VOLUME 28 · NUMBER 10 · APRIL 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Rituximab Plus Fludarabine and Cyclophosphamide Prolongs Progression-Free Survival Compared With Fludarabine and Cyclophosphamide Alone in Previously Treated Chronic Lymphocytic Leukemia

Tadeusz Robak, Anna Dmoszynska, Philippe Solal-Céligny, Krzysztof Warzocha, Javier Loscertales, John Catalano, Boris V. Afanasiev, Loree Larratt, Christian H. Geisler, Marco Montillo, Ilya Zyuzgin, Peter S. Ganly, Caroline Dartigeas, András Rosta, Jörg Maurer, Myriam Mendila, M. Wayne Saville, Nancy Valente, Michael K. Wenger, and Sergey I. Moiseev

From the Department of Hematology, Medical University, Lodz; Department of Hemato-Oncology and Bone Marrow Transplantation, Medical University, Lublin; Department of Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland; Department of Hematology, Clinique Victor Hugo, Le Mans; Department of Hematology, Centre Hospitalier Universitaire Bretonneau, Tours, France; Department of Hematology, Hospital Universitario de la Princesa, Madrid, Spain; Haematology Department and Dorevitch Pathology, Frankston Hospital, Frankston, Victoria, Australia; Bone Marrow Transplantation Centre and Department of Hematology, St Petersburg Pavlov State Medical University; Leningrad Regional Clinical Hospital, St Petersburg, Russia; Department of Hematology, Walter C. Mackenzie Health Sciences Centre, Edmonton, Alberta, Canada; Department of Hematology, Rigshospitalet, Copenhagen, Denmark; Divisione Ematologia, Ospedale Niguarda, Milano, Italy; Department of Haematology, Christchurch Hospital, Christchurch, New Zealand; Department of Medicine, National Institute of Oncology, Budapest, Hungary; Pharmaceuticals Division, F. Hoffmann-La Roche, Basel, Switzerland; Oncology Medical Research, Biogen Idec, Cambridge, MA; and Genentech, South San Francisco, CA.

Submitted October 9, 2009; accepted December 17, 2009; published online ahead of print at www.jco.org on March 1, 2010.

Supported by F. Hoffmann-La Roche, Genentech, and Biogen Idec.

Presented in part at the 50th Annual Meeting of the American Society of Hematology, December 6-9, 2008, San Francisco, CA.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Tadeusz Robak, MD, Department of Hematology, Medical University of Lodz, Ciolkowskiego 2, Lodz, Poland 93-510; e-mail: robaktad@csk.umed.lodz.pl.

0732-183X/10/2810-1756/$20.00

DOI: 10.1200/JCO.2009.26.4556

ABSTRACT

Purpose
Rituximab, a monoclonal antibody that targets the CD20 cell surface antigen, has clinical activity in patients with non-Hodgkin's lymphoma and other B-lymphocyte disorders when administered alone or in combination with chemotherapy. Promising results have previously been reported in nonrandomized studies in patients with chronic lymphocytic leukemia (CLL). This trial was designed to compare chemoimmunotherapy with chemotherapy alone in patients with previously treated CLL.

Patients and Methods
This international, multicenter, randomized trial compared six cycles of rituximab plus fludarabine and cyclophosphamide (R-FC) with six cycles of fludarabine and cyclophosphamide alone (FC) in patients with previously treated CLL. A total of 552 patients with Binet stage A (10%), B (59%), or C (31%) disease entered the study and were randomly assigned to receive R-FC (n = 276) or FC (n = 276).

Results
After a median follow-up time of 25 months, rituximab significantly improved progression-free survival in patients with previously treated CLL (hazard ratio = 0.65; $P < .001$; median, 30.6 months for R-FC *v* 20.6 months for FC). Event-free survival, response rate, complete response rate, duration of response, and time to new CLL treatment or death were also significantly improved. Although the rates of adverse events, grade 3 or 4 events, and serious adverse events were slightly higher in the R-FC arm, R-FC was generally well tolerated, with no new safety findings and no detrimental effect on quality of life.

Conclusion
R-FC significantly improved the outcome of patients with previously treated CLL.

J Clin Oncol 28:1756-1765. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common form of adult leukemia, with an incidence of approximately two to four cases per 100,000 inhabitants per year in Western countries (> 20 per 100,000 after the age of 70 years).[1,2] The disease generally follows an indolent course, with multiple relapses and remissions of decreasing quality and duration. Several prognostic factors have been identified, including disease stage, chromosomal aberrations (such as deletions of 17p, 13q, or 11q, or trisomy 12), immunoglobulin heavy-chain variable region (IgVH) mutational status, and overexpression of CD38 and/or the ζ-chain–associated protein kinase 70 (ZAP-70).[3] CLL remains incurable with conventional chemotherapy, and new treatment options are needed. Apart from watchful waiting for patients with asymptomatic disease, several therapies are currently available, including alkylating agents (with or without corticosteroids) and purine nucleoside analogs, alone or in combination, for more advanced or symptomatic disease. Fludarabine has been shown to be superior to alkylating agent–based chemotherapy in patients with CLL,[4,5] and combinations of fludarabine and cyclophosphamide (FC) have been shown to result in superior complete remission (CR) rates and duration of response (DR) compared with fludarabine alone.[6-8] Rituximab, a monoclonal antibody that targets the

CD20 antigen on B lymphocytes, has activity in CLL as monotherapy[9-13] and in combination with chemotherapy.[14-19] Some of the best phase II efficacy results have been produced with a combination of rituximab, fludarabine, and cyclophosphamide (R-FC) in both treatment-naïve[20,21] and previously treated patients.[22] Twenty-five percent of previously treated patients achieved a CR with R-FC treatment. Of these patients, 12 (32%) achieved molecular remission in bone marrow. Compared with historical controls, CR rates and survival were significantly better with R-FC than with FC alone in both previously treated and untreated patients.[21,23] The REACH (Rituximab in the Study of Relapsed Chronic Lymphocytic Leukemia) study (Roche Study No. BO17072; F. Hoffmann-La Roche, Basel, Switzerland) was initiated to directly compare R-FC with FC alone in patients with previously treated CLL.

PATIENTS AND METHODS

Study Design

This international, multicenter, open-label, phase III trial randomly assigned patients (1:1) with previously treated CLL to receive either R-FC or FC alone. Patients were stratified by country, previous treatment for CLL (alkylator refractory, alkylator sensitive, or fludarabine [or other nucleoside analog] exposed), time from diagnosis to random assignment (< 2, < 5, or < 10 years), and β_2-microglobulin ($\leq$ upper limit of normal [ULN] or $>$ ULN).

The primary objective was to demonstrate superior progression-free survival (PFS) for R-FC compared with FC alone. Secondary objectives were to compare event-free survival, disease-free survival, overall survival, overall response rate (ORR), CR rate, DR, molecular remission rate, time to new CLL treatment, safety, and quality of life (QOL) between the study arms and to characterize the pharmacokinetics of rituximab, fludarabine, and cyclophosphamide (data to be presented elsewhere). Evaluation of the relationship between baseline prognostic markers and clinical outcome in subsets of patients was also preplanned.

The study was conducted at 88 centers in 17 countries. All patients gave written informed consent, per Declaration of Helsinki recommendations. Safety and interim efficacy data were reviewed by an independent data safety monitoring board. F. Hoffmann-La Roche was the sponsor of the trial.

Eligibility Criteria

Patients age $\geq$ 18 years with CD20$^+$ CLL according to National Cancer Institute Working Group criteria,[24] who had received one prior line of therapy, which could be single-agent chlorambucil ($\pm$ prednisone/prednisolone), single-agent fludarabine (or other nucleoside analog), or an alkylator-containing combination regimen, but not an alkylator/nucleoside analog combination, were eligible. Patients could be sensitive or refractory to prior alkylating agents but had to be sensitive to fludarabine (defined as achieving a response that lasted $\geq$ 6 months). Prior treatment with interferon, rituximab, other monoclonal antibodies, or stem-cell transplantation was not permitted.

Patients had to have adequate hepatic (bilirubin $< 2\times$ ULN), renal (calculated creatinine clearance $\geq$ 60 mL/min; 50 mL/min was permitted for a short period during the trial), and bone marrow function (neutrophils $\geq 1 \times 10^9$/L; platelets $\geq 50 \times 10^9$/L); an Eastern Cooperative Oncology Group performance status ≤ 1; and a life expectancy of more than 6 months. Fertile patients had to use contraception. Exclusion criteria included transformation to aggressive B-cell malignancy; history of severe nucleoside analog–induced toxicity; clinically significant autoimmune hemolytic anemia; invasive malignancy in the last 2 years; other serious illness or medical conditions, including infection with HIV, hepatitis B or C, severe pulmonary or cardiac disease, recent myocardial infarction, uncontrolled diabetes or hypertension, seizure disorders requiring treatment, and comorbid conditions that might require systemic corticosteroids for more than 1 month; pregnancy or lactation; and recent use of other investigational drugs.

Study Treatment

Patients on both arms of the study received intravenous (IV) fludarabine 25 mg/m^2/d and cyclophosphamide 250 mg/m^2/d for 3 days, repeated every 28 days for a total of six cycles. Patients randomly assigned to rituximab received 375 mg/m^2 by IV infusion on day 1 of the first cycle (the day before chemotherapy) and 500 mg/m^2 IV on day 1 of subsequent cycles (the same day as chemotherapy), with premedication (oral acetaminophen and an antihistamine). Patients with an absolute lymphocyte count $\geq 25 \times 10^9$ cells/L before cycle 2 or subsequent cycles could have their rituximab dose split over 2 days, at the investigator's discretion.

Patients received supportive care as needed, including antibiotics, blood transfusions, and hematopoietic growth factors. Prophylaxis for tumor lysis syndrome (including allopurinol or rasburicase) and prophylactic antimicrobials (cotrimoxazole and acyclovir/valacyclovir) were required for all patients.

Chemotherapy dose reductions ($\leq$ two permitted, each by 25%) and delays (of $\geq$ 1 week) were scheduled for clinically significant grade 3 or 4 toxicities. Patients with renal impairment (creatinine clearance $<$ 70 mL/min) also required a 25% dose reduction in fludarabine (discontinuation if the clearance decreased to $\leq$ 30 mL/min).

Efficacy Assessments

Disease status was assessed by regular blood counts, clinical examination, and computed tomography (CT) scans throughout treatment and until 33 months after entering the study. Subsequent assessments were planned by clinical examination and blood counts every 6 months until 5 years, and then every year until 8 years. Response was assessed using the National Cancer Institute Working Group 1996 criteria,[24] with the addition of radiographs for assessment of best response and progression. Responses had to be confirmed with a CT scan $\geq$ 8 weeks after first documentation of response, and CRs also required bone marrow biopsy confirmation. All CT scans and clinical efficacy data underwent an independent review (Perceptive Informatics, Boston, MA).

Molecular response was assessed in peripheral blood and bone marrow at the time of CR and 6 months later (if CR was maintained). Patients were categorized as molecular responders (minimal residual disease [MRD] negative) if there was no detectable clonal IgVH rearrangement, as assessed by polymerase chain reaction using standard methods and a sensitivity cutoff of 1×10^{-4}.[25,26]

Safety and QOL Assessments

Adverse events (AEs), assessed clinically and by laboratory measurements throughout the study, were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). QOL was assessed at baseline, after three cycles and six cycles, and at 1 year using the Functional Assessment of Cancer Therapy–General (FACT-G) questionnaire (version 4.0).

Statistical Analysis

Recruitment of 550 patients was planned based on an estimated recruitment period of 55 months and a median PFS time of 20 months in the control arm. The sample size was required for 284 events to show a 40% improvement in median PFS (28 months) in the R-FC arm, corresponding to a 29% risk reduction (hazard ratio [HR] = 0.714), with 80% power and an overall α level of 5% (adjusted for one interim analysis after two thirds of the planned events).

All randomly assigned patients were included in the efficacy analyses, which were conducted on an intent-to-treat basis using investigator assessments of response/progression. Response rates were compared using χ^2 tests with 95% CIs applying the Anderson-Hauck method. Stratified and nonstratified log-rank tests and Cox regressions were used for time-to-event end points, with the median time calculated by Kaplan-Meier analysis. All statistical tests were two-sided. Exploratory analyses of prognostic factors were performed using logistic regression.

Safety data were summarized by grade, severity, and relationship to study medication, treatment arm, cycle, and phase; laboratory safety data were also summarized as shift tables. Additional safety analyses (not shown) were performed according to baseline characteristics (age, disease stage, creatinine clearance, and lymphocyte count).

QOL was analyzed by analysis of covariance, with treatment as the main factor and baseline FACT-G total score as a covariate. FACT-G

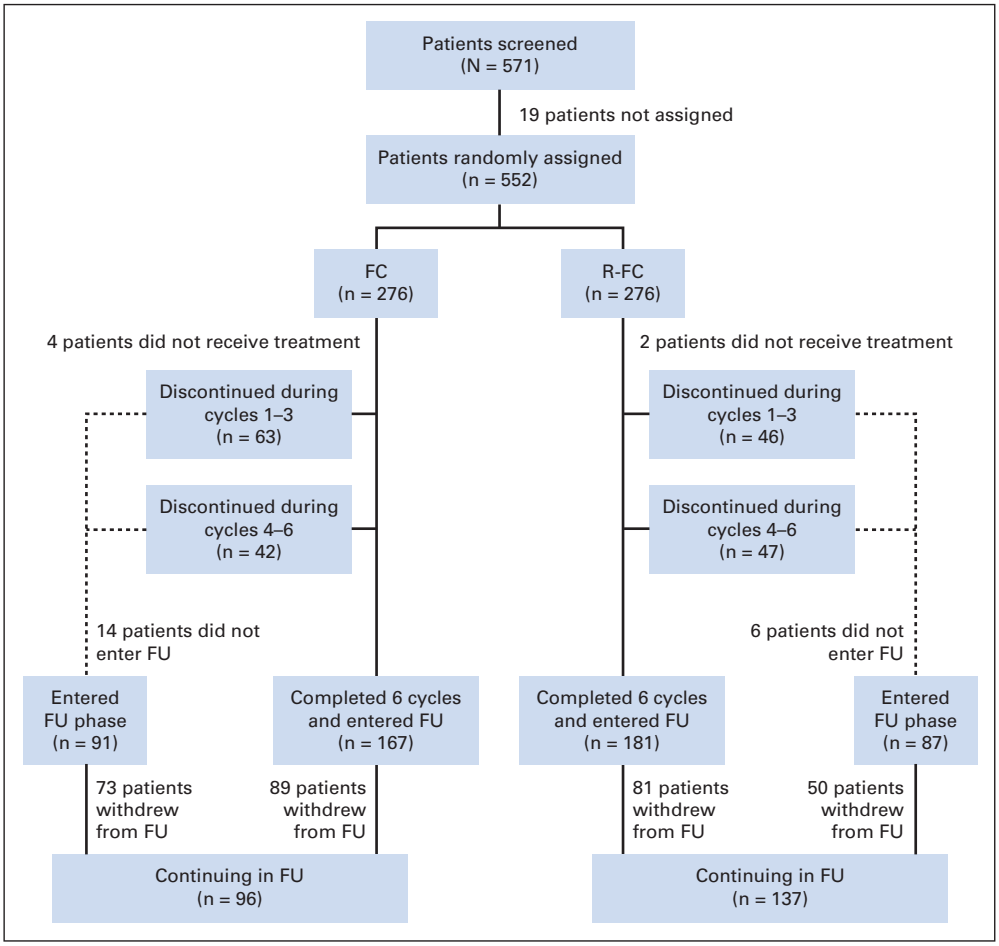

Fig 1. CONSORT diagram of the Rituximab in the REACH (Study of Relapsed Chronic Lymphocytic Leukemia) trial. FC, fludarabine and cyclophosphamide; R-FC, rituximab plus fludarabine and cyclophosphamide; FU, follow-up.

subscores (eg, physical, social/family) and total score over time were also summarized descriptively.

RESULTS

Study Population

Between July 2003 and August 2007, 552 patients were enrolled and randomly assigned (n = 276 per arm). Six randomly assigned patients (FC, n = 4; R-FC, n = 2) did not receive study treatment (Fig 1). Table 1 lists the patients' baseline characteristics, which were well balanced in the two arms.

Treatment

More patients in the R-FC arm (67.5%) completed six cycles of therapy compared with the patients in the FC arm (61.4%; Fig 1). Overall, most patients who stopped treatment early did so because of AEs, but more patients in the FC arm stopped as a result of insufficient response (stable or progressive disease) compared with R-FC arm (5% *v* 1%, respectively). More than 90% of patients received ≥ 90% of the planned dose of fludarabine (25 mg/m^2/d) and/or cyclophosphamide (250 mg/m^2/d) in cycle 1, but this proportion decreased to approximately 67% for fludarabine and 73% for cyclophosphamide in cycle 4 and to 59% for fludarabine and 64% for cyclophosphamide in cycle 6. There were no major differences in FC exposure between the two arms. The vast majority of patients who received rituximab received more than 90% of the planned dose at each cycle, including 96% of patients in cycle 1.

The median follow-up time was 25 months. More patients in the FC arm (n = 69, 25%) than in the R-FC arm (n = 47, 17%) started a subsequent treatment for CLL. Of these patients, 49% in the FC arm and 30% in the R-FC arm received rituximab as part of their first subsequent treatment.

Safety and QOL

Almost all patients experienced AEs, but 70% of events in both arms were grade 1 or 2 in severity, and the proportions of patients who discontinued therapy as a result of an AE were similar in the two arms (Table 2). Overall, the rates of AEs of any grade, grade 3 or 4 AEs, serious AEs, and fatal AEs were higher in the R-FC arm compared with the FC arm (Table 2). More second malignancies (7% in R-FC arm *v* 5% in FC arm) and more cases of hepatitis B (primary infections and reactivation; 3% in R-FC arm *v* < 1% in FC arm) were also reported in the R-FC arm. Most fatal AEs (in both arms) were a result of infections. However, despite the higher rate of grade 3 or 4 neutropenia in the R-FC arm, the overall incidence of infections (51% in FC arm and 49% in R-FC arm) and grade 3 or 4 infections (19% in FC arm and 18% in R-FC) did not differ. This may have been a result of the greater use of colony-stimulating factors in the R-FC arm (58% *v* 49% in the

Table 1. Baseline Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	FC (n = 276) No. of Patients	FC (n = 276) %*	R-FC (n = 276) No. of Patients	R-FC (n = 276) %*
Sex				
Male	181	66	187	68
Female	95	34	89	32
White	273	99	271	98
Age, years				
Median	62.0		63.0	
Range	35-81		35-83	
< 65	162	59	155	56
65-70	68	25	74	27
> 70	46	17	47	17
Binet stage				
A	31	11	24	9
B	160	58	166	60
C	85	31	86	31
"B" symptoms	85	31	72	26
ECOG performance status				
0	161	59	169	61
1	114	41	107	39
Median time from first diagnosis, years	3.69		3.79	
Median time from last progression, months	1.64		1.61	
Previous chemotherapy category				
Alkylator refractory	71	26	74	27
Alkylator sensitive	155	56	152	55
Fludarabine exposed†	50	18	48	17
Lymphocytes, $\times 10^9$/L				
≤ 25	97	36	89	33
> 100	57	21	52	19
β_2-microglobulin > ULN	205	78	203	76
IgVH				
Mutated	92	35	100	39
Unmutated	170	65	158	61
ZAP-70				
Positive	84	42	89	42
Negative	115	58	122	58
del11q				
Yes	59	22	56	21
No	204	78	214	79
del13q				
Yes	159	60	150	56
No	105	40	120	44
del17p				
Yes	24	9	18	7
No	239	91	251	93
Trisomy 12				
Yes	40	15	29	11
No	223	85	241	89
No. of cytogenetic abnormalities				
0	47	18	72	27
1	157	59	150	56
2	59	22	42	16
3	1	< 1	6	2
4	1	< 1	—	—
CD38‡				
Positive	79	48	91	57
Negative	85	52	69	43

Abbreviations: FC, fludarabine and cyclophosphamide; R-FC, rituximab plus fludarabine and cyclophosphamide; ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of normal; IgVH, immunoglobulin heavy-chain variable region; ZAP-70, zeta-chain-associated protein kinase 70.

*Percentages are based on No. of valid values.

†Includes three R-FC patients and five FC patients treated with sequential fludarabine and alkylating agents (originally allowed by the protocol). Prior treatment is missing for two FC patients.

‡CD38 was an optional assessment at baseline.

Table 2. Overview of AEs

AE	FC (n = 272) No. of Patients	FC (n = 272) %	R-FC (n = 274) No. of Patients	R-FC (n = 274) %
Any AE	260	96	270	99
Grade 3 or 4 AEs	200	74	219	80
Serious AEs	130	48	137	50
Fatal AEs	26	10	36	14
AE leading to discontinuation	69	25	72	26
AE leading to dose modification/interruption	105	39	141	51
Treatment-related deaths	14	5	19	7
All deaths	68	25	62	23
Grade 3 or 4 hematologic toxicity during treatment (laboratory data)				
Hemoglobin	52	19	53	19
Platelets	71	26	74	27
Neutrophils	229	84	245	89
Most common nonhematologic AEs (≥ 10% of patients, all grades)				
Nausea	96	35	110	40
Vomiting	51	19	58	21
Pyrexia	42	15	69	25
Fatigue	45	17	45	16
Asthenia	30	11	28	10
Chills	6	2	45	15
Constipation	30	11	40	15
Diarrhea	32	12	33	12
Cough	24	9	34	12
Headache	30	11	25	9
Most common grade 3 or 4 AEs (≥ 5% of patients)				
Neutropenia	108	40	116	42
Febrile neutropenia	32	12	33	12
Anemia	35	13	33	12
Thrombocytopenia	24	9	29	11
Granulocytopenia	12	4	18	7
Pancytopenia	13	5	9	3
Pneumonia	17	6	15	5
Other grade 3/4 AEs with a ≥ 2% difference in incidence between arms				
Hepatitis B	—	—	5	1.8
Possible infusion-related AEs				
AEs on day 1 or 2 of any treatment cycle	131	48	176	64
Grade 3 or 4 AEs on day 1 or 2 of cycle 1	11	4	17	6
Grade 3 or 4 AEs during rituximab infusion	—	—	18 (7)	

Abbreviations: AE, adverse event; FC, fludarabine and cyclophosphamide; R-FC, rituximab plus fludarabine and cyclophosphamide.

FC arm) and mandatory antimicrobial and antiviral prophylaxis in both arms. The frequency and severity of AEs tended to be higher in older patients and patients with poor renal function in both arms of the study. In contrast to reports from previous single-arm studies, there was no apparent increase in toxicity with R-FC (notably, infusion-related events or tumor lysis syndrome) in patients with high baseline lymphocyte counts or advanced-stage disease (data not shown). The incidence and severity of rituximab infusion-related reactions were similar to those reported in patients with non-Hodgkin's lymphoma (NHL). Overall, R-FC was well tolerated.

QOL scores were high at screening (median score, 79.5 of 112 points and 80.0 of 112 points in the FC and R-FC arms, respectively)

and did not change substantially over the study period. Differences between treatment arms were small at every time point, with no apparent trends.

Efficacy

The primary end point of the study was PFS, which improved significantly in the R-FC arm compared with the FC arm, with an HR of 0.65 (representing a 35% reduction in risk of progression or death) and a 10-month improvement in median PFS time from 20.6 to 30.6 months ($P < .001$; Table 3; Figs 2A and 2B). Significant improvements were observed in most secondary end points, including DR, time to new CLL treatment, CR, and ORR (Table 3). These findings were supported by the results of the independent review committee (IRC; Table 3), which were also statistically and clinically in favor of the R-FC arm. With a median follow-up time of 25 months, there was no statistically significant difference in survival between the two treatment arms (Fig 2C), although less than 10% of patients had died at this point.

MRD assessment was scheduled in patients achieving a CR. MRD results in peripheral blood were available for 32 of 39 patients for FC and 37 of 67 patients for R-FC. More patients receiving R-FC (16 [43%] of 37 patients) were MRD negative compared with patients receiving FC (10 [31%] of 32 patients). MRD in the bone marrow was assessed in only 12 patients (FC, n = 4; R-FC, n = 8), with no difference between the treatment arms.

The PFS (and ORR) benefit was consistent across key patient subgroups (Figs 3 and 4 and Appendix Figs A1 and A2, online only). Of note, both Binet stage B and C patients benefited from R-FC, as did patients with high lymphocyte counts, poor renal function, or poor prognostic factors such as del11q, unmutated IgVH, or positive ZAP-70. Univariate and multivariate Cox regression analyses for PFS confirmed the advantage of R-FC over FC and indicated the robustness of the results of the primary analysis. A likelihood ratio test for potential interaction of age, sex, disease stage, and prognostic markers for PFS did not reveal any significant interactions.

Table 3. Overview of Efficacy

Parameter	FC (n = 276)	R-FC (n = 276)	*P**	HR	95% CI	*P*† for HR
Investigator assessments of response/progression						
Median progression-free survival, months	20.6	30.6	< .001	0.65‡	0.51 to 0.82	< .001
Median overall survival, months	52	NR	.2874	0.83§	0.59 to 1.17	.2871
Best overall response rate, %						
Response (complete or partial)	58.0	69.9	.0034			
Complete response	13.0	24.3	< .001			
Partial response	44.9	45.7				
Stable disease	22.1	17.0				
Progressive disease	5.4	2.5				
Missing/not assessable	14.5	10.5				
Median duration of response, months‖	27.7	39.6	.0252	0.69§	0.50 to 0.96	.026
Median time to new treatment, months	34.3	NR	.0024	0.65§	0.49 to 0.86	.0026
Molecular response rate¶						
Patients assessed for MRD in blood						
No. of all patients	32	37				
%	12	13				
MRD negative in blood						
No. of patients assessed	10	16				
%	31	43				
Patients assessed for MRD in bone marrow						
No. of all patients	13	24				
%	5	9				
MRD negative in bone marrow						
No. of patients assessed	4	8				
%	31	33				
Independent review committee assessments of response/progression						
Median progression-free survival, months	21.9	27.0	.0218	0.76	0.60 to 0.96	.0222
Best overall response rate, %						
Response	49	61	.0048			
Complete response	3	9	.0046			

Abbreviations: FC, fludarabine and cyclophosphamide; R-FC, rituximab plus fludarabine and cyclophosphamide; HR, hazard ratio; NR, not reached; MRD, minimal residual disease.
*P values determined using the log-rank or χ^2 test.
†P values determined using the Wald test.
‡Nonstratified (unadjusted).
§Nonstratified (adjusted).
‖Only in patients with a complete or partial response.
¶Only in patients with a complete response as assessed by the investigator.

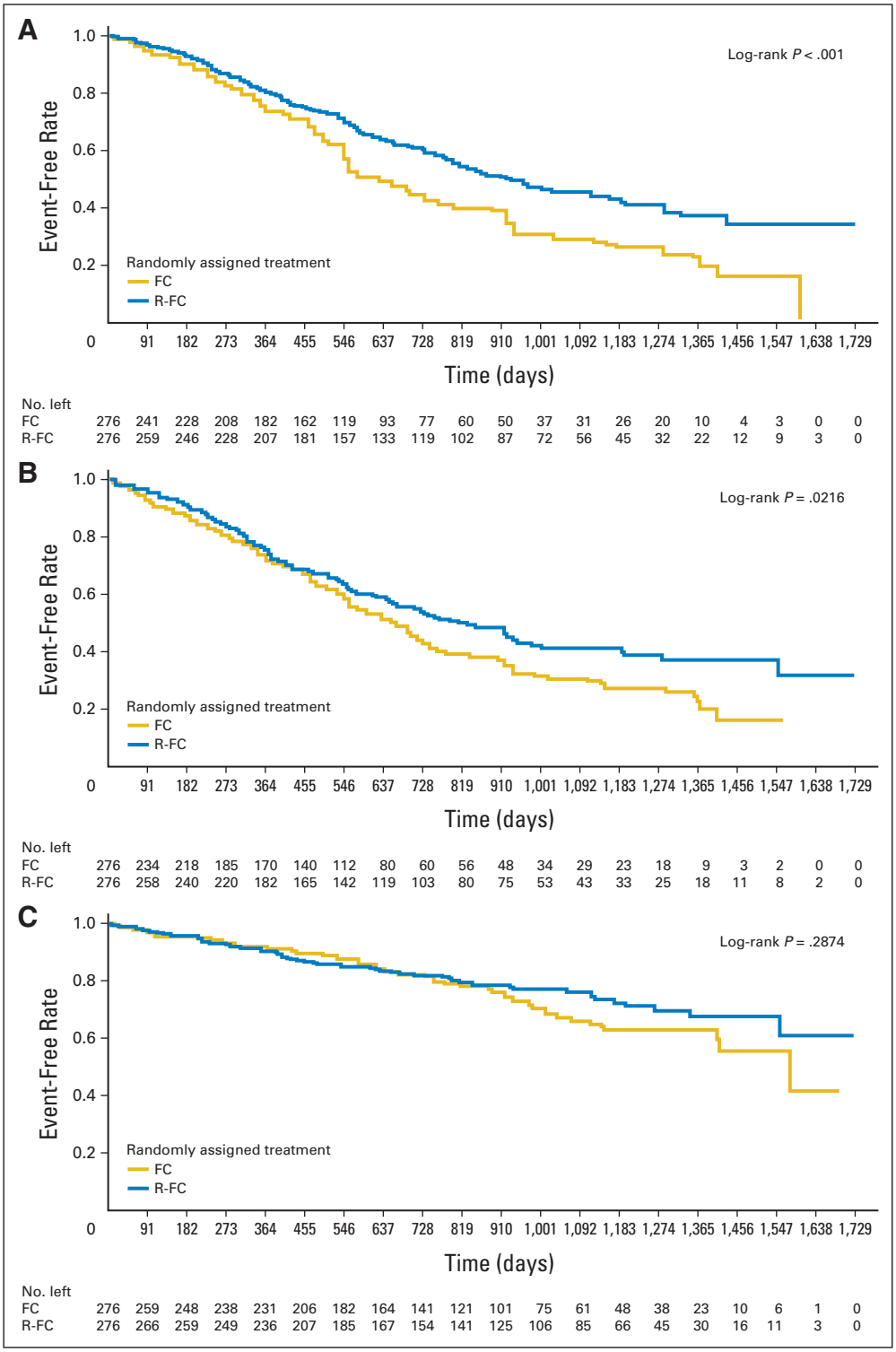

Fig 2. Kaplan-Meier plots of (A) progression-free survival by investigator assessment, (B) progression-free survival by independent review panel assessment, and (C) overall survival in the intent-to-treat population. FC, fludarabine and cyclophosphamide; R-FC, rituximab plus fludarabine and cyclophosphamide.

DISCUSSION

The REACH study is the largest randomized trial in patients with previously treated CLL reported to date. The trial showed that the addition of rituximab to FC chemotherapy significantly improved PFS, a finding supported by the IRC analysis. Investigator- and IRC-assessed CR rates were also significantly improved with R-FC, although CR rates reported by the IRC were much lower than those reported by the investigators. This was mainly because of the stringent IRC requirements for CT scan assessments, the need to follow strict algorithms without access to full clinical data (indicating, for example, transient or alternative reasons for changes in lymph node size or

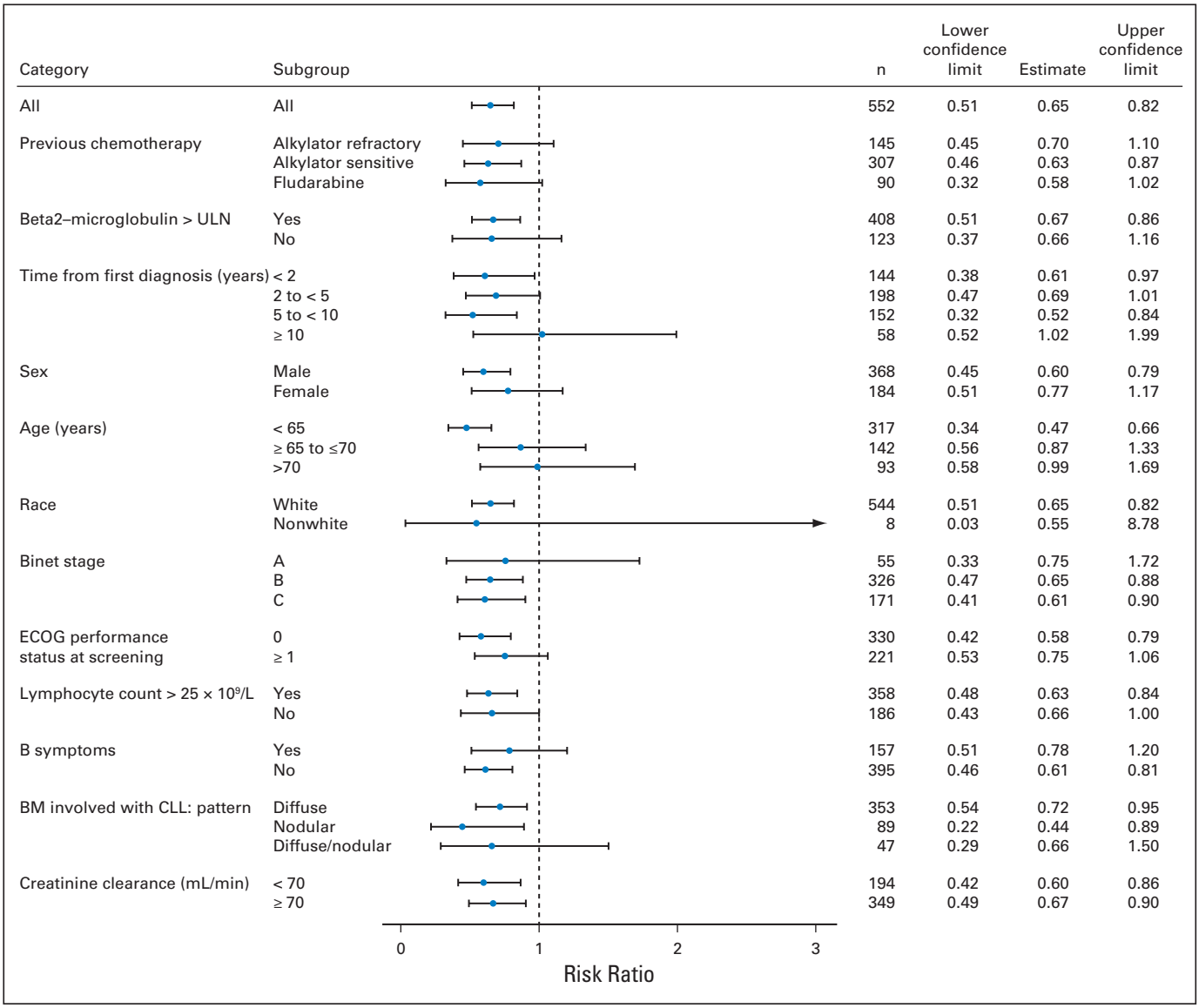

Fig 3. Hazard ratios and 95% CIs for progression-free survival (PFS) by subgroup (intent-to-treat population, investigator assessment). PFS was measured from day of random assignment until first documented disease progression, relapse after response, or death from any cause. Censoring occurred at last response assessment. ULN, upper limit of normal; ECOG, Eastern Cooperative Oncology Group; BM, bone marrow; CLL, chronic lymphocytic leukemia.

lymphocyte count), and lack of confirmatory bone marrow biopsies. The requirement for regular CT scans in this study went beyond the recognized requirements at the time[24] and more recent guidelines[27] and is not necessarily warranted in future studies or routine clinical practice.

Overall survival was not significantly improved in the R-FC arm. However, results were directionally consistent with the significant PFS benefit observed; the survival data were relatively immature; and post-trial cross over to rituximab had already occurred. Analysis of MRD was essentially inconclusive because of small patient numbers. Moreover, flow cytometry is now considered the method of choice for assessing MRD in CLL.[28] Other secondary efficacy end points were significantly better in the R-FC arm than the FC arm, and subgroup analyses also showed consistent trends in efficacy in almost all of the prespecified subgroups tested. In particular, R-FC was beneficial in patients with all disease stages and in some particularly poor prognosis subgroups (notably patients with unmutated IgVH, with del11q, and positive for ZAP-70). These findings from a randomized, international, multicenter study confirm the positive findings from single-institution phase II trials of R-FC in patients with previously treated CLL[22,23] and phase II and III trials of R-FC in patients with newly diagnosed CLL,[20,21,29,30] indicating that R-FC provides the longest PFS of any regimen yet tested in patients with CLL.

These findings are supported by evidence from many phase II CLL studies showing the efficacy of rituximab in combination with chemotherapy regimens other than FC, including fludarabine[14-16] and fludarabine-based regimens[31-34]; pentostatin- and cladribine-based regimens[18,19,35,36]; cyclophosphamide, doxorubicin, vincristine, and prednisone[37]; bendamustine[17]; alemtuzumab[38]; and high-dose corticosteroids.[39,40] These phase II studies demonstrate consistently

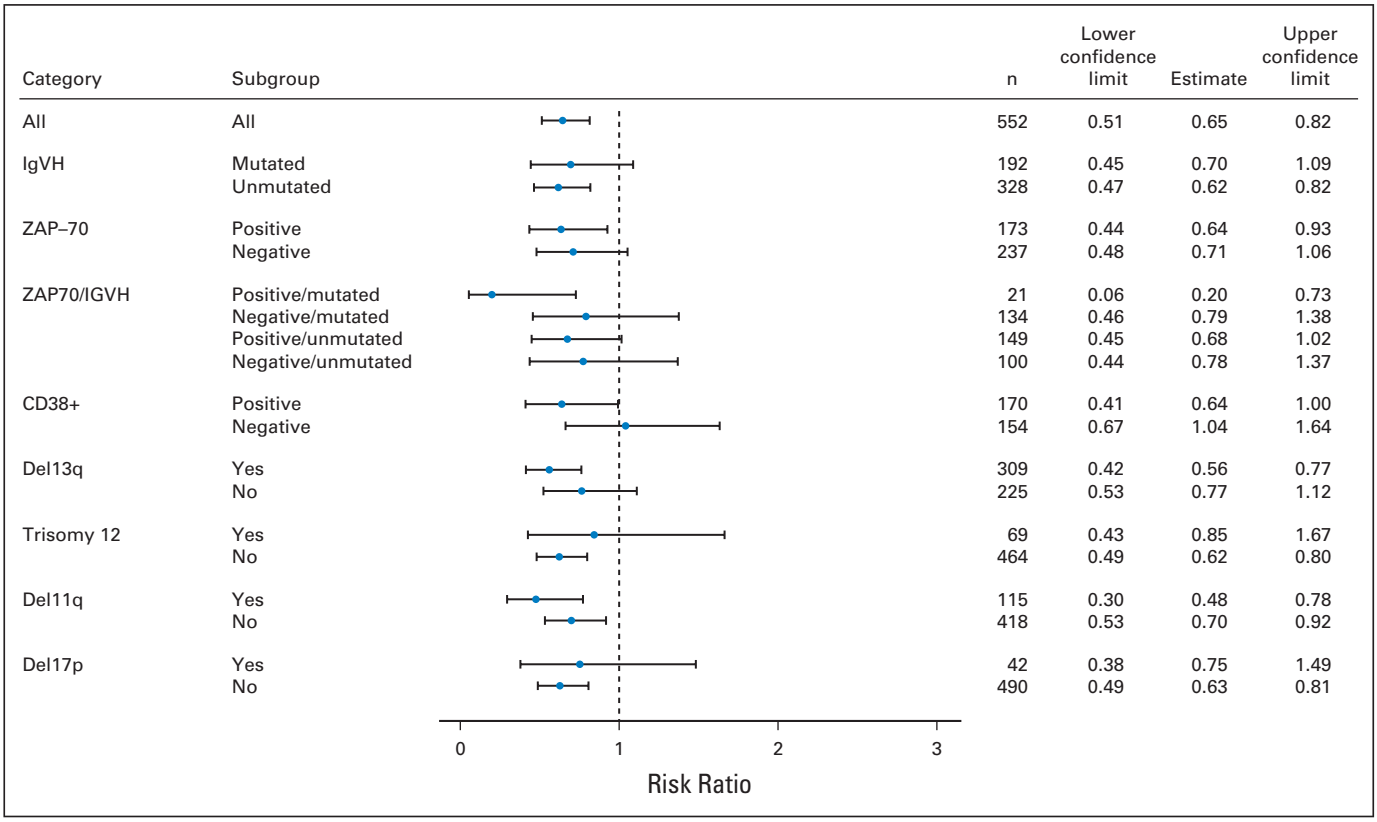

Fig 4. Hazard ratios and 95% CIs for progression-free survival (PFS) by subgroup (intent-to-treat population, investigator assessment). PFS was measured from day of random assignment until first documented disease progression, relapse after response, or death from any cause. Censoring occurred at last response assessment. IgVH, immunoglobulin heavy-chain variable region; ZAP-70, zeta-chain-associated protein kinase 70.

high ORRs and CR rates, generally in the range 70% to 95% and 0% to 43%, respectively, in previously treated patients and more than 90% and more than 40%, respectively, in previously untreated patients.

Administration of rituximab in combination with FC chemotherapy was well tolerated, consistent with the known safety profile of rituximab. Although grade 3 or 4 neutropenia was more frequent in the R-FC arm, there was no increase in overall or severe infections or the proportion of patients who had to stop treatment early as a result of toxicity, and the addition of rituximab had no detrimental effect on QOL. Second malignancies were reported more frequently in the R-FC arm, but a variety of neoplasms were reported with no predominant type, and there was no increase in myelodysplastic syndrome or related hematologic malignancies. Patients with CLL are known to be at increased risk of second malignancies, and a recent large study showed no increase in the incidence of second malignancy in patients with CLL treated with rituximab-based regimens.[41]

The R-FC regimen used in this study was developed by Keating et al[20] and Wierda et al[22] and includes a higher dose of rituximab (500 mg/m^2 in cycles 2 to 6) than used in patients with NHL. The decision to use a higher dose of rituximab was based on phase II data that demonstrated superior efficacy in patients with relapsed CLL treated with higher doses of rituximab monotherapy.[10] Rituximab had also been observed to have poorer efficacy in patients with CLL or small lymphocytic lymphoma[9,13] and to result in lower serum levels of rituximab compared with patients with follicular NHL.[13,42] This phenomenon is thought to be related to increased CD20 antigenemia and/or higher levels of circulating tumor cells in patients with CLL.[43]

Because of general European practice at the time of recruitment, only a minority of patients in the REACH study had previously been exposed to fludarabine during their initial therapy for CLL. This may be a limitation of the study because purine analog combinations are now more widely used as first-line therapy.[44] However, the results of R-FC treatment in the subgroup of fludarabine-exposed patients were consistent with the benefits seen in the study overall (Fig 3).

Overall, the results of the REACH study indicate that R-FC is efficacious and well tolerated and that it is an important treatment option for patients with previously treated CLL. These findings are consistent with recent results showing that R-FC is superior to FC when used as initial treatment for patients with CLL.[29]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Jörg Maurer, F. Hoffman-La Roche (C); Myriam Mendila, F. Hoffmann-La Roche (U); M. Wayne Saville, Biogen Idec (C); Nancy Valente, Genentech (C); Michael K.

Wenger, F. Hoffmann-La Roche (C) **Consultant or Advisory Role:** Tadeusz Robak, F. Hoffmann-La Roche (C); Philippe Solal-Céligny, F. Hoffmann-La Roche (C); Javier Loscertales, F. Hoffmann-La Roche (C); John Catalano, F. Hoffmann-La Roche (C); Marco Montillo, F. Hoffmann-La Roche (C), Mundipharma (C), Genzyme (C); Peter S. Ganly, F. Hoffmann-La Roche (C), Novartis (C) **Stock Ownership:** Myriam Mendila, F. Hoffmann-La Roche; M. Wayne Saville, Biogen Idec **Honoraria:** Tadeusz Robak, F. Hoffmann-La Roche; Philippe Solal-Céligny, F. Hoffmann-La Roche; Javier Loscertales, F. Hoffmann-La Roche; John Catalano, F. Hoffmann-La Roche; Loree Larratt, F. Hoffmann-La Roche; Christian H. Geisler, F. Hoffmann-La Roche; Marco Montillo, F. Hoffmann-La Roche, Mundipharma, Genzyme; András Rosta, F. Hoffmann-La Roche **Research Funding:** Tadeusz Robak, F. Hoffmann-La Roche; Anna Dmoszynska, F. Hoffmann-La Roche; Christian H. Geisler, Bayer Schering Pharma **Expert Testimony:** None **Other Remuneration:** Christian H. Geisler, F. Hoffmann-La Roche, Mundipharma

AUTHOR CONTRIBUTIONS

Conception and design: Tadeusz Robak, Philippe Solal-Céligny, Myriam Mendila, M. Wayne Saville, Michael K. Wenger

Financial support: Nancy Valente, Michael K. Wenger
Administrative support: Myriam Mendila, Michael K. Wenger
Provision of study materials or patients: Tadeusz Robak, Anna Dmoszynska, Philippe Solal-Céligny, Javier Loscertales, John Catalano, Boris V. Afanasiev, Loree Larratt, Christian H. Geisler, Marco Montillo, Ilya Zyuzgin, Peter S. Ganly, Caroline Dartigeas, Sergey I. Moiseev
Collection and assembly of data: Philippe Solal-Céligny, Krzysztof Warzocha, Javier Loscertales, John Catalano, Peter S. Ganly, Caroline Dartigeas, András Rosta, Myriam Mendila, Michael K. Wenger, Sergey I. Moiseev
Data analysis and interpretation: Tadeusz Robak, Anna Dmoszynska, Philippe Solal-Céligny, Ilya Zyuzgin, Peter S. Ganly, Jörg Maurer, Myriam Mendila, M. Wayne Saville, Nancy Valente, Michael K. Wenger
Manuscript writing: Tadeusz Robak, Philippe Solal-Céligny, John Catalano, Christian H. Geisler, Peter S. Ganly, M. Wayne Saville, Nancy Valente, Michael K. Wenger
Final approval of manuscript: Tadeusz Robak, Anna Dmoszynska, Philippe Solal-Céligny, Krzysztof Warzocha, Javier Loscertales, John Catalano, Boris V. Afanasiev, Loree Larratt, Christian H. Geisler, Marco Montillo, Ilya Zyuzgin, Peter S. Ganly, Caroline Dartigeas, András Rosta, Jörg Maurer, Myriam Mendila, M. Wayne Saville, Nancy Valente, Michael K. Wenger, Sergey I. Moiseev

REFERENCES

1. Horner MJ, Ries LAG, Krapcho M, et al (eds): SEER Cancer Statistics Review, 1975-2006, National Cancer Institute. http://seer.cancer.gov/csr/1975_2006/

2. Sant M, Allemani C, Santaquilani M, et al: EUROCARE-4: Survival of cancer patients diagnosed in 1995-1999—Results and commentary. Eur J Cancer 45:931-991, 2009

3. Gribben JG: How I treat CLL upfront. Blood 115:187-197, 2010

4. Johnson S, Smith AG, Loffler H, et al: Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukaemia: The French Cooperative Group on CLL. Lancet 347:1432-1438, 1996

5. Rai KR, Peterson BL, Appelbaum FR, et al: Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. N Engl J Med 343:1750-1757, 2000

6. Catovsky D, Richards S, Matutes E, et al: Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): A randomised controlled trial. Lancet 370:230-239, 2007

7. Eichhorst BF, Busch R, Hopfinger G, et al: Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. Blood 107:885-891, 2006

8. Flinn IW, Neuberg DS, Grever MR, et al: Phase III trial of fludarabine plus cyclophosphamide compared with fludarabine for patients with previously untreated chronic lymphocytic leukemia: US Intergroup Trial E2997. J Clin Oncol 25:793-798, 2007

9. Hainsworth JD, Litchy S, Barton JH, et al: Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: A phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 21:1746-1751, 2003

10. O'Brien SM, Kantarjian H, Thomas DA, et al: Rituximab dose-escalation trial in chronic lymphocytic leukemia. J Clin Oncol 19:2165-2170, 2001

11. Byrd JC, Murphy T, Howard RS, et al: Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. J Clin Oncol 19:2153-2164, 2001

12. Mavromatis B, Cheson BD: Monoclonal antibody therapy of chronic lymphocytic leukemia. J Clin Oncol 21:1874-1881, 2003

13. McLaughlin P, Grillo-López AJ, Link BK, et al: Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: Half of patients respond to a four-dose treatment program. J Clin Oncol 16:2825-2833, 1998

14. Byrd JC, Peterson BL, Morrison VA, et al: Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: Results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood 101:6-14, 2003

15. Byrd JC, Rai K, Peterson BL, et al: Addition of rituximab to fludarabine may prolong progression-free survival and overall survival in patients with previously untreated chronic lymphocytic leukemia: An updated retrospective comparative analysis of CALGB 9712 and CALGB 9011. Blood 105:49-53, 2005

16. Schulz H, Klein SK, Rehwald U, et al: Phase 2 study of a combined immunochemotherapy using rituximab and fludarabine in patients with chronic lymphocytic leukemia. Blood 100:3115-3120, 2002

17. Fischer K, Stilgenbauer S, Schweighofer C, et al: Bendamustine in combination with rituximab (BR) for patients with relapsed chronic lymphocytic leukemia (CLL): A multicentre phase II trial of the German CLL Study Group (GCLLSG). Blood 110: 3106, 2007 (abstr)

18. Lamanna N, Kalaycio M, Maslak P, et al: Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia. J Clin Oncol 24:1575-1581, 2006

19. Robak T, Smolewski P, Cebula B, et al: Rituximab plus cladribine with or without cyclophosphamide in patients with relapsed or refractory chronic lymphocytic leukemia. Eur J Haematol 79:107-113, 2007

20. Keating MJ, O'Brien S, Albitar M, et al: Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol 23:4079-4088, 2005

21. Tam CS, O'Brien S, Wierda W, et al: Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood 112:975-980, 2008

22. Wierda W, O'Brien S, Wen S, et al: Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. J Clin Oncol 23:4070-4078, 2005

23. Wierda W, O'Brien S, Faderl S, et al: A retrospective comparison of three sequential groups of patients with recurrent/refractory chronic lymphocytic leukemia treated with fludarabine-based regimens. Cancer 106:337-345, 2006

24. Cheson BD, Bennett JM, Grever M, et al: National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: Revised guidelines for diagnosis and treatment. Blood 87:4990-4997, 1996

25. van der Velden V, Cazzaniga G, Schrauder A, et al: Analysis of minimal residual disease by Ig/TCR gene rearrangements: Guidelines for interpretation of real-time quantitative PCR data. Leukemia 21: 604-611, 2007

26. Bruggemann M, Droese J, Bolz I, et al: Improved assessment of minimal residual disease in B cell malignancies using fluorogenic consensus probes for real-time quantitative PCR. Leukemia 14:1419-1425, 2000

27. Hallek M, Cheson BD, Catovsky D, 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 111:5446-5456, 2008

28. Rawstron AC, Villamor N, Ritgen M, et al: International standardized approach for flow cytometric residual disease monitoring in chronic lymphocytic leukaemia. Leukemia 21:956-9564, 2007

29. 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 112:325, 2008 (abstr)

30. Tam CS, Keating MJ: Chemoimmunotherapy of chronic lymphocytic leukemia. Best Pract Res Clin Haematol 20:479-498, 2007

31. Hillmen P, Pocock C, Cohen D, et al: NCRI CLL201 trial: A randomized phase II trial of fludarabine, cyclophosphamide and mitoxantrone (FCM) with or without rituximab in previously treated CLL. Blood 110:752, 2007 (abstr)

32. Faderl S, Wierda W, Ferrajoli A, et al: Update of experience with fludarabine, cyclophosphamide, mitoxantrone plus rituximab (FCM-R) in frontline therapy for chronic lymphocytic leukemia (CLL). Blood 110:627, 2007 (abstr)

33. Wierda WG, O'Brien S, Faderl S, et al: Combined cyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR), an active regimen for heavily treated patients with CLL. Blood 108:31, 2006 (abstr)

34. Bosch F, Abrisqueta P, Villamor N, et al: Rituximab, fludarabine, cyclophosphamide, and mitoxantrone: A new, highly active chemoimmunotherapy regimen for chronic lymphocytic leukemia. J Clin Oncol 27:4578-4584, 2009

35. Lamanna N, Heaney ML, Brentjens RJ, et al: Pentostatin, cyclophosphamide, rituximab, and mitoxantrone (PCRM): A new highly active regimen for patients with chronic lymphocytic leukemia (CLL) previously treated with PCR or FCR. Blood 110: 3115, 2007 (abstr)

36. Kay NE, Geyer SM, Call TG, et al: Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. Blood 109:405-411, 2007

37. Eichhorst BF, Busch C, Duehresen U, et al: CHOP plus rituximab (CHOP-R) in fludarabine (F) refractory chronic lymphocytic leukemia (CLL) or CLL with autoimmune hemolytic anemia (AIHA) or Richter's transformation (RT): First interim analysis of a phase II trial of the German CLL Study Group (GCLLSG). Blood 106:2126, 2005 (abstr)

38. Faderl S, Thomas DA, O'Brien S, et al: Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies. Blood 101:3413-3415, 2003

39. Castro JE, Sandoval-Sus JD, Bole J, et al: Rituximab in combination with high-dose methylprednisolone for the treatment of fludarabine refractory high-risk chronic lymphocytic leukemia. Leukemia 22:2048-2053, 2008

40. Bowen DA, Call TG, Jenkins GD, et al: Methylprednisolone-rituximab is an effective salvage therapy for patients with relapsed chronic lymphocytic leukemia including those with unfavorable cytogenetic features. Leuk Lymphoma 48: 2412-2417, 2007

41. Tsimberidou AM, Wen S, McLaughlin P, et al: Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. J Clin Oncol 27: 904-910, 2009

42. Berinstein NL, Grillo-López AJ, White CA, et al: Association of serum rituximab (IDEC-C2B8) concentration and anti-tumor response in the treatment of recurrent low-grade or follicular non-Hodgkin's lymphoma. Ann Oncol 9:995-1001, 1998

43. Manshouri T, Do KA, Wang X, et al: Circulating CD20 is detectable in the plasma of patients with chronic lymphocytic leukemia and is of prognostic significance. Blood 101:2507-2513, 2003

44. Eichhorst B, Hallek M, Dreyling M: Chronic lymphocytic leukemia: ESMO minimum clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 20:iv102-iv104, 2009 (suppl 4)

