

**ARZERRA™ (OFATUMUMAB) INJECTION
FOR INTRAVENOUS USE**

**FDA ONCOLOGIC DRUGS ADVISORY COMMITTEE
BRIEFING DOCUMENT**

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ABBREVIATIONS

AA	accelerated approval
ADCC	antibody dependent cell-mediated cytotoxicity
AE	adverse event
AUC	area under the concentration curve
BSA	body surface area
BFR	bulky fludarabine refractory
CDC	complement dependent cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisolone
CI	confidence interval
CLL	chronic lymphocytic leukemia
CL	clearance
C _{min}	minimum observed concentration
C _{max}	maximum observed concentration
COPD	chronic obstructive pulmonary disease
CR	complete remission
CRF	case report form
CT	computerized tomography
DLBCL	diffuse large B cell lymphoma
DMC	data monitoring committee
DLT	dose limiting toxicity
DR	double refractory
ECOG	Eastern Cooperative Oncology Group
FAS	full analysis set
FC	fludarabine + cyclophosphamide
FCR	fludarabine + cyclophosphamide + rituximab
FDA	Food and Drug Administration
FL	follicular lymphoma
HAHA	human anti-human antibodies
IgG	immunoglobulin G
IRC	independent review committee
MTD	maximum tolerated dose
NCI CTC	National Cancer Institute Common Toxicity Criteria
NCIWG	National Cancer Institute Working Group
NE	not evaluable
NHL	non-Hodgkin's lymphoma
nPR	nodular partial remission
PD	progressive disease
PFS	progression-free survival
PML	progressive multifocal leukoencephalopathy
PR	partial remission
PRCA	pure red cell aplasia
OS	overall survival
RA	rheumatoid arthritis
RR	response rate
SAE	serious adverse event
SD	stable disease

SPD	sum of the product of diameters
SOC	system organ class
$t_{1/2}$	terminal phase half-life
Tmax	time observed maximum concentration
Vss	volume of distribution at steady state

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EXECUTIVE SUMMARY

Introduction

GSK has submitted a Biologics License Application (BLA) to the FDA under the provisions of accelerated approval in 21 CFR 601.40 and 21 CFR 601.41 for approval of ofatumumab (ARZERRA) for the treatment of patients with chronic lymphocytic leukemia (CLL). The Sponsor and FDA are negotiating an indication statement for ARZERRA in the treatment of chronic lymphocytic leukemia (CLL) under the provisions of accelerated approval based on studies that have investigated response rate, a surrogate endpoint for clinical benefit.

This BLA is based on data from a pre-planned interim analysis of an ongoing, single-arm, two cohort study, Hx-CD20-406, of ofatumumab monotherapy with 154 CLL subjects who were either refractory to both fludarabine and alemtuzumab (double refractory, DR), or had bulky (at least 1 lymph node >5cm) fludarabine refractory disease (BFR) for whom alemtuzumab is considered less effective.

Ofatumumab is a unique human IgG1 monoclonal antibody that targets a distinct small loop epitope on the CD20 molecule. It binds CD20 relatively tightly and has a reduced off rate compared to rituximab. The mechanisms of actions of ofatumumab include complement dependent cytotoxicity (CDC) and antibody dependent cell-mediated cytotoxicity (ADCC). Ofatumumab has the ability to lyse CD20-expressing cells *in vitro* more efficiently than rituximab, especially in cells with a relatively low CD20 expression (such as CLL) and in cells expressing high levels of complement-regulatory proteins. *In vitro* studies further showed that it induced efficient killing of a panel of patient CLL tumor cells by CDC. These specifications led to a clinical development plan for ofatumumab in CLL.

Patients with fludarabine refractory CLL have poor survival (6-14 months) [Keating, 2002a, Tam, 2007]. Current salvage therapies have limited efficacy and substantial toxicities with response rates of approximately 25%, up to 60% major infections and a 16% rate of early death. In the Hx-CD20-406 study, 51% of subjects responded to ofatumumab monotherapy. The responses occurred quickly, were of clinically meaningful duration and consistent across important subgroups. The safety profile was favourable, with a lower rate of infection and early death reported with other salvage therapies. These results demonstrate a substantial improvement when viewed in the context of current therapies available for treating this stage of the disease. In order to confirm these findings under accelerated approval requirements, randomized phase III studies with ofatumumab and survival endpoint measures in frontline and relapsed CLL are ongoing. Based on the results of Hx-CD20-406, it is suggested that ofatumumab is given strong consideration for marketing authorization under accelerated approval regulations in order to make this new treatment option available to patients with refractory CLL.

Refractory CLL Patients Need New Treatment Options

Chronic lymphocytic leukemia is the most common leukemia in the United States. It is a B cell neoplasm characterized by the accumulation of circulating CD5, CD20, and CD23 positive lymphocytes, causing constitutional symptoms (fevers, chills, night sweats, weight loss), generalized lymphadenopathy, hepatosplenomegaly, cytopenias, and increased risk of infection from immunosuppression [Kay, 2002]. Median age at diagnosis is 65-70 years, and the median survival ranges from 5-20+ years depending on risk factors. As the disease progresses and patients become refractory to available therapies, the median survival is approximately 6-14 months [Keating, 2002a, Tam, 2007].

No therapy has been shown to cure CLL, so the treatment objectives are disease and symptom control. Advanced age, more than 2 prior therapies, and the presence of chromosomal abnormalities such as 17p and 11q deletions are associated with decreased response to therapy and reduced survival [Wierda, 2005, Döhner, 2000]. Infections secondary to the complications of the disease and/or treatment are the leading cause of death in this patient population.

There are currently four drugs approved for use in CLL: the alkylating agents chlorambucil and bendamustine, the purine analogue fludarabine and the anti-CD52 monoclonal antibody alemtuzumab. Chlorambucil and bendamustine induce remissions for 1-2 years as first line therapies, but relapses almost always occur [Catovsky, 2007; TREANDA prescribing information]. In subsequent lines of therapy, alkylating agents have limited efficacy and substantial chemotherapy-related toxicities [Rai, 2000, Bergmann, 2005; Aivado, 2002; Kath, 2001]. The purine analog fludarabine is superior to alkylators in the frontline setting [Catovsky, 2007].

Patients refractory to fludarabine have low response rates (25%) and a median overall survival of less than 12 months with salvage regimens [Keating, 2002a]. Alemtuzumab induces responses (33%) in fludarabine refractory CLL; however, infectious complications (19% opportunistic, 13% fatal) are problematic and limit its use [Keating, 2002b]. The anti-CD20 monoclonal antibody rituximab, although not approved for use in CLL, is being used in combination with chemotherapy, but has limited efficacy (20-25% response rate) as monotherapy, even at doses up to 2,250mg/m² [Hallek, 2008, Robak, 2008, Huhn, 2001, O'Brien, 2001a].

Patients refractory to both fludarabine and alemtuzumab (double refractory (DR)) have low responses rates (20%) and substantial toxicities (60% major infections, 16% early deaths), leading to poor survival (median 8 months) with salvage therapies [Tam, 2007]. Alemtuzumab is less effective (8-12% response rate) in patients with bulky (at least 1 lymph node > 5cm) fludarabine refractory (BFR) CLL [Keating, 2002a; Moreton, 2005, Fiegl, 2006]. Other salvage therapies in BFR patients also have low response rates (26%), and substantial toxicities (45% major infections, 10% early deaths) with a 14 month median survival [Tam, 2007].

Based on these findings, better treatment options for fludarabine refractory patients are needed.

Efficacy and Safety of Ofatumumab

Pivotal Study Hx-CD20-406

In the single arm, multi-center, open-label study Hx-CD20-406, subjects with either DR or BFR CLL received ofatumumab monotherapy (initial dose of 300 mg, followed one week later by 2000 mg once weekly for seven infusions, followed 5 weeks later by 2000 mg once every 4 weeks for 4 infusions, for a total of 12 intravenous infusions over a 24 week treatment period). Subjects were assessed for the primary endpoint of response by an Independent Endpoints Review Committee (IRC), and followed for duration of response and safety for up to 48 months. Response rate (RR) was assessed according to the National Cancer Institute Working Group (NCIWG) 1996 CLL guidelines for response which incorporates improvements in clinical symptoms, reduction in tumor size by physical examination, and improvements in objective hematological parameters.

An independent Data Monitoring Committee (DMC) reviewed the IRC-assessed primary endpoint of response data from 154 subjects as of 19 May 2008. This pre-planned interim analysis included data from 59 subjects in the DR group and 79 subjects in the BFR group: 16 subjects not categorized by the IRC as DR or BFR were not included in the efficacy analysis but were included in the safety analysis. Based upon the 58% and 47% response rates reported for the DR and BFR groups, the DMC informed the sponsor that the pre-defined criteria of observing response rates that exceeded 15% at the 1% significance level had been achieved in both groups.

Baseline Characteristics: Study Hx-CD20-406

Subjects (median age 64 years DR, 62 years BFR) had baseline characteristics of advanced and treatment refractory CLL (Rai stage III/IV: 54% DR, 70% BFR, Binet stage B or C: 90% DR, 95% BFR). They had received a median of 5 (DR) or 4 (BFR) prior regimens, approximately 50% were treated with prior rituximab-based therapy. Most subjects had chromosomal abnormalities (83% DR, 75% BFR), including 17p (30% DR, 18% BFR) and 11q (42% DR, 28% BFR) deletions.

Efficacy: Study Hx-CD20-406

In the fludarabine refractory CLL population with many adverse prognostic risk factors, 51% of subjects responded to ofatumumab monotherapy. The responses were of clinically meaningful duration and consistent across both the DR and BFR groups.

Efficacy Endpoint	DR N=59	BFR N=79	Combined DR+BFR N=138
Primary Endpoint			
RR, % (99% CI)	58 (40, 74)	47 (32, 62)	51 (40, 63)
Secondary Endpoints	Median duration, months		
Duration of Response	7.1	5.6	5.6
Progression Free Survival	5.7	5.9	5.7
Overall Survival	13.7	15.4	15.4

The 47-58% response rates and 5.6-7.1 month median duration of response are clinically meaningful in the context of the 20-26% response rates and 2-3 month median time to progression with available salvage therapies reported in the literature for similar refractory CLL populations [Tam, 2007]. The response rate will remain clinically meaningful even if no further responses in this ongoing study would occur. The full study aims to recruit 100 subjects in each of the pre-specified subgroups. The response rates for each group (100 subjects each) at the end of the study would still be at least 34% as a point estimate, and the lower boundary would exceed 15% at the 1% significance level at the final analysis.

A post-hoc landmark analysis of survival at 12 weeks showed a significant improvement in median overall survival amongst responders vs. non-responders (median survival not reached vs. 9.8 – 10.2 months) in both the DR and BFR groups.

The consistent response rates between the DR and BFR populations demonstrate independent corroboration of the treatment effect of ofatumumab. Responses were also consistent when analyzed by the individual components of the NCIWG 1996 CLL response criteria. Importantly, responses were observed in subjects with poor prognostic indicators such as advanced age and 17p and 11q chromosome deletions, as well as in subjects with prior rituximab-containing therapies.

Comparison of RR by Subgroup	DR N=59	BFR N=79	Combined DR+BFR N=138
RR, n (%)	34 (58)	37 (47)	71 (51)
Age, responders (%)			
≥65 years	14/27 (52)	15/33 (45)	29/60 (48)
≥70 years	6/10 (60)	8/19 (42)	14/29 (48)
Prior Therapeutic regimen, responders (%)			
Prior rituximab	19/35 (54)	19/43 (44)	38/78 (49)
No prior rituximab	15/24 (63)	18/36 (50)	33/60 (55)
Prior FCR ^a	8/16 (50)	7/16 (44)	15/32 (47)
No prior FCR ^a	26/43 (60)	30/63 (48)	56/106 (53)
Chromosomal Abnormalities, responders (%)			
17p deletion	7/17 (41)	2/14 (14)	9/31 (29)
11q deletion	15/24 (63)	14/22 (64)	29/46 (63)

a. FCR = fludarabine+cyclophosphamide+rituximab

Safety: Study Hx-CD20-406

Ofatumumab was well tolerated in this refractory population with no unexpected safety concerns identified. Non-serious adverse events (AEs) were expected and/or common in this subject population with infections, infusion reactions, and hematologic abnormalities being the most common AEs reported. AEs leading to withdrawal from treatment occurred in 14% of subjects. Fatal AEs occurred in 16% of subjects. Infections and infusion reactions were mostly mild to moderate. Anemia, neutropenia and

thrombocytopenia were also observed, but the median hematologic values remained within the normal range (neutrophil count) or increased (hemoglobin and platelet counts) during treatment in subjects with data available up to 52 weeks.

A total of 90% of 154 subjects received all 8 weekly doses, and 55% of subjects completed treatment with 12 doses of ofatumumab over 24 weeks. The most common causes for withdrawal from study treatment were infections (11 subjects) and progressive disease (4 subjects).

Almost all subjects (95%) experienced at least one adverse event, mostly mild to moderate infections, infusion reactions or hematologic abnormalities. The most common AEs were pyrexia (20%), cough (19%), diarrhea (18%), pneumonia (16%), neutropenia (16%), anemia (16%), and fatigue (15%).

Adverse Events during treatment and follow-up	Hx-CD20-406 N=154
Any AE, n (%)	146 (95)
Drug-related AEs, n (%)	98 (64)
All SAEs, n (%)	82 (53)
Drug-related SAEs, n (%)	25 (16)
Fatal (Grade 5) SAEs, n (%)	24 (16)
All AEs leading to withdrawal from treatment, n (%)	22 (14) ^a

a. 5 additional subjects had disease progression listed as the AE that resulted in discontinuation

Serious adverse events (SAEs) were reported by 82 subjects (53%) during treatment or follow up, with lower respiratory infections as the most common events (16%), followed by septic complications (2%).

As of the data cut-off date, 61 subjects had died. The majority of deaths (66%) occurred more than 60 days after last dose of ofatumumab, mostly due to disease progression or infections. Early deaths (within 8 weeks of initiation of treatment) occurred in 6 subjects.

Adverse Events of Interest during treatment and follow-up	Hx-CD20-406 N=154
Any Infection	108 (70)
Grade 3 or 4 Infection	39 (25)
Fatal Infection	16 (10)
Infusion Reaction at any time	99 (64)
Grade 3 or 4 infusion reaction	9 (6)
Grade 3 or 4 Neutropenia	19 (12)

Infections were mostly mild to moderate. The majority of Grade 3 or 4 infections occurred in subjects with baseline neutropenia. Major infections, defined as infections leading to hospitalization for >48 hours during or within 4 weeks of treatment, occurred in 28% of subjects. Higher major infection rates (54%) and fatal infection rates (13-49%) have been reported with available salvage therapies in similar patient populations [Perkins, 2002; Tam, 2007].

Infusion reactions were most common with the first infusion, occurring in 41% of subjects with the 1st infusion, 25% of subjects with the 2nd infusion, and declined further to 6% of subjects with the 12th infusion. One subject withdrew from treatment due to infusion reactions and no fatal infusion reactions were reported.

Grade 3 or 4 neutropenia (12%), anemia (5%) and thrombocytopenia (1%) were reported. However, in contrast to what would be expected with chemotherapy based salvage therapies, the median hemoglobin and platelet counts increased during treatment with ofatumumab in the patient population that completed the 24 week treatment protocol. The median neutrophil counts decreased during the initial weekly treatment period but remained above the lower limit of normal during the study.

As of the data cut-off date of 19 May 2008, no cases of tumor lysis syndrome or severe or fatal cases of mucocutaneous reactions were reported.

Ofatumumab Demonstrates Benefits over Available Therapies: A New Treatment Option for CLL Patients

Patients with CLL refractory to fludarabine and alemtuzumab, and patients with bulky-fludarabine-refractory disease need new therapeutic options since current therapies have poor efficacy and a high incidence of treatment or disease related side effects.

Compared to the 20-26% response rate and 2-3 month time-to-progression with current salvage therapy options for DR or BFR CLL refractory patients, the 47-58% response rate and 5.6-7.1 month median duration of response of ofatumumab indicate better efficacy over existing therapies, and are likely predictive of clinical benefit. This is supported by the significantly longer median overall survival amongst responders versus non-responders in the 12 week landmark analysis of overall survival. Randomized phase III ofatumumab trials with survival endpoints in both the frontline and relapsed CLL are ongoing.

The safety data in subjects from pivotal study Hx-CD20-406 and from the cumulative safety experience demonstrates that ofatumumab treatment has an acceptable safety profile. As stated above, severe and fatal infections are common and the most frequent cause of death in fludarabine refractory patients. The 28% incidence of major infections and 4% incidence of early deaths reported in Hx-CD20-406 should be evaluated in the context of the 45% incidence of major infections and 13% incidence of early deaths with existing therapies [Tam, 2007]. The 25% incidence of Grade 3-4 infections, 6% incidence of Grade 3 infusion reactions (none fatal), and 12% Grade 3-4 neutropenia with ofatumumab monotherapy appear favorable in the context of the 37% incidence of Grade 3-4 infections, 16% incidence of Grade 3-4 infusion-related rigors, and 70% incidence of Grade 3-4 neutropenia reported with alemtuzumab monoclonal antibody therapy in CLL patients who have received prior therapy [CAMPATH prescribing information].

The benefit to risk profile of ofatumumab demonstrates a substantial improvement when viewed in the context of current therapies available for treating the refractory CLL population with a very poor prognosis. Ofatumumab treatment offers a new treatment option for patients with fludarabine refractory CLL.

1. NEED FOR NEW THERAPIES IN CLL

1.1. B Cell Chronic Lymphocytic Leukemia

B cell chronic lymphocytic leukemia is a subtype of mature peripheral B cell neoplasms, characterized by the accumulation of circulating malignant lymphocytes that typically express cell surface markers CD5, CD20, and CD23. It is the most common type of leukemia in adults in the United States and Western Europe. The median age at diagnosis is 65-70 years, with a male to female ratio of 2:1. Initially, most patients present with asymptomatic lymphocytosis and do not need cytoreductive therapy [Kay, 2002]. Patients with active disease are characterized by a lymphocyte doubling time of less than 6 months, or progressive, even massive lymphadenopathy, hepatomegaly, splenomegaly, anemia and thrombocytopenia. Constitutional symptoms such as fever, night sweats, unintended weight loss, and extreme fatigue are common in advanced disease and can significantly impact quality of life [Cheson, 1996]. CLL also causes relative immunosuppression that increases the risk of infections that are ultimately the major cause of death in this patient population. Median survival at diagnosis ranges from 5 to 20+ years depending on risk factors, but is only 6 to 14 months for CLL refractory to available therapies [Tam, 2007].

1.2. CLL Treatment

No therapy has been shown to be curative for CLL or to prolong survival, so the treatment objective is disease control, mitigation of symptoms and prolongation of progression-free survival. Treatment is initiated when the patient presents with active disease. Although most patients with CLL will achieve responses with initial therapy, nearly all patients relapse and require further treatments. Advanced age, more than 2 prior therapies [Wierda, 2005], and the presence of chromosomal abnormalities such as 17p and 11q deletions [Döhner, 2000] are associated with decreased response to therapy. Treatment is often complicated by the increased susceptibility to infections that are the leading cause of death in heavily pre-treated patients.

The purine analog fludarabine, alone or in combination with other agents, can be considered as the backbone of CLL therapy in both the frontline and subsequent lines of therapy [Rai, 2000; Catovsky, 2007], and is indicated for alkylator resistant CLL. Bendamustine, an alkylating chemotherapy agent, was recently approved in the United States based on frontline CLL data in comparison with the alkylator chlorambucil [TREANDA prescribing information, 2008; Knauf, 2007]. However, available data shows that alkylators such as chlorambucil and bendamustine are not as effective in subsequent lines of therapy [Rai, 2000, Bergmann, 2005, Kath, 2001, Aivado, 2002]. Alemtuzumab was recently approved based on frontline CLL data in comparison to chlorambucil [Hillmen, 2007]. Rituximab, an anti-CD20 monoclonal antibody, is not approved for CLL and has limited efficacy as monotherapy [Huhn, 2001]. Response rates remained low when rituximab doses were increased from 375 mg/m² to 2,250 mg/m² in fludarabine refractory CLL [O'Brien, 2001a].

1.3. Fludarabine-Refractory CLL Treatment

For patients who are refractory to fludarabine, the prognosis is grim. Alemtuzumab, an anti-CD52 monoclonal antibody, targets both B and T cells and is approved for treatment of alkylator and purine analog resistant disease. Alemtuzumab has shown a 2% complete remission (CR) and 31% partial remission (PR) rate with a median time to progression of 4.7 months, but treatment is associated with significant infectious complications due to its profound immunosuppressive effects, including a 19% incidence of opportunistic infections, and a 13% incidence of fatal infections [Keating, 2002b].

For double-refractory patients (DR) who no longer respond to fludarabine and alemtuzumab, no approved or other standard therapies are available. In a retrospective study of 58 fludarabine and alemtuzumab refractory CLL patients treated at a single institution, the overall response rate to 20 different salvage therapies was 20%, and no responses were seen with monoclonal antibody therapies as single agents (0 responses in 14 subjects) [Tam, 2007]. The median time to treatment failure was only 2 months. Early deaths (defined as death within 8 weeks of starting therapy) occurred in 16% of patients and 60% of patients suffered major infections. Median survival for this DR group was only 8 months, and was 6 months for those treated with monoclonal antibodies as single agents. Therefore, the DR group, refractory to fludarabine and alemtuzumab therapies, constitutes an unmet medical need population that needs new effective therapies.

Bulky (lymphadenopathy >5 cm) fludarabine-refractory CLL patients (BFR) also have a high unmet medical need as evidenced by a developing consensus, supported by a number of literature reports, that BFR patients respond poorly to alemtuzumab therapy. Responses with alemtuzumab seen in treatment naïve CLL patients with bulky disease in the frontline registration study [Hillmen, 2007] were not seen in CLL patients with bulky disease treated with alemtuzumab in the study of fludarabine-resistant subjects. Only 2 of 17 BFR CLL patients achieved PR in this study with alemtuzumab [Keating, 2002b]. In another study, only 1 of 11 patients with BFR CLL responded, and a shorter survival vs. patients with non-bulky fludarabine-refractory CLL was seen (9 months vs. 30 months; $p < 0.001$) [Moreton, 2005]. A retrospective review of 37 bulky vs. 68 non-bulky CLL patients with at least 1 prior therapy treated with alemtuzumab also showed significantly lower response rates (8% bulky vs. 28% non-bulky) and shorter median overall survival (10 months bulky vs. 27.5 months non-bulky; $p < 0.001$) [Fiegl, 2006]. Treatment was associated with significant toxicities, especially serious (89%) and fatal infections (48%) [Perkins, 2002]. Based on a review of the literature, the recent British Committee for Standards in Haematology treatment guidelines do not recommend alemtuzumab in BFR CLL patients [Oscier, 2004].

Other salvage therapies beyond alemtuzumab are also not effective in BFR CLL patients. In a retrospective study by the MD Anderson Center [Tam, 2007], the 41 BFR CLL patients treated at that institution received 21 different salvage chemotherapies and other treatments. The overall response rate was 26%, with no responses seen with monoclonal antibody therapies as single agents. The median time to treatment failure was, at most, 3 months with purine analog combinations. A 10% incidence of early deaths and 45% incidence of major infections and a median survival of only 14 months were reported.

expression of CD20 molecules and in cells expressing high levels of complement regulatory proteins [Teeling, 2004].

(b) (3) (A)

Data Source: Teeling, 2004

These findings suggested that ofatumumab may be capable of inducing lysis of CLL cells which are known to express relatively low levels of CD20 on their surface. Ofatumumab induced CDC and antibody dependent cell-mediated cytotoxicity (ADCC) of a panel of freshly isolated patient CLL cells *in vitro*. In the presence of complement, such as in whole blood assays, ofatumumab was superior to rituximab and killed tumor cells effectively and rapidly by CDC [Teeling, 2004]

The ability of ofatumumab to efficiently kill patient CLL cells by CDC as well as ADCC mechanisms led to a clinical development plan for ofatumumab in CLL, focusing on fludarabine refractory CLL patients who are also refractory to alemtuzumab or have bulky lymphadenopathy and are therefore in greatest need of new treatment options.

2.2. Overview of Clinical Pharmacology

Clinical pharmacology, including pharmacokinetics and pharmacodynamics, and concentration-effect relationship data comes from the pivotal and supportive studies in CLL, as well as studies in follicular lymphoma (FL) and rheumatoid arthritis (RA). A description of these studies is shown in [Appendix Table 1](#).

2.2.1. Pharmacokinetics

Maximum ofatumumab serum concentrations were generally observed at or shortly after the end of the infusion. In the pivotal study in subjects with refractory CLL (Study Hx-CD20-406), the geometric mean maximal concentration (C_{max}) value was 63 µg/mL after the first infusion (300 mg); after the eighth weekly infusion (seventh infusion of

2000 mg), the geometric mean C_{max} value was 1482 µg/mL and geometric mean area under the concentration-time curve (AUC(0-∞)) value was 674,463 µg.h/mL; after the twelfth infusion with a longer dosing interval (fourth monthly infusion; 2000 mg), the geometric mean C_{max} value was 881 µg/mL and geometric mean AUC(0-∞) was 265,707 µg.h/mL.

Ofatumumab is eliminated in two ways: a target-independent route as with other IgG molecules and a target-mediated route related to binding to B cells. There was a rapid and sustained depletion of CD20⁺ B cells after the first ofatumumab infusion, leaving a reduced number of CD20⁺ cells available for the antibody to bind at subsequent infusions. As a result, ofatumumab clearance values were lower and t_{1/2} values were significantly larger after later infusions than after the initial infusion (Table 1); CL and t_{1/2} values were similar at fourth infusion and later. Ofatumumab volume of distribution values were low, consistent with distribution largely in the systemic circulation.

Table 1 Clearance, Volume of Distribution at Steady State and Half-Life Values for Ofatumumab After Infusion in Subjects with CLL (Study Hx-CD20-402 and Study Hx-CD20-406)

Infusion Number	Dose (mg)	n	Clearance (mL/h)	V _{ss} (L)	Half-Life (days)
1 ^a	500	27	63.7 (140%)	3.2 (44%)	1.3 (109%)
4 ^a	2000	24	8.5 (98%)	1.7 (44%)	11.5 (77%)
8 ^b	2000	127	9.5 (50%)	5.1 (42%)	15.8 (40%)
12 ^b	2000	77	10.1 (47%)	4.7 (30%)	13.9 (26%)

Data are presented as geometric mean (%CV).

a. Study Hx-CD20-402 (four weekly infusions)

b. Study Hx-CD20-406 (eight weekly infusions then four monthly infusions)

Significant covariates on ofatumumab pharmacokinetics were identified in a combined population pharmacokinetic analysis and in a multiple regression analysis in subjects who had received single or multiple infusions of ofatumumab as a single agent at doses ranging from 100 to 2000 mg, with similar findings. In both analyses, diagnosis (CLL, FL or RA) and measures of body size (body surface area (BSA), body weight, and/or height) were significant covariates for ofatumumab clearance and volume of distribution. In addition, an effect of gender on both ofatumumab clearance and volume of distribution at steady state was identified by the multiple regression analysis.

The effects of diagnosis on ofatumumab pharmacokinetics were largest, with higher CL (369% at first infusion; 31-36% at later infusions) and V_{ss} (22-65%) values observed in CLL than in FL or RA (multiple regression analysis), consistent with high initial B-cell counts in subjects with CLL. The effects of body size measures (5-11% with 10 kg increases in weight or 0.1 m² increases in BSA) and gender (14-25% lower in female subjects than in male subjects) on ofatumumab CL and V_{ss} values were modest and are

not considered to be clinically relevant; no dose adjustment is recommended based on body size or gender.

2.2.2. Pharmacodynamics

Rapid, efficient, and sustained depletion of peripheral B cells was observed for the majority of subjects at all dosing regimens tested, with the decrease beginning with the first ofatumumab infusion. In subjects with refractory CLL in Study Hx-CD20-406, the median decrease in B-cell counts was 23% after the first infusion and 92% after the eighth infusion. Peripheral B-cell counts remained low throughout the remainder of therapy in most subjects and gradually increased after the end of ofatumumab therapy, with the median decrease in B cell counts remaining 68% below baseline three months after the last infusion.

2.2.3. Concentration-Effect Relationships

In subjects with relapsed or refractory CLL (Study Hx-CD20-402), statistically significant relationships were seen between response and ofatumumab pharmacokinetics after the fourth infusion (241% higher AUC, 43% higher C_{max}, and 94% higher C_{min} values in subjects who responded); higher AUC values were associated with longer duration of response, delayed time to progression, and delayed time to next anti-CLL therapy. These findings contributed to the dose selection for the pivotal trial (Section 3.1.1).

In subjects with refractory CLL (Study Hx-CD20-406), response from screening to Week 24 was correlated with exposure at the eighth infusion (37% higher AUC, 23% higher C_{max}, and 91% higher C_{min} values at the eighth infusion in subjects who responded). No differences in exposure were seen at the twelfth infusion (last monthly infusion) between subjects who responded and subjects who did not respond. Longer progression-free survival was associated with higher exposure (AUC, C_{max}, and C_{min} values) at both the eighth and twelfth infusions.

These relationships should be interpreted with caution with respect to causality: higher exposures may result in more tumor reduction; however, lower or reduced tumor burden will result in reduced clearance and therefore higher exposures.

2.2.4. Immunogenicity

No anti-ofatumumab antibodies were detected in subjects who received ofatumumab in study Hx-CD20-406. In the 274 subjects who received ofatumumab in Study Hx-CD20-001, Study Hx-CD20-402, and Study Hx-CD20-403 Part A and B, only two samples were (borderline) positive for anti-ofatumumab antibodies. Conclusions regarding these results are limited in that the assay used to measure anti-ofatumumab antibodies was capable of detecting antibodies of only one isotype (IgG1) and was not capable of detecting antibodies to CH2 and CH3 domains. There was no evidence of any effect of the anti-ofatumumab antibodies on safety, pharmacokinetics, or pharmacodynamics.

An assay that can detect antibodies of multiple isotypes to any epitope on ofatumumab was subsequently developed and is being used to test for anti-ofatumumab antibodies in

the Study Hx-CD20-406. No human anti-human antibodies (HAHAs) were detected in any of the evaluable subjects (39% of subjects receiving all infusions).

The overall immunogenicity risk for ofatumumab is low. The ofatumumab (fully human) primary sequence, high purity drug product, route of administration, nature of the specific cellular target, and intended patient population all decrease the risk for induction of immune responses, and the likely impact of an immune response is considered to be low. The current clinical data are consistent with this assessment; antibody responses to date have been both very low in incidence and with no detectable impact on the safety, pharmacokinetics, or pharmacodynamics of ofatumumab.

2.3. Clinical Development of Ofatumumab in CLL

The clinical development plan for ofatumumab in CLL consists of 1 completed dose-escalation phase I/II study, 3 ongoing single arm studies (including the pivotal study for the BLA submission), and 2 ongoing phase III randomized studies. Additional studies in other oncology and non-oncology indications have been completed or are ongoing ([Table 2](#)).

Hx-CD20-402 is a completed dose-escalation phase I/II study in 33 subjects with relapsed or refractory CLL, treated in 3 different dose cohorts [[Coiffier, 2008](#)] that provided data for the dose selection in the pivotal study. No responses were observed in 3 subjects who received an initial dose of 100 mg ofatumumab followed by 3 weekly doses of 500 mg (Group A), nor in the 3 subjects who received an initial dose of 300 mg followed by 3 weekly doses of 1000 mg (Group B). In the 27 subjects who received an initial dose of 500 mg followed by 3 weekly doses of 2000 mg (Group C), 13 of the 26 evaluable subjects responded (1 nPR, 12 PR). Ofatumumab was well tolerated with no unexpected safety issues identified. The 2000 mg dose was therefore selected as the monotherapy dose for the ongoing pivotal Hx-CD20-406 study in refractory CLL that forms the basis for this BLA.

In addition, Hx-CD20-407 is an ongoing study of ofatumumab in combination with fludarabine + cyclophosphamide (FC) in frontline CLL, and Hx-CD20-416 is an ongoing study of ofatumumab monotherapy in subjects who relapsed after receiving ofatumumab in the pivotal Hx-CD20-406 study.

Phase III trials are ongoing with ofatumumab in combination with chlorambucil versus chlorambucil alone in frontline CLL, and with ofatumumab in combination with FC versus FC alone in relapsed CLL. Primary endpoint for both studies is improvement in progression-free survival ([Appendix Table 2](#)).

Table 2 Ofatumumab Clinical Development Program in CLL

	Phase I/II Studies	Ongoing Studies	Phase III Studies
First Line		Hx-CD20-407 ofatumumab + FC N=61 (enrollment complete)	OMB110911 ofatumumab + chlorambucil vs. chlorambucil Planned N=444 (ongoing)
Second Line	Hx-CD20-402 ofatumumab dose- ranging N=33 (completed)		OMB110913 ofatumumab + FC vs. FC Planned N=352 (ongoing)
Fludarabine- refractory		Hx-CD20-406 ofatumumab monotherapy Planned N=225 (ongoing)	
		Hx-CD20-416 ofatumumab monotherapy retreatment study Planned N=25	

Additional oncology studies include 3 follicular lymphoma (FL) studies: a completed phase I/II dose escalation study of ofatumumab in relapsed FL, an ongoing combination chemotherapy study in frontline FL, and an ongoing monotherapy study in rituximab-refractory FL ([Appendix Table 2](#)). There are 2 ongoing diffuse large B-cell lymphoma (DLBCL) studies: an ongoing single-arm monotherapy study in relapsed DLBCL and an ongoing combination chemotherapy studies in relapsed DLBCL prior to transplant. In addition, there is an ongoing single-arm monotherapy study in Waldenström's Macroglobulinemia. Furthermore, studies in rheumatoid arthritis and multiple sclerosis are either completed or ongoing ([Appendix Table 1](#)).

2.3.1. Regulatory Considerations

For the past 17 years the FDA has also approved promising new cancer drugs by the utilizing the accelerated approval regulation for serious, life-threatening diseases. The accelerated approval regulation facilitates drug approval based on evidence from a surrogate endpoint, such as overall response rate, which is likely to predict clinical benefit. Such a benefit can be an improvement over available therapies in either safety or efficacy measures. A confirmatory trial is needed to achieve standard approval following accelerated approval under current regulations.

The early activity demonstrated by ofatumumab in the phase I/II Hx-CD20-402 CLL study led to a study design that is acceptable under the accelerated approval regulation. In initial meetings with the FDA, Genmab A/S identified the population for whom existing therapies were inadequate, and where accelerated approval would be feasible based on promising results from a single arm study. Subsequently, Genmab A/S and GSK maintained a dialogue with the Division of Biologic Oncology Products during the

development of Arzerra™ (ofatumumab) through written communication and meetings via telephone and in person. The principal outcomes of this dialogue have included: modification of pivotal study Hx-CD20-406 to include FDA input; acceptability of response rate as the primary study endpoint; agreement that at 30% or higher response rate would be clinically meaningful to support consideration for accelerated approval; definition of the double refractory population as a patient population with an unmet medical need; recognition that the bulky fludarabine refractory population should be analyzed separately and the acceptance of which will be a review issue; acceptability of the proposed package of the BLA including size of the safety database; design and acceptability of a confirmatory study under accelerated approval regulations; and guidances including the non-clinical and CMC components of the BLA.

2.3.2. Proposed Indication and Dosage

The Sponsor and FDA are negotiating an indication statement for ARZERRA in the treatment of chronic lymphocytic leukemia (CLL) under the provisions of accelerated approval based on studies that have investigated response rate, a surrogate endpoint for clinical benefit.

The recommended dose of ofatumumab for double-refractory and bulky fludarabine-refractory indications is an initial dose of 300 mg, followed one week later by 2000 mg once weekly for seven infusions, followed 4 to 5 weeks later by 2000 mg once every 4 weeks for 4 infusions, for a total of 12 infusions.

3. STUDY HX-CD20-406

3.1. Study Design

Study Hx-CD20-406 is an ongoing, single arm, open-label, multi-center study of ofatumumab in subjects with CLL who are either refractory to both fludarabine and alemtuzumab, or who are refractory to fludarabine and had bulky lymphadenopathy. Single agent ofatumumab was administered as 8 weekly infusions followed by 4 monthly infusions over 24 weeks. The primary endpoint was response rate over a 24 week period.

3.1.1. Dose Regimen and Justification

The findings from the study of ofatumumab in relapsed or refractory CLL subjects in dose-ranging Study Hx-CD20-402 served as the rationale for the ongoing pivotal Study Hx-CD20-406. In Study Hx-CD20-402, subjects received ofatumumab weekly for four weeks.

The rationale for the dose selection for Study Hx-CD20-406 includes:

- In Study Hx-CD20-402, subjects in Group C (the highest dose group; three infusions of 2000 mg after an initial dose of 500 mg) had a 48% response rate, and the data suggested that higher exposures were correlated with response; thus, 2000 mg was selected to achieve maximal exposures. Simulations of concentration-time profiles showed that an initial infusion of 300 mg followed

by seven weekly infusions of 2000 mg each was expected to achieve high ofatumumab exposures.

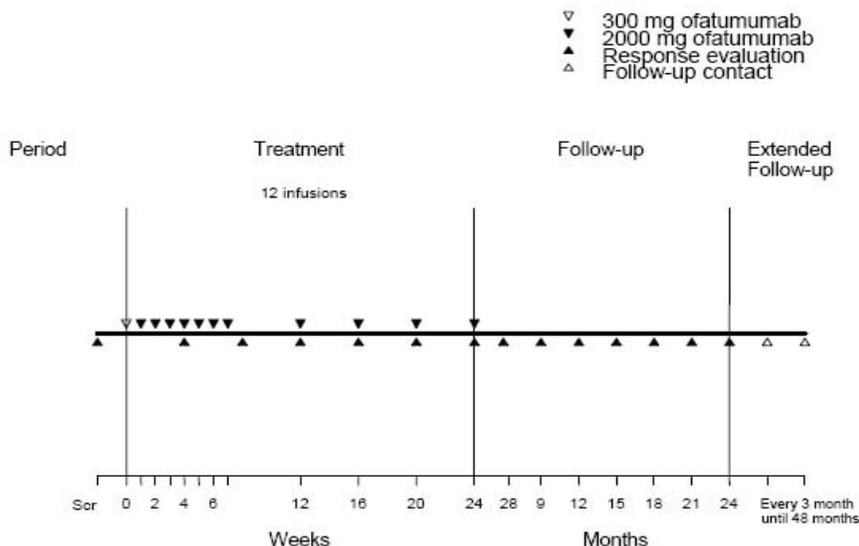
- In Study Hx-CD20-402, most subjects responded with a reduction lymph node size four weeks after initiation of therapy; however, a subgroup of subjects responded with a slower regression of their lymphadenopathy (i.e., between 4 and 11 weeks). In addition, some subjects with a rapid decrease in their lymphadenopathy experienced an increase in their lymphadenopathy toward the end of the trial or lost clinical response at Week 15 or Week 19. Increasing the number of weekly infusions to eight was considered to be of potential benefit to maximize response and response duration.
- It was postulated that prolonged therapy with infusions every four weeks after the cessation of the weekly infusions could minimize re-emergence of CLL cells and increase response duration.
- Adverse events (AEs) reported in previous clinical trials have primarily been observed on infusion days (notably on the day of the first infusion). A prolonged treatment schedule in Study Hx-CD20-406 was not expected to affect the overall safety profile of ofatumumab.
- The 300 mg initial dose was chosen to minimize the potential for first infusion reactions.

Therefore, an ofatumumab dose of 2000 mg repeated for up to 24 weeks (initial infusion of 300 mg, followed one week later by 2000 mg once weekly for seven infusions, followed five weeks later by an infusion of 2000 mg once every four weeks for four infusions, for a total of twelve infusions) was selected for the Hx-CD20-406.

3.1.2. Study Conduct

The study events are described in [Figure 3](#).

Figure 3 Hx-CD20-406 Study Events



Pre-medications (paracetamol, antihistamine, IV glucocorticoids) were given to minimize infusion related side effects.

Study Hx-CD20-406 has three distinct periods for data collection. During the treatment period, efficacy and safety assessments were to be performed every 4 weeks until Week 28. Subjects who completed the treatment period entered the follow-up period. During the follow-up period (Week 28 to Month 24), disease status was evaluated every 3 months. Subjects completing follow-up and subjects who were withdrawn from treatment or follow-up phases could enter the extended follow-up period and were followed for up to 48 months or until alternate CLL treatment was started. Only serious adverse events (SAEs) were recorded during the extended follow-up period, and the primary intention of this phase was to assess survival. Extended follow-up assessments occurred every three months up to Month 48 or until alternate CLL treatment was started. The efficacy assessments included measurements of blood counts, palpable lymph node size and number, spleen and liver size, and constitutional symptoms.

3.1.3. Eligibility Criteria

Adult subjects were eligible for participation if they had active CLL and

- were refractory to prior therapy defined as a minimum of 2 cycles of fludarabine and at least 12 administrations of alemtuzumab (double refractory, DR), or
- were refractory to prior therapy defined as a minimum of 2 cycles of fludarabine and had bulky lymphadenopathy, defined as lymph node size of >5 cm (bulky fludarabine refractory, BFR).

3.1.4. Primary and Secondary Endpoints

The primary objective of the study is to evaluate the efficacy of ofatumumab in these subject populations as measured by response rate over a 24 week period according to National Cancer Institute Working Group (NCIWG) 1996 response criteria for CLL as assessed by the Independent Endpoints Review Committee (IRC).

Secondary endpoints include duration of response, progression-free survival, overall survival, the individual components of the NCIWG response criteria, responses by sub-groups and safety endpoints.

3.1.4.1. NCIWG 1996 CLL Response Criteria

The IRC assessed subjects to determine their response status of responders or non-responders as follows: complete remission (CR), nodular partial remission (nPR), and partial remission (PR) were classified as responders, while stable disease (SD) and progressive disease (PD) were classified as non-responders. Responses were required to be maintained for at least two months (56 days). The definitions of each response category are shown in [Table 3](#).

Table 3 NCIWG 1996 CLL Response Criteria

Parameter	Complete Remission	Partial Remission	Progressive Disease
Lymphocytes	<4.0x10 ⁹ /L	≥50% reduction from baseline	≥50% increase to at least 5.0 x10 ⁹ /L
Lymphadenopathy	Absence by physical exam	≥50% reduction	≥50% increase for at least 2 weeks or new palpable node ≥1cm
Organomegaly	Normal size spleen and liver by physical exam	≥50% reduction if abnormal at baseline	≥50% increase
Constitutional Symptoms	None	Not defined	Not defined
Neutrophils	≥1.5x10 ⁹ /L	≥1.5x10 ⁹ /L or 50% improvement from baseline	Not defined
Platelets	>100x10 ⁹ /L	>100x10 ⁹ /L or 50% improvement from baseline	Not defined
Hemoglobin	>11.0 g/dL (untransfused)	>11.0 g/dL or 50% improvement from baseline (untransfused)	Not defined
Bone Marrow	Normocellular for age, <30% lymphocytes, no B-lymphoid nodules.	If done, ≥30% lymphocytes and/or B-lymphoid nodules	Not defined
Response Definition	All above met for at least two months. If persistent nodules in bone marrow =nPR	Meets criteria for first three for at least 2 months, and at least one other of above met	At least one of above met, or transformation to more aggressive histology

In accordance with the NCIWG 1996 CLL response criteria, CT scans were required only for the documentation of suspected CR, otherwise, CT scans were not required nor done to confirm PR. Subjects not meeting the criteria for CR, PR or PD were considered to have Stable Disease (SD). Transformation to a more aggressive histology, including Richter's syndrome or prolymphocytic leukemia with >55% prolymphocytes, was considered progressive disease.

Achieving a partial or complete remission in CLL is considered clinically beneficial because the NCIWG 1996 CLL response criteria assess not only reduction in tumor size, but also measure direct and indirect elements of clinical benefit such as improvement in constitutional symptoms and improvements in hematologic parameters.

3.1.5. Protocol Amendments

The study protocol had five amendments. Amendments to the protocol primarily resulted in changes to the inclusion and exclusion criteria and the number of subjects planned.

Amendment 1 modified the inclusion and exclusion criteria and clarified the study objectives. No subjects were enrolled prior to Amendment 1. Based on feedback from the Food and Drug Administration on 23 May 2006, Amendment 2 and 3 defined the subject eligibility definition consistent with the DR and BFR subject populations that are the focus of this briefing document. The intent of these amendments was to ensure that a more homogeneous subject population would be included in the trial and that an adequate number of subjects would be enrolled into each of these groups to test for efficacy in these populations. Furthermore, the subject populations, as now defined, represented populations with a clinically unmet need based on failure to respond to prior fludarabine or alemtuzumab therapy, and the study would no longer enroll subjects who had demonstrated lack of tolerability to these agents. As a result, 16 subjects who were intolerant/ineligible to fludarabine or intolerant to alemtuzumab and enrolled prior to Amendment 2 were included in the interim analysis, and are described and analyzed separately as Other. These 16 subjects are excluded from the efficacy analyses because they do not represent the pre-specified primary patient populations; however their data contribute to the safety analysis.

Amendment 4 is the most significant amendment with regard to the analysis of efficacy presented in this summary. Amendment 4 increased the sample size from 66 subjects to 100 subjects (per subject group) and introduced a primary endpoint interim analysis at the original full study cohort of 66 subjects per group. A stopping rule for futility was also introduced. Amendment 5 was an administrative amendment that did not change the conduct of the study.

3.1.6. The IRC Process

An independent endpoints review committee (IRC) was used in Study Hx-CD20-406 to determine eligibility and the primary endpoint of response rate from the investigator's clinical assessments and the laboratory components of the primary efficacy data. An expert panel of IRC members applied the protocol-specified method of response determination to assure an independent, consistent, and medically appropriate application of this composite measure of response in CLL. The IRC was a committee of 5 experts in

CLL treatment, including 2 authors of the NCIWG 1996 CLL response criteria. The IRC made determinations of eligibility and response independently, and was blinded to the results of other IRC member determinations. At least 2 IRC members evaluated eligibility for each of the 154 subjects.

3.1.7. Statistical Analyses

Primary evidence for the efficacy of ofatumumab in subjects with CLL was provided by a pre-specified interim analysis of Study Hx-CD20-406.

For the primary endpoint interim analysis, assuming an underlying response rate of 30%, 66 subjects are needed to exclude a 15% response rate at the 1% (2-sided) significance level with 63% power. For the primary endpoint final analysis, 100 subjects are needed to exclude a 15% response rate at the 4.7% (2-sided) significance level with 92% power. Given that the response rate with salvage chemotherapy in the target populations has been described as being 20-26%, and 0% with monoclonal antibodies as single agents [Tam, 2007], observing a 30% or higher response rate that excludes a 15% response rate at the 1% significance level would indicate meaningful efficacy in this highly refractory population.

An independent Data Monitoring Committee (DMC) reviewed the IRC-assessed primary endpoint of response data from 154 subjects as of 19 May 2008. This pre-planned interim analysis included data from 59 subjects in the DR group 79 subjects in the BFR group: 16 subjects were not categorized by the IRC as DR or BFR were not included in the efficacy analysis but was included in the safety analysis. Based upon the 58% and 47% response rates reported for the DR and BFR groups, the DMC informed the sponsor on 22 July 2008 that the pre-defined criteria of observing response rates that exceeded 15% at the 1% significance level had been achieved in both groups.

The analysis population was the full analysis set (FAS), which included all subjects who were exposed to study drug irrespective of their compliance to the planned course of treatment. This was the primary analysis population and was used for evaluation of all endpoints.

3.2. Study Population

At the time of the interim analysis (data cut-off date 19 May 2008) 154 subjects received treatment with ofatumumab.

The sponsor had estimated that this cohort of 154 subjects included 66 subjects who would meet the criteria for the DR group. Subsequent IRC assignment, as defined in the protocol as the required basis for determining subject group, confirmed 59 subjects as meeting the criteria for the DR group and 79 subjects met the criteria for the BFR group. Subjects who did not meet DR or BFR criteria were assigned to the Other group (16 subjects). This IRC categorization was used for classification of subject data in the interim analysis.

3.2.1. Subject Disposition

Subject disposition at the interim analysis of Study Hx-CD20-406 is summarized in [Table 4](#).

Table 4 Disposition of Subjects in Study Hx-CD20-406

Subject Disposition	Hx-CD20-406 N=154
Completed treatment (all 12 infusions)	85 (55)
Ongoing in follow-up n (%)	20 (13)
Withdrawn from follow up	65 (42)
Withdrawn from treatment (<12 infusions)	69 (45)
Progressive disease	35 (23)
AE	21 (14)
Other ^a	13 (8)

a. Includes disease transformation, subject decision, investigator decision and no response.

At the time of the interim analysis, 69 subjects (45%) were withdrawn from treatment prior to the completion of all scheduled ofatumumab treatments, and of those, 17 (11%) were no longer participating in the study. The most common reason for withdrawal from treatment was disease progression (35 subjects, 23%). Adverse events were another common reason for withdrawal from treatment, reported for 21 subjects (14%). These adverse events included preferred terms of pneumonia, sepsis, neutropenic sepsis, septic shock, neutropenia, myocardial infarction, pulmonary edema, hypersensitivity reaction, pure red cell aplasia, hemiparesis (as symptom of progressive disease), herpes zoster, progression of study disease (reported as AE), abdominal pain, urinary tract infection, and cardiac failure. An additional 3 subjects (2%) were withdrawn from follow-up due to adverse events.

Most subjects (111, 72%) continued to be followed after treatment completion or discontinuation. Of 111 subjects who continued to extended follow up, 66 were continuing to be followed at the time of the interim analysis.

3.2.2. Baseline Demographic Characteristics

The subjects in the DR and BFR groups were similar with regard to age, gender and race ([Table 5](#)). The median age overall was 63 years, and 43% of subjects were ≥65 years of age. More than 90% of subjects were Caucasian.

Table 5 Demographic Characteristics, Study Hx-CD20-406

Demographic Characteristics	DR N=59	BFR N=79	Other N=16	Study Total N=154
Age, years				
Median	64	62	63	63
Min – Max	41-86	43-84	53-82	41-86
≥65 yrs, n (%)	27 (46)	33 (42)	6 (38)	66 (43)
≥75 yrs, n (%)	4 (7)	10 (13)	2 (13)	16 (10)
Sex, n (%)				
Female	15 (25)	22 (28)	6 (38)	43 (28)
Male	44 (75)	57 (72)	10 (63)	111 (72)
Race, n (%)				
White	56 (95)	78 (99)	15 (94)	149 (97)
Asian	1 (2)	0	1 (6)	2 (1)
Hispanic or Latino	1 (2)	0	0	1 (1)
African-American/African	0	1 (1)	0	1 (1)
Other	1 (2)	0	0	1 (1)

3.2.3. Baseline Disease Characteristics

The characteristics of CLL were also similar between the DR and BFR groups (Table 6), including bulky lymphadenopathy. All BFR subjects and 93% of DR subjects had bulky lymphadenopathy at baseline by CT scan.

Table 6 Baseline Disease Characteristics, Study Hx-CD20-406

Disease Characteristics	DR N=59	BFR N=79	Other N=16	Study Total N=154
Duration of CLL in years, median (min, max)	6 (1, 19)	5.9 (1, 18)	7.5 (4, 17)	6.3 (1, 19)
Number of prior CLL regimens, median	5.0	4.0	6.5	5.0
ECOG performance status ^a , n (%)				
0	27 (46)	25 (32)	3 (19)	55 (36)
1	19 (32)	40 (51)	9 (56)	69 (45)
2	12 (20)	13 (16)	4 (25)	29 (19)
3	1 (2) ^b	0	0	1 (1)
Rai at screening, n (%)				
0	1 (2)	0	0	1 (1)
I	11 (19)	7 (9)	2 (13)	20 (13)
II	15 (25)	17 (22)	4 (25)	36 (23)
III	10 (17)	11 (14)	4 (25)	25 (16)
IV	22 (37)	44 (56)	6 (38)	72 (47)
Binet at screening, n (%)				
A	6 (10)	4 (5)	1 (6)	11 (7)
B	23 (39)	24 (30)	6 (38)	53 (34)
C	30 (51)	51 (65)	9 (56)	90 (58)
Chromosomal abnormalities, n (%)	n=57	n=78	n=16	n=151
17p deletion	17 (30)	14 (18) ^c	2 (13) ^d	33 (22) ^e
11q deletion	24 (42)	22 (28)	4 (25)	50 (33)
12q trisomy	3 (5)	8 (10)	5 (31)	16 (11)
13q deletion	5 (9)	13 (17)	1 (6)	19 (13)
No abnormalities found	8 (14)	19 (24)	3 (19)	30 (20) ^f
Median lymphocyte count at baseline (10 ⁹ /L)	14.7	28.5	72.4	19.7
Constitutional symptoms present at screening, n (%)	36 (61)	52 (66)	12 (75)	100 (65)
Bulky lymphadenopathy ^g present at baseline, n (%)	55 (93)	79 (100)	7 (44)	141 (92)
Organomegaly ^h present at baseline, n (%)	35 (59)	49 (62)	13 (81)	97 (63)

a. ECOG performance status at baseline

b. One subject was allowed to enroll in the study despite an ECOG performance status of 3, which due to an elbow surgery, and not related to CLL.

c. BFR subjects with assessment of 17p = 76.

d. Other subjects with assessment of 17p = 15.

e. Total subjects with assessment of 17p = 148.

f. Total subjects with assessment of no abnormalities = 150

g. Bulky lymphadenopathy defined as presence of at least one lymph node >5 cm by CT scan.

h. Organomegaly defined as enlarged liver or spleen or both.

Subjects had an overall median time since CLL diagnosis of 6.3 years, and a median of 5 prior CLL treatment regimens (DR: 5, BFR: 4).

According to the Modified Rai staging, 63% of subjects were considered to be high-risk (stage III and IV), with 36% of subjects considered to be intermediate-risk (stage I or II). Using the Binet staging system, 58% of subjects were classified as high risk (stage C), and 34% of subjects were classified as intermediate risk (stage B). The disease stage of subjects was similar between groups.

Subjects were assessed by FISH analysis for chromosomal abnormalities known or suspected to affect response to CLL treatment, specifically 17p deletion, 11q deletion, 12q trisomy, and 13q deletion. Of these, 17p and 11q deletions are associated with poor response to CLL treatment. Most subjects in each group had chromosomal abnormalities detected. The most common were 11q deletion and 17p deletion, with these abnormalities more prevalent in the DR group. The rate of other chromosomal abnormalities was similar across groups.

The overall median lymphocyte count was $19.7 \times 10^9/L$, with a lower median lymphocyte count in the DR compared to the BFR and the Other group. Subjects in the DR group were exposed to a greater number of prior therapies than those in the BFR group, which is likely the reason for the lower median lymphocyte count.

Constitutional symptoms of CLL (fever, extreme fatigue, weight loss, night sweat) were present in 65% of subjects at baseline, and were similar in the DR and BFR groups. Overall, 63% of subjects had organomegaly (enlarged liver and/or spleen) at baseline, and the incidence of organomegaly was similar across groups.

3.2.4. Prior CLL Therapy

Most of the subjects have been previously treated with 5 or more prior therapies ([Table 7](#)).

Table 7 Summary of Prior CLL Therapies, Study Hx-CD20-406

Prior CLL Therapies	DR N=59	BFR N=79	Other N=16	Study Total N=154
Number of prior CLL Therapies, n (%)				
1	2 (3)	10 (13)	0	12 (8)
2	5 (8)	5 (6)	0	10 (6)
3	6 (10)	13 (16)	1 (6)	20 (13)
4	9 (15)	12 (15)	0	21 (14)
5	10 (17)	20 (25)	3 (19)	33 (21)
>5	27 (46)	19 (24)	12 (75)	58 (38)

The majority of subjects in all groups received prior treatment with rituximab, either as monotherapy or as part of combination therapy ([Table 8](#)).

Table 8 Summary of Prior Rituximab-Containing CLL Therapies, Study Hx-CD20-406

Prior Rituximab-Containing CLL Therapy, n (%)	DR N=59	BFR N=79	Other N=16	Total N=154
Any rituximab ^a	35 (59)	43 (54)	10 (63)	88 (57)
Rituximab monotherapy	11 (19)	17 (22)	7 (44)	35 (23)
Fludarabine + rituximab ^b (FR)	5 (8)	19 (24)	3 (19)	27 (18)
Fludarabine + cyclophosphamide + rituximab ^c (FCR)	22 (37)	20 (25)	2 (13)	44 (29)

a. Subjects may have received more than one type of rituximab treatment regimen.

b. Any fludarabine + rituximab combination except FCR

c. Any fludarabine + cyclophosphamide + rituximab combination

Subjects in study Hx-CD20-406 were refractory to approved and commonly used CLL therapies according to the protocol-defined definition of refractory status (Table 9). Most subjects were refractory to CLL therapies including alkylating agents (chlorambucil, bendamustine, cyclophosphamide, melphalan); the purine analog, fludarabine and the anti-CD52 monoclonal antibody, alemtuzumab. Approximately 50% of subjects did not respond to their latest rituximab-based therapy for at least 6 months.

Table 9 Refractory Status of DR and BFR Subjects, Study Hx-CD20-406

Analysis	Definition	Number of Subjects, (%)
Refractory per protocol	DR: No response or partial remission or better lasting <6 months to at least 2 cycles of fludarabine containing regimen and at least 12 doses of alemtuzumab BRF: No response or partial remission or better lasting <6 months to at least 2 cycles of fludarabine containing regimen	DR: 59/59 (100) BFR: 79/79 (100)
Refractory per protocol with prior alkylator therapy	As above, plus prior treatment at any time with chlorambucil, bendamustine, cyclophosphamide or melphalan, regardless of number of cycles of therapy	DR: 55/59 (93) BFR: 73/79 (92)
Refractory to latest alkylator therapy	DR: Refractory to latest treatment containing chlorambucil, bendamustine, cyclophosphamide or melphalan and latest fludarabine-containing therapy, and latest alemtuzumab containing therapy. BFR: Refractory to latest treatment containing chlorambucil, bendamustine, cyclophosphamide or melphalan and latest fludarabine-containing therapy.	DR: 46/59 (78) BFR: 65/79 (82)
Refractory to last therapy prior to ofatumumab	Refractory to any last therapy, regardless of dose or number of cycles	DR: 56/59 (95) BFR: 71/79 (90)
No response to rituximab	No response lasting at least 6 months after latest rituximab-based therapy.	DR: 31/59 (53) BFR: 33/79 (42)

3.3. Primary Efficacy Endpoint: Response Rate

Efficacy results for Study Hx-CD20-406 are presented in [Table 10](#) for the DR, BFR and combined DR+BFR subjects (combined group).

Table 10 Summary of Response Assessed by IRC, Study Hx-CD20-406

Response	DR N=59	BFR N=79	Combined DR + BFR N=138
Response Rate			
Responders, n (%)	34 (58)	37 (47)	71 (51)
99% CI (%)	(40, 74)	(32, 62)	(40, 63)
Response			
CR, n (%)	0	1 (1)	1 (1)
nPR, n (%)	0	0	0
PR, n (%)	34 (58)	36 (46)	70 (51)
SD, n (%)	18 (31)	32 (41)	50 (36)
PD, n (%)	2 (3)	8 (10)	10 (7)
NE, n (%)	5 (8)	2 (3)	7 (5)

CR = complete remission, nPR = nodular partial remission, PR = partial remission, SD = stable disease, PD = progressive disease, NE = not evaluable

The IRC-assessed response rate was 58% in the DR group, 47% in the BFR group, and 51% for the combined group. In all groups, the 99% confidence intervals demonstrated that the response rate exceeded the pre-planned null hypothesis response rate of 15%. The observed response rates in the combined group, DR and BFR groups all exceeded 30%. Additional sensitivity analyses of the response rate were conducted based on investigator assessments (42% in the DR group, 34% in the BFR group) and a strictly algorithm-based analysis based on the CLL response criteria. All analyses exceeded 15% at the 1% significance level in both the DR and BFR groups.

Nearly all (70 of 71) responses were PR (58% in DR, 46% in BFR). One CR was observed in the BFR group. Response rates were similar between groups. Stable disease was observed for 50 subjects (31% in DR, 41% in BFR). Subjects who were responders or who had stable disease accounted for nearly 90% of the combined group population. Only 10 subjects experienced progressive disease (3% in DR, 10% in BFR) as best response to ofatumumab treatment.

Seven subjects (5%) were considered not evaluable because they did not have the first assessment at Week 4. In the DR group, 5 subjects were not evaluable: 2 subjects died prior to Week 4, and 2 subjects had disease progression prior to Week 4, and 1 subject was considered not evaluable because the investigator assessment of response at Week 12 could not be confirmed. In the BFR group, 2 subjects were not evaluable: both died prior to Week 4.

The response rate in the total study population, which includes DR, BFR and Other subjects, was 52% (80/154), with 78 PR, 1 nPR and 1 CR. In the Other group, the response rate was 56%, with 8 PR and 1 nPR response observed.

3.4. Secondary Efficacy Endpoints

The secondary endpoints included duration of response, onset of response, progression-free survival (PFS), time to next CLL treatment, and overall survival (OS), assessed with Kaplan-Meier estimates. Median survival times were derived and presented with corresponding two-sided 95% confidence intervals.

Individual components of the of the NCIWG 1996 CLL response criteria were also analyzed as secondary endpoints (Section 3.5) in addition to a documented response to ofatumumab treatment by the pre-specified composite measure. These individual components included effects on lymphocytes counts, reduction in lymphadenopathy, the resolution of constitutional symptoms, resolution of organomegaly and improvement in hematologic parameters. These analyses provided further evidence suggestive of clinically meaningful benefits induced by ofatumumab treatment.

3.4.1. Duration of Response

Duration of response was defined as the time from initial response to disease progression or death, and was defined only for subjects who responded (CR, nPR or PR) during the 24 week period from the start of treatment. The median time to onset of response, median duration of response, and the median duration of response after last infusion are shown in [Table 11](#).

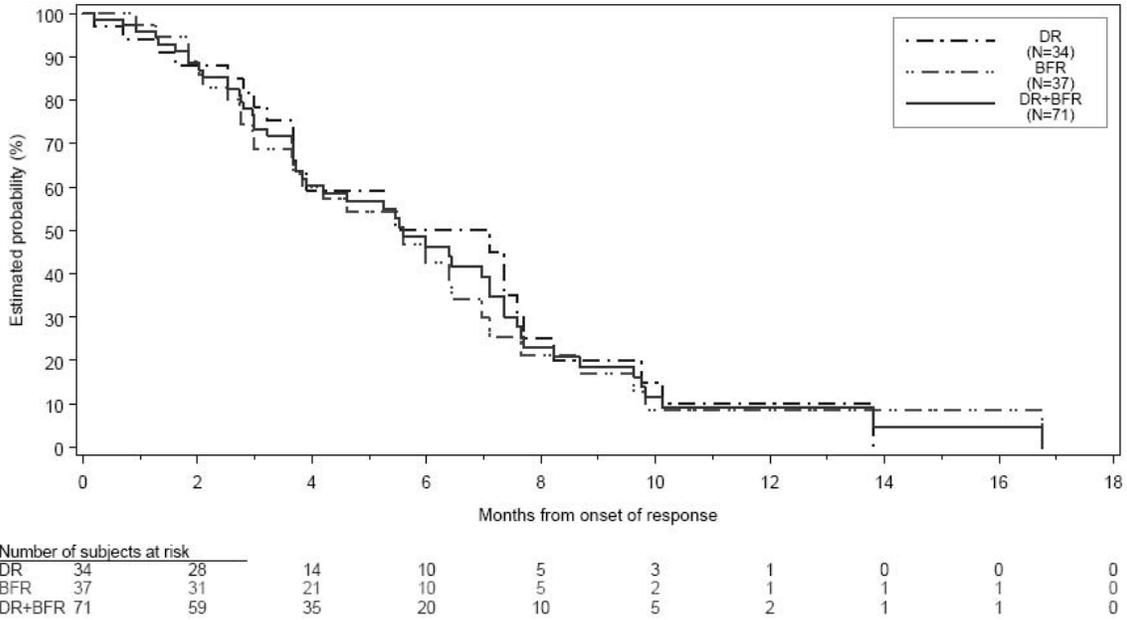
Table 11 Summary of Onset and Duration of Response (Responders only), Study Hx-CD20-406

Onset and Duration of Response	DR N=34	BFR N=37	Combined DR+BFR N=71
Median time to onset of response (months)	1.8	1.8	1.8
	95% CI: 1.0, 1.9	95% CI: 1.0, 1.9	95% CI: 1.0, 1.8
Median duration of response (months)	7.1	5.6	5.6
	95% CI: 3.7, 7.6	95% CI: 3.6, 7.0	95% CI: 3.8, 7.1
Median duration of response after last infusion (months)	2.5	1.9	2.1
	95% CI: 0.9, 5.0	95% CI: 0.9, 2.8	95% CI: 1.1, 2.8

N=number of subjects in each analysis with an observed event.

Figure 4 shows the median duration of response in subjects who responded in each group, and combined.

Figure 4 Duration of Response, Study Hx-CD20-406

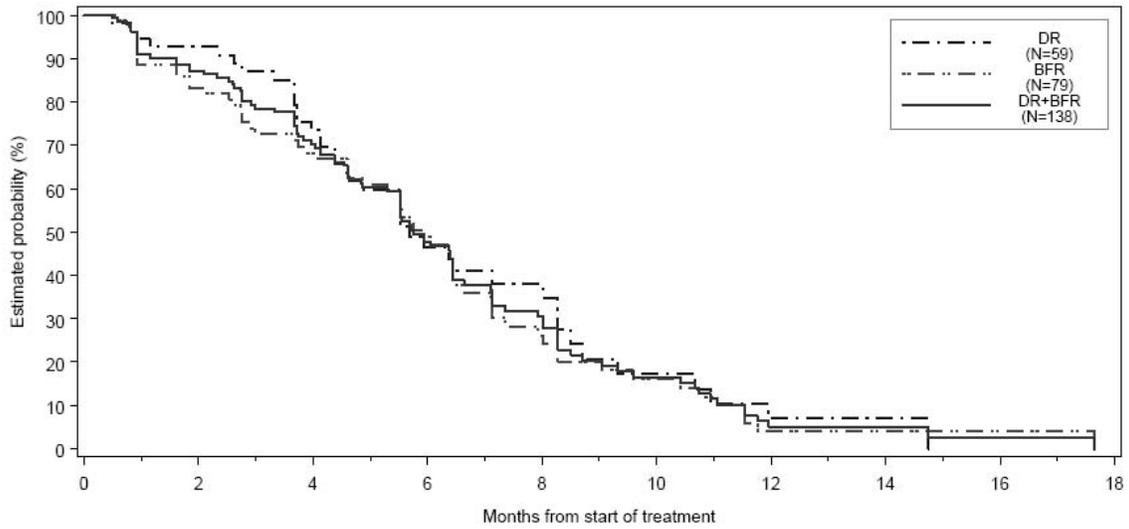


Response to ofatumumab was closely correlated with the treatment period. There was a rapid onset of response after initiation of treatment (1.8 months combined group). The response was sustained during the treatment period and for 2 months after discontinuation of treatment in the majority of subjects. The onset and duration of response was similar across groups.

3.4.2. Progression-free survival

Progression-free survival (PFS) was defined as the time from baseline until progression of CLL or death. The progression events were defined in the protocol, and progression dates were verified by the IRC. The median PFS was 5.7 months (DR: 5.7 months, BFR: 5.9 months) (Figure 5).

Figure 5 Progression-Free Survival, Study Hx-CD20-406

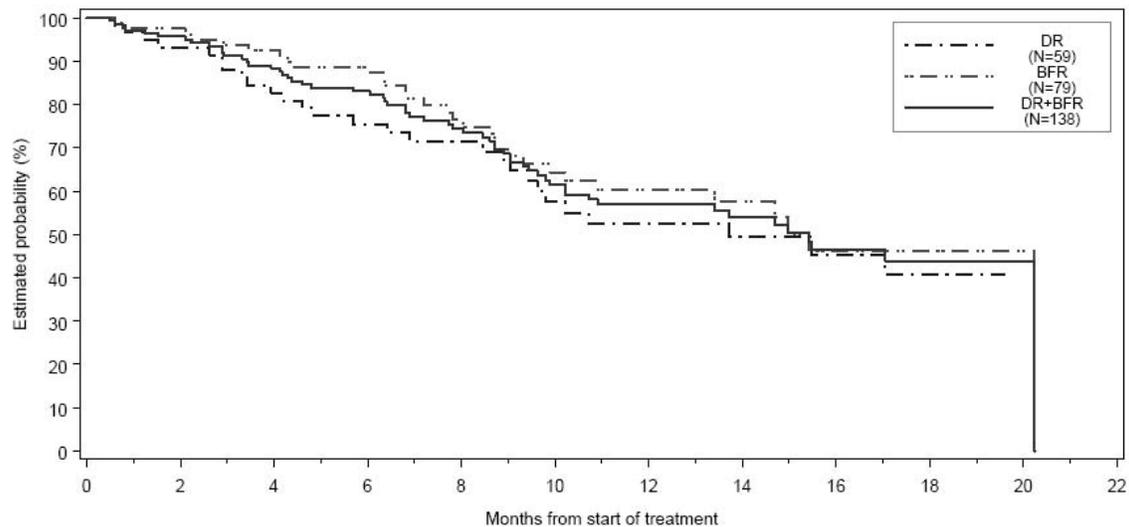


Number of subjects at risk										
DR	59	49	38	19	11	5	2	1	0	0
BFR	79	62	47	31	13	8	1	1	1	0
DR+BFR	138	111	85	50	24	13	3	2	1	0

3.4.3. Overall Survival

Overall survival was defined as the time from baseline (allocation of treatment) to death, and is shown in Figure 6. The median overall survival was 15.4 months in the combined group (DR: 13.7 months, BFR: 15.4 months).

Figure 6 Overall Survival, Study Hx-CD20-406



Number of subjects at risk												
DR	59	54	47	39	32	24	19	15	11	4	0	0
BFR	79	77	73	65	46	33	27	19	10	4	2	0
DR+BFR	138	131	120	104	78	57	46	34	21	8	2	0

At the time of the interim analysis, 27 DR and 31 BFR subjects (58 combined group) had died. The median overall survival was similar across groups. The median overall

survival after the completion of the study may be longer since some subjects were still responding at the time of the interim analysis.

3.4.3.1. Overall Survival by Response

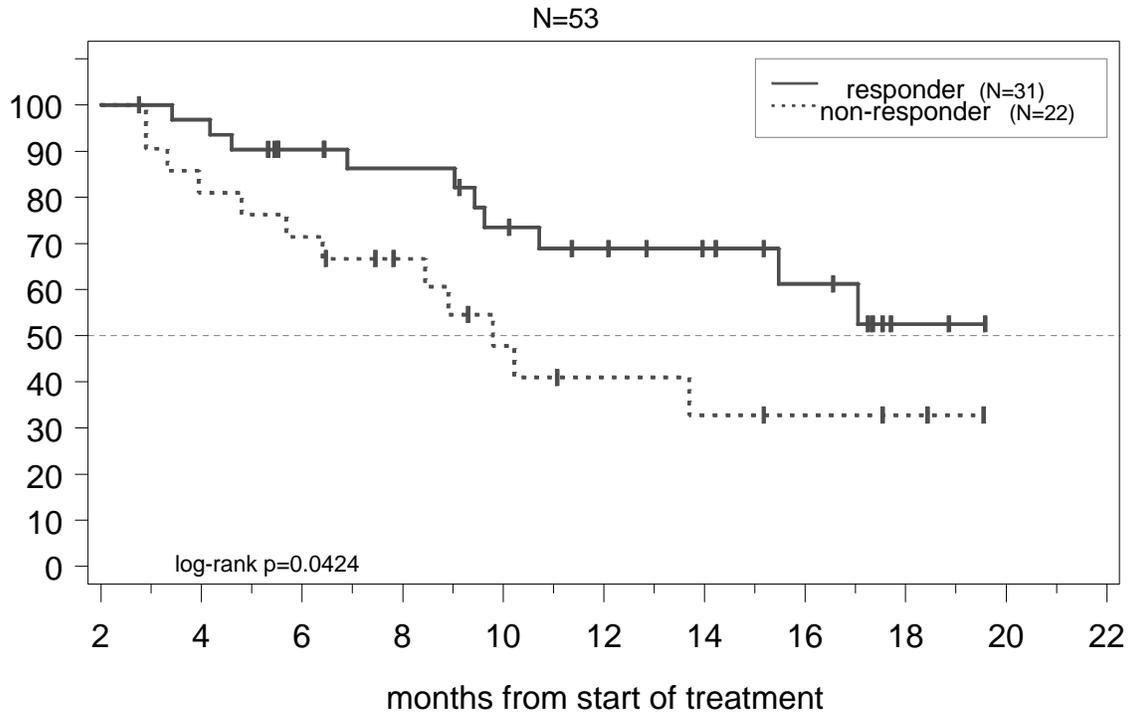
Responders in the DR and BFR populations had significantly longer median overall survival than non-responders (median not reached for responders vs. 10 months in non-responders) when tested with a post-hoc landmark analysis at Week 12.

Analyses to determine whether response is a predictor of survival can be subject to biases. Survivorship bias is a factor since subjects must be alive and still participating in the study to have a confirmed response. Selection bias occurs if subjects who respond to treatment may have had favorable prognostic characteristics that would have predisposed them to a longer overall survival regardless of treatment. Landmark analyses of overall survival in responders vs. non-responders have been performed to minimize bias in the evaluation of the relationship of response and overall survival. In a landmark analysis, only subjects who survive until the analysis time-point are included. A direct comparison between responders and non-responders may be misleading since subjects that die shortly after the start of treatment do not have the opportunity to become responders and are by default allocated to the non-responder group. The landmark analysis should be conducted at a time point that maximizes the number of responders as well as maximizing the duration of follow-up. The landmark analysis at Week 12 is the earliest time-point at which a response identified at Week 4 could be confirmed, and satisfied both of these conditions.

At Week 12, 53 of 59 DR subjects ([Figure 7](#)) and 75 of 79 BFR subjects were included in the landmark analysis ([Figure 8](#)).

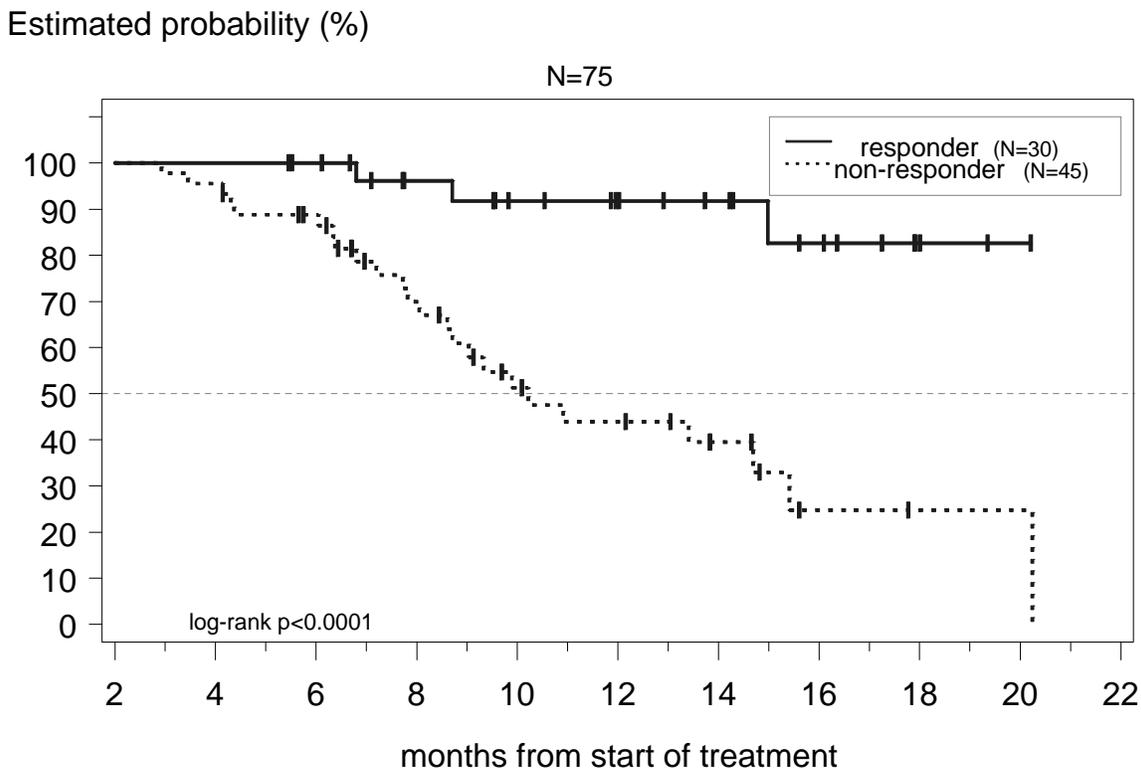
Figure 7 Overall Survival per Response in Week 12 Survivors, DR Group, Study Hx-CD20-406

Estimated probability (%)



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Figure 8 Overall Survival per Response in Week 12 Survivors, BFR Group, Study Hx-CD20-406



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Subjects responding to ofatumumab are likely to live longer than non-responders. In the DR group, response to ofatumumab was associated with at least a 10 month longer median overall survival ($p=0.0424$); the median overall survival was not yet reached for responders. In the BFR group, response to ofatumumab was associated with a greater than 10 month increase in median overall survival ($p<0.0001$); the median overall survival was not reached for responders.

The post-hoc landmark analysis of median overall survival at Week 12 supports the use of response rate as a surrogate for clinical benefit of ofatumumab in these fludarabine-refractory populations.

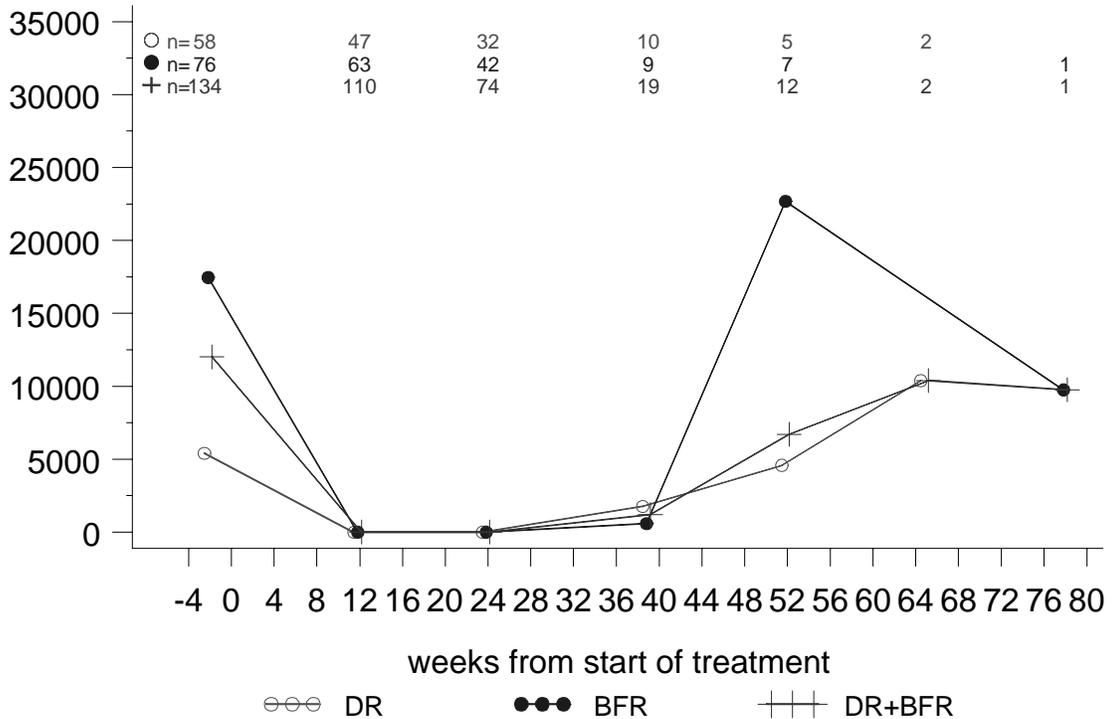
3.4.4. Malignant B Cells in Peripheral Blood

Malignant B cells are $CD45^+CD5^+CD19^+$ or $CD45^+CD5^+CD20^+$ cells. Ofatumumab binds to CD20 and could interfere with the $CD45^+CD5^+CD20^+$ assay, therefore, the $CD45^+CD5^+CD19^+$ assay was also used. Immunophenotyping was done at baseline and every 3 months thereafter. Figure 9 shows the median $CD45^+CD5^+CD20^+$ B cells decreasing over the 24 week treatment period.

Figure 9 Median CD45⁺CD5⁺CD20⁺ B Cells, Study Hx-CD20-406

Trend over time: Median values

Median CD45+CD5+CD20+ (cells/mm³)



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Likewise, after only 1 week of ofatumumab treatment, the overall median reduction of CD45⁺CD5⁺CD19⁺ cells in the combined group was 23% (DR: 19%, BFR: 24%). By the next assessment at Week 7, there was a 92% overall median reduction (DR: 91%, BFR: 93%). The median levels appeared to increase after the treatment period ended, but the number of subjects was limited (data not shown).

Treatment with ofatumumab was associated with a rapid and profound depletion of malignant B cells in peripheral blood. This effect was sustained throughout the treatment period, with a gradual increase in malignant B cells after discontinuation of therapy.

3.5. Improvements in Individual Components of Response Criteria, Study HX-CD20-406

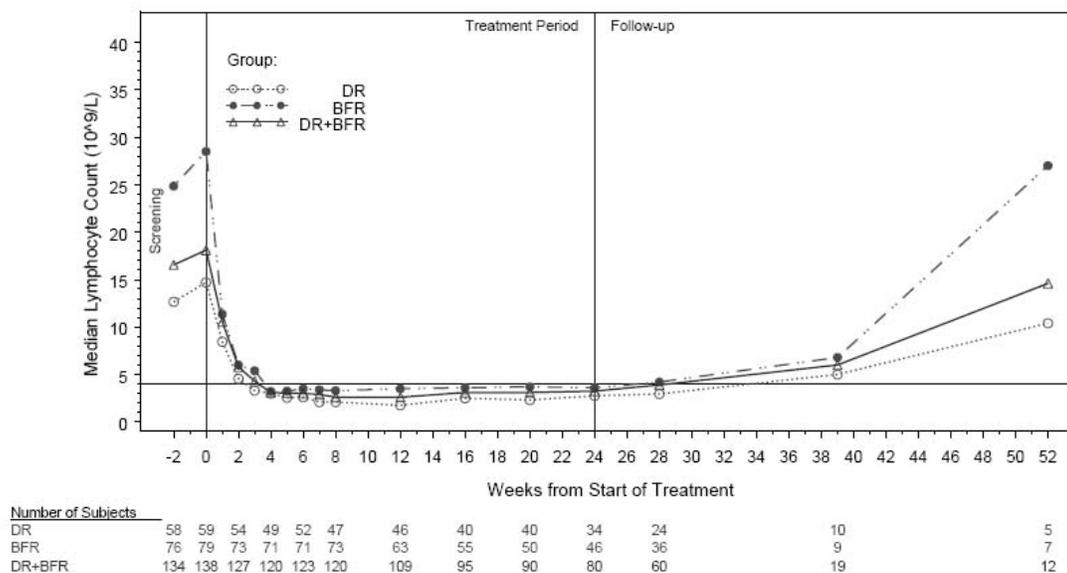
Individual components of the of the NCIWG 1996 response criteria were also analyzed as secondary endpoints in addition to a documented response to ofatumumab treatment by the pre-specified composite measure [Table 3].

3.5.1. Reduction in Lymphocyte Count

Within 1 week following initiation of ofatumumab treatment, the combined group median lymphocyte count decreased by 41% (DR: 42%, BFR: 60%). By Week 4, the combined

group median lymphocyte count reduced by 83% (DR: 81%, BFR: 89%). Figure 10 shows the median lymphocyte count over time for DR, BFR and combined groups.

Figure 10 Median Lymphocyte Count, Study Hx-CD20-406



Initiation of treatment with ofatumumab resulted in a rapid decrease in median lymphocyte counts to levels within the normal range that was sustained throughout the treatment period. After ofatumumab treatment ended, the median lymphocyte count remained within the normal range for several weeks, followed by a gradual increase in median lymphocyte count that remained below baseline levels. However, this increase did not appear to be as rapid as the increase observed between the screening and baseline visits.

3.5.2. Resolution of Lymphadenopathy

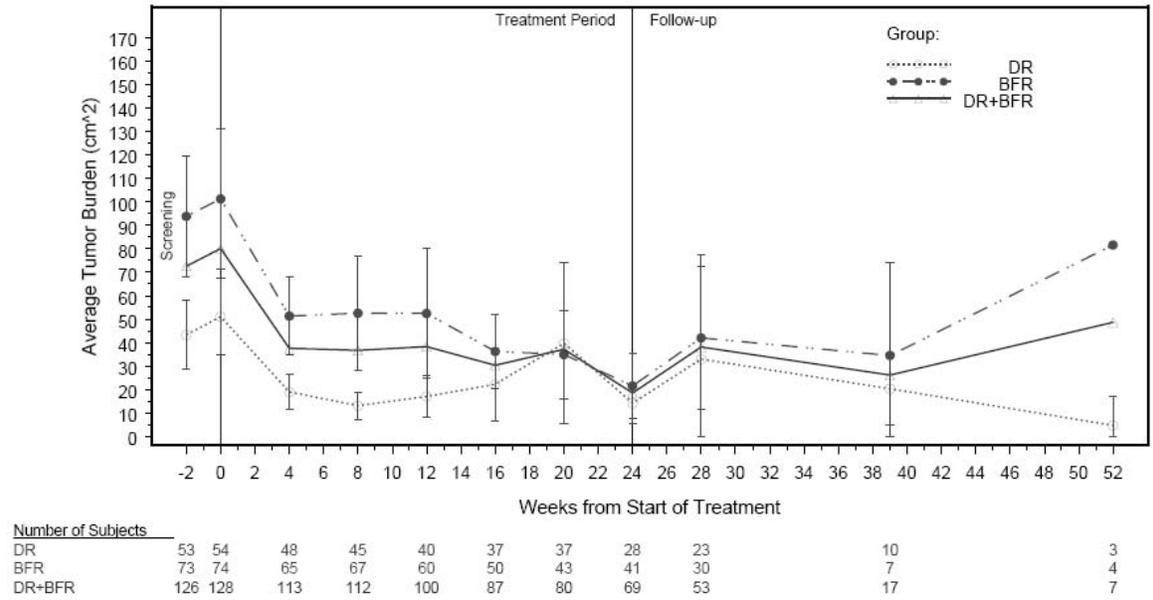
Lymphadenopathy can cause physical discomfort in CLL subjects, particularly in those with bulky disease (lymph nodes >5 cm). Decrease in size or resolution of lymphadenopathy (all nodes <1 cm) can alleviate discomfort and improve a subject's cosmetic appearance. Lymphadenopathy was assessed by physical exam at each visit as part of the assessment of response. For each assessed lymph node, the diameter in two separate dimensions of the largest palpable node from each of the assessed sites (cervical, axillary, supraclavicular, inguinal, and femoral) was measured and recorded as the sum of the products of greatest diameters (SPD). Lymph nodes with the largest diameter <1 cm were considered normal and were not considered in the response evaluation. Lymph node size, as measured by physical examination and reported as SPD, was assessed from baseline until Month 24.

Within 4 weeks following initiation of ofatumumab treatment, median lymph node SPD decreased by 60% in the combined group (DR: 71%, BFR: 51%). At Week 8, the overall median decrease in SPD versus baseline was 69% (DR: 76%, BFR: 63%). Reductions in

median SPD continued during the treatment period. At Week 24, the reduction in median SPD versus baseline in the combined group was 81% (DR: 78%, BFR 83%).

Figure 11 shows the change in the average tumor burden (the sum total of SPD at each time-point divided by the number of evaluable subjects) during screening, during the treatment period, and during follow-up, stratified by group. For subjects with missing baseline data, latest screening or unscheduled data were carried forward to baseline. Data were excluded upon death, study withdrawal, or initiation of next CLL therapy. Due to the limited number of evaluable subjects, data beyond Week 52 was not included.

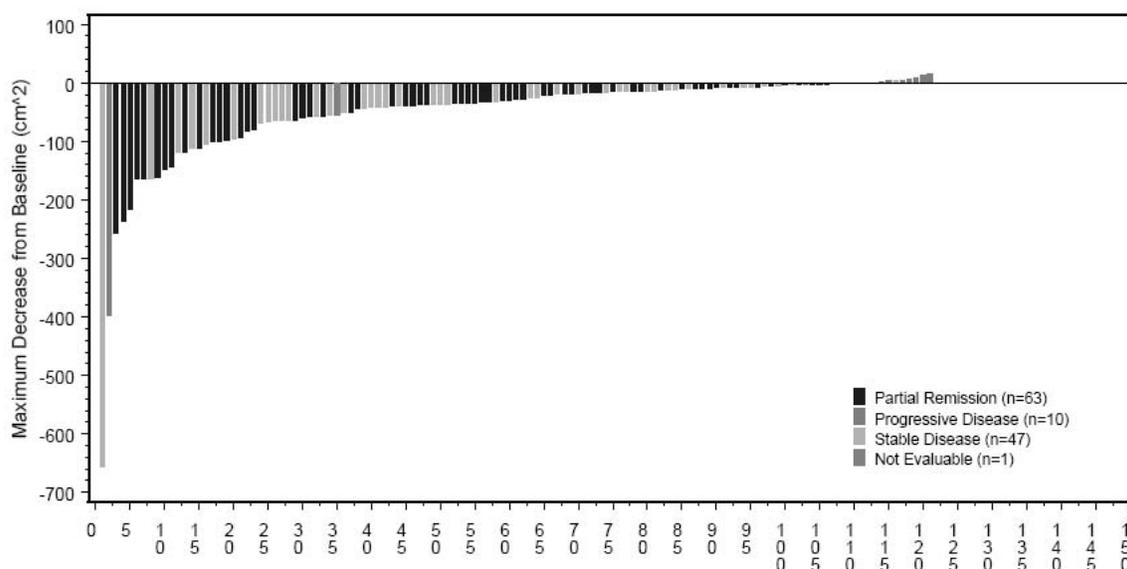
Figure 11 Average Palpable Tumor Burden (in cm²) Over Time in Subjects with Lymphadenopathy at Baseline, Study Hx-CD20-406



After the end of treatment, the degree of lymphadenopathy remained below baseline for another 6 months through Week 52, although data was limited by the declining number of evaluable subjects. The pattern of decrease in the average tumor burden was consistent in both the DR and BFR groups.

The maximum decrease in SPD was quantified in cm² for each subject in the combined group, by response and is presented in Figure 12.

Figure 12 Maximum Decrease in SPD from Baseline in Subjects with Lymphadenopathy at Baseline, Study Hx-CD20-406 (Combined DR+BFR)



Most subjects (82%, 99/121) experienced a reduction in SPD of at least 5 cm² during the study, with 18 subjects experiencing a decrease ≥ 100 cm². The decrease in SPD during treatment with ofatumumab was not only limited to responders, as subjects with SD or even PD also saw an impressive reduction in tumor load in the lymph node compartment.

The number of consecutive months that subjects experienced a >50% reduction or complete resolution of lymphadenopathy in the combined group was measured to determine the duration of meaningful improvement in lymphadenopathy. A 50% or greater decrease meets the criteria for a partial remission for this parameter, while complete resolution meets the criteria for a complete remission. Table 12 summarizes the improvements and complete resolution of lymphadenopathy for subjects with baseline palpable lymphadenopathy.

Table 12 Duration of Improvement of Lymphadenopathy in Subjects with Palpable Lymphadenopathy at Baseline, Study Hx-CD20-406

	Combined Group (DR+BFR) n=129	
	> 50% Decrease	100% Decrease
Duration of Improvement of Lymphadenopathy		
at least 2 months, n (%)	70 (54)	17 (13)
at least 4 months, n (%)	47 (36)	8 (6)
at least 6 months, n (%)	13 (10)	2 (2)

After initiation of treatment with ofatumumab, the majority of subjects with baseline lymphadenopathy had at least a 50% reduction of lymphadenopathy at some time during the study. The decrease was rapid, with an approximate 50% decrease in average tumor

burden in the palpable lymph nodes by Week 4. The decrease continued throughout the treatment period, and did not return to baseline after the end of treatment. The decrease in the lymph node SPD as best response exceeded 100 cm² in some subjects. The benefit was clinically meaningful and durable, with more than half of subjects, including both responders and non-responders, experiencing a period of reduction in lymphadenopathy lasting at least 2 consecutive months, and for at least 6 consecutive months in some subjects.

3.5.3. Constitutional Symptoms

Night sweats, weight loss, fever, and extreme fatigue are debilitating constitutional symptoms commonly associated with active CLL. Resolution of constitutional symptoms improves the feeling of well-being, which can be a meaningful clinical benefit. Constitutional symptoms were reported by subjects and results captured by investigators every 4 weeks during the treatment follow-up period as part of assessment of response.

Complete resolution of all constitutional symptoms was analyzed over time and by response. Complete resolution of all constitutional symptoms was defined as presence of at least one symptom at baseline followed by the absence of all symptoms thereafter. Data was not included after initiation of next CLL therapy, study withdrawal or death.

At baseline, 77 subjects suffered from constitutional symptoms (31 DR, 46 BFR), 60 subjects had no constitutional symptoms (28 DR, 32 BFR) and data were missing for one BFR subject. More than three-quarters of subjects with baseline constitutional symptoms experienced complete resolution of all symptoms for at least 2 months during the study (79%, 61/77). All but one of these 61 subjects experienced complete resolution during the treatment period. Nearly all responders with baseline constitutional symptoms experienced complete resolution (93%, 40/43) (Figure 14). Notably, all subjects without constitutional symptoms at baseline remained symptom-free during the study.

In each of the DR and BFR groups, the change in percentage of subjects with constitutional symptoms over time is presented in Figure 13. Data were limited by the declining number of evaluable subjects over time, and were too limited to be included beyond Week 52.

Figure 13 Constitutional Symptoms Over Time by Group, in Subjects with at Least One Symptom Present at Baseline

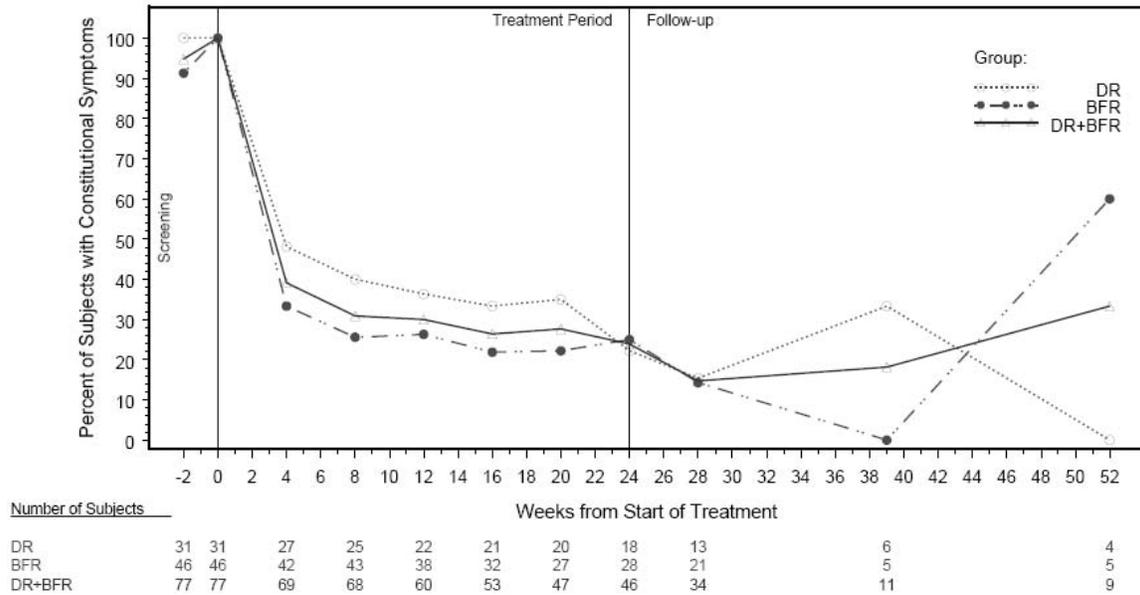
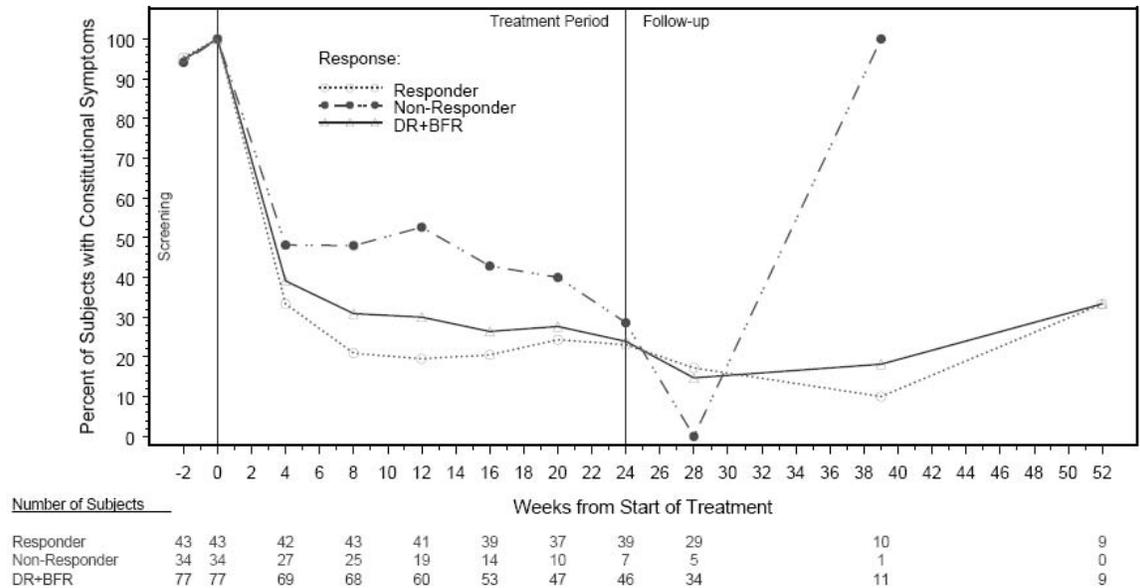


Figure 14 Constitutional Symptoms Over Time by Response, in Subjects with at Least One Symptom Present at Baseline



To provide further detail on the duration of the benefit of resolution of constitutional symptoms, [Table 13](#) summarizes the consecutive number of months that subjects were symptom-free for each of the DR, BFR, and combined groups. The absence of constitutional symptoms for at least 2 consecutive months is a component of complete remission according to the NCIWG 1996 CLL response criteria. More than half of subjects in the combined group with baseline constitutional symptoms were symptom-free for at least 2 months, with some subjects symptom-free for at least 6 months.

Table 13 Duration of Constitutional Symptom-Free Period in Subjects with Symptoms at Baseline

Duration of Symptom-Free Period	DR n=31	BFR n=46	Combined DR+BFR n=77
at least 2 months, n (%)	15 (48)	29 (63)	44 (57)
at least 4 months, n (%)	12 (39)	20 (43)	32 (42)
at least 6 months, n (%)	7 (23)	7 (15)	14 (18)

Includes only subjects with baseline constitutional symptoms
Duration of time is in consecutive months

In summary, more than half of the subjects in each group with baseline constitutional symptoms experienced complete resolution of symptoms regardless of response. The resolution was rapid, with more than half of subjects experiencing complete resolution by Week 4. The complete resolution was sustained through the treatment period, and remained below baseline after the end of treatment. The complete resolution was durable, with more than half of subjects, including both responders and non-responders, experiencing a symptom-free period for at least 2 consecutive months, and for at least 6 consecutive months in some subjects.

3.5.4. Resolution of Hepatomegaly and Splenomegaly (Organomegaly)

CLL subjects may experience abdominal discomfort, fullness, or early satiety resulting from hepatomegaly or splenomegaly. Hepatomegaly and splenomegaly were assessed by physical exam at each visit as part of the assessment of response. Complete resolution of hepatomegaly was defined as the presence of an enlarged palpable liver at baseline followed by absence of hepatomegaly post-baseline. Complete resolution of splenomegaly was defined as the presence of an enlarged palpable spleen at baseline followed by absence of splenomegaly post-baseline.

More than two-thirds of subjects in the DR and BFR groups experienced complete resolution of hepatomegaly for at least 2 months during the study (71%, 24/34), and all occurred during the treatment period. A total of 17 of 24 subjects experienced complete resolution of hepatomegaly during response. The absence of hepatomegaly was maintained in all subjects without baseline hepatomegaly and only one subject had new or worsening hepatomegaly as best response during the study period. [Figure 15](#) shows the maximum decrease in hepatomegaly in subjects with hepatomegaly at baseline.

More than half of subjects in the DR and BFR groups experienced complete resolution of splenomegaly some time during the study (60%, 42/70), and all occurred during the treatment period. A total of 34 of 42 subjects experienced complete resolution of splenomegaly during response. The absence of splenomegaly was maintained in the majority of subjects without baseline splenomegaly and only two subjects had worsening of splenomegaly as best response during the study period. [Figure 16](#) shows the maximum decrease in splenomegaly in subjects with splenomegaly at baseline.

Figure 15 Maximum Decrease in Hepatomegaly in Combined Group (DR+BFR) Subjects with Hepatomegaly at Baseline, Study Hx-CD20-406

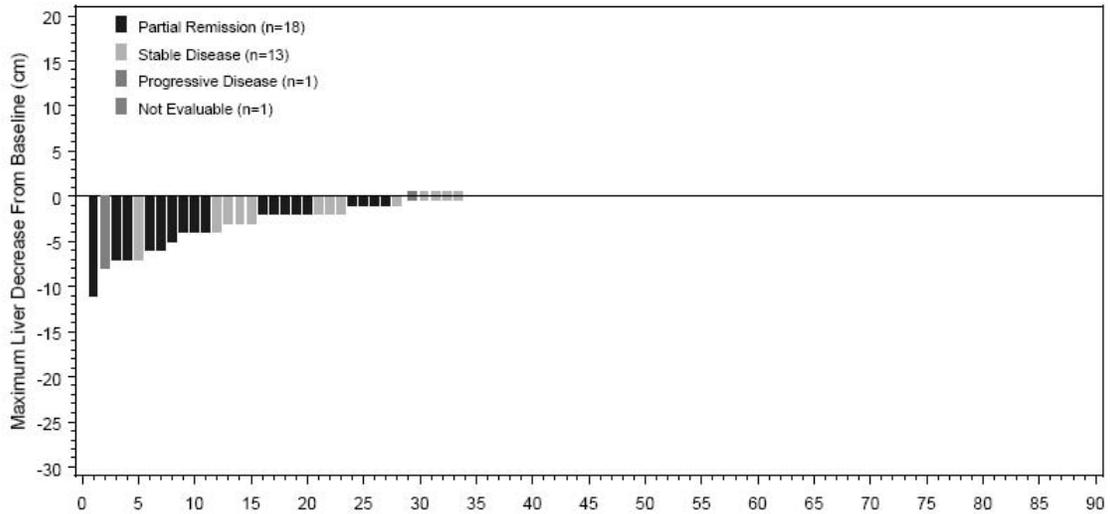
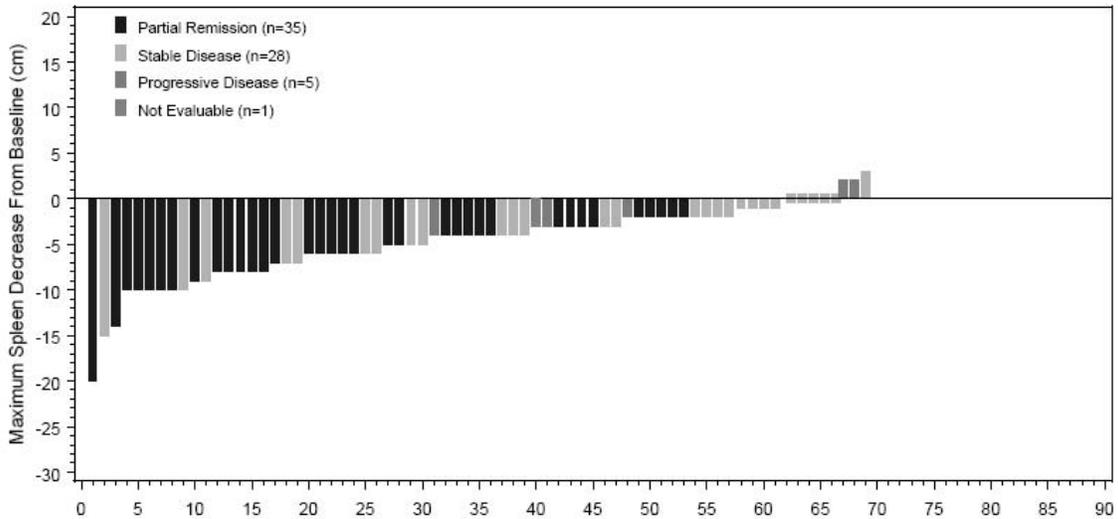


Figure 16 Maximum Decrease in Splenomegaly in Combined Group (DR+BFR) Subjects with Splenomegaly at Baseline, Study Hx-CD20-406



To provide further detail on the duration of benefit of reduction or complete resolution of organomegaly, the number of consecutive months that subjects experienced each type of reduction was analyzed for the DR and BFR group. A 50% or greater decrease lasting at least 2 months met the criteria for partial remission and complete resolution met the criteria for complete remission. [Table 14](#) summarizes the duration of resolution for subjects with baseline hepatomegaly and for the subset of subjects with baseline hepatomegaly >10 cm. [Table 15](#) summarizes the duration of resolution data for subjects

with baseline splenomegaly and for the subset of subjects with baseline organomegaly >10 cm.

Table 14 Duration of Hepatomegaly Decrease in Combined Group (DR+BFR) Subjects with Hepatomegaly at Baseline, Study Hx-CD20-406

Duration of Hepatomegaly Decrease	Baseline Hepatomegaly n=39		Baseline >10 cm Hepatomegaly n=2	
	>50% Decrease	100% Decrease	>50% Decrease	100% Decrease
at least 2 months, n (%)	24 (62)	20 (39)	1 (50)	0
at least 4 months, n (%)	15 (38)	14 (39)	0	0
at least 6 months, n (%)	5 (13)	4 (10)	0	0

Includes only subjects with baseline hepatomegaly
Duration of time is in consecutive months

Table 15 Duration of Splenomegaly Decrease in Combined Group (DR+BFR) Subjects with Splenomegaly at Baseline, Study Hx-CD20-406

Duration of Splenomegaly Decrease	Baseline Splenomegaly n=76		Baseline >10 cm Splenomegaly n=13	
	>50% Decrease	100% Decrease	>50% Decrease	100% Decrease
at least 2 months, n (%)	42 (55)	30 (39)	4 (31)	1 (8)
at least 4 months, n (%)	33 (43)	21 (28)	3 (23)	1 (8)
at least 6 months, n (%)	9 (12)	7 (9)	0	0

Includes only subjects with baseline splenomegaly
Duration of time is in consecutive months

Subjects with baseline hepatomegaly or splenomegaly, including those with massive organomegaly (>10 cm), experienced clinically meaningful, durable reductions in liver and/or spleen size after initiation of ofatumumab treatment. A decrease in organomegaly was observed throughout the treatment period, and did not appear to return to baseline after the end of treatment, and in responders for up to a year. More than half of subjects had a reductions lasting at least 2 consecutive months. Reductions were also observed for a durable period in some subjects with baseline massive organomegaly. Complete resolution of organomegaly occurred in more than one-third of subjects with baseline organomegaly for at least 2 months, meeting the criteria of a complete remission for this parameter, including two subjects with massive organomegaly >10 cm at baseline.

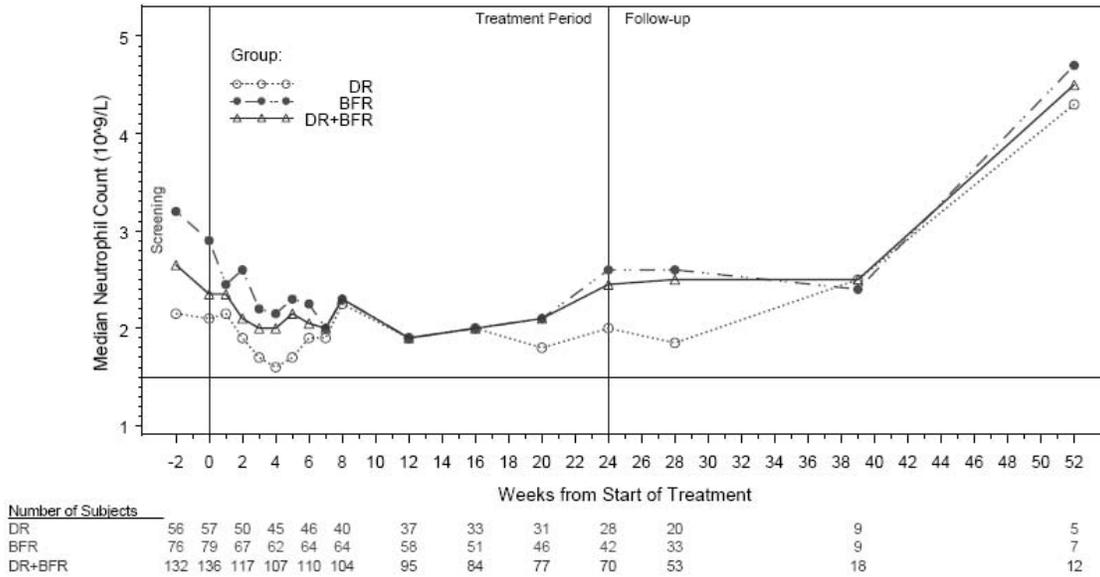
3.5.5. Changes in Neutrophil Count

Refractory CLL itself, cumulative damage from prior treatments, and advanced age can contribute to neutropenia in this study population. Treatment-induced neutropenia may increase the risk of developing serious and possibly life-threatening infections that are frequent complications and a major cause of death. Chemotherapy usually causes neutropenia during treatment, exacerbating this risk.

Changes in neutrophil counts were analyzed over time in the DR, BFR and combined group, and by response. Subjects were excluded from the analysis once they received concomitant growth factors for neutropenia (G-CSF or GM-CSF). Data were also excluded upon death, study withdrawal, or initiation of next CLL therapy.

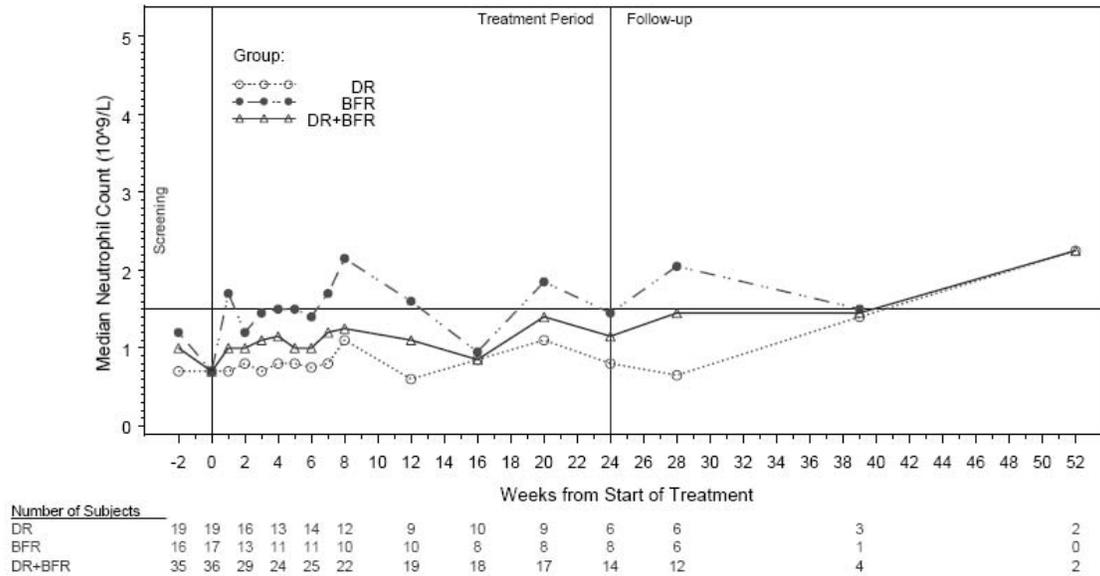
In the DR and BFR group, median neutrophil counts at baseline were normal ($2.3 \times 10^9/L$). The median neutrophil counts fluctuated but remained above the normal threshold level for CLL of $1.5 \times 10^9/L$ during the treatment period and during follow-up in both the DR and BFR groups (Figure 17).

Figure 17 Median Neutrophil Count Over Time By Group, Study Hx-CD20-406



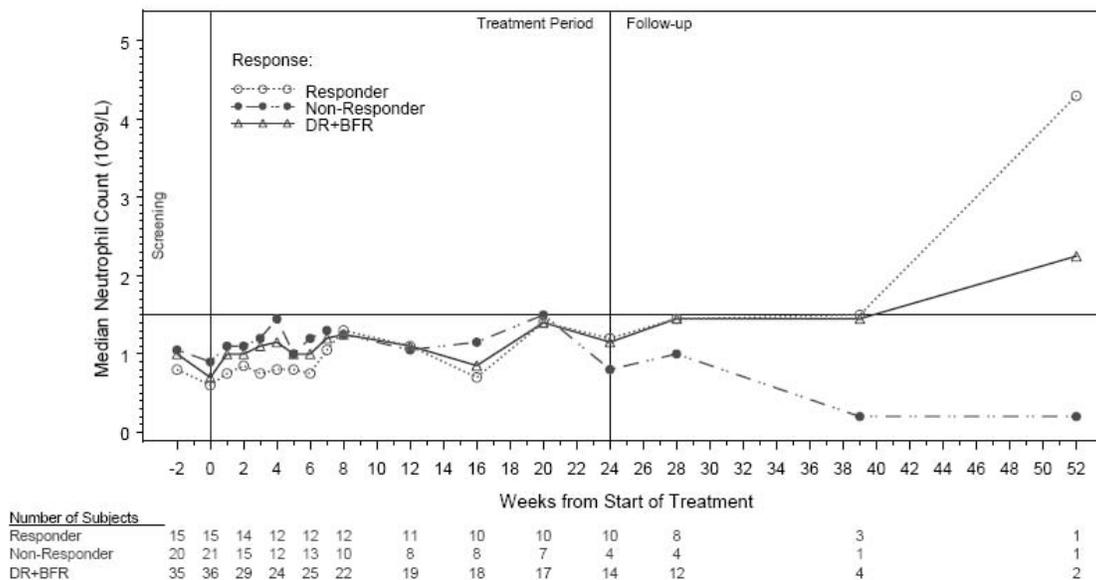
Median neutrophil counts were also analyzed in a subset of subjects with baseline neutropenia ($<1.5 \times 10^9/L$). At baseline, 36 subjects were neutropenic (19 DR, 17 BFR), with neutrophil counts below the normal value for CLL of $1.5 \times 10^9/L$ (Figure 18).

Figure 18 Median Neutrophil Count ($10^9/L$) over Time in Subjects with Baseline Neutropenia, Study Hx-CD20-406



For patients with data during follow-up through Week 52, median neutrophil counts remained at or near $1.5 \times 10^9/L$ although data were limited by the declining number of evaluable subjects. The pattern of neutrophil levels appeared similar in both the DR and BFR groups and by response (Figure 19). The median neutrophil count did not improve to above $1.5 \times 10^9/L$ during the study period for subjects with baseline neutropenia.

Figure 19 Median Neutrophil Count ($10^9/L$) over Time in Subjects with Baseline Neutropenia, by Response, Study Hx-CD20-406



Nevertheless, increases in neutrophil counts from $<1 \times 10^9/L$ to $>1 \times 10^9/L$ post-baseline, and an increase to normal ($>1.5 \times 10^9/L$) post-baseline were observed in this study at some time-point in a limited number of subjects. Increases from $<1.5 \times 10^9/L$ to $>1.5 \times 10^9/L$ post-baseline were also observed. Table 16 summarizes the duration of time in consecutive months that subjects improved neutrophil counts to $>1 \times 10^9/L$ or $>1.5 \times 10^9/L$ in the DR and BFR group.

Table 16 Duration of Change in Neutrophil Count in Combined Group (DR+BFR) Subjects with Baseline Neutrophil Count Less than 1 or $1.5 \times 10^9/L$, Study Hx-CD20-406

Duration of Change in Neutrophil Count	$<1 \times 10^9/L$ at baseline to $>1 \times 10^9/L$ post-baseline n=22	$<1 \times 10^9/L$ at baseline to $>1.5 \times 10^9/L$ post-baseline n=22	$<1.5 \times 10^9/L$ at baseline to $>1.5 \times 10^9/L$ post-baseline n=36
at least 2 months	5 (23)	3 (14)	6 (36)
at least 4 months	4 (18)	1 (5)	2 (6)
at least 6 months	1 (5)	0	0

Excludes subject visits from the date of first time on growth factors

For subjects with missing baseline data, latest screening/unscheduled data were carried forward to baseline

Duration of time is in consecutive months

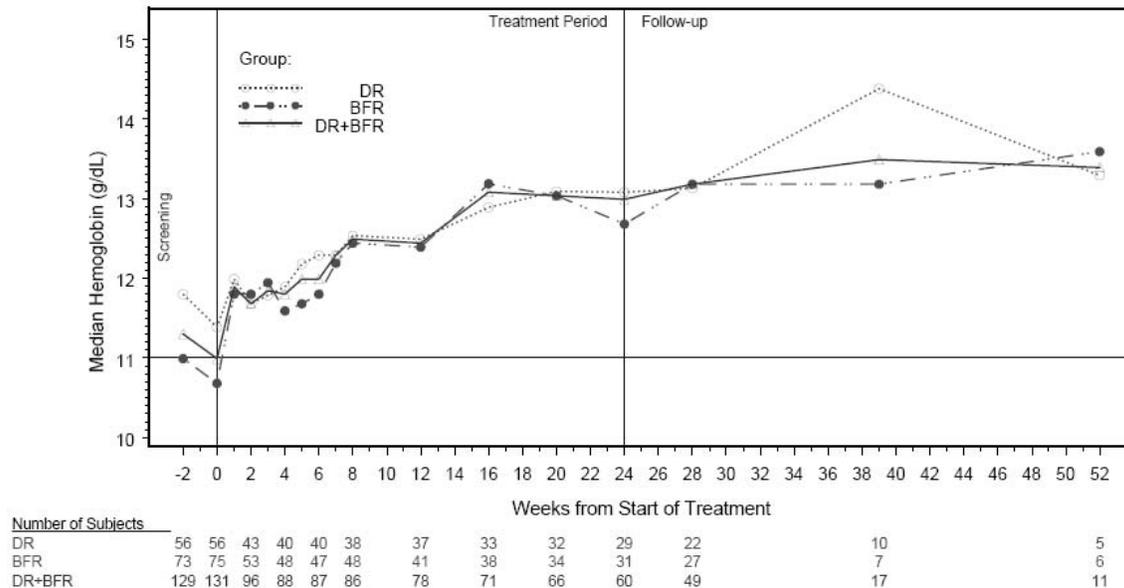
These data showed that the median neutrophil counts did not worsen overall during the treatment period, in fact, some improvement was seen in the BFR group (data not shown). It is acknowledged that the analysis over time is limited by survival bias, as patients who die or withdraw from the study no longer contribute to the dataset. It should be kept in mind that cytotoxic chemotherapy in this subject population would most likely have worsened the median neutrophil counts.

3.5.6. Improvement in Hemoglobin Values

Refractory CLL itself, the damage from prior treatments and advanced age can contribute to low hemoglobin values in patients with CLL. Anemia can cause fatigue, limiting activities of daily living, and may require red cell transfusions or treatment with erythropoietin. Normalization or a clinically meaningful increase in hemoglobin may relieve subjects of the signs and symptoms of anemia.

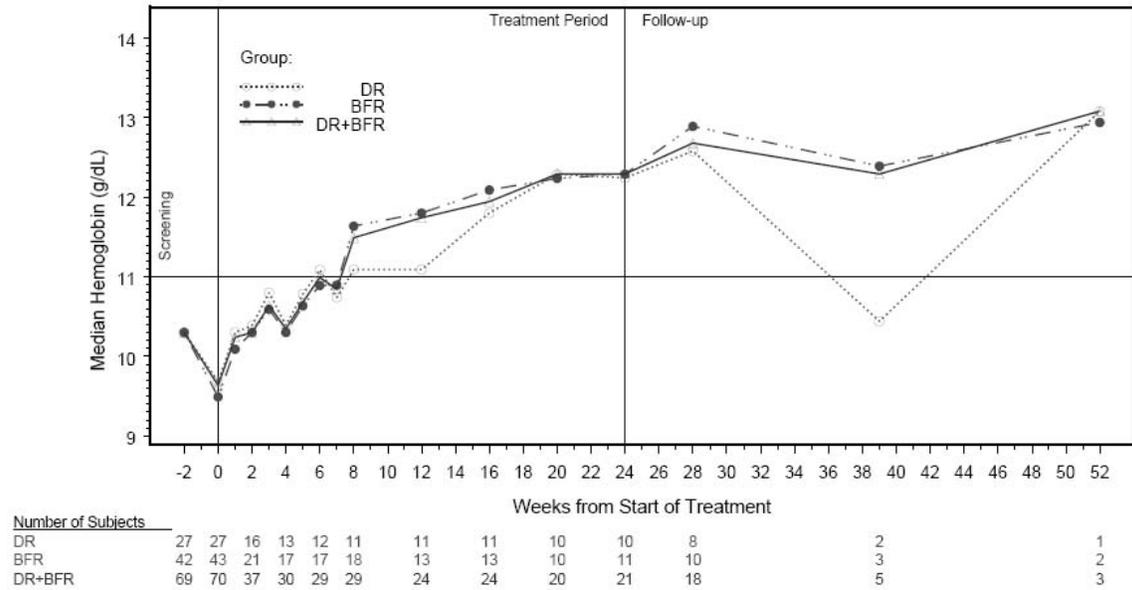
Hemoglobin values were assessed at all visits by a central laboratory. Subjects were excluded from the analysis once they received concomitant red cell transfusions or erythropoietin treatment. Data were excluded following initiation of next CLL therapy, after study withdrawal and death. The results showed that median hemoglobin values increased steadily from baseline through the treatment period and into the follow-up period for subjects with data up to one year. [Figure 20](#) shows improvement median hemoglobin concentration over time.

Figure 20 Median Hemoglobin Concentration over Time, Study Hx-CD20-406



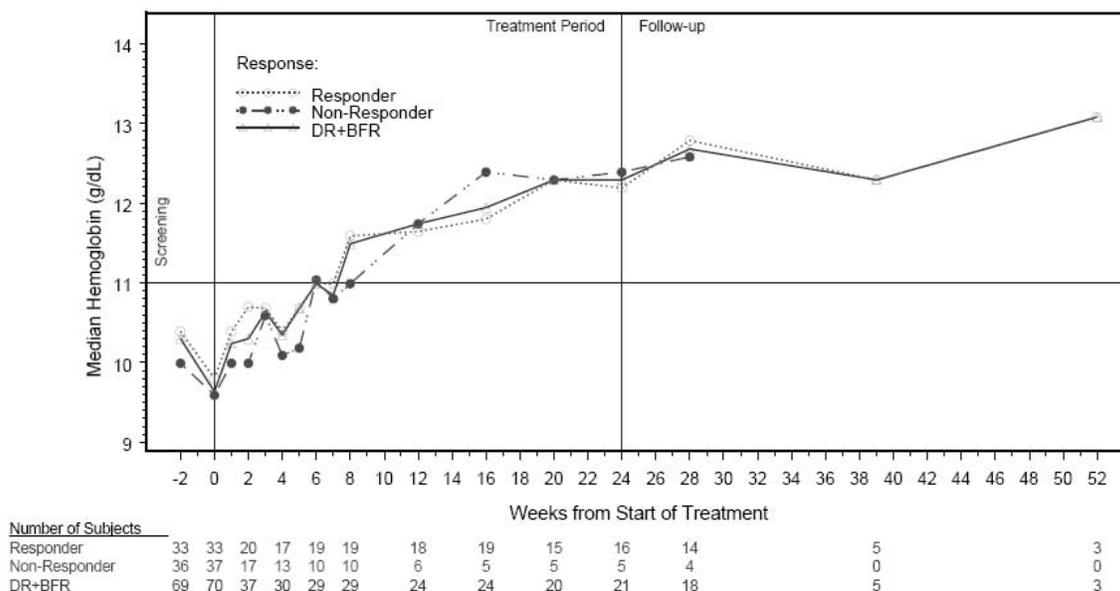
The NCIWG 1996 CLL response criteria defined hemoglobin levels >11.0 g/dL or a 50% improvement over baseline as a clinically beneficial response. Median hemoglobin values were also analyzed in a subset of subjects with baseline hemoglobin <11 g/dL ([Figure 21](#)). At baseline, 68 subjects (26 DR, 42 BFR), had hemoglobin levels <11g/dL. Data from the limited number of evaluable subjects beyond Week 52 was not included.

Figure 21 Median Hemoglobin over Time in Subjects with Anemia at Baseline, Study Hx-CD20-406



Median hemoglobin values improved steadily after ofatumumab treatment began, and by Week 8 were above 11 g/dL in the DR and BFR group. The improvement continued through Week 24 during the treatment period. Although the data is limited by the number of evaluable subjects during follow-up, median hemoglobin values remained normal through Week 52, with the exception of a transient decrease in the two evaluable DR subjects at Week 39. The pattern of improvement was consistent in both the DR and BFR groups regardless of response (Figure 22).

Figure 22 Median Hemoglobin over Time in Subjects with Anemia at Baseline, by Response, Study Hx-CD20-406 (DR+BFR)



An increase in hemoglobin of ≥ 2 g/dL from baseline is considered clinically meaningful and is the goal of treatment of anemia with erythropoietin. This improvement was observed in this study in a subset of subjects with baseline anemia. There were subjects in each of the groups with baseline hemoglobin < 10 g/dL that had improvement to > 12 g/dL, and subjects with baseline hemoglobin < 11 g/dL had improvements to > 11 g/dL. A small number of subjects in the DR and BFR group experienced clinically meaningful increases in hemoglobin counts for at least 2 months, with some having durable improvements for 4 or 6 months (Table 17).

Table 17 Duration of Change in Hemoglobin Count in Combined Group (DR+BFR) Subjects with Baseline Hemoglobin Count Less than 10 g/dL or Less than or Equal to 11 g/dL, Study Hx-CD20-406

Duration of Change in Hemoglobin Count	≤ 11 g/dL at baseline and ≥ 2 g/dL increase post-baseline n=70	< 10 g/dL at baseline and > 12 g/dL post-baseline n=47	< 11 g/dL at baseline and > 11 g/dL post-baseline n=70
at least 2 months	12 (17)	2 (4)	19 (27)
at least 4 months	4 (6)	1 (2)	13 (19)
at least 6 months	1 (1)	0	4 (6)

Excludes subject visits from the date of first time on growth factors

For subjects with missing baseline data, latest screening/unscheduled data were carried forward to baseline

Duration of time is in consecutive months

It should be noted that the analysis over time is limited by survival bias, as patients who die or withdraw from the study no longer contribute to the dataset. For patients who remained on study, the improvement was sustained through the treatment period, and did not decline to baseline after the end of treatment. This benefit was achieved without

transfusions or growth factor support, suggesting recovery of bone marrow function allowed by ofatumumab treatment. Given the fact that decreases in hemoglobin values would be expected with cytotoxic therapies, patients with fludarabine-refractory CLL may derive clinical benefit from the increase in hemoglobin associated with ofatumumab treatment.

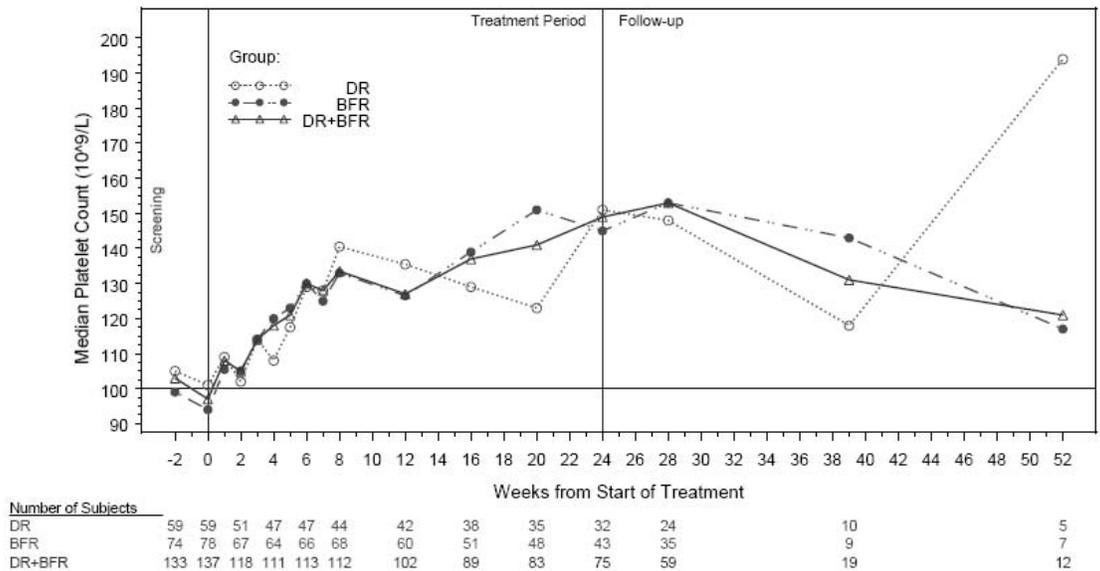
3.5.7. Improvement in Platelet Counts

Changes in platelet counts were analyzed over time in each of the DR, BFR and combined groups, and by response. Subjects were excluded from the analysis once they received platelet transfusions. Data were also excluded upon death, study withdrawal, or initiation of next CLL therapy.

Almost half of the subjects (46%, 46/100) with low platelets at baseline had documented improvement in platelet levels at some time during the study, with most of the improvements occurring during the treatment period. Nearly all of the subjects with normal or high platelet levels at baseline maintained their levels during the study (97%, 36/37). Only one subject had a worsening of a normal platelet level as best response during the study.

Median platelet counts increased steadily after ofatumumab treatment from $97 \times 10^9/L$ to more than $120 \times 10^9/L$ within 8 weeks, continued to rise to above $140 \times 10^9/L$, and remained above baseline values during follow-up, through Week 52. The pattern of improvement was consistent in both the DR and BFR groups (Figure 23).

Figure 23 Median Platelet Count over Time, Study Hx-CD20-406



Median platelet counts were also analyzed in a subset of subjects with baseline thrombocytopenia. At baseline, 73 subjects (29 DR, 44 BFR), had platelet counts below $100 \times 10^9/L$. Figure 24 presents the change in median platelet count during screening, during the treatment period, and during follow-up, stratified by group. Figure 25 presents the same data by response.

Figure 24 Median Platelet Count over Time in Subjects with Baseline Thrombocytopenia, Study Hx-CD20-406

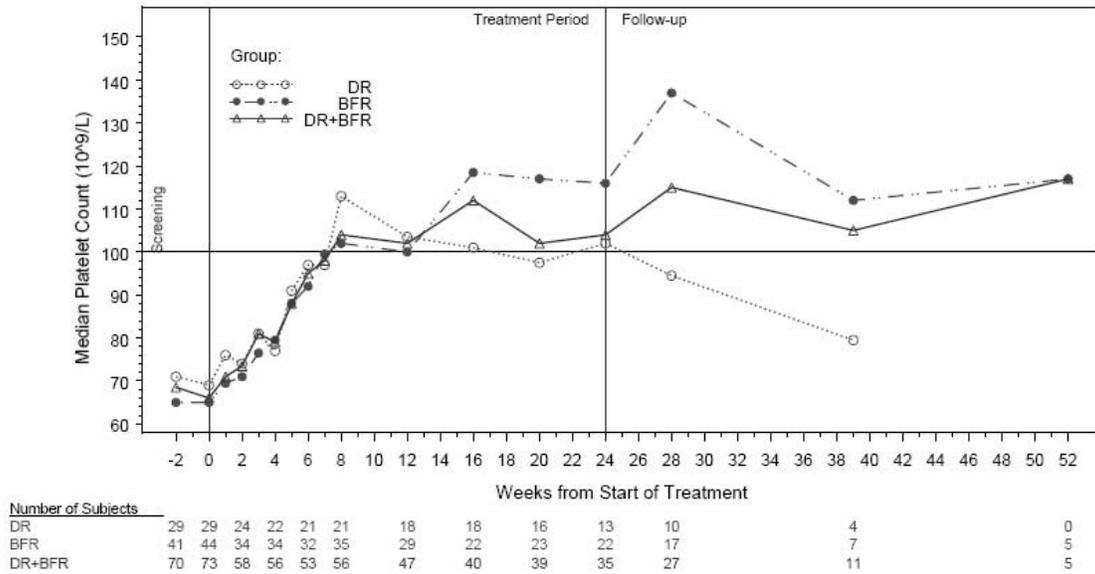
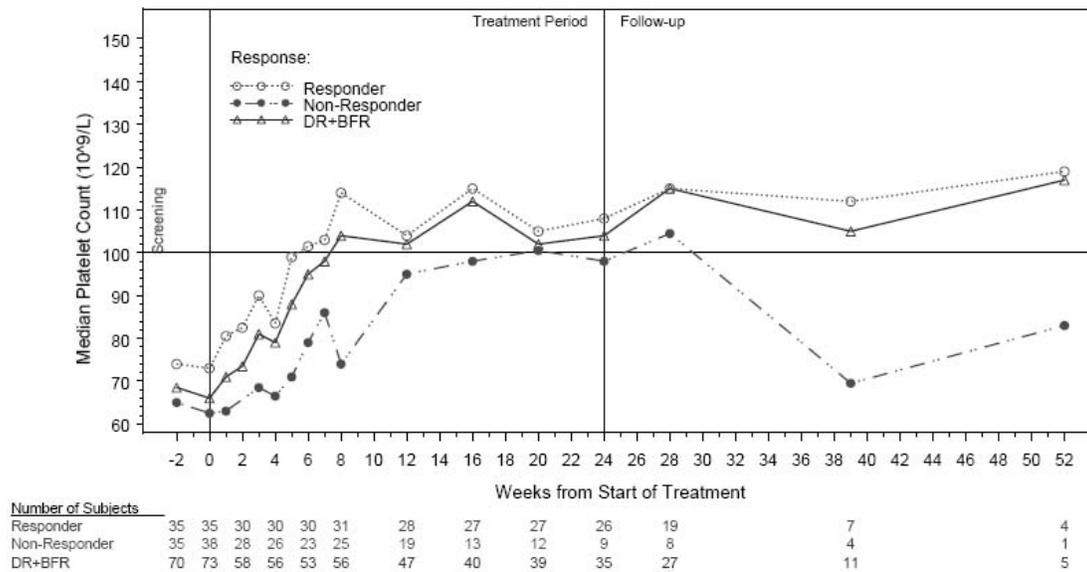


Figure 25 Median Platelet Count over Time in Subjects with Baseline Thrombocytopenia, by Response, Study Hx-CD20-406



A majority of subjects (66%) with baseline platelet levels of $<100 \times 10^9/L$ experienced a 50% increase in platelet count, or platelet levels above $100 \times 10^9/L$. Some subjects in the combined group improved from $<30 \times 10^9/L$ to $>30 \times 10^9/L$, thereby reducing the risk of bleeding from Grade 3 or Grade 4 thrombocytopenia. Normalization of platelet counts to above $100 \times 10^9/L$ was observed in 46% of subjects in both groups. The improvement was steady and was sustained through the treatment period. During the course of the study, 10% of subjects received platelet transfusions.

The median platelet counts steadily increased to above $100 \times 10^9/L$ by Week 8 in the combined group and in responders. The median platelet counts remained near or above $100 \times 10^9/L$ through Week 24 during the treatment period. Although the number of evaluable subjects was limited and interpretation affected by survival bias, for those subjects who had achieved a response and who remained on study, the median platelet counts remained above $100 \times 10^9/L$ through Week 52 for the combined group, the BFR and DR group. Non-responders also had an increase of median platelet counts, however, the median platelet level did not reach $100 \times 10^9/L$ until Week 22, compared to Week 6 for responders.

A smaller number of subjects in the combined group experienced clinically meaningful increases in platelet counts for at least 2 months, with some having durable improvements for 4 or 6 months. Table 18 summarizes the duration of time in consecutive months that subjects in the combined group experienced improved platelet counts.

Table 18 Duration of Change in Platelet Count in Combined Group (DR+BFR) Subjects with Baseline Platelet Count Less than $100 \times 10^9/L$ and Less than $<30 \times 10^9/L$, Study Hx-CD20-406

Duration of Change in Hemoglobin Count	$<100 \times 10^9/L$ at baseline to $>50\%$ increase or $>100 \times 10^9/L$ post-baseline n=73	$<30 \times 10^9/L$ at baseline to $>30 \times 10^9/L$ post-baseline n=13
at least 2 months	29 (40)	3 (23)
at least 4 months	17 (23)	1 (8)
at least 6 months	6 (8)	0

Excludes subject visits from the date of first time on growth factors

For subjects with missing baseline data, latest screening/unscheduled data were carried forward to baseline

Duration of time is in consecutive months

In summary, an increase in median platelet values was observed in the combined group, regardless of response, and in subject with baseline thrombocytopenia. It is acknowledged that the analysis over time is limited by survival bias, as subjects who die or withdraw from the study no longer contribute to the dataset. However, for subjects who remained on study, the improvement was sustained through the treatment period, and did not decrease to baseline after the end of treatment. This benefit was achieved without transfusions, suggesting recovery of bone marrow function allowed by ofatumumab treatment. Given the fact that decreases in platelet counts would be expected with cytotoxic therapies, patients with fludarabine-refractory CLL may derive clinical benefit from the increase in platelet counts associated with ofatumumab treatment.

3.5.8. Summary of Improvements in Individual Components of Response Criteria

To meet the criteria for response according to the NCIWG 1996 CLL response criteria,, responses were required to be maintained for at least two months (56 days). Table 19 shows the subjects who had resolution or improvement in each of the response criteria parameters for a minimum of two months.

Table 19 Summary of Clinical Improvements with a Minimum of 2 Months Duration in Subjects with Abnormalities at Baseline, Study Hx-CD20-406

Section Number	Efficacy Endpoint	DR N=59	BFR N=79	Combined DR+BFR N=138
		Subjects with benefit / Subjects with abnormality at baseline, (%)		
3.5.1	≥50% improvement in Lymphocyte count	31/42 (74)	44/64 (69)	75/106 (71)
3.5.1	Normalization of Lymphocyte count (≤4x10 ⁹ /L)	20/42 (48)	26/64 (41)	46/106 (43)
3.5.3	Complete Resolution of Constitutional Symptoms ^a	15/31 (48)	29/46 (63)	44/77 (57)
3.5.2	≥50% improvement in Lymphadenopathy ^b	34/55 (62)	36/74 (49)	70/129 (54)
3.5.2	Complete resolution of Lymphadenopathy	9/55 (16)	8/74 (11)	17/129 (13)
3.5.4	≥50% improvement in Splenomegaly	16/30 (53)	26/46 (57)	42/76 (55)
3.5.4	Complete resolution of Splenomegaly	14/30 (47)	16/46 (35)	30/76 (39)
3.5.4	≥50% improvement in Hepatomegaly	11/18 (61)	13/21 (62)	24/39 (62)
3.5.4	Complete resolution of Hepatomegaly	9/18 (50)	11/21 (52)	20/39 (51)
3.5.6	Hemoglobin <11 g/dL to >11 g/dL post-baseline	8/26 (31)	11/42 (26)	19/68 (28)
3.5.7	Platelet counts <100x10 ⁹ /L to >50% increase or >100x10 ⁹ /L post-baseline	12/29 (41)	17/44 (39)	29/73 (40)
3.5.5	Neutrophils <1.5x10 ⁹ /L to >1.5x10 ⁹ /L post-baseline	1/19 (5)	5/17 (29)	6/36 (17)

- a. Complete resolution of constitutional symptoms (fever, night sweats, fatigue, and weight loss) defined as the presence of any symptoms at baseline, followed by no symptoms present.
- b. Lymphadenopathy measured by sum of the products of greatest diameters (SPD) as assessed by physical examination

Improvement or complete resolution of disease symptoms (maintained for ≥2 months) was observed in a large proportion of subjects, including subjects considered non-responders by NCIWG 1996 criteria. Improvements in hematologic values were also observed in subjects with abnormal baseline values, particularly for platelet counts and hemoglobin. The effect on neutrophils was less profound (consistent with the observed effects on median neutrophils over time), nevertheless, 17% of subjects who were neutropenic at baseline had normalization for at least 2 months.

3.6. Comparison of Response rates according to Baseline Factors, Study Hx-CD20-406

Response rates were similar across subgroups with no statistically significant differences observed with regard to age, prior therapy or palpable lymph nodes at baseline (Table 20).

Table 20 Comparison of Response Rate by Characteristics at Baseline

Subgroup	DR N=59	BFR N=79	Combined DR+BFR N=138
RR, n (%)	34 (58)	37 (47)	71 (51)
Prior Therapeutic regimen, responders (%)			
Prior rituximab	19/35 (54)	19/43 (44)	38/78 (49)
No prior rituximab	15/24 (63)	18/36 (50)	33/60 (55)
Prior FC ^a	14/19 (74)	18/32 (56)	32/51 (63)
No prior FC	20/40 (50)	19/47 (40)	39/87 (45)
Prior FCR ^b	8/16 (50)	7/16 (44)	15/32 (47)
No Prior FCR	26/43 (60)	30/63 (48)	56/106 (53)
Age, responders (%)			
≥65 years	14/27 (52)	15/33 (45)	29/60 (48)
≥70 years	6/10 (60)	8/19 (42)	14/29 (48)
Largest Palpable lymph node at Baseline, responders (%)			
>0 to 2 cm	11/18 (61)	7/11 (64)	18/29 (62)
>2 to <5cm	11/18 (61)	7/17 (41)	18/35 (51)
≥5 cm	8/18 (44)	20/47 (43)	28/65 (43)
Chromosomal Abnormalities, responders (%)			
17p deletion	7/17 (41)	2/14 (14)	9/31 (29)
11q deletion	15/24 (63)	14/22 (64)	29/46 (63)

a. FC = fludarabine+ cyclophosphamide; FC alone as qualifying therapy for inclusion in the trial

b. FCR = fludarabine + cyclophosphamide + rituximab; FCR with or without other drugs as qualifying therapy for inclusion in the study

Ofatumumab induced responses in the refractory subject population regardless of prior CLL therapies, including use of fludarabine and rituximab alone or in combination with other therapies. Older subjects, who typically have lower response rates to CLL therapies, responded to ofatumumab in a similar manner to the overall population. Lymph node size at baseline did not appear to significantly affect the response to ofatumumab in either the DR or BFR groups, although the response rate in subjects with large lymph nodes >5 cm were numerically lower compared to subjects with smaller lymph node enlargements.

Deletions of 17p and 11q were the most common chromosomal abnormalities detected overall and in both the DR and BFR groups. Deletions of 17p usually result in very poor response to other CLL treatment. Subjects with a 17p deletion had a similar response rate to subjects without 17p deletion overall and in the DR group. BFR subjects with 17p deletions had a lower response rate that was statistically significant compared to subjects without 17p deletions (55% vs. 14%, p=0.0073).

Deletions of 11q are also associated with poor response to CLL treatment. Despite this, subjects with 11q deletions had similar response rates to subjects without 11q deletions, in both the DR and BFR groups.

Table 21 shows the response rates for subjects who were refractory to available CLL therapies.

Table 21 Refractory Status and Response Rates in DR and BFR Groups

DR Group	Fludarabine and Alemtuzumab Refractory (DR)	Prior Alkylator, Refractory to Fludarabine and Alemtuzumab Containing Regimen	Refractory to Latest Alkylator and Fludarabine and Alemtuzumab	Refractory to Last Therapy	No Response >6 months after latest Rituximab-Based Therapy
Refractory (%)	100	93 (55/59)	78 (46/59)	95 (56/59)	53 (31/59)
Response rate (%)	58 (34/59)	56 (31/55)	59 (27/46)	55 (31/56)	55 (17/31)
BFR Group	Bulky Fludarabine Refractory (BFR)	Prior Alkylator, Refractory to Fludarabine and Alemtuzumab Containing Regimen	Refractory to Latest Alkylator and Fludarabine and Alemtuzumab	Refractory to Last Therapy	No Response >6 months after latest Rituximab-Based Therapy
Refractory (%)	100	92 (73/79)	82 (65/79)	90 (71/79)	42 (33/79)
Response rate (%)	47 (37/79)	47 (34/73)	48 (31/65)	49 (35/71)	48 (16/33)

Response rates were consistent within both the DR and BFR groups, regardless of being refractory to any type of available CLL therapies, including alkylating-agents (chlorambucil and bendamustine), fludarabine, alemtuzumab and rituximab.

3.7. Efficacy Summary

The efficacy results from pivotal study Hx-CD20-406 demonstrate compelling efficacy of ofatumumab monotherapy in two fludarabine-refractory populations, with response rates of 47-58%. The responses occurred quickly and were durable, and were consistent across subgroups. Landmark analysis at 12 weeks showed that responders in both DR and BFR groups had markedly longer median survival than non-responders. Moreover, additional subjects who were non-responders by NCIWG 1996 CLL response criteria experienced improvement or resolution of clinical symptoms and hematological parameters of CLL. Overall, the pre-planned interim analysis from pivotal study Hx-CD20-406 showed efficacy suggestive of clinical benefit for ofatumumab monotherapy in the treatment of subjects with fludarabine-refractory CLL.

3.8. Overview of Safety

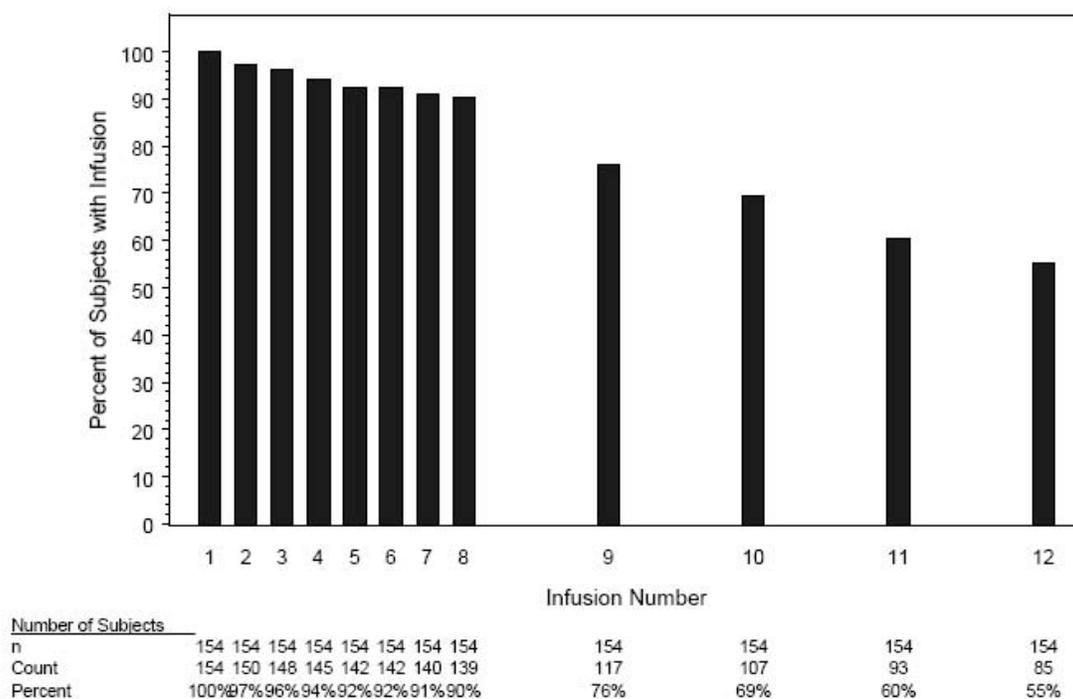
The safety data from the Hx-CD20-406 studies demonstrated that treatment with ofatumumab was generally well tolerated in the study population with advanced, heavily pre-treated, highly refractory CLL that are at high risk for rapid disease progression and infectious complications. Common adverse events fall predominantly into three categories: infections, infusion reactions and hematologic abnormalities (neutropenia and anemia). No unexpected adverse events were observed.

The safety profile of ofatumumab is based on the evaluation of 12 studies (completed or ongoing) in 648 subjects who have received at least one dose of ofatumumab (Appendix 1). The primary safety data are provided from the pivotal study Hx-CD20-406 in 154 fludarabine-refractory CLL subjects. Supportive studies are discussed in Section 3.8.7

3.8.1. Exposure to Ofatumumab

In Study Hx-CD20-406, the intended dosing regimen was 12 infusions of ofatumumab over duration of 24 weeks. The exposures for 154 subjects included in the interim analysis are discussed in this section, and the percent of subjects receiving each infusion is presented in Figure 26.

Figure 26 Percent of Subjects Receiving Infusions Over the Course of Treatment, Study Hx-CD20-406



Infusions 1-8 were given weekly, followed five weeks later by monthly infusions 9-12. Most subjects (139/154; 90%) received all 8 weekly infusions, and 55% (85 subjects) received all 12 infusions (completed 24 weeks of treatment). The most common causes for withdrawal from treatment were infections (11 subjects) and progressive disease (4 subjects).

The median dose per infusion was 300 mg for the first infusion, and 2000 mg for infusions 2-12. The median cumulative dose was 22,300 mg.

3.8.2. Adverse Events

The safety population for Study Hx-CD20-406 includes 154 subjects included in the planned interim analysis (cut-off date 19 May 2008). This cut-off date was based on 66 double-refractory (DR) subjects who received ofatumumab and had data available for analysis of the primary efficacy endpoint.

Clinical assessments were performed by investigators. Standard safety evaluations included assessment of AEs, laboratory evaluations (hematology and clinical biochemistry), human anti-human antibody (HAHA) testing, and vital signs during the treatment and follow-up phases. As per study protocol, deterioration of study disease was not to be reported as an AE unless it fulfilled the SAE criteria.

An independent external Data Monitoring Committee (DMC) was appointed to conduct ongoing regular safety surveillance of the study. The DMC's safety reviews included evaluations of all SAEs, all non-serious AEs of common terminology criteria for adverse events (CTCAE) Grade 3 and 4, and all other relevant safety data.

As of the cut-off date for the interim analysis (19 May 2008), 146 (95%) of the 154 subjects treated with ofatumumab had a total of 1209 AEs during treatment or follow-up. The majority of AEs (81%) occurred during the treatment period. A total of 98 (64%) subjects had 494 (41% of 1209) AEs considered by the investigator to be related to ofatumumab (Table 22).

Table 22 Summary of AEs in Subjects in Study Hx-CD20-406 (Treatment or Follow-up)

Adverse Events	Hx-CD20-406			
	DR N=59	BFR N=79	Other N=16	Total N=154
Any AE, n (%)	54 (92)	76 (96)	16 (100)	146 (95)
Drug-related AEs, n (%)	36 (61)	48 (61)	14 (88)	98 (64)
AEs ≥Grade 3, n (%)	38 (64)	38 (48)	12 (75)	88 (57)
Infusion Reaction AEs, n (%)	38 (64)	48 (61)	13 (81)	99 (64)
Infections, n (%)	41 (69)	54 (68)	13 (81)	108 (70)
All AEs leading to withdrawal from treatment, n (%)	12 (20)	8 (10)	2(13)	22 (14) ^a
All SAEs, n (%)	32 (54)	38 (48)	12 (75)	82 (53)
Fatal (Grade 5) SAEs, n (%)	12 (20)	10 (13)	2 (13)	24 (16)

a. 5 additional subjects had disease progression listed as the AE that resulted in discontinuation

A total of 61 subjects died as of the cut-off date for safety reporting (19 May 2008):

- 24 fatal SAEs occurred during treatment or follow-up (DR: 12/59, 20%; BFR: 10/79, 13%; Other: 2/16, 13%). Early death, defined as death occurring within the first 8 weeks of treatment, occurred in 6 of the 24 subjects (5 due to infection, 1 due to myocardial infarction). The causes of death for the other 18 subjects were disease progression (6 subjects), infections (11 subjects), and cardiac failure (1 subject).

- 37 deaths occurred during extended follow-up. Seven fatal SAEs occurred before initiation of new CLL treatment, and 30 deaths occurred after the initiation of alternative CLL treatment and were therefore not reported as SAEs. Further details regarding deaths during extended follow-up are presented in Section 3.8.5.

3.8.2.1. Common AEs

The most frequently reported AEs were pyrexia, cough, diarrhea, pneumonia, neutropenia, anemia, fatigue and dyspnea (Table 23). Other AEs reported at incidences of >10% were rash, bronchitis, upper respiratory tract infection and nausea. No clinically relevant differences were observed among the subgroup populations with regard to types of AEs.

Table 23 AEs experienced by >=10% of CLL Subjects in Any Group or Total in Study Hx-CD20-406

System Organ Class Preferred Term	DR N=59	BFR N=79	Other N=16	Total N=154
Any AEs, n (%)	54 (92)	76 (96)	16 (100)	146 (95)
General disorders and administration site conditions, n (%)				
Pyrexia	15 (25)	9 (11)	7 (44)	31 (20)
Fatigue	9 (15)	13 (16)	1 (6)	23 (15)
Edema peripheral	5 (8)	8 (10)	1 (6)	14 (9)
Chills	6 (10)	5 (6)	2 (13)	13 (8)
Disease progression	1 (2)	5 (6)	3 (19)	9 (6)
Respiratory, thoracic and mediastinal disorders, n (%)				
Cough	11 (19)	14 (18)	5 (31)	30 (19)
Dyspnea	11 (19)	8 (10)	3 (19)	22 (14)
Gastrointestinal disorders, n (%)				
Diarrhea	11 (19)	12 (15)	5 (31)	28 (18)
Nausea	7 (12)	9 (11)	1 (6)	17 (11)
Blood and lymphatic system disorders, n (%)				
Neutropenia	9 (15)	10 (13)	6 (38)	25 (16)
Anemia	10 (17)	13 (16)	2 (13)	25 (16)
Infections and infestations, n (%)				
Pneumonia	10 (17)	11 (14)	4 (25)	25 (16)
Bronchitis	11 (19)	6 (8)	0	17 (11)
Upper respiratory tract infection	2 (3)	13 (16)	2 (13)	17 (11)
Lower respiratory tract infection	1 (2)	3 (4)	3 (19)	7 (5)
Urinary tract infection	2 (3)	2 (3)	2 (13)	6 (4)
Skin and subcutaneous tissue disorders, n (%)				
Rash	8 (14)	6 (8)	5 (31)	19 (12)
Urticaria	3 (5)	8 (10)	1 (6)	12 (8)
Dry skin	0	1 (1)	2 (13)	3 (2)
Erythema	1 (2)	0	2 (13)	3 (2)
Musculoskeletal and connective tissue disorders, n (%)				
Back pain	7 (12)	3 (4)	2 (13)	12 (8)
Musculoskeletal pain	2 (3)	0	3 (19)	5 (3)
Psychiatric disorders, n (%)				
Insomnia	6 (10)	4 (5)	1 (6)	11 (7)
Nervous system disorders, n (%)				
Paresthesia	3 (5)	2 (3)	2 (13)	7 (5)
Dizziness	0	1 (1)	2 (13)	3 (2)

For the majority of system organ classes (SOCs), AEs were most frequently reported among subjects in the Other group than in the DR or BFR groups. Due to the small number of subjects in this subgroup (N=16), no firm conclusions could be drawn. However, it should be noted that these subjects were in the study for a longer period (median follow up of 269 days vs. 195 days) than those in the other 2 groups, which may account for a higher rate of AEs reported. In addition, the median baseline lymphocyte

counts for these subjects were higher ($72.4 \times 10^9/L$ vs. $19.5 \times 10^9/L$) than those in the other 2 groups, possibly contributing to an increase in infusion reactions.

3.8.2.2. AEs Related to Study Treatment

A total of 98 (64% of 154) subjects experienced 494 AEs (41% of all 1209 AEs) considered to be drug-related.

With the exception of neutropenia (21 subjects, 14%), individual AEs considered to be drug-related were reported by <10% of subjects (Table 24). Hematologic adverse events are described in more detail in Section 3.8.2.3.

Other frequently reported drug-related AEs included rash, urticaria, fatigue, chill, pyrexia, pneumonia, dyspnea, cough, diarrhea, and nausea.

Infusion reactions have been listed separately in Section 3.8.6.2

Table 24 Drug-related AEs experienced by $\geq 5\%$ of CLL Subjects in Any Group or Total in Study Hx-CD20-406

System Organ Class Preferred Term	DR N=59	BFR N=79	Other N=16	Total N=154
Any Event, n (%)	36 (61)	48 (61)	14 (88)	98 (64)
Blood and lymphatic system disorders, n (%)				
Neutropenia	9 (15)	6 (8)	6 (38)	21 (14)
Anemia	2 (3)	5 (6)	1 (6)	8 (5)
Skin and subcutaneous tissue disorders, n (%)				
Rash	5 (8)	2 (3)	5 (31)	12 (8)
Urticaria	3 (5)	7 (9)	1 (6)	11 (7)
Hyperhidrosis	3 (5)	4 (5)	1 (6)	8 (5)
Pruritus	3 (5)	4 (5)	0	7 (5)
General disorders and administration site conditions, n (%)				
Fatigue	3 (5)	7 (9)	1 (6)	11 (7)
Chills	3 (5)	5 (6)	2 (13)	10 (6)
Pyrexia	5 (8)	1 (1)	3 (19)	9 (6)
Infections and Infestations, n (%)				
Pneumonia	5 (8)	4 (5)	0	9 (6)
Respiratory, thoracic and mediastinal disorders, n (%)				
Dyspnea	5 (8)	3 (4)	1 (6)	9 (6)
Cough	5 (8)	4 (5)	0	9 (6)
Gastrointestinal disorders, n (%)				
Diarrhea	5 (8)	3 (4)	2 (13)	10 (6)
Nausea	3 (5)	5 (6)	1 (6)	9 (6)
Vascular disorders, n (%)				
Hypotension	2 (3)	4 (5)	1 (6)	7 (5)

3.8.2.3. Hematologic Adverse Events

A total of 29 subjects (19%) had 42 events associated with decreased neutrophil counts. The most common reported event was neutropenia: 25 subjects (16%) had 35 events.

Fifteen of the 29 subjects (52%) who had AEs associated with a decreased neutrophil count were neutropenic at baseline, as defined by the CTCAE v3 criteria (\geq Grade 1; $<1.8 \times 10^9/L$). Of these, eleven subjects (73%) with baseline neutropenia received G-CSF as concomitant medication during the course of the study.

Of the 42 events associated with decreased neutrophil count, 1 event was fatal (neutropenic sepsis), 10 events were Grade 4 (9 neutropenia, 1 neutrophil count decreased), 21 events were Grade 3 (16 neutropenia, 1 neutrophil count decreased, 2 neutropenic sepsis and 2 febrile neutropenia), and 10 events were Grade 1-2.

A total of 29 subjects (19%) had 39 events associated with decreased hemoglobin. The majority of these events were anemia (25 subjects [16%], 33 events). Approximately one-third of these events (14/39) were considered by the investigator to be related to ofatumumab treatment. Four events were serious (1 anemia, 1 autoimmune hemolytic anemia, 2 hemolytic anemia) and one of these 4 serious events (hemolytic anemia) was considered by the investigator to be related to ofatumumab.

None of the 39 AEs associated with decreased hemoglobin were fatal. A total of 3 events were Grade 4 (1 anemia, 1 anemia hemolytic autoimmune, and 1 hemolytic anemia), 12 events were Grade 3 (10 anemia, 1 hemoglobin decreased, 1 hemolytic anemia), and 24 events were Grade 1-2 (22 anemia, 2 hemoglobin decreased).

Four subjects (3%) had 5 events of decreased platelet count (3 events of thrombocytopenia and 2 events of decreased platelet count). Four of these events were considered by the investigator to be related to ofatumumab. An SAE of thrombocytopenia was reported for 1 subject and the event was considered by the investigator to be not related to ofatumumab.

These AEs should be considered in the context of all the available hematology assessments; for subjects with data available during the 6 month treatment period, there was an increase in median hemoglobin values from 10.9 g/dL to 12.6 g/dL at baseline and Week 24, respectively, and an increase in median platelet values from $96 \times 10^9/L$ to $137 \times 10^9/L$. The neutrophil counts showed a mild decrease during the first weeks of treatment, but median neutrophil counts remained $>1.5 \times 10^9/L$ during the remainder of treatment. Subjects with baseline neutropenia did not appear to have a decrease in their median neutrophil counts during the treatment period.

This hematologic profile compares favorably to the frequency and severity of hematologic adverse events that would be expected with cytotoxic therapy options in this clinical setting.

3.8.2.4. Biochemistry Adverse Events

Eight subjects (5%) had NCI-CTC \geq Grade 3 uric acid elevations. Three of these subjects had hyperuricemia reported as an AE of which one was considered by the investigator to be related to ofatumumab. No AEs of tumor lysis syndrome were reported as of the cut-off date (19 May 2008).

3.8.3. Serious Adverse Events

The protocol defined SAE reporting period was from the day the subject signed the informed consent until the end of Month 48 (end of extended follow-up period) or until initiation of alternative CLL treatment.

A total of 82 subjects (53%) had 152 SAEs, and 25 subjects (16%) had 39 SAEs that were considered by the investigator to be related to ofatumumab ([Table 25](#)). The most common drug-related SAEs were infections (14 subjects, 9%), and neutropenia (8 subjects, 5%).

Table 25 Summary of SAEs experienced by More Than One Subject During Treatment or Follow-up, Study Hx-CD20-406

System Organ Class Preferred Term	DR N=59	BFR N=79	Other N=16	Total N=154
Subjects with SAEs, n (%)	32 (54)	38 (48)	12 (75)	82 (53)
Infections and infestations, n (%)				
Pneumonia	8 (14)	9 (11)	2 (13)	19 (12)
Sepsis	3 (5)	4 (5)	0	7 (5)
Herpes zoster	2 (3)	1 (1)	0	3 (2)
Bronchopneumonia	2 (3)	1 (1)	0	3 (2)
Neutropenic sepsis	1 (2)	1 (1)	1 (6)	3 (2)
Sinusitis	1 (2)	2 (3)	0	3 (2)
Urinary tract infection	1 (2)	1 (1)	1 (6)	3 (2)
Bronchitis	2 (3)	0	0	2 (1)
Septic shock	2 (3)	0	0	2 (1)
Blood and lymphatic system disorders, n (%)				
Neutropenia	3 (5)	2 (3)	4 (25)	9 (6)
Febrile neutropenia	0	1 (1)	1 (6)	2 (1)
Hemolytic anemia	0	2 (3)	0	2 (1)
General disorders and administration site conditions, n (%)				
Disease progression	1 (2)	5 (6)	3 (19)	9 (6)
Pyrexia	4 (7)	3 (4)	0	7 (5)
Cardiac disorders, n (%)				
Myocardial infarction	1 (2)	2 (3)	0	3 (2)
Cardiac failure	1 (2)	0	1 (6)	2 (1)
Myocardial ischemia	0	2 (3)	0	2 (1)
Injury, poisoning and procedural complications, n (%)				
Fall	0	2 (3)	0	2 (1)
Gastrointestinal disorders, n (%)				
Small intestinal obstruction	1 (2)	1 (1)	0	2 (1)
Vascular disorders, n (%)				
Deep vein thrombosis	0	2 (3)	0	2 (1)
Eye disorders, n (%)				
Diplopia	1 (2)	1 (1)	0	2 (1)
Psychiatric disorders, n (%)				
Confusional state	2 (3)	0	0	2 (1)

Excludes SAEs during extended follow-up.

Overall, the SOC of ‘infections and infestations’ was the most common category of SAEs reported, and 51 (33%) subjects had at least 1 such event considered as SAEs. A total of 14 (9%) subjects had SAEs of infections considered to be related to study drug. Serious infections and infestations are discussed in detail in Section 3.8.6.1.2.

Of all SAEs reported, lower respiratory infections (pneumonia, bronchopneumonia, bronchitis) were the most common (24 subjects, 16%), followed by septic complications (sepsis, neutropenic sepsis) (3 subjects, 2%). Eight subjects (5%) had SAEs of lower respiratory infections that were considered by the investigator to be drug-related. All 3 SAEs of septic complications were considered by the investigator to be drug-related.

Other common SAEs reported during treatment and follow-up were neutropenia (6%), disease progression (6%), and pyrexia (5%).

A total of 19 (12%) subjects discontinued due to their SAEs. The most common reason for discontinuation due to SAE was pneumonia (6 subjects) and sepsis (6 subjects).

Table 26 summarizes the incidence of all SAEs, regardless of study period (treatment or follow-up) or initiation of alternative CLL treatment, and relative to last dose of study medication.

The majority of the SAEs (58%) occurred during treatment. A total of 39 SAEs (39/152, 26%) occurred within 30 days of the last infusion of ofatumumab. Infections were the most common SAEs, regardless of the time since last infusion. There were no differences in the type of SAEs reported on treatment as compared to after completion of treatment.

Table 26 Summary of SAEs, Analyzed by Days Since Last Infusion, Study Hx-CD20-406

Days Since Last Infusion	DR N=59	BFR N=79	Other N=16	Total N=154
Number of Events	69	61	22	152
On treatment, n (%)	41 (59)	33 (54)	14 (64)	88 (58)
1 – 30 days, n (%)	20 (29)	16 (26)	3 (14)	39 (26)
>30 – 60 days, n (%)	4 (6)	4 (7)	2 (9)	10 (7)
>60 days, n (%)	4 (6)	8 (13)	3 (14)	15 (10)

Clinically important events such as serious cardiac events, small bowel obstruction, neoplasms, and autoimmune anemias were reported in this study.

Cardiac events were reported in 7 subjects (2 DR, 4 BFR and 1 Other). None of the 9 events were considered as related to ofatumumab by the investigator. Two subjects had cardiac failure, two subjects had myocardial infarction, two subjects had myocardial ischemia, and one subject had perimyocarditis. Two subjects (1 DR, 1 BFR) were diagnosed with small bowel obstruction during the study. In both cases, the events resolved and were considered by the investigator to be unrelated to ofatumumab treatment. Five subjects had five SAEs of new or secondary neoplasms reported. One subject had Hodgkin’s Lymphoma, which was considered related to ofatumumab. One subject had CLL transformation, one subject had Mantle Cell Lymphoma, one subject had breast cancer, and one subject had coecal adenocarcinoma; all were considered not related to ofatumumab.

3.8.3.1. Serious AEs Reported in Extended Follow-up

Of the 154 subjects, 111 entered extended follow-up after completion of treatment and follow up, or following withdrawal from treatment or follow-up. According to the protocol, during this period only SAEs were reported, up to the time of initiation of new CLL treatment. Nine of 111 subjects that entered the extended follow-up had 11 SAEs

before initiation of new CLL treatment. None of the SAEs reported in the 9 subjects were considered drug-related by the investigator.

3.8.4. AEs Leading to Withdrawal

In this study, 27 (17%) subjects had AEs that led to withdrawal from treatment (21 subjects) or follow-up (6 subjects) as of the data cut-off date of 19 May 2008. Of the 27 subjects, 5 subjects discontinued due to AEs considered to be disease progression by the investigators. Of the other 22 subjects, 14 subjects died due to infections. The most common AEs that resulted in withdrawal were pneumonia (6 subjects: 4 DR, 2 BFR) and sepsis (6 subjects: 4 DR, 2 BFR).

The proportion of subjects with AEs leading to withdrawal (excluding 5 subjects who discontinued due to disease progression but were listed as AEs) was numerically higher in the DR group (11 subjects) than in the BFR group (8 subjects).

The majority of subjects had AEs leading to discontinuation that were considered by the investigator to be not related to study drug (23/27, 85%). Four subjects had AEs that were considered to be related to study medication; 2 in the DR group of pneumonia and hypersensitivity, 1 pneumonia in the BFR group, and 1 neutropenia in the Other group.

Nineteen subjects had 20 SAEs resulting in withdrawal from treatment or follow-up and 11 subjects were withdrawn due to SAEs with fatal outcome. Four AEs leading to withdrawal of 4 subjects were judged by the investigator as drug-related (Grade 5 pneumonia, Grade 4 pneumonia, Grade 3 hypersensitivity, and Grade 2 neutropenia).

An additional 45 (41%) subjects withdrew from all study activities due to SAEs in extended follow up. The reason for withdrawal of 43 of these 45 subjects was death. Fatal SAEs were reported as the cause of death of 37 subjects with the most common fatal SAE being disease progression in 10 subjects. The cause of death was not specified for 6 subjects. Withdrawal of the 2 remaining subjects during extended follow-up was due to “too unwell to attend further follow-up appointments - for palliative care only” and lost to follow-up.

3.8.5. Deaths

A total of 61 subjects died during study as of 19 May 2008.

Table 27 Summary of Deaths, Analyzed by Days Since Last Infusion, Study Hx-CD20-406

Days From Last Infusion	DR N=59	BFR N=79	Other N=16	Total N=154
1 – 30 days, n (%)	8 (14)	5 (6)	1 (6)	14 (9)
>30 – 60 days, n (%)	5 (8)	1 (1)	1 (6)	7 (5)
>60 days, n (%)	14 (24)	25 (32)	1 (6)	40 (26)

Early death is defined as death occurring within 8 weeks of start of ofatumumab treatment. Six of 154 subjects (4%; 4 DR subjects and 2 BFR subjects) died within 8 weeks after the start of treatment, 5 were due to infection, and 1 due to myocardial infarction. Most subjects died >60 days after the last dose of ofatumumab.

More subjects died after the start of new CLL treatment than prior to the start of new CLL treatment (Table 28).

Table 28 Summary of Deaths, Analyzed by Timing of Next CLL Treatment in Study Hx-CD20-406

Number of Events leading to death	DR (N=59)	BFR (N=79)	Other (N=16)	Total (N=154)
	n=27	n=31	n=3	n=61
Prior to next CLL treatment	13 (48)	11 (35)	2 (67)	26 (43)
After new CLL treatment	14 (52)	20 (65)	1 (33)	35 (57)

Of the total 61 deaths, 24 were reported during treatment or follow-up (the AE reporting period for the study) and 37 were reported during extended follow-up (7 before and 30 after initiation of new CLL treatment). Of the 24 deaths during this time period, 4 were considered related to ofatumumab, but only 1 occurred within 30 days of ofatumumab treatment: pneumonia in a DR subject 25 days after the 8th infusion.

Of the 24 deaths during treatment or follow up, 4 subjects died during response to ofatumumab, defined as within 30 days of last ofatumumab dose and an investigator assessed response status of PR, nPR or CR at the time-point closest to the onset of the fatal SAE.

Sixteen of the 24 deaths during treatment and follow-up were due to infections: 10 (17%) of 59 DR subjects, 5 (6%) of 79 BFR subjects and 1 (6%) of 16 Other subjects. Disease progression, including CLL transformation and hemiparesis due to CLL CNS involvement, was the cause of death in 6 subjects during treatment or follow-up. One subject died due to cardiac failure and 1 subject (Other group) died due to myocardial infarction, both were considered unrelated to ofatumumab by the investigator.

3.8.6. Adverse Events of Special Interest

In this section, the following events of interest generally known to be associated with anti-CD20 therapies are discussed:

- Infections
- Infusion reactions
- Autoimmune hematologic complications
- Tumor lysis syndrome
- Mucocutaneous reactions

3.8.6.1. Infections

Subjects with advanced, pre-treated CLL are prone to infections due to immune defects inherent to the primary disease as well as to therapy-related immunosuppression [Morrison, 2007]. Infection-related AE preferred terms were grouped to better understand if the pattern of infection in the refractory CLL population could be explained by the underlying disease in this heavily pre-treated, immunocompromised subject population or if there was evidence that ofatumumab might have contributed to the infection rate in the study population.

3.8.6.1.1. All Infections

Of the 154 subjects enrolled in the study, 108 subjects (70%) had infections of any severity grade reported as AEs (21% of 1209 AEs). Respiratory tract infections were the most common events. Infections of the lower respiratory tract (pneumonias) were more common than upper respiratory tract infections. The second most frequently reported events were septic complications. The frequency of infections was similar between the DR and BFR subgroups (Table 29).

The majority of infections were of Grade 1 or 2 in severity (91 subjects, 59%). Fatal infections occurred in 16 of 154 subjects (10%) during treatment or follow-up. During extended follow-up, an additional 14 subjects died due to infections (6 pneumonia, 7 sepsis, 1 aspergillus infection). No cases of hepatitis B reactivation have been reported across the clinical program to date, but subjects with active hepatitis B were excluded from the studies.

Table 29 Summary of All Infections, Study Hx-CD20-406

	DR N=59		BFR N=79		Other N=16		Total N=154	
	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)
Any infections	104	41 (69)	111	54 (68)	35	13 (81)	250	108 (70)
All Respiratory Tract Infections	67	31 (53)	67	38 (48)	17	8 (50)	151	77 (50)
Lower respiratory tract infections	44	24 (41)	29	21 (27)	13	7 (44)	86	52 (34)
Pneumonias	19	15 (25)	17	14 (18)	7	6 (38)	43	35 (23)
Bronchial infections	16	11 (19)	8	6 (8)	0	0	24	17 (11)
Lung infections	4	3 (5)	1	1 (1)	0	0	5	4 (3)
Upper respiratory tract infections	23	15 (25)	38	24 (30)	4	3 (19)	65	42 (27)
Septic complications	6	6 (10)	6	5 (6)	1	1 (6)	13	12 (8)
Other infections	31	22 (37)	38	25 (32)	17	10 (63)	86	57 (37)

In 32 subjects (21%), the infections were considered related to ofatumumab treatment by the investigator (Table 30).

Table 30 Summary of All Drug-Related Infections in Study Hx-CD20-406

	DR N=59		BFR N=79		Other N=16		Total N=154	
	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)
Any drug-related infections	20	12 (20)	29	17 (22)	5	3 (19)	54	32 (21)
All Respiratory Tract Infections	15	8 (14)	13	11 (14)	3	1 (6)	31	20 (13)
Lower respiratory tract infections	14	8 (14)	8	7 (9)	1	1 (6)	23	16 (10)
Pneumonias	8	6 (10)	5	5 (6)	0	0	13	11 (7)
Bronchial infections	1	1 (2)	2	2 (3)	0	0	3	3 (2)
Lung infections	2	1 (2)	0	0	0	0	2	1 (1)
Upper respiratory tract infections	1	1 (2)	5	4 (5)	2	1 (6)	8	6 (4)
Septic complications	0	0	3	3 (4)	0	0	3	3 (2)
Other infections	5	5 (8)	13	8 (10)	2	2 (13)	20	15 (10)

A total of 11 subjects (7%) withdrew from study treatment due to 12 infections (6 events of sepsis, 4 events of pneumonia, and one each of urinary tract infection and Herpes Zoster).

3.8.6.1.2. Infections Reported as SAEs

A total of 51 subjects (33%) had infections that were reported as SAEs. In 14 subjects (9%), these events were considered drug-related by the investigators. Subjects in the DR group had a higher frequency of drug-related infection SAEs compared to subjects in the BFR and Other group (Table 31).

Fatal infections occurred in 16 subjects (10%).

Table 31 Summary of Drug-Related Serious Infections in Study Hx-CD20-406

	DR N=59		BFR N=79		Other N=16		Total N=154	
	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)
All drug-related infection SAEs	11	9 (15)	6	4 (5)	1	1 (6)	18	14 (9)
All Respiratory Tract Infections	7	6 (10)	2	2 (3)	0	0	9	8 (5)
Septic complications	0	0	3	3 (4)	0	0	3	3 (2)
Other infections	4	4 (7)	1	1 (1)	1	1 (6)	6	6 (4)

3.8.6.1.3. Grade 3 and Grade 4 Infections

A total of 31 subjects (20%) had 39 Grade 3 infections; in 27 subjects, these events were also reported as SAEs. The incidence of Grade 3 infections was similar among the three subgroups of subjects. In 8 subjects with Grade 3 infections, the events were considered drug-related by the investigator. Six of these infections were also reported as SAEs.

Eight subjects (5%) had Grade 4 infections, all of which were also reported as SAEs. The majority of these infections (6 events in 6 subjects) were respiratory tract infections, with pneumonias being the most common events (4 subjects, 4 events). Grade 4 infections in 6 subjects (3%) were considered drug-related

3.8.6.1.4. Grade 5 (Fatal) Infections

A total of 16 subjects (10%) had fatal infections during treatment and follow-up, (Table 32). The fatal infections in 4 of the 16 subjects were considered by the investigator to be related to study drug.

The most common cause of death from infections during treatment and follow-up was sepsis (7 subjects), followed by pneumonia (6 subjects). The 3 other infections were one case each of progressive multifocal leukoencephalopathy (PML), fusarium infection, and peritoneal infection.

Of these 16 deaths, 9 (6 DR, 3 BFR) occurred within 30 days of the last dose of ofatumumab, 5 (3 DR, 1 BFR, 1 Other) occurred within 30 to 60 days after last dose of ofatumumab, and 2 (1 DR, 1BFR) occurred beyond 60 days after the last dose of ofatumumab.

During extended follow-up, an additional 14 subjects died due to infections (6 pneumonia, 7 sepsis, and 1 aspergillus infection). Two of these 14 deaths occurred within 30 days of the last dose, 1 being categorized as an early death (within 8 weeks of starting treatment). Both deaths occurred after the start of new CLL therapy.

Table 32 Summary of All and Drug-Related Fatal Infections in Study Hx-CD20-406 (During Treatment and Follow-up)

	DR N=59		BFR N=79		Other N=16		Total N=154	
	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)
All Fatal Infections								
Any fatal infection	10	10 (17)	5	5 (6)	1	1 (6)	16	16 (10)
All Respiratory Tract Infections	4	4 (7)	2	2 (3)	0	0	6	6 (4)
Lower respiratory tract infections	4	4 (7)	2	2 (3)	0	0	6	6 (4)
Pneumonias	4	4 (7)	2	2 (3)	0	0	6	6 (4)
Septic complications	4	4 (7)	3	3 (4)	0	0	7	7 (5)
Other infections ¹	2	2 (3)	0	0	1	1 (6)	3	3 (2)
Drug-Related Fatal Infections								
Any drug-related fatal infection	3	3 (5)	1	1 (1)	0	0	4	4 (3)
All Respiratory Tract Infections	2	2 (3)	0	0	0	0	2	2 (1)
Lower respiratory tract infections	2	2 (3)	0	0	0	0	2	2 (1)
Pneumonias	2	2 (3)	0	0	0	0	2	2 (1)
Septic complications	0	0	1	1 (1)	0	0	1	1 (1)
Other infections	1	1 (2)	0	0	0	0	1	1 (1)

Analysis of Risk Factors for Infection

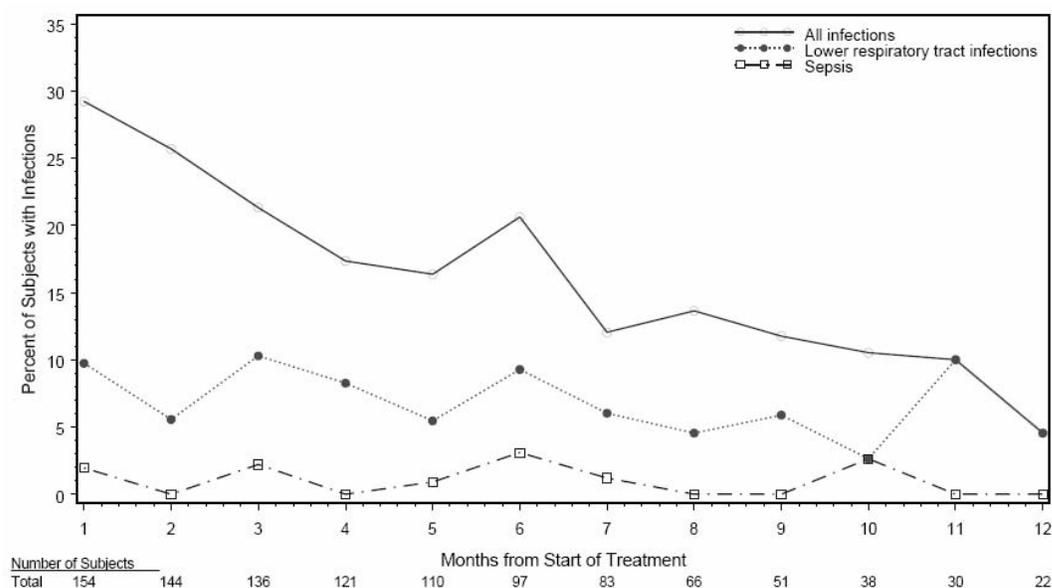
The potential for ofatumumab to increase the risk of infection was analyzed by four different confounding risk factors related to aspects of disease status or to clinical characteristics that emerged during treatment:

- Rai Stage - Subjects with advanced stage CLL (Rai Stage III or IV) at screening had more \geq Grade 3 infections (including fatal infections) than those with less advanced disease (Rai Stage I or II) (24% vs. 5%, respectively). This analysis indicated that advanced stage CLL was a major risk factor for infections.
- Number of prior CLL therapies - Receiving greater than two prior therapies has been shown to be an adverse prognostic factor in CLL therapy [Wierda, 2005]. Subjects with ≥ 3 prior therapies had more infections than those with < 3 prior therapies (76% vs. 59%, respectively). Fatal infections were more common in heavily pre-treated subjects (5% of subjects with 1-2 prior therapies compared to 20% of subjects with ≥ 3 prior therapies). These data suggest that the higher number of prior therapies, and not ofatumumab treatment, was a major risk factor for developing infections in this study.
- Neutrophil counts at baseline - Neutropenia increases the risk of infection. Baseline Grade 3 or 4 neutropenia was associated with a higher incidence of serious or fatal

infections. The 17 subjects with baseline Grade 3 and 4 neutropenia had a higher incidence of \geq Grade 3 infections than the 76 subjects with normal baseline neutrophil counts (53%, 9/17 vs. 37%, 28/76). Fatal infections were also more frequent in subjects with Grade 3 or 4 baseline neutropenia than subjects with normal baseline neutrophil counts (24%, 4/17 vs. 16%, 12/76).

- Infections over time - The total number of subjects with infections was plotted against the study period in months, and there was no increase, but rather, a decrease of infections over time across all 3 subgroups of subjects was observed (Figure 27). The proportion of subjects with infections decreased from 29% at Month 1 to 21% at Month 6, and decreased further to 5% at Month 12. It is acknowledged that such analysis is subject to survival bias because subjects who died during the observation period could not have contributed to the observed infection rate.

Figure 27 Subjects with Selected Infections Over Time in Study Hx-CD20-406



In summary, the frequency, types and severity of infections seen in the study were consistent with what can be expected in subjects with fludarabine-refractory disease. The data does not suggest that ofatumumab had altered or increased the risk of infection in this population in a clinically significant way.

3.8.6.2. Infusion Reactions

Infusion reactions are commonly associated with anti-CD20 antibody therapy. These reactions typically include a constellation of symptoms including rash, cough, pain, chills and rigors, pyrexia and fever, and dyspnea. Infusion reactions were broadly defined as signs and symptoms that could be infusion related, occurred on infusion days and started after the beginning of the ofatumumab infusion. The events were usually mild, and generally allowed for the administration of the fully intended infusion dose.

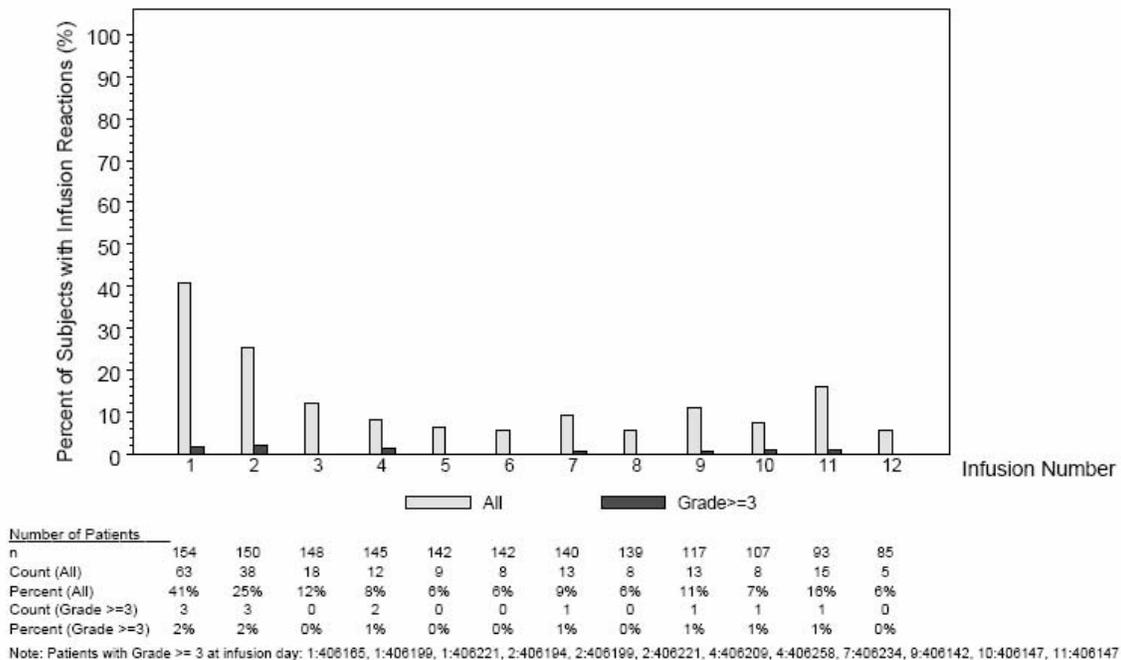
Pre-medication consisting of paracetamol (1000 mg or equivalent) and an antihistamine (cetirizine 10 mg or equivalent) was to be administered before each ofatumumab infusion. Additionally, administration of IV steroids (prednisolone, 100 mg or equivalent) was mandatory before the first 2 weekly and the first monthly infusion (infusion 9). For all other infusions, IV steroid administration was optional (3rd to 8th infusion) or could be administered at reduced doses (10th to 12th). During the study, more than 80% of subjects received IV steroids as pre-medication before ofatumumab infusion.

Dose interruptions as a means to treat infusion reactions were most frequent during the first dose (33 subjects, 21%), but decreased with subsequent doses. Despite the dose interruptions, there was only 1 subject who did not ultimately receive the full intended dose.

Overall, 64% of subjects had any kind of infusion reactions during or following any of the 12 scheduled infusions. The events were usually mild (\leq Grade 2), most common with the first infusion and, with the exception of 1 subject, did not preclude the administration of the fully intended infusion dose. In this study, 41% of subjects had infusion reaction AEs following the first infusion declining to 25% with the second infusion, and to 6% with the last infusion (Figure 28). One subject stopped treatment due to an infusion reaction. A total of 5 subjects had infusion reactions classified as SAEs. One subject discontinued due to an infusion reaction and subsequently developed PML. No fatal infusion reactions occurred on any infusion day.

Although direct comparisons cannot be made due to differences in pre-medication schedules and subject populations, the frequency of these reactions appear to be lower than rates described with intravenous use of rituximab or alemtuzumab [Keating, 2002b; O'Brien, 2001a]. Collectively, these results suggest that ofatumumab was relatively well tolerated and that infusion reactions were common yet manageable.

Figure 28 Percent of Subjects with Infusion Reactions by Infusion in Study Hx-CD20-406



3.8.6.3. Autoimmune Hematologic Complications

Autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP) and pure red cell aplasia (PRCA) are well-known complications that can occur in subjects with CLL; however, they were rarely observed with ofatumumab.

In Study Hx-CD20-406, 3 of 154 subjects (2%) were diagnosed with AIHA (one in the DR group and 2 in the BFR group). All 3 events were reported as SAEs and considered by the investigator as unrelated to ofatumumab. None of the subjects had a history of hemolytic anemia, but hemolysis was evident in 2 out of 3 cases at baseline with positive Coombs test and low haptoglobin levels.

One case of Grade 2 PRCA was reported 46 weeks after the last dose of ofatumumab. The subject had a prior history of hemolytic anemia (1 year prior to entry into the study following fludarabine therapy). The PRCA was considered as not related to study drug by the investigator and the subject was withdrawn from study. No cases of ITP were reported in this study.

Based on the study data, there does not appear to be an increased risk for the development of hemolytic reactions during treatment with ofatumumab.

3.8.6.4. Tumor Lysis Syndrome

No TLS events were reported as of the interim analysis cut-off date for Study Hx-CD20-406.

3.8.6.5. Mucocutaneous Reactions

Using the terms indicating severe mucocutaneous reactions (paraneoplastic pemphigus, Stevens-Johnson Syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis), a review of the entire AE database for the ofatumumab oncology studies included in the BLA submission through the safety cut-off date did not reveal a single case of these events.

3.8.7. Safety in Other Studies

Data from 5 additional supportive studies (Hx-CD20-402, Hx-CD20-407, Hx-CD20-001, Hx-CD20-405, and Hx-CD20-409), both ongoing and completed, in subjects with CLL or FL also support the safety profile of ofatumumab ([Appendix Table 1](#), [Appendix Table 2](#)). These studies evaluated the safety and efficacy of ofatumumab as monotherapy in relapse/refractory CLL, relapsed/refractory FL, and as combination therapy with fludarabine and cyclophosphamide (FC) or with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in the frontline CLL and FL settings, respectively, and included 208 subjects. Supportive safety data (SAEs only) were also analyzed from 286 subjects in studies of ofatumumab in diffuse large B cell lymphoma (DLBCL), rheumatoid arthritis (RA) and chronic obstructive pulmonary disease (COPD) ([Appendix Table 1](#)). No additional safety concerns were seen from these additional supportive studies applicable to the CLL study population.

3.8.8. Safety Conclusions

The safety data from the Hx-CD20-406 studies demonstrate that treatment with ofatumumab was generally well tolerated in the study population with advanced, heavily pre-treated, highly refractory CLL with a high risk for rapid disease progression and infectious complications. Adverse events were common and were predominantly mild to moderate infections, infusion reactions and hematologic abnormalities, side effects that were to be expected in this patient population for both frequency and severity. These events were mostly manageable. No unexpected adverse events were observed. SAEs were the minority of all AEs. A review of safety data for the 90 Day Safety Update to the BLA, which includes 206 subjects in Study Hx-CD20-406 and 1138 subjects in the ofatumumab oncology and non-oncology clinical development program, did not result in any changes to the safety profile of ofatumumab.

The 25% incidence of Grade 3 or 4 infections, 23-32% incidence of major infections, 6% incidence of Grade 3 infusion reactions (none fatal), and 12% Grade 3 or 4 neutropenia with ofatumumab monotherapy should be evaluated in the context of the 37% incidence of Grade 3 or 4 infections, 45-60% major infections, 16% incidence of Grade 3 or 4 infusion-related rigors, and 70% incidence of Grade 3 or 4 neutropenia with available therapies [[Tam, 2007](#), [CAMPATH](#) prescribing information].

4. BENEFITS AND RISKS CONCLUSIONS

4.1. Therapeutic Justification

Patients with CLL refractory to fludarabine and alemtuzumab or patients with bulky-fludarabine-refractory disease present an extraordinary treatment challenge. The prognosis for this patient population is grim with existing therapies. All salvage therapies are characterized by low response rates and a high rate of treatment related complications. Both patient populations urgently need new effective therapies. Given the data presented in this submission, ofatumumab offers a new treatment option with efficacy and safety advantages over existing therapies for patients with fludarabine refractory CLL.

4.2. Efficacy

The results in the pivotal study Hx-CD20-406 demonstrated a high response rate (58% in the DR group, 47% in the BFR group). Although these data were not generated from a randomized study, the efficacy results appear considerably higher in the context of the 20-26% observed with other salvage therapies reported in the literature ([Appendix Table 3](#)). Subjects in the DR and BFR groups responded similarly, supporting the initial decision to offer both groups the same treatment modality. The response rate in the BFR group was higher than those reported in the literature with alemtuzumab ([Appendix Table 3](#)). Responses in both groups occurred rapidly (median time to onset of response 1.8 months), were of a clinically meaningful duration (median duration of response of 5.6 months) and were even accompanied by clinical improvements in a subgroup of subjects who did not fulfil all response criteria. A post-hoc landmark analysis at 12 weeks provides evidence that response to ofatumumab was associated with a several month longer median survival compared to subjects who did not achieve response. This supports the other evidence presented in the BLA that the response to ofatumumab is reasonably likely to predict clinical benefit in the target population.

Subgroup analyses showed consistently high response rates across subgroups typically associated with poor outcomes, specifically subjects 65 years of age or older, subjects with more than 2 prior therapies, and subjects with chromosomal abnormalities, including subjects with DR CLL and 17p and 11q deletions. In addition, consistently high response rates were observed in subjects refractory to available CLL therapies, including alkylating-agents (chlorambucil and bendamustine), fludarabine, alemtuzumab (DR group), and prior rituximab-based therapies.

The compelling response rates, duration of response, clinical improvements in the individual components of response, and consistent responses amongst subgroups indicate that ofatumumab has efficacy advantages over existing therapies in both the DR and BFR populations.

4.3. Safety

Overall, there were no unexpected safety findings across the ofatumumab clinical development program and the safety profile demonstrated an acceptable level of

tolerability. The safety profile is consistent with what would be predicted by the mechanism of action for an anti-CD20 monoclonal antibody. A relatively high incidence of adverse events was noted in this refractory CLL population, but the majority were mild to moderate in severity and well managed. The most common adverse events were infections, non-serious infusion reactions, and hematologic adverse events

Infections are a common complication and a major cause of death in patients with refractory CLL. A review of data on infection in the literature showed that incidence of major infections (32% DR, 23% BFR) was lower than what has been described in the literature (60% DR, 45% BFR) with salvage therapies. Analyses of infections seen in the pivotal study indicated that the underlying disease rather than ofatumumab was a major risk factor for Grade 3 or 4 or fatal infections. In addition, early deaths with ofatumumab (7% DR, 3% BFR) were lower than reported with salvage therapies (16% DR, 10% BFR) ([Appendix Table 3](#)) [[Tam, 2007](#)].

Infusion reactions occurred frequently with the first infusion, but subsided with further infusions. The intensity of these reactions was mostly Grade 1-2, and almost all subjects received a full scheduled dose at each infusion. Implementation of a pre-medication schedule is recommended and probably has limited the number and the intensity of infusion reactions, and has allowed for the administration of the fully intended dose in a majority of subjects.

Unlike most other salvage treatment options, improvements in some hematological parameters were observed, suggestive of bone marrow recovery in subjects who had received many prior cytotoxic therapies.

4.4. Benefit:Risk Assessment

The efficacy data and the safety profile demonstrated in study Hx-CD20-406 must be interpreted in the context of available therapies in different fludarabine refractory populations.

Ofatumumab has demonstrated efficacy and safety advantages over available therapies in CLL patients who are refractory to fludarabine and have a need for new therapies due to poor response rates and high treatment-related toxicities with currently used subsequent therapies for CLL. Alkylating agents like chlorambucil have limited efficacy in fludarabine-refractory populations whereas ofatumumab has shown a high response rate and a safety profile different from classical cytotoxic agents in the populations treated in study Hx-CD20-406 [[Rai, 2000](#)]. The recent approval of the alkylating agent bendamustine for the treatment of CLL was based on frontline treatment, and efficacy of bendamustine in the fludarabine-refractory setting was absent [[TREANDA](#) prescribing information]. Despite the availability of bendamustine in Germany since 1971, a review of the available literature found only 16 CLL patients with prior fludarabine (4 considered fludarabine-refractory), who were treated with bendamustine, and only three responded. There were no responses among the fludarabine-refractory patients, and up to 50% of fludarabine-refractory patients experienced dose-limiting infectious and hematologic toxicities [[Bergmann, 2005](#), [Aivado, 2002](#), [Kath, 2001](#)]. Fludarabine is not expected to be effective in a fludarabine-refractory population, and combining

fludarabine with alkylating-agents increases toxicities [O'Brien, 2001b]. Alemtuzumab has not demonstrated efficacy in the alemtuzumab-refractory DR population, and has limited responses in the bulky fludarabine-refractory populations [Keating, 2002b, Moreton, 2005]. Rituximab, a monoclonal antibody against CD20, has been used in combination with chemotherapy in a fludarabine- and rituximab-naïve patient population, but responses have been associated with chemotherapy-related toxicities [O'Brien, 2001a, Robak, 2008]. In contrast, ofatumumab showed compelling activity and a favorable side effects profile in the pivotal study with 59 DR and 79 BFR subjects. These findings demonstrate clinically important advantages over available CLL therapies, including bendamustine, and thus meet criteria for accelerated approval.

Figure 29 shows graphically the response rates in Study Hx-CD20-406 compared to other salvage therapies in DR and BFR populations. Figure 30 compares the major infection rate in Hx-CD20-406 with salvage therapies in DR and BFR populations. Salvage therapies currently used include monoclonal antibodies, single-agent cytotoxic therapies, purine analog combinations, and investigational therapies.



Data Source: Tam, 2007

Data Source: [Tam](#), 2007

Ofatumumab monotherapy demonstrated one of the highest response rates reported in the DR and BFR CLL populations, with longer overall median survival than available salvage regimens. Ofatumumab monotherapy was associated with a lower major infection rate and lower early death rate than reported with available salvage regimens ([Appendix Table 3](#)).

Collectively, these results confer a positive benefit-risk relationship and support the approval of ofatumumab in CLL patients who have received prior therapy, especially for CLL patients refractory to fludarabine and alemtuzumab, or for patients refractory to fludarabine with bulky lymphadenopathy for whom alemtuzumab is unlikely to benefit.

4.5. Overall Conclusions

From the Sponsor's perspective, the data submitted for FDA review meet the regulatory goal of providing sufficient evidence to support accelerated approval of ofatumumab for DR and BFR CLL populations in whom salvage therapies are largely ineffective and have significant toxicities. In this setting, FDA may grant approval based on a meaningful effect on a surrogate endpoint that is reasonably likely to predict clinical benefit if the drug provides an advantage over available therapy. The FDA has signalled that a compelling response rate (with adequate duration) is an accepted surrogate endpoint for accelerated approval. These data from Hx-CD20-406 demonstrate ofatumumab meets these regulatory requirements. Both the response rate and the safety profile are better than available therapies for CLL patients in these two difficult to treat populations.

It is therefore suggested that ofatumumab, after review by the FDA, should be approved and made available to the intended patient population as a new, important treatment option.

5. REFERENCES

Aivado M, Shulte K, Henze L, et al. Bendamustine in the Treatment of Chronic Lymphocytic Leukemia: Results and Future Perspectives. *Semin Oncol.* 2002;29 Suppl 13:19-22.

Bergmann M, Goebeler M, Herold M et al. Efficacy of Bendamustine in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase I/II study of the German CLL Study Group. *Hematologica.* 2005;90(10):1357-64.

CAMPATH (alemtuzumab) prescribing information, Bayer Healthcare, October 2008.

Catovsky D, Richards S, Matutes E, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukemia (the LRF CLL4 Trial): a randomized controlled trial. *Lancet.* 2007;370:230-239.

Cheson BD, Bennett JM, Grever M, Kay N, Keating MJ, O'Brien S, Rai KR. National Cancer Institute-Sponsored Working Group Guidelines for Chronic Lymphocytic Lymphoma: Revised Guidelines for Diagnosis and Treatment. *Blood.* 1996;87:4990-4997.

Coiffier B, Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia. A phase I-II study. *Blood* 2008; 111:1094-1100.

Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med* 2000;343:1910-1916

Fiegl M, et al. Routine clinical use of alemtuzumab in patients with heavily pre-treated B-cell chronic lymphocytic leukemia. *Cancer.* 2006;107:2408-16.

Hallek M, Fingerle-Rowson G, Fink A, et al. Immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus fludarabine and cyclophosphamide (FC) improves response rates and progression-free survival (PFS) of previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL). *Blood (ASH Annual Meeting Abstracts)* 2008;112: Abstract 325.

Hillmen P, Skotnicki AB, Robak T, Jaksic B, Dmoszynska A, Wu J, Sirard C, Mayer J. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *J Clin Oncol.* 2007;25:5616-5623.

Huhn D, von Schilling C, Wilhelm M, et al. Rituximab therapy of patients with B-cell chronic lymphocytic leukemia. *Blood.* Huhn, D., et al. 2001;98:1326-1331.

Kath R, Blumenstengel K, Fricke H, Höffken K. Bendamustine monotherapy in advanced and refractory chronic lymphocytic leukemia. *J Cancer Res Clin Oncol.* 2001;127:48-54.

Kay, NE, Hamblin, TJ, Jelinek, DF, et al. Chronic Lymphocytic Leukemia. *Hematology* 2002;1:193-213.

Keating MJ, O'Brien S, Kontoyiannis D et al. Results of first salvage therapy for patients refractory to a fludarabine regimen in chronic lymphocytic leukemia. *Leuk Lymphoma*. 2002a; 43:755-1762.

Keating MJ, Flinn IF, Jain VJ, Binet JB, Hillmen PH, Byrd JB, Albitar MA, Brettman LB, Santabarbara PS, Wacker BW, Rai KR. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. *Blood*. 2002b;99:3554-3561.

Knauf WU, et al. Bendamustine Versus Chlorambucil in Treatment-Naïve Patients with B-Cell Chronic Lymphocytic Leukemia (B-CLL): Results of an International Phase III Study. *Blood*. (ASH Annual Meeting Abstracts) November, 2007;110:2043.

Moreton P, Kennedy B, Lucas G. et al. Eradication of minimal residual disease in B-cell chronic lymphocytic leukemia after alemtuzumab therapy is associated with prolonged survival. *J Clin Oncol*. 2005; 23: 2971-2979.

Morrison V, Management of Infectious Complications in Patients with Chronic Lymphocytic Leukemia, *Hematology* 2007;332-338

O'Brien SM, Kantarjian H, Thomas DA, Giles FJ, Freireich EJ, Cortes J, Lerner S, Keating MJ. Rituximab dose-escalation trial in chronic lymphocytic leukemia. *J Clin Oncol*. 2001a;19:2165-2170.

O'Brien S, et al. Results of fludarabine and cyclophosphamide combination regimen in chronic lymphocytic leukemia. *JCO*. 2001b;19:1414-20

Oscier D, Fegan C, Hillmen P, Illidge T, Johnson S, Maguire P, Matutes E, Milligan D. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. *Br J Haematol*. 2004;125:294-317.

Perkins JG, Flynn JM, Howard RS, Byrd JC. Frequency and type of serious infections in fludarabine-refractory B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma: implications for clinical trials in this patient population. *Cancer*. 2002;94:2033-2039.

Rai KR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. *NEJM* 2000;343:1750-7.

Rai KR, Freter CE, Mercier RJ et al. Alemtuzumab in previously treated chronic lymphocytic leukemia patients who also had received fludarabine. *J Clin Oncol*. 2002; 20: 3891-3897.

Robak T, et al. Rituximab, fludarabine, and cyclophosphamide (R-FC) prolongs progression free survival in relapsed or refractory chronic lymphocytic leukemia (CLL)

compared to FC alone: final results from the international randomized phase III REACH trial. *Blood* (ASH Annual Meeting Abstracts) 2008; 112: Late-Breaking Abstract 1

Tam CS, O'Brien S, Lerner S, et al. The natural history of fludarabine-refractory chronic lymphocytic leukemia patients who fail alemtuzumab or have bulky lymphadenopathy. *Leuk Lymphoma*. 2007;48:1931-1939.

Teeling JL, French RR, Cragg MS, et al. Characterization of new human CD20 monoclonal antibodies with potent cytolytic activity against non-Hodgkin lymphomas. *Blood*. 2004;104:1793-800.

TREANDA (bendamustine hydrochloride) prescribing information, Cephalon, Inc., March 2008.

Wierda WW, O'Brien SO, Wen SW, Faderl SF, Garcia-Manero GG, Thomas DT et al. Chemoimmunotherapy with Fludarabine, Cyclophosphamide, and Rituximab for Relapsed and Refractory Chronic Lymphocytic Leukemia. *J Clin Oncol*. 2005; 23: 4070.

6. APPENDIX

Appendix Table 1 Overview of Subjects Contributing to Safety Analysis of Ofatumumab

Study ID	Ofatumumab Monotherapy		Ofatumumab Combination Therapy	Ofatumumab Blinded Treatment
	Number of subjects any dose	Number of subjects 2000 mg	Number of subjects 500 mg or 1000 mg	Number of subjects placebo or 700 mg
CLL studies				
Hx-CD20-406	154	154	NA	NA
Hx-CD20-402	33	27	NA	NA
Hx-CD20-407	NA	NA	28	NA
CLL Sub-totals	187	181	28	NA
FL studies				
Hx-CD20-001	40	NA	NA	NA
Hx-CD20-405	74	NA	NA	NA
Hx-CD20-409	NA	NA	33	NA
FL Sub-totals	114	NA	33	NA
Clinical safety database	362			
Other Oncology Indications				
GEN415/DLBCL	4	NA	NA	NA
Non-oncology Indications				
Hx-CD20-403 (RA)	201	NA	NA	NA
GEN410 (RA)	NA	NA	NA	54
GEN411 (RA)	NA	NA	NA	12
GEN413 (RA)	10	NA	NA	NA
Hx-CD20-408 (COPD)	5	NA	NA	NA
Total of subjects in other indications	286			
Grand Total of Subjects who received at least one dose of ofatumumab	648			

Study GEN415 is an open-label, single-arm, multi-center phase 2 study with ofatumumab in subjects with relapsed diffuse large B-Cell lymphoma (DLBCL) ineligible for transplant or after relapse of autologous transplant.

Ofatumumab monotherapy studies in RA include completed study Hx-CD20-403, and ongoing studies OFA110635(GEN410), OFA110634(GEN411), GEN413 and OFA110867.

Hx-CD20-408 was a study of ofatumumab monotherapy in COPD.

Appendix Table 2 Pivotal CLL and Supportive Oncology (CLL and FL) Studies Included in Clinical Safety Database

Study No./ Status	Phase	Design/ Main Inclusion Criteria/Objectives	No. treated	Dose of ofatumumab (number of infusions)
Hx-CD20-406 Ongoing	II	OL, SA, F/A-ref CLL, O-mono, 1° efficacy, 2° safety, PK, HAHA	154 active	300mg (x1) + 2000mg (x11)
Hx-CD20-402 Completed	I/II	OL, DE, rel/ref CLL, O-mono, 1° safety, efficacy 2° PK	33 active	100mg (x1) + 500 mg (x3), 300mg (x1) + 1000 mg (x3) or 500mg (x1) + 2000mg (x3)
Hx-CD20-001 Completed	I/II	OL, DE, rel/ref FL, O-mono, 1° safety, efficacy 2° PK	40 active	300, 500, 700 or 1000mg (x4)
Hx-CD20-405 Ongoing	II	OL, SA, R-ref FL, O-mono, 1° efficacy, 2° long term efficacy, safety, PK	74 active	300mg (x1) + 1000mg (7x) 300mg (x1) + 500mg (x7)
Hx-CD20-407 Ongoing	II	OL, PA, untreated CLL, O+FC, 1° efficacy, 2° safety, PK	28 active	300mg (x1) + 500 or 1000mg (x5)
Hx-CD20-409 Ongoing	II	OL, PA, untreated FL, O+CHOP, 1° efficacy, 2° safety, PK	33 active	300mg (x1) + 500 or 1000mg (x5)
Total number of Subjects			362	

Abbreviations: 1°, primary objective; 2°, secondary objective; A, alemtuzumab; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CLL, chronic lymphocytic leukemia; DE, dose escalation; FC, fludarabine plus cyclophosphamide; FL, follicular lymphoma; F, fludarabine; HAHA, human anti-human antibody; O, ofatumumab; O-mono, ofatumumab monotherapy; OL, open-label; PA, parallel arm; PK, pharmacokinetics; Ref, refractory; Rel, relapsed; R, rituximab; SA, Single arm.

Appendix Table 3 Comparison of Hx-CD20-406 to Other Therapies for CLL

	Hx-CD20-406				Salvage Therapies in Fludarabine-refractory CLL				Alemtuzumab in Bulky Fludarabine-refractory CLL		
	DR+BFR N=138	DR N=59	BFR N=79	Total N=154	Tam DR N=58	Tam BFR N=41	Tam Total N=99	Perkins N=27	Fiegl N=37	Moreton N=11	Keating N=17
SUBJECT CHARACTERISTICS											
Median age, years	63	64	62	63	58	61	58	67	66	58	66
Median # Prior Therapies	5	5	4	5	4	4	4	2	3	3	3
EFFICACY											
Response rate	51%	58%	47%	52%	20%	26%	23%	11.4%	8%	9%	12%
Median Duration of response	5.6m	7.1m	5.6m	6m	2-3m	2.3m	2-3m	na	na	na	na
Median PFS	5.7m	5.7m	5.9m	6m	na	na	na	na	na	na	na
Median OS	15.4m	13.7m	15.4m	17.1m	8m	14m	9m	13m	10m	9m	na
SAFETY											
Major infections	27%	32%	23%	28%	60%	45%	54%	na	na	na	na
Serious infections	33%	37%	29%	33%	na	na	na	89%	na	na	na
Sepsis	8%	10%	6%	8%	na	na	na	na	na	na	15%
Fatal infections	11%	17%	6%	10%	na	na	8%	48%	na	na	13%
Early death	4%	7%	3%	4%	16%	10%	13%	na	12%	na	na

na = not available, m = months, PFS = Progression-free survival, OS = overall survival