20 July 2017
EMA/538285/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Gazyvaro

International non-proprietary name: obinutuzumab

Procedure No. EMEA/H/C/002799/0000

Note

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

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List of abbreviations

ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AEPI	adverse event of particular interest
BSIZ	baseline tumor size
CHMP	Committee for Medicinal Products for Human Use
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisolone
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CRu	unconfirmed complete response
CSR	clinical study report
CVP	cyclophosphamide, vincristine, and prednisone
DFS	disease-free survival
DLBCL	diffuse large B-cell lymphoma
DoR	duration of response
EFS	event-free survival
ESMO	European Society for Medical Oncology
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FC	fludarabine and cyclophosphamide
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
G-benda	obinutuzumab + bendamustine
GELF	Groupe d'Etude des Lymphomes Folliculaires
GI	gastrointestinal
HAHA	human anti-human antibodies
HR	hazard ratio
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
iNHL	indolent non-Hodgkin's lymphoma
IRC	Independent Review Committee
IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous
mAb	monoclonal antibody
MZL	marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NHL	non-Hodgkin's lymphoma
ORR	objective response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic(s)
PR	partial response
SAE	serious adverse event
sBLA	Supplemental Biologics License Application
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	stable disease
SLL	small lymphocytic lymphoma
SMQ	Standardised MedDRA Queries
SOC	system organ class

TLS	tumor lysis syndrome
TTNALT	time to new anti-lymphoma treatment

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Limited submitted to the European Medicines Agency on 7 October 2016 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 a new indication for Gazyvaro in combination with chemotherapy, followed by Gazyvaro maintenance therapy in patients achieving a response, for the treatment of patients with previously untreated advanced follicular lymphoma; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the RMP are updated in accordance. In addition, the due date for provision of the final clinical study report of study BO21223/GALLIUM listed in the Gazyvaro RMP as Category 3 has been updated. Furthermore, the Annex II is brought in line with the latest QRD template (version 10). In addition, clarification or editorial changes to the SmPC are proposed for accuracy and clarity.

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

Gazyvaro, was designated as an orphan medicinal product EU/3/12/1054 on 10 October 2012 and EU/3/15/1504 on 19 June 2015. Gazyvaro was designated as an orphan medicinal product in the following indication: Treatment of chronic lymphocytic leukaemia and Treatment of follicular lymphoma.

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) EMEA-33-2010 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 applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

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

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Sinan B. Sarac Co-Rapporteur: Pierre Demolis

Timetable	Actual dates
Submission date	7 October 2016
Start of procedure:	29 October 2016
CHMP Co-Rapporteur Assessment Report	26 December 2016
CHMP Rapporteur Assessment Report	22 December 2016
PRAC Rapporteur Assessment Report	22 December 2016
PRAC members comments	04 January 2017
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	12 January 2017
CHMP members comments	16 January 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 January 2017
Request for supplementary information	26 January 2017
Procedure Re-start	20 March 2017
CHMP Rapporteur Assessment Report	26 April 2017
PRAC Rapporteur Assessment Report	20 April 2017
PRAC members comments	26 April 2017
Updated PRAC Rapporteur Assessment Report	26 April 2017
PRAC Outcome	05 May 2017
CHMP members comments	08 May 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	11 May 2017
2nd Request for supplementary information	18 May 2017
Procedure Re-start	21 June 2017
CHMP Rapporteur Assessment Report	05 July 2017
CHMP members comments	10 July 2017
Updated CHMP Rapporteur Assessment Report	11 July 2017
The CHMP adopted a report on market exclusivity on	20 July 2017
Opinion	20 July 2017

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The benefit of adding rituximab to combination chemotherapy during the initial treatment of advanced NHL has been documented in multiple clinical trials over the past decade.

Efficacy and safety results of the pivotal, randomized, open-label, Phase III study BO21223 (GALLIUM) in patients with previously untreated advanced indolent non –Hodgkin lymphoma NHL compare obinutuzumab to established treatment with rituximab.

2.1.2. Disease or condition

Non-Hodgkin's lymphoma (NHL) includes all types of malignant lymphomas except from Hodgkin's disease. These include a heterogeneous group of malignancies, ranging from slow-growing iNHL, which comprise about a third of all NHLs, to more aggressive forms of NHL. The main subtypes of iNHL are follicular lymphoma, marginal zone lymphomas, and small lymphocytic lymphoma. Follicular lymphomas are indolent (slow-growing) NHL and the second-most-common form of non-Hodgkin's lymphomas overall.

2.1.3. Epidemiology , Aetiology and pathogenesis

Follicular lymphomas (FLs) are the second most frequent subtype of nodal lymphoid malignancies in Western Europe. The annual incidence of this disease in the EU has rapidly increased during recent decades and has risen from 2–3/100 000 during the 1950s to 5/100 000 recently [1], representing approximately 22% of all NHLs and 70% of indolent NHL. Marginal zone lymphomas account for approximately 5-10% of NHL cases.

2.1.4. Biologic features and risk factors, screening tools/prevention

NHL is distinguished from Hodgkin's disease only by the absence of binucleate giant cells. Follicular lymphomas are indolent (slow-growing) NHL and the second-most-common form of non-Hodgkin's lymphomas overall, defined as a lymphoma of follicle center B-cells (centrocytes and centroblasts), which has at least a partially follicular pattern. It is positive for the B-cell markers CD10, CD19, CD22, and usually CD20, but almost always negative for CD5.

Follicular lymphoma is defined as a mature B-cell neoplasm in the 2008 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues. Follicular lymphoma cells are malignant counterparts of normal germinal center B cells. Approximately 85% of patients with FL have a genomic translocation t(14;18)(q32;q21), [2] which results in the overexpression of the BCL-2 protein, a member of a family of proteins that blocks programmed cell death or apoptosis.

2.1.5. Clinical presentation and diagnosis and stage/prognosis

Diagnosis should be based on a surgical specimen/excisional lymph node biopsy and in the cases without easily accessible lymph nodes core biopsies can be carried. Fine needle aspirations are inappropriate for a reliable diagnosis. The histological report should give the diagnosis according to the World Health Organization (WHO) classification. Grading of lymph node biopsies is carried out

according to the number of blasts/high-power field (Table 1). FL grade 3B (with sheets of blasts) is considered an aggressive lymphoma and treated as such, whereas grade 1, 2 and 3A should be treated as indolent disease [3]. Review, especially of grade 3A or 3B, by an expert haematopathologist is performed if the infiltration pattern is atypical (diffuse areas, even with small cells).

Since treatment largely depends on the stage of the disease, initial staging should be thorough, particularly in the small proportion of patients with early stages I and II (10%–15%) including a computed tomography (CT) scan of the neck, thorax, abdomen and pelvis, and a bone marrow aspirate and biopsy; Positron emission tomography (PET)–CT is particularly important to confirm localised stage I/II before involved-field radiotherapy.

A complete blood count, routine blood chemistry including lactate dehydrogenase (LDH), β2 microglobulin and uric acid as well as screening tests for human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C are required. The staging is carried out according to the Ann Arbor classification system with mention of bulky disease (>7 cm) when appropriate.

For prognostic purposes, a 'Follicular Lymphoma-specific International Prognostic Index' (FLIPI, see Table 1) has been established [4]. A revised FLIPI 2 (incorporating β2 microglobulin, diameter of largest lymph node, bone marrow involvement and haemoglobin level) has been suggested for patients requiring treatment which may be more informative on progression-free survival (PFS) [5].

Table 1: Follicular Lymphoma-specific International Prognostic Index' (FLIPI) risk factors

	Definition of risk factors	
Parameter	**FLIPI 1**	**FLIPI 2**
Nodal sites	>4 lymph node regions (definition in [5])	Long diameter of largest lymph node >6 cm
Age	>60 years	>60 years
Serum marker	Elevated LDH	Elevated β2 microglobulin
Stage	Advanced (III–IV according to Ann Arbor classification)	Bone marrow involvement
Haemoglobin	<12 g/dl	<12 g/dl

0–1 risk factors, low risk; 2 risk factors, intermediate risk; 3–5 risk factors, high risk.

LDH, lactate dehydrogenase.

2.1.6. Management

Current treatment options for patients with previously untreated advanced follicular lymphoma according to recommendations for initial treatment of follicular lymphoma in ESMO and NCCN guidelines, treatment options for newly diagnosed patients with FL include "watch and wait", radiotherapy, and systemic treatments.

Systematic treatments include chemoimmunotherapy (R-CHOP, R-CVP, R-benda) and in selected cases (elderly/infirm patients) rituximab monotherapy (or R-chlorambucil for elderly patients). For patients who achieve response (CR/PR) rituximab maintenance is indicated.

About the product

Obinutuzumab (GAZYVA®, GAZYVARO®; also known as GA101 and RO5072759) is a glycoengineered, humanized Type II CD20 monoclonal antibody of the immunoglobulin G1 (IgG1) isotype. It consists of two heavy chains and two light chains with inter- and intra-chain disulfide bonds, as is typical of IgG1 antibodies. Obinutuzumab was derived by humanization of the parental B-Ly1 mouse antibody and is produced in the Chinese Hamster Ovary (CHO) K1 cell line. It has been glycoengineered to improve a number of characteristics compared with the anti-CD20 antibody, rituximab. The calculated molecular mass of intact obinutuzumab is 146,321 Da (peptide chains only, with heavy chain C-terminal lysine residue and heavy chain N-terminal glutamines).

Obinutuzumab recognizes a type II epitope of the CD20 molecule found on B cells. It has high-affinity binding to the CD20 antigen, low complement-dependent cytotoxicity (CDC) activity, high direct cell death induction and high antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). Based on these features and nonclinical studies, obinutuzumab was expected to have improved efficacy with similar toxicity to rituximab, which is an established treatment for patients with B-cell malignancies, including chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL) and other B-cell disorders.

Obinutuzumab was first approved for use in combination with chlorambucil in the first-line treatment of patients with CLL in the United States (US) (November 2013), the European Union (EU) (July 2014) and many other countries based on the results of the pivotal Phase III trial, study BO21004 (CLL-11). Obinutuzumab was later approved for use in combination with bendamustine in patients with follicular lymphoma (FL) who did not respond to a rituximab-containing regimen, in the US (February 2016) and in the EU (June 2016), based on the results of the pivotal Phase III trial, GAO4753g (GADOLIN).

This application is seeking approval of an additional indication for obinutuzumab in patients with previously untreated FL based on the results of the pivotal Phase III trial, BO21223 (GALLIUM). The proposed indication is as follows:

"Gazyvaro in combination with chemotherapy, followed by Gazyvaro maintenance therapy in patients achieving a response, is indicated for the treatment of patients with previously untreated advanced follicular lymphoma."

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by

the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

An ERA has not been submitted as part of this application (see discussion on non-clinical aspects).

2.2.2. Discussion on non-clinical aspects.

No new non-clinical-related information is relevant for the present application.

Since obinutuzumab is a monoclonal antibody and as such it is a protein (molecular mass ~150 kDa), it is exempted from the submission of an ERA as according to the Guideline on Environmental Risk Assessment (ERA) for Non-GMO Human Medicinal Products [EMEA/CHMP/SWP/4447/00 corr. 2] an ERA is not required proteins and peptides, as "due to their nature they are unlikely to result in a significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

GCP

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

The MAH 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**

Table 2: Clinical Pharmacology studies

Protocol No.	Location of Synopsis Location of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3 Clinical Study Reports								
5.3.1 Reports of Biopharmaceutic Studies								
5.3.1.1 Bioavailability (BA) Study Reports								
No Study Conducted								
5.3.1.2 Comparative BA/BE Study Reports								
No Study Conducted								
5.3.1.3 In vitro – In vivo Correlation Study Reports								
No Study Conducted								
5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies								
Quantification of RO5072759 in human serum by ELISA (amended)	No synopsis available (Report No. 1028962) (amendment)	NA	NA	NA	NA	MA	NA	NA

Protocol No.	Location of Synopsis Location of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Semi-quantitative determination of antibodies directed to RO5072759 in human serum by ELISA (amended)	No synopsis available (Report No. 1032264) (amendment)	NA	NA	NA	NA	MA	NA	NA
5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials								
No Study Conducted								
5.3.3 Reports of Human Pharmacokinetic (PK) Studies								
5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports								
No Study Conducted								
5.3.3.2 Patient PK and Initial Tolerability Study Reports								
No Study Conducted								
5.3.3.3 Intrinsic Factors PK Study Reports								
No Study Conducted								
5.3.3.4 Extrinsic Factors PK Study Reports								
No Study Conducted								

Protocol No.	Location of Synopsis Location of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.3.5 Population PK Study Reports								
Population PK analysis for obinutuzumab in patients with FL or MZL (Study BO21223)	No synopsis available (Report No. 1072889)	NA	NA	NA	NA	MA	NA	NA
5.3.4 Reports of Human Pharmacodynamic (PD) Studies								
No Study Conducted								

Table 3: Overview of Clinical efficacy studies

Protocol No.	Location of Synopsis Location of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.5 Reports of Efficacy and Safety Studies								
5.3.5.1 Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (Previously Untreated Follicular Lymphoma)								
BO21223 (GALLIUM)	Synopsis Primary CSR BO21223 Report Primary CSR BO21223 (Report No. 1067980)	**Primary:** Efficacy (PFS) **Secondary:** Efficacy (ORR, CR at EOI [± FDG-PET], EFS, DFS, DoR, PROs, Safety, Pharmacokinetics, Pharmacodynamics **Exploratory:** MRD (*BCL/IgH*), Conversion rate, (PR to CR, or SD to PR/CR) during maintenance.	Open label, multicenter, randomized 2-arm Phase III study. (G-chemo vs. R-chemo).	**Induction:** Obinutuzumab 1000 mg IV on D1 of 6-8 cycles (+ D8 & D15 of C1) (G-chemo arm) (plus one of: CHOP [6 × 21d cycles], CVP [8 × 21d cycles], or bendamustine [6 × 28d cycles]). **Maintenance:** (for CR/PR responders at EOI) obinutuzumab monotherapy (1000 mg) (G-Chemo arm) every 2 mo until PD for up to 2 yrs.	Total:1401 FL: 1202 (601 in G-chemo arm) MZL: 195 other NHL: 4	Documented CD20+ FL (Grade 1-3a), sMZL, nMZL, eMZL Stage III/IV or bulky Stage II requiring treatment.	Total: 30 months (6 months induction plus 24 months maintenance) .	Study ongoing; full primary CSR available.

Protocol No.	Location of Synopsis Location of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.5.2 Reports of Uncontrolled Clinical Studies								
BO21000 (GAUDI)	Synopsis Final Study Report BO21000 Final Clinical Study Report BO21000 (Report No. 1068428)	**Primary:** Safety **Secondary:** Efficacy (EOT response, BOR, CR, PFS, EFS), pharmacokinetics, pharmacodynamics.	Open label, multicenter, Phase Ib study (G-CHOP, G-benda)	Induction: Obinutuzumab: 1000 mg IV (Day 1 of 6-8 cycles (+Days 8 of Cycle 1) combined with either: CHOP for 6-8 × 21d cycles or bendamustine for 4-6 × 28d cycles. Maintenance: (for CR/PR responders at EOI)†: Obinutuzumab once every 3 mo for 2 yrs (or PD).	first-line FL*: 81	Documented CD20+ FL patients with no prior systemic therapy*.	6-8 cycles of Induction treatment (total 24 weeks)	Study completed; Final CSR covering final safety and efficacy data including maintenance treatment and follow-up is provided in this submission†.

CR = complete response; DFS = disease-free survival; DoR = duration of response; EFS = event-free survival; ELISA = enzyme-linked immunosorbent assay; EOI = end of induction; EOT = end of treatment ; INV = investigator; IRC = independent review committee; TTNLT = time to next anti-leukemia treatment; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome.

* BO21000/GAUDI also enrolled patients with relapsed/refractory FL. Only the data from the first-line patients will be used to support this submission.

† Primary BO21000 CSR for first-line patients (Report No. 1050659) included data from the induction treatment period has been submitted previously as part of the initial BLA.

Study, Phase	Study Design	Population	Efficacy Endpoints	Patients	Dose, Route, Regimen
Pivotal Study					
BO21223 (GALLIUM) Phase III	Open-label, multicenter, randomized (G-chemo followed by G maintenance vs. R-chemo followed by R maintenance)	Histologically documented CD20+, previously untreated iNHL (FL, splenic MZL, nodal MZL, or extranodal MZL)	**Primary**: (INV-PFS) in FL population **Secondary**: Overall population: INV-PFS FL and overall population: IRC-PFS, CR and ORR at EOI (with and without PET, by INV and IRC), OS, EFS, DFS, DOR, TTNLT, change in PROs **Exploratory**: MRD by BCL2/IgH (in FL) Conversion rate (PR to CR, or SD to PR/CR) during maintenance (Key analyses of PFS, CR rate, and ORR will be repeated based on IRC assessments)	**Randomized at clinical cutoff date**: 1202 patients with FL: G-chemo (n = 601) R-chemo (n = 601)	Obinutuzumab (in combination with chemotherapy) induction: 1000 mg for eight 21-day cycles (CHOP[a]/CVP[b] arms) or six 28-day cycles (bendamustine[c] arm). Obinutuzumab on Day 1, 8, 15 of Cycle 1 and Day 1 for subsequent cycles. Responders (CR, PR) in G-chemo arm receive obinutuzumab 1000 mg every 2 months maintenance for a maximum of 2 years or until progression, and responders in R-chemo arm receive rituximab 375 mg/m^2 every 2 months maintenance therapy for a maximum of 2 years or until progression.

Study, Phase	Study Design	Population	Efficacy Endpoints	Patients	Dose, Route, Regimen
Supporting Study					
BO21000 (GAUDI) Phase Ib	Open-label, multicenter, 2-part [d] (G-benda, G-CHOP)	Documented CD20+relapsed/ refractory FL or documented CD20+ FL with no prior systemic therapy	**Primary**: Safety **Secondary**: ORR, CR rates, PFS, EFS Exploratory: CR30, DOR	**Patients Enrolled and Included in this Report**: 81 patients with previously-untreated FL: G-benda (n=40) G-CHOP (n=41)	G-CHOP arm[e]: Obinutuzumab (1000 mg absolute [flat] dose) was administered on Days 1 and 8 of the first 3-week cycle (i.e., 21 days), and then on Day 1 for subsequent 3-week cycles (i.e., six-eight 21-day cycles). G-benda arm[f]: Obinutuzumab (1000 mg absolute [flat] dose) was administered on Days 1 and 8 of the first 4-week cycle (i.e., 28 days) and then on Day 1 for subsequent 4-week cycles (i.e., four–six 28-day cycles). Responders (CR, PR) were eligible (at the investigator's discretion) to receive maintenance obinutuzumab 1000 mg every 3 months until progression or for a maximum of 2 years.

2.3.2. Pharmacokinetics

The primary and secondary pharmacology of obinutuzumab and chemotherapy drugs has been previously investigated.

Population Pharmacokinetics

Population PK model (Report 1072889):

Analysis objectives:

- To update a previously developed population model [Report No. 1065581] that describes pharmacokinetics of obinutuzumab following intravenous administration in patients with CD20+ B-cells malignancies.
- To re-estimate population PK parameters of the model
- To determine post-hoc estimates for derived PK parameters (steady-state AUC_T, Cmax, Ctrough, terminal half-life and effective half-life)
- To re-estimate the inter-individual variability of model parameters in the patient population
- To re-estimate the residual variability of the dependent variable (obinutuzumab concentration) in the patient population
- To confirm and re-estimate the effects of previously identified covariate factors that influence disposition of obinutuzumab, and to estimate the effects of new covariates
- To determine whether the presence of anti-drug antibodies (ADAs) affects pharmacokinetics of obinutuzumab following intravenous administration in patients with CD20+ B-cells malignancies
- To perform model-based simulations of clinically relevant dosing regimens.

The analyzed dataset:

The population PK model was previously built using data from studies BO20999, BO21000, BO21003, BO21004, GAO4753g, and GAO4915g. These data included 16301 serum concentration values of obinutuzumab from a total of 961 patients with chronic lymphocytic leukemia (CLL), FL (406 patients), MZL (35 patients), other indolent non-Hodgkin lymphoma (iNHL) subtypes, diffuse large B-cell lymphoma (DLBCL), or mantle cell lymphoma (MCL). The current population PK analysis added the data from study BO21223 (7550 concentration values from a total of 493 patients with FL [408], MZL [84], and CLL [1]) to the previous data set, thus including a total of 23,851.

Model characteristics:

The PK model comprises two clearance pathways: a linear clearance and a nonlinear time varying clearance pathway (target mediated drug disposition: TMDD). This model was applied to the data and the model parameters were re-estimated consecutively to the inclusion of the data from study BO21223. The estimated parameters are reported below (Table 4) as well as the parameters of the prior model (table 14) for analysis and comparison purpose.

Table 4: Parameter estimates for final model of the prior analysis (model 171imp).

Parameter		Estimate	RSE(%)	95%CI
k_{des} (1/day)	$\exp(\theta_1)$	0.11	7.2	0.0956 - 0.127
CL_T (L/day)	$\exp(\theta_2)$	0.154	9.12	0.129 - 0.184
CL_{inf} (L/day)	$\exp(\theta_3)$	0.0742	2.67	0.0705 - 0.0782
V_1 (L)	$\exp(\theta_4)$	2.72	1.22	2.65 - 2.78
V_2 (L)	$\exp(\theta_5)$	1.23	3.95	1.14 - 1.33
Q (L/day)	$\exp(\theta_6)$	1.32	11.4	1.06 - 1.65
$CL_{inf,WT}$	θ_7	0.639	14.5	0.458 - 0.82
$V_{1,WT}$	θ_8	0.378	10.1	0.304 - 0.453
$V_{2,WT}$	θ_9	1.08	14.5	0.77 - 1.38
$k_{des,CHOP}$	$\exp(\theta_{10})$	0.309	11.1	0.249 - 0.384
$k_{des,bendamustine}$	$\exp(\theta_{11})$	0.591	14.4	0.445 - 0.784
$k_{des,FC}$	$\exp(\theta_{12})$	2.64	33.0	1.39 - 5.05
$k_{des,MZL}$	$\exp(\theta_{13})$	0.299	25.6	0.181 - 0.493
$CL_{T,CLL}$	$\exp(\theta_{14})$	2.25	13.6	1.72 - 2.94
$CL_{T,MCL}$	$\exp(\theta_{15})$	2.80	40.0	1.28 - 6.14
$CL_{T,BSIZ}$	θ_{16}	0.351	15.4	0.245 - 0.456
$CL_{T,SEX}$	$\exp(\theta_{17})$	1.45	10.0	1.19 - 1.77
CL_{SLL}	$\exp(\theta_{18})$	1.38	11.5	1.1 - 1.73
CL_{CLL}	$\exp(\theta_{19})$	1.47	3.68	1.37 - 1.58
CL_{MCL}	$\exp(\theta_{20})$	2.07	18.3	1.45 - 2.96
CL_{BSIZ}	θ_{21}	0.09	18.2	0.0578 - 0.122
CL_{SEX}	$\exp(\theta_{22})$	1.18	3.51	1.1 - 1.26
CL_{AGE}	θ_{23}	-0.241	29.3	-0.379 - -0.103
CL_{ALB}	θ_{24}	-0.682	16.7	-0.906 - -0.459
$V_{1,SEX}$	$\exp(\theta_{25})$	1.19	1.54	1.16 - 1.23

Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage
ω^2_{kdes}	Ω(1,1)	0.82	8.56	0.682 - 0.958	CV=90.6%	25.6%
ω^2_{CLT}	Ω(2,2)	1.21	19.7	0.74 - 1.67	CV=110%	26.9%
ω^2_{CLinf}	Ω(3,3)	0.199	7.16	0.171 - 0.227	CV=44.6%	6.1%
ω^2_{V1}	Ω(4,4)	0.0341	7.01	0.0295 - 0.0388	CV=18.5%	10.7%
ω^2_{V2}	Ω(5,5)	0.23	12.1	0.175 - 0.284	CV=47.9%	39.3%
ω^2_{Q}	Ω(6,6)	0.956	17.8	0.623 - 1.29	CV=97.8%	50.2%
ω^2_{EPS}	Ω(7,7)	0.224	8.02	0.189 - 0.259	CV=47.3%	2.4%
σ^2	Σ(1,1)	1	Fixed			2.2 %
σ_L	θ_{26}	1.77	9.72	1.43 - 2.11		
σ_H	θ_{27}	0.111	3.78	0.103 - 0.119		
σ_{50} (ug/mL)	θ_{28}	8.26	14.9	5.85 - 10.7		

SE: Standard Error: RSE: Relative Standard Error, %RSE=100·SE/PE, where PE is a parameter estimate;. 95% CI: 95% confidence interval. SD: Standard Deviation; CV: coefficient of variation, CV = 100*SD %.

Source: 171impParEst.csv, 171impParEstExp.csv.

Table 5: Parameter estimates for final model 009imp

Parameter		Estimate	RSE(%)	95%CI
k_{des} (1/day)	$\exp(\theta_1)$	0.112	7.61	0.0969 - 0.131
CL_T (L/day)	$\exp(\theta_2)$	0.145	5.93	0.129 - 0.163
CL_{inf} (L/day)	$\exp(\theta_3)$	0.0753	1.93	0.0726 - 0.0782
V_1 (L)	$\exp(\theta_4)$	2.59	1.02	2.54 - 2.64
V_2 (L)	$\exp(\theta_5)$	1.47	2.53	1.4 - 1.55
Q (L/day)	$\exp(\theta_6)$	1.32	9.18	1.11 - 1.59
$CL_{inf, WT}$	θ_7	0.721	9.08	0.593 - 0.849
$V_{1, WT}$	θ_8	0.437	7.43	0.374 - 0.501
$V_{2, WT}$	θ_9	0.776	12.5	0.585 - 0.967
$k_{des,CHOP-CVP}$	$\exp(\theta_{10})$	0.285	9.26	0.238 - 0.342
$k_{des,bendamustine}$	$\exp(\theta_{11})$	0.466	10.1	0.382 - 0.567
$k_{des,FC}$	$\exp(\theta_{12})$	2.88	34.6	1.46 - 5.67
$CL_{T,MZL}$	$\exp(\theta_{13})$	1.4	11.3	1.12 - 1.75
$CL_{T,CLL}$	$\exp(\theta_{14})$	2.28	13.1	1.77 - 2.95
$CL_{T,MCL}$	$\exp(\theta_{15})$	2.98	39.9	1.36 - 6.51
$CL_{T,BSIZ}$	θ_{16}	0.345	10.7	0.273 - 0.418
$CL_{T,SEX}$	$\exp(\theta_{17})$	1.48	7.12	1.29 - 1.7
CL_{SLL}	$\exp(\theta_{18})$	1.38	11.5	1.1 - 1.73
CL_{CLL}	$\exp(\theta_{19})$	1.45	3.41	1.36 - 1.55
CL_{MCL}	$\exp(\theta_{20})$	2.04	18.4	1.43 - 2.93
CL_{BSIZ}	θ_{21}	0.0596	19.5	0.0368 - 0.0824
CL_{SEX}	$\exp(\theta_{22})$	1.18	2.61	1.12 - 1.24
CL_{AGE}	θ_{23}	-0.211	24.1	-0.311 - -0.111
CL_{ALB}	θ_{24}	-0.493	19.1	-0.677 - -0.309
$V_{1,SEX}$	$\exp(\theta_{25})$	1.19	1.33	1.16 - 1.22
$CL_{T,ADA}$	$\exp(\theta_{29})$	3.09	21.3	2.04 - 4.69
$k_{des,ADA}$	$\exp(\theta_{30})$	1.74	17.4	1.24 - 2.45

Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage
ω^2_{kdes}	Ω(1,1)	0.821	7.96	0.693 - 0.949	CV=90.6%	22.8%
ω^2_{CLT}	Ω(2,2)	1.09	15.2	0.768 - 1.42	CV=104%	22.5%
ω^2_{CLinf}	Ω(3,3)	0.163	6.76	0.141 - 0.184	CV=40.4%	6.2%
ω^2_{V1}	Ω(4,4)	0.0355	5.67	0.0316 - 0.0395	CV=18.9%	10.6%
ω^2_{V2}	Ω(5,5)	0.143	10.8	0.112 - 0.173	CV=37.8%	43.4%
ω^2_{Q}	Ω(6,6)	0.997	13.9	0.726 - 1.27	CV=99.9%	47.7%
ω^2_{EPS}	Ω(7,7)	0.191	7.33	0.163 - 0.218	CV=43.6%	3.8%
σ^2	Σ(1,1)	1	Fixed			2.6 %
σ_L	θ_{26}	1.59	7.87	1.34 - 1.83		
σ_H	θ_{27}	0.121	2.6	0.115 - 0.127		
σ_{50} (ug/mL)	θ_{28}	7.55	11.9	5.79 - 9.3		

SE: Standard Error: RSE: Relative Standard Error, %RSE=100·SE/PE, where PE is a parameter estimate;. 95% CI: 95% confidence interval. SD: Standard Deviation; CV: coefficient of variation, CV = 100*SD %.

Source: 009impParEst.csv.

Table 6: Covariates identified with significant impact on obinutuzumab PK

Parameter	Covariate	Reference Value	Covariate Value[a]	Covariate Effect Value [95%CI](%)
CL_{inf}	Body weight	75 kg	50 kg	-25.3 [-21.4;-29.1]
			115 kg	36.1 [28.8;43.8]
	Albumin	40 g/L	29.0 g/L	17.2 [24.3;10.4]
			48.6 g/L	-9.2 [-12.4;-5.8]
	Sex	Female	Male	17.7 [11.8;23.9]
	Disease type	FL, MZL or DLBCL	CLL	45.2 [35.8;55.3]
			SLL	38.0 [10.2;72.9]
			MCL	104.3 [42.5;192.9]
	Age	65 years	38 years	12.0 [18.2;6.2]
			82 years	-4.8 [-7;-2.6]
	Baseline tumor size	3000 mm^2	344 mm^2	-12.1 [-7.7;-16.3]
			27500 mm^2	14.1 [8.5;20]
CL_T	Sex	Female	Male	48.3 [29;70.5]
	Disease type	FL or DLBCL	CLL	128.3 [76.5;195.3]
			MCL	197.8 [36.1;551.5]
			MZL	40.2 [12.4;75]
	Baseline tumor size	3000 mm^2	344 mm^2	-52.7 [-44.7;-59.5]
			27500 mm^2	115 [83.2;152.3]
	ADA detection	Not detected	Detected	209.2 [103.8;369.1]
V_1	Body weight	75 kg	50 kg	-16.2 [-14.1;-18.4]
			115 kg	20.6 [17.3;23.9]
	Sex	Female	Male	18.6 [15.6;21.8]
V_2	Body weight	75 kg	50 kg	-27.0 [-21.1;-32.4]
			115 kg	39.3 [28.4;51.2]
k_{des}	CHOP or CVP	Not Administered	Administered	-71.5 [-76.2;-65.8]
	FC	Not Administered	Administered	187.6 [45.9;466.9]
	Bendamustine	Not Administered	Administered	-53.4 [-61.8;-43.3]
	ADA detection	Not detected	Detected	74.4 [24;145.4]

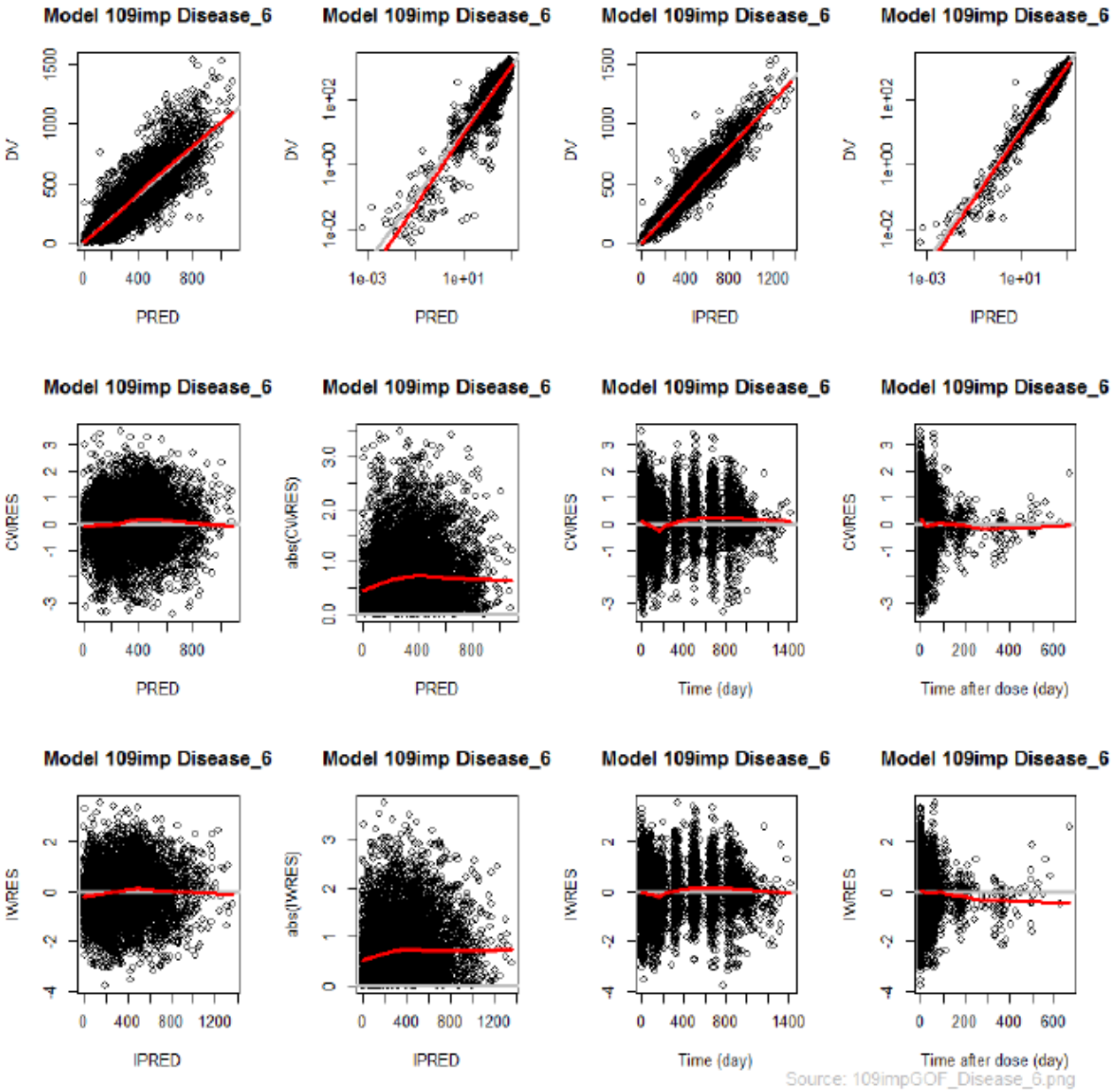
a. The values of the continuous covariates represent 2.5th and 97.5th percentiles of the values in the combined data set.

Source: 009impCovEffectsTable.csv.

Model qualification/ validation:

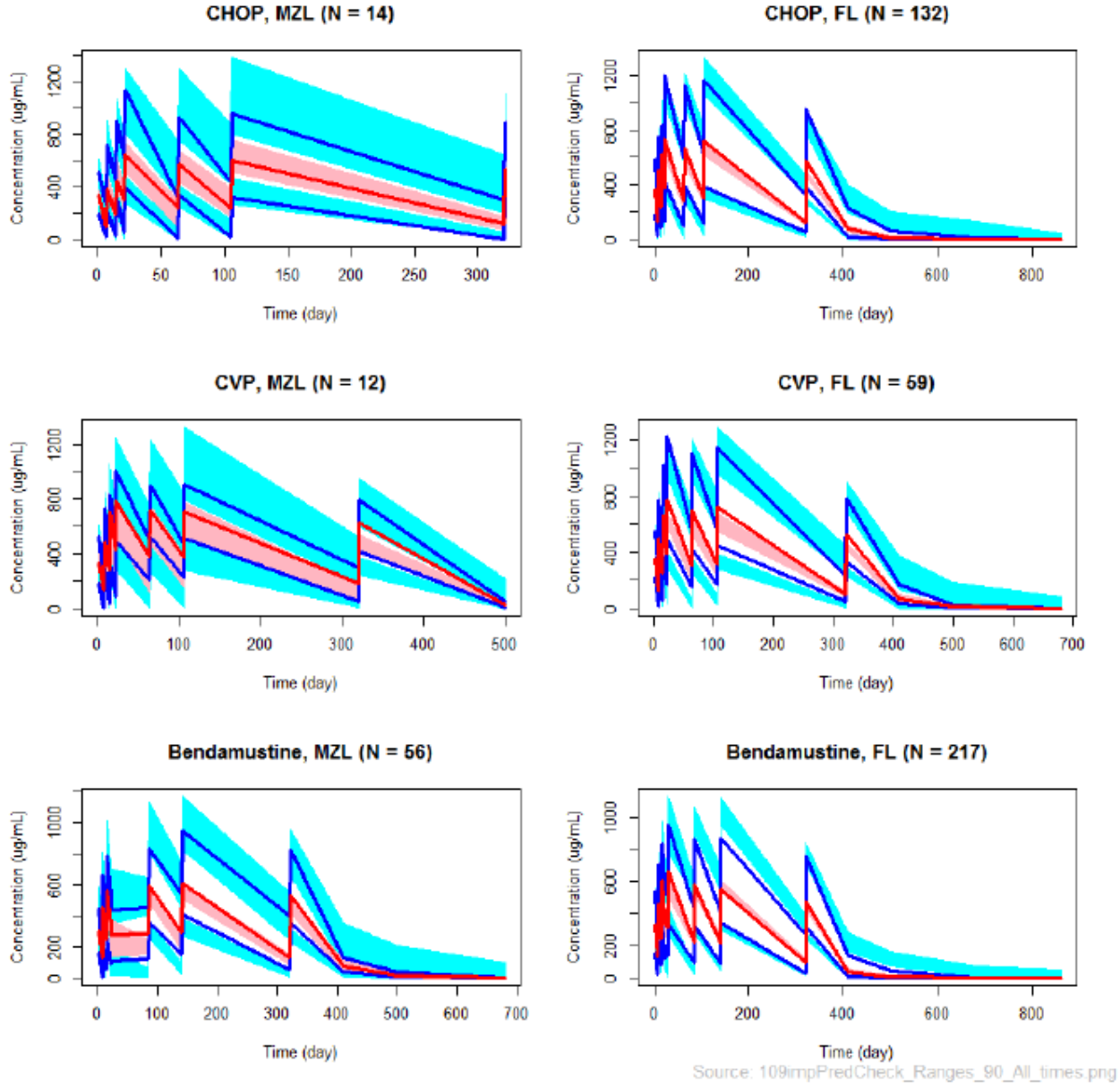
The model evaluation included graphical examination of the goodness of plots (Figure 1) and Visual predictive checks (Figure 2).

Figure 1: Goodness of fit for model 009imp: Study BO21223, patients with FL



Source: 109impGOF_Disease_6.png

Figure 2: Visual predictive check model 009imp: Study BO21223



Systemic exposure to obinutuzumab predictions:

The model was used for the predictions of systemic exposure to obinutuzumab in the target population but also in MZL patients when co-treated with chemotherapy (CHOP or CVP) and obinutuzumab 21-day cycles (during the induction phase) or with bendamustine and obinutuzumab 28 day cycles.

Table 7: Summary of conditional predictions for C_{max}, C_{trough} and AUC following G-CHOP/CVP dosing regimen, by iNHL subtype

The covariate factors and patients' individual random effects were used to compute PK parameters in each group following G-CHOP/CVP dosing regimen (1000 mg on Days 1, 8, and 15 of cycle 1, and on Day 1 of cycles 2-8, cycle duration 21 days; then every 8 weeks). Residual variability was not included in the simulations. CV was computed as standard deviation of the log-transformed data. MZL: marginal zone lymphoma; FL: follicular lymphoma.

	Statistic	iNHL Subtype	
		MZL	FL
Number of patients		26	191
Induction (Cycle 8, Day 148 to 169)			
C_{max} (µg/mL)	Mean (SD)	668.5 (218.2)	706.2 (209.1)
	Median (Range)	648.8 (195.4-1157.7)	671.8 (284.2-1459.8)
	Geometric Mean (CV)	629.3 (0.38)	676.4 (0.3)
C_{trough} (µg/mL)	Mean (SD)	421.2 (200.9)	431.4 (176.7)
	Median (Range)	388.8 (16.6-831.8)	396.2 (45.2-1072.8)
	Geometric Mean (CV)	338.3 (0.89)	394.6 (0.44)
AUC_T (µg/mL*day)	Mean (SD)	11048 (4476)	11429 (4049)
	Median (Range)	10446 (1512-20590)	10773 (2519-26080)
	Geometric Mean (CV)	9849 (0.56)	10723 (0.37)
Maintenance (Cycle 4 of Maintenance, Day 372 to 428)			
C_{max} (µg/mL)	Mean (SD)	426.9 (123)	436.9 (115.1)
	Median (Range)	416.7 (211.8-670.6)	410.9 (190.3-860.1)
	Geometric Mean (CV)	409.4 (0.3)	422.7 (0.26)
C_{trough} (µg/mL)	Mean (SD)	144.4 (86.7)	133.3 (70.5)
	Median (Range)	110.5 (1.4-313.9)	115.8 (15.2-392.4)
	Geometric Mean (CV)	104.9 (1.1)	115.5 (0.56)
AUC_T (µg/mL*day)	Mean (SD)	13848 (6077)	13375 (5094)
	Median (Range)	11755 (3276-24760)	12090 (4031-32340)
	Geometric Mean (CV)	12387 (0.52)	12474 (0.38)

Table 8: Summary of conditional predictions for C_{max}, C_{trough} and AUC following G-bendamustine dosing regimen, by iNHL subtype

The covariate factors and patients' individual random effects were used to compute PK parameters in each group following G-Bendamustine dosing regimen (1000 mg on Days 1, 8, and 15 of cycle 1, and on Day 1 of cycles 2-6, cycle duration 28 days; then every 8 weeks). Residual variability was not included in the simulations. CV was computed as standard deviation of the log-transformed data. MZL: marginal zone lymphoma; FL: follicular lymphoma.

Statistic		iNHL Subtype	
		MZL	FL
Number of patients		58	217
Induction (Cycle 6, Day 141 to 169)			
C_{max} (µg/mL)	Mean (SD)	548.4 (157.9)	533.1 (146)
	Median (Range)	524.8 (171-899)	521.5 (214.2-1003.2)
	Geometric Mean (CV)	524.3 (0.32)	513.4 (0.28)
C_{trough} (µg/mL)	Mean (SD)	310.5 (137.4)	279.6 (116.9)
	Median (Range)	288.3 (3.2-630.9)	259.9 (15.3-667.5)
	Geometric Mean (CV)	266.1 (0.75)	254.8 (0.46)
AUC_τ (µg/mL* day)	Mean (SD)	11478 (4190)	10702 (3653)
	Median (Range)	10600 (1094-21033)	10169 (2007-22341)
	Geometric Mean (CV)	10553 (0.47)	10088 (0.35)
Maintenance (Cycle 4 of Maintenance, Day 365 to 421)			
C_{max} (µg/mL)	Mean (SD)	399 (105.1)	386.8 (98.7)
	Median (Range)	380.4 (221.5-754.6)	378.5 (195.8-683.1)
	Geometric Mean (CV)	386.4 (0.25)	374.7 (0.25)
C_{trough} (µg/mL)	Mean (SD)	138.3 (84.5)	116.7 (63.8)
	Median (Range)	117.3 (28.5-535.2)	104.3 (13.5-351.8)
	Geometric Mean (CV)	118.9 (0.55)	100.8 (0.56)
AUC_τ (µg/mL* day)	Mean (SD)	13217 (5370)	11937 (4448)
	Median (Range)	11762 (6012-35160)	11319 (3829-25760)
	Geometric Mean (CV)	12321 (0.37)	11174 (0.36)

2.3.3. Pharmacodynamics

The mechanism of action as well as the primary and secondary pharmacology of obinutuzumab and chemotherapy drugs has been previously investigated.

2.3.4. PK/PD modelling

As part of the study BO21223, B-cells counts and tumor size were measured in patients with FL and MZL. A PK-PD modelling has been attempted by the applicant in order to assess the relationship these PD endpoints and the systemic exposure. The PPK model described above was used in order to estimate the systemic exposure to obinutuzumab.

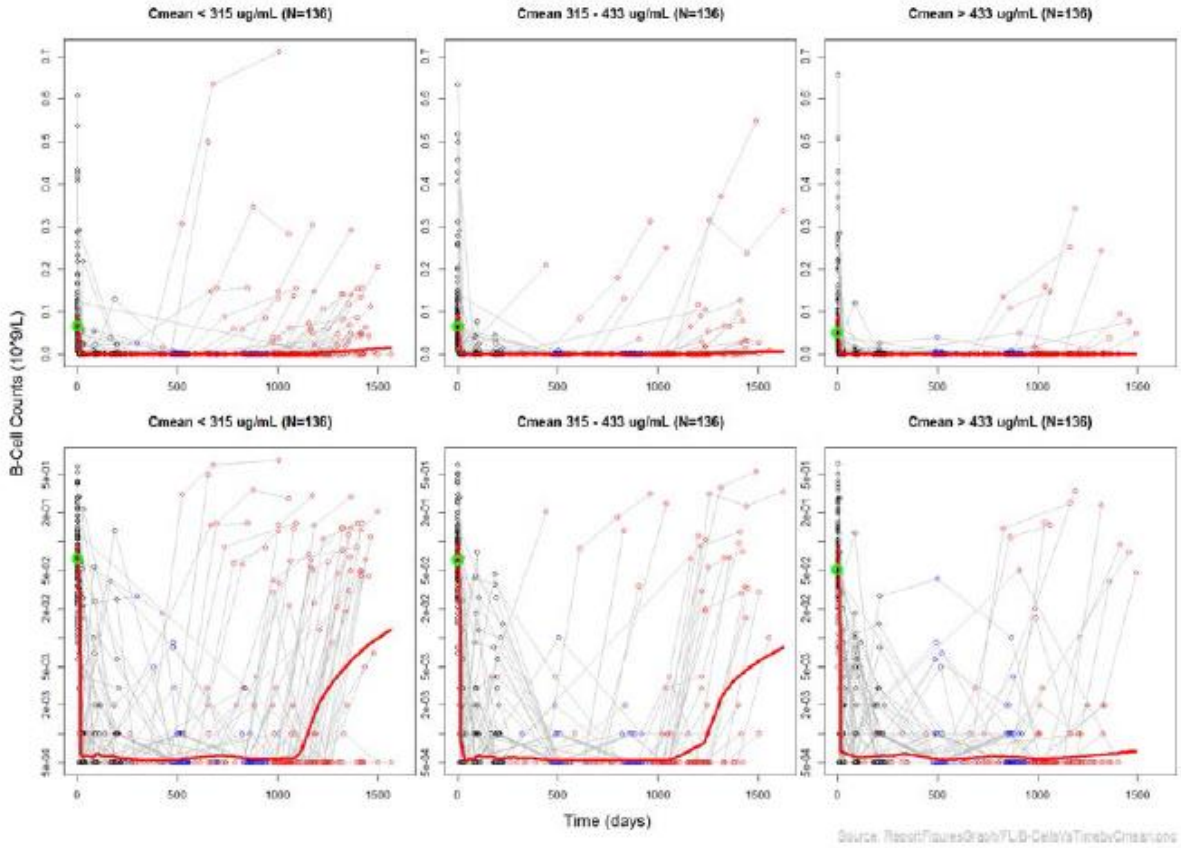
Relationship between obinutuzumab exposure and time course of B-cell counts:

The graphical analysis performed to assess the relationship between the observed values of B-cell counts and obinutuzumab exposure (Cmean) indicated that in all exposure groups B-cell counts declined from their baseline values to nearly zero after start of drug administration. B-cells remained

at very low levels for most patients (for majority of patients at BLQ levels) for most of the observation period (Figure 3).

Figure 3: B-cell counts over time by obinutuzumab exposure (C_{mean}), FL patients

Observed values over time (**points** and **thin gray lines**), on arithmetic scale (**top**) or semi-log scale (**bottom**) by categories of predicted C_{mean}. **Black**, **blue**, and **red** points denote observations during Induction, Maintenance, and during follow-up or following early discontinuation. **Red bold lines** are lowess smooth lines. The green circle at time zero illustrates median of the observed data at baseline. Values on lower plots of $5*10^{-4}$ were equal to zero (changed for visualization). 24 values at baseline ranging from 1 to 181 and 1 value of 3.4 at 90 days in the highest C_{mean} category not shown.

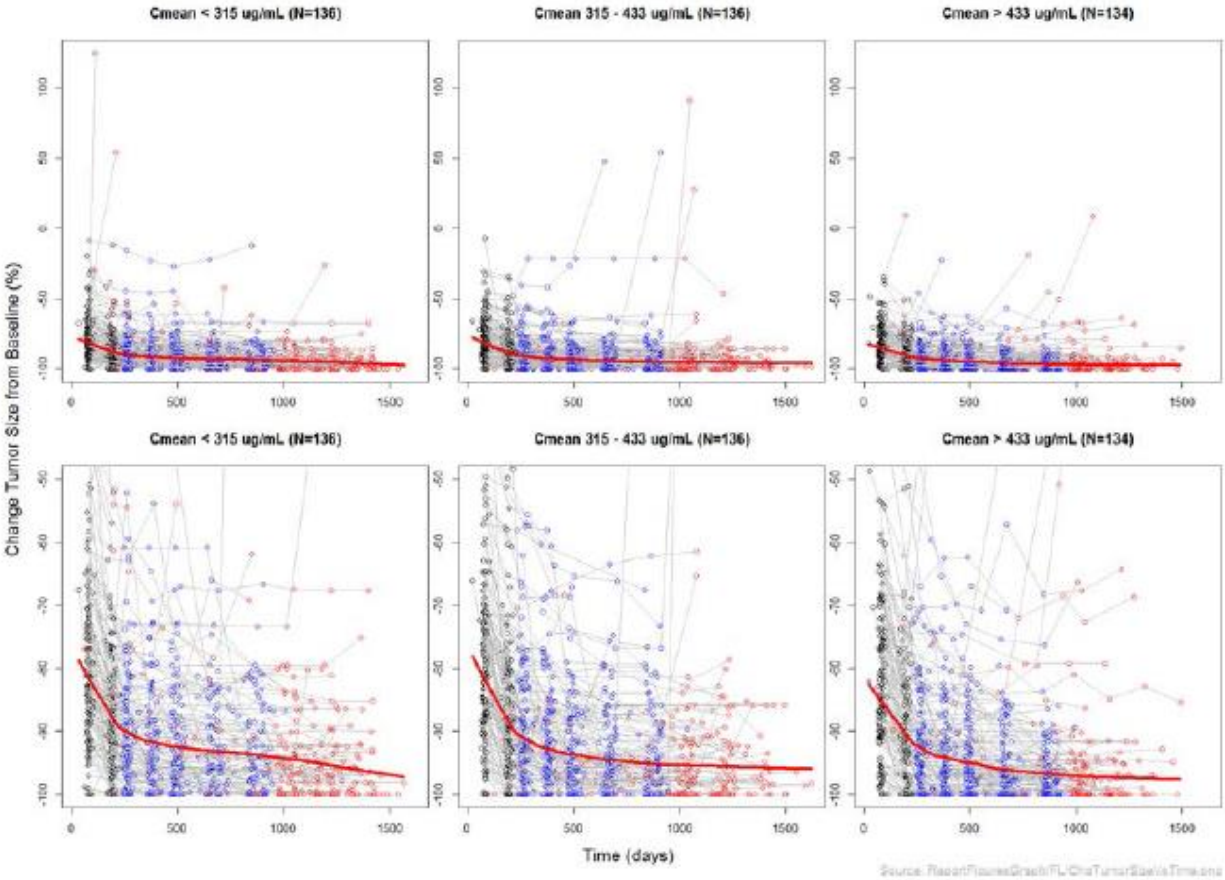


- Relationship between obinutuzumab exposure and tumor size decrease:

A graphical analysis was performed to assess the relationship between the change in tumor size and obinutuzumab exposure (Figure 198). Tumor size decreased during Induction from a median of approximately 5000 mm^2 to 500 mm^2 with a slow additional decrease during Maintenance. Change in tumor size was similar in all exposure categories.

Figure 4: % change of tumour size over time by obinutuzumab exposure (C_{mean}), FL patients

Observed values over time (**points** and **thin gray lines**) by categories of predicted C_{mean}. **Black**, **blue**, and **red** points denote observations during Induction, Maintenance, and during follow-up or following early discontinuation. **Red bold lines** are lowess smooth lines. Plots in the lower panel are zoomed in versions of the plots in the upper panel.



Reduction in tumor size is observed in all Cmean groups. However, no optimal target mean concentration could be defined.

In the submitted PopPK report (September 2016), ADAs were detected in 29 patients from study BO21223 (5.8%). By comparison, ADAs were detected in 17 patients (5.5%) from study BO21004, 2 patients (2%) from study GAO4915g, 1 patient (0.5%) from study GAO4753g. All ADAs detected in Study BO21223 were detected prior to initiation of obinutuzumab treatment only. In an update, 1/565 patient (0.2% of patients with a post-baseline assessment) developed HAHA at induction completion. While the clinical significance of HAHA is not known, a potential correlation between HAHA and clinical course cannot be ruled out. Patients with detected ADAs had higher initial time-dependent clearance and a higher rate of decline of this clearance, but the same time-independent clearance as patients without ADAs, indicating a transient effect of ADAs on obinutuzumab concentrations only.

The rate of ADAs observed in study BO21223 is comparable to that observed in previous studies. ADAs do not exhibit a neutralizing activity as obinutuzumab PKs appears to have no clinically impact on systemic exposure.

2.3.5. Discussion on clinical pharmacology

Obinutuzumab is currently approved in patients with CLL in combination with chlorambucil non eligible to full-dose fludarabine and in patients with FL in combination with bendamustine who did not respond to rituximab or rituximab-containing regimen. In the current variation the applicant seeks the use of obinutuzumab in combination with chemotherapy (CHOP, CVP or bendamustine) in previously untreated patients with FL.

The claimed induction dosing scheme for the pursued new indication is slightly different from that currently approved. Indeed, when administered with CHOP or CVP shorter administration cycles are to be followed (eight 21-day cycles instead of six 28-day cycles). Consequently, the total dose of obinutuzumab in the induction phase is higher (8000 mg versus 6000) for patients treated with CHOP or CVP in the new indication.

The pharmacokinetics of obinutuzumab has been characterized using non compartmental analysis (NCA) in early studies but also and mainly through a population-PK approach (PPK) using all available, consisting mostly in sparse data collected during clinical studies.

Study BO21223 is pivotal for the claimed indication. The study included PK sampling (approximately 23 samples per obinutuzumab-treated patient) from a planned sample of 460 patients with FL or MZL who received obinutuzumab. The obinutuzumab PK data from Study BO21223 were added to the population PK dataset and the population PK model was updated. The presence of ADAs was also analyzed in all patients receiving obinutuzumab. Therefore, the previously developed PPK model was updated by the inclusion of data collected in study BO21223. The PPK model was refined and the model parameters were re-estimated. This update is provided by the applicant in report 1072889 and analyzed below.

The current population PK model of obinutuzumab (with the inclusion of data from BO21223) was consistent with a previously developed model in patients with CLL, FL, other iNHL subtypes, DLBCL, and MCL. The model confirmed the influence of previously identified covariates (body weight, sex, tumor size and serum albumin at baseline, disease types [CLL, FL/DLBCL, MCL], iNHL subtypes [SLL], and concomitant chemotherapies [CHOP, CVP, bendamustine, FC]). The PK model also better quantified the influence of a MZL diagnosis compared to FL, with a slightly higher time-dependent clearance and a similar linear clearance. Doxorubicin (administered as part of CHOP regimen) had no influence on obinutuzumab PK.

As typical for mAbs, obinutuzumab exposure is lower in patients with high body weight (following Q3W regimen, mean AUC_T and Ctrough at Cycle 8 of induction and Cycle 4 of maintenance is 31-39% higher for WT < 60 kg and 28% - 37% lower for WT >90 kg compared to patients weighting 60 – 90 kg), and is also lower in male patients (31%-43% lower in male FL patients compared to females). As most of the targeted agents, obinutuzumab exposure depends on tumor burden and therefore decreases in patients with high tumor size at baseline (following Q3W regimen in FL patients, mean AUC_T and Ctrough at Cycle 8 of induction and Cycle 4 of maintenance is 5% -7% higher for BSIZ < 2777 mm^2 and 1% - 2% lower for BSIZ >8998 mm^2, compared to BSIZ of 2777 - 8998 mm^2).

The approach used by the applicant to characterize the PKs of obinutuzumab in the new target population (untreated patients with FL) and according to claimed dosing scheme could be considered acceptable. As expected, higher systemic exposure to obinutuzumab is observed in patients treated with bendamustine and obinutuzumab every 21 days comparatively to those receiving other chemotherapy (CHOP or CVP) and obinutuzumab every 28 days. The systemic exposure appears to be approximately proportional to the dose.

Body weight appears to be the most determinant factor for systemic exposure. For instance, systemic exposure in FL patients is estimated to be approximately doubled in patients weighing less than 60 Kg comparatively to those weighing more than 90 kg. In order to explore the the adequacy of the proposed dosing scheme PFS was compared in normal weighted (BMI $\leq$ 30 mg/m^2) and in obese patients (BMI$>$ 30 mg/m^2 and body weight $\leq$ 90 kg or $>$ 90 kg), and no significant difference was observed (see discussion on clinical efficacy) thus confirming the fixed dose/regimen of obinutuzumab.

Even though tumor size was identified as a significant covariate in the final model, the influence of tumor size on the systemic exposure to obinutuzumab remains limited.

The influence of obinutuzumab on the PKs of the co-administered chemotherapies has not been formally investigated, however it is generally accepted –due to the nature of obinutuzumab- that any significant impact of on the PKs of concomitant chemotherapies is unlikely (See discussion on clinical safety).

The PKs of obinutuzumab is adequately elucidated in the new group of patients (untreated patients with FL) treated with the claimed dosing scheme. The concentration time-course of obinutuzumab is accurately described by a two-compartment PK model with both time-dependant and time-independent clearance components (TMDD). The prior model was refined by the inclusion of the data collected in the pivotal study BO21223.

Since obinutuzumab is given more frequently when combined with CHOP/CVP (every 21 days), higher obinutuzumab systemic exposure is observed compared to when obinutuzumab is given in combination with bendamustine (every 28 days). The systemic exposure appears to be approximately proportional to the dose.

The influence of obinutuzumab on the PKs of the co-administered chemotherapies has not been formally investigated. But it could be agreed that significant impact of obinutuzumab on the PKs of the drugs used in chemotherapies is unlikely.

No relationship between obinutuzumab exposure and time course of B-cell counts was established. The relationship between the observed values of B-cell counts and obinutuzumab exposure (Cmean) indicated that in all exposure groups B-cell counts declined from their baseline values to nearly zero after start of drug administration. B-cells remained at very low levels for most patients.

The rate of ADAs observed in study BO21223 is comparable to that observed in previous studies. ADAs do not exhibit a neutralizing activity as obinutuzumab PKs appears to have no clinically impact on systemic exposure (See discussion on clinical safety).

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology aspects of obinutuzumab in the proposed indication have been sufficiently characterised.

2.4. Clinical efficacy

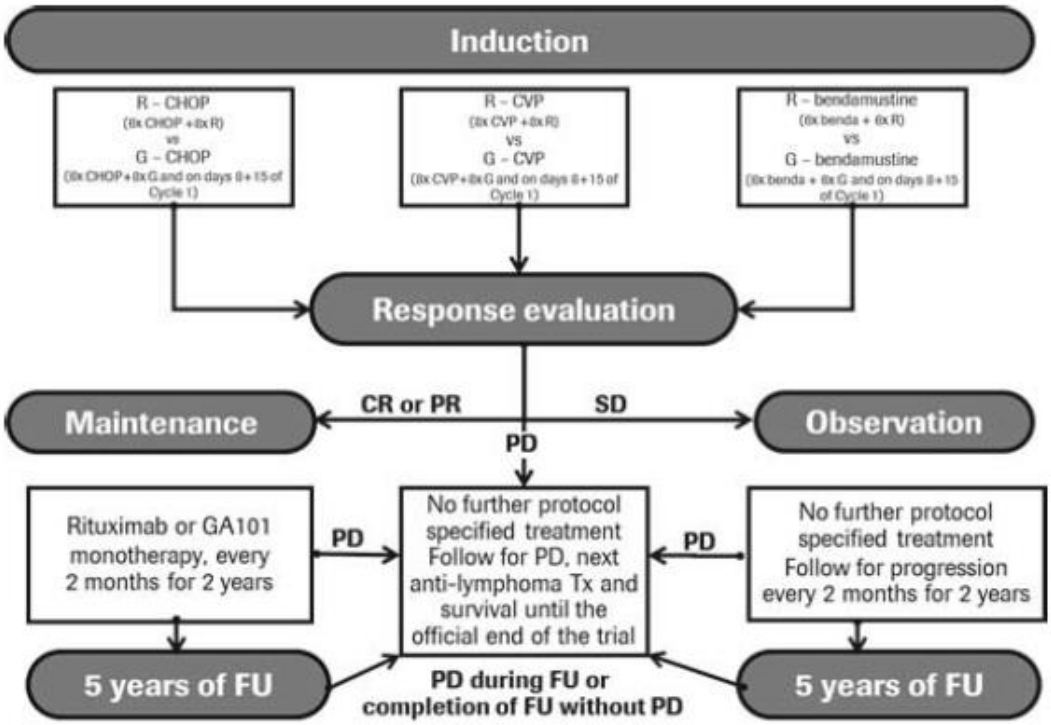
2.4.1. Dose response study(ies).

No dose response study was submitted.

2.4.2. Main study(ies)

Study BO21223 (Gallium)

Figure 5: Overview of study design



Methods

Study participants

Adult patients with previously untreated indolent NHL were eligible for the study.

Inclusion Criteria:

Patients had to meet the following inclusion criteria to be eligible for the study entry:

- Histologically documented, CD20-positive, indolent B-cell NHL consisting of one of the following: FL (Grades 1-3a), splenic MZL, nodal MZL, or extranodal MZL

  Tissue diagnostic procedures had to be performed within 12 months prior to randomization. Biopsy material from an excisional or core biopsy had to be submitted for retrospective central confirmation. Tissue samples dated >12 months prior to randomization were accepted only if tissue material was available for retrospective confirmation, if there was no clinical indication for transformation of disease, and if the request for additional biopsy was unethical treatment of the patient. Bone marrow alone was not suitable to make the diagnosis of FL.

  Approximately 200 patients with MZL (splenic, nodal, or extranodal) were to be randomized. After reaching the cap of 200, recruitment of patients with MZL was stopped.

In patients with splenic MZL without splenic tissue available for histologic review, the diagnosis could be confirmed by the presence of splenomegaly and typical morphologic and immunophenotypic findings in the blood and bone marrow.

Bone marrow had to be submitted for retrospective central confirmation.

- Stage III or IV disease or Stage II bulky disease
    - Bulky disease is defined as a tumor diameter of ≥ 7 cm.
- For patients with FL: requirement for treatment, defined as meeting at least one of the following criteria:
    - Bulky disease, defined as a nodal or extranodal (except spleen) mass ≥ 7 cm in the greatest diameter
    - Local symptoms or compromise of normal organ function due to progressive nodal disease or extranodal tumor mass
    - Presence of B symptoms (fever, drenching night sweats, or unintentional weight loss of > 10% of normal body weight over a period of 6 months or less)
    - Presence of symptomatic extranodal disease (e.g., pleural effusions, peritoneal ascites)
    - Cytopenias due to underlying lymphoma (i.e., absolute neutrophil count 1.0 x 10^9/L, haemoglobin >10 g/dL, and/or platelet count > 100 x 10^9/L)
    - Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm
    - Symptomatic splenic enlargement
- For patients with symptomatic splenic, nodal, or non-gastric extranodal MZL:
    - disease that was de novo or had relapsed following local therapy (i.e., surgery or radiotherapy) and required therapy, as assessed by the investigator
- For patients with symptomatic gastric extranodal MZL: Helicobacter pylori-negative disease that was de novo or had relapsed following local therapy (i.e., surgery or radiotherapy) and required therapy, as assessed by the investigator, or H. pylori-positive disease that remained stable, progressed, or relapsed following antibiotic therapy and required therapy, as assessed by the investigator (see Appendix G of the protocol for additional details regarding gastric extranodal MZL)
- At least one bi-dimensionally measurable lesion (> 2 cm in its largest dimension by CT scan or magnetic resonance imaging [MRI])

  In patients with splenic MZL, an enlarged spleen on CT scan or extending at least 2 cm below the costal margin by physical examination constituted measurable disease providing that no explanation other than lymphomatous involvement was likely. For an enlarged liver to constitute the only measurable disease parameter, a liver biopsy showing proof of NHL in the liver was required.
- Able and willing to provide written informed consent and to comply with the study protocol
- Age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2 (see Appendix H of the protocol)
- Adequate hematologic function (unless abnormalities are related to NHL), defined as follows:

- Hemoglobin ≥ 9.0 g/dL
- Absolute neutrophil count ≥ 1.5 x 10^9/L
- Platelet count ≥ 75 x 10^9/L

- For men who were not surgically sterile: agreement to use a barrier method of contraception during the treatment phase and for at least 3 months after the last dose of obinutuzumab and rituximab or bendamustine or according to institutional guidelines for CHOP or CVP chemotherapy, whichever is longer. In addition, male patients had to agree to request that their partners use an additional method of contraception, such as oral contraceptives, intrauterine device, barrier method of contraception, or spermicidal gel.
- For women of reproductive potential who were not surgically sterile: agreement to use two adequate methods of contraception, such as oral contraceptives, intrauterine device, or barrier method of contraception in conjunction with spermicidal jelly during the treatment period and for at least 12 months after the last dose of obinutuzumab or rituximab, for at least 3 months after the last dose of bendamustine or according to institutional guidelines for CHOP or CVP chemotherapy, whichever is longer.

Exclusion Criteria:

The following criteria excluded patients from study entry:

- History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (e.g., patients in whom dosing with rituximab would be contraindicated for safety reasons)
- Known hypersensitivity to any of the study drugs
- Known sensitivity to murine products
- History of sensitivity to mannitol
- Central nervous system lymphoma, leptomeningeal lymphoma, or histologic evidence of transformation to a high-grade or diffuse large B-cell lymphoma
- Grade 3b FL, SLL, or WM
- Ann Arbor Stage I disease (see Appendix H of the protocol)
- For patients with FL: prior treatment for NHL by chemotherapy, immunotherapy, or radiotherapy

  Low-dose methotrexate (MTX) in rheumatoid arthritis (typically 7.5 mg to a maximum of 20 mg/week) was not considered chemotherapy for lymphoma. It was recommended to stop MTX 2-3 weeks prior to starting immunochemotherapy since the combination of MTX and immunochemotherapy increases the risk of immunosuppression and of infection
- For patients with non-follicular lymphoma: prior treatment with chemotherapy or immunotherapy
- Regular treatment with corticosteroids during the 4 weeks prior to the start of Cycle 1, unless administered for indications other than NHL at a dose equivalent to ≤ 30 mg/day prednisone

  Patients receiving corticosteroid treatment with ≤ 30 mg/day of prednisone or equivalent had to be documented to be on a stable dose of at least 4 weeks' duration prior to randomization.

  If glucocorticoid treatment was urgently required for medical reasons (e.g., complications imminent if not treated at least with glucocorticoids; strong discomfort/pain of the patient due

to lymphoma), prednisone 100 mg or equivalent could be given for a maximum of 5 sequential days, but all tumor assessments had to be completed prior to the start of glucocorticoid treatment.

Glucocorticoid treatment had to be stopped prior to randomization.

In cases when a glucocorticoid pre-treatment/pre-phase was done externally prior to considering the patient for study inclusion, glucocorticoids had to be stopped for at least 7 days before screening assessments can begin.

- Patients with a history of confirmed progressive multifocal leukoencephalopathy (PML)
- History of prior other malignancy with the exception of:
    - Curatively treated basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the cervix at any time prior to study
    - Other cancers not specified above which have been curatively treated by surgery alone and from which subject is disease-free for ≥5 years without further treatment
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, severe arrhythmia, myocardial infarction within the previous 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- For patients who received CHOP: LVEF < 50% by MUGA scan or echocardiogram
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics, except if for tumor fever) within 4 weeks prior to the start of Cycle 1

  Patients with suspected active or latent tuberculosis (latent tuberculosis had to be confirmed by positive Interferon-γ release assay)
- Vaccination with a live vaccine within 28 days prior to randomization
- Recent major surgery (within 4 weeks prior to the start of Cycle 1), other than for diagnosis
- Any of the following abnormal laboratory values (unless any of these abnormalities are due to underlying lymphoma):
    - Creatinine > 1.5 times the upper limit of normal (ULN) (unless creatinine clearance normal) or calculated creatinine clearance < 40 mL/min (using Cockcroft-Gault formula; see Appendix I of the protocol)
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 x ULN
    - Total bilirubin > 1.5 x ULN (or > 3 x ULN for patients with documented Gilbert syndrome)
    - International normalized ratio (INR) or prothrombin time (PT) > 1.5 x ULN in the absence of therapeutic anticoagulation
    - Partial thromboplastin time (PTT) or activated PTT (aPTT) > 1.5 x ULN in the absence of a lupus anticoagulant

- Positive test results for chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg] serology)

  Patients with occult or prior HBV infection (defined as negative hepatitis B surface antigen [HBsAg] and positive total hepatitis B core antibody [HBcAb]) could be included if HBV DNA was undetectable, provided that they were willing to undergo monthly DNA testing. Patients who had protective titers of hepatitis B surface antibody [HBsAb] after vaccination or prior but cured hepatitis B were eligible.

- Positive test results for hepatitis C (hepatitis C virus [HCV] antibody serology testing)

  Patients positive for HCV antibody were eligible only if PCR was negative for HCV RNA.

- Known history of HIV seropositive status.

  In countries where mandatory testing by health authorities is required, HIV testing was performed.

- Positive test results for human T-lymphotropic 1 (HTLV 1) virus HTLV testing was required in patients from endemic countries (Japan, countries in the Caribbean basin, South America, Central America, sub-Saharan Africa, and Melanesia).

- Pregnant or lactating

- Life expectancy < 12 months

- Participation in another clinical trial with drug intervention within 28 days prior to start of Cycle 1 and during the study.

Treatments

Rituximab

In the R-chemo arm, six to eight standard doses of rituximab at 375 mg/m^2 were administered by IV infusion with the accompanying chemotherapy regimen during induction.

- R-CHOP: Rituximab was administered on Day 1 of Cycles 1-6 (21-day cycles). CHOP was administered on Day 1, with prednisone/prednisolone/methylprednisolone administered on Days1–5, of Cycles 1-6.

- R-CVP: Rituximab was administered on Day 1 of Cycles 1–8 (21-day cycles). CVP was administered on Day 1, with prednisone/prednisolone/methylprednisolone administered on Days1–5, of Cycles 1-6.

- R-bendamustine: Rituximab was administered on Day 1 of Cycles 1-6 (28-day cycles). Bendamustine was administered on Days 1 and 2 of Cycles 1-6, with prednisone/prednisolone/methylprednisolone also administered on Day 1 of Cycle 1. Patients randomized to receive R-chemo who achieved a CR or PR at the end of induction therapy continued to receive R-maintenance at 375 mg/m^2 every 2 months until disease progression, or for 2 years.

Obinutuzumab

In the G-chemo arm, eight to ten doses of obinutuzumab at 1000 mg were administered by IV infusion with the accompanying chemotherapy regimen during induction. More details are provided in Section 4.3.2 of the protocol.

- G-CHOP: Obinutuzumab was administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2–6(21-day cycles). CHOP was administered on Day 1, with prednisone/prednisolone/methylprednisolone also administered on Days1–5 of Cycles 1–6.
- G-CVP: Obinutuzumab was administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2-8 (21-day cycles). CVP was administered on Day 1, with prednisone/prednisolone/methylprednisolone also administered on Days1–5 of Cycles 1–8.
- G-bendamustine: Obinutuzumab was administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2-6 (28-day cycles). Bendamustine was administered on Days 1 and 2 of Cycles 1-6, with prednisone/prednisolone/methylprednisolone administered on Day 1 of Cycle 1.

Patients randomized to receive G-chemo who achieved a CR or PR at the end of induction therapy continued to receive G-maintenance at 1000 mg every 2 months until disease progression, or for 2 years.

CHOP

A total of six 21-day cycles of CHOP were administered. If CHOP was discontinued for any reason other than toxicity, patients were to be discontinued from study treatment and entered follow-up directly without maintenance. CHOP was administered according to the standard preparation and infusion procedures of each investigational site.

CVP

A total of eight 21-day cycles of CVP was administered. If CVP was discontinued for any reason other than toxicity, patients were to be discontinued from study treatment and entered follow-up directly without maintenance. CVP was administered according to the standard preparation and infusion procedures of each investigational site.

Bendamustine

A total of six 28-day cycles of bendamustine was administered. If bendamustine was discontinued for any reason other than toxicity, patients were to be discontinued from study treatment and entered follow-up directly without maintenance.

Premedication

All rituximab or obinutuzumab infusions were administered after premedication with oral acetaminophen/paracetamol and an antihistamine. Patients who were considered to have a high tumor burden and who were considered at risk for tumor lysis by the investigator also received tumor lysis prophylaxis prior to the initiation of treatment.

Cyclophosphamide, doxorubicin, and bendamustine have a moderate risk of emesis. It was recommended that infusions be administered following premedication with a serotonin antagonist or per institutional practice.

Objectives

The primary objective of this study was:

- To evaluate the efficacy of obinutuzumab plus chemotherapy (G-chemo) followed by obinutuzumab maintenance (G-maintenance) therapy compared with rituximab plus chemotherapy (R-chemo) followed by rituximab maintenance (R-maintenance) therapy in patients with previously untreated advanced FL, as measured by investigator-assessed PFS.

The following secondary objective applied to patients with previously untreated advanced indolent NHL (i.e., overall population):

- To evaluate and compare investigator-assessed PFS between the two arms

The following secondary objectives applied to patients with previously untreated advanced indolent NHL (i.e., overall population) and to the subset of patients with previously untreated advanced FL (i.e., follicular population):

- To evaluate and compare Independent Review Committee (IRC)-assessed PFS between the two arms. In the US, IRC-assessed PFS will be the basis of regulatory decisions.
- To evaluate and compare overall response (OR) and complete response (CR) after the end of induction treatment, as assessed by the investigator, between the two arms, with and without 18F-fluorodeoxyglucose positron emission tomography (FDG-PET)
- To evaluate and compare OR and CR after the end of induction treatment, as assessed by the IRC, between the two arms, with and without FDG-PET
- To evaluate and compare overall survival (OS), event-free survival (EFS), disease-free survival (DFS), duration of response (DOR), and time to next anti-lymphoma treatment (TTNLT) between the two arms

  EFS, DFS, and DOR are based on investigator assessment.
- To evaluate and compare the safety profiles between the two arms during induction and maintenance
- To assess patient-reported outcomes (PROs) in both arms. HRQoL was assessed using two self-administered validated questionnaires, FACT-Lym and EuroQol EQ-5D-3L.

The exploratory objectives for this study were as follows:

- To evaluate and compare the proportion of patients who transformed to aggressive histology at first relapse between the two arms
- To evaluate the proportion of patients with a partial response (PR) or stable disease (SD) at the end of induction treatment who converted to CR or to PR/CR, respectively, during maintenance treatment or post-induction observation, as assessed by the investigator
- To characterize the pharmacokinetics and pharmacodynamics of obinutuzumab in combination with chemotherapy
- To compare the efficacy of obinutuzumab versus rituximab within each chemotherapy subset
- To assess the prognostic and predictive ability of baseline clinical factors, which may include activities of daily living (ADLs), instrumental activities of daily living (IADLs), Follicular Lymphoma International Prognostic Index 2 (FLIPI2) score, International Prognostic Index (IPI) score, and FDG-PET imaging
- To assess the prognostic and predictive ability of biomarkers (such as Fcγ receptor polymorphisms) pertaining to the biology of FL and factors relating to the host immune system (such as immunohistochemistry [IHC] and gene expression assessment of specific targets or gene profiles) To assess the prognostic and predictive value of BCL2/IgH rearrangement and other markers of minimum residual disease (MRD) in patients with FL at baseline, during induction, at the completion of induction therapy, during maintenance therapy or observation,

and during follow-up (IgH clonality could be used as a marker of MRD in patients without an identifiable BCL2/IgH translocation at baseline)

- To correlate FDG-PET results with efficacy parameters
- A dedicated analysis to adequately assess PFS in the MZL subcohort was performed
- To identify and characterize changes in tumor gene expression and cell surface markers that occur in patients who have relapsed and/or transformed after initial treatment with a rituximab- or obinutuzumab-containing regimen.

Outcomes/endpoints

Primary Efficacy Endpoint

Progression free survival (PFS) is the primary efficacy endpoint of the study. PFS is defined as time from the day of randomization until the first documented day of disease progression, symptomatic deterioration, disease transformation, or death from any cause, whichever occurred first. Patients who did not experience documented disease progression or death were censored at the last valid (SD, PR, CR) tumor assessment prior to the clinical cut-off date.

Secondary Efficacy Endpoints

Secondary efficacy endpoints were EFS, TTNLT, DFS, and DOR and additionally - on account of the primary endpoint crossing the pre-specified boundary- key secondary endpoints were tested in hierarchical order by the fixed sequence testing procedure.

- CR rate at the end of induction therapy in the FL population based on tumor assessment without PET
- CR rate at the end of induction therapy in the overall population based on tumor assessment without PET
- Overall survival in the FL population; Overall survival in the overall population

  OS, defined as the time from the date of randomization to the date of death from any cause. OS for patients who were not reported to have died at the time of the analysis were censored at the date when they were last known to be alive as documented by the investigator.
- ORR at the end of induction therapy in the FL population based on tumor assessment without PET
- ORR at the end of induction therapy in the overall population based on tumor assessment without PET. The ORR is defined as the percentage of patients with CR or PR as the end-of-induction response. All other cases are designated non-responders.

All analyses are based on the investigator's assessment. Analyses of PFS, CR rate, and ORR are based on IRC assessments in the application for the FDA registration.

EFS, defined as the time from the date of randomization to the date to disease progression/relapse, death from any cause, or initiation of a NALT. If the specified event (disease progression/relapse, death, or initiation of a NALT) did not occur, EFS was censored at the date of last tumor assessment. For patients without an event who have not had post-baseline tumor assessments, EFS was censored on the date of randomization.

Time to next anti-lymphoma treatment (TTNLT) is defined as the time from the date of randomization to the start date of the next anti-lymphoma treatment or death from any cause. Patients without a TTNLT event were censored at the date at which the patient was last known to be alive.

Disease-free survival (DFS), defined as the time from the date of the first occurrence of a documented CR to the date of disease progression, relapse, or death from any cause (PFS event). DFS is evaluated for the subgroup of patients with a response of CR at any time prior to NALT. DFS for patients who have had no documented disease progression, relapse, or have not died after CR, were censored at the last disease assessment date.

Duration of response, defined as the time from the date of the first occurrence of a documented CR or PR to the date of disease progression, relapse, or death from any cause (PFS event) for the subgroup of patients with a response of CR or PR any time prior to NALT. For patients achieving a response who have not experienced disease progression, relapse, or died prior to the time of the analysis, the duration of response was censored on the date of last disease assessment.

Sample size

The primary analysis of the study tested the equality of PFS distributions in the R-chemo and G-chemo arms the following null hypothesis with use of a two-sided stratified log rank test at an overall 5% significance level:

- Equality of PFS distributions in the G-chemo and R-chemo arms in the FL population by investigator assessment: H0: PFSG-chemo = PFSR-chemo versus H1: SG-chemo ≠ SR-chemo In the FL subset, estimates on the number of events required to demonstrate efficacy with respect to PFS were based on the following assumptions:
- Two-sided log rank test at the 0.05 level of significance
- Powered for the FL population
- Eighty percent power to detect a hazard ratio (HR) for G-chemo versus R-chemo of 0.74, corresponding to an improvement in 3-year PFS from 70.7% to 77.4% or in median PFS from 6 years to 8.1 years (35%). Note that estimates of median PFS were not likely to be reached in either study arm at either interim or final PFS analysis
- Exponential distribution of PFS
- An annual dropout rate of 2.5%

Performance of interim analysis on PFS: one futility analysis when approximately 30% of the total (investigator-assessed) PFS events had occurred and one efficacy analysis when approximately 67% of the total (investigator-assessed) PFS events had occurred. Efficacy and (nonbinding) futility boundaries were calculated using the Lan-DeMets approximation to the O-Brien-Fleming boundary shape. Resulting significance levels at the interim and final analyses are documented in the SAP.

In addition, a futility analysis based on CR rates at the end of induction as determined by CT (or MRI, but not PET), was performed on the first 170 randomized patients with FL.

With the above assumptions, 370 PFS events were required to achieve 80% power for the primary analysis. Recruitment was staggered in order to recruit the first 170 patients at a smaller number of sites, followed by the activation of all sites after the IDMC meeting for futility based on CR rates. It was expected that during the first stage, after a 6-month ramp up, 18 patients per month would be recruited, and after the IDMC meeting and another 4-month ramp up, an accrual rate of 37 patients per month was expected.

The 1200 patients with FL enrolled over 49 months and followed for an additional 29 months after randomization of the last patients were required to provide 370 PFS events, with a total duration for PFS follow-up of approximately 78 months (6.5 years).

Although the primary efficacy endpoint is the investigator-assessed PFS, PFS based on IRC assessments was also analyzed to support the primary analysis. In the United States, IRC-assessed PFS will be the basis for regulatory decisions. Approximately 200 additional patients with non-follicular lymphoma (i.e., with MZL) were enrolled. This number was selected on the basis of estimation from the enrolment feasibility assessment prior to the start of the study. This estimation indicated that at least 200 patients with MZL would likely be enrolled in 49 months, in addition to the planned enrollment of 1200 patients with FL. As such, data from the patients with MZL can be interpreted in context of subgroup analyses. However, this subgroup was not powered to detect statistically significant differences.

Randomisation

1202 eligible patients with FL who fulfilled the inclusion/exclusion criteria were randomly assigned in a 1:1 ratio to either G-chemo followed by G-maintenance in responders or R-chemo followed by R-maintenance in responders. In addition, 195 patients with MZL were randomly assigned in a 1:1 ratio to the two treatment arms. There were an additional 4 patients with non-FL.

Randomization was stratified for the following factors:

1. Chemotherapy regimen (CHOP, CVP, or bendamustine)

2. FLIPI (for FL: low, intermediate, or high)/IPI (for MZL: low/low-intermediate or high-intermediate/high) group (see the protocol for further details)

3. Geographic region (Western Europe, Eastern Europe, South and Central America, North America, other)

Blinding (masking)

This was an open-label study; however the IRC was blinded to treatment assignment throughout. Clinical Scientists from the MAH's study team reviewed eCRF data for ambiguous, contradictory and/or potentially erroneous data entry as part of routine data cleaning. For these activities, they were not blinded to treatment allocation on an individual patient basis. However, no aggregated efficacy or safety analyses by treatment arm were conducted by the Sponsor using unblinded data before the IDMC released the data following the interim analysis.

At the pre-specified interim analysis for efficacy, the IDMC recommended that the study be fully analyzed because the pre-specified boundary for the primary endpoint, investigator-assessed PFS, had been crossed and the results were considered clinically meaningful. The Sponsor endorsed this recommendation and the interim analysis is now considered the primary analysis of efficacy. The Sponsor was only exposed to aggregate efficacy or safety analyses by treatment arm after the IDMC recommendation and Sponsor decision.

Statistical methods

A two-sided stratified log-rank test (0.05 significance level) stratified by chemotherapy regimen (CHOP, CVP, or bendamustine) and Follicular Lymphoma International Prognostic Index (FLIPI) risk group (low, intermediate, or high) in patients with FL, or international prognostic index (IPI) risk group (low or low-intermediate vs. high-intermediate or high) was used for the primary analysis. Kaplan-Meier methodology was used to estimate PFS distribution for each treatment arm. Estimates of

treatment effect were expressed as hazard ratios through the use of a stratified Cox proportional hazards analysis, including 95% confidence intervals.

PFS was compared using a two-sided log-rank test stratified by chemotherapy regimen (CHOP, CVP, or bendamustine), FL international prognostic index (FLIPI) risk group (low, intermediate, or high) in patients with FL or international prognostic index (IPI) risk group (low or low-intermediate vs. high-intermediate or high) in patients with non-follicular lymphoma.

Estimates of the treatment effect are expressed as hazard ratios, estimated with the use of a stratified Cox model, including 95% confidence limits. An unstratified log-rank test was also performed as a sensitivity analysis. Kaplan-Meier methodology was used to estimate median (if reached), 2-year and 3-year PFS and 95% CIs for each treatment arm, and the Kaplan-Meier curve is provided for a visual description of the difference across treatment arms.

Three interim analyses were planned: two for futility (one on CR and one on PFS) and one for efficacy (on PFS).

The first interim analysis was based on differences in end-of-induction CR rates in the first 170 enrolled patients with FL. The IDMC reviewed the data on 24 October 2012 and recommended that the study continue.

The second interim analysis (futility on PFS) was conducted when 30% of the required investigator-assessed PFS events (i.e., approximately 111 events) had occurred. The clinical data cutoff for the second interim analysis was 20 February 2014. The IDMC reviewed the data on 31 July 2014 and recommended that the study continue.

The third interim analysis (efficacy) was planned after 67% of the events had occurred (i.e. approximately 248 events), and all patients had been enrolled and followed for an estimated minimum of 11 months. The clinical cutoff date for the third interim analysis was 31 January 2016. This analysis is now referred to as the primary analysis. The IDMC reviewed the data on 20 May 2016 and recommended that the study be fully analyzed at this time, as the primary endpoint had been met. The IDMC recommendations are provided.

PFS was analyzed for the follicular lymphoma population based on assessments by the investigators as well as by the IRC; both investigator- and IRC-assessed PFS endpoints were analyzed in the same manner. In the US, IRC-assessed PFS will be the basis of regulatory decisions. It was anticipated that in the worst case, the number of corresponding IRC events at clinical cutoff would be, at most, 10% lower than the number of investigator-assessed events. Such a worst case loss in number of events would result in a reduction in the power of approximately 5% to detect the assumed treatment difference. All analyses of PFS and secondary efficacy endpoints were performed for the FL population and the overall population, with the exception of PFS, which was analysed only in the overall population as a secondary efficacy endpoint (PFS for the follicular population is the primary efficacy endpoint). Patients were analyzed according to the treatment arm to which they were randomized.

To adjust for multiple statistical testing of the primary and key secondary efficacy endpoints, thereby controlling the overall Type I error rate at a two-sided 0.05 level of significance, the fixed sequence testing procedure (Westfall and Krishen 2001) was used. These endpoints were tested in the following order:

- PFS in the overall population
- CR rate at the end of induction therapy in the FL population based on tumor assessment without PET

- CR rate at the end of induction therapy in the overall population based on tumor assessment without PET
- Overall survival in the FL population
- Overall survival in the overall population
- ORR at the end of induction therapy in the FL population based on tumor assessment without PET
- ORR at the end of induction therapy in the overall population based on tumor assessment without PET

The primary efficacy analysis population is the intent-to-treat follicular lymphoma population (FL ITT), defined as all randomized patients with follicular histology. Efficacy analyses were conducted according to the intent-to-treat (ITT) principle, where patients were grouped according to their randomized treatment arm regardless of what treatments were actually received.

The primary and key secondary efficacy parameters were also determined in the intent-to-treat population, defined as all randomized patients (overall population, ITT).

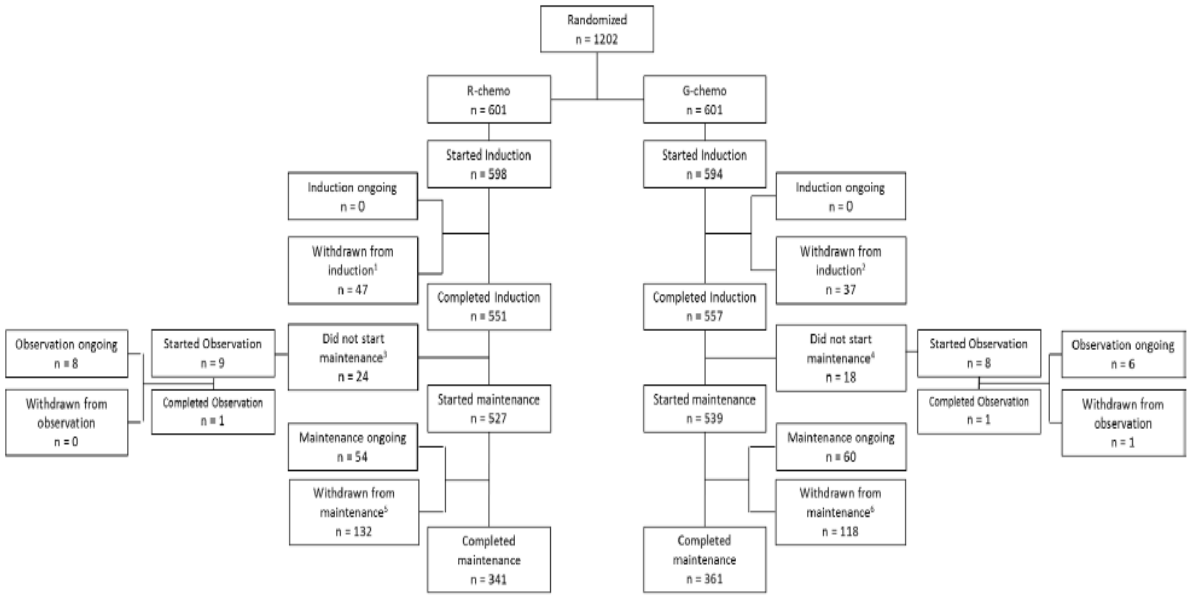
Pharmacokinetic analyses and the evaluable population are defined in a separate analysis plan. Patient data was included in the pharmacokinetic analysis if they contained sufficient dosing information and at least one adequately documented and quantifiable concentration per patient.

The safety analysis population included all patients who received any amount of study drug (obinutuzumab, rituximab, or chemotherapy [CHOP, CVP, or bendamustine]), and patients were analyzed according to the treatment received (i.e., a patient who received obinutuzumab at least once for any reason was analyzed under the G-chemo treatment arm; if only chemotherapy and/or rituximab was received, the patient was analysed under the R-chemo treatment arm).

Results

Participant flow

Figure 6: Patient Disposition at the Clinical Cut-off Date (31 January 2016; FL Population)



Note: Study design described in Section 1.2.1.1.

[1] Reasons for withdrawal from R-chemo induction treatment were as follows: AEs (n=19); progressive disease (n=14); physician decision (n=5); withdrawal by subject (n=3); protocol violation (n=2); other (n=2); death (n=1); and non-compliance (n=1).

[2] Reasons for withdrawal from G-chemo induction treatment were as follows: AEs (n=19); progressive disease (n=5); withdrawal by subject (n=5); death (n=3); other (n=2); protocol violation (n=2); and physician decision (n=1).

[3] 24 patients did not start R-maintenance treatment due to: progressive disease between induction and maintenance (n=10); started observation (i.e., stable disease) (n=9); withdrawal by subject (n=3); physician decision (n=1); and other (n=1).

[4] 19* patients did not start G-maintenance treatment due to: progressive disease between induction and maintenance (n=10); started observation (i.e., stable disease) (n=8), and withdrawal by subject (n=1). *Patient 53851 entered maintenance but did not complete induction.

[5] Reasons for withdrawal from R-maintenance treatment were as follows: progressive disease (n=64); AEs (n=38); physician decision (n=11); withdrawal by subject (n=10); death (n=4); other (n=3); lost to follow-up (n=1); and protocol violation (n=1).

[6] Reasons for withdrawal from G-maintenance treatment were as follows: AEs (n=51); progressive disease (n=37); physician decision (n=15); withdrawal by subject (n=5); other (n=4); death (n=6); non-compliance (n=2); and lost to follow-up (n=1).

Recruitment

Patients were recruited from 177 investigational sites in 18 countries.

The highest recruiting countries were United Kingdom (293 patients), Germany (237 patients), Canada (138 patients), Australia (136 patients), and Japan (129 patients).

Period of trial: 6 July 2011 (first patient enrolled) to 31 January 2016 (cutoff date for this Clinical Study Report). The study is ongoing.

Conduct of the study

Protocol amendments were prepared by the Sponsor, and were submitted to the IRB/EC and to Regulatory Authorities in accordance with local regulatory requirements.

Approval was obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

There were four amendments to the study protocol. A summary of the protocol amendments, including the rationale and key changes, is given in Table 3. Version BO21223-A1 was the original protocol. The methodology sections of this report are based on the most recent version of the protocol (Version A5).

Table 9: Summary of Protocol Amendments

Protocol Amendment (Date)	Rationale and Key Changes
Version A1 (26 July 2011)	On the basis of a decision by the Sponsor, Study BO21223 was amended to allow for an early futility analysis of the first 170 randomized patients with follicular lymphoma based on the end-of-induction treatment complete response rates. The statistical methods sections were updated accordingly. PET was also made mandatory at screening and at end of induction therapy for the first 170 patients with follicular lymphoma at all sites where PET scanners were available. The determination of minimal residual disease (MRD) based on polymerase chain reaction detection of BCL2/IgH-rearrangements within the malignant clone for all patients with follicular lymphoma was also implemented. Additional minor changes as detailed in the protocol amendment summary of changes for protocol amendment A1.
Version A2 (16 July 2012)	The protocol was amended to implement a DNA substudy in those patients who give consent to the Roche Clinical Repository (RCR) and to DNA collection. Additional minor changes as detailed in the protocol amendment summary of changes for protocol amendment A2.
Version A3 (France only) (18 November 2012)	Study BO21223 was amended to address questions received from France's Agence Nationale de Sécurité Medicament (ANSM) on 17 October 2012. This protocol version was a country-specific amendment implemented in France. Progressive multifocal encephalopathy (PML) was added as an exclusion criterion, and additional information regarding PML diagnosis, evaluation, and guidance on how to manage a potential PML case was included. These changes were implemented into version A4. Details on the changes are given in the protocol amendment summary of changes for protocol amendment A3.
Version A4 (28 May 2013)	On the basis of a decision by the Sponsor, Study BO21223 was amended to allow a clarification of measuring and assessing the spleen and splenic response for marginal zone lymphoma (MZL) patients. Additional minor changes as detailed in the protocol amendment summary of changes for protocol amendment A4.

Protocol Amendment (Date)	Rationale and Key Changes
Version A5 (22 Mar 2014)	Study BO21223 was amended following identification of higher incidence of thrombocytopenia and hemorrhagic events in Study BO21004/CLL11, especially during the first cycle in patients receiving obinutuzumab as compared to the control arms in the pivotal Study BO21004/CLL11. Guidelines regarding management of patients with thrombocytopenia, especially during the first cycle, including those who were receiving concomitant anticoagulants or platelet inhibitors was added. Additional minor changes as detailed in the protocol amendment summary of changes for protocol amendment A5.

Overall, 828/1401 patients (59.1%) had at least one protocol deviation:

Table 10: All Protoicol deviations (overall population)

Analysis Population: Intent-to-Treat Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

	R-chemo (N=699)	G-chemo (N=702)	Total (N=1401)
Total number of patients with at least one protocol deviation	412 (58.9%)	416 (59.3%)	828 (59.1%)
Total number of protocol deviations	997	929	1926
3_OTHER TUMOUR OR RESPONSE RELATED ASSESSMENTS	187 (26.8%)	194 (27.6%)	381 (27.2%)
2_MISSING TA OR PERFORMED AT THE WRONG TIME	181 (25.9%)	189 (26.9%)	370 (26.4%)
5_MISSING SCREENING ASSESSMENTS	66 (9.4%)	92 (13.1%)	158 (11.3%)
1_OTHER VIOLATIONS OF STUDY MEDICATION	65 (9.3%)	60 (8.5%)	125 (8.9%)
7_SPLEEN/LIVER PALPATION ND OR OUTSIDE TIME WINDOW	45 (6.4%)	45 (6.4%)	90 (6.4%)
1_HBV OR HCV MISSED TEST	42 (6.0%)	26 (3.7%)	68 (4.9%)
6_IN RA LESION EITHER NOT ASSESSED OR DIFF METHOD	20 (2.9%)	23 (3.3%)	43 (3.1%)
9_SAE/AESI REPORTING DELAYED/MISSED	10 (1.4%)	17 (2.4%)	27 (1.9%)
7_USE OF EXPIRED OR NON STUDY STOCK	21 (3.0%)	5 (0.7%)	26 (1.9%)
1I_SAFETY ECG RELATED	9 (1.3%)	8 (1.1%)	17 (1.2%)
4_FAILURE TO REDUCE OR DELAY FOR TOXICITY	6 (0.9%)	9 (1.3%)	15 (1.1%)
2_OTHER VIOLATIONS OF NON STUDY MEDICATION	6 (0.9%)	7 (1.0%)	13 (0.9%)
1A_HISTOLOGICALLY DOCUMENTED DISEASE	4 (0.6%)	8 (1.1%)	12 (0.9%)
6_NEW ANTI LYMPHOMA THERAPY BEFORE OR WITHOUT PD	6 (0.9%)	5 (0.7%)	11 (0.8%)
3_OVERDOSE OF STUDY MEDICATION	5 (0.7%)	4 (0.6%)	9 (0.6%)
1Z_PREVIOUS MALIGNANCIES	2 (0.3%)	6 (0.9%)	8 (0.6%)
4_ADMINISTRATION DEVIATIONS.	4 (0.6%)	4 (0.6%)	8 (0.6%)
2_STAGE 2 BULKY (>7CM) DISEASE	1 (0.1%)	6 (0.9%)	7 (0.5%)
5_RECEIVED INCORRECT IMP	5 (0.7%)	2 (0.3%)	7 (0.5%)
1U_SAFETY LVEF RELATED	4 (0.6%)	2 (0.3%)	6 (0.4%)
7_WRITTEN INFORMED CONSENT	3 (0.4%)	2 (0.3%)	5 (0.4%)
1Y-22_ KNOWN HIV, HTLV/1, HBV OR HCV	1 (0.1%)	2 (0.3%)	3 (0.2%)
23_PREGNANCY NO BASELINE TEST	2 (0.3%)	1 (0.1%)	3 (0.2%)
3_GELF CRITERION REQUIREMENT FOR TREATMENT	1 (0.1%)	2 (0.3%)	3 (0.2%)
1U_CORTICOSTEROID >30MG/DAY (4 WEEKS)	1 (0.1%)	1 (0.1%)	2 (0.1%)
8_SAFETY PREGNANCY TEST RELATED	1 (0.1%)	1 (0.1%)	2 (0.1%)
1B_LABS NOT MET	0	1 (0.1%)	1 (<0.1%)
1D_STAGE 3 OR 4 DISEASE	1 (0.1%)	0	1 (<0.1%)
6_>1 MEASURABLE LESION	1 (0.1%)	0	1 (<0.1%)
6_GRADE 3B FL, SLL OR WM	0	1 (0.1%)	1 (<0.1%)
7_ANN ARBOR STAGE 1	1 (0.1%)	0	1 (<0.1%)
8_AND 9_PRIOR IMMUNO, CHEMO OR RADIO THERAPY	1 (0.1%)	0	1 (<0.1%)

Output contains all major protocol deviations: these are related to study inclusion or exclusion criteria, conduct of the trial, patient management, or patient assessment.

Program: /opt/BIOSTAT/prod/cdt7159z/t_dv_c.sas
Output: /opt/BIOSTAT/prod/cdt7159n/12I223a/reports/t_dv_c_223_IT.out
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Baseline data

Table 11: Demographic data (FL population)

Protocol(s): BO21223 (L21223A)
Analysis Population: Intent-to-Treat Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

	R-chemo (N=601)	G-chemo (N=601)	Total (N=1202)
Age (yr) at Baseline			
Mean	57.7	58.2	57.9
SD	12.2	11.5	11.9
Median	58.0	60.0	59.0
Min - Max	23 - 85	26 - 88	23 - 88
n	601	601	1202
Age Group I (yr) at Baseline			
< 40	44 (7.3%)	35 (5.8%)	79 (6.6%)
40 - 59	279 (46.4%)	263 (43.8%)	542 (45.1%)
60 - 69	172 (28.6%)	206 (34.3%)	378 (31.4%)
>= 70	106 (17.6%)	97 (16.1%)	203 (16.9%)
n	601	601	1202
Age Group II (yr) at Baseline			
< 60	323 (53.7%)	298 (49.6%)	621 (51.7%)
>= 60	278 (46.3%)	303 (50.4%)	581 (48.3%)
n	601	601	1202
Age Group III (yr) at Baseline			
< 65	414 (68.9%)	412 (68.6%)	826 (68.7%)
>= 65	187 (31.1%)	189 (31.4%)	376 (31.3%)
n	601	601	1202
Sex			
Male	280 (46.6%)	283 (47.1%)	563 (46.8%)
Female	321 (53.4%)	318 (52.9%)	639 (53.2%)
n	601	601	1202
Ethnicity			
Hispanic or Latino	18 (3.0%)	36 (6.0%)	54 (4.5%)
Not Hispanic or Latino	538 (89.5%)	529 (88.0%)	1067 (88.8%)
Not Reported	30 (5.0%)	23 (3.8%)	53 (4.4%)
Unknown	15 (2.5%)	13 (2.2%)	28 (2.3%)
n	601	601	1202
Race			
American Indian or Alaska Native	1 (0.2%)	0	1 (<0.1%)
Asian	98 (16.3%)	100 (16.6%)	198 (16.5%)
Black or African American	1 (0.2%)	3 (0.5%)	4 (0.3%)
Native Hawaiian or Other Pacific Islander	0	1 (0.2%)	1 (<0.1%)
White	481 (80.0%)	487 (81.0%)	968 (80.5%)
Other	17 (2.8%)	10 (1.7%)	27 (2.2%)
Multiple	3 (0.5%)	0	3 (0.2%)
n	601	601	1202
Height (cm) at Baseline			
Mean	168.43	168.26	168.34
SD	10.08	10.03	10.05
Median	169.00	168.00	168.00
Min - Max	101.0 - 196.0	142.7 - 196.5	101.0 - 196.5
n	600	600	1200
Weight (kg) at Baseline			
Mean	75.16	76.34	75.75
SD	17.04	17.94	17.50
Median	74.00	75.00	74.25
Min - Max	32.4 - 158.0	35.3 - 155.0	32.4 - 158.0
n	599	601	1200
Baseline Body Surface Area (m2)			
Mean	1.84	1.86	1.85
SD	0.23	0.24	0.23
Median	1.84	1.83	1.84
Min - Max	1.1 - 2.8	1.2 - 2.6	1.1 - 2.8
n	599	600	1199
Baseline Body Mass Index (kg/m2)			
Mean	26.44	26.81	26.63
SD	5.90	5.27	5.60
Median	25.29	26.27	25.69
Min - Max	16.1 - 97.1	15.7 - 64.5	15.7 - 97.1
n	599	600	1199

Program: /opt/BIOSTAT/prod/cdt7159z/k21223d/t_dm_c.sas
Output: /opt/BIOSTAT/prod/cdt7159n/l21223a/reports/t_dm_c_foly_223_IT.out
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Table 12: Baseline data (FL population)

Protocol(s): BO21223 (L21223A)
Analysis Population: Intent-to-Treat Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

	R-chemo (N=601)	G-chemo (N=601)	Total (N=1202)
ECOG at Baseline			
0-1	576 (96.2%)	585 (97.5%)	1161 (96.8%)
2	23 (3.8%)	15 (2.5%)	38 (3.2%)
n	599	600	1199
Ann Arbor Stage at Diagnosis			
I	8 (1.3%)	10 (1.7%)	18 (1.5%)
II	44 (7.4%)	41 (6.9%)	85 (7.1%)
III	209 (35.0%)	208 (34.8%)	417 (34.9%)
IV	336 (56.3%)	339 (56.7%)	675 (56.5%)
n	597	598	1195
FLIPI No. of Adverse Factors Categories 1			
Low (0,1)	125 (20.8%)	128 (21.3%)	253 (21.0%)
Intermediate (2)	223 (37.1%)	224 (37.3%)	447 (37.2%)
High (>=3)	253 (42.1%)	249 (41.4%)	502 (41.8%)
n	601	601	1202
FLIPI No. of Adverse Factors Categories 2			
Low (0)	55 (9.4%)	51 (8.8%)	106 (9.1%)
Intermediate (1-2)	290 (49.5%)	296 (51.1%)	586 (50.3%)
High (>=3)	241 (41.1%)	232 (40.1%)	473 (40.6%)
n	586	579	1165
Bone Marrow Involvement at Baseline			
Positive	295 (49.3%)	318 (53.7%)	613 (51.5%)
Negative	291 (48.7%)	266 (44.9%)	557 (46.8%)
Indeterminate	12 (2.0%)	8 (1.4%)	20 (1.7%)
n	598	592	1190
Extranodal Involvement			
Yes	396 (65.9%)	392 (65.2%)	788 (65.6%)
No	205 (34.1%)	209 (34.8%)	414 (34.4%)
n	601	601	1202
Time from Initial Diagnosis to Randomization (months)			
Mean	7.28	6.25	6.77
SD	16.48	13.78	15.20
Median	1.41	1.48	1.45
Min - Max	0.0 - 168.1	0.1 - 121.6	0.0 - 168.1
n	601	598	1199
Time from Initial Diagnosis to Randomization (months) Category			
<6	474 (78.9%)	490 (81.9%)	964 (80.4%)
6-12	32 (5.3%)	35 (5.9%)	67 (5.6%)
>12	95 (15.8%)	73 (12.2%)	168 (14.0%)
n	601	598	1199
Bulky Disease at Baseline (7cm threshold)			
Yes	271 (45.2%)	255 (42.5%)	526 (43.8%)
No	329 (54.8%)	345 (57.5%)	674 (56.2%)
n	600	600	1200
Number of Indicator Lesions at Baseline			
1	37 (6.2%)	34 (5.7%)	71 (5.9%)
2	58 (9.7%)	47 (7.8%)	105 (8.8%)
3	67 (11.2%)	68 (11.3%)	135 (11.3%)
4	87 (14.5%)	109 (18.2%)	196 (16.3%)
5	88 (14.7%)	98 (16.3%)	186 (15.5%)
6	263 (43.8%)	244 (40.7%)	507 (42.3%)
n	600	600	1200
Liver Assessment Palpable at Baseline			
Yes	55 (9.4%)	50 (8.4%)	105 (8.9%)
No	528 (90.6%)	543 (91.6%)	1071 (91.1%)
n	583	593	1176
Liv. Dist. BCE/Medio-Clavicular Line (cm) at Baseline			
0-3	149 (93.1%)	145 (92.9%)	294 (93.0%)
>3-6	4 (2.5%)	10 (6.4%)	14 (4.4%)
>6	7 (4.4%)	1 (0.6%)	8 (2.5%)
n	160	156	316
Spleen Assessment Palpable at Baseline			
Yes	90 (15.4%)	78 (13.2%)	168 (14.3%)
No	493 (84.6%)	515 (86.8%)	1008 (85.7%)
n	583	593	1176

Program: /opt/BIOSTAT/prod/cdt7159z/k21223d/t_dm_bdc.sas
Output: /opt/BIOSTAT/prod/cdt7159n/l21223a/reports/t_dm_bdc_foly_223_IT.out
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Table 13: baseline B-symptom status (FL population)

Protocol(s): B021223 (L21223A)
Analysis Population: Intent-to-Treat Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

	R-chemo (N=601)	G-chemo (N=601)	Total (N=1202)
>=1 B-symptom present			
Yes	206 (34.3%)	201 (33.4%)	407 (33.9%)
No	394 (65.7%)	400 (66.6%)	794 (66.1%)
n	600	601	1201
Fever			
Yes	17 (2.8%)	25 (4.2%)	42 (3.5%)
No	583 (97.2%)	576 (95.8%)	1159 (96.5%)
n	600	601	1201
Night Sweats			
Yes	155 (25.8%)	144 (24.0%)	299 (24.9%)
No	445 (74.2%)	457 (76.0%)	902 (75.1%)
n	600	601	1201
Weight Loss			
Yes	100 (16.7%)	102 (17.0%)	202 (16.8%)
No	500 (83.3%)	499 (83.0%)	999 (83.2%)
n	600	601	1201

Program: /opt/BIOSTAT/prod/cdt7159z/t_dm_bsym.sas
Output: /opt/BIOSTAT/prod/cdt7159n/12T223a/reports/t_dm_bsym_foly_223_IT.out
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Demographic and Baseline Characteristics (Overall Population)

In the overall population, the median age was 60.0 years (range: 23 to 88 years). The G-chemo arm had more patients > 60 years old than the R-chemo arm (53.0% vs 47.8%, respectively). The majority of patients were White (82.4% [1154/1401] of patients). Overall, more female than male patients were randomized (739/1401 patients [52.7%] vs. 662/1401 patients [47.3%]).

The majority of patients had an ECOG performance status of 0-1 (96.8%). Overall, 60.2% of patients were classified as stage IV according to Ann Arbor criteria. Baseline B-symptoms (fever, night sweats, weight loss) were present in 34.5% of patients. FCγ receptor polymorphism results were available for 1332/1401 patients (95.1%) for the FCγreceptor IIa and IIIa, and 1245/1401 patients (88.9%) for the FCγ receptor IIb analyses. For FCγ receptor IIa, overall the 131HR genotype was most frequent (47.5% of patients) and the frequency was comparable in both treatment arms. For FCγ receptor IIIa, the 158FF genotype was most frequent (44.9% of patients) in the R-chemo arm, but the 158VF genotype was most frequent (48.5% of patients) in the G-chemo arm. For FCγ receptor IIb/IIc, overall the 232II genotype was most frequent (78.1% of patients) and the frequency was comparable in both treatment arms.

Demographic and Baseline Characteristics (MZL Population)

Regarding geographic region, the R-chemo arm had more patients from Eastern Europe than the G-chemo arm (16.7% versus 10.1%; respectively). There were 32/195 patients (16.4%) who received CHOP chemotherapy (18/96 patients [18.8%] in the R-chemo arm and 14/99 patients [14.1%] in the G-chemo arm). There were 24/195 patients (12.3%) who received CVP chemotherapy (12/96 patients [12.5%] in the R-chemo arm and 12/99 patients [12.1%] in the G-chemo arm). There were 139/195

patients (71.3%) who received bendamustine chemotherapy (66/96 patients [68.8%] in the R-chemo arm and 73/99 patients [73.7%] in the G-chemo arm).

Central Pathology Assessments (Overall Population)

As randomization was stratified according to FLIPI group for FL (low, intermediate, or high) or IPI group for MZL (low/low-intermediate or high-intermediate/high), among other criteria, patients were randomized separately depending on their diagnosis (FL or MZL). The investigator provided the diagnosis as two categories, FL or non-FL, to IxRS. The investigator reported the diagnosis in the eCRF in three categories: FL, non-FL (with subtypes), or other. Three patients had an eCRF diagnosis of other: (diffuse large B-cell lymphoma [transformed FL]; R-chemo), (DBCL; G-chemo), and CLL; G-chemo).

Numbers analysed

Table 14: Analysis populations (FL population)

t_ds_anpop_foly_223_IT APPROVED Analysis Populations - Follicular Lymphoma Patients (Intent-to-Treat Patients)

Protocol(s): B021223 (L21223A)
Analysis Population: Intent-to-Treat Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

	R-chemo (N=601)	G-chemo (N=601)
Randomized Patients		
Assigned Treatment	601	601
Safety Evaluable Population		
Treatment Received: G-chemo	1	594
Treatment Received: R-chemo	597	0

Outcomes and estimation

The HR for the primary endpoint of PFS by INV in the FL population was 0.66, p-value 0.0012. The median PFS by INV was not reached in any arm at the time of analysis. The results of the primary endpoint analysis are further supported by PFS by IRC

Table 15: Fixed sequence testing procedure (INV- assessment)

Efficacy Parameter	INV-Assessment	
	Estimate	p-value
*PFS in FL population†	HR = 0.66 (0.51, 0.85)	0.0012
*PFS in overall population†	HR = 0.68 (0.54, 0.85)	0.0009
CR rate without PET at the EOI therapy in the FL population‡	Δ = −4.3% (−9.1, 0.4)	0.07
CR rate without PET at the EOI therapy in the overall population‡	Δ = −4.2% (−8.6, 0.1)	0.0466
OS in the FL population†	HR = 0.75 (0.49, 1.17)	0.21
OS in the overall population†	HR = 0.79 (0.55 ,1.15)	0.23
ORR without PET at the EOI therapy in the FL population‡	Δ = 1.7% (−2.1, 5.5)	0.33
ORR without PET at the EOI therapy in the overall population‡	Δ = 1.5% (−2.1, 5.1)	0.36

EOI = end of induction, HR = Hazard ratio, Δ = absolute difference in %.
*Significant according to Fixed Sequence Testing Procedure.
† stratified log-rank test
‡ Chi-square test

Primary endpoint: PFS by INV

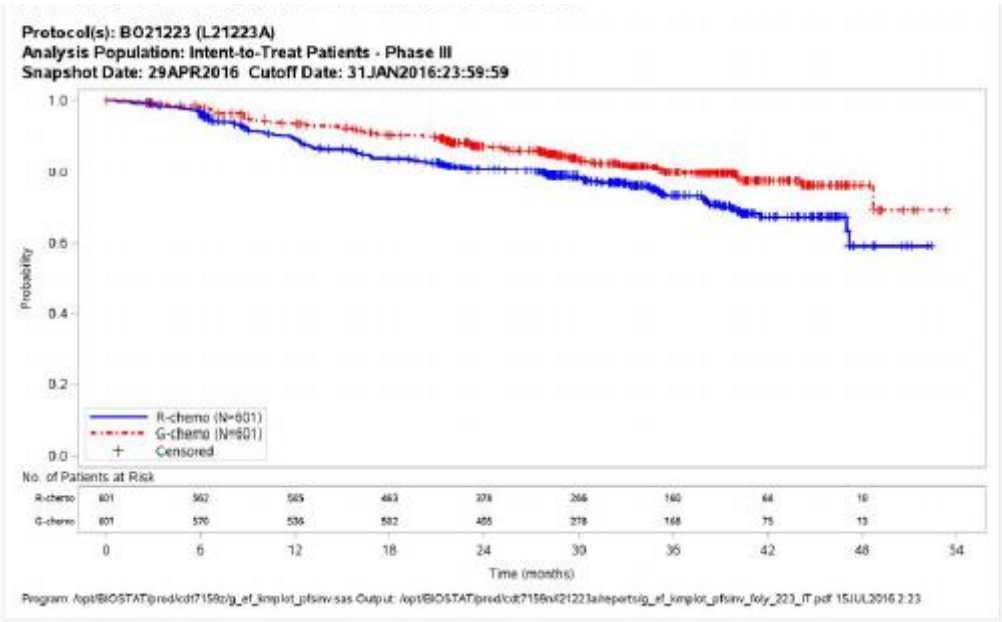
Table 16: Summary of PFS by Investigator's assessment (FL- ITT population)

Protocol(s): B021223 (L21223A)
Analysis Population: Intent-to-Treat Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

	R-chemo (N=601)	G-chemo (N=601)
Patients included in analysis	601 (100.0%)	601 (100.0%)
Patients with event (%)	144 (24.0%)	101 (16.8%)
Earliest contributing event		
Death	14	21
Disease Progression	130	80
Patients without event (%)*	457 (76.0%)	500 (83.2%)
Time to event(months)		
Median	NE	NE
95% CI for Median	(47.1, NE)	NE
25% and 75%-ile	34.9, NE	46.7, NE
Range	0.0 to 52.4	0.0 to 53.4
Time Point Analysis		
0.5 year		
Patients remaining at risk	562	570
Event free proportion	96.59	98.46
95% CI	(94.76, 97.79)	(97.06, 99.19)
1 year		
Patients remaining at risk	505	536
Event free proportion	89.74	93.94
95% CI	(86.95, 91.95)	(91.66, 95.61)
1.5 years		
Patients remaining at risk	463	502
Event free proportion	84.17	90.73
95% CI	(80.90, 86.93)	(88.04, 92.84)
2 years		
Patients remaining at risk	378	405
Event free proportion	80.94	87.66
95% CI	(77.43, 83.96)	(84.63, 90.13)
2.5 years		
Patients remaining at risk	266	278
Event free proportion	78.37	83.71
95% CI	(74.63, 81.63)	(80.17, 86.67)
3 years		
Patients remaining at risk	160	168
Event free proportion	73.29	80.03
95% CI	(68.83, 77.21)	(75.87, 83.55)
Stratified Analysis		
p-value (log-rank)	0.0012	
Hazard Ratio	0.66	
95% CI	(0.51, 0.85)	
Unstratified Analysis		
p-value (log-rank)	0.0013	
Hazard Ratio	0.66	
95% CI	(0.51, 0.85)	

*Censored.
Summaries of time to event (median, percentiles) are based on Kaplan-Meier estimates.
95% CI for median was computed using the method of Brookmeyer and Crowley.
Stratification factors: FLIPI, Chemotherapy Regimen.

Figure 7: Kaplan-Meier plot of PFS by Investigator's assessment (FL ITT population)



Secondary endpoint: PFS by IRC

Table 17: Summary of PFS by IRC assessment (FL ITT population)

Protocol(s): B021223 (L21223A)
Analysis Population: Intent-to-Treat Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

	R-chemo (N=601)	G-chemo (N=601)
Patients included in analysis	601 (100.0%)	601 (100.0%)
Patients with event (%)	125 (20.8%)	93 (15.5%)
Earliest contributing event		
Death	19	24
Disease Progression	106	69
Patients without event (%)*	476 (79.2%)	508 (84.5%)
Time to event(months)		
Median	51.2	NE
95% CI for Median	(47.1, NE)	(48.7, NE)
25% and 75%-ile	40.3, NE	48.7, NE
Range	0.0 to 52.4	0.0 to 53.4
Time Point Analysis		
0.5 year		
Patients remaining at risk	563	569
Event free proportion	97.09	98.62
95% CI	(95.36, 98.18)	(97.26, 99.31)
1 year		
Patients remaining at risk	500	528
Event free proportion	90.19	94.05
95% CI	(87.44, 92.36)	(91.78, 95.71)
1.5 years		
Patients remaining at risk	460	491
Event free proportion	84.92	89.73
95% CI	(81.69, 87.63)	(86.92, 91.97)
2 years		
Patients remaining at risk	372	385
Event free proportion	82.01	87.19
95% CI	(78.54, 84.97)	(84.10, 89.71)
2.5 years		
Patients remaining at risk	263	270
Event free proportion	80.27	85.06
95% CI	(76.62, 83.41)	(81.67, 87.88)
3 years		
Patients remaining at risk	160	162
Event free proportion	77.86	81.85
95% CI	(73.77, 81.39)	(77.89, 85.17)
Stratified Analysis		
p-value (log-rank)	0.0138	
Hazard Ratio	0.71	
95% CI	(0.54, 0.93)	
Unstratified Analysis		
p-value (log-rank)	0.0131	
Hazard Ratio	0.71	
95% CI	(0.55, 0.93)	

*Censored.
Summaries of time to event (median, percentiles) are based on Kaplan-Meier estimates.
95% CI for median was computed using the method of Brookmeyer and Crowley.
Stratification factors: FLIPI, Chemotherapy Regimen.

Program: /opt/BIOSTAT/prod/cdt7159s/k21223d/t_ef_tte_strunstr.sas
Output: /opt/BIOSTAT/prod/cdt7159n/121223a/reports/t_ef_tte_strunstr_pfsradl_foly_223_IT.out
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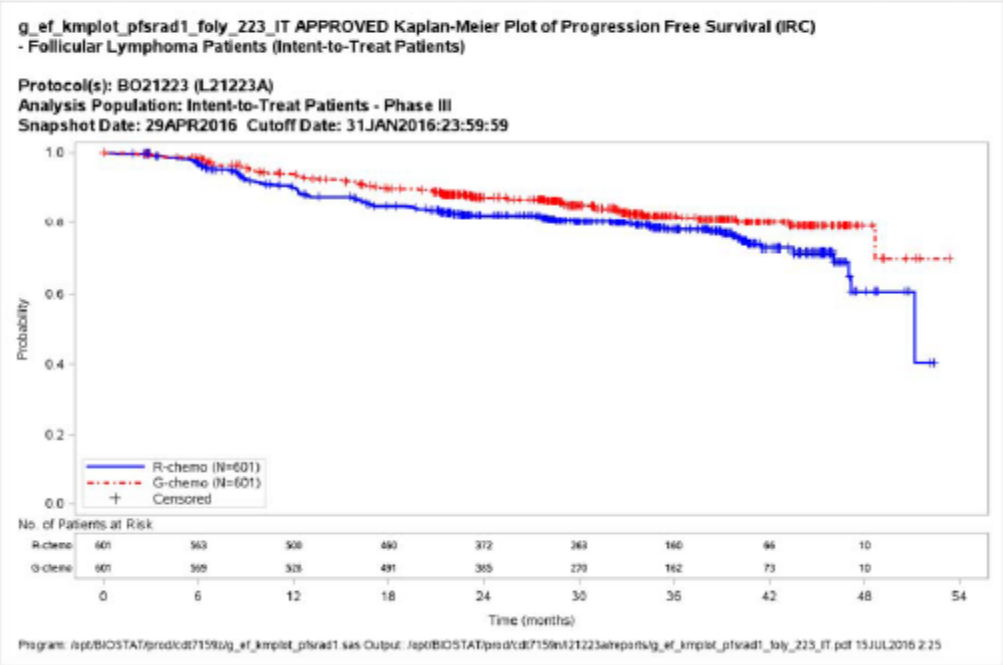
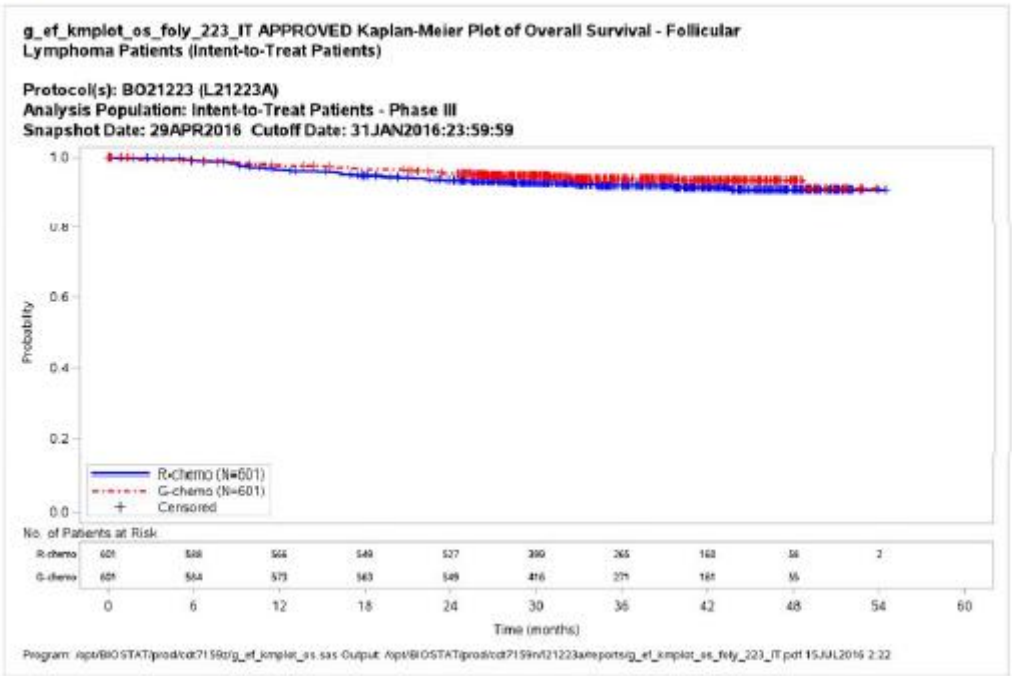
Figure 8 Kaplan-Meier Plot of Progression-Free Survival by IRC Assessment (FL ITT Population)



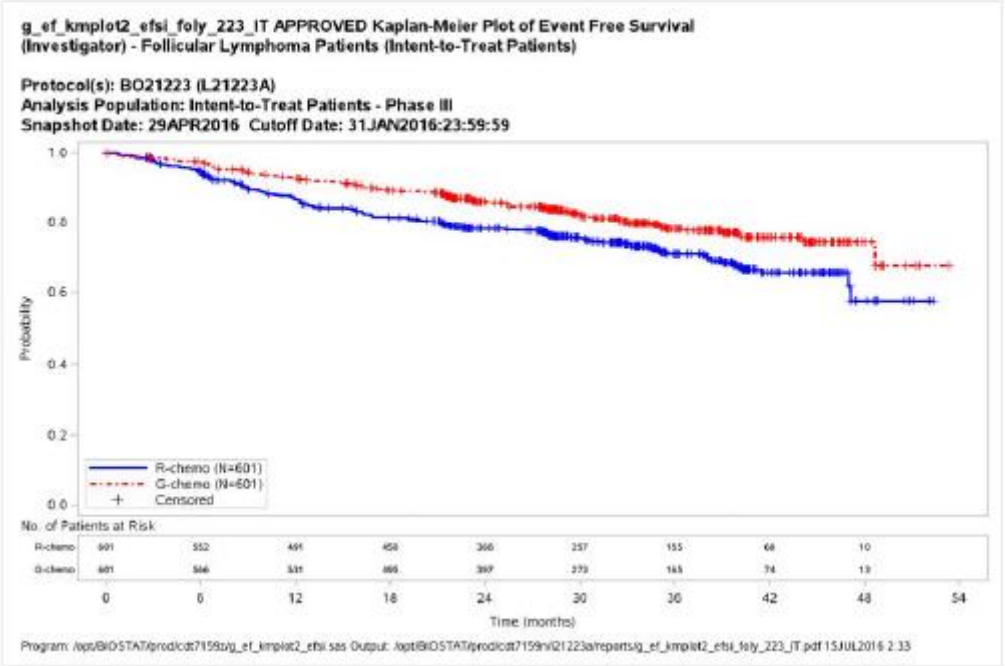
Secondary endpoint: OS

Figure 9 Kaplan-Meier Plot of Overall Survival (FL ITT Population)



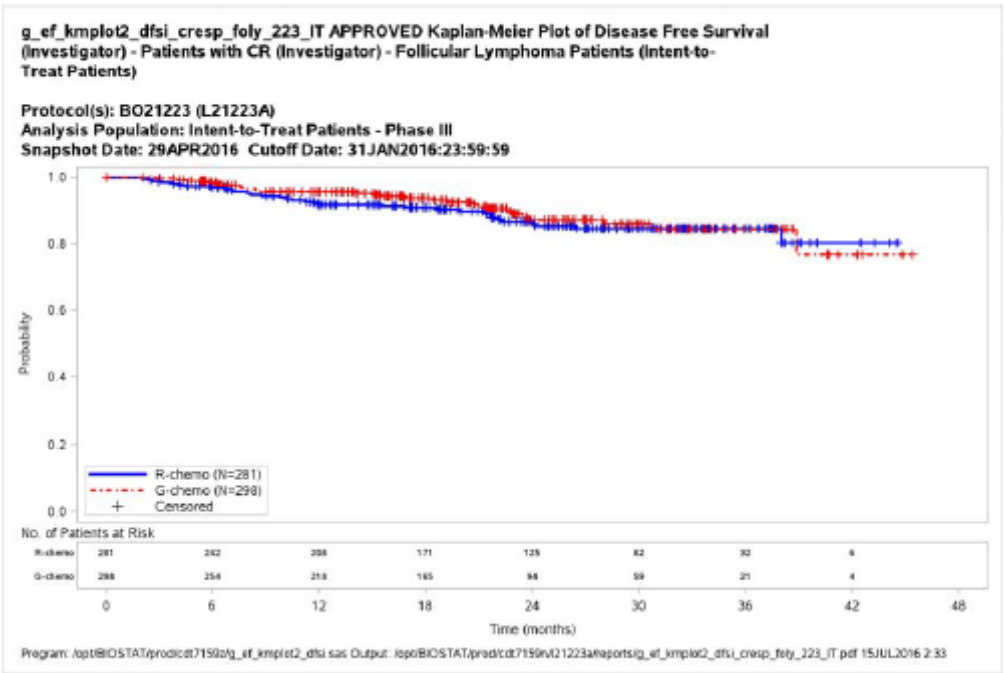
Secondary endpoint: EFS

Figure 10 Kaplan-Meier Plot of Event-Free Survival by Investigator Assessment (FL ITT Population)



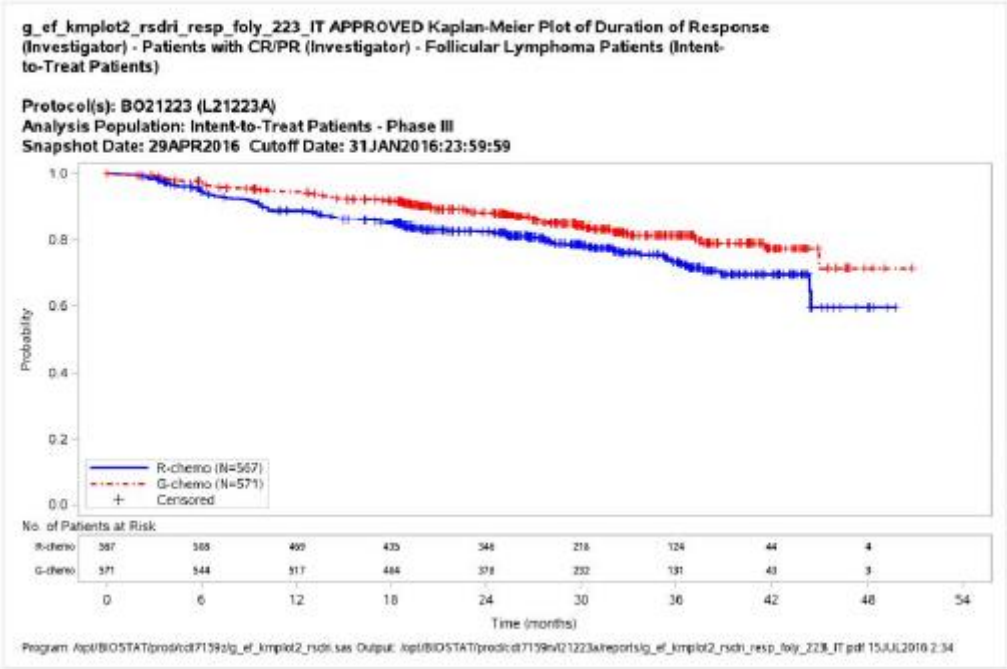
Secondary endpoint: DFS

Figure 11 Kaplan-Meier Plot of Disease-Free Survival in Patients with CR by Investigator Assessment (FL ITT Population)



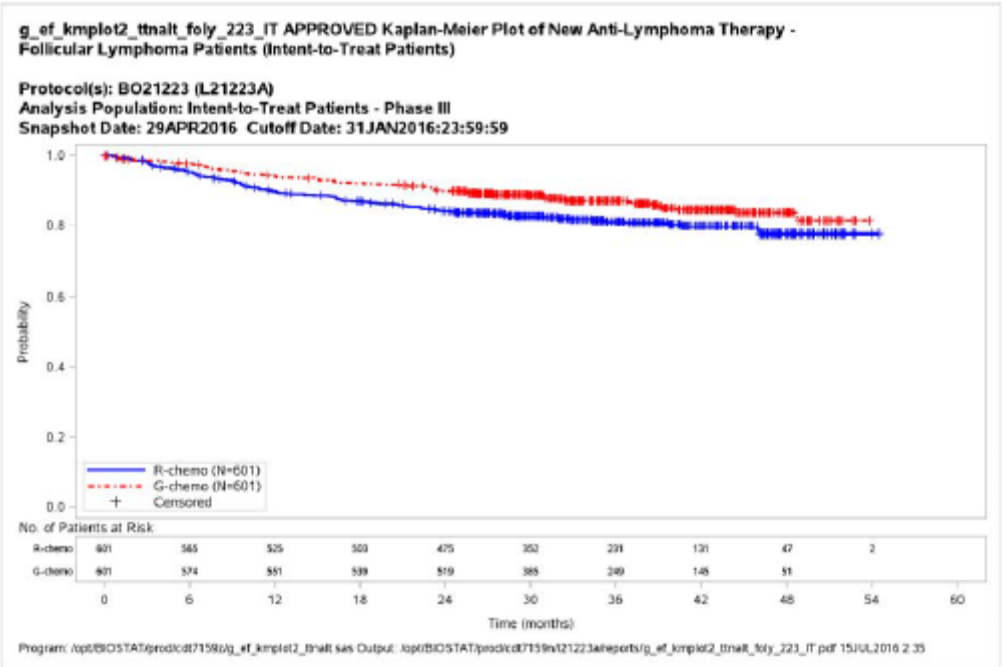
Secondary endpoint: DOR

Figure 12 Kaplan-Meier Plot of Duration of Response in Patients with CR/PR by Investigator Assessment (FL ITT Population)



Secondary endpoint: Time to new anti-lympoma treatment (TTNALT)

Figure 13 Kaplan-Meier Plot of Time to New Anti-Lymphoma Treatment (FL ITT Population)



Ancillary analyses

Sensitivity analysis for PFS by INV

The robustness of the PFS results (by investigator or IRC review) was assessed by performing a series of pre-specified sensitivity analyses applying alternative censoring rules or specific analysis criteria

Table 18: Summary of sensitivity analyses for PFS (INV – assessed and IRC – assessed FL ITT population

Analysis	Censoring rules/specific analysis criteria	Stratified HR (95% CI) (p-value) (No. of events G–chemo vs. R–chemo)	
		INV-Assessed PFS	IRC-Assessed PFS
Unstratified log-rank test		0.66 (0.51, 0.85) (p=0.0013) 101 vs. 144	0.71 (0.55, 0.93) (p=0.0131) 93 vs. 125
Re-randomization test	Re-run randomization algorithm a large number (10,000, based on IVRS stratification) of times to assess the sensitivity of the stratified log-rank test to the dynamic randomization procedure.	p=0.0011	p=0.0153
Impact of loss to follow-up ("worst case analysis")	Assigns event outcomes to patients who withdrew prior to disease progression in the obinutuzumab arm at the next scheduled disease assessment date and censored outcomes to patients in the rituximab arm at the last disease assessment date.	0.90 (0.72, 1.14) (p=0.40) 139 vs. 144	1.17 (0.92, 1.48) (p=0.20) 153 vs. 125
Impact of missed tumor assessment	If patients missed or had an incomplete response assessment prior to the date of the clinical data cutoff or prior to PD, they were counted as having progressed on the day after their last complete response assessment.	0.77 (0.63, 0.94) (p=0.0104) 169 vs. 207	0.83 (0.67, 1.03) (p=0.09) 161 vs. 185
Impact of NALT	Censoring at the initiation of non-protocol-specified anti-lymphoma therapy prior to disease progression, to assess potential confounding of the treatment effect estimates by subsequent therapy.	0.64 (0.49, 0.83) (p=0.0008) 95 vs. 137	0.72 (0.54, 0.95) (p=0.0183) 87 vs. 116
Impact of treatment discontinuation	Patients who discontinued the study treatment for other reasons than disease progression or death were counted as having progressed at the time of discontinuation (event was date of last dose for early treatment discontinuations).	0.78 (0.64, 0.95) (p=0.0135) 181 vs. 221	0.83 (0.67, 1.01) (p=0.06) 175 vs. 206
Impact of late death	Patients who died more than 6 months after their last response assessment and showed no sign of progression were censored at the last available response assessment.	0.64 (0.49, 0.83) (p=0.0007) 95 vs. 140	0.72 (0.55, 0.95) (p=0.0200) 88 vs. 118
Impact of non-evaluable* last tumor assessment	Accepting non-evaluable* tumor assessment as last response assessment for censoring purposes.	0.66 (0.51, 0.86) (p=0.0016) 101 vs. 144	0.70 (0.53, 0.91) (p=0.0073) 95 vs. 132

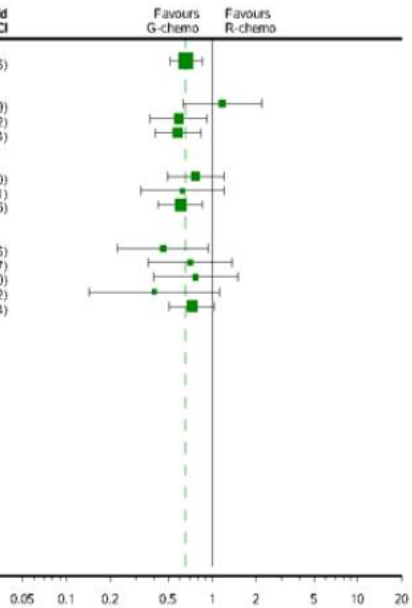
PFS in subgroups

Figure 14 Subgroup Analysis of Investigator-Assessed PFS by Stratification Factors (FL ITT Population)

g_ef_fshr_strat_pfsinv_foly_223_IT APPROVED Forest Plot of Hazard Ratio by Subgroup (Part 1)
- PFS - Investigator - Follicular Lymphoma Patients (Intent-to-Treat Patients)

Protocol(s): BO21223 (L21223A)
Analysis Population: Intent-to-Treat Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

		R-chemo (N=601)			G-chemo (N=601)				
Stratification Factors	Total n	n	Events	1 Year KM rate	n	Events	1 Year KM rate	Hazard Ratio	95% Wald CI
All Patients	1202	601	144	89.736	601	101	93.939	0.66	(0.51, 0.85)
IPI/FLIPI									
FL FLIPI Low	253	125	18	93.059	128	22	94.357	1.17	(0.63, 2.19)
FL FLIPI Intermediate	447	223	49	90.176	224	31	96.246	0.59	(0.37, 0.92)
FL FLIPI High	502	253	77	87.765	249	48	91.662	0.58	(0.41, 0.84)
Chemotherapy Regimen									
CHOP	398	203	46	93.841	195	35	93.636	0.77	(0.50, 1.20)
CVP	118	57	20	78.963	61	16	95.000	0.63	(0.32, 1.21)
BENDAMUSTINE	686	341	78	89.021	345	50	93.928	0.61	(0.43, 0.86)
Geographic Region									
Asia	185	93	22	93.049	92	11	94.212	0.46	(0.22, 0.95)
Eastern Europe	157	79	21	85.941	78	15	92.137	0.71	(0.36, 1.37)
North America	152	77	20	92.006	75	15	95.730	0.77	(0.39, 1.50)
Other	128	66	13	92.188	62	5	98.305	0.40	(0.14, 1.12)
Western Europe	580	286	68	88.621	294	55	93.007	0.73	(0.51, 1.04)



Unstratified hazard ratio is displayed.
CI = confidence interval
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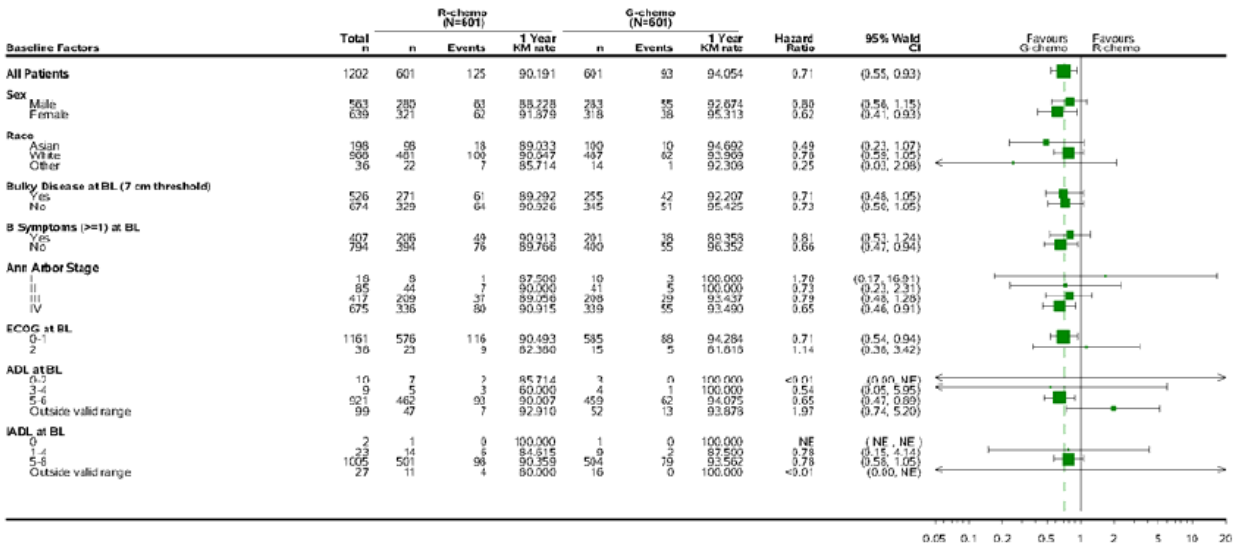
Figure 15: Subgroup analysis of IRC-assessed PFS by baseline demographics and disease characteristics (FL ITT population)

Protocol(s): BO21223 (L21223A)
Analysis Population: Intent-to-Treat Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59



Unstratified hazard ratio is displayed.
CI = confidence interval.
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Concordance rate between PFS by INV and IRC

Agreement between the IRC and the Investigator on the type of PFS event (i.e., agreement on assignment of PD, death or no event per patient) was high (92.1% overall) and balanced between arms (91.0% in the R-chemo arm vs. 93.2% in the G-chemo arm). In particular, for the R-chemo arm, the Investigator and IRC agreed that progression had not occurred in 444 of 601 patients (73.9%) and that progression had occurred in 91 of 601 patients (15.1%). Similarly, for the G-chemo arm, the Investigator and the IRC agreed that progression had not occurred in 486 of 601 patients (80.9%) and had occurred in 54 of 601 patients (9.0%). The majority of discordance between IRC-and Investigator PFS events was related to cases where the Investigator registered a progression event, but the IRC did not (54 patients; Table 29). Note that once the Investigator had diagnosed progression, no more CT scans were expected to be available to the IRC, preventing subsequent registration of disease progression. A small subset of these cases (7/54) were related to disease transformation.

Table 19: Summary of investigator and IRC –assessed PFS events (FL ITT population)

IRC Assessment	Death (n=19)	PD Event (n=106)	No Event (n=476)	Total (n=601)
Treatment Group: R-chemo (N=601)				
Investigator Assessment				
Death	12 (2.0%)	2 (0.3%)	0	14
PD Event	7 (1.2%)	91 (15.1%)	32 (5.3%)	130
No Event	0	13 (2.2%)	444 (73.9%)	457
Cohen's kappa				
kappa estimate	0.75			
95% CI	(0.69, 0.81)			
Treatment Group: G-chemo (N=601)				
IRC Assessment	Death (n=24)	PD Event (n=69)	No Event (n=508)	Total (n=601)
Investigator Assessment				
Death	20 (3.3%)	1 (0.2%)	0	21
PD Event	4 (0.7%)	54 (9.0%)	22 (3.7%)	80
No Event	0	14 (2.3%)	486 (80.9%)	500
Cohen's kappa				
kappa estimate	0.76			
95% CI	(0.69, 0.83)			
Treatment Group: ALL (N=1202)				
IRC Assessment	Death (n=43)	PD Event (n=175)	No Event (n=984)	Total (n=1202)
Investigator Assessment				
Death	32 (2.7%)	3 (0.2%)	0	35
PD Event	11 (0.9%)	145 (12.1%)	54 (4.5%)	210
No Event	0	27 (2.2%)	930 (77.4%)	957
Cohen's kappa				
kappa estimate	0.75			
95% CI	(0.71, 0.80)			

Table 20: Summary of time difference between investigator and IRC- assessed disease progression (FL ITT population)

Protocol(s): BO21223 (L21223A)
Analysis Population: Intent-to-Treat Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

	Total (N=1202)	R-chemo (N=601)	G-chemo (N=601)
Overall concordance	1107 (92.1%)	547 (91.0%)	560 (93.2%)
PD Events per IRC	175	106	69
Agreement with investigator PD event	145 (82.9%)	91 (85.8%)	54 (78.3%)
PD event date agreement	97 (55.4%)	64 (60.4%)	33 (47.8%)
PD event later per investigator	44 (25.1%)	24 (22.6%)	20 (29.0%)
PD event earlier per investigator	4 (2.3%)	3 (2.8%)	1 (1.4%)
Censored per investigator	27 (15.4%)	13 (12.3%)	14 (20.3%)
PD event, Death per investigator	3 (1.7%)	2 (1.9%)	1 (1.4%)
Death as event (IRC or Investigator)	46	21	25
Death as event per IRC	43	19	24
Death as event per investigator	35	14	21
Agreement	32 (69.6%)	12 (57.1%)	20 (80.0%)
Deaths as event by IRC, PD by investigator	11 (23.9%)	7 (33.3%)	4 (16.0%)
Deaths as event by investigator, PD by IRC	3 (6.5%)	2 (9.5%)	1 (4.0%)
Censored per IRC	984	476	508
Agreement with investigator	930 (94.5%)	444 (93.3%)	486 (95.7%)
PD event by investigator	54 (5.5%)	32 (6.7%)	22 (4.3%)
Absolute difference of time to event in days* (between Investigator timing and IRC timing)			
Mean (Std)	64.6 (141.3)	54.7 (125.8)	78.4 (160.3)
Range	0 - 841	0 - 841	0 - 787
Median	0.0	0.0	0.0
25%-ile	0.0	0.0	0.0
75%-ile	65.0	51.0	81.0
n	177	103	74

IRC and investigator dates are considered to be in agreement if they are within 30 days apart to account for potential slight differences in visit date assignments by IRC and investigator
* includes PD events and deaths

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Modified by PDRD

Disease Transformation

Of the 1202 patients with Follicular Lymphoma enrolled in the study, 210 patients (17.5%) had documented progression (130/601 patients in the R-chemo arm [21.6%], and 80/601 patients in the G-chemo arm [13.3%]). Disease transformation (to a high grade malignancy or DLBCL) was reported for 29/601 patients (4.8%) in the R-chemo arm, and 18/601 patients (3.0%) in the G-chemo arm (Table 33), with a difference in transformation rates of - 1.8% (95% CI: - 4.1, 0.4). When considered as a percentage of patients with disease progression, 22.3% of patients in the R-chemo arm (29/130) and 22.5% of patients in the G-chemo arm (18/80) progressed with disease transformation.

Table 21 Proportion of patients with disease transformation (FL ITT population)

t_ef_dt_foly_223_IT APPROVED Proportion of Patients with Disease Transformation - Follicular Lymphoma Patients (Intent-to-Treat Patients)

Protocol(s): BO21223 (L21223A)
Analysis Population: Intent-to-Treat Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

	R-chemo (N=601)	G-chemo (N=601)
Patients with histologic transformation	29 (4.8%)	18 (3.0%)
95% CI for patients with transformation*	(3.26, 6.86)	(1.78, 4.69)
Difference in proportion of transforming patients (G-Chemo vs R-Chemo)	-1.83	
95% CI for difference#	(-4.10, 0.44)	

* 95% CI for one sample binomial using Clopper-Pearson method
\# Approximate 95% CI for difference of two proportions using Hauck-Anderson method

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Response conversion during maintenance treatment

At the end of the induction therapy, 794/1201 patients (66.1%) achieved a PR (379 patients (63.1%) in the R-chemo arm vs. 415 patients (69,1%) in the G-chemo arm). A total of 493 patients with an end of induction response of PR also had an available end of maintenance response assessment. Of these patients, an improvement in response to CR during maintenance was observed in 97/222 patients (43.7%) in the R-chemo arm, compared with 134/271 patients (49.4%) on the G-chemo arm.

End of Maintenance Response (FL ITT Population)

A non-pre-specified end of maintenance response (EOMR) analysis was conducted. EOMR was defined as the first response assessment that occurred after the last dose of maintenance treatment. The population included all patients randomized other than those who had not yet reached the end of the maintenance assessment. Patients with disease progression or death at any time or with missing response assessments at the end of maintenance were considered non-responders. This analysis is similar to that exploring conversion, but includes all randomized patients in the study long enough, i.e., also early withdrawals and non-responders, within the denominator.

Based on the Investigator assessment, 712/1058 patients with FL (67.3%) achieved a CR or PR at the end of maintenance phase: 341 patients (64.0% [95% CI: 59.7, 68.1]) in the R-chemo arm and 371 patients (70.7% [95% CI: 66.6, 74.5]) in the G-chemo arm, an absolute difference of 6.7% (95% CI: 1.0, 12.4; p-value = 0.0197, CMH test) in favor of G-chemo at this time point. Similarly, an absolute difference in CR rate of 2.5% (95% CI: - 3.5, 8.4; p-value = 0.39, CMH test) was found in favor of G-chemo at this time point (Table 22)

Table 22: Overall end of maintenance response without PET by investigator (FLITT population)

t_ef_rspstrm_invetm_foly_223_IT APPROVED - End of maintenance response without PET by Investigator - Follicular
Lymphoma Patients (Intent-to-Treat Patients)

Protocol(s): BO21223 (L21223A)
Analysis Population: Intent-to-Treat Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

	R-chemo (N=601)		G-chemo (N=601)
n	533		525
Overall Response (CR,PR)	341 (64.0%)		371 (70.7%)
95% CI (Clopper-Pearson)	(59.74, 68.06)		(66.57, 74.53)
Difference (G-Chemo vs. R-Chemo)		6.69	
95% CI (Hauck-Anderson)		(0.95, 12.43)	
P-Value* (Cochran-Mantel-Haenszel)		0.0197	
Odds Ratio (G-Chemo vs. R-Chemo)		1.36	
95% CI		(1.05, 1.76)	
Complete Response (CR)	195 (36.6%)		205 (39.0%)
95% CI (Clopper-Pearson)	(32.49, 40.83)		(34.85, 43.37)
Difference (G-Chemo vs. R-Chemo)		2.46	
95% CI (Hauck-Anderson)		(-3.48, 8.41)	
P-Value* (Cochran-Mantel-Haenszel)		0.3871	
Odds Ratio (G-Chemo vs. R-Chemo)		1.12	
95% CI		(0.87, 1.44)	
Partial Response (PR)	146 (27.4%)		166 (31.6%)
95% CI (Clopper-Pearson)	(23.65, 31.39)		(27.66, 35.79)
Difference (G-Chemo vs. R-Chemo)		4.23	
95% CI (Hauck-Anderson)		(-1.36, 9.82)	
P-Value* (Cochran-Mantel-Haenszel)		0.1389	
Odds Ratio (G-Chemo vs. R-Chemo)		1.22	
95% CI		(0.94, 1.59)	
Stable Disease (SD)	1 (0.2%)		0
95% CI (Clopper-Pearson)	(0.00, 1.04)		(0.00, 0.70)
Difference (G-Chemo vs. R-Chemo)		-0.19	
95% CI (Hauck-Anderson)		(-0.65, 0.28)	
P-Value* (Cochran-Mantel-Haenszel)		0.2733	
Odds Ratio (G-Chemo vs. R-Chemo)		<0.01	
95% CI		(0.00, NE)	

n is based on number of patients that reached end of maintenance response assessment, or withdrew prematurely
* P-Values based on stratified Cochran-Mantel-Haenszel. Stratification factors: IPI/FLIPI, Chemotherapy Regimen.

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(Table 22 cont)

	R-chemo (N=601)		G-chemo (N=601)
Progressive Disease (PD)	70 (13.1%)		41 (7.8%)
95% CI (Clopper-Pearson)	(10.38, 16.30)		(5.66, 10.45)
Difference (G-Chemo vs. R-Chemo)		-5.32	
95% CI (Hauck-Anderson)		(-9.10, -1.55)	
P-Value* (Cochran-Mantel-Haenszel)		0.0039	
Odds Ratio (G-Chemo vs. R-Chemo)		0.55	
95% CI		(0.37, 0.83)	
Unable to Evaluate (NE)	26 (4.9%)		21 (4.0%)
95% CI (Clopper-Pearson)	(3.21, 7.07)		(2.49, 6.05)
Difference (G-Chemo vs. R-Chemo)		-0.88	
95% CI (Hauck-Anderson)		(-3.46, 1.70)	
P-Value* (Cochran-Mantel-Haenszel)		0.5222	
Odds Ratio (G-Chemo vs. R-Chemo)		0.83	
95% CI		(0.46, 1.49)	
Missing (NA)	95 (17.8%)		92 (17.5%)
95% CI (Clopper-Pearson)	(14.67, 21.34)		(14.37, 21.05)
Difference (G-Chemo vs. R-Chemo)		-0.30	
95% CI (Hauck-Anderson)		(-5.00, 4.40)	
P-Value* (Cochran-Mantel-Haenszel)		0.9043	
Odds Ratio (G-Chemo vs. R-Chemo)		0.98	
95% CI		(0.71, 1.35)	

n is based on number of patients that reached end of maintenance response assessment, or withdrew prematurely
* P-Values based on stratified Cochran-Mantel-Haenszel. Stratification factors: IPI/FLIPI, Chemotherapy Regimen.

When response was assessed by IRC, the IRC assessed EOMR was similar to the Investigator assessed EOMR with 65.1% (95% CI: 60.9, 69.2) for the R-chemo arm and 70.9% (95%

CI: 66.8, 74.8) for the G-chemo arm; and CR rates were 42.6% (95% CI: 38.4, 46.9) and 45.2% (95% CI: 40.9, 49.6), respectively.

Table 23: Summary of Efficacy parameters in the Overall and FL population

Efficacy Parameter	IRC-Assessed Endpoints			
	Overall Population		Follicular Population	
	R-Chemo (N=699)	G-Chemo (N=702)	R-Chemo (N=601)	G-Chemo (N=601)
Progression-Free Survival				
Patients with event	151 (21.6%)	113 (16.1%)	125 (20.8%)	93 (15.5%)
HR (stratified), 95% CI	0.73 (0.57, 0.93) p-value=0.0109		0.71 (0.54, 0.93) p-value=0.0138	
KM 2-year estimate	81.8% (78.6, 84.6)	86.8% (83.9, 89.2)	82.0% (78.5, 85.0)	87.2% (84.1, 89.7)
KM 3-year estimate	77.4% (73.6, 80.7)	81.1% (77.5, 84.2)	77.9% (73.8, 81.4)	81.9% (77.9, 85.2)
Overall Response at End-of-Induction				
Overall Response (CR, PR)				
Without PET				
n (%)	606 (86.7%)	630 (89.7%)	529 (88.0%)	548 (91.2%)
Δ, 95% CI	3.1% (−0.4, 6.5) p-value=0.06		3.2% (−0.4, 6.7) p=0.07	
With PET				
n (%)	275/330 (83.3%)	280/321 (87.2%)	254/298 (85.2%)	263/297 (88.6%)
Δ, 95% CI	3.9% (−1.7, 9.5) p-value=0.22		3.3% (−2.3, 8.9) p-value=0.30	

Efficacy Parameter	IRC-Assessed Endpoints			
	Overall Population		Follicular Population	
	R-Chemo (N=699)	G-Chemo (N=702)	R-Chemo (N=601)	G-Chemo (N=601)
Complete Response at End-of-Induction				
Complete Response (CR)				
Without PET				
n (%)	181 (25.9%)	189 (26.9%)	159 (26.5%)	171 (28.5%)
Δ	1.0 (−3.7, 5.7) p-value=0.72		2.0% (−3.1, 7.1) p-value=0.50	
With PET				
n (%)	196/330 (59.4%)	223/321 (69.5%)	178/298 (59.7%)	212/297 (71.4%)
Δ	10.1% (2.6, 17.6) p-value=0.0094		11.7% (3.9, 19.4) p-value=0.0056	

CR=complete response, HR=Hazard ratio, IRC=Independent Review Committee, KM=Kaplan Meier, PET=positron emission tomography, PR=partial response, Δ=absolute difference in %.
p-values and hazard ratios were calculated using the stratified log-rank test and stratified Cox regression for time-to-event endpoints, respectively.
Stratification factors were chemotherapy and FLIPI/IPI. p-values for response proportion difference were calculated using the stratified Cochran-Mantel-Haenszel method.

HRQoL

Equal proportions of patients in the G-chemo and R-Chemo arms had improvement in their FACT-Lym questionnaire scores during treatment and throughout maintenance and follow-up as defined by a ≥ 3

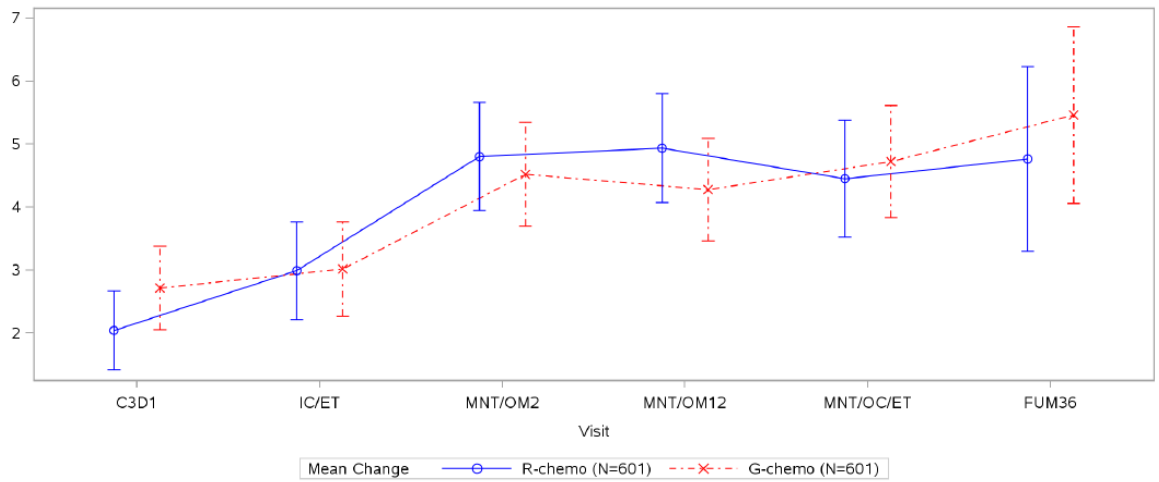
point increase from baseline in the Lymphoma subscale, a ≥ 6 point increase from baseline in the FACT Lym TOI and a ≥ 7 point increase from baseline in the FACT Lym Total score (Table 39). By the Month 2 maintenance assessment, although the number of patients available for assessment was lower, approximately 50% of the patients still in the treatment arms were reporting clinically meaningful improvement.

Table 24: Summary of meaningful improvement in FACT-Lym

FACT-Lym Subscale (definition of meaningful improvement)	R-chemo n=601	G-chemo n=601
Lymphoma subscale (≥3 point increase)		
Cycle 3, Day 1 (Induction treatment)	217 (40.8%)	229 (45.1%)
End of Induction visit	238 (47.6%)	233 (47.0%)
Maintenance visit Month 2	212 (56.5%)	233 (57.4%)
Maintenance visit Month 12	216 (56.1%)	227 (53.7%)
Maintenance Completion visit	205 (55.0%)	218 (56.2%)
FACT TOI (≥6 point increase)		
Cycle 3, Day 1 (Induction treatment)	163 (30.5%)	162 (31.7%)
End of Induction visit	203 (40.0%)	189 (38.0%)
Maintenance visit Month 2	182 (48.3%)	192 (47.1%)
Maintenance visit Month 12	190 (49.1%)	202 (47.6%)
Maintenance Completion visit	174 (46.4%)	191 (49.1%)
FACT Total (≥7 point increase)		
Cycle 3, Day 1 (Induction treatment)	179 (33.5%)	173 (33.9%)
End of Induction visit	206 (40.6%)	197 (39.6%)
Maintenance visit Month 2	180 (47.7%)	191 (46.8%)
Maintenance visit Month 12	188 (48.5%)	197 (46.5%)
Maintenance Completion visit	171 (45.5%)	191 (49.1%)

Note: Percentages are calculated on the number of patients who completed the questionnaire at each visit.

Figure 16: Change from baseline in patient-reported FACT-Lym Lymphoma subscale scores during treatment (FL ITT population)



Scheduled visits up until follow-up month 36 only are included. C3D1 = CYCLE 3 DAY 1,
IC/ET = INDUCTION COMPLETION/EARLY TERMINATION VISIT, MNT/OM2 = MAINT/OBS MONTH 2, MNT/OM12 = MAINT/OBS MONTH 12,
MNT/OC/ET = MAINTENANCE OR OBSERVATION COMPLETION/EARLY TERMINATION VISIT, FUM36 = FOLLOW-UP MONTH 36
Vertical bars at each time point represent Confidence Interval for Mean.

Mean baseline FACT-Lym Lymphoma subscale score: R-chemo: 45.0 ± 9.4 vs. G-chemo: 45.5 ± 9.9 (maximum 60).

Summary of main study

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

Table 25: Summary of Efficacy for trial

Title: A multicenter, Phase III, open-label, randomized study in previously untreated patients with advanced indolent non-Hodgkin's lymphoma evaluating the benefit of GA101 (RO5072759) plus chemotherapy compared with rituximab followed by GA101 or rituximab maintenance therapy in responders		
Study identifier	**BO21223**	
Design	Phase III, randomised (1:1), open-label	
	Duration of study	6 July 2011 (first patient enrolled) to 31 January 2016 (cutoff date for this Clinical Study Report). The study Is ongoing.
Hypothesis	Superiority	
Treatments groups	R-chemo (rituximab + chemotherapy)	Six to eight doses of rituximab 375 mg/m2 were administered by IV infusion with the accompanying chemotherapy regimen during induction. Rituximab was administered on Day 1 of each cycle (2-6 or 2-8, depending on accompanying chemotherapy regimen). CHOP was administered on Day 1 of Cycles 1−6. CVP was administered on Day 1 of Cycles 1–8. Bendamustine was administered on Days 1 and 2 of Cycles 1−6. Patients randomized to rituximab plus chemotherapy who achieved a CR or PR at the end of induction therapy continued to receive rituximab 375 mg/m2 every 2 months until disease progression or for up to 2 years.
	G-chemo (obinutuzumab + chemotherapy)	Eight to ten doses of obinutuzumab 1000 mg were administered by IV infusion with the accompanying chemotherapy regimen during induction. Obinutuzumab was administered on Days 1, 8, and 15 of Cycle 1, and on Day 1 of subsequent cycles (2-6 or 2-8, depending on accompanying chemotherapy regimen). CHOP was administered on Day 1 of Cycles 1−6. CVP was administered on Day 1 of Cycles 1–8. Bendamustine was administered on Days 1 and 2 of Cycles 1−6. Patients randomized to receive obinutuzumab plus chemotherapy who achieved a CR or PR at the end of induction therapy continued to receive obinutuzumab 1000 mg every 2 months until disease progression or for up to 2 years.

Endpoints and definitions	Primary endpoint:	PFS by INV	Progression-free survival assessed by investigator
	Secondary endpoint:	PFS by IRC	Progression-free survival assessed by independent review committee.
	Secondary endpoint	OS	Overall survival
	Secondary endpoint	DOR	Duration of response
	Secondary endpoint	EFS	Event-free survival
	Secondary endpoint	DFS	Disease-free survival
	Secondary endpoint	TTNALT	Time to new anti-lymphoma treatment
Database lock	<date>		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	R-chemo	O-chemo	
	Number of subject (FL patients only)	601	601	
	PFS by INV (median in months)	NE	NE	
	95% CI	47.1, NE	48.1, NE	
	PFS by IRC (median in months)	51.2	NE	
	95% CI	47.1, NE	48.7, NE	
	OS (median in months)	NE	NE	
	DOR (median in months)	NE	NE	
	EFS (median in months)	NE	NE	
	DFS (median in months)	NE	NE	
	TTNALT (median in months)	NE	NE	
Effect estimate per comparison	Primary endpoint : PFS by INV	Comparison groups	R-chemo vs. G-chemo	

		HR	0.66
		95%CI	0.51, 0.85
		P-value	0.0012
	Secondary endpoint: PFS by IRC.	Comparison groups	R-chemo vs. G-chemo
		HR	0.71
		95%CI	0.54, 0.93
		P-value	0.0138
	Secondary endpoint: OS	Comparison groups	R-chemo vs. G-chemo
		HR	0.75
		95%CI	0.49, 1.17
		P-value	0.21
	Secondary endpoint: DOR	Comparison groups	R-chemo vs. G-chemo
		HR	0.66
		95%CI	0.50, 0.87
		P-value	
	Secondary endpoint: EFS	Comparison groups	R-chemo vs. G-chemo
		HR	0.65
		95%CI	0.51, 0.83
		P-value	0.0006
	Secondary endpoint: DFS	Comparison groups	R-chemo vs. G-chemo
		HR	0.81
		95%CI	0.48, 1.35
		P-value	-
	Secondary endpoint: TTNALT	Comparison groups	R-chemo vs. G-chemo
		HR	0.68
		95%CI	0.51,0.91
		P-value	0.0094
Notes	EFS, OS, DFS, DOR and TTNALT are not adjusted for multiplicity.		

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

N/A

Clinical studies in special populations

N/A

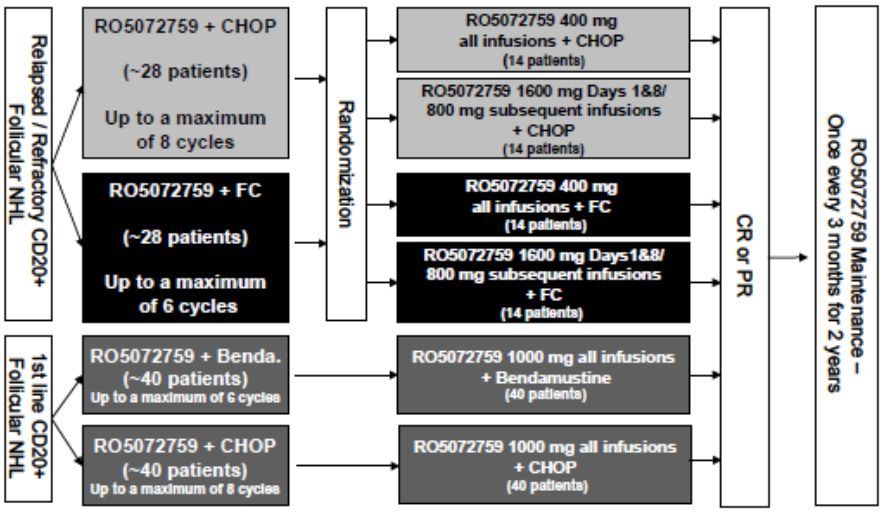
Supportive study

The data to support the current application to extend the use of obinutuzumab to previously untreated patients with FL comes from one pivotal Phase III study, with supporting data from a Phase Ib study:

BO21000 (GAUDI): *An open-label, multi-center, randomized, Phase Ib study to investigate the safety and efficacy of RO5072759 given in combination with CHOP, FC or bendamustine chemotherapy in patients with CD20+ B-cell follicular non-Hodgkin's lymphoma.*

In Study BO21000, the number of scheduled obinutuzumab doses was lower than in Study BO21223 since only two doses of obinutuzumab were scheduled in Cycle 1 (on Day 1 and 8 in BO21000 vs. Day 1, 8, and 15 in BO21223), fewer treatment cycles were scheduled during induction (4 or 6 for G-benda and 6 or 8 for G-CHOP in BO21000 vs. 6 for G-benda and 8 for G-CHOP or G-CVP in BO21223), and because of less frequent maintenance dosing (every 3 months for a total of 8 maintenance doses in BO21000 vs. every 2 months for a total of 12 maintenance doses in BO21223). The number of planned chemotherapy cycles was also lower in BO21000 than in BO21223.

Figure 16: BO21000 Study design



Note: This study used the 2007 revised response criteria for NHL, and unconfirmed response (CRu) is not part of these revised criteria. Patients whose response would have been labeled CRu according to the original 1999 criteria were therefore classified under PR in this study. Patients who completed maintenance therapy were then followed for 2 years after receiving the last dose of obinutuzumab or until progression or NALT, whichever occurred first. Monitoring for recurrent disease continued in patients who were in continuous response (i.e., CR/PR), and all patients were followed for survival every 6 months until the end of the study. The end of the study was defined as the time point when the last patient had completed 2 years of follow-up after receiving the last dose of maintenance therapy

Table 26: Comparison of key entry criteria in studies BO21233 and BO21000

	BO21223	BO21000 (Previously-Untreated Patients)
Age	≥ 18 years of age	≥ 18 years of age
Sex	Male and female	Male and female
CD20 Status	$CD20^+$ disease based on local testing followed by central confirmation [a]	$CD20^+$ disease based on local testing followed by central confirmation [a]
Patient Population	Patients with previously-untreated $CD20^+$ B-cell FL (Grades 1-3), splenic MZL, nodal MZL or extranodal MZL [b]	Patients with previously-untreated $CD20^+$ B-cell FL
Disease Stage	Ann Arbor Stage III or IV disease or Stage II bulky disease [c] (stage I excluded)	Ann Arbor Stage I–IV
Life expectancy	> 12 months	> 12 weeks
Measurable disease	All patients had to have at least one bi-dimensionally measurable lesion (> 1.5 cm in its largest dimension by CT scan)	All patients had to have at least one bi-dimensionally measurable lesion (> 1.5 cm in its largest dimension by CT scan)
Performance Status	0–2	0–2
Concomitant disease	Patients with evidence of significant, uncontrolled concomitant diseases (e.g., significant cardiovascular disease or pulmonary disease) were excluded.	Patients with evidence of significant, uncontrolled concomitant diseases (e.g., significant cardiovascular disease or pulmonary disease) were excluded.

Table 27 Overview of Efficacy in Previously-Untreated FL Population in Study BO21000

Efficacy Parameter	**Previously-Untreated FL Population**	
	G-benda (N = 41)	**G-CHOP (N = 40)**
End of Treatment Response		
Patients with CR (95% CI)	15 (36.6%) (22.1; 53.1)	14 (35.0%) (20.6; 51.7)
Patients with PR	23 (56.1%)	24 (60.0%)
EOT response rate (95% CI)	92.7% (80.1; 98.5)	95.0% (83.1; 99.4)
Best Overall Response		
Patients with CR	28 (68.3%)	32 (80.0%)
Patients with PR	10 (24.4%)	6 (15.0%)
BOR rate (95% CI)	92.7% (80.1; 98.5)	95.0% (83.1; 99.4)
Complete Response at 30 months[a]		
Patients with response	24 (63.2%)	21 (58.3 %)
95% CI	(46.0; 78.2)	(40.8; 74.5)
Progression-Free Survival		
Number (%) of patients with event	6 (14.6 %)	11 (27.5 %)
Median, months (95% CI)	56.0 (NE, NE)	NE
3-year PFS rate	0.90 (0.80; 0.99)	0.84 (0.72; 0.96)
Event-Free Survival		
Patients with event (%)	8 (19.5 %)	13 (32.5 %)
Median, months (95% CI)	56.0 (NE, NE)	NE
Duration of Response		
Number of patients with response	38	38

Patients with PD after CR/PR	5 (13.2 %)	11 (28.9 %)
Median duration, months (95% CI)	53.6 (NE, NE)	NE
Time to New Anti-Lymphoma Treatment		
Patients with event	5 (12.2 %)	9 (22.5 %)
Median time to NALT (95% CI)	NE (58; NE)	NE (NE, NE)

BOR ☐ best overall response, CI ☐ confidence interval, CR ☐ complete response, EOT ☐ end of treatment, NALT ☐ new anti-lymphoma treatment, NE ☐ Not estimable, PD ☐ progressive disease, PFS ☐ Progression-free Survival, PR ☐ partial response.

[a] CR30 was a post-hoc exploratory analysis. All other parameters were pre-specified in protocol.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The Applicant has provided one pivotal, randomised (1:1), open-label, phase III study (BO21223) to support the proposed extension of the indication. The study included patients with previously untreated stage III/IV or stage II Bulky disease (>7cm) Follicular Lymphoma (FL). Patients with Grade 3b FL are excluded from the study as reflected in the SmPC, since they usually are more aggressive and treated as DLBCL. The recent GOYA study comparing R-CHOP with G-CHOP in patients with DLBCL showed that the latter was not superior to the first. Patients with Grade 3b FL are in clinical practise perceived to behave as DLBCL.

The choice of backbones (CHOP, CVP or bendamustine) and regimens are fully acceptable, since R-CHOP, R-CVP and R-B followed by rituximab maintenance are considered standard of care in this patient population.

Randomisation and the three stratification factors are acceptable. The stratification factors are: Chemotherapy regimen (CHOP, CVP, or bendamustine), FLIPI (for FL: low, intermediate, or high)/IPI (for MZL: low/low-intermediate or high-intermediate/high) group and geographic region (Western Europe, Eastern Europe, South and Central America, North America, other). It is noted that randomization occurred separately for the patients with FL and MZL. The Western Europe region only included countries within the European Union.

The trial was adequately powered for the FL population (in line with the claimed indication), with 3 planned interim analyses (2 for futility, one for efficacy) using the O'Brien-Fleming sequential procedure for controlling the overall 0.05 type-1 error, with a nominal type-1 error of 0.012 for the efficacy interim analysis. Calculations were based upon a hazard ratio of 0.741 representing a 26% reduction risk of disease progression. Assuming a 6-year PFS in the R-Chemo arm and exponentially distributed PFS times, this corresponds to a 2.1-years increase of median PFS with Gazyvaro compared to SOC. Analysis in the MZL cohort was exploratory only; therefore no power calculation was performed for this subgroup of subjects.

The primary objective of this study is to compare efficacy between R-chemo and G-chemo in terms of Progression-free survival as assessed by Investigator. PFS is fully acceptable in patients with FL, since the course of the disease typically stretches over years to decades. The Applicant has included PFS by IRC as a secondary objective. This is acknowledged since the study is open-label. To adjust for multiple statistical testing of the primary and key secondary efficacy endpoints, the Applicant has applied a fixed sequence testing procedure. Other secondary objectives/endpoints include OS, EFS, TTNALT, DFS and DOR. The testing of EFS, TTNALT, DFS and DOR were not adjusted for multiplicity, and the results should therefore be interpreted with caution.

The Applicant applied 3 planned IA's. However, the first two IAs were concerned with futility, while the last IA was related to PFS (efficacy) and was planned after 67% of the events had occurred.

The protocol was amended 4 times. None of the amendments are considered critical for conduct of the study or the interpretation of data. With regard to protocol deviations, the overall number of deviations is similar between the two arms. In the updated analysis 427 patients in the G-chemo arm and 418 patients in the R-chemo arm had at least one deviation. The subcategory "other tumour or response related assessments" comprised 194 patients in the G-chemo arm and 187 patients in the R-chemo arm. The pattern of deviations is more or less similar, the majority of deviations in the subcategory included "missing" or "out of window" MRD assessments, missing laboratory assessments or related to patients with MZL who were not the target population. The deviations were considered having no direct impact on the primary endpoint.

In general, the baseline demographic characteristics are well balanced between the two treatment arms. The majority of patients are white, below 65 years of age. Mean age is approximately 58 years. There are slightly more patients in the age group 60-69 years in the G-chemo arm. If any, this is in favour of the R-chemo arm. The baseline disease characteristics are well balanced. The majority of patients had ECOG score of 0 or 1, Ann Arbor stage 3 or 4, FLIPI score intermediate or high. Slightly more patients had Bulky disease at baseline in the R-chemo arm, however, the difference is not considered major. Baseline B-symptoms are well balanced without any major differences. Overall, at baseline, patients in the two treatment arms had similar levels of HRQoL (as measured by the FACT-Lym questionnaire) and health status (as measured by the EQ-5D questionnaire). Patients in both treatment arms had some impairment of physical function, functional wellbeing, emotional and social function at baseline as a result of their disease, similar to that reported in the literature in a sample of newly diagnosed patients with FL (Pettengell et al, 2009), and in other cancer and non-cancer populations (Janda et al 2009; Brucker at al 2005).

Efficacy data and additional analyses

The dosing rationale was based on a comprehensive review of safety, efficacy and PK data in Phase I studies. A unit dose of 1000 mg for all infusions was chosen as the dose to be used in future Phase II and Phase III studies since it was the dose most likely to be well tolerated and efficacious in a majority of NHL patients regardless of their initial tumor burden. Furthermore, PK modelling suggested that additional doses of obinutuzumab on Days 8 and 15 of Cycle 1 would saturate the target-mediated clearance, achieve a steady state of drug early, and maintain it for the duration of treatment. In addition, when used as monotherapy in the iNHL Phase II extension portion of the BO20999 study, obinutuzumab showed greater efficacy with doses around 1000 mg compared with lower doses of 400 mg, with a doubling of response rate in rituximab-refractory patients. The maintenance regimen of 2-monthly dosing for up to two years was also familiar to clinicians as this regimen is used for R-maintenance in patients with previously untreated FL and had been shown to be safe in the Phase I/II obinutuzumab Studies BO21003 and BO21000.

The median PFS by INV was not reached in any arm at the time of analysis. The HR for PFS in the FL population was 0.66, p-value 0.0012. The results of the primary endpoint are further supported by the key secondary endpoint, PFS by IRC. The concordance rate between the two analyses is considered acceptable and in line with what has previously been accepted. The IRC-assessment hazard ratio is 0.71 [95% CI: 0.54, 0.93] and is in the range of the expected reduction risk in FL population. The study was stopped for efficacy based on IDMC recommendations as planned and described in the protocol.

In order to confirm the proposed dosing scheme -since body weight was the most determinant factor for systemic exposure (See Clinical Pharmacology)- PFS was compared in normal weighted and in obese patients and similar PFS observed in patients with BMI $\leq$ 30 mg/m^2 or $>$ 30 mg/m^2 and body weight $\leq$ 90 kg or $>$ 90 kg. The lack of relationship between exposure and PFS previously reported in Study BO21223, confirm the recommended fixed dose/regimen of 1000 mg of obinutuzumab for previously untreated patients with FL across the whole range of body weight. These findings are also consistent with saturation of CD20+ tumor cells during the course of treatment. Therefore, a body weight-adjusted dosing is unlikely to improve PFS in patients with extreme body weight, such as obese patients.

OS data in the updated analysis were also consistent with the primary analysis, showing no significant effect of G-chemo as compared to R-chemo. The Applicant will provide updated OS data at the time of the final analysis post authorisation. This is as expected, due to the natural history of the disease, the OS data are not mature, but there is no indication of any detrimental effect.

In terms of OS across subgroups, findings of higher number of AEs of fatal outcome in the G-benda and R-benda arms as compared to the other chemotherapy backbones are discussed under Clinical Safety. A comparison between chemotherapy backbones is difficult in view that this is not a randomised comparison and that there are likely confounding factors due to patient selection. Indeed, although small numbers, patients in the R-benda and G-benda subgroup were of older age > 80 years, had more baseline comorbidity and/or new anti-lymphoma treatment than patients in the CHOP subgroups. More mature OS data are needed to further investigate the impact of these findings.

With regard to secondary endpoints, EFS, DOR and TTNALT data are consistent with the primary endpoint and show a benefit in favour of G-chemo. It needs to be highlighted that EFS, DOR andDFS were not adjusted for multiplicity. With regard to DFS, data are not mature, but there is no indication of any detrimental effect.

When comparing progression disease events between investigators and IRC at the end of treatment induction, agreement is relatively high, reaching 0.75 kappa values in both arms. However, the

agreement between both assessment bodies is lower when it involves the whole range of events (CR, PR, SD, PD and unevaluable). The observed discrepancies between investigators and IRC PFS assessments were all addressed, especially in case of conflicting assessments (not evaluable response or disease progression vs positive response). Conflicting situations were equally observed in both arms (8.3% and 8.9% respectively in G- and R-Chemo). A focus on all possible impacts on the patient management from these specific conflicting situations showed no detrimental effect on the affected patients.

Several pre-specified sensitivity analysis of PFS were conducted. All analyses, except for one, were consistent with the primary analyses. The "impact of loss to follow-up" (worst case analysis) showed no difference between the two treatment arms. Thus, even when patients in G-chemo arm withdrew prior to disease progression and were consequently counted as "events" in the sensitivity analysis, the result indicate that G-chemo is at least non-inferior to R-chemo. Overall, the sensitivity analyses show that the primary estimate is robust and reliable.

Subgroups analyses in both the IRC and INV assessed PFS are consistent with the primary estimate. With regard to subgroup analysis of PFS by INV by stratification factors, no relevant difference in terms of chemotherapy backbone or region was shown. There seems to be no difference between G-chemo and R-chemo in patients with FLIPI score low. This may be due to the fact that these patients in general have low disease activity, leading to difficulties in showing a difference between the two treatment arms or the fact that patients with FLIPI score low only comprised 21% of the ITT population. No explanation could be found as to why obinutuzumab had no effect in the FLIPI low score subgroup, however these results were reported in the SmPC.

No significant difference according to transformation of the disease is seen in the G-chemo population versus the R-chemo population, which is reassuring.

Over the course of treatment, HRQoL was similar in the two treatment arms. Patients in both arms experienced clinically meaningful improvements in lymphoma-specific symptoms and the summary scales that included this subscale (i.e., TOI, Lym-Total). No clear differences were detected in HRQoL between the two treatment arms and at no timepoint during the study, however, the value of these subjective data are limited in an open-label study.

The Applicant has also provided a supportive study, BO21000, a small phase 1b study that investigates obinutuzumab in combination with CHOP and bendamustine. The study is divided in two parts, where the second part of the study included previously untreated patients. Since study BO21000 main objective is safety, the interpretation of efficacy should be cautious, however, the secondary endpoints included efficacy measures, such as PFS, TTNALT, DOR, ORR and EFS, and seems to provide supportive evidence for the findings in the pivotal study.

It is noted that patients with Grade 3b FL were excluded from the pivotal study. These patients are in the clinical setting often treated with R-CHOP. The GOYA study comparing R-CHOP with O-CHOP in patients with DLCBL showed that the latter was not superior to the first. Patients with Grade 3b FL are in clinical practise perceived to behave as DLBCL, and are as such treated the same way.

2.4.4. Conclusions on the clinical efficacy

The Applicant has provided the BO21223 study, that demonstrate a statistically significant and clinically relevant improvement of PFS in patients with FL being treated with obinutuzumab +chemotherapy (bendamustine, CHOP or CVP) compared with Rituximab+chemotherapy, thus the study met its primary endpoint. The primary results are confirmed by PFS by IRC and all sensitivity analyses support these findings. Furthermore, the findings are consistent across all relevant subgroups

and stratification factors.

Updated analysis of PFS and OS were performed with 6.6 months additional median follow-up (data cut-off as of 10 September 2016). The investigator-assessed PFS demonstrated a HR of 0.68 (95% CI: 0.54, 0.87), p=0.0016, being consistent with the primary analysis. The updated OS data were also consistent with the primary analysis, showing no significant effect of G-chemo as compared to R-chemo.

2.5. Clinical safety

Introduction

The primary safety data for patients receiving first-line treatment for FL are derived from the pivotal Phase III study BO21223 (GALLIUM) with 595 patients treated with G-chemo, but safety of the overall population (FL + MZL and other NHL) are provided with 698 patients treated with G-chemo.

The safety of obinutuzumab from the GALLIUM study is supported by data from 81 patients from the Phase Ib study BO21000 (GAUDI) of obinutuzumab in combination with chemotherapy (induction therapy), followed by obinutuzumab maintenance monotherapy in patients with FL.

Safety data are presented separately for the induction, maintenance and follow-up phases. Data have been collected up to 31 January 2016, which corresponds to the clinical cut-off date for the third interim analysis for efficacy. Safety data from Studies BO21223 and BO21000 are presented separately as of the different drug exposures during induction (difference in number of cycles and doses), the different maintenance dosage schedules (every 2 months in BO21223 and every 3 months in BO21000), different eligibility requirements for maintenance, and the large difference in population sizes between the studies (595 vs 81 patients).

Safety data collection

Safety monitoring comprised the collection of adverse events (AEs), serious adverse events (SAEs), protocol-specified hematology, clinical chemistry, urinalysis variables, vital signs, pharmacodynamic parameters, and immunological tests. SAE was defined as any experience that suggested a significant hazard, contraindication, side effect, or precaution (see ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2). The severity of all adverse events was graded on a five-point scale (Grade 1 to 5) and reported in detail on the eCRF according to the National Cancer Institute Common Terminology Criteria (NCI CTCAE) version 4.0 for Study BO21223 and version 3.0 for Study BO21000. All deaths are summarized by analysis population, including AEs that resulted in death. Deaths were outcomes, not events. Progression of lymphoma was not recorded as an AE or SAE if it was clearly consistent with the suspected progression of the patient's underlying cancer. Hospitalization due solely to the progression of underlying lymphoma was not reported as an SAE.

All AEs (related and unrelated) were recorded up to 28 days after the last dose of study drug, Grade ≥ 3 AEs (related and unrelated) were recorded up to 6 months after the last dose of study drug, Grade 3 or 4 infections (related and unrelated) were recorded up to 24 months after the last dose of study drug.

All grade events of infusion related reactions (IRRs), neutropenia, infections (including progressive multifocal leukoencephalopathy (PML), tumor lysis syndrome (TLS), thrombocytopenia (including acute thrombocytopenia and hemorrhagic events), gastrointestinal (GI) perforation, cardiac events, second malignancies and hepatitis B reactivation were identified as AEPIs (adverse events of particular

interest).

Safety Population

The safety population included all patients who received any amount of study drug (obinutuzumab, rituximab, or chemotherapy [CHOP, CVP, or bendamustine]). The FL safety population consisted of 1192 patients: 597patients in the R-chemo arm and 595 in the G-chemo arm. Of 1202 randomized patients with FL, 10 patients (four patients in the R-chemo arm and six patients in the G-chemo arm) did not receive any amount of study drug (obinutuzumab, rituximab, or chemotherapy [CHOP, CVP, or bendamustine]) and therefore, per protocol, were excluded from the FL safety population. Three patients in the G-chemo arm received one or more doses of rituximab in error – these patients are also included in the G-chemo arm for safety analyses.

Table 18 Demographic Data in Study BO21223 (FL Population)

Analysis Population: Intent-to-Treat Patients - Phase III

	R-chemo (N=601)	G-chemo (N=601)	Total (N=1202)
Age (yr) at Baseline			
Mean	57.7	58.2	57.9
SD	12.2	11.5	11.9
Median	58.0	60.0	59.0
Min - Max	23 - 85	26 - 88	23 - 88
n	601	601	1202
Age Group I (yr) at Baseline			
< 40	44 (7.3%)	35 (5.8%)	79 (6.6%)
40 - 59	279 (46.4%)	263 (43.8%)	542 (45.1%)
60 - 69	172 (28.6%)	206 (34.3%)	378 (31.4%)
>= 70	106 (17.6%)	97 (16.1%)	203 (16.9%)
n	601	601	1202
Age Group II (yr) at Baseline			
< 60	323 (53.7%)	298 (49.6%)	621 (51.7%)
>= 60	278 (46.3%)	303 (50.4%)	581 (48.3%)
n	601	601	1202
Age Group III (yr) at Baseline			
< 65	414 (68.9%)	412 (68.6%)	826 (68.7%)
>= 65	187 (31.1%)	189 (31.4%)	376 (31.3%)
n	601	601	1202
Sex			
Male	280 (46.6%)	283 (47.1%)	563 (46.8%)
Female	321 (53.4%)	318 (52.9%)	639 (53.2%)
n	601	601	1202
Ethnicity			
Hispanic or Latino	18 (3.0%)	36 (6.0%)	54 (4.5%)
Not Hispanic or Latino	538 (89.5%)	529 (88.0%)	1067 (88.8%)
Not Reported	30 (5.0%)	23 (3.8%)	53 (4.4%)
Unknown	15 (2.5%)	13 (2.2%)	28 (2.3%)
n	601	601	1202
Race			
American Indian or Alaska Native	1 (0.2%)	0	1 (<0.1%)
Asian	98 (16.3%)	100 (16.6%)	198 (16.5%)
Black or African American	1 (0.2%)	3 (0.5%)	4 (0.3%)
Native Hawaiian or Other Pacific Islander	0	1 (0.2%)	1 (<0.1%)
White	481 (80.0%)	487 (81.0%)	968 (80.5%)
Other	17 (2.8%)	10 (1.7%)	27 (2.2%)
Multiple	3 (0.5%)	0	3 (0.2%)
n	601	601	1202
Height (cm) at Baseline			
Mean	168.43	168.26	168.34
SD	10.08	10.03	10.05
Median	169.00	168.00	168.00
Min - Max	101.0 - 196.0	142.7 - 196.5	101.0 - 196.5
n	600	600	1200
Weight (kg) at Baseline			
Mean	75.16	76.34	75.75
SD	17.04	17.94	17.50
Median	74.00	75.00	74.25
Min - Max	32.4 - 158.0	35.3 - 155.0	32.4 - 158.0
n	599	601	1200
Baseline Body Surface Area (m2)			
Mean	1.84	1.86	1.85
SD	0.23	0.24	0.23
Median	1.84	1.83	1.84
Min - Max	1.1 - 2.8	1.2 - 2.6	1.1 - 2.8
n	599	600	1199
Baseline Body Mass Index (kg/m2)			
Mean	26.44	26.81	26.63
SD	5.90	5.27	5.60
Median	25.29	26.27	25.69
Min - Max	16.1 - 97.1	15.7 - 64.5	15.7 - 97.1
n	599	600	1199

Patient exposure

In Study BO21223, the median observation time (randomization to last available assessment) among FL patients at the cutoff date was 34.4 months (range: 0.1 – 54.5 months) in the R-chemo arm and 34.8 months (range: 0.0 – 53.8 months) in the G-chemo arm. The median duration of post-treatment follow-up at the cutoff date of 31 January 2016 was 9.2 months (range: 0.0–42.3 months) in the R-chemo arm and 9.4 months (range: 0.0–46.9 months) in the G-chemo arm.

Of 676 patients with previously untreated FL treated with an obinutuzumab-based chemoimmunotherapy induction regimen in the two studies, 620 patients went on to receive obinutuzumab maintenance for up to 2 years as monotherapy.

Table 29 Numbers of Patients Contributing to the Evaluation of Safety of Obinutuzumab as Treatment for Previously Untreated FL

	Obinutuzumab		*Comparator: Rituximab*	
	Induction	Maintenance[a]	*Induction*	*Maintenance[a]*
Pivotal Study BO21223 Phase III	FL: 595 Total iNHL: 698	FL: 548 Overall iNHL: 638	*FL: 597* *Overall iNHL: 692*	*FL: 535* *Overall iNHL: 638*
Supporting Study BO21000 Phase Ib (first-line cohort, FL)	FL: 81	FL: 72	---	
Total obinutuzumab safety population	FL: 676 Overall iNHL: 779	FL: 620 Overall iNHL: 710	-	

[a] All patients in the maintenance phase were also in the induction phase.
FL = follicular lymphoma

Exposure during induction

Table 30 Exposure during Induction in Study BO21223 (FL Safety Population)

	R-chemo (N=597)	G-chemo (N=595)	
	Study Drug	Study Drug	
	RITUXIMAB	GA101	RITUXIMAB
Dose intensity during Induction			
<60 %	0	2 (0.3%)	1 (33.3%)
80 - <90 %	3 (0.5%)	0	1 (33.3%)
>=90 %	594 (99.5%)	593 (99.7%)	0
Missing	0	0	1 (33.3%)
n	597	595	3
Duration of exposure in Induction			
n	597	595	2
Mean (SD)	24.36 (3.68)	24.68 (3.87)	14.14 (14.14)
Median	25.14	25.14	14.14
Min - Max	2.6 - 32.3	3.3 - 35.3	4.1 - 24.1
Total dose during Induction (mg)			
n	597	595	2
Mean (SD)	4544.9 (1031.6)	8600.4 (1524.5)	2200.0 (1697.1)
Median	4526.5	8000.0	2200.0
Min - Max	525 - 7230	20 - 10093	1000 - 3400
Total nr. of doses during Induction			
n	597	595	2
Mean (SD)	6.6 (1.3)	8.6 (1.5)	3.0 (2.8)
Median	6.0	8.0	3.0
Min - Max	1 - 8	1 - 10	1 - 5
Nr. of missed cycles during Induction			
n	597	595	2
Mean (SD)	0.0 (0.0)	0.0 (0.2)	4.0 (4.2)
Median	0.0	0.0	4.0
Min - Max	0 - 0	0 - 4	1 - 7
Nr. of missed doses during Induction			
n	597	595	2
Mean (SD)	0.0 (0.0)	0.0 (0.3)	4.0 (4.2)
Median	0.0	0.0	4.0
Min - Max	0 - 0	0 - 6	1 - 7

Table 31 Summary of Extent of Exposure to Chemotherapy during Induction in Study BO21223 (FL Safety Population)

	R-chemo n=597		**G-chemo n=595**	
	Median treatment duration†, weeks (range)	**Dose intensity* of ≥90%, (%)**	**Median treatment duration†, weeks (range)**	**Dose intensity* of ≥90%, (%)**
Chemotherapy				
bendamustine	24.3 (3.9-30.0)	89.3%	24.3 (3.9-31.4)	90.5%
cyclophosphamide	19.3 (2.6-28.1)	95.8%	20.1 (3.1-29.1)	90.6%
doxorubicin	19.1 (4.1-24.0)	95.1%	19.9 (3.1-27.1)	90.2%
prednisone	19.9 (2.4-28.9)	93.4%	20.9 (3.1-29.7)	94.1%
vincristine	19.3 (2.6-28.1)	83.4%	20.1 (3.1-29.1)	80.7%

* Defined as total cumulative dose actually received /total planned dose x 100%.
† Planned duration of chemotherapy treatment during induction was 24 weeks for patients receiving bendamustine (6 × 28-day cycles) or CVP (8 × 21-day cycles), and 18 weeks for patients receiving CHOP (6 × 21-day cycles).

Exposure during maintenance

Table 32 Study Drug Exposure during Maintenance in Study BO21223 (FL Safety Population)

t_ex2_foly_223_SEM APPROVED Study Drug Exposure During Maintenance - Follicular Lymphoma Patients (Patients Who Entered Maintenance Phase)

Protocol(s): BO21223 (K21223D)
Analysis Population: Patients Who Entered Maintenance Phase - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

	R-chemo (N=526)	G-chemo (N=540)	
	RITUXIMAB	OBINUTUZUMAB	RITUXIMAB [a]
Dose intensity during Maintenance			
<60 %	0	0	0
60 - <80 %	0	0	0
80 - <90 %	4 (0.8%)	0	0
>=90 %	522 (99.2%)	539 (99.8%)	1 (33.3%)
Missing	0	1 (0.2%)	2 (66.7%)
n	526	540	3
Duration of exposure in Maintenance			
n	526	540	3
Mean (SD)	80.16 (27.97)	82.67 (25.15)	34.24 (55.75)
Median	92.14	92.29	4.14
Min - Max	2.1 - 117.7	0.0 - 117.3	0.0 - 98.6
Total dose during Maintenance			
n	526	539	2
Mean (SD)	7018.68 (2507.04)	10450.87 (2995.82)	4380.00 (5345.73)
Median	7679.00	12000.00	4380.00
Min - Max	555.0 - 12000.0	1000.0 - 12087.7	600.0 - 8160.0
Total nr. of doses during Maintenance			
n	526	539	2
Mean (SD)	10.1 (3.3)	10.5 (3.0)	6.5 (7.8)
Median	12.0	12.0	6.5
Min - Max	1 - 12	1 - 12	1 - 12
Nr. of missed doses during Maintenance			
n	526	539	2
Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.5 (0.7)
Median	0.0	0.0	0.5
Min - Max	0 - 1	0 - 1	0 - 1

Time unit is in weeks, dose unit is mg.
Treatment duration is the date of the last dose of study medication minus the date of the first maintenance dose plus 28 days.
Or if new antileukemia therapy was started within these 28 days exposure duration is the time interval between first maintenance dose and start of new anti-lymphoma therapy minus 1 day.
Dose intensity is the total dose actually received divided by the total planned dose.
[a] The G-chemo heading shows the patients who received obinutuzumab as planned (in column 'GA101'), and in the column entitled 'Rituximab' it shows the three patients with a medication error who received at least one dose of both obinutuzumab and rituximab.

Adverse events

Table 33 Overview of Adverse Events in Safety Populations of Pivotal Study BO21223 and Supporting Study BO21000 (Entire Study Period)

	BO21223				BO21000 (FL, previously untreated)
	FL Safety Population		Overall Safety Population		
	R-chemo (N = 597)	G-chemo (N = 595)	R-chemo (N = 692)	G-chemo (N = 698)	G-chemo N = 81
Patients with					
Any AE	587 (98.3%)	592 (99.5%)	682 (98.6%)	695 (99.6%)	81 (100%)
Fatal AE	20 (3.4%) [a]	24 (4.0%) [a]	26 (3.8%) [a]	36 (5.2%) [a]	1 (1%) [b]
Grade 3-5 AE	405 (67.8%)	444 (74.6%)	479 (69.2%)	528 (75.6%)	67 (83%)
Serious AE	238 (39.9%)	274 (46.1%)	286 (41.3%)	340 (48.7%)	36 (44%)
AE leading to Treatment Withdrawal	85 (14.2%)	97 (16.3%)	104 (15.0%)	125 (17.9%)	10 (12%)
AE leading to Antibody Interruption	338 (56.6%)	395 (66.4%)	402 (58.1%)	474 (67.9%)	55 (68%)
Related AE	547 (91.6%)	564 (94.8%)	634 (91.6%)	663 (95.0%)	78 (96%)
AEs of Particular Interest					
IRR	349 (58.5%)	406 (68.2%)	401 (57.9%)	486 (69.6%)	60 (74%)
Neutropenia	269 (45.1%)	301 (50.6%)	311 (44.9%)	352 (50.4%)	45 (56%)
Infection	418 (70.0%)	460 (77.3%)	481 (69.5%)	545 (78.1%)	64 (79%)
TLS	3 (0.5%)	6 (1.0%)	3 (0.4%)	6 (0.9%)	0
Thrombocytopenia	45 (7.5%)	68 (11.4%)	50 (7.2%)	87 (12.5%)	7 (9%)
Acute Thrombocytopenia	0	7 (1.2%)	1 (0.1%)	8 (1.1%)	0
Hemorrhagic Events	62 (10.4%)	57 (9.6%)	72 (10.4%)	70 (10.0%)	11 (14%)
GI Perforation	3 (0.5%)	4 (0.7%)	3 (0.4%)	4 (0.6%)	0
Cardiac Events	58 (9.7%)	78 (13.1%)	67 (9.7%)	102 (14.6%)	11 (14%)
Second or Unspecified Tumor Malignancies [c]	30 (5.0%)	43 (7.2%)	38 (5.5%)	50 (7.2%)	7 (9%)
Hepatitis B Reactivation [d]	7/53 (13.2%)	5/29 (17.2%)	7/57 (12.3%)	5/34 (14.7%)	0 [e]

AE = adverse event; FL = follicular lymphoma; GI = gastrointestinal, IRR = infusion-related reaction; TLS = tumor lysis syndrome
[a] Fatal AEs for BO21223 include outcomes that were available in the database as of the snapshot date (29 April 2016) where the AE onset date was on or before the cutoff date (31 January 2016)
[b] Two additional deaths, due to neutropenic sepsis and acute myeloid leukemia, respectively, were reported in follow-up.
[c] AEs reported under the secondary malignancies SMQ (not the SOC) are shown.
[d] Data are based on DNA lab tests, and Hepatitis B Reactivation is based on the protocol definition. Denominators are the number of patients who had positive core antibody results at baseline (patients at risk).
[e] Patients with positive hepatitis B surface antigen or total hepatitis B core antibody at baseline screening were excluded from Study BO21000. Two patients had a protocol deviation of hepatitis testing not done at screening.

Table 34 Adverse Events with an Incidence Rate of at least 10% in Either Treatment Arm in Study BO21223 (FL Safety Population)

t_ae_5per_emerge_foly_223_SE APPROVED Adverse Events with an Incidence At Least 5% - Treatment-Emergent AEs - Follicular Lymphoma Patients (Safety-Evaluable Patients)
Protocol(s): BO21223 (L21223A)
Analysis Population: Safety-Evaluable Patients - Phase III Snapshot Date: 29APR2016 Cutoff Date:31JAN2016:23:59:59

MedDRA System Organ Class MedDRA Preferred Term	R-chemo (N=597)	G-chemo (N=595)
Total number of patients with at least one adverse event	576 (96.5%)	579 (97.3%)
Overall total number of events	6351	6936
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total number of patients with at least one adverse event	302 (50.6%)	341 (57.3%)
NEUTROPENIA	260 (43.6%)	289 (48.6%)
LEUKOPENIA	71 (11.9%)	69 (11.6%)
ANAEMIA	60 (10.1%)	53 (8.9%)
THROMBOCYTOPENIA	45 (7.5%)	68 (11.4%)
GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	411 (68.8%)	445 (74.8%)
NAUSEA	278 (46.6%)	279 (46.9%)
CONSTIPATION	188 (31.5%)	210 (35.3%)
DIARRHOEA	131 (21.9%)	160 (26.9%)
VOMITING	122 (20.4%)	139 (23.4%)
ABDOMINAL PAIN	64 (10.7%)	61 (10.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total number of patients with at least one adverse event	365 (61.1%)	402 (67.6%)
FATIGUE	218 (36.5%)	214 (36.0%)
PYREXIA	127 (21.3%)	164 (27.6%)
CHILLS	56 (9.4%)	99 (16.6%)
INFECTIONS AND INFESTATIONS		
Total number of patients with at least one adverse event	335 (56.1%)	362 (60.8%)
UPPER RESPIRATORY TRACT INFECTION	107 (17.9%)	112 (18.8%)
NASOPHARYNGITIS	109 (18.3%)	102 (17.1%)
URINARY TRACT INFECTION	54 (9.0%)	64 (10.8%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total number of patients with at least one adverse event	292 (48.9%)	351 (59.0%)
INFUSION RELATED REACTION	292 (48.9%)	351 (59.0%)
METABOLISM AND NUTRITION DISORDERS		
Total number of patients with at least one adverse event	88 (14.7%)	97 (16.3%)
DECREASED APPETITE	74 (12.4%)	69 (11.6%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total number of patients with at least one adverse event	225 (37.7%)	235 (39.5%)
BACK PAIN	96 (16.1%)	79 (13.3%)
ARTHRALGIA	79 (13.2%)	88 (14.8%)
NERVOUS SYSTEM DISORDERS		
Total number of patients with at least one adverse event	238 (39.9%)	271 (45.5%)
HEADACHE	101 (16.9%)	122 (20.5%)
PSYCHIATRIC DISORDERS		
Total number of patients with at least one adverse event	111 (18.6%)	118 (19.8%)
INSOMNIA	71 (11.9%)	86 (14.5%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total number of patients with at least one adverse event	241 (40.4%)	249 (41.8%)
COUGH	144 (24.1%)	152 (25.5%)
DYSPNOEA	73 (12.2%)	87 (14.6%)
OROPHARYNGEAL PAIN	60 (10.1%)	65 (10.9%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total number of patients with at least one adverse event	258 (43.2%)	261 (43.9%)
RASH	108 (18.1%)	93 (15.6%)
PRURITUS	83 (13.9%)	75 (12.6%)
ALOPECIA	68 (11.4%)	80 (13.4%)

Table35 Adverse Events Reported with a Difference of at Least 2% Between the Treatment Arms in Study BO21223 (FL Safety Population)

Protocol(s): BO21223 (K21223D)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date:
31JAN2016:23:59:59

MedDRA System Organ Class MedDRA Preferred Term	R-chemo (N=597)	G-chemo (N=595)
Total number of patients	551 (92.3%)	557 (93.6%)
Total number of AE	3035	3699
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Number of patients with at least one AE	278 (46.6%)	321 (53.9%)
NEUTROPENIA	260 (43.6%)	289 (48.6%)
THROMBOCYTOPENIA	45 (7.5%)	68 (11.4%)
FEBRILE NEUTROPENIA	29 (4.9%)	43 (7.2%)
Number of AE	772	931
GASTROINTESTINAL DISORDERS		
Number of patients with at least one AE	318 (53.3%)	359 (60.3%)
CONSTIPATION	188 (31.5%)	210 (35.3%)
DIARRHOEA	131 (21.9%)	160 (26.9%)
VOMITING	122 (20.4%)	139 (23.4%)
DYSPEPSIA	34 (5.7%)	49 (8.2%)
Number of AE	667	769
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Number of patients with at least one AE	155 (26.0%)	211 (35.5%)
PYREXIA	127 (21.3%)	164 (27.6%)
CHILLS	56 (9.4%)	99 (16.6%)
Number of AE	249	343
INFECTIONS AND INFESTATIONS		
Number of patients with at least one AE	106 (17.8%)	150 (25.2%)
HERPES ZOSTER	39 (6.5%)	59 (9.9%)
SINUSITIS	38 (6.4%)	55 (9.2%)
RHINITIS	26 (4.4%)	41 (6.9%)
PHARYNGITIS	13 (2.2%)	26 (4.4%)
Number of AE	136	220
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Number of patients with at least one AE	292 (48.9%)	351 (59.0%)
INFUSION RELATED REACTION	292 (48.9%)	351 (59.0%)
Number of AE	461	586
METABOLISM AND NUTRITION DISORDERS		
Number of patients with at least one AE	22 (3.7%)	38 (6.4%)
HYPOKALAEMIA	22 (3.7%)	38 (6.4%)
Number of AE	34	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Number of patients with at least one AE	116 (19.4%)	110 (18.5%)
BACK PAIN	96 (16.1%)	79 (13.3%)
MYALGIA	26 (4.4%)	40 (6.7%)
Number of AE	156	147
NERVOUS SYSTEM DISORDERS		
Number of patients with at least one AE	101 (16.9%)	122 (20.5%)
HEADACHE	101 (16.9%)	122 (20.5%)
Number of AE	153	184
PSYCHIATRIC DISORDERS		
Number of patients with at least one AE	71 (11.9%)	86 (14.5%)
INSOMNIA	71 (11.9%)	86 (14.5%)
Number of AE	81	99
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Number of patients with at least one AE	73 (12.2%)	87 (14.6%)
DYSPNOEA	73 (12.2%)	87 (14.6%)
Number of AE	86	97
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Number of patients with at least one AE	168 (28.1%)	160 (26.9%)
RASH	108 (18.1%)	93 (15.6%)
ALOPECIA	68 (11.4%)	80 (13.4%)
Number of AE	203	199
VASCULAR DISORDERS		
Number of patients with at least one AE	31 (5.2%)	57 (9.6%)
HYPOTENSION	18 (3.0%)	33 (5.5%)
HOT FLUSH	14 (2.3%)	26 (4.4%)
Number of AE	37	67

Adverse Events by Severity

The majority of AEs reported in the study were NCI CTC AE Grade 1 or 2 in severity in each arm (8022/9341 events [85.9%] in the R-chemo arm and 8767/10311 [85.0%] in the G chemo arm (see Table 16).

The numbers of AEs that were Grade 3-5 (1,319 in the R-chemo arm and 1,544 in the R-chemo arm) were much lower than the numbers of Grade 1-2 AEs (see paragraph above). In the R-chemo arm vs. the G-chemo arm of the study, 67.8% of patients and 74.6% of patients, respectively, experienced Grade 3-5 AEs. The percentages of patients with FL with at least one Grade 3-5 AE in the R-chemo arm vs. G-chemo arm, respectively, were 36.2% vs. 35.3% Grade 3; 28.3% vs. 35.3% Grade 4 (driven by a higher incidence of Grade 4 neutropenia in the G-chemo arm (29.5% in the R-chemo arm vs. 36.6% in the G-chemo arm); and 3.4% vs. 4.0% Grade 5.

Table 36 Summary of Adverse Events by Highest CTC Grade in Study BO21223 (FL Safety Population)

		NCI CTC AE grade				
	Total	**1**	**2**	**3**	**4**	**5**
R-chemo (N=597)						
Pts with at least 1 AE	585 (98.0%)	22 (3.7%)	158 (26.5%)	216 (36.2%)	169 (28.3%)	20 (3.4%)
Total no. of AEs	9341	5017	3005	933	366	20
G-chemo (N=595)						
Pts with at least 1 AE	592 (99.5%)	15 (2.5%)	133 (22.4%)	210 (35.3%)	210 (35.3%)	24 (4.0%)
Total no. of AEs	10311	5531	3236	1044	474	26

AE: adverse event; NCI CTC = National Cancer Institute Common Toxicity Criteria
Multiple occurrences of the same AE in the same individual are counted in the total number of AEs.

Adverse events of special interest

A higher incidence of AEs (all grades and Grade 3-5) in the G-chemo arm compared to the R-chemo arm was observed for the following AEPIs: IRRs, neutropenia, thrombocytopenia, infections (no PML case was reported), and second malignancies. The incidence of hemorrhagic events and gastrointestinal perforations were comparable between the study arms.

IRRs

Table 37 Summary of IRRs in Study BO21223 (FL Safety Population)

	R-chemo (N=597)	G-chemo (N=595)
No. of patients with at least one AE	349 (58.5%)	406 (68.2%)
No. of patients with grade 1 AEs	115 (19.3%)	110 (18.5%)
No. of patients with grade 2 AEs	194 (32.5%)	222 (37.3%)
No. of patients with grade 3 AEs	38 (6.4%)	61 (10.3%)
No. of patients with grade 4 AEs	2 (0.3%)	13 (2.2%)
No. of patients with grade 5 AEs	0 (0.0%)	0 (0.0%)
No. of patients with grade 3-5 AEs	40 (6.7%)	74 (12.4%)
No. of patients with missing grade AE	0 (0.0%)	0 (0.0%)
No. of patients with serious AE	14 (2.3%)	33 (5.5%)
Total No. of AEs:	1540	2023
No. of grade 1 AEs	867	1105
No. of grade 2 AEs	595	765
No. of grade 3 AEs	75	124
No. of grade 4 AEs	3	29
No. of grade 5 AEs	0	0
No. of grade 3-5 AEs	78	153
No. of AEs with missing grade	0	0
No. of serious AEs	31	82
No. of AEs with missing seriousness	0	0
No. of AEs related to antibody	1226	1696
No. of AEs related to CHOP	178	162
No. of AEs related to CVP	82	146
No. of AEs related to Bendamustine	359	425
Total No. of patients with at least one AE:	349	406
No. of patients with AEs related to antibody	292 (83.7%)	353 (86.9%)
No. of patients with AEs related to CHOP	61 (17.5%)	59 (14.5%)
No. of patients with AEs related to CVP	18 (5.2%)	29 (7.1%)
No. of patients with AEs related to Bendamustine	137 (39.3%)	158 (38.9%)
Total No. of patients with at least one AE:	349	406
No. of patients with antibody dose reduced due to AE	0 (0.0%)	0 (0.0%)
No. of patients with antibody interrupted due to AE	183 (52.4%)	226 (55.7%)
No. of patients with antibody withdrawn due to AE	0 (0.0%)	4 (1.0%)
No. of patients with chemotherapy dose reduced due to AE	8 (2.3%)	15 (3.7%)
No. of patients with chemotherapy interrupted due to AE	11 (3.2%)	21 (5.2%)
No. of patients with chemotherapy withdrawn due to AE	1 (0.3%)	5 (1.2%)
No. of patients with any treatment dose reduced due to AE	8 (2.3%)	15 (3.7%)
No. of patients with any treatment interrupted due to AE	189 (54.2%)	231 (56.9%)
No. of patients with any treatment withdrawn due to AE	1 (0.3%)	7 (1.7%)
No. of patients with at least one AE unresolved or ongoing	23 (6.6%)	31 (7.6%)
No. of patients with treatment received for AE	249 (71.3%)	322 (79.3%)
No. of patients without treatment received for AE	100 (28.7%)	84 (20.7%)

Table 38: Summary of IRRs by cycle during induction (FL safety population)

Treatment Cycles	R-chemo (N=597)	G-chemo (N=595)
Cycle 1		
Patients with at least one AE	260 (43.6%)	356 (59.8%)
Number of AEs	757	1285
Number of grade 3-5 AEs	45	112
Number of fatal AEs	0	0
Number of serious AEs	14	63
Number of AEs leading to antibody withdrawal	0	15
Number of AEs leading to chemotherapy withdrawal	0	5
n	597	595
Cycle 2		
Patients with at least one AE	109 (18.4%)	69 (11.8%)
Number of AEs	243	155
Number of grade 3-5 AEs	15	8
Number of fatal AEs	0	0
Number of serious AEs	12	6
Number of AEs leading to antibody withdrawal	0	0
Number of AEs leading to chemotherapy withdrawal	0	0
n	591	584
Cycle 3		
Patients with at least one AE	76 (13.0%)	45 (7.7%)
Number of AEs	155	80
Number of grade 3-5 AEs	4	1
Number of fatal AEs	0	0
Number of serious AEs	2	0
Number of AEs leading to antibody withdrawal	0	0
Number of AEs leading to chemotherapy withdrawal	0	0
n	586	581
Cycle 4		
Patients with at least one AE	48 (8.3%)	44 (7.6%)
Number of AEs	85	82
Number of grade 3-5 AEs	2	0
Number of fatal AEs	0	0
Number of serious AEs	0	0
Number of AEs leading to antibody withdrawal	0	0
Number of AEs leading to chemotherapy withdrawal	0	1
n	580	576
Cycle 5		
Patients with at least one AE	46 (8.1%)	40 (7.0%)
Number of AEs	85	70
Number of grade 3-5 AEs	3	5
Number of fatal AEs	0	0
Number of serious AEs	0	5
Number of AEs leading to antibody withdrawal	0	0
Number of AEs leading to chemotherapy withdrawal	0	0
n	567	568
Cycle 6		
Patients with at least one AE	30 (5.4%)	33 (5.9%)
Number of AEs	58	62
Number of grade 3-5 AEs	4	5
Number of fatal AEs	0	0
Number of serious AEs	3	2
Number of AEs leading to antibody withdrawal	0	0
Number of AEs leading to chemotherapy withdrawal	0	0
n	551	563
Cycle 7		
Patients with at least one AE	8 (3.4%)	8 (3.3%)
Number of AEs	17	26
Number of grade 3-5 AEs	0	3
Number of fatal AEs	0	0
Number of serious AEs	0	1
Number of AEs leading to antibody withdrawal	0	0
Number of AEs leading to chemotherapy withdrawal	1	0
n	236	243
Cycle 8		
Patients with at least one AE	5 (2.1%)	6 (2.5%)
Number of AEs	11	15
Number of grade 3-5 AEs	2	0
Number of fatal AEs	0	0
Number of serious AEs	0	0
Number of AEs leading to antibody withdrawal	0	0
Number of AEs leading to chemotherapy withdrawal	0	2
n	235	241

Neutropenia

Table 39 Summary of Neutropenia in Study BO21223 (FL Safety Population)

	R-chemo (N=597)	G-chemo (N=595)
No. of patients with at least one AE	269 (45.1%)	301 (50.6%)
No. of patients with grade 1 AEs	9 (1.5%)	9 (1.5%)
No. of patients with grade 2 AEs	24 (4.0%)	19 (3.2%)
No. of patients with grade 3 AEs	85 (14.2%)	98 (16.5%)
No. of patients with grade 4 AEs	151 (25.3%)	175 (29.4%)
No. of patients with grade 5 AEs	0 (0.0%)	0 (0.0%)
No. of patients with grade 3-5 AEs	236 (39.5%)	273 (45.9%)
No. of patients with missing grade AE	0 (0.0%)	0 (0.0%)
No. of patients with serious AE	44 (7.4%)	50 (8.4%)
Total No. of AEs:	714	802
No. of grade 1 AEs	44	35
No. of grade 2 AEs	84	85
No. of grade 3 AEs	276	338
No. of grade 4 AEs	310	344
No. of grade 5 AEs	0	0
No. of grade 3-5 AEs	586	682
No. of AEs with missing grade	0	0
No. of serious AEs	68	64
No. of AEs with missing seriousness	0	0
Total No. of patients with at least one AE:	269	301
No. of patients with antibody dose reduced due to AE	0 (0.0%)	0 (0.0%)
No. of patients with antibody interrupted due to AE	105 (39.0%)	164 (54.5%)
No. of patients with antibody withdrawn due to AE	13 (4.8%)	13 (4.3%)
No. of patients with chemotherapy dose reduced due to AE	32 (11.9%)	46 (15.3%)
No. of patients with chemotherapy interrupted due to AE	59 (21.9%)	59 (19.6%)
No. of patients with chemotherapy withdrawn due to AE	4 (1.5%)	2 (0.7%)
No. of patients with any treatment dose reduced due to AE	32 (11.9%)	46 (15.3%)
No. of patients with any treatment interrupted due to AE	107 (39.8%)	165 (54.8%)
No. of patients with any treatment withdrawn due to AE	14 (5.2%)	15 (5.0%)
No. of patients with at least one AE unresolved or ongoing	10 (3.7%)	13 (4.3%)
No. of patients with treatment received for AE	201 (74.7%)	239 (79.4%)
No. of patients without treatment received for AE	68 (25.3%)	62 (20.6%)

Prolonged neutropenia and late onset neutropenia

Prolonged neutropenia was defined as low neutrophil counts at the last visit before last antibody administration (LAA) followed by an assessment of low neutrophil count between Day 24 and Day 41 after LAA. Prolonged neutropenia occurred in 3/537 patients (0.6%) in the R chemo arm and 5/533 patients (0.9%) in the G chemo arm.

Late onset neutropenia (i.e., low neutrophil count at LAA with absolute neutrophil count within normal range at last previous visit prior to LAA) occurred in 22/537 patients (4.1%) in the R chemo arm and 21/533 patients (3.9%) in the G chemo arm.

Infections

Table 40 Summary of Infections in Study BO21223 (FL Safety Population)

	R-chemo (N=597)	G-chemo (N=595)
No. of patients with at least one AE	418 (70.0%)	460 (77.3%)
No. of patients with grade 1 AEs	90 (15.1%)	81 (13.6%)
No. of patients with grade 2 AEs	235 (39.4%)	260 (43.7%)
No. of patients with grade 3 AEs	87 (14.6%)	101 (17.0%)
No. of patients with grade 4 AEs	4 (0.7%)	8 (1.3%)
No. of patients with grade 5 AEs	2 (0.3%)	10 (1.7%)
No. of patients with grade 3-5 AEs	93 (15.6%)	119 (20.0%)
No. of patients with missing grade AE	0 (0.0%)	0 (0.0%)
No. of patients with serious AE	86 (14.4%)	108 (18.2%)
Total No. of AEs:	1180	1421
No. of grade 1 AEs	430	473
No. of grade 2 AEs	625	782
No. of grade 3 AEs	118	145
No. of grade 4 AEs	5	11
No. of grade 5 AEs	2	10
No. of grade 3-5 AEs	125	166
No. of AEs with missing grade	0	0
No. of serious AEs	119	146
No. of AEs with missing seriousness	0	0
Total No. of patients with at least one AE:	418	460
No. of patients with antibody dose reduced due to AE	0 (0.0%)	0 (0.0%)
No. of patients with antibody interrupted due to AE	67 (16.0%)	90 (19.6%)
No. of patients with antibody withdrawn due to AE	19 (4.5%)	25 (5.4%)
No. of patients with chemotherapy dose reduced due to AE	5 (1.2%)	5 (1.1%)
No. of patients with chemotherapy interrupted due to AE	28 (6.7%)	34 (7.4%)
No. of patients with chemotherapy withdrawn due to AE	6 (1.4%)	6 (1.3%)
No. of patients with any treatment dose reduced due to AE	5 (1.2%)	5 (1.1%)
No. of patients with any treatment interrupted due to AE	70 (16.7%)	93 (20.2%)
No. of patients with any treatment withdrawn due to AE	19 (4.5%)	28 (6.1%)
No. of patients with at least one AE unresolved or ongoing	48 (11.5%)	83 (18.0%)
No. of patients with treatment received for AE	364 (87.1%)	415 (90.2%)
No. of patients without treatment received for AE	54 (12.9%)	45 (9.8%)

Trombocytopenia, Acute Thrombocytopenia, and Hemorrhagic Events

Table 41 Summary of Thrombocytopenia AEs in Study BO21223 (FL Safety Population)

Protocol(s): BO21223 (L21223A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

	R-chemo (N=597)	G-chemo (N=595)
No. of patients with at least one AE	45 (7.5%)	68 (11.4%)
No. of patients with grade 1 AEs	16 (2.7%)	15 (2.5%)
No. of patients with grade 2 AEs	13 (2.2%)	17 (2.9%)
No. of patients with grade 3 AEs	12 (2.0%)	23 (3.9%)
No. of patients with grade 4 AEs	4 (0.7%)	13 (2.2%)
No. of patients with grade 5 AEs	0 (0.0%)	0 (0.0%)
No. of patients with grade 3-5 AEs	16 (2.7%)	36 (6.1%)
No. of patients with missing grade AE	0 (0.0%)	0 (0.0%)
No. of patients with serious AE	1 (0.2%)	4 (0.7%)
Total No. of AEs:	68	133
No. of grade 1 AEs	27	46
No. of grade 2 AEs	22	24
No. of grade 3 AEs	15	37
No. of grade 4 AEs	4	26
No. of grade 5 AEs	0	0
No. of grade 3-5 AEs	19	63
No. of AEs with missing grade	0	0
No. of serious AEs	1	11
No. of AEs with missing seriousness	0	0
Total No. of patients with at least one AE:	45	68
No. of patients with antibody dose reduced due to AE	0 (0.0%)	0 (0.0%)
No. of patients with antibody interrupted due to AE	5 (11.1%)	19 (27.9%)
No. of patients with antibody withdrawn due to AE	1 (2.2%)	1 (1.5%)
No. of patients with chemotherapy dose reduced due to AE	6 (13.3%)	9 (13.2%)
No. of patients with chemotherapy interrupted due to AE	3 (6.7%)	7 (10.3%)
No. of patients with chemotherapy withdrawn due to AE	1 (2.2%)	2 (2.9%)
No. of patients with any treatment dose reduced due to AE	6 (13.3%)	9 (13.2%)
No. of patients with any treatment interrupted due to AE	7 (15.6%)	19 (27.9%)
No. of patients with any treatment withdrawn due to AE	1 (2.2%)	2 (2.9%)
No. of patients with at least one AE unresolved or ongoing	9 (20.0%)	8 (11.8%)
No. of patients with treatment received for AE	6 (13.3%)	21 (30.9%)
No. of patients without treatment received for AE	39 (86.7%)	47 (69.1%)

Tumor Lysis Syndrome (TLS)

Table 42 Summary of Tumor Lysis Syndrome in Study BO21223 (FL Safety Population)

	R-chemo (N=597)	G-chemo (N=595)
No. of patients with at least one AE	3 (0.5%)	6 (1.0%)
No. of patients with grade 1 AEs	0 (0.0%)	0 (0.0%)
No. of patients with grade 2 AEs	0 (0.0%)	0 (0.0%)
No. of patients with grade 3 AEs	3 (0.5%)	5 (0.8%)
No. of patients with grade 4 AEs	0 (0.0%)	1 (0.2%)
No. of patients with grade 5 AEs	0 (0.0%)	0 (0.0%)
No. of patients with grade 3-5 AEs	3 (0.5%)	6 (1.0%)
No. of patients with missing grade AE	0 (0.0%)	0 (0.0%)
No. of patients with serious AE	1 (0.2%)	3 (0.5%)
Total No. of AEs:	3	6
No. of grade 1 AEs	0	0
No. of grade 2 AEs	0	0
No. of grade 3 AEs	3	5
No. of grade 4 AEs	0	1
No. of grade 5 AEs	0	0
No. of grade 3-5 AEs	3	6
No. of AEs with missing grade	0	0
No. of serious AEs	1	3
No. of AEs with missing seriousness	0	0
Total No. of patients with at least one AE:	3	6
No. of patients with antibody dose reduced due to AE	0 (0.0%)	0 (0.0%)
No. of patients with antibody interrupted due to AE	0 (0.0%)	3 (50.0%)
No. of patients with antibody withdrawn due to AE	0 (0.0%)	0 (0.0%)
No. of patients with chemotherapy dose reduced due to AE	0 (0.0%)	0 (0.0%)
No. of patients with chemotherapy interrupted due to AE	0 (0.0%)	3 (50.0%)
No. of patients with chemotherapy withdrawn due to AE	0 (0.0%)	0 (0.0%)
No. of patients with any treatment dose reduced due to AE	0 (0.0%)	0 (0.0%)
No. of patients with any treatment interrupted due to AE	0 (0.0%)	3 (50.0%)
No. of patients with any treatment withdrawn due to AE	0 (0.0%)	0 (0.0%)
No. of patients with at least one AE unresolved or ongoing	0 (0.0%)	0 (0.0%)
No. of patients with treatment received for AE	1 (33.3%)	5 (83.3%)
No. of patients without treatment received for AE	2 (66.7%)	1 (16.7%)

Gastrointestinal perforation

Gastrointestinal perforation was reported in three patients (0.5%) in the R-chemo arm and in four patients (0.7%) in the G-chemo arm. The events included fistulas in two patients in the R-chemo arm (one of whom had a history of diverticulitis and intermittent constipation at study entry) and one patient in the G-chemo arm (with a history of sigmoiditis at study entry); each of these three patients had extranodal involvement at study entry.

Cardiac events

The incidence of cardiac AEs (SOC of "Cardiac Disorders") was 9.7% in the R-chemo arm and 13.1% in the G-chemo arm. The most frequently occurring cardiac events, for patients in the R-chemo and G-chemo arms, respectively, were palpitations (2.7% vs. 2.5%), tachycardia (1.2% vs. 2.7%), atrial fibrillation (1.3% vs. 1.7%), sinus tachycardia (0.5% vs. 1.3%), and angina pectoris (0.8% vs. 0.7%).

The percentage of patients with Grade 3 to 5 cardiac AEs was similar in the two arms: 2.8% for R-

chemo and 3.7% for G-chemo), with four patients in each arm experiencing Grade 4 events and two in each arm experiencing Grade 5 events. The fatal events were cardiac arrest and myocardial infarction in the R-chemo arm, and two cases of cardiogenic shock in the G-chemo arm. Each fatal cardiac AE occurred in elderly patients ($\geq$65 years old) with pre-existing conditions.

Serious cardiac AEs were reported in 2.0 % of patients in the R-chemo arm and 4.4% in the G-chemo arm. The incidence of Grade 3-5 AEs and serious AEs in patients without pre-existing cardiac conditions was low and balanced between arms.

Of the patients who experienced cardiac events, one patient in the R chemo arm (due to cardiac failure and cardiogenic shock) and two patients in the G chemo arm (one due to tachycardia and the other due to ventricular dysfunction) had a study treatment withdrawn due to the event. Ten patients in the R-chemo arm and 20 patients in the G-chemo arm had a dose interruption of any drug due to cardiac events. Twenty-six patients in the R-chemo arm and 41 patients in the G-chemo arm had treatment for cardiac events, and the cardiac events had resolved in most patients by the data cutoff date (for 41/58 patients in the R-chemo arm and 66/78 patients in the G-chemo arm).

Some of the patients had cardiac events that occurred during or within 24 hours of the end of an infusion and were therefore considered infusion-related events (10 patients [1.7%] who experienced cardiac events in the R-chemo arm and 26 patients [4.4%] who experienced cardiac events in the G-chemo arm). When excluding cardiac AEs reported as IRRs (such as palpitations, tachycardia, and bradycardia occurring within 24 hours of infusion), the incidence of cardiac AEs was comparable between arms: 8.2% of patients in the R-chemo arm vs. 9.6% in the G-chemo arm.

Twenty-six patients in the R-chemo arm and 41 patients in the G-chemo arm had treatment for cardiac events, and the cardiac events had resolved in most patients by the data cutoff date (for 41/58 patients in the R-chemo arm and 66/78 patients in the G-chemo arm).

There were four fatal cardiac AEs in total, two in each arm (cardiac arrest and myocardial infarction in the R-chemo arm, and two cases of cardiogenic shock in the G-chemo arm). The fatal cardiac AEs in the G-chemo arm occurred in elderly patients (> 65 years old) with preexisting cardiac conditions.

Table 43 Summary of Cardiac Events in Study BO21223 (FL Safety Population)

	R-chemo (N=597)	G-chemo (N=595)
No. of patients with at least one AE	58 (9.7%)	78 (13.1%)
No. of patients with grade 1 AEs	27 (4.5%)	33 (5.5%)
No. of patients with grade 2 AEs	14 (2.3%)	23 (3.9%)
No. of patients with grade 3 AEs	11 (1.8%)	16 (2.7%)
No. of patients with grade 4 AEs	4 (0.7%)	4 (0.7%)
No. of patients with grade 5 AEs	2 (0.3%)	2 (0.3%)
No. of patients with grade 3-5 AEs	17 (2.8%)	22 (3.7%)
No. of patients with missing grade AE	0 (0.0%)	0 (0.0%)
No. of patients with serious AE	12 (2.0%)	26 (4.4%)
Total No. of AEs:	74	117
No. of grade 1 AEs	34	66
No. of grade 2 AEs	18	27
No. of grade 3 AEs	15	18
No. of grade 4 AEs	5	4
No. of grade 5 AEs	2	2
No. of grade 3-5 AEs	22	24
No. of AEs with missing grade	0	0
No. of serious AEs	13	29
No. of AEs with missing seriousness	0	0
Total No. of patients with at least one AE:	58	78
No. of patients with antibody dose reduced due to AE	0 (0.0%)	0 (0.0%)
No. of patients with antibody interrupted due to AE	9 (15.5%)	20 (25.6%)
No. of patients with antibody withdrawn due to AE	1 (1.7%)	1 (1.3%)
No. of patients with chemotherapy dose reduced due to AE	0 (0.0%)	0 (0.0%)
No. of patients with chemotherapy interrupted due to AE	2 (3.4%)	3 (3.8%)
No. of patients with chemotherapy withdrawn due to AE	1 (1.7%)	1 (1.3%)
No. of patients with any treatment dose reduced due to AE	0 (0.0%)	0 (0.0%)
No. of patients with any treatment interrupted due to AE	10 (17.2%)	20 (25.6%)
No. of patients with any treatment withdrawn due to AE	1 (1.7%)	2 (2.6%)
No. of patients with at least one AE unresolved or ongoing	17 (29.3%)	12 (15.4%)
No. of patients with treatment received for AE	26 (44.8%)	41 (52.6%)
No. of patients without treatment received for AE	32 (55.2%)	37 (47.4%)

Serious adverse event/deaths/other significant events

Table 44 Serious Adverse Events and Grade 3-5 Adverse Events in Patients With and Without Pre-existing Cardiac Conditions in Study BO21223 (FL Safety Population)

	Patients without pre-existing cardiac conditions		Patients with pre-existing cardiac conditions	
	R-chemo	G-chemo	R-chemo	G-chemo
Total number of patients	535	509	62	86
Number of patients with at least one cardiac SAE	6 (1.1%)	13 (2.6%)	6 (9.7%)	13 (15.11%)
Number of patients with at least one cardiac Grade 3-5 AE	10 (1.9%)	9 (1.8%)	7 (11.3%)	13 (15.1%)

Secondary malignancies

Table 45 Second Malignancies by SOC; AEs that Started at Least 6 Months after the First Dose of Study Medication in Study BO21223 (FL Safety Population)

Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

MedDRA System Organ Class MedDRA Preferred Term	R-chemo (N=597)	G-chemo (N=595)
Total number of patients with at least one adverse event	42 (7.0%)	62 (10.4%)
Overall total number of events	46	75
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Total number of patients with at least one adverse event	42 (7.0%)	62 (10.4%)
BASAL CELL CARCINOMA	6 (1.0%)	11 (1.8%)
SQUAMOUS CELL CARCINOMA	5 (0.8%)	5 (0.8%)
PROSTATE CANCER	3 (0.5%)	4 (0.7%)
SEBORRHOEIC KERATOSIS	2 (0.3%)	4 (0.7%)
LIPOMA	2 (0.3%)	3 (0.5%)
BREAST CANCER	0	4 (0.7%)
MELANOCYTIC NAEVUS	2 (0.3%)	2 (0.3%)
SKIN PAPILLOMA	2 (0.3%)	2 (0.3%)
BOWEN'S DISEASE	3 (0.5%)	0
COLON ADENOMA	1 (0.2%)	2 (0.3%)
ACUTE MYELOID LEUKAEMIA	0	2 (0.3%)
ANOGENITAL WARTS	1 (0.2%)	1 (0.2%)
COLON CANCER	2 (0.3%)	0
HODGKIN'S DISEASE	0	2 (0.3%)
INVASIVE DUCTAL BREAST CARCINOMA	1 (0.2%)	1 (0.2%)
MALIGNANT MELANOMA	1 (0.2%)	1 (0.2%)
MYELODYSPLASTIC SYNDROME	0	2 (0.3%)
RECTAL ADENOCARCINOMA	1 (0.2%)	1 (0.2%)
SQUAMOUS CELL CARCINOMA OF SKIN	0	2 (0.3%)
ACUTE LYMPHOCYTIC LEUKAEMIA	0	1 (0.2%)
ADENOCARCINOMA	1 (0.2%)	0
ADENOCARCINOMA OF COLON	0	1 (0.2%)
ADENOMA BENIGN	1 (0.2%)	0
BENIGN NEOPLASM	0	1 (0.2%)
BENIGN NEOPLASM OF SKIN	0	1 (0.2%)
BENIGN NEOPLASM OF THYROID GLAND	0	1 (0.2%)
COLORECTAL CANCER	1 (0.2%)	0
EYE HAEMANGIOMA	0	1 (0.2%)
FOLLICULAR THYROID CANCER	0	1 (0.2%)
GASTRIC CANCER	1 (0.2%)	0
HAEMANGIOMA OF LIVER	0	1 (0.2%)
HEPATIC NEOPLASM	0	1 (0.2%)
HODGKIN'S DISEASE NODULAR SCLEROSIS	0	1 (0.2%)
INTRADUCTAL PROLIFERATIVE BREAST LESION	1 (0.2%)	0
INTRAOCULAR MELANOMA	1 (0.2%)	0
LEIOMYOMA	0	1 (0.2%)
LIPOFIBROMA	1 (0.2%)	0
LUNG ADENOCARCINOMA	1 (0.2%)	0
MENINGIOMA	0	1 (0.2%)
MENINGIOMA BENIGN	1 (0.2%)	0

NASAL NEOPLASM	0	1 (0.2%)
NEOPLASM	1 (0.2%)	0
NEOPLASM SKIN	1 (0.2%)	0
NEUROENDOCRINE CARCINOMA OF THE SKIN	1 (0.2%)	0
NON-SMALL CELL LUNG CANCER	0	1 (0.2%)
NON-SMALL CELL LUNG CANCER STAGE IV	0	1 (0.2%)
PAPILLARY THYROID CANCER	0	1 (0.2%)
RENAL CANCER	0	1 (0.2%)
RENAL CELL CARCINOMA	1 (0.2%)	0
SCHWANNOMA	0	1 (0.2%)
SQUAMOUS CELL CARCINOMA OF LUNG	0	1 (0.2%)
THYROID CANCER	0	1 (0.2%)
TRANSITIONAL CELL CARCINOMA	0	1 (0.2%)
Total number of events	46	75

Table 46 Summary of Second Malignancies by SMQ; AEs that Started at Least 6 Months after the First Dose of Study Medication in Study BO21223 (FL Safety Population)

Protocol(s): BO21223 (L21223A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

MedDRA System Organ Class MedDRA Preferred Term	R-chemo (N=597)	G-chemo (N=595)
Total number of patients with at least one adverse event	30 (5.0%)	43 (7.2%)
Overall total number of events	33	51
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Total number of patients with at least one adverse event	30 (5.0%)	43 (7.2%)
BASAL CELL CARCINOMA	6 (1.0%)	11 (1.8%)
SQUAMOUS CELL CARCINOMA	5 (0.8%)	5 (0.8%)
PROSTATE CANCER	3 (0.5%)	4 (0.7%)
BREAST CANCER	0	4 (0.7%)
BOWEN'S DISEASE	3 (0.5%)	0
ACUTE MYELOID LEUKAEMIA	0	2 (0.3%)
COLON CANCER	2 (0.3%)	0
HODGKIN'S DISEASE	0	2 (0.3%)
INVASIVE DUCTAL BREAST CARCINOMA	1 (0.2%)	1 (0.2%)
MALIGNANT MELANOMA	1 (0.2%)	1 (0.2%)
RECTAL ADENOCARCINOMA	1 (0.2%)	1 (0.2%)
SQUAMOUS CELL CARCINOMA OF SKIN	0	2 (0.3%)
ACUTE LYMPHOCYTIC LEUKAEMIA	0	1 (0.2%)
ADENOCARCINOMA	1 (0.2%)	0
ADENOCARCINOMA OF COLON	0	1 (0.2%)
COLORECTAL CANCER	1 (0.2%)	0
FOLLICULAR THYROID CANCER	0	1 (0.2%)
GASTRIC CANCER	1 (0.2%)	0
HEPATIC NEOPLASM	0	1 (0.2%)
HODGKIN'S DISEASE NODULAR SCLEROSIS	0	1 (0.2%)
INTRADUCTAL PROLIFERATIVE BREAST LESION	1 (0.2%)	0
INTRAOCULAR MELANOMA	1 (0.2%)	0
LUNG ADENOCARCINOMA	1 (0.2%)	0
NASAL NEOPLASM	0	1 (0.2%)
NEOPLASM	1 (0.2%)	0
NEOPLASM SKIN	1 (0.2%)	0
NEUROENDOCRINE CARCINOMA OF THE SKIN	1 (0.2%)	0
NON-SMALL CELL LUNG CANCER	0	1 (0.2%)
NON-SMALL CELL LUNG CANCER STAGE IV	0	1 (0.2%)
PAPILLARY THYROID CANCER	0	1 (0.2%)
RENAL CANCER	0	1 (0.2%)
RENAL CELL CARCINOMA	1 (0.2%)	0
SQUAMOUS CELL CARCINOMA OF LUNG	0	1 (0.2%)
THYROID CANCER	0	1 (0.2%)
TRANSITIONAL CELL CARCINOMA	0	1 (0.2%)
Total number of events	33	51

Investigator text for AEs encoded using MedDRA v18.1.
Percentages are based on N in the column headings.
AEs with onset date before the first drug intake are not taken into account.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Updated data with regard to secondary malignancies showed a 6.0% of the patients in the R-chemo

arm had an event as compared to a 7.9% of the patients in the G-chemo arm.

Hepatitis B Reactivation

Overall, 53 patients in the R-chemo arm and 29 patients in the G-chemo arm were hepatitis B core antibody positive at baseline, and therefore at risk of developing hepatitis B reactivation. Five patients experienced AEs of HBV reactivation: two in the R-chemo arm and three in the G-chemo arm; all the events reported in the G-chemo arm were Grades 1 or 2.

Patients could receive prophylactic anti-viral medication to prevent HBV reactivation in countries where they are administered as part of the standard of care or national guidelines. Of the patients with hepatitis B core antibody positive at baseline, 15 in the R-chemo arm and 7 in the G-chemo arm received prophylaxis for hepatitis B on-study. Of the 5 patients who experienced the AE PT of Hepatitis B reactivation, both patients in the R-chemo arm and one of the 3 patients in the G-chemo arm, received prophylaxis for hepatitis B.

Serious adverse event/deaths

Table 47 Serious AEs over the entire study period -in >1% of patients in either arm by PT

MedDRA System Organ Class MedDRA Preferred Term	R-chemo (N=597)	G-chemo (N=595)
Total number of patients with at least one adverse event	238 (39.9%)	274 (46.1%)
Overall total number of events	450	590
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total number of patients with at least one adverse event	47 (7.9%)	56 (9.4%)
FEBRILE NEUTROPENIA	19 (3.2%)	29 (4.9%)
NEUTROPENIA	25 (4.2%)	22 (3.7%)
Total number of events	73	85
GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	28 (4.7%)	43 (7.2%)
DIARRHOEA	6 (1.0%)	8 (1.3%)
ABDOMINAL PAIN	5 (0.8%)	8 (1.3%)
VOMITING	7 (1.2%)	3 (0.5%)
Total number of events	40	58
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total number of patients with at least one adverse event	34 (5.7%)	30 (5.0%)
PYREXIA	17 (2.8%)	18 (3.0%)
Total number of events	37	36
INFECTIONS AND INFESTATIONS		
Total number of patients with at least one adverse event	86 (14.4%)	108 (18.2%)
PNEUMONIA	25 (4.2%)	29 (4.9%)
HERPES ZOSTER	8 (1.3%)	6 (1.0%)
URINARY TRACT INFECTION	5 (0.8%)	8 (1.3%)
INFECTION	7 (1.2%)	5 (0.8%)
LOWER RESPIRATORY TRACT INFECTION	3 (0.5%)	8 (1.3%)
LUNG INFECTION	6 (1.0%)	5 (0.8%)
SEPSIS	2 (0.3%)	8 (1.3%)
BRONCHITIS	3 (0.5%)	6 (1.0%)
GASTROENTERITIS	1 (0.2%)	7 (1.2%)
Total number of events	119	146
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total number of patients with at least one adverse event	21 (3.5%)	41 (6.9%)
INFUSION RELATED REACTION	11 (1.8%)	27 (4.5%)
Total number of events	24	50
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total number of patients with at least one adverse event	30 (5.0%)	33 (5.5%)
DYSPNOEA	6 (1.0%)	6 (1.0%)
PULMONARY EMBOLISM	2 (0.3%)	6 (1.0%)
Total number of events	32	36
VASCULAR DISORDERS		
Total number of patients with at least one adverse event	7 (1.2%)	12 (2.0%)
HYPOTENSION	0	6 (1.0%)
Total number of events	7	13

Table 48 Grade 3-5 AEs Reported in ≥ 2% of Patients in Either Treatment Arm in Study BO21223 (FL Safety Population)

	FL Population	
	R-chemo n = 597	**G-chemo n = 595**
Neutropenia	226 (37.9%)	**261 (43.9%)**
Leukopenia	50 (8.4%)	51 (8.6%)
Febrile neutropenia	29 (4.9%)	**41 (6.9%)**
Infusion-related reaction	22 (3.7%)	**40 (6.7%)**
Thrombocytopenia	16 (2.7%)	**36 (6.1%)**
Pneumonia	26 (4.4%)	29 (4.9%)
Anemia	13 (2.2%)	24 (4.0%)
Dyspnoea	9 (1.5%)	17 (2.9%)
Hypertension	10 (1.7%)	14 (2.4%)

Deaths

Table 49: Summary of deaths [Snapshot date 29.04.2016 ; cut-off date 31.01.2016]

		R-chemo (N=597)	G-chemo (N= 595)
Subject status	Alive	551 (92.3%)	560 (94.1%)
	Dead	46 (7.7%)	35 (5.9%)
Cause of death	Adverse event	20 (3.4%)	23 (3.9%)
	Progressive disease	22 (3.7%)	12 (2.0%)
	Other	4 (0.7%)	0 (0.0%)

Laboratory findings

B-cell depletion and recovery

Almost all patients who had a B-cell result reported showed B-cell depletion at the last antibody administration. Of the 452 patients in the R-chemo arm with a B-cell result, 445 patients showed B-cell depletion at the LAA. Of the 457 patients in the G chemo arm with a B-cell result, 454 patients had B-cell depletion at the LAA.

Immunoglobulin depletion was defined as levels below 0.5 g/L, 5.0 g/L and 0.3 g/L for IgA, IgG and IgM, respectively, at any time during the study. The proportion of patients experiencing immunoglobulin depletion at the last dose of antibody was:

- IgA: 9.5% in the R-chemo arm and 6.4% in the G-chemo arm.
- IgG: 11.6% in the R-chemo arm and 9.4% in the G-chemo arm
- IgM: 29.0% in the R-chemo arm and 29.7% in the G-chemo arm

Immunoglobulin depletion was comparable between the treatment arms. At the time of data cutoff, only a few patients (3.4 – 10.7%) with immunoglobulin depletion had recovered, hence the time to recovery could not be calculated in a meaningful way.

Chemistry

The highest NCI-CTCAE Grade for chemistry parameters throughout the study is shown in Table 41 (also see Section 8.12.12.2 in primary BO21223 CSR). Grade 3 and/or Grade 4 abnormalities were reported for the following chemistry parameters on both treatment arms during the study: albumin (low), ALT (high), AST (high), calcium (low and high), CrCL (low), BSA corrected CrCL (low), creatinine (high and low), potassium (low and high), sodium (low), bilirubin (high), and uric acid (high). High uric acid (any grade and Grade 3, in particular) was more frequently (≥ 5% difference) reported in the G-chemo arm. Abnormalities of the following parameters were also more frequently reported (≥ 5% difference) in the G-chemo arm: low albumin, high ALT, high AST, low calcium, high potassium and low sodium.

Anti-therapeutic antibodies

The detection of human anti-human (HAHA) anti-drug antibodies against obinutuzumab was performed using a validated ELISA. The sensitivity of the method was 18.4 ng–equiv./mL antibody titer in human serum. For the positive control, a purified rabbit polyclonal antibody directed against obinutuzumab was used. The mean drug tolerance factor was 95.6 (the tolerated ratio of drug to positive control), allowing the detection of anti-obinutuzumab antibodies with a sensitivity level of 0.500 µg/mL at obinutuzumab serum concentrations of up to 47.8 ≥g/mL.

Immunogenicity testing of study samples in the G chemo arm was performed using a 3 tiered approach (screening, confirmation, and titration). The confirmatory assay was statistically evaluated during validation to allow for the presence of approximately 1% false positive results. For samples confirmed positive, titration was performed and an antibody titer value was reported. The titer was defined as the highest sample dilution that resulted in a response at or above the assay cut point.

At baseline, 25 patients (5.1%) in the G chemo arm had positive HAHA results. As these patients had not been exposed to obinutuzumab before, these results can be regarded as false positive. One patient in the G chemo arm had a detectable positive HAHA result for anti obinutuzumab antibodies after Cycle 1, Day 1.

Safety in special populations

Table 50 Adverse Events by Age Group and Sex in Study BO21223 (FL Safety Population)

	R-chemo (N=597)		G-chemo (N=595)	
	<65 (N=410)	>=65 (N=187)	<65 (N=412)	>=65 (N=183)
Number of patients with AEs	402 (98.0%)	185 (98.9%)	411 (99.8%)	181 (98.9%)
Number of events	6378	2965	7243	3068
Male patients with AEs	190 (96.9%)	80 (97.6%)	194 (99.5%)	85 (98.8%)
Male patients	196 (47.8%)	82 (43.9%)	195 (47.3%)	86 (47.0%)
Female patients with AEs	212 (99.1%)	105 (100.0%)	217 (100.0%)	96 (99.0%)
Female patients	214 (52.2%)	105 (56.1%)	217 (52.7%)	97 (53.0%)
Number of patients with:				
Related AEs	378 (92.2%)	169 (90.4%)	392 (95.1%)	172 (94.0%)
Serious AEs	146 (35.6%)	92 (49.2%)	167 (40.5%)	107 (58.5%)
AEs leading to withdrawal from any treatment	52 (12.7%)	33 (17.6%)	52 (12.6%)	45 (24.6%)
AEs leading to death	7 (1.7%)	13 (7.0%)	9 (2.2%)	15 (8.2%)
AEs treated	390 (95.1%)	180 (96.3%)	401 (97.3%)	178 (97.3%)
AEs resolved	398 (97.1%)	184 (98.4%)	410 (99.5%)	180 (98.4%)
AEs unresolved	281 (68.5%)	139 (74.3%)	301 (73.1%)	147 (80.3%)

Table 51 Adverse Events by Creatinine Clearance < 50 mL/min and ≥ 50 mL/min in Study BO21223 (FL Safety Population)

	CrCL at Baseline < 50 mL/min		CrCL at Baseline ≥ 50 mL/min	
	R-chemo (N = 23)	G-chemo (N = 27)	R-chemo (N = 573)	G-chemo (N = 568)
Total no. of AEs	363	535	8974	9776
Total no. of deaths	4 (17.4%)	4 (14.8%)	42 (7.3%)	31 (5.5%)
Total no. patients with at least one:				
AE	22 (95.7%)	27 (100.0%)	564 (98.4%)	565 (99.5%)
Grade 3-5	18 (78.3%)	23 (85.2%)	386 (67.4%)	421 (74.1%)
Grade 5	2 (8.7%)	2 (7.4%)	18 (3.1%)	22 (3.9%)
Serious AE	11 (47.8%)	20 (74.1%)	227 (39.6%)	254 (44.7%)
AE leading to treatment withdrawal	5 (21.7%)	10 (37.0%)	80 (14.0%)	87 (15.3%)

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been conducted

Discontinuation due to adverse events

No dose reductions were permitted for obinutuzumab in either study (nor for rituximab in Study BO21223). Certain AEs warranted slowing of antibody infusion rate, interruptions, or dose delays. Chemotherapy regimen modifications included dose delays and reduction of certain chemotherapy components under certain circumstances.

A patient was considered to have withdrawn from study treatment if they discontinued all of the components of their allocated treatment.

Post marketing experience

There is currently no Post Marketing Experience with obinutuzumab in this indication. No new safety concerns have been identified since the last RMP was submitted.

2.5.1. Discussion on clinical safety

The size of the safety database with approximately 600 patients exposed to obinutuzumab in both the induction phase and the maintenance phase is acceptable. Demographic and patient characteristics were balanced between the treatment arms.

Dose intensity and duration of treatment was overall comparable between treatment arms in both induction and maintenance phase. During induction, most patients received all planned doses of obinutuzumab or rituximab. Overall, 99.5% of patients in the R-chemo arm and 99.7% of patients in the G-chemo arm received at least 90% of the planned cumulative dose of therapeutic antibody.

In the FL population of Study BO21223, the treatment arms were generally well-balanced with respect to demographic factors. The median age of patients was 59.0 years (range: 23 to 88 years) and very similar in each study arm. The majority of patients were less than 65 years of age (68.7%). Overall, more female than male patients were randomized in the study (53.2% female). The majority of patients were White (80.5%). The median BSA was 1.84 m^2 and the median BMI was 25.69 kg/ m^2, and these characteristics were also very similar in both treatment arms.

Baseline disease characteristics including B-symptom data, bone marrow involvement, FLIPI scores and other parameters, were also balanced overall between the two arms of the study. The treatment arms were well balanced with regard to the baseline stratification factors: FLIPI (low, intermediate and high), chemotherapy regimen (CHOP, CVP, bendamustine) and geographic region (Eastern Europe, Western Europe, North America, Asia, Other). AEs and SAEs were defined according to acceptable standards. The causal relationship of AEs to the investigational products was assessed by investigators. Deaths were outcomes, not events, and progression of lymphoma was not recorded as AEs or SAEs.

In the G-chemo arm, only four patients missed either the Cycle1 Day 8, or Cycle 1 Day 15 dose (note, the other 11 patients in this listing were withdrawn from treatment after Cycle 1 Day 1 so only received one dose of study medication in total).

During maintenance, most patients received all planned doses of obinutuzumab or rituximab. Overall, 99.2% of patients in the R-chemo arm and 99.8% of patients in the G-chemo arm received at least 90% of the planned cumulative dose of therapeutic antibody. The median duration of treatment with rituximab and obinutuzumab during maintenance was the same in the two arms (92 weeks).

Overall, AEs are more frequently observed in the G-chemo arm. This is not unexpected and is in line with the previous findings in studies with obinutuzumab. However, the incidence of AEs leading to withdrawal of study treatment is considered similar. Thus, even though AEs occur more frequently in the G-chemo, patients seem to adhere to treatment. Looking at AEs with an incidence rate of at least 10%, the most relevant differences are seen with regard to neutropenia, diarrhoea, pyrexia and infusion related reactions (IRR). These are all well-known AEs related to anti-CD20 antibodies and are adequately reflected in the SmPC. Looking at the AEs reported with a difference of at least 2%, it is observed that the difference in neutropenia does not translate into a relevant difference in terms febrile neutropenia. Differences are observed with regard to other AEs, but none are considered clinically significant and the majority of these AEs are adequately handled in the clinical setting.

More AEs occurred during induction phase, where the majority of Grade 3-5 AEs were observed. During both induction, maintenance and follow-up, more AEs occurred in the G-chemo arm. This is as expected and do not pose any major clinical concerns or challenges.

There are no relevant difference between the two treatment arms in terms of Grade 1-3 and 5 AEs was reported, however, a significant difference is observed in Grade 4 AEs. The updated data as of clinical cutoff of 10 September 2016 showed consistency between these data and the primary analysis data concerning the AEs, SAEs, fatal AEs, and resolved AEs. A difference less than 2% was reported in either sex compared with the overall FL patient population.

No significant difference in safety between the two treatment arms was observed related to gender. With regard to age, there seems to be more SAEs, AEs leading to withdrawal and death in patients >=65 years, which was expected.

With regard to adverse events of particular/special interest IRR, a well-known AE related to anti-CD20 antibodies, is more frequently observed in patients treated with obinutuzumab, especially during the first couple of cycles of treatment. Most of the IRR resolved with either treatment modifications or spontaneously. IRR is well described in the SmPC, were precautionary measures in terms of premedication are given.

Neutropenia was another adverse event of particular/special interest; slightly more Grade 3 and 4 AEs are observed in the G-chemo arm. This is not unexpected. No Grade 5 AEs are observed. Neutropenia in itself is not a major concerns, however, prolonged neutropenia give rise to more infections. Overall,

more infections and Grade 3-5 infections were reported in the G-chemo arm compared to the R-chemo arm. The incidence of Grade 3-5 infections was lower among G-chemo patients who received G-CSF prophylaxis compared with those who did not. Granulocyte-colony stimulating factors (G-CSF) could be considered in patients who experience neutropenia.The incidence and rate of infection is higher for obinutuzumab compared to rituximab, also in the maintenance phase. This could be related to prolonged B-cell depletion and longer recovery. Patients that received bendamustine seems to be at higher risk. Updated B-cell assessments as of data cutoff of 10-september-2016 are still immature and no conclusion can be drawn. B-cell depletion and recovery data will be submitted in the final clinical study report.

Serious cardiac AEs were reported in 2.0 % of patients in the R-chemo arm and 4.4% in the G-chemo arm; the imbalance between the arms was largely due to more reports of atrial fibrillation, bradycardia, and acute myocardial infarction (mostly in elderly patients with previous or concurrent coronary disease) in the G-chemo arm.

When IRRs were excluded the difference in the incidence of cardiac events was reduced. The number of cardiac Grade 3-5 and serious AEs in patients without cardiac conditions was low and balanced between arms. Overall, the risk of cardiac events in patients with pre-existing conditions is notable, and these patients should be monitored closely if treated with obinutuzumab. This is adequately reflected in the SmPC. The updated cardiac AEs were similar to the first analysis. The numbers are small and overall a similar proportion of patients had cardiac grade 3-5 events in both treatment arms when cardiac IRRs were excluded. Most patients in the R-chemo and G-chemo arms with grade 3-5 cardiac events had predisposing factors, hypertension being the most frequent, other factors were diabetes and pre-existing cardiac conditions. The 4 fatal events were in patients who received bendamustine during induction. Patients who receive bendamustine are often more frail compared to those who receive CHOP. The cardiac events are adequately reflected in the SmPC.

With regard to secondary malignancies, there are slightly more events in the G-chemo arm, 6.0% in the R-chemo arm and 7.9% in the G-chemo arm comparable to the proportion observed in the primary analysis. Although, no apparent pattern can be observed, hematological malignancies were only observed in the G-chemo arm. The number for each different cancer is small, it could be chance findings and was driven mainly by a difference in non-melanoma skin cancers and hematological malignancies. Cytogenetic tests performed in patients with secondary AML/MDS, however were inconclusive as to whether the cases were treatment related or de novo.

With regard to other adverse events of particular/special interest (thrombocytopenia, TLS, GI perforation) no clinically relevant differences were observed.

There was a higher rate of thrombocytopenia in the G-chemo arm compared to the R-chemo arm, especially in cycle 1, but the incidence of hemorrhage was low. Patients should be carefully monitored as addressed in the SmPC. Concomitant treatment with agents like platelet inhibitors and anticoagulants could increase the risk. Thrombocytopenia was only seen in few patients in the maintenance phase. This AE is known with Gazyvaro.

The risk of TLS is already flagged in the FL population. Patients considered at risk should receive prophylaxis. This is adequately reflected in the SmPC.

Hepatitis B reactivation is a known risk of anti-CD20 antibodies. The numbers are small, but seems comparable between the treatment groups. Screening should be performed and local guidelines followed. This is adequately addressed in the SmPC. No case of PML was observed.

The above findings are also reflected in the pattern of SAEs and Grade 3-5 AEs, where more are seen in the G-chemo arm, mainly driven by infections, neutropenia, IRR and thrombocytopenia. Overall, the

higher toxicity of obinutuzumab compared to rituximab is as expected from the mechanism of action and seems manageable.

Updated data with regard to secondary malignancies, showed slightly more events in the G-chemo arm: 6.0% in the R-chemo arm and 7.9% in the G-chemo arm. Hematological malignancies malignancies (Hodgkin disease, acute myeloid leukemia, acute lymphocytic leukemia and myelodysplastic syndromes) were only observed in the G-chemo arm. Although no clear pattern in the type of tumor and the onset, latency, or chemotherapy regimen, in either treatment arm was observed, the difference was mainly driven by a difference in non-melanoma skin cancers and hematological malignancies. Cytogenetic tests performed in patients with secondary AML/MDS, however were inconclusive as to whether the cases were treatment related or de novo.

The frequency of death was similar in the R-chemo and G-chemo arm, (3.4% vs. 4.0%, respectively). The causes of death due to adverse events are overall as expected and with no apparent differences between treatment arms. However, the number of deaths and number of AEs with fatal outcome in the R-Benda and G-Benda arm are high compared to the other chemo backbones. This is in contrast to common clinical understanding of the safety profile of bendamustine, which is considered to be more tolerable than CHOP and CVP. The updated analysis as of clinical cutoff date 10 september 2016 revealed 1 more patient in the R-benda subgroup with a fatal outcome. Although small numbers, more patients in the R-benda and G-benda subgroup were confounded by older age > 80 years, baseline comorbidity and/or new anti-lymphoma treatment than patients in the CHOP subgroups. Thus no specific cause could be identified which could explain the higher incidence of fatal AEs in the G-benda (5.9%)and R-benda (4.4%) subgroup, when compared to patients who received CVP- and CHOP–containing regimens (range of 1.6% to 2.0%).

No concerns regarding anti-drug antibodies were identified.

No formal drug-drug interaction studies have been conducted with obinutuzumab. This is acceptable as such interactions are not expected with this monoclonal antibody. A comparison of serum pharmacokinetic parameters from studies of obinutuzumab monotherapy with pharmacokinetic parameters from studies of obinutuzumab in combination with chemotherapy (BO21000) suggests that concomitant chemotherapy has minimal impact on the pharmacokinetics of obinutuzumab.

Delayed reporting of AEs was reported, however this was widely spread and not confined to specific sites with no trends detected. Updated safety data as of the 5th May 2017 showed an increase of adverse events between the snapshot dates 29 April 2016 and 5 May 2017 by 8.3 % and 7.9 % in the R-chemo arm and G-chemo arm respectively. The number of patients with any AE (all grades), Grade 3-5 AEs, Fatal AEs, SAEs or AE leading to withdrawal from any treatment was only slightly affected and did not differ between the treatments. The updated safety data did not cause a difference between treatment arms of ≥ 2 %. An increase in number of patients experiencing a Grade 3-5 AE of 2.2 % in the R-chemo arm and 2.0 % in the G-chemo arm was mainly driven by neutropenia. The incidence of neutropenia is highest in the G-chemo arm. No differences between treatment arms was identified by AE grade, nature or severity. The incidence by treatment phase and by chemotherapy was also unaffected by the safety update. The small numerical differences in incidences caused by the safety update did not change the overall safety profile of either treatment and no concerning changes in incidences between treatments has been identified.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics and section 4.8 has been updated accordingly.

The final report from study BO21223 as foreseen in the RMP- focus on safety updates; events of thrombocytopenia, late onset and prolonged neutropenia, prolonged B-cell depletion, immunogenicity, will be specifically investigated.

2.5.2. Conclusions on clinical safety

Overall, the safety of the combination of obinutuzumab with chemotherapy is acceptable and as expected. There are more AEs and SAEs, but the withdrawal rates are comparable between the two treatment arms, thus, indicating that patients adhered to treatment. The observed toxicities are manageable in clinical practice.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

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

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

- Within this procedure, the MAH has submitted an updated Risk Management Plan (RMP version 3.0) and based on the latest approved RMP (version 2.2), including data from the pivotal study BO21223/GALLIUM in previously untreated patients with advanced follicular lymphoma as well as data from the supportive study BO21000/GAUDI.

  In addition, the MAH proposed to update the due date for the final clinical study report of study BO21223/GALLIUM listed in the Gazyvaro Risk Management Plan "Category 3: Required additional pharmacovigilance activities".

  The PRAC considered the risk management plan version 3.1 to be acceptable. The PRAC endorsed PRAC Rapporteur assessment reports are attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 3.1 with the following content:

Safety concerns

Table 52: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Infusion related reactions Tumor lysis syndrome Thrombocytopenia Neutropenia Late onset and prolonged neutropenia Prolonged B-cell depletion Infections Hepatitis B reactivation Progressive multifocal leukoencephalopathy Worsening of pre-existing cardiac conditions GI perforation
Important potential risks	Impaired immunization response Immunogenicity Second malignancies Immune-mediated glomerulonephritis
Missing information	Use in children Use in pregnancy and lactation

Pharmacovigilance plan

Table 53: Ongoing and planned studies in the post-authorisation pharmacovigilance plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
Study BO21004: Obinutuzumab + chlorambucil compared to rituximab + chlorambucil or chlorambucil alone in previously untreated CLL patients with comorbidities. Category 3	Primary: demonstration of clinically relevant statistical superiority in PFS obinutuzumab + Clb compared to rituximab + Clb and Clb alone and RClb compared to Clb in previously untreated CLL patients with comorbidities. Includes secondary objective to evaluate and compare the safety profile of patients.	IRRs (confirmation of decrease in IRRs since protocol amendment introducing split dosing, slow infusion and reinforcing pre-existing risk minimization measures) (complete) Prolonged B-cell depletion Immunogenicity Immune-mediated glomerulonephritis	Study ongoing	Q1 2014 (Stage 2 analysis CSR; completed) Q2 2018 (Final CSR)

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Study BO21005: Obinutuzumab in combination with CHOP versus rituximab and CHOP in previously untreated patients with CD20-positive DLBCL Category 3	Primary: demonstrate superiority in PFS of obinutuzumab plus chemotherapy vs. rituximab plus chemotherapy in previously untreated DLBCL patients Includes secondary objective to evaluate and compare the safety profiles of patients treated with the combination of obinutuzumab and CHOP with rituximab and CHOP	Thrombocytopenia Late onset and prolonged neutropenia Prolonged B-cell depletion Immunogenicity Immune-mediated glomerulonephritis	Study ongoing	Q1 2019
Study BO21223: Obinutuzumab plus chemotherapy compared with rituximab plus chemotherapy in previously untreated patients with advanced indolent lymphoma followed by GA101[1] or rituximab maintenance therapy in responders Category 3	Primary: Efficacy of obinutuzumab plus chemotherapy followed by obinutuzumab maintenance therapy compared with rituximab plus chemotherapy followed by rituximab maintenance therapy in previously untreated advanced follicular lymphoma. Includes secondary objective to evaluate and compare the safety profiles between the two arms	Thrombocytopenia Late onset and prolonged neutropenia Prolonged B-cell depletion Immunogenicity Immune-mediated glomerulonephritis	Study ongoing (Primary analysis completed)	Q4 2021
Study MO28543: Obinutuzumab in combination with chemotherapy in patients with previously untreated or relapsed/refractory CLL Category 3	Primary: To evaluate the safety and tolerability of obinutuzumab alone or in combination with chemotherapy	IRRs	Study ongoing	Q1 2019

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Study GAO4753g: Obinutuzumab in combination with bendamustine compared with bendamustine in patients with rituximab-refractory indolent NHL Category 3	To evaluate clinical benefit in terms of PFS of obinutuzumab in combination with bendamustine compared with bendamustine alone in patients with indolent NHL refractory to prior rituximab-containing therapy. Includes secondary objective evaluate and compare the safety profiles of patients treated with bendamustine and obinutuzumab and bendamustine alone.	Thrombocytopenia Prolonged B-cell depletion	Study ongoing	(Primary CSR complete). Updated OS results: Study Completion is expected Q4 2019. Submission of the Final Study report Q4 2020. Regular safety updates will be provided with the PSURs.

Risk minimisation measures

Table 54: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Infusion related reactions	EU SmPC Sections 4.2, 4.4 and 4.8	None proposed
Tumor lysis syndrome	EU SmPC Sections 4.2, 4.4 and 4.8	None proposed
Thrombocytopenia	EU SmPC Sections 4.4 and 4.8	None proposed
Neutropenia	EU SmPC Sections 4.4, 4.5 and 4.8	None proposed
Late onset and prolonged neutropenia	EU SmPC Sections 4.4 and 4.5	None proposed
Prolonged B-cell depletion	EU SmPC Sections 4.4 and 5.1	None proposed
Infections	EU SmPC Sections 4.4 and 4.8	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hepatitis B-reactivation	EU SmPC Sections 4.4 and 4.8	None proposed
Progressive multifocal leukoence-phalopathy	EU SmPC Sections 4.4 and 4.8	None proposed
Worsening of pre-existing cardiac conditions	EU SmPC Sections 4.4 and 4.8	None proposed
GI perforation	EU SmPC Section 4.8	None proposed
Impaired immunization response	EU SmPC Section 4.4	None proposed
Immunogenicity	EU SmPC Sections 4.4 and 5.1	None proposed
Second malignancies	None	None proposed
Immune-mediated glomerulo-nephritis	None	None proposed
Use in children	EU SmPC Section 4.2	None proposed
Use in pregnancy and lactation	EU SmPC Sections 4.4 and 4.6	None proposed

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed and accepted by the CHMP.

2.7.1. 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:

- No significant changes impacting the readability of the package leaflet are made. The new additions follow the same structure and use similar descriptions and terminology as used in the approved package leaflet.
- The target group of users has not fundamentally changed: the age range of patients with previously untreated follicular lymphoma is similar to the age range of participants interviewed during the Gazyvaro user test. Gazyvaro is already approved in the follicular lymphoma setting.
- Moreover, posology proposed in this application does not essentially differ to the currently approved follicular lymphoma indication.

3. Benefit-Risk Balance

Benefits

Beneficial effects

This is a type II variation to extend the indication of GAZYVARO in combination with chemotherapy, followed by Gazyvaro maintenance therapy in patients achieving a response, for the treatment of patients with previously untreated advanced follicular lymphoma.

The MAH has provided the interim results of one pivotal, randomized, open-label, Phase III study BO21223 (GALLIUM) in patients with previously untreated advanced indolent non –Hodgkin lymphoma NHL. Obinutuzumab in combination with chemotherapy significantly decreases the risk of relapse compared to R-chemo with HR for PFS at 0.66, p-value 0.0012. In a disease characterized by several relapses, where the patient finally becomes refractory to the different chemotherapy agents, this is clinically highly relevant, as time-to relapse is further postponed. Secondary endpoints, such as EFS, DOR and TTNALT are consistent with the primary endpoint and show a benefit in favour of G-chemo. With regard to DFS, as expected in a disease entity with a relatively long survival, data are not mature, but there is no indication of any detrimental effect.

The median PFS by INV was not reached in any arm at the time of analysis. Due to the course of FL, median PFS may take considerable long time to reach. An updated analysis after 6.6 months additional median follow-up with a data cut-off of 10 September 2016 was performed. The investigator-assessed PFS increased to 281/370 = 76% of total planned events with a HR of 0.68 (95% CI: 0.54, 0.87), p=0.0016, being consistent with the primary analysis. The HR estimate for secondary time–to-event endpoints are consistent with data from the primary analysis. OS data were also consistent with the primary analysis, showing no significant effect of G-chemo as compared to R-chemo. A PFS blinded assessment was performed by an Independent review committee (IRC) in order to support primary outcomes resulting in a hazard ratio of 0.71 - in the range of the expected reduction risk in FL population, but not statistically significant in regard to the type-1 error set in the trial for the 3rd interim analysis (0.012). The concordance rate between the two analyses is considered acceptable and in line with what has previously been accepted. The study was stopped for efficacy based on IDMC recommendations as planned and described in the protocol.

Uncertainty in the knowledge about the beneficial effects

There seems to be no difference between G-chemo and R-chemo in patients with FLIPI score low, but patients with FLIPI score low only comprised 21% of the ITT population and no explanation could be found as to why obinutuzumab had no added effect in the FLIPI low score subgroup. This information was reflected in section 5.1 of the SmPC.

There are no data on the activity of Gazyvaro in Follicular Lymphoma grade 3b patients. These patients were excluded from the clinical studies GALLIUM and GOYA, (see SmPC section 5.1) as in clinical practice they are more aggressively treated, similar to DLBCL. Data from DLBCL patients from the GOYA trial indicated similar activity for Gazyvaro and Rituximab in patients with DLBCL.

Update on the overall survival data (still immature at the time of the updated analysis) will be provided with the final report from Study BO21223 (see RMP).

Risks

Unfavourable effects

Overall, AEs are more frequently observed in the G-chemo arm. This is not unexpected and is in line

with the previous findings in studies with obinutuzumab. However, the incidence of AEs leading to withdrawal of study treatment is considered similar. Thus, even though AEs occur more frequently in the G-chemo, patients seem to adhere to treatment. Looking at AEs with an incidence rate of at least 10%, the most relevant differences are seen with regard to neutropenia, diarrhoea, pyrexia and infusion related reactions (IRR). These are all well-known AEs related to anti-CD20 antibodies and are adequately reflected in the SmPC.

More AEs occurred during induction phase, where the majority of Grade 3-5 AEs were observed. During both induction, maintenance and follow-up, more AEs occurred in the G-chemo arm. This is as expected and do not pose any major clinical concerns or challenges.

Slightly more Grade 3 and 4 AEs are observed in the G-chemo arm. This is not unexpected. Neutropenia in itself is not a major concerns, however, prolonged neutropenia give rise to more infections. Overall, more infections and Grade 3-5 infections were reported in the G-chemo arm compared to the R-chemo arm. The incidence of Grade 3-5 infections was lower among G-chemo patients who received G-CSF prophylaxis compared with those who did not. Thus Granulocyte-colony stimulating factors (G-CSF) could be considered in patients who experience neutropenia.

Uncertainty in the knowledge about the unfavourable effects

Considering that the results from the subgroup analysis in FLIPI low patients are currently inconclusive, section 4.4 of the SmPC was amended to include a recommendation that the therapy choice in these patients should take into account the overall safety profile of obinutuzumab plus chemotherapy and the patient situation. Final report from Study BO21223 will provide more information on adverse events such as thrombocytopenia, late onset and prolonged neutropenia, prolonged B-cell depletion and immunogenicity (see RMP).

Subgroup analyses of outcome by chemotherapy backbone showed that the number of deaths and number of AEs with fatal outcome in the R-Benda and G-Benda arm are higher compared to the other chemo backbones. Although small numbers, patients in the R-benda and G-benda subgroup were of older age > 80 years and had more baseline comorbidity and/or new anti-lymphoma treatment than patients in the CHOP subgroups. No specific cause could be identified which could explain the higher incidence of fatal AEs in the G-benda (5.9%)and R-benda (4.4%) subgroup, when compared to patients who received CVP- and CHOP–containing regimens (range of 1.6% to 2.0%). Final study report is expected to provide mature data (see RMP).

Effects Table

Table 55: Effects Table for Gazyvaro in FL (data cut-off: 31 January 2016)

Effect	Short Description	Unit	G-chemo	R-chemo	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS by INV	Progression-free survival assessed by investigator	Median in months	NE (48.1, NE)	NE (47.1, NE)	HR = 0.66 (95%CI; 0.51, 0.85), p-value = 0.0012	

Effect	Short Description	Unit	G-chemo	R-chemo	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
Neutropenia (Grade 3-5)		N(%)	261 (43.9%)	226 (37.9%)		
Febrile neutropenia (Grade 3-5)		N(%)	41 (6.9%)	29 (4.9%)		
IRR (Grade 3-5)		N(%)	40 (6.7%)	22 (3.7%)		
Thrombocytopenia (Grade 3-5)		N(%)	36 (6.1%)	16 (2.7%)		
Infections (Grade 3-5)		N(%)	108 (18.2%)	86 (14.4%)		

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The PFS gain is considered clinically meaningful for patients with FL with HR = 0.68 (95% CI: 0.54, 0.87), p=0.0016 from the updated analysis - consistent with the primary analysis (HR = 0.66 [95% CI: 0.51, 0.85]). Overall survival data are as expected immature at this stage, but will be updated at the final CSR.

There are no new safety findings and the observed toxicities are overall manageable in the clinical setting. However, the adverse event profile of obinutuzumab including uncertainties (i.e. risk of secondary malignancies) is in line with well-known so far safety in CLL.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

Data to support the efficacy of obinutuzumab in combination with chemotherapy in patients with previously untreated FL are provided from one pivotal Phase III study (study BO21223/GALLIUM), with additional data from the supporting study BO21000 (GAUDI). Study BO21223, showed that treatment with obinutuzumab in combination with chemotherapy resulted in a statistically significant and clinically meaningful reduction in the risk of progression or death as assessed by the investigator, compared

with rituximab in combination with chemotherapy. The results of the primary endpoint are further supported by the key secondary endpoint, PFS by IRC. Due to the course of FL, median PFS may take considerable long time to reach, however the difference in PFS between the two treatment arms in patients with FL, favoring obinutuzumab +chemo followed by obinutuzumab maintenance is statistically significant and clinically important and seems robust. Results from secondary endpoints are consistent with the primary endpoint. OS data in the updated analysis were also consistent with the primary analysis, showing no difference in the effect of G-chemo as compared to R-chemo. The Applicant will provide updated efficacy data including OS data at the time of the final analysis post authorisation.

Obinutuzumab plus chemotherapy induction followed by obinutuzumab maintenance in patients with previously-untreated FL was associated with a tolerable and manageable safety profile. Overall, no unexpected safety signals were detected in study BO21223 or study BO21000.

The final study report from the pivotal study will be provided.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by a majority of 26 out of 27 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of Indication to include a new indication for Gazyvaro in combination with chemotherapy, followed by Gazyvaro maintenance therapy in patients achieving a response, for the treatment of patients with previously untreated advanced follicular lymphoma; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the RMP are updated in accordance. In addition, the due date for provision of the final clinical study report of study BO21223/GALLIUM listed in the Gazyvaro RMP as Category 3 has been updated. Furthermore, the Annex II is brought in line with the latest QRD template (version 10). In addition, clarification or editorial changes to the SmPC are proposed for accuracy and clarity.

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

Divergent position to the majority recommendation is appended to this report.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers, by a majority of 26 out of 27 votes, that the new therapeutic indication brings significant clinical benefit in comparison with existing

therapies (see appendix 1).

5. EPAR changes

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

Scope

Extension of Indication to include a new indication for Gazyvaro in combination with chemotherapy, followed by Gazyvaro maintenance therapy in patients achieving a response, for the treatment of patients with previously untreated advanced follicular lymphoma; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the RMP are updated in accordance. In addition, the due date for provision of the final clinical study report of study BO21223/GALLIUM listed in the Gazyvaro RMP as Category 3 has been updated. Furthermore, the Annex II is brought in line with the latest QRD template (version 10). In addition, clarification or editorial changes to the SmPC are proposed for accuracy and clarity.

Summary

Please refer to the published Assessment Report Gazyvaro H-2799-II-016.