

# Safety and efficacy of obinutuzumab with CHOP or bendamustine in previously untreated follicular lymphoma

Andrew Grigg,<sup>1</sup> Martin J.S. Dyer,<sup>2</sup> Marcos González Díaz,<sup>3</sup> Martin Dreyling,<sup>4</sup> Simon Rule,<sup>5</sup> Guiyuan Lei,<sup>6</sup> Andrea Knapp,<sup>7</sup> Elisabeth Wassner-Fritsch<sup>7</sup> and Paula Marlton<sup>8</sup>

<sup>1</sup>Department of Clinical Haematology, Austin Hospital, Heidelberg, Australia; <sup>2</sup>Ernest and Helen Scott Haematological Research Institute, University of Leicester, UK; <sup>3</sup>Department of Hematology, University Hospital of Salamanca, Spain; <sup>4</sup>Department of Medicine III, LMU, Munich, Germany; <sup>5</sup>Department of Haematology, Derriford Hospital, Plymouth, UK; <sup>6</sup>Roche Products Ltd, Welwyn Garden City, UK; <sup>7</sup>F. Hoffmann-La Roche Ltd, Basel, Switzerland and <sup>8</sup>Department of Haematology, Princess Alexandra Hospital and University of Queensland School of Medicine, Brisbane, Australia



Haematologica 2017  
Volume 102(4):765-772

## ABSTRACT

The GAUDI study assessed safety and preliminary efficacy of induction therapy with obinutuzumab plus chemotherapy, followed by maintenance therapy with obinutuzumab alone, in previously untreated patients with follicular lymphoma. Assignment to chemotherapy was decided on a per-center basis before the patients' enrollment. Patients (n=81) received four to six cycles of obinutuzumab plus bendamustine every 4 weeks or six to eight cycles of obinutuzumab plus CHOP every 3 weeks. Patients with an end-of-treatment response were eligible for obinutuzumab maintenance therapy every 3 months for 2 years or until disease progression. Induction treatment was completed by 90% of patients in the obinutuzumab plus bendamustine group and 95% in the obinutuzumab plus CHOP group, while maintenance was completed by 81% and 72% of patients, respectively. All patients experienced at least one adverse event during induction, most commonly infusion-related reactions (58%), the majority of which were grade 1/2. The most common hematologic adverse event was grade 3/4 neutropenia (36% during induction and 7% during maintenance). One treatment-related death occurred during the maintenance phase. At the end of induction, 94% of patients had achieved an overall response, with complete response based on computed tomography in 36%. The progression-free survival rate at 36 months was 90% in the obinutuzumab plus bendamustine group and 84% in the obinutuzumab plus CHOP group. These results demonstrate that induction therapy with obinutuzumab plus bendamustine or obinutuzumab plus CHOP, followed by obinutuzumab maintenance, is associated with tolerable safety and promising efficacy. This study is registered at ClinicalTrials.gov as NCT00825149.

## Introduction

Chemoimmunotherapy utilizing the type I anti-CD20 monoclonal antibody rituximab is the standard-of-care treatment for advanced follicular lymphoma (FL),<sup>1</sup> with the chemotherapy component generally consisting of bendamustine or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) in the first-line setting.<sup>2</sup> However, as some patients do not respond to treatment, and most will relapse after an initial response,<sup>3</sup> new treatments with improved anti-tumor efficacy are needed.

Obinutuzumab (GA101; G) is a glyco-engineered type II, humanized, anti-CD20 monoclonal antibody that has reduced core fucosylation compared with rituximab.

## Correspondence:

andrew.grigg@austin.org.au

Received: July 11, 2016.

Accepted: December 22, 2016.

Pre-published: December 23, 2016.

doi:10.3324/haematol.2016.152272

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: [www.haematologica.org/content/102/4/765](http://www.haematologica.org/content/102/4/765)

©2017 Ferrata Storti Foundation

Material published in *Haematologica* is covered by copyright. All rights are reserved to the Ferrata Storti Foundation. Use of published material is allowed under the following terms and conditions:

<https://creativecommons.org/licenses/by-nc/4.0/legalcode>.

Copies of published material are allowed for personal or internal use. Sharing published material for non-commercial purposes is subject to the following conditions:

<https://creativecommons.org/licenses/by-nc/4.0/legalcode>, sect. 3. Reproducing and sharing published material for commercial purposes is not allowed without permission in writing from the publisher.



In preclinical studies, obinutuzumab showed increased direct cell death and antibody-dependent cellular cytotoxicity, but reduced complement activation, when compared with rituximab *in vitro* and improved survival in human lymphoma xenograft models *in vivo*.<sup>4,8</sup> In a clinical setting, obinutuzumab monotherapy was well tolerated with promising activity in relapsed or refractory patients with indolent non-Hodgkin lymphoma (NHL), including FL.<sup>9-12</sup>

Obinutuzumab has been investigated in combination with chemotherapy. In the open-label, phase 1b GAUDI study, induction therapy with obinutuzumab plus either CHOP (G-CHOP) or fludarabine and cyclophosphamide (G-FC), followed by obinutuzumab maintenance, was associated with encouraging efficacy and safety outcomes for patients with relapsed or refractory FL.<sup>13,14</sup> The GAUDI study also investigated the safety and efficacy of G-CHOP or obinutuzumab plus bendamustine (G-B) followed by obinutuzumab maintenance in patients with previously untreated FL. Data from the induction phase, and preliminary data from the maintenance phase, for patients receiving first-line treatment showed a safety profile consistent with that reported for the relapsed or refractory subset.<sup>15-16</sup>

This paper presents the final analysis of the subset of previously untreated patients from the open-label, multicenter, phase 1b GAUDI study, the primary aim of which was to establish the safety and efficacy of G-CHOP and G-B induction therapy in patients with previously untreated CD20<sup>+</sup> FL.

## Methods

### Patients

Eligible patients were aged  $\geq 18$  years, had documented CD20<sup>+</sup> FL with no prior systemic therapy, were deemed in need of treatment by the investigator, had  $\geq 1$  bi-dimensionally measurable lesion ( $>1.5$  cm at its largest dimension by computed tomography scan), had a life expectancy  $>12$  weeks, an Eastern Cooperative Oncology Group performance status of 0-2, and no disease transformation based on lymph node biopsy or re-biopsy within 5 months of the start of treatment.

Key exclusion criteria included central nervous system lymphoma, a history of malignancy within 2 years of study entry, and evidence of significant, uncontrolled comorbidities.

All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines, and was approved by the appropriate local ethics committees.

### Treatment

Assignment to chemotherapy regimen was decided on a per-center basis before enrollment. Patients received obinutuzumab [1000 mg intravenously (iv), days 1 and 8 of cycle 1, and day 1 of subsequent cycles] plus bendamustine (4-6 cycles at 4-week intervals: 90 mg/m<sup>2</sup> iv on days 2 and 3 of cycle 1, and days 1 and 2 of subsequent cycles) or CHOP (6-8 cycles at 3-week intervals: cyclophosphamide, 750 mg/m<sup>2</sup> iv day 1; doxorubicin, 50 mg/m<sup>2</sup> iv day 1; vincristine, 1.4 mg/m<sup>2</sup> capped at 2 mg iv day 1; prednisone, 100 mg orally days 1-5). The first obinutuzumab infusion was administered at an initial rate of 50 mg/h escalating to a maximum of 400 mg/h while subsequent infusions were administered at an initial rate of 100 mg/h escalating to the same maximum rate. Patients with a complete response or partial response at the end of induction were eligible for maintenance with obinutuzumab

monotherapy (1000 mg iv) starting 12 weeks after the last chemoimmunotherapy dose and administered every 3 months for 2 years or until disease progression. Details of prophylactic medication and chemotherapy dose modifications are provided in the *Online Supplementary Appendix*.

### Assessments

The primary endpoint was safety of induction treatment for G-B and G-CHOP. Secondary endpoints included overall response rate, complete response rate, progression-free survival, obinutuzumab pharmacokinetics, B-cell depletion and recovery, and safety of obinutuzumab maintenance therapy. Adverse events and serious adverse events were monitored according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Response rates were assessed by computed tomography scan according to the revised response criteria for non-Hodgkin lymphoma.<sup>17</sup> Further details of assessments are provided in the *Online Supplementary Appendix*.

### Statistical analysis

Eighty patients were planned for the safety evaluation. All patients who received  $\geq 1$  dose of G-chemotherapy were eligible for the safety and efficacy analyses. With approximately 40 patients per regimen, there was at least an 80% chance of observing an adverse event with a true incidence  $\geq 4\%$ . The two-sided 95% confidence interval for overall response rate for each regimen was expected to be  $\pm 0.11$  from the observed rate, assuming an expected overall response rate of 0.85 based on data from previous studies of rituximab plus CHOP or bendamustine.<sup>18</sup>

For the efficacy evaluation, response rates and 95% Pearson-Clopper confidence intervals were estimated. Progression-free survival was assessed using Kaplan-Meier methodology.

## Results

### Patients' disposition and baseline characteristics

Eighty-one patients were enrolled between August 2010 and September 2011; 41 were allocated to the G-B group and 40 to the G-CHOP group. Results of the final analysis are presented.

Baseline characteristics, including prognostic indicators as measured by the FL International Prognostic Index (FLIPI) score,<sup>19</sup> are summarized in Table 1. Most patients (91%) had Ann Arbor stage III-IV disease, had an intermediate/high FLIPI score (82%), and had extra-nodal involvement (67%); 43% had bulky disease.

The treatment allocation and study flow are summarized in Figure 1. All patients entered in the study received at least one dose of treatment. During the induction period, 90% of patients in the G-B group completed four cycles of treatment, and 85% received the maximum six cycles. In the G-CHOP group, 95% of patients completed six cycles and 33% received the maximum eight cycles. Due to the protocol design, whereby patients received obinutuzumab in combination with four to six cycles of bendamustine or six to eight cycles of CHOP, the mean cumulative dose of obinutuzumab during induction was lower in the G-B group (6534 mg) than in the G-CHOP group (7271 mg). Fifteen patients in the G-B group received steroid prophylaxis after cycle 1, six of whom had not experienced an infusion-related reaction. Nine patients (G-B, 5; G-CHOP, 4) discontinued the study during induction or completed induction but did not proceed to maintenance for reasons summarized in the legend to Figure 1.

Seventy-two patients started the maintenance phase; 81% of G-B patients and 72% of G-CHOP patients completed the maximum eight cycles of obinutuzumab, with mean cumulative doses for patients who started maintenance of 7222 mg and 6833 mg, respectively. Seventeen patients discontinued maintenance for reasons summarized in the legend to Figure 1; seven patients in the G-B group (19% of patients entering maintenance) and ten patients in the G-CHOP group (28%). Eleven discontinuations occurred during the first to fourth administrations and six during the fifth to eighth administrations.

Overall, 73 patients entered follow-up [G-B, 38 (93%); G-CHOP, 35 (88%)], comprising eight patients who entered post-induction without proceeding to maintenance and 65 patients who entered post-maintenance (55 who completed maintenance and 10 who discontinued maintenance prematurely). Eight patients did not enter follow-up for various reasons, most commonly insufficient therapeutic response (4 patients with progressive disease and 1 with stable disease). At the time of analysis, 14 of the 73 patients had discontinued follow-up, most commonly due to disease progression. The median observation time (time from first drug administration to last date alive) on study was 51 months (range, 0.3-60).

**Safety**

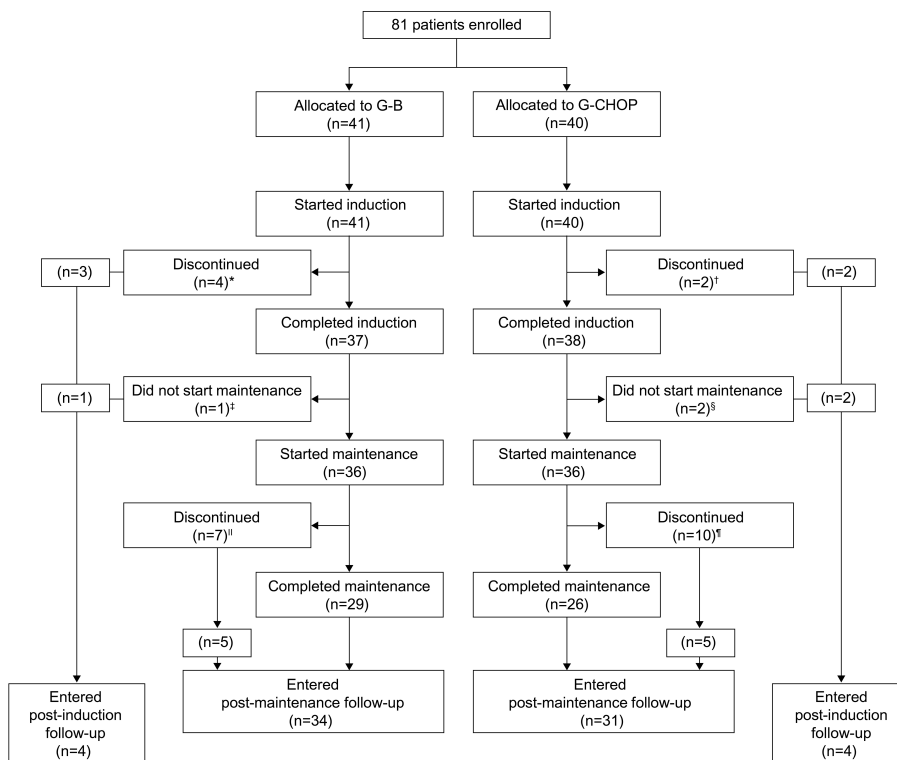
Hematologic adverse events and the most common non-hematologic adverse events by treatment group and phase are shown in Tables 2 and 3, respectively.

**Induction.** All patients experienced at least one adverse event during the induction phase, with 64% (G-B, 51%; G-CHOP, 78%) experiencing grade 3/4 adverse events. Infusion-related reactions were the most common adverse events (occurring in 58% of patients); the majority occurred during cycle 1 and were grade ≤2 in intensity. Dose delays or modifications (including infusion interruptions due to

**Table 1. Patients' baseline demographics and disease characteristics.**

Characteristic	G-B (N=41)	G-CHOP (N=40)	Total (N=81)
Age, years, median (range)	57.0 (34-84)	53.5 (27-74)	55.0 (27-84)
Male, n. (%)	17 (41)	19 (48)	36 (44)
Ann Arbor stage, n. (%)			
I	2 (5)	—	2 (2)
II	3 (7)	2 (5)	5 (6)
III	15 (37)	10 (25)	25 (31)
IV	21 (51)	28 (70)	49 (60)
Bulky disease (≥7 cm), n. (%)			
Yes	17 (41)	18 (45)	35 (43)
No	24 (59)	22 (55)	46 (57)
Bone marrow involvement, n. (%)			
Negative	20 (49)	19 (48)	39 (48)
Positive	19 (46)	21 (53)	40 (49)
Indeterminate	2 (5)	—	2 (2)
FLIPI score, n. (%)			
Low risk (0-1)	8 (20)	7 (18)	15 (19)
Intermediate risk (2)	14 (34)	15 (38)	29 (36)
High risk (3-5)	19 (46)	18 (45)	37 (46)
FLIPI 2* score, n. (%)			
Low risk (0-1)	16 (39)	12 (30)	28 (35)
Intermediate risk (2)	6 (15)	13 (33)	19 (23)
High risk (3-5)	17 (41)	13 (33)	30 (37)
Unknown	2 (5)	2 (5)	4 (5)
Hemoglobin, n. (%)			
<120 g/L	13 (32)	8 (20)	21 (26)
≥120 g/L	28 (68)	32 (80)	60 (74)
Extra-nodal involvement, n. (%)			
Yes	24 (59)	30 (75)	54 (67)
No	17 (41)	10 (25)	27 (33)

\*Analysis of FLIPI 2 scores<sup>28</sup> was not specified in the study protocol and data were calculated retrospectively. FLIPI: Follicular Lymphoma International Prognostic Index; G-B: obinutuzumab plus bendamustine; G-CHOP: obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.



**Figure 1. Disposition of patients in the study.** \*Reasons for discontinuation from G-B induction therapy: insufficient therapeutic response (n=2), administrative/other (n=1), and withdrawal of consent (n=1; this patient did not enter post-induction follow-up). †Reasons for discontinuation from G-CHOP induction therapy: adverse event (AE)/intercurrent illness (n=1) and administrative/other (n=1). ‡Reasons patients did not start G-maintenance treatment (G-B group): AE/intercurrent illness (n=1). §Reasons patients did not start G-maintenance treatment (G-CHOP group): administrative/other (n=2). ¶Reasons for withdrawal from maintenance treatment (G-B group): AE/intercurrent illness (n=5) and insufficient therapeutic response (n=2). ¶Reasons for withdrawal from maintenance treatment (G-CHOP group): AE/intercurrent illness (n=4), insufficient therapeutic response (n=3), administrative/other (n=2), and death (n=1).

**Table 2.** Hematologic adverse events\* occurring in >5% of patients in either group during any treatment phase, n. (%).

G-B	Induction (N=41)		Maintenance (N=36)	
	All grades	Grade 3/4	All grades	Grade 3/4
Total patients with ≥1 AE	16 (39)	15 (37)	8 (22)	6 (17)
Neutropenia	12 (29)	12 (29)	5 (14)	5 (14)
Anemia	3 (7)	3 (7)	3 (8)	1 (3)
Thrombocytopenia	4 (10)	2 (5)	2 (6)	2 (6)
Febrile neutropenia	—	—	1 (3)	1 (3)

G-CHOP	Induction (N=40)		Maintenance (N=36)	
	All grades	Grade 3/4	All grades	Grade 3/4
Total patients with ≥1 AE	23 (58)	22 (55)	—	—
Neutropenia	18 (45)	17 (43)	—	—
Anemia	2 (5)	1 (3)	—	—
Thrombocytopenia	1 (3)	1 (3)	—	—
Febrile neutropenia	4 (10)	4 (10)	—	—

Total	Induction (N=81)		Maintenance (N=72)	
	All grades	Grade 3/4	All grades	Grade 3/4
Total patients with ≥1 AE	39 (48)	37 (46)	8 (11)	6 (8)
Neutropenia	30 (37)	29 (36)	5 (7)	5 (7)
Anemia	5 (6)	4 (5)	3 (4)	1 (1)
Thrombocytopenia	5 (6)	3 (4)	2 (3)	2 (3)
Febrile neutropenia	4 (5)	4 (5)	1 (1)	1 (1)

\*Hematologic adverse events were defined as adverse events in the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class 'Blood and Lymphatic System Disorders'. AE: adverse event; G-B: obinutuzumab plus bendamustine; G-CHOP: obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

infusion-related reactions) were required in 65% of patients (G-B, 59%; G-CHOP, 73%). Fifty patients (G-B, 23; G-CHOP, 27) had 74 (G-B, 33; G-CHOP, 41) dose delays or interruptions of obinutuzumab because of adverse events (no dose reductions were allowed per protocol), most commonly because of infusion-related reactions: 17 patients in the G-B group, and 19 patients in the G-CHOP group. Twenty-nine patients (36% overall: 29% of G-B patients and 43% of G-CHOP patients) had 43 (G-B, 16; G-CHOP, 27) dose delays or modifications to chemotherapy because of adverse events, most commonly neutropenia. Only one patient in the G-CHOP group discontinued induction due to an infusion-related reaction.

The most common grade 3/4 hematologic adverse event was neutropenia, which occurred in 36% of patients (G-B, 29%; G-CHOP, 43%) during induction, although febrile neutropenia was rare (Table 2). Of note, primary granulocyte colony-stimulating factor (G-CSF) prophylaxis was not used in this trial. Neutropenia resolved within 3-33 days from onset in the G-B group and 4-32 days of onset in the G-CHOP group. Three patients had neutropenia unresolved by day 28; in two patients in the G-B group it resolved on days 30 and 33 and in one patient in the G-CHOP group it resolved on day 32. Eight patients in the G-B group and five patients in the G-CHOP group experienced dose delays due to neutropenia. In the G-B group, all 12 patients who experienced grade 3/4 neutropenia subsequently received G-CSF, as did 14 of 17 patients experiencing neutropenia in the G-CHOP group. One patient in the G-CHOP group developed grade 3 thrombocytopenia during cycle 1, which led to a delay in starting cycle 2.

Grade 3/4 non-hematologic adverse events overall were uncommon (Table 3). Grade 3/4 infections occurred in 13 patients (16%), predominantly in the context of neutropenia (9 patients). *P. jirovecii* pneumonia was reported in one patient.

**Table 3.** Non-hematologic adverse events occurring in >15% of patients in either group, % total (% G-B, % G-CHOP).

	All grades	Grade 3/4
Induction [N=81 (G-B, 41; G-CHOP, 40)]		
Infusion-related reaction	58 (59, 58)	7 (10, 5)
Infections and infestations*	58 (54, 63)	16 (10, 23)
Nausea	51 (59, 43)	4 (5, 3)
Fatigue	37 (39, 35)	4 (2, 5)
Headache	32 (34, 30)	1 (0, 3)
Diarrhea	26 (34, 18)	1 (2, 0)
Constipation	26 (20, 33)	—
Cough	23 (22, 25)	1 (0, 3)
Vomiting	20 (17, 23)	1 (0, 3)
Pyrexia	19 (22, 15)	2 (5, 0)
Dyspepsia	15 (12, 18)	1 (0, 3)
Alopecia	11 (2, 20)	—
Mucosal inflammation	10 (2, 18)	—
Maintenance [N=72 (G-B, 36; G-CHOP, 36)]		
Infections and infestations*	65 (72, 58)	15 (17, 14)
Cough	15 (19, 11)	—

\*Reported as Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class 'Infections and Infestations' as adverse events of special interest. G-B: obinutuzumab plus bendamustine; G-CHOP: obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

**Maintenance.** Overall, 27 of 72 eligible patients experienced grade 3-5 adverse events during maintenance. Nine patients withdrew from obinutuzumab treatment due to an adverse event, five in the G-B group (due to giardiasis with anemia, neutropenic infection, flare-up of Crohn disease, nasopharyngitis, and neutropenia in one patient each) and four in the G-CHOP group (3 due to infection and 1 due to peripheral sensory neuropathy). Eight patients (G-B, 6; G-CHOP, 2) had obinutuzumab dose delays or interruptions. The only treatment-related death



**Table 4. Summary of efficacy parameters.**

Variable	G-B (N=41)	G-CHOP (N=40)	Total (N=81)
Overall response rate, % (95% CI)	93 (80.1, 98.5)	95 (83.1, 99.4)	94 (86.2, 98.0)
CR at end of induction, % (95% CI)	37 (22.1, 53.1)	35 (20.6, 51.7)	36 (25.4, 47.2)
CR at 30 months, % (95% CI)	63 (46.0, 78.2)	58 (40.8, 74.5)	61 (NA, NA)
PFS at 36 months, % (95% CI)	90 (0.80, 0.99)	84 (0.72, 0.96)	87 (0.79, 0.94)
Progression/death (n)	6	11	17
Deaths due to progressive disease (n)	1	2	3

CI: confidence interval; CR: complete response; G-B: obinutuzumab plus bendamustine; G-CHOP: obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; NA: not analyzed; PFS: progression-free survival.

occurred in a patient in the G-CHOP group, 59 days after the only dose of maintenance treatment, due to lactic acidosis in the context of an underlying respiratory infection (pathogen not identified) in the absence of neutropenia.

The most common class of non-hematologic adverse events was infections, with 11 patients (G-B, 6; G-CHOP, 5) experiencing a variety of grade 3 infections and one patient in the G-B group having a grade 4 neutropenic infection. No further cases of *P. jirovecii* pneumonia were reported during maintenance.

Eight patients experienced hematologic adverse events during maintenance, all in the G-B group (Table 2); it should be noted that blood tests were only mandatory prior to each 3-monthly cycle. Six patients (8%) developed grade 3/4 neutropenia (n=5) or febrile neutropenia (n=1), noted 81-91 days after the last dose of obinutuzumab. The duration of neutropenia was highly variable, ranging from 4 days to more than 265 days, remaining unresolved at the last follow-up at 265 days in one patient. Only two patients experienced febrile/infective complications. Three patients with prompt resolution of neutropenia (of 4, 8, and 22 days duration after 5, 1, and 2 doses of maintenance, respectively) were re-challenged following response to G-CSF (n=2) or spontaneous resolution (n=1) and went on to complete eight cycles of maintenance without further neutropenia or G-CSF. The other three patients had prolonged neutropenia of 85-265 days' duration; of these, one completed maintenance and two discontinued therapy.

G-CSF was used variably in these patients with neutropenia. Two patients did not receive G-CSF. One with grade 4 neutropenia after the first maintenance dose recovered (white cell count  $\geq 1 \times 10^9$  cells/L) within 8 days and resumed maintenance. The other patient with grade 3 neutropenia after the seventh dose of maintenance received the eighth and final dose of maintenance after improvement to grade 1 but subsequently had ongoing grade 3 neutropenia that had not resolved at 265 days; a marrow biopsy was not performed.

The other four patients in this group received G-CSF. As mentioned, two responded quickly and resumed maintenance. A third developed grade 4 neutropenia after the fifth dose of maintenance, received G-CSF for 3 days without effect and remained persistently neutropenic (white cell count ranging from  $0.24-0.8 \times 10^9$  cells/L) until recovery ( $3.9 \times 10^9$  cells/L) 8 months after onset; a marrow biopsy was not performed. The fourth patient withdrew from the study 3 months after the first maintenance dose due to a late-onset neutropenic infection. Grade 4 neu-

tropenia and febrile neutropenia were recurrent in this patient over an 8-month period with seven discrete episodes (1 of febrile neutropenia) lasting from 9-21 days despite ongoing titrated G-CSF therapy. These were associated with grade 2-4 thrombocytopenia on several occasions. Bone marrow examinations during four of the episodes (this was the only patient in the group who had a bone marrow examination for investigation of neutropenia) all showed similar findings with maturation arrest of the myeloid series, adequate megakaryopoiesis and no evidence of lymphoma. Prednisolone therapy was instituted at 8 months and neutropenia resolved; maintenance G-CSF was slowly weaned and stopped 15 months after initial onset of the neutropenia with no further recurrence after 33 months of subsequent follow up.

**Follow-up.** No serious adverse events were observed in the eight patients who entered follow-up directly after induction. Three patients experienced serious adverse events during post-maintenance follow-up. In the G-B group, one patient had lower abdominal pain (grade 3); in the G-CHOP group, one patient had an abnormal liver function test (grade 4) and one had dyspnea (grade 3).

Blood tests were conducted every 3 months during follow-up. One of 38 evaluable G-B patients experienced grade 3 neutropenia during follow-up 6 months after completing maintenance. Spontaneous recovery was recorded after 85 days and no further neutropenic events were recorded at the 12-month follow-up.

### Efficacy

The overall response rate was 94% at the end of induction and the complete response rate was 37% at the end of induction and 61% at 30 months (Table 4). The estimated progression-free survival rate at 36 months was 87% (Figure 2). At the final analysis, 17 events defining progression/death had occurred in 81 patients: one event (progression) occurred during induction, six during maintenance (5 progression and 1 death, including one patient in the G-CHOP group with transformation to diffuse large B-cell lymphoma), and ten after maintenance. A summary of efficacy parameters by study group is presented in Table 4.

### Pharmacokinetics

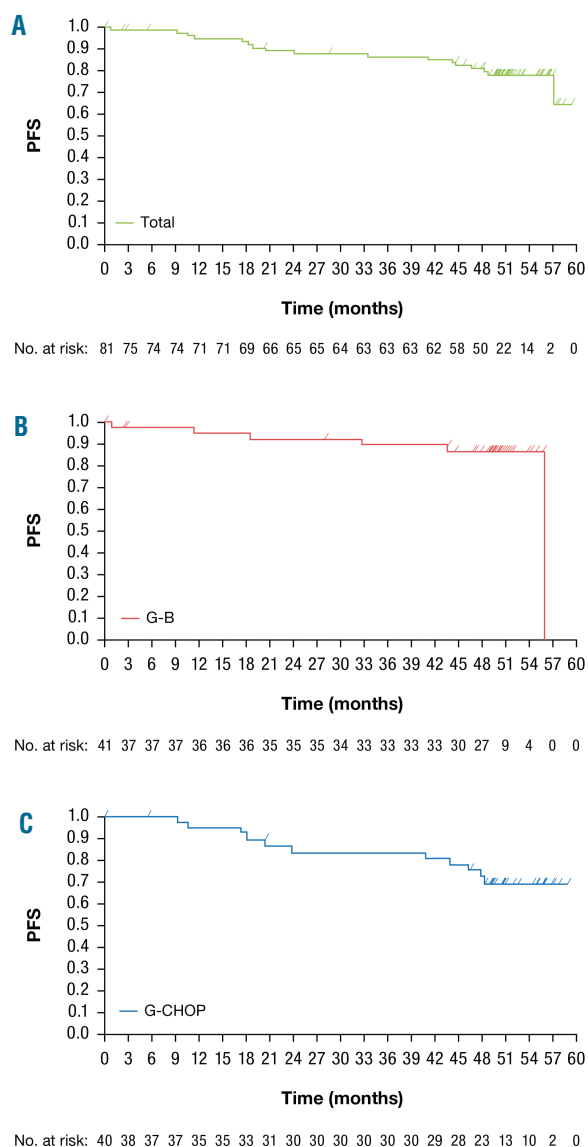
Patients in both treatment groups had similar mean serum concentrations of obinutuzumab during induction and maintenance, with a similar half-life observed for both treatments (G-B, 37.3 days; G-CHOP, 35.5 days; Figure 3).  $C_{max}$  and  $C_{min}$  values increased over the induction period.

## Pharmacodynamics

B-cell levels decreased rapidly in both treatment groups following the first obinutuzumab infusion, with all patients showing B-cell depletion throughout the treatment period (Figure 4). The majority of patients remained depleted throughout follow-up. The median time from end of treatment to B-cell recovery was 24 months for the G-B group and 29 months for the G-CHOP group.

Median levels of T cells and natural killer cells were reduced after the first cycle and were low throughout induction treatment, with full recovery to baseline levels during maintenance or follow-up. By day 28 of follow-up, levels of CD3<sup>+</sup>, CD4<sup>+</sup>, CD8<sup>+</sup>, and CD16<sup>+</sup>/56<sup>+</sup> cells had recovered to 59%, 42%, 78%, and 44% of baseline levels, respectively.

Median IgG levels fell from a baseline of 8.3 g/L (normal range, 5-12 g/L) to 7.54 g/L after the end of induction, but



**Figure 2. Progression-free survival.** Progression-free survival (PFS) for (A) the total study population, the (B) G-B group, and (C) the G-CHOP group. G-B: obinutuzumab plus bendamustine; G-CHOP: obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

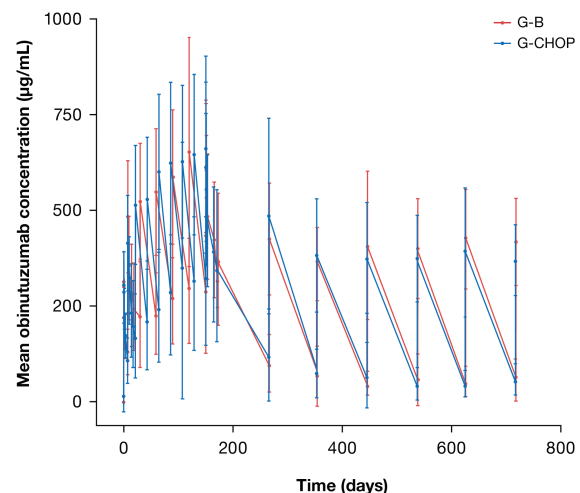
remained within the normal range and steady thereafter to the end of maintenance [6.95 g/L (based on 66 patients)] and during follow-up [6.76 g/L at 60 weeks of follow-up (49 patients) and 6.5 g/L at 122 weeks (31 patients)]. One patient had hypogammaglobulinemia of IgG (lowest value, 2.74 g/L) during follow-up without clinical consequences and was treated monthly with gammaglobulins until recovery at 28 months after onset. Median levels of IgA and IgM were decreased compared with baseline during the induction phase and remained so throughout maintenance; median levels generally remained within the normal range for IgA (0.5-3.5 g/L) and IgM (0.3-2.3 g/L).

## Discussion

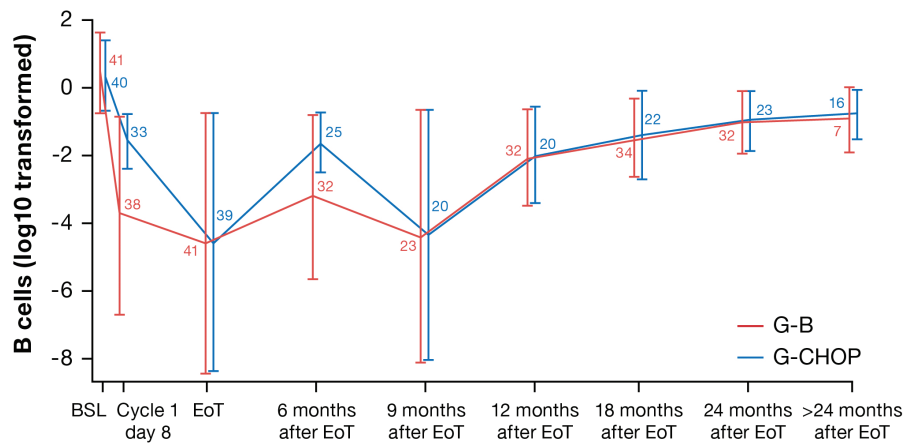
The results of this study in patients with previously untreated FL demonstrate that induction therapy with G-B or G-CHOP followed by obinutuzumab maintenance is associated with a tolerable safety profile and promising efficacy. The decision to start therapy was at the discretion of the investigator, although as 60% of patients with an assessable FLIPI 2 score had intermediate-high risk disease, 43% of patients had bulky disease (>7.5cm), 91% had Ann Arbor stage III-IV, and 67% had extranodal disease, the study population is likely to represent a cohort in which therapy was justified.

The majority of patients completed the minimum number of prescribed cycles of G-chemotherapy. There were no new safety signals compared with previous studies of G-monotherapy<sup>9,10,12</sup> or G-chemotherapy (G-CHOP or G-FC) followed by G-maintenance<sup>14</sup> in relapsed or refractory FL. Seventy-six percent of patients (55 of 72 who started maintenance) completed the treatment course. Non-hematologic adverse events were mostly grade 1/2. One death, due to non-neutropenic sepsis, occurred during the study.

The most common toxicity was infusion-related reactions in cycle 1, which were generally low grade and at a rate consistent with or lower than in previous studies of



**Figure 3. Mean serum concentration of obinutuzumab throughout the induction and maintenance periods.** G-B: obinutuzumab plus bendamustine; G-CHOP: obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.



**Figure 4. B-cell levels throughout the induction and maintenance periods.** BSL: baseline; EoT: end of treatment; G-B: obinutuzumab plus bendamustine; G-CHOP: obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

obinutuzumab in relapsed or refractory indolent NHL.<sup>9,10,12,14</sup> In particular, the rate of grade 3/4 infusion-related reactions (7%) compares favorably with the rate of 21% in the currently indicated use of obinutuzumab in combination with chlorambucil for chronic lymphocytic leukemia.<sup>20</sup>

Grade 3/4 neutropenia was experienced by 36% of patients (29% of G-B patients and 43% of G-CHOP patients) during induction. In previous studies of patients with indolent NHL receiving induction treatment of rituximab with bendamustine or CHOP, grade 3/4 neutropenia occurred in 29% to 49% of patients given rituximab plus bendamustine and in 69% to 87% of those given rituximab plus CHOP.<sup>2,21</sup> The incidence of febrile neutropenia and grade 3/4 infections during induction was modest (5% and 16%, respectively).

Grade 3/4 neutropenia was also documented in seven G-B patients, but no G-CHOP patients, during the maintenance phase (n=6) or follow-up (n=1) indicating a potential increase in susceptibility to neutropenia with this combination, although febrile neutropenia only occurred in one of these patients. As neutropenia was monitored only by routine blood tests every 3 months, the incidence and timing of onset is unclear. Delayed onset neutropenia, occurring more than 1 month after the last antibody administration, is a well-recognized complication of rituximab therapy with an incidence of 8% to 25%, and is often associated with myeloid maturation arrest on bone marrow examination as observed in one patient who underwent a marrow investigation in this context.<sup>22-24</sup> Neutropenia resolved quickly in three patients; however, in the other four, the neutropenia lasted from 85 days to more than 8 months with variable responses to G-CSF. Additional data from ongoing trials are awaited to examine further the incidence, clinical significance and natural history of neutropenia in this context.

In this study complete response was defined by com-

puted tomography findings, which in FL can be difficult to interpret in the short term and may give lower complete response rates than with assessment based on positron emission tomography.<sup>25</sup> With this caveat, the complete response rate at 30 months was 61% and was substantially higher after obinutuzumab maintenance than after induction; whether this represents the natural history of nodal regression in FL after therapy or a true anti-lymphoma effect of maintenance is impossible to determine in the absence of prospective randomized data.

The progression-free rate at 36 months was 87%. Comparison of these results with those from similar studies of rituximab-chemotherapy induction followed by rituximab maintenance (the progression-free survival at 36 months in the PRIMA study was 75%) are not strictly valid as study populations may differ,<sup>26,27</sup> however, the impression from this study is that obinutuzumab-chemotherapy is unlikely to be inferior.

Based on the clinical potential seen for obinutuzumab in this and other phase 1 and 2 studies, the confirmatory phase 3 GALLIUM study is ongoing, comparing obinutuzumab plus chemotherapy with rituximab plus chemotherapy, followed by immunotherapy maintenance with obinutuzumab or rituximab, respectively, in previously untreated patients with indolent NHL (NCT01332968).

#### Acknowledgments

Research support for this study was provided by F. Hoffmann-La Roche Ltd. The authors would like to thank the patients and their families, and the study investigators, study coordinators, and nurses who assisted with the obinutuzumab clinical program. This study was sponsored by F. Hoffmann-La Roche Ltd. Medical writing support, under the direction of the lead author, was provided by Susan Browne, PhD, Gardiner-Caldwell Communications (Macclesfield, UK). Support for third-party writing assistance was provided by F. Hoffmann-La Roche Ltd.

#### References

1. Dreyling M, Ghielmini M, Marcus R, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2014;25(Suppl 3):iii76-iii82.
2. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet.* 2013;381(9873):1203-1210.
3. Keating GM. Rituximab: a review of its use in chronic lymphocytic leukaemia, low-grade or follicular lymphoma and diffuse large B-cell lymphoma. *Drugs.* 2010;70(11):1445-1476.
4. Glennie MJ, French RR, Cragg MS, Taylor

- RP. Mechanisms of killing by anti-CD20 monoclonal antibodies. *Mol Immunol.* 2007;44(16):3823-3837.
5. Heinrich DA, Weinkauff M, Hutter G, et al. Differential regulation patterns of the anti-CD20 antibodies obinutuzumab and rituximab in mantle cell lymphoma. *Br J Haematol.* 2015;168(4):606-610.
  6. Herter S, Herting F, Mundigl O, et al. Preclinical activity of the type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab in vitro and in xenograft models. *Mol Cancer Ther.* 2013;12(10):2031-2042.
  7. Herting F, Friess T, Bader S, et al. Enhanced anti-tumor activity of the glycoengineered type II CD20 antibody obinutuzumab (GA101) in combination with chemotherapy in xenograft models of human lymphoma. *Leuk Lymphoma.* 2014;55(9):2151-2160.
  8. Mössner E, Brünker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. *Blood.* 2010;115(22):4393-4402.
  9. Salles G, Morschhauser F, Lamy T, et al. Phase 1 study results of the type II glycoengineered humanized anti-CD20 monoclonal antibody obinutuzumab (GA101) in B-cell lymphoma patients. *Blood.* 2012;119(22):5126-5132.
  10. Salles GA, Morschhauser F, Solal-Céligny P, et al. Obinutuzumab (GA101) in patients with relapsed/refractory indolent non-Hodgkin lymphoma: results from the phase II GAUGUIN study. *J Clin Oncol.* 2013;31(23):2920-2926.
  11. Sehn LH, Assouline SE, Stewart DA, et al. A phase 1 study of obinutuzumab induction followed by 2 years of maintenance in patients with relapsed CD20-positive B-cell malignancies. *Blood.* 2012;119(22):5118-5125.
  12. Sehn LH, Goy A, Offner FC, et al. Randomized phase II trial comparing obinutuzumab (GA101) with rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin lymphoma: final analysis of the GAUSS study. *J Clin Oncol.* 2015;33(30):3467-3474.
  13. Davies A, Radford J, Cartron G, et al. Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: final data from the maintenance phase of the phase 1b GAUDI study (BO21000). *Blood.* 2013;122(21):1814.
  14. Radford J, Davies A, Cartron G, et al. Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000). *Blood.* 2013;122(7):1137-1143.
  15. Dyer MJ, Grigg A, González Díaz M, et al. Obinutuzumab (GA101) in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or bendamustine in patients with previously untreated follicular lymphoma (FL): results of the phase 1b GAUDI study (BO21000). *Blood.* 2012;120(21):3686.
  16. Dyer MJ, Grigg A, González Díaz M, et al. Obinutuzumab (GA101) in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or bendamustine for the first-line treatment of follicular non-Hodgkin lymphoma: final results from the maintenance phase of the phase 1b GAUDI study. *Blood.* 2014;124(21):1743.
  17. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007;25(5):579-586.
  18. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood.* 2005;106(12):3725-3732.
  19. Solal-Céligny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood.* 2004;104(5):1258-1265.
  20. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med.* 2014;370(12):1101-1110.
  21. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood.* 2014;123(19):2944-2952.
  22. Voog E, Morschhauser F, Solal-Céligny P. Neutropenia in patients treated with rituximab. *N Engl J Med.* 2003;348(26):2691-2694.
  23. Nitta E, Izutsu K, Sato T, et al. A high incidence of late-onset neutropenia following rituximab-containing chemotherapy as a primary treatment of CD20-positive B-cell lymphoma: a single-institution study. *Ann Oncol.* 2007;18(2):364-369.
  24. Lemieux B, Tartas S, Traulle C, et al. Rituximab-related late-onset neutropenia after autologous stem cell transplantation for aggressive non-Hodgkin's lymphoma. *Bone Marrow Transplant.* 2004;33(9):921-923.
  25. Trotman J, Luminari S, Boussetta S, et al. Prognostic value of PET-CT after first-line therapy in patients with follicular lymphoma: a pooled analysis of central scan review in three multicentre studies. *Lancet Haematol.* 2014;1(1):e17-e27.
  26. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet.* 2011;377(9759):42-51.
  27. Morschhauser F, Seymour J, Feugier P, et al. Impact of induction chemotherapy regimen on response, safety and outcome in the PRIMA study. *Ann Oncol.* 2011;22(Suppl 4):89.
  28. Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. *J Clin Oncol.* 2009;27(27):4555-4562.