ORIGINAL ARTICLE

Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions

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ABSTRACT

BACKGROUND

The monoclonal anti-CD20 antibody rituximab, combined with chemotherapeutic agents, has been shown to prolong overall survival in physically fit patients with previously untreated chronic lymphocytic leukemia (CLL) but not in those with coexisting conditions. We investigated the benefit of the type 2, glycoengineered antibody obinutuzumab (also known as GA101) as compared with that of rituximab, each combined with chlorambucil, in patients with previously untreated CLL and coexisting conditions.

METHODS

We randomly assigned 781 patients with previously untreated CLL and a score higher than 6 on the Cumulative Illness Rating Scale (CIRS) (range, 0 to 56, with higher scores indicating worse health status) or an estimated creatinine clearance of 30 to 69 ml per minute to receive chlorambucil, obinutuzumab plus chlorambucil, or rituximab plus chlorambucil. The primary end point was investigator-assessed progression-free survival.

RESULTS

The patients had a median age of 73 years, creatinine clearance of 62 ml per minute, and CIRS score of 8 at baseline. Treatment with obinutuzumab–chlorambucil or rituximab–chlorambucil, as compared with chlorambucil monotherapy, increased response rates and prolonged progression-free survival (median progression-free survival, 26.7 months with obinutuzumab–chlorambucil vs. 11.1 months with chlorambucil alone; hazard ratio for progression or death, 0.18; 95% confidence interval [CI], 0.13 to 0.24; P<0.001; and 16.3 months with rituximab–chlorambucil vs. 11.1 months with chlorambucil alone; hazard ratio, 0.44; 95% CI, 0.34 to 0.57; P<0.001). Treatment with obinutuzumab–chlorambucil, as compared with chlorambucil alone, prolonged overall survival (hazard ratio for death, 0.41; 95% CI, 0.23 to 0.74; P=0.002). Treatment with obinutuzumab–chlorambucil, as compared with rituximab–chlorambucil, resulted in prolongation of progression-free survival (hazard ratio, 0.39; 95% CI, 0.31 to 0.49; P<0.001) and higher rates of complete response (20.7% vs. 7.0%) and molecular response. Infusion-related reactions and neutropenia were more common with obinutuzumab–chlorambucil than with rituximab–chlorambucil, but the risk of infection was not increased.

CONCLUSIONS

Combining an anti-CD20 antibody with chemotherapy improved outcomes in patients with CLL and coexisting conditions. In this patient population, obinutuzumab was superior to rituximab when each was combined with chlorambucil. (Funded by F. Hoffmann–La Roche; ClinicalTrials.gov number, NCT01010061.)

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CHRONIC LYMPHOCYTIC LEUKEMIA (CLL), which is characterized by a neoplastic accumulation of B lymphocytes,[1] is the most common leukemia in Western countries. The majority of patients with CLL are older than 70 years of age, and many present with coexisting conditions.[2,3]

In the past, CLL was treated with chemotherapy without improving survival.[4-8] The addition of the monoclonal anti-CD20 antibody rituximab to fludarabine and cyclophosphamide has been shown to prolong overall survival in physically fit patients with previously untreated CLL.[9-11] However, randomized trials have not shown that targeting the CD20 antigen in patients with CLL and coexisting conditions would result in a similar benefit. Previous phase 2 trials suggested that combining rituximab with the alkylating drug chlorambucil was a reasonable treatment approach for such patients.[12,13]

Rituximab is a chimeric type 1 antibody that kills CLL cells primarily by means of complement-dependent and antibody-dependent cellular cytotoxicity after binding to CD20.[14] Obinutuzumab (also known as GA101) is a humanized, glycoengineered type 2 antibody also targeted against CD20.[15] In preclinical studies, obinutuzumab showed superior efficacy, as compared with rituximab, by inducing direct cell death and enhanced antibody-dependent cellular cytotoxicity (with less complement-dependent cytotoxicity).[16-20] We wondered whether this difference in mechanism of action would translate into a clinical benefit for patients with CLL.

We conducted a phase 3, randomized trial to determine whether anti-CD20 antibody–based chemoimmunotherapy (with chlorambucil as the chemotherapy backbone) would be beneficial in patients with CLL and coexisting conditions and whether targeting of the CD20 antigen by obinutuzumab could improve outcomes as compared with rituximab.

METHODS

PATIENTS

In this open-label, three-group study, we enrolled patients with CD20-positive CLL that was diagnosed according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia.[21] Previously untreated patients requiring treatment (i.e., those with Binet stage C or symptomatic disease) were included. Central screening before randomization was performed to exclude patients with an incorrect diagnosis or without a need for therapy. Enrolled patients were required to have a clinically meaningful burden of coexisting conditions, as reflected by a score higher than 6 on the Cumulative Illness Rating Scale (CIRS) (range, 0 to 56, with higher scores indicating worse health status) or a creatinine clearance of 30 to 69 ml per minute as assessed with the use of the Cockcroft–Gault formula.[22,23] Additional eligibility criteria are summarized in the Supplementary Appendix, available with the full text of this article at NEJM.org. All patients provided written informed consent.

STUDY OVERSIGHT AND CONDUCT

The study was approved by the institutional review board or independent ethics committee at each participating institution and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The study was designed by the German CLL Study Group and the sponsor (F. Hoffmann–La Roche). The sponsor gathered and, in conjunction with the German CLL Study Group, analyzed the data. The first author wrote all manuscript drafts. All the authors vouch for the completeness and accuracy of the data and the adherence of the study to the protocol (available at NEJM.org). A medical-communications agency paid by the sponsor provided initial versions of figures and editing support. (Details of the conduct of the study are provided in the Supplementary Appendix.) There were no agreements concerning confidentiality of the data among the sponsor, the German CLL Study Group, and the academic authors.

RANDOMIZATION AND TREATMENT

This multinational trial was conducted in 26 countries; 189 centers enrolled patients. Enrollment was preceded by a safety run-in phase.[24] Between April 2010 and July 2012, patients were enrolled and randomly assigned to one of the following treatment groups on a 1:2:2 basis: chlorambucil alone, obinutuzumab plus chlorambucil, or rituximab plus chlorambucil. After 118 patients had been assigned to the chlorambucil-alone group, this group was closed on the basis of predefined criteria, and randomization to the two antibody groups was performed on a 1:1 basis. Randomization was stratified according to geographic region and Binet stage. Patients assigned to the

chlorambucil-alone group in whom progressive disease developed during treatment or within 6 months after the end of treatment were allowed to cross over to the obinutuzumab–chlorambucil group.

Patients received chlorambucil alone, obinutuzumab–chlorambucil, or rituximab–chlorambucil in six 28-day cycles. Chlorambucil was administered orally at a dose of 0.5 mg per kilogram of body weight on days 1 and 15 of each cycle (equivalent to the median dose in a previous trial showing noninferiority of chlorambucil to fludarabine in elderly patients with CLL).[25] A rationale for the selection of the chlorambucil dose is provided in the Supplementary Appendix. Obinutuzumab was administered intravenously at a dose of 1000 mg on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2 through 6 (on the basis of previous pharmacokinetic studies and modeling).[26] After amendment of the study protocol, the first infusion of obinutuzumab was administered over a period of 2 days. Rituximab was administered intravenously at a dose of 375 mg per square meter of body-surface area on day 1 of cycle 1 and 500 mg per square meter on day 1 of cycles 2 through 6. Prophylaxis for infusion-related reactions and the tumor lysis syndrome included fluid intake and premedication with allopurinol, paracetamol (acetaminophen), antihistamines, and glucocorticoids.

ASSESSMENTS AND END POINTS

Assessments at baseline included immunophenotyping of circulating lymphocytes, central analysis of genomic aberrations by means of fluorescence in situ hybridization, and mutational analysis of the immunoglobulin heavy-chain variable-region gene (*IGHV*) by means of DNA sequencing.[27,28] The site investigators were provided with guidelines for CIRS assessment.[29] Adverse events were reported according to the National Cancer Institute Common Toxicity Criteria (version 4.0).[30] The response to therapy at 3 months after the end of treatment and the status with respect to remission during follow-up were assessed according to the guidelines of the International Workshop on Chronic Lymphocytic Leukemia.[21] Complete and partial responses were confirmed by means of computed tomographic scanning, and complete responses were confirmed by means of bone marrow biopsy. Minimal residual disease was analyzed centrally according to international guidelines[21,31] by means

of an allele-specific oligonucleotide polymerase-chain-reaction assay at baseline and 3 months after the end of treatment.[32,33]

The primary end point was progression-free survival, as assessed by the site investigators. Key secondary end points were progression-free survival as assessed by an independent review committee, response rates and the rate of negative testing for minimal residual disease after the end of treatment, event-free survival, the time to new treatment, overall survival, adverse events, and patient-reported outcomes. A data and safety monitoring board reviewed the data regularly once randomization was opened.

STATISTICAL ANALYSIS

The statistical design of the study is outlined in the Supplementary Appendix. Progression-free survival as the primary end point was used to calculate the sample for the study. Time points for the three pairwise comparisons were determined on the basis of the predefined numbers of progression-free survival events needed for each comparison. Assumptions for median progression-free survival were 12 months for the chlorambucil-alone group, 20 months for the rituximab–chlorambucil group, and 27 months for the obinutuzumab–chlorambucil group. The number of required events was based on a two-sided log-rank test at an alpha level of 5% with a power of at least 80%.

The primary analyses for the comparisons of the obinutuzumab–chlorambucil group and the rituximab–chlorambucil group with the chlorambucil-alone group were conducted in July 2012 and August 2012, respectively, and were updated in May 2013, when the primary analysis of the comparison between the obinutuzumab–chlorambucil group and the rituximab–chlorambucil group was performed. The efficacy boundary was crossed at a preplanned interim analysis. All results presented here are from the analyses of May 2013; earlier results are summarized in Table S1 in the Supplementary Appendix.

The primary analysis was a two-sided log-rank test stratified according to Binet stage. The type 1 error was controlled through the closed-testing procedure (the global test was a three-group log-rank test). The comparison between the obinutuzumab–chlorambucil group and the rituximab–chlorambucil group included two interim looks at the data and an O'Brien–Fleming efficacy boundary with a Lan–DeMets alpha-spending function

to adjust for multiple comparisons. Secondary end points were analyzed with the use of a two-sided test at a 5% alpha level without adjustment for multiple comparisons.

RESULTS

PATIENTS

A total of 781 patients were enrolled and treated with chlorambucil alone, obinutuzumab–chlorambucil, or rituximab–chlorambucil. The num-

bers of patients who were enrolled and assigned to each treatment group are shown in Figure S1 in the Supplementary Appendix. Pairwise comparisons of the three treatment groups were performed in different study cohorts.

Age and clinical characteristics at baseline were well balanced among the treatment groups (Table 1, and Tables S2 and S3 in the Supplementary Appendix). The patients had a median age of 73 years, creatinine clearance of 62 ml per minute, and CIRS score of 8 at baseline. Most

Table 1. Baseline Characteristics, Intention-to-Treat Population.*

Characteristic	Obinutuzumab–Chlorambucil vs. Chlorambucil Alone		Rituximab–Chlorambucil vs. Chlorambucil Alone		Obinutuzumab–Chlorambucil vs. Rituximab–Chlorambucil	
	Obinutuzumab–Chlorambucil (N=238)	Chlorambucil Alone (N=118)	Rituximab–Chlorambucil (N=233)	Chlorambucil Alone (N=118)	Obinutuzumab–Chlorambucil (N=333)	Rituximab–Chlorambucil (N=330)
Age — yr						
Median	74	72	73	72	74	73
Range	39–88	43–87	40–90	43–87	39–89	40–90
Cumulative Illness Rating Scale†						
Score — median (range)	8 (1–20)	8 (0–18)	8 (0–18)	8 (0–18)	8 (0–22)	8 (0–18)
Affected organ system or disorder — no. (%)						
Cardiac	120 (50)	62 (53)	111 (48)	62 (53)	171 (51)	165 (50)
Hypertension	168 (71)	88 (75)	155 (67)	88 (75)	228 (68)	225 (68)
Vascular	91 (38)	34 (29)	68 (29)	34 (29)	114 (34)	95 (29)
Respiratory	85 (36)	43 (36)	85 (36)	43 (36)	121 (36)	127 (38)
Eye, ear, throat, or larynx	86 (36)	53 (45)	102 (44)	53 (45)	131 (39)	141 (43)
Upper gastrointestinal	80 (34)	39 (33)	70 (30)	39 (33)	104 (31)	102 (31)
Lower gastrointestinal	50 (21)	25 (21)	38 (16)	25 (21)	68 (20)	55 (17)
Hepatic or biliary	39 (16)	21 (18)	40 (17)	21 (18)	56 (17)	66 (20)
Renal	104 (44)	45 (38)	111 (48)	45 (38)	137 (41)	145 (44)
Genitourinary	83 (35)	44 (37)	76 (33)	44 (37)	114 (34)	114 (35)
Musculoskeletal	106 (45)	45 (38)	96 (41)	45 (38)	148 (44)	135 (41)
Endocrine or metabolic	127 (53)	64 (54)	117 (50)	64 (54)	183 (55)	161 (49)
Neurologic	46 (19)	33 (28)	48 (21)	33 (28)	72 (22)	72 (22)
Psychiatric	39 (16)	11 (9)	36 (15)	11 (9)	59 (18)	49 (15)
Median calculated creatinine clearance — ml/min	61.4	63.8	61.8	63.8	62.5	62.6
Binet stage — no. (%)						
A	55 (23)	24 (20)	49 (21)	24 (20)	74 (22)	74 (22)
B	98 (41)	50 (42)	100 (43)	50 (42)	142 (43)	135 (41)
C	85 (36)	44 (37)	84 (36)	44 (37)	117 (35)	121 (37)
Unmutated *IGHV* — no./total no. (%)	129/210 (61)	58/99 (59)	126/204 (62)	58/100 (58)	188/305 (62)	182/298 (61)
del(17p) on FISH — no./total no. (%)	16/203 (8)	10/96 (10)	9/196 (5)	10/97 (10)	22/295 (7)	20/287 (7)

* The intention-to-treat population included all patients randomly assigned to a treatment group. There were no significant differences in the listed baseline characteristics between groups in the three pairwise comparisons. Pairwise comparisons of the three treatment groups were performed in different study cohorts and therefore are always displayed side by side. FISH denotes fluorescence in situ hybridization, and *IGHV* the immunoglobulin heavy-chain variable-region gene.
† Scores on the Cumulative Illness Rating Scale range from 0 to 56, with higher scores indicating worse health status.

patients (82%) had more than three coexisting conditions, and nearly one third (27%) had at least one coexisting condition that was not well controlled at baseline according to CIRS grading.

The median number of treatment cycles and the total dose of chlorambucil administered per patient were similar among the treatment groups. As a consequence of different dosing schedules, the median total dose of obinutuzumab was higher than that of rituximab (Table S4 in the Supplementary Appendix).

SAFETY

Adverse events occurred more frequently in the antibody groups than in the chlorambucil-alone group and were most frequent with obinutuzumab–chlorambucil treatment (Table 2, and Tables S5 and S6 in the Supplementary Appendix). The incidence of grade 3 or 4 neutropenia was highest with the combination of obinutuzumab and chlorambucil and was lowest with chlorambucil alone. Rates of grade 3 to 5 infection ranged from 11 to 14% and did not differ significantly among the treatment groups. Most reported infections were of bacterial origin. Infusion-related reactions were more frequent with obinutuzumab–chlorambucil treatment than with rituximab–chlorambucil treatment. In the obinutuzumab–chlorambucil group, grade 3 or 4 infu-

sion-related reactions occurred in 20% of patients during the first infusion of obinutuzumab, but there were no grade 3 or 4 reactions during subsequent obinutuzumab infusions. No deaths were associated with infusion-related reactions. Neither the lymphocyte counts nor the tumor burden at baseline was a strong predictor of obinutuzumab-related infusion reactions. Prophylactic measures had only a moderate effect on the frequency of infusion-related reactions (Fig. S2 and Tables S7 and S8 in the Supplementary Appendix). The tumor lysis syndrome was reported in 15 patients in the study and resolved in all cases. Frequencies of newly diagnosed neoplasms were similar among the treatment groups (Table S9 in the Supplementary Appendix).

As compared with both patients receiving obinutuzumab–chlorambucil and those receiving chlorambucil alone, patients receiving rituximab–chlorambucil were less likely to discontinue therapy early owing to adverse events. This imbalance between the obinutuzumab–chlorambucil group and the rituximab–chlorambucil group was primarily due to infusion-related reactions in the obinutuzumab–chlorambucil group (Tables S10 and S11 in the Supplementary Appendix). The most frequent serious adverse events were infections, infusion-related reactions, and neoplasms (Table S6 in the Supplementary

Table 2. Adverse Events of Grade 3 or Higher, Safety Population.*

Event	Obinutuzumab–Chlorambucil vs. Chlorambucil Alone		Rituximab–Chlorambucil vs. Chlorambucil Alone		Obinutuzumab–Chlorambucil vs. Rituximab–Chlorambucil	
	Obinutuzumab–Chlorambucil (N=241)	Chlorambucil Alone (N=116)	Rituximab–Chlorambucil (N=225)	Chlorambucil Alone (N=116)	Obinutuzumab–Chlorambucil (N=336)	Rituximab–Chlorambucil (N=321)
	number of patients (percent)					
Any event	175 (73)	58 (50)	125 (56)	58 (50)	235 (70)	177 (55)
Infusion-related reactions	51 (21)	—	9 (4)	—	67 (20)	12 (4)
Neutropenia	84 (35)	18 (16)	60 (27)	18 (16)	111 (33)	91 (28)
Anemia	11 (5)	5 (4)	10 (4)	5 (4)	14 (4)	12 (4)
Thrombocytopenia	27 (11)	5 (4)	8 (4)	5 (4)	35 (10)	10 (3)
Leukopenia	13 (5)	0	3 (1)	0	15 (4)	3 (1)
Infections	27 (11)	16 (14)	30 (13)	16 (14)	40 (12)	44 (14)
Pneumonia	8 (3)	4 (3)	11 (5)	4 (3)	13 (4)	17 (5)
Febrile neutropenia	4 (2)	5 (4)	4 (2)	5 (4)	8 (2)	4 (1)

* The safety population included all patients who received at least one dose of study medication. Shown are adverse events of grade 3, 4, or 5 with an incidence of 3% or higher in any treatment group, irrespective of whether the event was considered related or unrelated to treatment by the investigators.
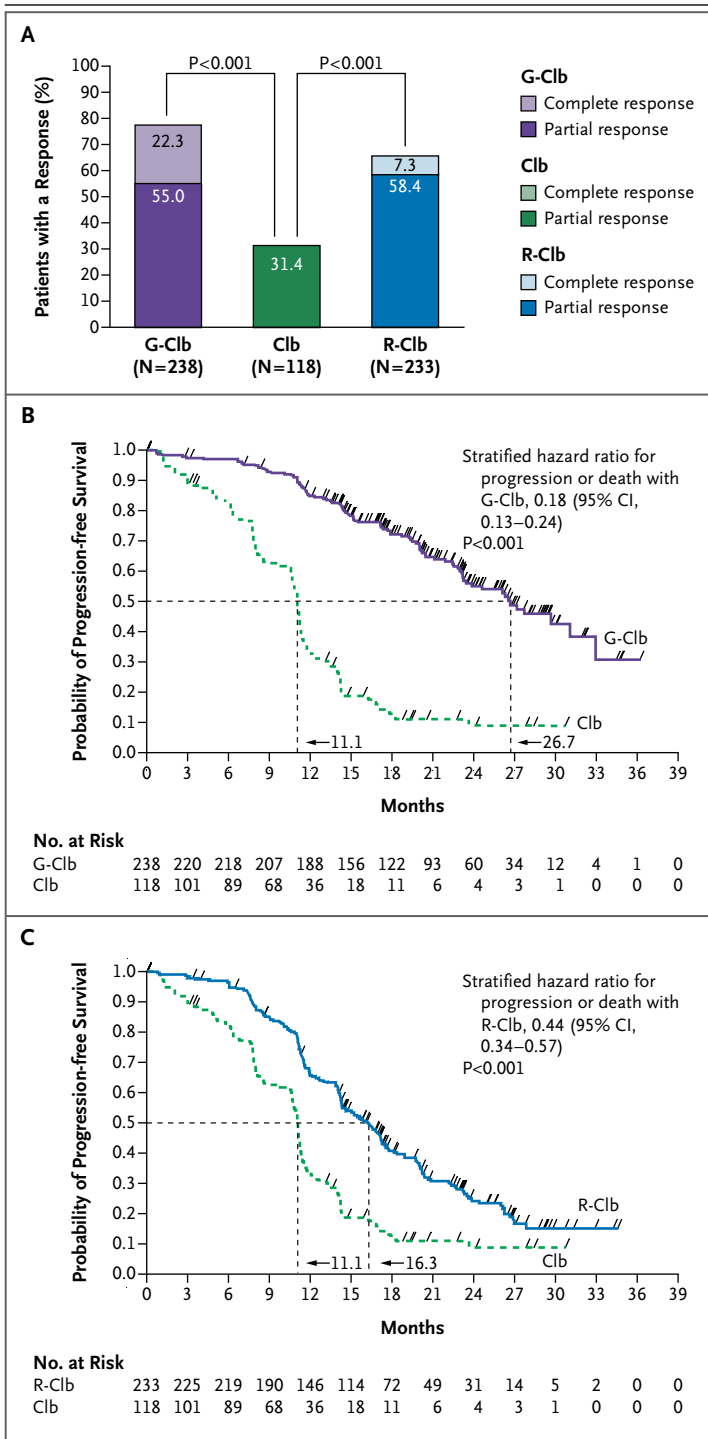
Figure 1. Response Rates and Progression-free Survival with Obinutuzumab–Chlorambucil or Rituximab–Chlorambucil versus Chlorambucil Alone.

Panel A shows response rates at 3 months after the end of treatment. Complete response included complete response with incomplete bone marrow recovery; partial response included nodular partial response. The response assessment was not available for one patient in the rituximab–chlorambucil group because the analysis occurred before the patient had a 3-month follow-up visit. Panel B shows progression-free survival with obinutuzumab–chlorambucil versus chlorambucil alone, and Panel C shows progression-free survival with rituximab–chlorambucil versus chlorambucil alone. Progression-free survival was assessed by the site investigators. P values were calculated with the use of a stratified log-rank test. CI denotes confidence interval, Clb chlorambucil alone, G-Clb obinutuzumab–chlorambucil, and R-Clb rituximab–chlorambucil.

most common grade 5 adverse events were newly diagnosed neoplasms and cardiac events in the antibody groups and infections in the chlorambucil-alone group (Table S12 in the Supplementary Appendix).

EFFICACY

Overall response rates at 3 months after the end of treatment were increased in the obinutuzumab–chlorambucil and rituximab–chlorambucil groups as compared with the chlorambucil-alone group; complete responses were seen exclusively after antibody treatment (Fig. 1A). Therapy with obinutuzumab–chlorambucil or rituximab–chlorambucil, as compared with chlorambucil alone, was associated with significant improvement in the median progression-free survival (26.7 months with obinutuzumab–chlorambucil vs. 11.1 months with chlorambucil alone; hazard ratio for progression or death, 0.18; 95% confidence interval [CI], 0.13 to 0.24; P<0.001; and 16.3 months with rituximab–chlorambucil vs. 11.1 months with chlorambucil alone; hazard ratio, 0.44; 95% CI, 0.34 to 0.57; P<0.001) (Fig. 1B and 1C). This benefit was seen in all analyzed subgroups, except in patients with del(17p) (Fig. S3 in the Supplementary Appendix). Quality of life did not deteriorate during or after antibody therapy as compared with treatment with chlorambucil alone (Fig. S4 in the Supplementary Appendix).

Treatment with obinutuzumab–chlorambucil, as compared with rituximab–chlorambucil, resulted in higher rates of overall, complete, and molecular responses (Fig. 2A and 2B, and Table S13

Appendix). The percentage of patients who died because of an adverse event was lower in the obinutuzumab–chlorambucil group (4%) than in the rituximab–chlorambucil and chlorambucil-alone groups (6% and 9%, respectively). The

in the Supplementary Appendix). Among all patients for whom a result for minimal residual disease was available plus those who had progressive disease or who died, the rate of negative testing for minimal residual disease in bone marrow and peripheral blood was significantly higher after obinutuzumab–chlorambucil treatment than after rituximab–chlorambucil treatment (bone marrow, 19.5% vs. 2.6%; blood, 37.7% vs. 3.3%, respectively) (Fig. 2B). Negative testing for minimal residual disease in blood after obinutuzumab–chlorambucil treatment was associated with a favorable disease course during follow-up (Fig. S5 and S6 in the Supplementary Appendix). A significant prolongation in progression-free survival was observed with obinutuzumab–chlorambucil treatment as compared with rituximab–chlorambucil treatment (median progression-free survival, 26.7 vs. 15.2 months; hazard ratio, 0.39; 95% CI, 0.31 to 0.49; P<0.001) (Fig. 2C). The progression-free survival benefit with obinutuzumab–chlorambucil as compared with rituximab–chlorambucil was supported in all preplanned subgroup analyses, although the hazard ratios for patients with del(17p) or other karyotypes had 95% confidence intervals that included 1. The robustness of the results for progression-free survival was confirmed by various prespecified analyses (Fig. S3 and S7 in the Supplementary Appendix).

As of the most recent assessment of overall survival, treatment with obinutuzumab–chlorambucil provided a significant benefit as compared with chlorambucil monotherapy (hazard ratio for death, 0.41; 95% CI, 0.23 to 0.74; P=0.002) (Fig. 3A); the rates of death were 9% and 20%, respectively. No significant benefit was noted for rituximab–chlorambucil over chlorambucil alone (hazard ratio, 0.66; 95% CI, 0.39 to 1.11; P=0.11) (Fig. 3B); the rates of death were 15% and 20%, respectively. A significant benefit also was not noted for obinutuzumab–chlorambucil over rituximab–chlorambucil (hazard ratio, 0.66; 95% CI, 0.41 to 1.06; P=0.08) (Fig. 3C); the rates of death were 8% and 12%, respectively. Overall survival medians were not reached.

DISCUSSION

This phase 3 study compared treatment with chlorambucil alone, obinutuzumab–chlorambucil, and rituximab–chlorambucil in patients with
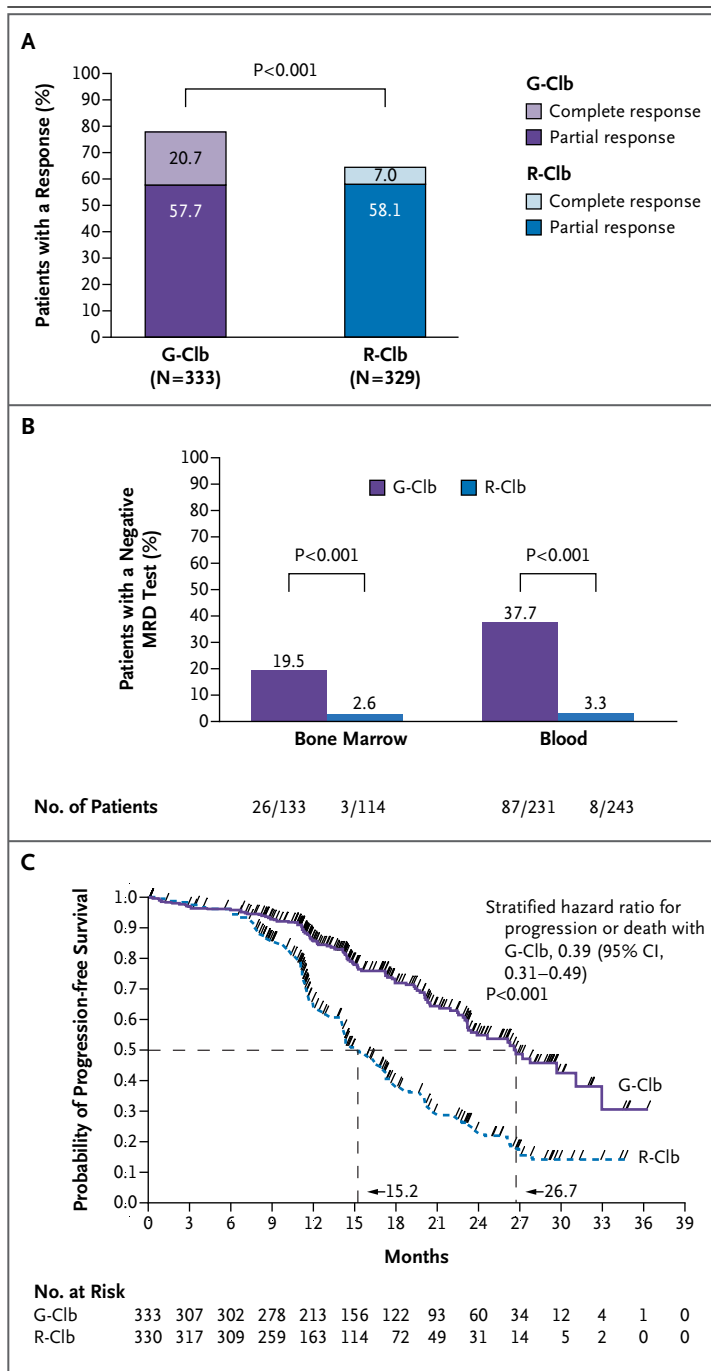

Figure 2. Response Rates and Progression-free Survival with Obinutuzumab–Chlorambucil versus Rituximab–Chlorambucil.

Panel A shows response rates at 3 months after the end of treatment. Complete response included complete response with incomplete bone marrow recovery; partial response included nodular partial response. Panel B shows molecular response rates; MRD denotes minimal residual disease. Panel C shows progression-free survival, as assessed by the site investigators. P values were calculated with the use of a stratified log-rank test. G-Clb denotes obinutuzumab–chlorambucil, and R-Clb rituximab–chlorambucil.
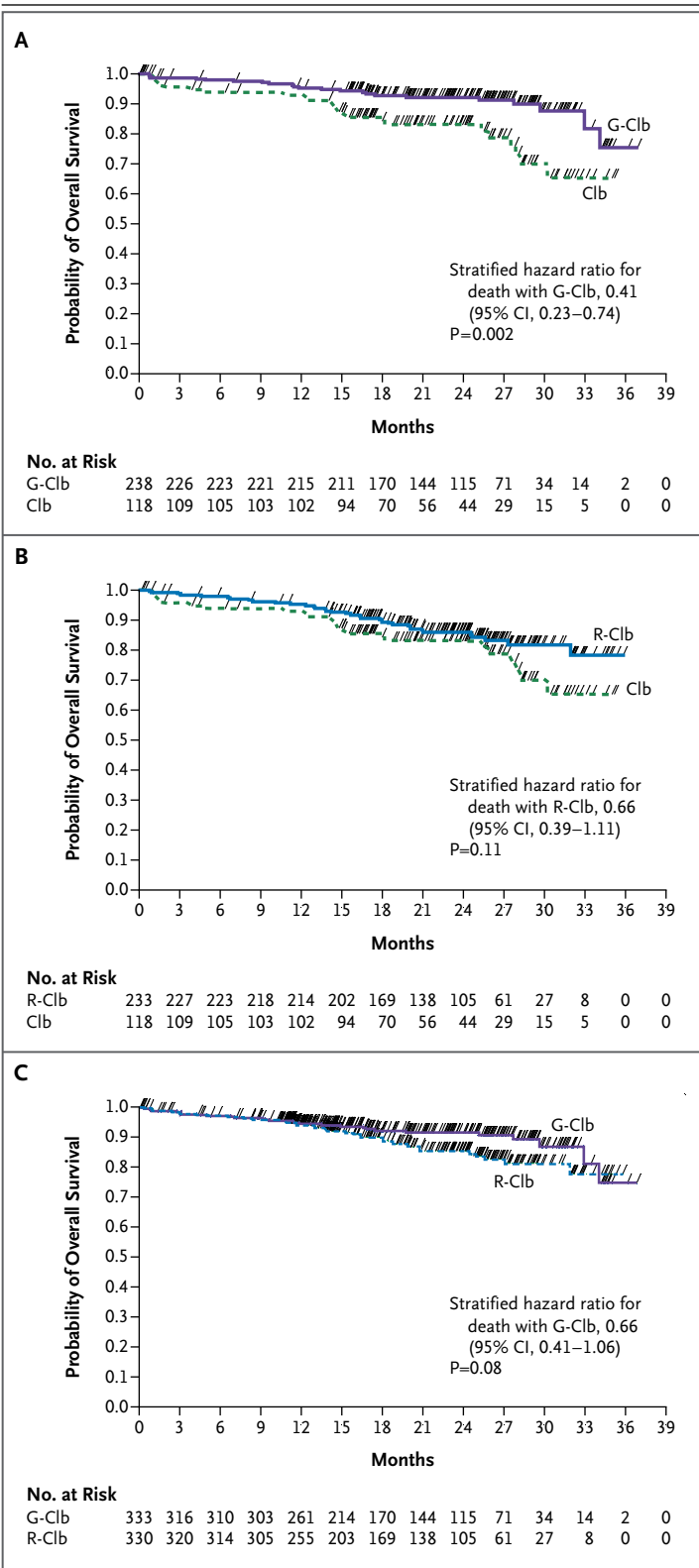
Figure 3. Overall Survival in the Intention-to-Treat Population.

Overall survival is shown for obinutuzumab–chlorambucil versus chlorambucil alone in Panel A, rituximab–chlorambucil versus chlorambucil alone in Panel B, and obinutuzumab–chlorambucil versus rituximab–chlorambucil in Panel C. P values were calculated with the use of a log-rank test. Clb denotes chlorambucil alone, G-Clb obinutuzumab–chlorambucil, and R-Clb rituximab–chlorambucil.

previously untreated CLL and coexisting conditions. Most enrolled patients were older than 70 years of age and had clinically meaningful health problems in addition to CLL. Although elderly patients with coexisting conditions represent the majority of patients with CLL,[2,3] they have been underrepresented in prior clinical trials. In contrast to treatment in younger, physically fit patients with CLL, chlorambucil monotherapy has remained a standard of care in older patients with coexisting conditions; no treatment has proved to be superior to chlorambucil in this patient population.[25,34] Our study shows that the combination of an anti-CD20 antibody with chlorambucil results in a better response and prolongation of progression-free survival in these patients. The patients treated with obinutuzumab and chlorambucil had an overall survival advantage over patients receiving chlorambucil alone. Previous trials of various treatments (e.g., fludarabine [alone or in combination with cyclophosphamide], bendamustine, and alemtuzumab)[4,6,8,35] did not show a survival advantage over treatment with chlorambucil alone.

To date, targeting of the CD20 antigen is the only therapeutic approach that has been shown to prolong survival among patients with previously untreated CLL.[9] New monoclonal anti-CD20 antibodies have been developed that were purported to be more efficacious than rituximab on the basis of preclinical studies.[36] With the exception of the glycoengineered type 2 antibody obinutuzumab, however, none have been directly compared with rituximab in patients with CLL. This study showed more complete responses and longer progression-free survival with obinutuzumab than with rituximab, when both were given in combination with chlorambucil. The trial met its primary end point (im-

proved progression-free survival), and this finding was robustly supported by analyses of all secondary end points and various preplanned sensitivity and subgroup analyses.

The rate of induction of negative status for minimal residual disease was more than 10 times as high with obinutuzumab–chlorambucil as it was with rituximab–chlorambucil. The capacity of a treatment to result in low levels of minimal residual disease in bone marrow or peripheral blood was recently associated with improved overall survival, irrespective of the clinically assessed response status.[37] With longer follow-up, the higher rate of eradication of minimal residual disease that was observed with obinutuzumab as compared with rituximab may lead to an overall survival benefit in addition to the improvement in progression-free survival.

Although response rates observed with rituximab–chlorambucil treatment were similar to those reported in previous phase 2 trials,[12,13] progression-free survival with rituximab–chlorambucil treatment was shorter in our study than in those trials. Some of the early trials showed longer progression-free survival with chlorambucil-alone treatment than we observed in our study.[5,6,35] However, these differences may be attributable to differences in patient populations, chlorambucil dosing schedules, and methods used for rigorous data collection. All these factors were kept constant across our treatment groups and therefore would not account for findings that favored obinutuzumab–chlorambucil over the other two treatments. The dose of obinutuzumab was higher than the dose of rituximab, and it is unclear to what extent this higher dose contributed to the greater activity of obinutuzumab–chlorambucil as compared with that of rituximab–chlorambucil. High-dose rituximab monotherapy in patients with CLL has been shown to have a dose–response relationship.[38] In combination with chemotherapy, however, high-dose rituximab did not result in an additional benefit.[39]

The combination of obinutuzumab or ritux-

imab with chlorambucil adds not only efficacy but also toxicity to the treatment. An increased incidence of neutropenia was observed with both antibodies but did not result in an increased incidence of infection. Infusion-related reactions, including severe reactions leading to withdrawal of therapy, were identified as a particular risk of obinutuzumab–chlorambucil treatment. Several prophylactic measures were implemented during the conduct of the trial (e.g., premedication with glucocorticoids and administration of the first dose of obinutuzumab over a period of 2 days), with a moderate effect on the frequency of infusion-related reactions. An important observation was that all grade 3 or 4 infusion-related reactions occurred during the first infusion of obinutuzumab but not during subsequent infusions. Rapid and profound B-cell depletion by obinutuzumab[40] might be the reason for the greater frequency and intensity of infusion-related reactions during the first dose of obinutuzumab as compared with rituximab. Lymphocyte counts and lymphadenopathy were not strong predictors of infusion-related reactions. In the absence of validated risk factors, all patients with CLL, irrespective of the leukemic burden, should therefore be closely monitored during the first infusion of obinutuzumab. Growing experience with this antibody will be key in reducing the risk of infusion-related reactions.

In conclusion, this randomized, phase 3 study showed that the combination of an anti-CD20 antibody (obinutuzumab or rituximab) with chlorambucil improves the outcomes in previously untreated patients with CLL and coexisting conditions. Obinutuzumab–chlorambucil provided an overall survival advantage over chlorambucil alone and induced deeper and longer remissions than did rituximab–chlorambucil.

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