U.S. Food and Drug Administration Approval: Obinutuzumab in Combination with Chlorambucil for the Treatment of Previously Untreated Chronic Lymphocytic Leukemia

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Abstract

On November 1, 2013, the U.S. Food and Drug Administration (FDA) approved obinutuzumab (GAZYVA; Genentech, Inc.), a CD20-directed cytolytic antibody, for use in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL). In stage 1 of the trial supporting approval, patients with previously untreated CD20-positive CLL were randomly allocated (2:2:1) to obinutuzumab + chlorambucil (GClb, $n = 238$), rituximab + chlorambucil (RClb, $n = 233$), or chlorambucil alone (Clb, $n = 118$). The primary endpoint was progression-free survival (PFS), and secondary endpoints included overall response rate (ORR). Only the comparison of GClb to Clb was relevant to this approval and is described herein. A clinically meaningful and statistically significant improvement in PFS with medians of 23.0 and 11.1 months was observed in the GClb and Clb arms, respectively (HR, 0.16; 95% CI, 0.11–0.24; $P < 0.0001$, log-rank test). The ORRs were 75.9% and 32.1% in the GClb and Clb arms, respectively, and the complete response rates were 27.8% and 0.9% in the GClb and Clb arms, respectively. The most common adverse reactions ($\geq 10\%$) reported in the GClb arm were infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, and musculoskeletal disorders. Obinutuzumab was the first Breakthrough Therapy–designated drug to receive FDA approval. *Clin Cancer Res; 20(15); 3902–7. ©2014 AACR.*

Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in Western countries (1). It is estimated that there will be 15,720 new cases of CLL and 4,600 deaths because of CLL in 2014 in the United States (2). CLL is predominant in older individuals with a median age at diagnosis of 71 years. CLL has a variable natural history with a 5-year relative survival rate of approximately 82% (3).

CLL is characterized by increasing levels of clonal lymphocytes in the blood, bone marrow, and lymphatic tissues (4). The diagnosis of CLL requires at least 5×10^9 B lymphocytes/L (5,000/µL) in the peripheral blood and confirmation of clonality by flow cytometry. CLL cells coexpress the T-cell antigen CD5 and B-cell surface antigens CD19, CD20, and CD23 (5).

Approved therapies for CLL include chlorambucil, cyclophosphamide, fludarabine, alemtuzumab, bendamustine, ofatumumab, and rituximab. For previously untreated patients with progressive CLL, recommended treatment regimens primarily consist of chemoimmunotherapies. However, in patients with coexisting medical conditions, often including the elderly, aggressive treatment regimens are poorly tolerated (6). Allogeneic stem-cell transplantation is the only potentially curative treatment for CLL (7).

This report summarizes the FDA review of the Biologics License Application (BLA) for obinutuzumab used in combination with chlorambucil for the initial therapy of patients with CLL.

Chemistry

Obinutuzumab is an Fc-glycoengineered humanized anti-CD20 monoclonal antibody of the IgG1 subclass with a molecular mass of approximately 150 kDa (8). It recognizes the type II epitope of the CD20 antigen rather than the type I epitope recognized by rituximab. Obinutuzumab is a sterile, clear, colorless to slightly brown, preservative-free liquid concentrate for i.v. administration and is supplied at a concentration of 25 mg/mL in 1,000 mg single-use vials.

Pharmacology and Toxicology

Obinutuzumab binds to CD20 expressed on the surface of pre-B and mature B lymphocytes (B-cells). Upon binding to CD20, obinutuzumab mediates B-cell lysis (i) through antibody-dependent cellular cytotoxicity and phagocytosis; (ii) by directly activating internal cell death signaling pathways; and (iii) by antibody activation of complement-dependent cytotoxicity.

Toxicology studies were conducted using cynomolgus monkeys. Obinutuzumab binds human and cynomolgus monkey CD20 with similar affinity. Repeat-dose toxicology studies of up to 26 weeks' duration using i.v. administration of obinutuzumab or 4 weeks' duration using s.c. administration were conducted. Toxicities observed from repeat-dose studies were consistent with the intended pharmacology of obinutuzumab or were the apparent result of cross-species immunogenicity effects. The primary effects of obinutuzumab included hypersensitivity reactions and marked decreases in circulating B cells, with corresponding lymphoid tissue B-cell depletion in the spleen and lymph nodes. Transient natural killer cell reductions were also observed, as were opportunistic infections secondary to immunosuppression.

Administration of obinutuzumab to pregnant monkeys during gestation was associated with complete depletion of B lymphocytes in infants. Obinutuzumab did not affect embryo–fetal development, parturition, postnatal survival, or the growth and development of infants. Obinutuzumab crosses the blood–placental barrier and is secreted in the milk of pregnant monkeys. Because of the depletion of B cells and possible opportunistic infections, use of obinutuzumab during pregnancy is not recommended.

Clinical Pharmacology

The steady-state pharmacokinetic parameters for obinutuzumab were derived using a population-based pharmacokinetic (pop-PK) analysis. The geometric mean (CV%) volume of distribution of obinutuzumab is approximately 3.8 L (23%). The elimination of obinutuzumab is composed of a linear clearance pathway and a time-dependent nonlinear clearance pathway. As obinutuzumab treatment progresses, the impact of the time-dependent pathway diminishes in a manner suggesting target-mediated drug disposition. The geometric mean (CV%) terminal obinutuzumab clearance and half-life are approximately 0.09 (46%) L/day and 28.4 (43%) days, respectively.

Body weight, disease type, and tumor size were associated with changes in obinutuzumab exposures, but the impact of these factors on obinutuzumab exposure did not warrant a dose modification at this time. Mild or moderate renal impairment [i.e., baseline creatinine clearance (CLcr) > 30 mL/min] did not affect obinutuzumab exposure. There are insufficient data available to determine the effect of severe renal impairment (CLcr < 30 mL/min) or any degree of hepatic impairment on obinutuzumab exposure. No treatment modifications are recommended in these populations because these elimination pathways are not expected to be a major factor affecting exposure as monoclonal antibodies are generally catabolized by ubiquitous proteolytic enzymes.

Clinical Trial

Design

Study CLL11 was an open-label, three-arm, randomized, multicenter, two-stage, phase III trial in patients with previously untreated CLL. Randomization was stratified by Binet stage and country/region. The trial was conducted at 155 centers in 24 countries and in collaboration with the German CLL Study Group. In stage 1 of the trial, patients were randomly allocated (2:2:1) to obinutuzumab plus chlorambucil (GClb), rituximab plus chlorambucil (RClb), or chlorambucil (Clb) alone. In stage 2, the randomization continued between GClb and RClb (1:1). Stage 2 results were not available at the time of the BLA review.

Key eligibility criteria were age of 18 years or older, previously untreated documented CD20-positive CLL requiring treatment, and coexisting medical conditions or creatinine clearance (CrCl) < 70 mL/min or both. Exclusion criteria included CrCl < 30 mL/min, active infections, positive hepatitis B (HBsAg or anti-HBc positive, patients positive for anti-HBc could be included if hepatitis B viral DNA was not detectable) and hepatitis C serology, and immunization with live virus vaccine within 28 days before randomization.

For the purpose of analysis, stage 1 of the clinical trial was further divided into stages 1a (GClb vs. Clb) and 1b (RClb vs. Clb). In the stage 1a analysis, 356 patients were randomly allocated to GClb ($n = 238$) or to Clb ($n = 118$). The stage 1b analysis is not relevant to this approval and will not be described further. Patients in the Clb arm with disease progression during or within 6 months of end of treatment could cross over to GClb, but only 19% had done so at the time of analysis cutoff date.

The trial began with patients on the GClb arm receiving obinutuzumab, 1,000 mg by i.v. infusion on days 1, 8, and 15 of the first treatment cycle and on the first day of cycles 2 to 6. Later in the trial, because of infusion reactions, the protocol was amended to split the first dose in the first cycle only between day 1 (100 mg) and day 2 (900 mg), and this regimen was administered to 45 (19%) patients. Patients on both arms received chlorambucil, 0.5 mg/kg orally on days 1 and 15 of a 28-day cycle for a maximum of 6 cycles. After the last treatment, patients were followed until disease progression, next leukemia treatment, and death.

Dose modification of obinutuzumab was not allowed. Dose reductions for chlorambucil were allowed, and once reduced the dose could not be reescalated. Patients who experienced a grade 4 infusion reaction or a grade 3 infusion reaction at rechallenge were permanently discontinued from the study treatment, and patients with an infection, grade 3 or 4 cytopenia, or grade 2 or higher nonhematologic toxicity had their study treatment temporarily interrupted until resolution.

To reduce infusion reactions, premedication with an i.v. glucocorticoid, acetaminophen, and an antihistamine before the first infusion became mandatory during the trial. Subsequent premedications could be reduced in the absence of an infusion reaction. Consideration was given to holding antihypertensive agents before and throughout the infusion because infusion reactions sometimes included hypotension. Infusion reactions were managed by interrupting or reducing the infusion rate and administering concomitant medications such as steroids and antihistamines. Upon resolution of symptoms, the infusion was resumed at one-half the previous rate. Obinutuzumab was to be administered at a location with immediately available emergency resuscitation equipment.

Patients with a high tumor burden (WBC $\geq 25 \times 10^9$/L or bulky lymphadenopathy) were to receive adequate hydration and antihyperuricemics before the initiation of treatment for prophylaxis of tumor lysis syndrome.

Disease assessment was performed at baseline, after 3 cycles, 28 days after the last trial treatment, 3 months after the end of treatment, and then every 3 months until 3 years from last treatment. Further follow-up visits were scheduled every 6 months until 5 years, and then annually for 8 years after the last patient entered the trial. A CT scan was performed in patients who had achieved a complete response (CR) or partial response 2 to 3 months after end of treatment. In patients who had a CR (or cytopenic CR), a bone marrow aspirate and biopsy were obtained. A CT scan was also performed when progression of disease was detected by physical examination.

The primary efficacy endpoint was progression-free survival (PFS) based on investigator's assessment. However, the regulatory decision was based on independent review committee (IRC)–assessed PFS. The IRC was composed of a panel of CLL experts (each patient reviewed by two reviewers and one adjudicator if required) who assessed response and progression based on peripheral blood counts, bone marrow biopsy results, reports of physical examination, and radiology reports. Secondary efficacy endpoints included best overall response, event-free survival, duration of response, disease-free survival, time to new antileukemic therapy, and overall survival. Response was determined using the NCI/International Workshop on CLL guideline (5). End of trial was defined as 8 years after the last patient was enrolled.

Results

Demographics

Patient demographics and disease characteristics, including CLL prognostic factors were balanced at baseline between treatment arms (Table 1). The median age was 73 years, 76% of patients had multiple coexisting medical conditions and 68% had a CrCl <70 mL/min.

Efficacy

The IRC-assessed median PFS was 23.0 months in the GClb arm versus 11.1 months in the Clb arm [Fig. 1 (HR, 0.16; 95% CI, 0.11–0.24; $P < 0.0001$ stratified log-rank test)]. The investigator-assessed median PFS durations

were 23.0 months in the GClb arm and 10.9 months in the Clb arm (HR, 0.14; 95% CI, 0.09–0.21; $P < 0.0001$ stratified log-rank test). The results of the secondary endpoints were supportive of the primary endpoint; however, there was no multiplicity adjustment plan for testing the secondary endpoints. Table 2 lists the results of the primary and key secondary endpoints. The overall survival (OS) data were not mature at the analysis cutoff date. The median observation time was 14.2 months, and the median number of treatment cycles was 6. Eighty-one percent and 67% of patients in the GClb and Clb arms, respectively, received all 6 treatment cycles.

Safety

The safety dataset included 240 patients who received one or more doses of obinutuzumab with Clb and 116 patients who received Clb only. Although Clb dose modifications or delays occurred twice as often in the GClb arm (32% vs. 15%), the median cumulative dose was comparable in the two arms (370 mg vs. 384 mg). The most frequently reported adverse reactions with an incidence of 5% or greater and occurring at least 2% more frequently in the GClb arm were infusion-related reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, leukopenia, and musculoskeletal pains (Table 3). The most common serious adverse reaction was infusion-related reaction (11%). Grade 3 to 4 neutropenia was more common in the GClb arm (34%) than in the Clb arm (16%). The incidence of infections was not higher in the GClb arm, but 32% of patients in the GClb arm received G-CSF compared with 14% in the Clb arm. Growth factors were allowed for neutropenia per investigator or institutional guidelines. Tumor lysis syndrome occurred in 4% of patients in the GClb arm.

The incidence of infusion reactions was 69% with the first infusion of obinutuzumab, and the incidence of reactions with subsequent infusions was 3% with the second 1,000 mg and <1% thereafter. Symptoms of infusion-related reactions occurring in greater than 20% of patients included hypotension, nausea, chills, and pyrexia. Changes to the administration of obinutuzumab during the trial (including glucocorticoid, analgesic, and antihistamine treatment, omission of antihypertensive medications in the morning of the first infusion, and administration of the cycle 1 day 1 dose over 2 days) seemed to reduce the incidence of infusion reactions.

Late-occurring neutropenia ($\geq$28 days after treatment) was seen in 16% of patients on the GClb arm and 12% of patients on the Clb arm. Although there were no instances of hepatitis B reactivation or progressive multifocal leukoencephalopathy in the randomized trial, there were rare cases of each on other trials using obinutuzumab.

Discussion

The regular approval (licensing) of obinutuzumab for use in combination with chlorambucil for the treatment of patients with previously untreated CLL was based on the demonstration of a clinically meaningful and statistically

Table 1. Baseline demographics and disease characteristics (CLL11, stage 1a)

Category	Parameter	GClb	Clb	Total
Gender	n	238	118	356
	Female	98 (41%)	43 (36%)	141 (40%)
	Male	140 (59%)	75 (64%)	215 (60%)
Age (y)	n	238	118	356
	≥75	107 (45%)	44 (37%)	151 (42%)
	≥65	196 (82%)	92 (78%)	288 (81%)
	Median	74.0	72.0	73.0
	Range	39–88	43–87	39–88
Race	n	238	118	356
	Caucasian	229 (96%)	108 (92%)	337 (95%)
ECOG PS	n	238	118	356
	0 to 1	211 (89%)	105 (89%)	316 (89%)
Binet stage	n	238	118	356
	A	55 (23%)	24 (20%)	79 (22%)
	B	98 (41%)	50 (42%)	148 (42%)
	C	85 (36%)	44 (37%)	129 (36%)
IgV$_H$	n	210	99	309
	Unmutated	129 (61%)	58 (59%)	187 (61%)
	Mutated	76 (36%)	36 (36%)	112 (36%)
Chromosomal abnormalities	n	203	96	299
	17p−	16 (8%)	10 (10%)	26 (9%)
	11q−	33 (16%)	14 (15%)	47 (16%)
	+12	33 (16%)	16 (17%)	49 (16%)
	13q−	58 (29%)	32 (33%)	90 (30%)
ZAP-70 expression	n	189	97	286
	Positive	83 (44%)	48 (49%)	131 (46%)
	Negative	106 (56%)	49 (51%)	155 (54%)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

robust improvement in PFS in a single randomized trial. For diseases such as CLL, PFS may be considered an acceptable endpoint for regular approval as it takes considerable time to reach the OS endpoint and additional subsequent ther-apies may confound an OS analysis (9). However, a recent update of study CLL11, including an analysis of stage 2, reported significant improvements in OS for the GClb arm compared with the Clb arm and in PFS for the GClb arm compared with the RClb arm (10). These data have not been reviewed by the FDA.

The main adverse reactions that occurred in the GClb arm were infusion reactions and myelosuppression. Other important toxicities included in the labeling were the risks of hepatitis B virus reactivation and JC virus infection resulting in progressive multifocal leukoence-phalopathy, which were observed in patients treated with obinutuzumab in other clinical trials. The FDA review of the randomized trial comparison of GClb to Clb concluded that there was a favorable benefit–risk outcome for the treatment of patients with previously untreated CLL.

CLL largely affects older patients who often have multiple comorbidities. However, this population is not sufficiently enrolled in most pivotal clinical trials (6). In the CLL11 trial, the median age was 73 years, and 81% of the patients were aged 65 years or older; thus, this was one of the few randomized trials that adequately represented the typical

Table 2. Summary of efficacy results (CLL11, stage 1a)

Endpoints	GClb	Clb
Median PFS by IRC (months)	23.0	11.1
HR, P-value (stratified log-rank test[a])	0.16 (0.11, 0.24),	
	<0.0001	
Median PFS by investigator (months)	23.0	10.9
HR, P-value (stratified log-rank test[a])	0.14 (0.09, 0.21),	
	<0.0001	
Best overall response rate	75.9%	32.1%
Complete response	27.8%	0.9%
Median duration of response (months)[b]	15.2	3.5

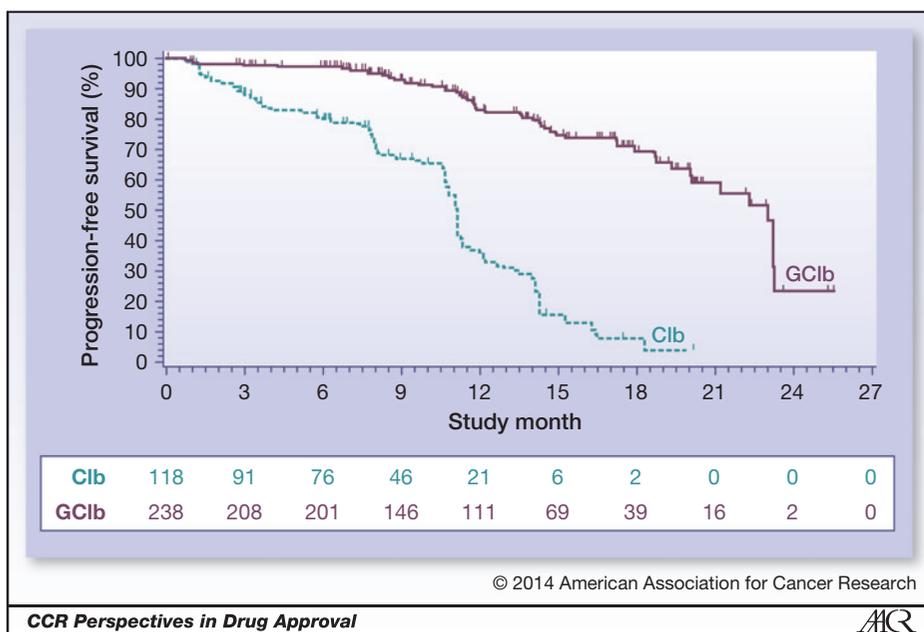[a]Stratified by Binet stage at baseline.
[b]Among patients who had response.

Figure 1. Kaplan–Meier estimates of IRC-assessed PFS (CLL11, stage 1a). Clb, chlorambucil; GClb, obinutuzumab + chlorambucil.

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age of the CLL population. The results of trial CLL11 indicate that the combination of obinutuzumab + chlorambucil is more effective than chlorambucil alone, has an acceptable safety profile, and is an appropriate regimen for elderly patients with previously untreated CLL and comorbidities. Because aggressive treatments for older patients with comorbidities are poorly tolerated, chlorambucil was considered an acceptable active control for this trial. However, in future trials in this patient population the GClb regimen would be an appropriate control.

In July 2012, the Food and Drug Administration Safety and Innovation Act was signed to provide designation of a drug as a Breakthrough Therapy for serious or life-threatening diseases. This designation is intended to expedite the

Table 3. Treatment-emergent adverse reactions with ≥5% incidence and ≥2% difference between the two arms (CLL11, stage 1a)

	Obinutuzumab + chlorambucil, *n* = 240				Chlorambucil, *n* = 116			
	Grades 1–4		Grades 3 and 4		Grades 1–4		Grades 3 and 4	
Adverse Event	*n*	%	*n*	%	*n*	%	*n*	%
Injury, poisoning, and procedural complications								
Infusion-related reaction	165	69	50	21	0	0	0	0
Blood and lymphatic system disorders								
Neutropenia	96	40	82	34	21	18	18	16
Thrombocytopenia	36	15	26	11	8	7	4	3
Anemia	29	12	9	4	12	10	6	5
Leukopenia	16	7	13	5	0	0	0	0
Respiratory, thoracic, and mediastinal disorders								
Cough	23	10	0	0	8	7	1	<1
General disorders and administration site conditions								
Pyrexia	25	10	1	<1	8	7	0	0
Musculoskeletal and connective tissue disorders								
Arthralgias[a]	13	5	2	1	3	3	1	1
Musculoskeletal pains[b]	23	10	2	1	8	7	0	0

[a]Includes the preferred terms: arthralgia, gouty arthritis, arthritis, and osteoarthritis.
[b]Includes the preferred terms: musculoskeletal pain, musculoskeletal chest pain, bone pain, myalgia intercostal, neck pain, pain in extremity, and back pain.

development of new drugs with preliminary clinical evidence that indicates the drug may offer a substantial improvement over available therapies (11). Obinutuzumab was the first Breakthrough Therapy product to receive FDA approval. Because the Breakthrough Therapy designation request for obinutuzumab was received close to the time of BLA submission, the development plan could not receive the full benefits of the program. Drugs that receive Breakthrough Therapy designation earlier in their development are eligible to receive intensive interaction and guidance from the FDA.

Obinutuzumab is the third CD20-directed cytolytic antibody (after ofatumumab and rituximab) to receive FDA approval and provides a major advance in the treatment of patients with CLL.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, et al. Cancer treatment and survivorship statistics. CA Cancer J Clin 2012;62: 220–41.
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9–29.
3. American Cancer Society. Cancer facts & figures 2013 [Internet]. Atlanta: American Cancer Society; 2013 [cited 2014 Jan 31]. Available from: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-036845.pdf.
4. Dighiero G, Hamblin TJ. Chronic lymphocytic leukaemia. Lancet 2008; 371:1017–29.
5. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the international workshop on chronic lymphocytic leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111: 5446–56.
6. Eichhorst B, Goede V, Hallek M. Treatment of elderly patients with chronic lymphocytic leukemia. Leuk Lymphoma 2009;50:171–8.
7. Fischer K, Cramer P, Busch R, Böttcher S, Bahlo J, Schubert J, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2012;30:3209–16.
8. Mössner E, Brünker P, Moser S, Püntener U, Schmidt C, Herter S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood 2010;115:4393–402.
9. Chakravarty A, Sridhara R. Use of progression-free survival as surrogate marker in oncology trials: some regulatory issues. Stat Methods Med Res 2008;17:515–18.
10. Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner C, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 2014;370:1101–10.
11. Guidance for Industry: Expedited programs for serious conditions-drugs and biologics. FDA; June 2013 [cited 2014 Jan 31]. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf.