Regulatory Issues: FDA

U.S. Food and Drug Administration Approval: Rituximab in Combination with Fludarabine and Cyclophosphamide for the Treatment of Patients with Chronic Lymphocytic Leukemia

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Compare the survival benefits of rituximab in combination with fludarabine and cyclophosphamide to those of alemtuzumab, bendamustine, and ofatumumab in patients with CLL.
2. Identify CLL patients for whom rituximab in combination with fludarabine and cyclophosphamide may be an appropriate first-line regimen.

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ABSTRACT

Purpose. To describe the clinical studies that led to the FDA approval of rituximab in combination with fludarabine and cyclophosphamide (FC) for the treatment of patients with chronic lymphocytic leukemia (CLL).

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Materials and Methods. The results of two multinational, randomized trials in CLL patients comparing rituximab combined with fludarabine and cyclophosphamide versus FC were reviewed. The primary endpoint of both studies was progression-free survival (PFS).

Results. The addition of rituximab to FC decreased the risk of a PFS event by 44% in 817 previously untreated patients and by 24% in 552 previously treated patients. Median survival times could not be estimated. Exploratory analysis in patients older than 70 suggested that there was

no benefit to patients when rituximab was added to FC. The safety profile observed in both trials was consistent with the known toxicity profile of rituximab, FC, or CLL.

Conclusions. On the basis of the demonstration of clinically meaningful prolongation of PFS, the FDA granted regular approval to rituximab in combination with FC for the treatment of patients with CLL. The magnitude of the treatment effect in patients 70 years and older is uncertain. *The Oncologist* 2011;16:97–104

INTRODUCTION

The incidence of chronic lymphocytic leukemia (CLL) in the United States occurred at an age-adjusted incidence rate of 4.2 per 100,000 people per year from 2003 to 2007. CLL is more frequently diagnosed in men, and the median age at diagnosis is 72 years [1].

The natural history of CLL is variable, with median survival exceeding 10 years in early-stage patients, and there are no data demonstrating improved outcomes following treatment in patients with asymptomatic, early-stage disease [2]. Median survival is 2–3 years for patients who present with high-risk disease and is also shorter for patients who have progressed following multiple lines of chemotherapy [3]. The disease remains incurable with conventional therapy. Responses can be achieved with a variety of chemotherapy combinations and single agents, but no treatment has demonstrated a survival advantage.

Table 1 summarizes the basis and type of approvals of CLL drugs in the past decade. Fludarabine, cyclophosphamide, and chlorambucil were approved based on durable

objective tumor responses prior to the institution of the accelerated approval regulations.

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen that is found on the surface of normal and malignant B-cell lymphocytes. Rituximab is currently approved for the following indications: relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma (NHL) as a single agent; previously untreated follicular, CD20-positive, B-cell NHL in combination with cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy; non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent, after first-line CVP chemotherapy; previously untreated diffuse large B-cell CD20 positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone or other anthracycline-based chemotherapy regimens; and in combination with methotrexate for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor antagonist therapies.

Table 1. Bases for approval of CLL drugs

Drug	Initial approval	Basis for approval
Alemtuzumab	May 7, 2001 (accelerated approval)	ORR in three single-arm studies in previously treated patients ($n = 149$); ORR was 21%–33%; median duration of response was 7–11 mo(s)
	September 19, 2007 (regular approval)	Improved PFS vs. chlorambucil in a randomized, active-controlled study ($n = 297$); HR favoring alemtuzumab was 0.58 [95% CI 0.43, 0.77 ($p < .0001$, stratified log-rank test)]
Bendamustine	March 20, 2008 (regular approval)	Improved PFS vs. chlorambucil in a randomized, active-controlled study ($n = 301$); HR favoring bendamustine was 0.27 [95% CI 0.17, 0.43 ($p < .0001$, stratified log-rank test)]
Ofatumumab	October 26 2009 (accelerated approval)	ORR of 42% in a single-arm study in patients refractory to fludarabine and alemtuzumab, most of whom also received alkylating agent drugs; median duration of response was 6.5 mo(s)
Abbreviations: CLL, chronic lymphocytic leukemia; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival.		

Genentech (a member of the Roche group) submitted these supplemental Biologics License Applications (sBLAs) on May 15, 2009. The applications page contained the final study results based on prespecified interim analyses of study ML17102, “A Phase 3 Trial of Combined Immunotherapy with Fludarabine, Cyclophosphamide and Rituximab (FCR) versus Chemotherapy with Fludarabine and Cyclophosphamide (FC) Alone in Patients with Previously Untreated CLL” [4] and final results of study BO17072, “An Open-Label, Multicenter, Randomized, Comparative Phase 3 Study to Evaluate the Efficacy and Safety of FCR versus FC Alone in Previously Treated Patients with CD20 Positive CLL” [5].

CLINICAL STUDIES

Materials and Methods

Study ML17102 (first-line treatment) was originally an international cooperative group trial (German CLL Study Group) that was converted into an industry-sponsored trial one year after patient enrollment started. The study was conducted in Europe, Australia, New Zealand, and Israel. Germany enrolled the majority of patients (63%). The trial recruited and randomized 817 patients, and data in the clinical study report and datasets included data from enrollment of the first patient on July 21, 2003, until data cutoff for the complete study report analysis on July 4, 2007. The last patient was enrolled in April 2006.

BO17072 (previously treated) is an industry-sponsored, international trial conducted in Europe, Australia, New Zealand, Canada, and a single center in the United States that enrolled 2 patients. The trial recruited 552 patients, and data in the clinical study report and datasets for this study included data from enrollment of the first patient, in July 2003, until data cutoff for the complete report analysis on July 23, 2008. The last patient was enrolled in August 2007.

Both trials were open-label, randomized (1:1) trials comparing the efficacy of FCR to FC. Eligibility was limited to patients 18 years or older, Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1, and an established diagnosis of CLL. Study ML17102 enrolled patients with active disease who required treatment for CLL. No previous treatment was allowed in study ML17102. Study BO17072 enrolled patients who received one prior chemotherapy regimen. Patients previously exposed to fludarabine were required to be fludarabine-sensitive (i.e., have achieved a partial response (PR) or complete response (CR) lasting at least 6 months). Both studies excluded patients who previously received monoclonal antibodies, who were candidates or recipients of an allogeneic or autologous hematopoietic progenitor cell transplant. Study BO17072

also excluded patients with prior prolonged fludarabine-induced severe cytopenias or history of fludarabine-induced autoimmune cytopenias.

Study medication was administered in six treatment cycles (28 days duration each). The FC regimen consisted of fludarabine 25 mg/m² per day, intravenously on days 1–3, and cyclophosphamide, 250 mg/m² per day, intravenously on days 1–3. The FCR regimen used the same doses and schedule of FC, with the addition of rituximab 375 mg/m² by intravenous infusion on day 1, cycle 1 in study BO17072, and on day 0, cycle 1 in study ML17102. Subsequently, rituximab was administered at 500 mg/m² on day 1 of cycles 2–6.

Both studies mandated response evaluations after 3 and 6 treatment cycles and 2 months after treatment discontinuation. Patients in CR or PR after the third cycle continued treatment for a total of 6 cycles. Patients with progressive disease (PD) after 3 cycles discontinued treatment. In study ML17102, patients with stable disease (SD) after 3 cycles discontinued treatment, whereas in study BO17072, patients with SD after 3 cycles may have continued treatment at the discretion of the investigator.

Toxicity attributed to FC was managed by dose reduction and supportive care. Combination chemotherapy (FC) was terminated for recurrent grade 3–4 (CTCAE v 2.0) cytopenias deemed unrelated to bone marrow involvement with CLL or for recurrent grade 3–4 nonhematological toxicity after two dose reductions. Rituximab infusions were discontinued prematurely for adverse events (AE) of grade 3 or greater in severity that occurred during infusion, and the severity of the AE prevented the infusion from resuming. Rituximab was terminated for the second occurrence of infusional toxicity, bronchospasm, or dyspnea that required discontinuation of the infusion. Protocol-specified treatment was also permanently discontinued for patients who initiated alternative anticancer therapy or withdrew consent, or at the investigator’s discretion.

The criteria for response, progression, and relapse were derived from the National Cancer Institute-Sponsored Working Group (NCI-WG) 1996 criteria [6]. Disease progression, as defined in the 1996 NCI-WG criteria, required at least one of the following: $\geq 50\%$ increase in the sum of the products of at least two lymph nodes; appearance of a new lymph node; $\geq 50\%$ increase in the size of hepatosplenomegaly as determined by measurement below the relevant costal margin or by computed tomography (CT) scan; appearance of palpable hepatomegaly or splenomegaly that was not previously present; $\geq 50\%$ increase in the absolute number of circulating lymphocytes to at least 5×10^9 cells/L; or transformation to a more aggressive histology (e.g., Richter’s syndrome or prolymphocytic leukemia with $>55\%$ prolymphocytes).

Table 2. Demographics and disease baseline characteristics

	ML17102		BO17072	
	FC (<i>n</i> = 409) <i>n</i> (%)	FCR (<i>n</i> = 408) <i>n</i> (%)	FC (<i>n</i> = 276) <i>n</i> (%)	FCR (<i>n</i> = 276) <i>n</i> (%)
Male	304 (74)	303 (74)	181 (66)	187 (68)
65 yr(s)	119 (29)	126 (30)	114 (41)	121 (34)
Binet stage A	14 (3)	9 (2)	31 (11)	24 (9)
Binet stage B	261 (64)	268 (66)	160 (58)	166 (60)
Binet stage C	133 (33)	131 (32)	85 (31)	86 (31)
B symptoms	197 (49)	167 (41)	85 (31)	72 (26)
Hepatomegaly	137 (33)	126 (31)	83 (30)	66 (24)
Splenomegaly	273 (67)	294 (72)	175 (63)	191 (70)

Abbreviations: FC, fludarabine and cyclophosphamide; FCR, fludarabine, cyclophosphamide, and rituximab.

Follow-up for all randomized patients who received at least one dose of treatment was monthly for 3 months, then every 3 months for 1 year, followed by every 6 months until 5 years. In patients with CR, PR, and SD, response was to be assessed at each visit until progression was documented. Assessments included physical examination; measurement of lymphadenopathy, liver, and spleen size by CT scan; ECOG score; and standard hematology and biochemistry tests according to the study schedule and whenever clinically indicated. The major difference in the disease assessments between trials is that, in the second-line study, routine monitoring with CT scans was mandatory until progression or month 33 due to the requirement for an independent review committee (IRC) radiological assessment. In ML17102, a CT scan was not required to confirm PD; however, the protocol recommended repeat imaging as clinically necessary and at final staging (i.e., after 9–12 months or maximum response). The protocol also allowed for the use of other imaging modalities (e.g., ultrasound or magnetic resonance imaging) in addition to CT.

The primary endpoint in both studies was progression-free survival (PFS), defined as the time between randomization and the date of the first documentation of disease progression, relapse, or death due to any cause. The start of a new CLL treatment was not considered an event nor a reason for censoring PFS time. In study ML17102, determinations of progression events and of objective tumor response for the purpose of the primary and secondary efficacy endpoint analyses were based on investigator assessments. In study BO17072, an IRC assessment was used to determine when and if a PFS event occurred for purposes of the primary efficacy analysis for regulatory considerations in the United States. The IRC review for each subject was per-

formed by three board-certified radiologists and one board-certified oncologist with expertise in CLL. The tumor responses identified by the IRC radiologists were to be linked to the scan dates for presentation to the oncologist. The oncologist utilized the IRC radiologists' determination of response and date of response (or progression) at each visit for all study patients. The derivation of the study endpoints was programmed by Roche (based on the information provided by the IRC oncologist) and was not the responsibility of the IRC.

Additional endpoints for both studies included overall survival, event-free survival, disease-free survival (limited to patients who achieved a CR), overall response rate (ORR), and duration of response.

The final sample size for protocol ML17102 was based on data from the German CLL-4 trial and assumed the median PFS time to be 40 months in the FC arm and 54 months in the FCR arm. The final analysis was planned at the time of 357 PFS events. With this sample size and assumptions, the study was designed to detect a 35% improvement in progression-free survival (hazard ratio (HR) 0.74), at 2-sided 5% α and 80% power at the time of the final analysis. One interim analysis was to be conducted after two thirds (i.e., 238 of 357 patients) of the required events had occurred.

On the basis of external data relevant to assumptions regarding PFS times in the FC control arm, the final sample size in study BO17072 (protocol amendment dated December 2006) was 550 patients. The final number of events for PFS analysis was 284 events. The study was initially designed to detect a 30% increase in PFS and a 6-month improvement in median PFS between the study arms with 80% power and a 2-sided α of 5%.

Table 3. Efficacy results in age subgroups

Age subgroup	ML17102		BO17072	
	No. of pts	Hazard ratio for PFS (95% CI)	No. of pts	Hazard ratio for PFS (95% CI)
<65 yr(s)	572	0.52 (0.39, 0.70)	313	0.61 (0.45, 0.84)
≥65 yr(s)	245	0.62 (0.39, 0.99)	233	0.99 (0.70, 1.40)
<70 yr(s)	736	0.51 (0.39, 0.67)	438	0.67 (0.51, 0.87)
≥70 yr(s)	81	1.17 (0.51, 2.66)	108	1.22 (0.73, 2.04)

Abbreviation: PFS, progression-free survival.

RESULTS

Patient Characteristics

Eight hundred seventeen patients (409 in the FC arm and 408 in the FCR arm) in study ML17102 were enrolled between July 21, 2003, and April 4, 2006. Study BO17072 enrolled 552 patients (276 in each arm) between July 31, 2003, and August 10, 2007. Table 2 summarizes the demographics and baseline characteristics of the patients enrolled in both trials. In both trials, demographic and disease baseline characteristics were well balanced between arms. The median age was 61 years in both arms of study ML17102, whereas in study BO17072, median age was 62 years for the FC arm and 63 years for the FCR arm.

On the basis of the FDA analysis of the data, in the previously treated population (study BO17072), 18% and 17% of patients were fludarabine-exposed and fludarabine-sensitive (FC and FCR arms, respectively), 56% and 55% were alkylator-sensitive (FC and FCR arms, respectively), and 26% and 27% were alkylator-refractory (FC and FCR arms, respectively). Sensitivity to a prior treatment was defined as the achievement of a CR or PR that lasted at least 6 months.

Clinical Pharmacology

The pharmacokinetic profile of rituximab in patients with CLL was studied in 21 patients who received FCR and 11 patients who received FC in study BO17072 and was similar to the pharmacokinetics described in the Rituxan (Genentech, Inc.) product labeling for patients with NHL. The estimated median terminal half-life of rituximab in the CLL population was 32 days (range 14–62 days). There was no evidence (based on the pharmacokinetic profile) of drug interactions between rituximab and chemotherapy.

Efficacy

Study ML17102 (First-Line Study). The primary efficacy analysis occurred after completion of accrual and based on 254 of investigator-identified PFS events at the interim

analysis. Results demonstrated a statistically significant treatment effect for FCR as compared to FC in favor of the FCR arm with a HR of 0.56 (95% CI: 0.43, 0.71; p -value < .0001, log-rank test). The median PFS times were 31.5 and 39.8 months for the FC and FCR arms, respectively. The magnitude of the treatment effect, however, appeared to be decreased in patients older than 70 years (Table 3).

Study BO17072 (Second-Line Study). The primary efficacy analysis, based on 285 IRC-determined PFS events (clinical data cutoff July 23, 2008) demonstrated a statistically significant difference in PFS that favored the FCR arm. The HR for PFS (FCR versus FC) was 0.76 (95% CI: 0.60, 0.96; p -value = .0218, log-rank test). The median PFS was 26.7 and 21.7 months for the FCR and FC arms, respectively. The analysis of PFS based on investigator-determined events is consistent with and supportive of the IRC-determined results.

Across both studies, 243 of 676 rituximab-treated patients (36%) were 65 years or older and 100 rituximab-treated patients (15%) were 70 years or older. A planned exploratory subset analysis of the second-line study in patients age 65 years and older suggested a trend towards decreased treatment effects among older patients. An additional exploratory analysis in patients age 70 years and older (approximating the median age at diagnosis for patients with CLL), together with the subset analysis in patients age 65 years and older, suggested decreasing treatment effects as the population subset evaluated became older. The HR for PFS crossed 1 in both studies in the subset of patients older than 70 years. Table 3 summarizes the efficacy results in subgroups defined by age.

Secondary Efficacy Endpoints

At the time of data cutoffs for the PFS analyses in both studies, the majority of patients were alive. Therefore, median survival times could not be estimated and no definitive conclusions can be made regarding the treatment effect of rit-

uximab, when combined with FC chemotherapy, on survival.

In accordance with the NCI-WG 1996 criteria, an observed tumor response required confirmation of durability through at least 8 weeks after the initial observation. In the first-line treatment trial, 86% and 73% of patients in FCR and FC arms, respectively, were identified by investigators as responders (achieved CR or PR). In the trial investigating FCR in previously treated patients, 54% and 45% of patients in the FCR and FC arms, respectively, were identified by the IRC as responders. In the first-line study, 2% of patients in the control arm and 1% of patients in the FCR discontinued treatment after the third cycle because of stable disease. In the second-line study, 5% of patients in the FC arm and 1% of patients in the FCR arm discontinued treatment after the third cycle because of insufficient therapeutic response.

SAFETY RESULTS

The safety database contained data from 274 rituximab-treated patients enrolled in study BO17072 and 402 rituximab-treated patients enrolled in study ML17102. According to FDA's analysis of the data submitted to the sBLA in study ML17102, 77% of patients in the FCR group received >90% of the planned rituximab dosing (cumulative dose of 2875 mg/m²). The proportion of patients receiving >90% of the planned fludarabine and cyclophosphamide doses for a given treatment cycle decreased from 90% to 47% in the FC arm and from 93% to 50% in the FCR arm between cycle 1 and cycle 6.

In the second-line setting, 82% of patients in the FCR group received >90% of planned rituximab dosing. As in the first-line setting, the proportion of patients receiving >90% of the planned fludarabine and cyclophosphamide doses for a given treatment cycle decreased from 98% to 36% in the FC arm and from 98% to 40% in the FCR arm between cycle 1 and cycle 6. No patient withdrew from the studies because of infusional toxicity, and rituximab was discontinued in one patient because of toxicity in the first-line study.

Across both studies, patients who were 70 years or older received a lower dose intensity for fludarabine and for cyclophosphamide compared to younger patients in both arms; the dose intensity for FC was similar in the FCR- and FC-treated groups. In study ML17102, the dose intensity of rituximab was similar in older and younger patients; however, in study BO17072, patients 70 years or older received a lower dose intensity of rituximab as compared to those younger than 70 years.

At FDA's request, an unplanned and premature analysis of survival was conducted for both studies to assess for pos-

sible toxic effects. Although immature, the survival data did not suggest a detrimental effect on overall survival among rituximab-treated patients. The HR for survival slightly favored the FCR-treated arms in both studies.

In the first-line setting, the leading cause of death in both the FCR and FC groups was infections; the rate of deaths due to infections was 5% versus 3% in FC and FCR arms, respectively. Although the leading cause of death from infection was sepsis, many of the sepsis events occurred following pneumonia. Overall, the incidence of grade 3–4 infections was 17% in the FC arm and 18% in the FCR arm.

In the second-line setting, the FC-treated group had a higher percentage of infectious deaths (7%) than the FCR-treated group (5%). The leading cause of infectious death was sepsis, followed by pneumonia. In some of the patients who died of sepsis, the death occurred in the context of PD or neutropenia while on treatment for progression, making the determination of the exact cause of death difficult. The addition of rituximab to the FC regimen did not increase the incidence of toxic deaths.

The leading cause of death in study BO17072 was PD. Death due to disease progression occurred more frequently in the control arm during the first and second years on protocol. After the second year, the incidence of deaths attributed to disease progression was similar in both arms.

Infusion-related adverse reactions were defined as any of the following adverse events occurring during or within 24 hours from the start of infusion: nausea, pyrexia, chills, hypotension, vomiting, and dyspnea. Fifty-nine percent of FCR-treated patients experienced an infusion reaction of any severity in the second-line setting. Because only grade 3 and 4 adverse reactions were collected in the first-line study, a reliable estimate of the infusional toxicity cannot be determined in this setting.

In study ML17102, the following severe and life-threatening (NCI circulating tumor cell grade 3 and 4) adverse reactions occurred more frequently in FCR-treated patients compared to FC-treated patients: infusion reactions (9% vs 0), neutropenia (30% vs. 19%), febrile neutropenia (9% vs. 6%), leukopenia (23% vs. 12%), and pancytopenia (3% vs. 1%). In study BO17072, the following grade 3 or 4 adverse reactions occurred more frequently in FCR-treated patients compared to FC-treated patients: infusion reactions (7% vs 0), neutropenia (49% vs. 44%), febrile neutropenia (15% vs. 12%), thrombocytopenia (11% vs. 9%), hypotension (2% vs. 0%), and hepatitis B (2% vs. 0%).

The incidence of grade 3 and 4 adverse reactions was higher among patients receiving FCR who were 70 years or older compared to younger patients for neutropenia [44% vs. 31% (ML17102); 56% vs. 39% (BO17072)], febrile

neutropenia [16% vs. 6% (ML17102)], anemia [5% vs. 2% (ML17102); 21% vs. 10% (BO17072)], thrombocytopenia [19% vs. 8% (BO17072)], pancytopenia [7% vs. 2% (ML17102); 7% vs. 2% (BO17072)], and infections [30% vs. 14% (BO17072)].

DISCUSSION

On February 17, 2010, FDA approved the labeling expansion of rituximab under 21 CFR 601.2 in combination with fludarabine and cyclophosphamide for the treatment of patients with CLL. This approval was based on the review of two studies that demonstrated both clinically relevant and statistically significant improvement in the primary endpoint of PFS. The addition of rituximab to the FC regimen decreased the risk of progression or death by 44% [HR 0.56 (95% CI: 0.43, 0.71); $p < .001$, log-rank test] in the first-line setting and by 24% [HR 0.76 (95% CI: 0.60, 0.96); $p = .022$, log-rank test] in the second-line setting. The IRC PFS analysis in the second-line setting was supported by the study investigators' PFS analysis.

An improvement in the endpoint PFS has served as the basis for prior FDA approvals for the treatment of patients with CLL, specifically alemtuzumab and bendamustine. The natural history and clinical course of untreated or minimally-treated CLL, which make it an appropriate disease for consideration of PFS as an approval endpoint, are the long natural history of the disease and the potential for administration of subsequent effective treatments, which themselves may obscure survival effects if administered in an unbalanced or uncontrolled manner after completion of study therapy.

In the United States, alemtuzumab, bendamustine, and ofatumumab have been approved by the FDA in the last 10 years. The initial approval for alemtuzumab and the current approval for ofatumumab were under the Accelerated Approval regulations. Under the Accelerated Approval regulations (21 CFR subpart H), FDA may grant marketing approval for a new drug product or biologic on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint (21 CFR 314.50) that is reasonably likely (based on epidemiologic, therapeutic, pathophysiologic, or other evidence) to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoints to clinical benefit, or of the observed clinical benefit to ultimate outcome.

Alemtuzumab was first approved under subpart H in 2001, on the basis of an improved overall response rate

(surrogate endpoint). Further randomized studies demonstrated an improvement in PFS.

In 2009, ofatumumab was approved under the accelerated approval regulations on the basis of response rate in a refractory population. Particularly in CLL, ORR can be difficult to interpret due to variability in how the NCI-WG criteria can be interpreted [7]. This variability underscores the need to confirm the benefit following accelerated approval and why ORRs of different products cannot be reliably compared to each other.

In the United States, rituximab has been marketed since 1997 and has a well-established toxicity profile. In patients with CLL, the majority of the drug-related adverse reactions in the two studies were attributable to the backbone chemotherapy regimen, FC. However, the addition of rituximab to FC chemotherapy resulted in an increase incidence of cytopenias and infusion-related reactions. The higher incidence of these adverse reactions did not translate into increased incidence of toxic deaths or long-term morbidity.

One of the major review issues regarding these two efficacy supplements involved the risk–benefit assessment for patients in the geriatric population, particularly patients older than 70 years. The median age at diagnosis of patients with CLL is 72 years. The population evaluated in the two studies supporting the CLL labeling expansion was 10 years younger than the median age at diagnosis of CLL patients in the United States.

The proportion of patients in both studies who were older than 70 was limited; however, the PFS HR for this exploratory subgroup was ≥ 1 in both studies (IRC analysis in the second-line setting). It is not clear whether decreased drug exposure (all drugs) due to cytopenias was the primary reason for this effect. Toxicities were increased in the older population (≥ 70 years) in both arms compared to the younger population.

Of particular concern in patients with CLL is the potential for overtreatment for the majority of patients with CLL who are older than 70 years and may not tolerate intensive treatment regimens. A recent randomized study conducted by the German CLL study group demonstrated that PFS was not improved with the substitution of fludarabine compared to chlorambucil in patients older than 65 years [8]. Additionally, there was a worrisome trend toward reduced survival observed in the German study among older patients treated with fludarabine. Additional studies with rituximab and other monoclonal antibodies in combination with less intensive chemotherapy regimens (compared to FC) may help determine the optimal therapy for older patients.

On the basis of the total number of adverse reactions in both studies and analysis of drug exposure, the backbone regimen of FC appeared to cause substantial toxicity. It is

not clear whether FC at the doses used in these studies should be offered to patients with CLL who are older than 65 years, based on the German CLL study group trial, or older than 70 years, based on the two rituximab studies described in this report. Nevertheless, FC is a standard regimen offered to many CLL patients in the United States, and the data from studies BO17072 and ML17102 support the addition of rituximab to fludarabine and cyclophosphamide when this combination regimen chemotherapy is planned. The FDA clinical review team encourages pharmaceutical manufacturers and cancer cooperative groups to determine optimal regimens for elderly patients that will ultimately prolong the lives of patients with CLL, especially if less toxic regimens can achieve similar effects. This may include designing studies that combine rituximab with different chemotherapy regimens, such as those with lower doses of FC or in combination with single-agent fludarabine, chlorambucil, or bendamustine.

CONCLUSION

The labeling expansion was approved based on improvement in PFS with a modest and acceptable increase in toxicity observed in two studies when rituximab was added to fludarabine and cyclophosphamide chemotherapy. The PFS results in two studies support the robustness of the results. The treatment effect of rituximab on PFS was supported by an increase in overall response rates. No statistically significant effects on survival were observed; however, the analyses of survival were immature at the time of the sBLA submission.

AUTHOR CONTRIBUTIONS

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