ORIGINAL ARTICLE

Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia

J.C. Byrd, J.R. Brown, S. O'Brien, J.C. Barrientos, N.E. Kay, N.M. Reddy, S. Coutre, C.S. Tam, S.P. Mulligan, U. Jaeger, S. Devereux, P.M. Barr, R.R. Furman, T.J. Kipps, F. Cymbalista, C. Pocock, P. Thornton, F. Caligaris-Cappio, T. Robak, J. Delgado, S.J. Schuster, M. Montillo, A. Schuh, S. de Vos, D. Gill, A. Bloor, C. Dearden, C. Moreno, J.J. Jones, A.D. Chu, M. Fardis, J. McGreivy, F. Clow, D.F. James, and P. Hillmen, for the RESONATE Investigators*

ABSTRACT

BACKGROUND

In patients with chronic lymphoid leukemia (CLL) or small lymphocytic lymphoma (SLL), a short duration of response to therapy or adverse cytogenetic abnormalities are associated with a poor outcome. We evaluated the efficacy of ibrutinib, a covalent inhibitor of Bruton's tyrosine kinase, in patients at risk for a poor outcome.

METHODS

In this multicenter, open-label, phase 3 study, we randomly assigned 391 patients with relapsed or refractory CLL or SLL to receive daily ibrutinib or the anti-CD20 antibody ofatumumab. The primary end point was the duration of progression-free survival, with the duration of overall survival and the overall response rate as secondary end points.

RESULTS

At a median follow-up of 9.4 months, ibrutinib significantly improved progression-free survival; the median duration was not reached in the ibrutinib group (with a rate of progression-free survival of 88% at 6 months), as compared with a median of 8.1 months in the ofatumumab group (hazard ratio for progression or death in the ibrutinib group, 0.22; P<0.001). Ibrutinib also significantly improved overall survival (hazard ratio for death, 0.43; P=0.005). At 12 months, the overall survival rate was 90% in the ibrutinib group and 81% in the ofatumumab group. The overall response rate was significantly higher in the ibrutinib group than in the ofatumumab group (42.6% vs. 4.1%, P<0.001). An additional 20% of ibrutinib-treated patients had a partial response with lymphocytosis. Similar effects were observed regardless of whether patients had a chromosome 17p13.1 deletion or resistance to purine analogues. The most frequent nonhematologic adverse events were diarrhea, fatigue, pyrexia, and nausea in the ibrutinib group and fatigue, infusion-related reactions, and cough in the ofatumumab group.

CONCLUSIONS

Ibrutinib, as compared with ofatumumab, significantly improved progression-free survival, overall survival, and response rate among patients with previously treated CLL or SLL. (Funded by Pharmacyclics and Janssen; RESONATE ClinicalTrials.gov number, NCT01578707.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Byrd at B302 Starling-Loving Hall, 320 W. 10th Ave., Columbus, OH 43210, or at john.byrd@osumc.edu.

*A complete list of investigators in the Study of Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia (RESONATE) is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 31, 2014, at NEJM.org.

DOI: 10.1056/NEJMoa1400376

Chronic lymphoid leukemia (CLL) is characterized by a variable natural history that is partly predicted by clinical and genomic features.[1] Therapy for CLL has evolved from monotherapy with alkylating agents to chemoimmunotherapy.[2,3] Each of the combination regimens has shown prolonged rates of progression-free survival, as compared with similar regimens that do not contain antibodies.

Treatment of patients with relapsed CLL often includes regimens such as bendamustine and rituximab,[4] ofatumumab,[5] or investigational agents.[6-8] Ofatumumab was approved by the Food and Drug Administration (FDA) and the European Medicines Agency on the basis of a single-group study involving patients who had resistance to fludarabine and alemtuzumab therapy; with an overall response rate of 58%,[5] ofatumumab has been recommended in international consensus guidelines as a therapeutic option for patients with previously treated CLL.[9,10]

A short duration of response to initial therapy or adverse cytogenetic abnormalities have been associated with a poor outcome among patients receiving conventional therapy.[9,11,12] Identifying new therapies that prolong survival remains an important need for these patients.

Ibrutinib (Imbruvica, Pharmacyclics and Janssen) is a first-in-class, oral covalent inhibitor of Bruton's tyrosine kinase, an essential enzyme in B-cell receptor signaling, homing, and adhesion.[13-15] On the basis of response rates in single-group, phase 2 studies, ibrutinib was recognized by the FDA as a breakthrough therapy and was granted accelerated approval for patients with mantle-cell lymphoma (in November 2013) and CLL (in February 2014) who had received at least one previous therapy. Among patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL), those who received ibrutinib had a response rate of 71%, according to investigator assessment, and a progression-free survival rate of 75% at 2 years.[13] In this study, drug toxicity did not result in the discontinuation of ibrutinib in most patients. On the basis of early results of the phase 2 trial, we initiated a multicenter, open-label, randomized, phase 3 trial, the Study of Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia (RESONATE), to compare once-daily oral ibrutinib with an active control single-agent therapy, ofatumumab, in patients with relapsed or refractory CLL or SLL.

Methods

Patients

Patients with CLL or SLL requiring therapy[16] were eligible for enrollment if they had received at least one previous therapy and were considered to be inappropriate candidates for purine analogue treatment because they had a short progression-free interval after chemoimmunotherapy or because they had coexisting illnesses, an age of 70 years or more, or a chromosome 17p13.1 deletion (Text S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status[17] of less than 2 (on a scale from 0 to 5, with higher scores indicating greater disability), an absolute neutrophil count of at least 750 cells per microliter, a platelet count of at least 30,000 cells per microliter, and adequate liver and kidney function. Patients requiring warfarin or strong CYP3A4/5 inhibitors were excluded. All patients provided written informed consent.

Study Oversight

The study was approved by the institutional review board or independent ethics committee at each participating institution and was conducted in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The study was sponsored by Pharmacyclics and Janssen. All the authors and their research teams collected the data. Representatives of Pharmacyclics designed the study, confirmed the accuracy of the data, and compiled the data for analysis; Janssen representatives had no active role in the study. The authors had full access to the data and analyses for the compilation of this report. The first author wrote the first draft of the manuscript, which was reviewed, modified, and approved in its final version by all the authors. Editorial assistance was provided by two professional medical editors funded by Pharmacyclics. All the authors vouch for the accuracy and completeness of the data reported and the fidelity of the study to the protocol (available at NEJM.org) and made the decision to submit the manuscript for publication.

Study Review

An independent review committee, whose members were unaware of study-group assignments and

lymphocyte counts, assessed progression and response. An independent data and safety monitoring committee evaluated safety and reviewed data from the protocol-specified interim analysis.

RANDOMIZATION AND TREATMENT

From June 2012 through April 2013, we enrolled 391 patients at 67 sites in the United States, Australia, and seven European countries. Patients were randomly assigned to receive either oral ibrutinib (at a dose of 420 mg once daily) until disease progression or the occurrence of unacceptable toxic effects or intravenous ofatumumab for up to 24 weeks at an initial dose of 300 mg at week 1, followed by a dose of 2000 mg weekly for 7 weeks and then every 4 weeks for 16 weeks, consistent with local labeling. Patients were stratified according to whether they had resistance to purine analogue chemoimmunotherapy (defined as no response or a relapse within 12 months after the last dose of a purine analogue) and whether they had a chromosome 17p13.1 deletion.

During this study, promising data from the phase 2 trial[13] led investigators to request, and the steering committee to recommend, crossover of patients in the ofatumumab group to the ibrutinib group. This revision was supported by the data and safety monitoring committee and was discussed with health authorities. Approximately 4 months after the last patient underwent randomization, a protocol amendment allowed patients in the ofatumumab group who had disease progression, as confirmed by an independent review committee, to receive ibrutinib.

STUDY END POINTS

The primary end point was the duration of progression-free survival, as assessed by the independent review committee, according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia.[11] (Details regarding criteria for a complete response, partial response, stable disease, and progressive disease are provided in Table S1 in the Supplementary Appendix.) On the basis of a clarification adopted in 2012, treatment-related lymphocytosis was not considered to be progressive disease.[11] Key secondary end points included the duration of overall survival and the response rate. The criteria of the International Workshop on Chronic Lymphocytic Leukemia require the use of computed tomography (CT) to evaluate response and persistent improvement for at least 2 months to confirm response.[11]

Patients were monitored weekly for the first 8 weeks, every 4 weeks until month 6, and then every 12 weeks, with full response assessments performed every 12 weeks. Toxicity was graded according to the criteria of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0; the criteria of the International Workshop on Chronic Lymphocytic Leukemia were used to evaluate hematologic toxicity. Reports of eye-related adverse events were collected proactively on the basis of preclinical toxicology studies in dogs that revealed corneal abnormalities in animals receiving ibrutinib at a dose of 150 mg per kilogram of body weight per day (equivalent dose in humans, 81 mg per kilogram per day).[18-20] Pathologists at a central laboratory assessed the results of interphase fluorescence in situ hybridization (FISH) to evaluate cytogenetic factors (a procedure that was also performed at local site laboratories), measurements of serum β_2-microglobulin, and mutational analysis of immunoglobulin heavy-chain variable (*IGHV*) genes. (The presence of unmutated genes is usually associated with a poorer response to therapy and a worse outcome.)

STATISTICAL ANALYSIS

The primary end point, progression-free survival, was used in the calculation of the study sample size. The number of required events was based on a target hazard ratio for progression or death of 0.60, as calculated with the use of a two-sided log-rank test at an alpha level of 0.05, with a study power of at least 90%. The efficacy boundary (two-sided $P<0.028$) was crossed at the preplanned interim analysis, and the results from that analysis are presented in this report. The primary analysis was a two-sided log-rank test stratified according to the presence or absence of the chromosome 17p13.1 deletion and the disease refractory status at randomization. The type I error was controlled through adjustment of the significance level with the use of the O'Brien–Fleming boundary[21] for the interim analysis and with the use of a hierarchical closed-testing procedure for primary and ordered secondary end points.

RESULTS

PATIENTS

The baseline characteristics of the patients were generally well balanced between the two study groups (Table 1, and Table S2 in the Supplemen-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Ibrutinib (N=195)	Ofatumumab (N=196)
Patients with small lymphocytic lymphoma — no. (%)	10 (5)	8 (4)
Median age (range) — yr	67 (30–86)	67 (37–88)
Male sex — no. (%)	129 (66)	137 (70)
Cumulative Illness Rating Scale score >6 — no. (%)†	38 (32)	39 (32)
Creatinine clearance <60 ml/min — no. (%)	62 (32)	61 (31)
Median hemoglobin (range) — g/dl	11 (7–16)	11 (6–16)
Median platelet count (range) — per mm^3	116,500 (20,000–441,000)	122,000 (23,000–345,000)
Median lymphocyte count (range) — per mm^3	29,470 (90–467,700)	29,930 (290–551,030)
ECOG performance status — no. (%)‡		
0	79 (41)	80 (41)
1	116 (59)	116 (59)
Bulky disease ≥5 cm — no. (%)§	124 (64)	101 (52)
Interphase cytogenetic abnormalities — no. (%)		
Chromosome 11q22.3 deletion	63 (32)	59 (30)
Chromosome 17p13.1 deletion ¶	63 (32)	64 (33)
β_2-microglobulin >3.5 mg/liter — no. (%)	153 (78)	145 (74)
Previous therapies		
Median no. (range)	3 (1–12)	2 (1–13)
≥3 — no. (%)	103 (53)	90 (46)
Type of therapy — no. (%)		
Alkylator	181 (93)	173 (88)
Bendamustine	84 (43)	73 (37)
Purine analogue	166 (85)	151 (77)
Anti-CD20	183 (94)	176 (90)
Alemtuzumab	40 (21)	33 (17)
Allogeneic transplantation	3 (2)	1 (1)
Median time from last therapy (range) — mo	8 (1–140)	12 (0–184)
Resistance to purine analogues — no. (%)‖	87 (45)	88 (45)

* There were no significant differences between the two groups at baseline, except with respect to the presence of bulky disease of 5 cm or more (P=0.04) and the median time from last therapy (P=0.02).
† Scores on the Cumulative Illness Rating Scale range from 0 to 52, with higher scores indicating worse health status. Scores on this test were required only for patients 65 years of age or older, and coexisting illnesses were not included in the scoring.
‡ Scores on the Eastern Cooperative Oncology Group (ECOG) performance status range from 0 to 5, with higher scores indicating greater disability.
§ Measurement was based on the largest diameter of the longest lymph node at screening, according to the assessment of the independent review committee.
¶ Patients were stratified at randomization according to the presence or absence of this genetic abnormality.
‖ Resistance was defined as no response or a relapse within 12 months after the last dose of a CD20-based chemoimmunotherapy regimen that included a purine analogue.

tary Appendix). The majority of patients had advanced-stage disease. Patients in the ibrutinib group had undergone a median of three previous therapies, and those in the ofatumumab group had undergone a median of two previous therapies. The majority of patients had received previous treatment with purine analogues, alkylating agents, and anti-CD20 antibodies, which were frequently ad-

ministered in combination. The percentage of patients with bulky disease (≥5 cm) was higher in the ibrutinib group than in the ofatumumab group (64% vs. 52%). Approximately 57% of the patients in the two study groups had a deletion at either chromosome 17p13.1 or chromosome 11q22.3. The median follow-up time was 9.4 months (range, 0.1 to 16.6), and 86% of patients were still receiving ibrutinib at the time of this analysis (Fig. S1 in the Supplementary Appendix).

EFFICACY

Progression-free Survival

Ibrutinib significantly prolonged the duration of progression-free survival, with the median not reached at a median follow-up of 9.4 months, as compared with a median duration of progression-free survival of 8.1 months with ofatumumab. The hazard ratio for progression or death in the ibrutinib group was 0.22 (95% confidence interval [CI], 0.15 to 0.32; P<0.001) (Fig. 1A). This represents a 78% reduction in the risk of progression or death among patients treated with ibrutinib, as compared with ofatumumab. At 6 months, 88% of patients in the ibrutinib group were still alive with no disease progression, as compared with 65% in the ofatumumab group. The effect of ibrutinib on progression-free survival was observed regardless of baseline clinical characteristics or molecular features (Fig. 2).

Among patients with a chromosome 17p13.1 deletion, the median duration of progression-free survival was not reached in the ibrutinib group, as compared with a median of 5.8 months in the ofatumumab group (hazard ratio for progression or death, 0.25; 95% CI, 0.14 to 0.45). At 6 months, 83% of the patients with this deletion in the ibrutinib group, as compared with 49% of those with this deletion in the ofatumumab group, were alive with no disease progression. Richter's transformation (CLL that has evolved into an aggressive, rapidly growing large-cell lymphoma) was confirmed in two patients in each study group. Prolymphocytic leukemia developed in an additional patient in the ibrutinib group.

Overall Survival

Ibrutinib, as compared with ofatumumab, significantly prolonged the rate of overall survival (hazard ratio for death in the ibrutinib group, 0.43; 95% CI, 0.24 to 0.79; P=0.005), with the risk of death reduced by 57% (Fig. 1B). At 12 months, the overall survival rate was 90% in the ibrutinib group and 81% in the ofatumumab group. At the time of this analysis, 57 patients in the ofatumumab group had crossed over to receive ibrutinib after confirmed disease progression. The survival effect was based on an analysis in which data were censored at the time of crossover. At 12 months, the survival effect was also observed in the uncensored sensitivity analysis (hazard ratio for death, 0.39; P=0.001), with an overall survival rate of 90% in the ibrutinib group and 79% in the ofatumumab group (Fig. S2 in the Supplementary Appendix).

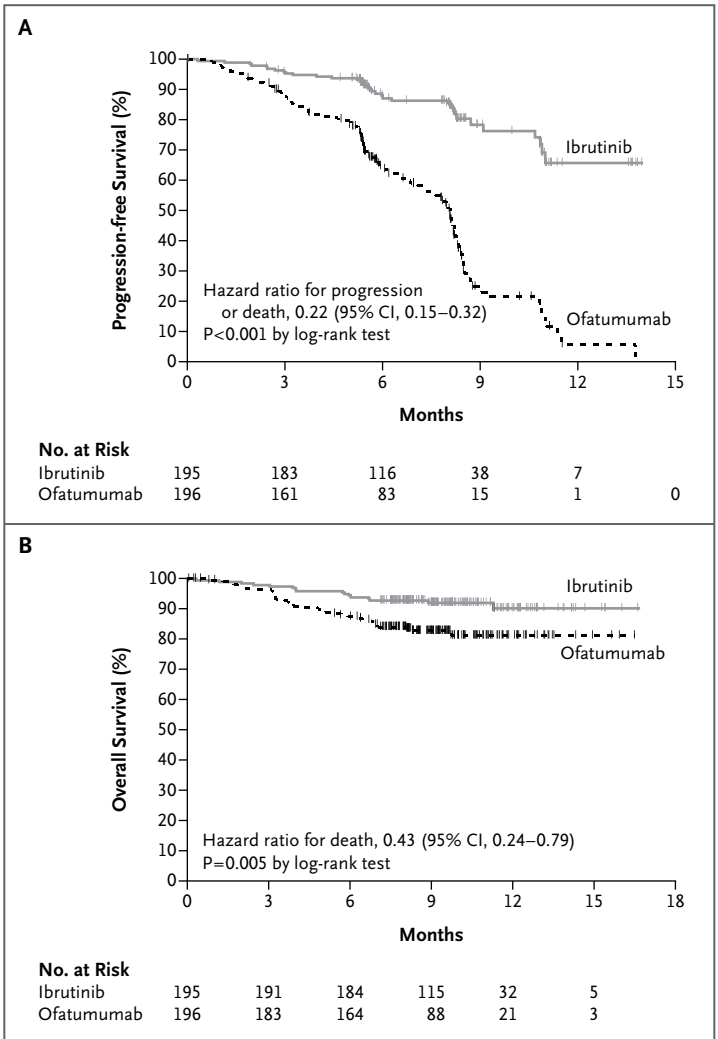

Figure 1. Progression-free and Overall Survival.

The durations of progression-free survival (Panel A) and overall survival (Panel B) were significantly longer in the ibrutinib group than in the ofatumumab group. At a median follow-up of 9.4 months, the median duration of progression-free survival was not reached in the ibrutinib group (with a rate of progression-free survival of 88% at 6 months), as compared with a median of 8.1 months in the ofatumumab group; the median duration of overall survival was not reached in either study group.

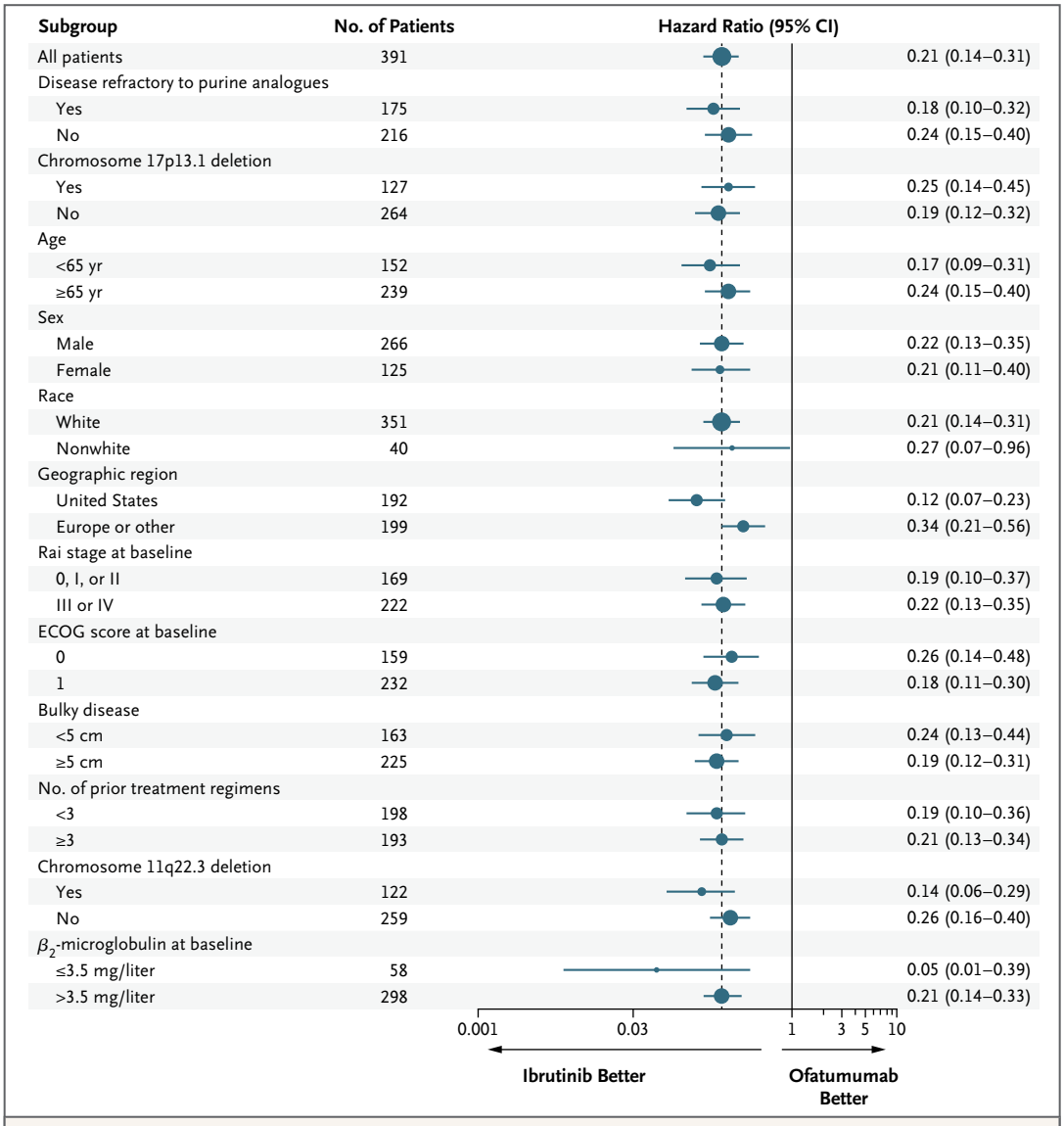

Figure 2. Subgroup Analyses of Progression-free Survival.

Shown are forest plots of hazard ratios for death or disease progression among subgroups of patients in the ibrutinib group and the ofatumumab group. The size of the circle is proportional to the size of the subgroup. The dashed vertical line indicates the overall treatment effect for all patients. The only test for heterogeneity that was significant was for geographic region (P=0.02), although the treatment effect remained significant within each region (P<0.001). The Rai staging system ranges from 0 (low risk) to I or II (intermediate risk) to III or IV (high risk). The Eastern Cooperative Oncology Group (ECOG) score ranges from 0 to 5, with higher scores indicating greater disability. Race was self-reported.

The difference in overall survival supporting the superiority of ibrutinib was preserved in all the subgroups defined according to pretreatment and genetic features (Fig. S3 in the Supplementary Appendix).

Response

The independently assessed response rate was significantly higher in the ibrutinib group than in the ofatumumab group (Fig. 3A). Overall, 43% of the patients in the ibrutinib group had a partial response, as compared with 4% in the ofatumumab group (odds ratio, 17.4; 95% CI, 8.1 to 37.3; P<0.001). In addition, 20% of the patients receiving ibrutinib had a partial response with lymphocytosis (resulting in a 63% response rate). Lymphocytosis was observed in 69% of the patients who were treated with ibrutinib and was

not considered to be disease progression.[11] The condition resolved in 77% of these patients during follow-up. In a recent study, patients with a partial response with lymphocytosis had rates of progression-free survival that were similar to those in patients with a partial response.[22] Investigator-assessed response rates were higher than independently assessed response rates in the two study groups (Fig. 3B).

SAFETY

Treatment exposure was longer among patients receiving ibrutinib than among those receiving ofatumumab (median duration, 8.6 months [range, 0.2 to 16.1] vs. 5.3 months [range, 0 to 7.4]). The profiles of cumulative adverse events that occurred in at least 10% of the patients are presented without adjustment for duration of exposure in Table 2. The most frequent nonhematologic adverse events that occurred in at least 20% of the patients were diarrhea, fatigue, pyrexia, and nausea in the ibrutinib group and fatigue, infusion-related reactions, and cough in the ofatumumab group. Overall, 57% of the patients in the ibrutinib group and 47% of the patients in the ofatumumab group had at least one adverse event of grade 3 or higher. Serious adverse events are summarized in Table S3 in the Supplementary Appendix. Adverse events of grade 3 or higher that occurred more frequently in the ibrutinib group than in the ofatumumab group included diarrhea (4% vs. 2%) and atrial fibrillation (3% vs. 0%); the latter event required cessation of therapy in one patient. An additional four patients in the ibrutinib group and one patient in the ofatumumab group had grade 1 or 2 atrial fibrillation. Bleeding-related adverse events of any grade (most commonly, petechiae, and including ecchymoses) were more common in the ibrutinib group than in the ofatumumab group (44% vs. 12%). Major hemorrhage (any hemorrhagic event of grade 3 or higher or resulting in transfusion of red cells or in hospitalization) was reported in two patients (1%) in the ibrutinib group (including one patient with a subdural hematoma) and three patients (2%) in the ofatumumab group.

Other adverse events that were more commonly noted among patients receiving ibrutinib than among those receiving ofatumumab included rash (8% vs. 4%), pyrexia (24% vs. 15%), and blurred vision (10% vs. 3%); all these events were generally grade 1 or 2 in severity. The incidence of cataracts was 3% and 1%, respectively. Infections of any grade were more common in the ibrutinib group (70% vs. 54%), whereas the frequency of infections of grade 3 or higher was similar in the two study groups (24% vs. 22%) (Table S4 in the Supplementary Appendix). Infusion reactions, peripheral sensory neuropathy, urticaria, night sweats, and pruritus were more common in the ofatumumab group. Basal-cell and squamous-cell carcinomas were reported in 4% of the patients in the ibrutinib group and in 2% in the ofatumumab group; nonskin cancers

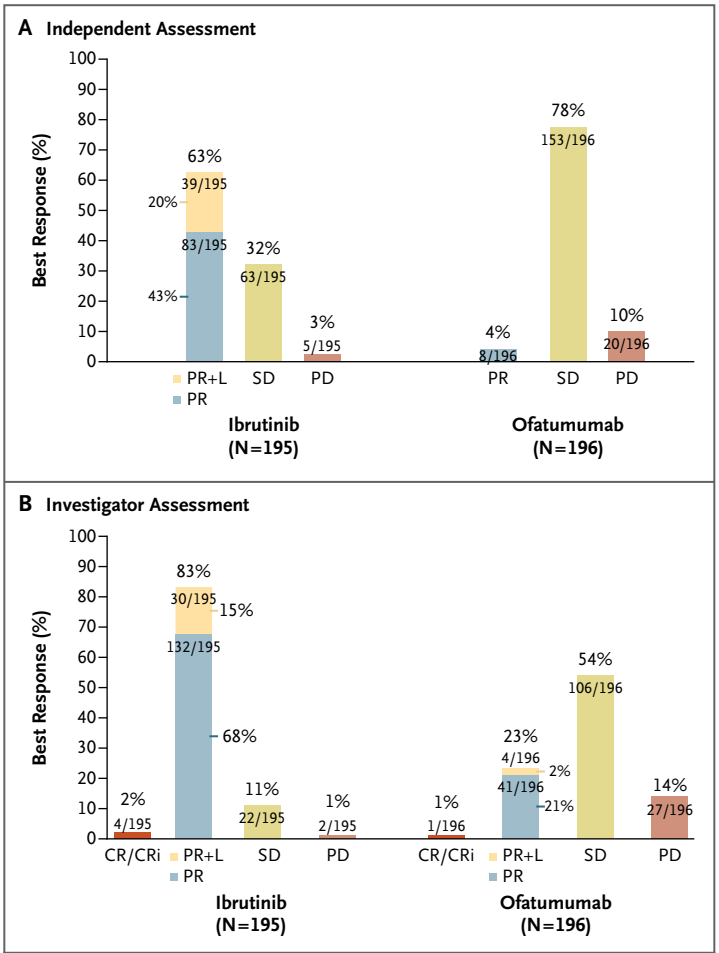

Figure 3. Best Response to Therapy, as Assessed by Independent Reviewers and by Investigators.

Shown are rates of patients' best response to therapy, according to independent assessment (Panel A) and investigator assessment (Panel B) with respect to complete response (CR), complete response with incomplete hematopoietic recovery (CRi), partial response (PR), partial response with lymphocytosis (PR+L), stable disease (SD), and progressive disease (PD). Data were unknown, missing, or could not be evaluated for 5 patients in the ibrutinib group in both the independent assessment and the investigator assessment and for 15 patients in the ofatumumab group in the independent assessment and 17 patients in the group in the investigator assessment.

Table 2. Adverse Events.*

Adverse Event	Ibrutinib (N=195)		Ofatumumab (N=191)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event occurring during treatment	194 (99)	99 (51)	187 (98)	74 (39)
Diarrhea	93 (48)	8 (4)	34 (18)	3 (2)
Fatigue	54 (28)	4 (2)	57 (30)	3 (2)
Nausea	51 (26)	3 (2)	35 (18)	0
Pyrexia	46 (24)	3 (2)	28 (15)	2 (1)
Anemia	44 (23)	9 (5)	33 (17)	15 (8)
Neutropenia	42 (22)	32 (16)	28 (15)	26 (14)
Cough	38 (19)	0	44 (23)	2 (1)
Thrombocytopenia	33 (17)	11 (6)	22 (12)	8 (4)
Arthralgia	34 (17)	2 (1)	13 (7)	0
Upper respiratory tract infection	31 (16)	1 (1)	20 (10)	3 (2)
Constipation	30 (15)	0	18 (9)	0
Vomiting	28 (14)	0	12 (6)	1 (1)
Headache	27 (14)	2 (1)	11 (6)	0
Petechiae	27 (14)	0	2 (1)	0
Muscle spasm	25 (13)	0	16 (8)	0
Dyspnea	23 (12)	4 (2)	20 (10)	1 (1)
Peripheral edema	22 (11)	0	15 (8)	0
Back pain	22 (11)	2 (1)	12 (6)	1 (1)
Sinusitis	21 (11)	1 (1)	12 (6)	0
Dizziness	22 (11)	0	10 (5)	0
Contusion	21 (11)	0	6 (3)	0
Stomatitis	21 (11)	1 (1)	4 (2)	1 (1)
Pain in limb	20 (10)	1 (1)	8 (4)	0
Pneumonia	19 (10)	13 (7)	13 (7)	9 (5)
Urinary tract infection	19 (10)	7 (4)	10 (5)	1 (1)
Myalgia	19 (10)	1 (1)	7 (4)	0
Blurred vision	19 (10)	0	6 (3)	0
Night sweats	10 (5)	1 (1)	24 (13)	0
Peripheral sensory neuropathy	8 (4)	0	24 (13)	0
Infusion-related reaction	0	0	53 (28)	6 (3)

* Listed are all adverse events that occurred in at least 10% of the patients in either group. Five patients in the ofatumumab group did not receive a study drug. All serious adverse events are listed in Tables S3 and S4 in the Supplementary Appendix.

were seen in 3% and 1% of the patients, respectively.

Discontinuation of treatment because of adverse events occurred in 4% of the patients in each study group. Fatal events occurred in 4% of the patients in the ibrutinib group and in 5% of those in the ofatumumab group (Table S5 in the Supplementary Appendix). These events were most commonly infectious in nature. Adverse events resulting in dose reductions occurred in

4% of the patients treated with ibrutinib, with only diarrhea (which occurred in three patients) leading to a dose reduction in more than one patient. Changes in creatinine levels from baseline were similar in the two study groups, with a decrease in creatinine clearance of any grade observed in 16% of the patients in the ibrutinib group and in 17% of those in the ofatumumab group.

DISCUSSION

Among patients with relapsed CLL or SLL, including those who had a short duration of response to prior therapy or who had adverse cytogenetic abnormalities, ibrutinib was superior to ofatumumab with respect to progression-free survival, overall survival, and response rate at a median follow-up of 9.4 months. The positive effect of ibrutinib was observed in subgroups of patients with a high-risk chromosome 17p13.1 deletion and with resistance to previous purine analogue therapy. Similar benefits with respect to progression-free survival were observed regardless of age, clinical stage, and factors such as status with respect to mutations in *IGHV*. The effect of ibrutinib on overall survival was significant, an effect that was robust despite the crossover of 57 patients to the ibrutinib group after they had disease progression while receiving ofatumumab; this effect was also observed in subgroup and sensitivity analyses.

Except for a few differences, our findings are largely similar to those of other trials of ibrutinib or ofatumumab. In each of the two groups in our study, the response rate as determined by independent assessors was lower than the response rate as determined by investigators. In the phase 2 study of ibrutinib monotherapy,[13] in which response was assessed by investigators, the response rate was 71%, which is similar to the 70% response rate assessed by investigators in our study. The independently assessed response rate in the ofatumumab group in our study appears to be lower than that in the pivotal study that was based on 1996 National Cancer Institute guidelines for CLL,[23] which did not require CT scanning to confirm response.[24] This difference may be due in part to the requirement in our study for serial CT scanning, which was performed every 12 weeks, to confirm response. Another ofatumumab study that compared response assessment between patients who underwent CT scanning and those who did not undergo CT scanning showed substantial differences in the rates of response between the two subgroups, with lower response rates seen in the group that underwent CT scanning.[25] Furthermore, the investigator-assessed response rate among patients in the ofatumumab group in our study (21%) was similar to the rate (23%) in a recent study that used 2008 criteria of the International Workshop on Chronic Lymphocytic Leukemia.[26] Reassuringly, the results with respect to progression-free survival in the ofatumumab group in our study (median, 8.1 months) are similar to those in historical reports (median, approximately 6 months).[5]

Previous reports of ofatumumab therapy showed that patients with refractory CLL had a median survival of 12 months[26] and 15 months,[5] with no plateau in deaths. With a median follow-up of 9.4 months in our study, an early separation in the curves for overall survival favored ibrutinib; however, the median was not reached in either study group. At later time points, the survival curve for ofatumumab began to flatten, which may in part be a reflection of the influence of ibrutinib on patients in the ofatumumab group who crossed over to ibrutinib therapy.

Ibrutinib was associated with toxic effects that were expected on the basis of the results of phase 2 studies. It appears that the drug can be safely administered even in a heavily pretreated and elderly population with baseline coexisting conditions, such as the one in our study. In the ibrutinib group, 32% of the patients had a decreased creatinine clearance, 64% had cytopenias, and 32% had a score on the Cumulative Illness Rating Scale of more than 6 (ranging from 0 to 52, with higher scores indicating worse health status). Toxic effects did not result in frequent dose reductions or treatment discontinuations.

One strength of a randomized, controlled trial is that background disease-related complications may be differentiated from a treatment effect with a new agent. However, it is important to note that patients in the ibrutinib group had a reporting period for adverse events that was more than 3 months longer than that in the

ofatumumab group (median duration, 8.6 months vs. 5.3 months), and no exposure-adjusted analysis of adverse events was performed.

The frequencies of renal complications and increased creatinine levels were similar in the two study groups. Although the overall rate of infections was higher in the ibrutinib group, the frequency of infections of grade 3 or higher did not differ significantly between the two groups. Ocular symptoms were collected proactively and were reported more frequently among patients in the ibrutinib group, including a small proportion of patients who reported blurred vision. The development of cataracts in 3% of the patients receiving ibrutinib (as compared with 1% in the control group) bears noting, since longer exposure may be associated with an increased risk.

Atrial fibrillation of any grade was noted in 10 patients in the ibrutinib group, as compared with 1 patient in the ofatumumab group, and led to the discontinuation of ibrutinib in 1 patient. Potential reasons for the higher rate of atrial fibrillation among patients receiving ibrutinib are being explored. In clinical studies in which serial electrocardiographic studies were performed, no evidence of arrhythmias was observed among patients receiving ibrutinib.[13,27]

An adverse event of interest with ibrutinib from early studies was major hemorrhage, including subdural hematoma. In our study, we excluded patients requiring warfarin but not those requiring other forms of anticoagulation. The rate of major hemorrhage was similar in the two study groups, with one subdural hematoma noted in a patient receiving ibrutinib. Although mild bleeding episodes were more common in the ibrutinib group, adherence to appropriate drug-withholding guidelines perioperatively and precautions regarding the use of antiplatelet agents and anticoagulants resulted in no unexpected major bleeding complications in the ibrutinib group. Further studies of the mechanism of bleeding, including bruising, that was observed among patients receiving ibrutinib have been conducted[28] or are planned.

In conclusion, ibrutinib was superior to ofatumumab in difficult-to-treat patients with relapsed or refractory CLL or SLL, as measured by progression-free survival, overall survival, and response. The improvement was observed across all subgroups that were examined, including patients who were resistant to chemoimmunotherapy and those with a chromosome 17p13.1 deletion, which confirms single-agent ibrutinib as an effective therapy for CLL or SLL. Phase 3 studies examining the effect of ibrutinib in previously untreated patients with CLL or SLL are ongoing (ClinicalTrials.gov numbers, NCT02048813 and NCT01722487).

Supported by Pharmacyclics and Janssen.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients and their families; Jennifer Lin for assistance with data analysis and interpretation; Christine Barker for trial management; and Patricia Gosling, Ph.D., of Pharmacyclics and Karen Pemberton, Ph.D., funded by Pharmacyclics, for their editorial assistance in the preparation of the manuscript.

APPENDIX

The authors are as follows: John C. Byrd, M.D., Jennifer R. Brown, M.D., Ph.D., Susan O'Brien, M.D., Jacqueline C. Barrientos, M.D., Neil E. Kay, M.D., Nishitha M. Reddy, M.B., B.S., Steven Coutre, M.D., Constantine S. Tam, M.D., Stephen P. Mulligan, M.B., B.S., Ph.D., Ulrich Jaeger, M.D., Steve Devereux, M.D., Paul M. Barr, M.D., Richard R. Furman, M.D., Thomas J. Kipps, M.D., Florence Cymbalista, M.D., Christopher Pocock, M.D., Ph.D., Patrick Thornton, M.D., Federico Caligaris-Cappio, M.D., Tadeusz Robak, M.D., Julio Delgado, M.D., Stephen J. Schuster, M.D., Marco Montillo, M.D., Anna Schuh, M.D., Sven de Vos, M.D., Devinder Gill, M.D., Adrian Bloor, Ph.D., F.R.C.Path., Claire Dearden, M.D., Carol Moreno, M.D., Jeffrey J. Jones, M.D., Alvina D. Chu, M.D., Maria Fardis, Ph.D., Jesse McGreivy, M.D., Fong Clow, D.Sc., Danelle F. James, M.D., and Peter Hillmen, M.B., Ch.B., Ph.D.

The authors' affiliations are as follows: Ohio State University Comprehensive Cancer Center, Columbus (J.C. Byrd, J.J.J.); Dana–Farber Cancer Institute, Boston (J.R.B.); M.D. Anderson Cancer Center, Houston (S.O.); Hofstra North Shore–LIJ School of Medicine, Hempstead (J.C. Barrientos), University of Rochester Cancer Center, Rochester (P.M.B.). and New York–Presbyterian Hospital and Weill Cornell Medical College, New York (R.R.F.) — all in New York; Mayo Clinic, Rochester, MN (N.E.K.); Vanderbilt–Ingram Cancer Center, Nashville (N.M.R.); Stanford University School of Medicine and Stanford Cancer Institute, Stanford (S.C.), Moores UCSD Cancer Center, San Diego (T.J.K.), David Geffen School of Medicine at UCLA, Los Angeles (S.V.), and Pharmacyclics, Sunnyvale (A.D.C., M.F., J.M., F.C., D.F.J.) — all in California; Peter MacCallum Cancer Centre and St. Vincent's Hospital, Melbourne, VIC (C.S.T.), Royal North Shore Hospital, Sydney, NSW (S.P.M.), and Princess Alexandra Hospital, Brisbane, QLD (D.G.) — all in Australia; Medical University of Vienna, Vienna (U.J.); Kings College Hospital, National Health Service (NHS) Foundation Trust Denmark Hill, London (S.D.), East Kent Hospitals, Canterbury (C.P.), Oxford Biomedical Research Centre, Oxford (A.S.), Christie NHS Foundation Trust Hematology and Transplant Unit, Manchester (A.B.), Royal Marsden Hospital and the Institute of Cancer Research, Sutton (C.D.), and Leeds Teaching Hospitals, St. James Institute of Oncology, Leeds (P.H.) — all in the United Kingdom; Hôpital Avicenne, Paris (F.C.); Beaumont Hospital, Dublin, Ireland (P.T.); Universita Vita-Salute San Raffaele (F.C-C.) and Niguarda Ca' Granda Hospital (M.M.), Milan; Medical University of Lodz and Copernicus Memorial Hospital, Lodz, Poland (T.R.); Hospital Clinic (J.D.) and Hospital de la Santa Creu Sant Pau (C.M.), Barcelona; and Abramson Cancer Center of the University of Pennsylvania, Philadelphia (S.J.S.).

REFERENCES

1. Hallek M. Chronic lymphocytic leukemia: 2013 update on diagnosis, risk stratification and treatment. Am J Hematol 2013;88:803-16.
2. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet 2010;376:1164-74.
3. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 2014;370:1101-10.
4. Fischer K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2011;29:3559-66.
5. Wierda WG, Kipps TJ, Mayer J, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2010;28:1749-55. [Erratum, J Clin Oncol 2010;28:3670.]
6. Badoux XC, Keating MJ, Wen S, et al. Phase II study of lenalidomide and rituximab as salvage therapy for patients with relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol 2013;31:584-91.
7. Chen CI, Bergsagel PL, Paul H, et al. Single-agent lenalidomide in the treatment of previously untreated chronic lymphocytic leukemia. J Clin Oncol 2011; 29:1175-81.
8. Ferrajoli A, Lee BN, Schlette EJ, et al. Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. Blood 2008;111:5291-7.
9. Eichhorst B, Dreyling M, Robak T, Montserrat E, Hallek M. Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2011;22:Suppl 6:vi50-vi54.
10. Zelenetz AD, Wierda WG, Abramson JS, et al. Non-Hodgkin's lymphomas, version 1.2013. J Natl Compr Canc Netw 2013;11:257-72.
11. Hallek M, Cheson B, Catovsky D, et al. Response assessment in chronic lymphocytic leukemia treated with novel agents causing an increase of peripheral blood lymphocytes. Blood 2012 June 4 (e-letter) (http://bloodjournal.hematologylibrary.org/content/111/12/5446/reply).
12. Zelenetz AD, Abramson JS, Advani RH, et al. NCCN Clinical Practice Guidelines in Oncology: non-Hodgkin's lymphomas. J Natl Compr Canc Netw 2010;8: 288-334.
13. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013;369:32-42. [Erratum, N Engl J Med 2014;370:786.]
14. Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. Proc Natl Acad Sci U S A 2010;107:13075-80.
15. Ponader S, Chen SS, Buggy JJ, et al. The Bruton tyrosine kinase inhibitor PCI-32765 thwarts chronic lymphocytic leukemia cell survival and tissue homing in vitro and in vivo. Blood 2012;119:1182-9.
16. 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 2008; 111:5446-56. [Erratum, Blood 2008;112: 5259.]
17. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.
18. Byrd JC, O'Brien S, James DF. Ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013;369:1278-9.
19. Neffendorf JE, Gout I, Hildebrand GD. Ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013; 369:1277.
20. Rushworth SA, MacEwan DJ, Bowles KM. Ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013; 369:1277-8.
21. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
22. Woyach JA, Smucker K, Smith LL, et al. Prolonged lymphocytosis during ibrutinib therapy is associated with distinct molecular characteristics and does not indicate a suboptimal response to therapy. Blood 2014;123:1810-7.
23. 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 1996; 87:4990-7.
24. Lemery SJ, Zhang J, Rothmann MD, et al. U.S. Food and Drug Administration approval: ofatumumab for the treatment of patients with chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab. Clin Cancer Res 2010;16:4331-8.
25. Flinn IW, Harwin WN, Ward P, et al. Phase II trial of ofatumumab (OFA) for older patients and patients who refuse fludarabine-based regimens with previously untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Blood 2012;120:719. abstract.
26. Moreno C, Montillo M, Panayiotis P, et al. A multicenter, phase IV observational study of ofatumumab in chronic lymphocytic leukemia (CLL): a European Research Initiative on CLL (ERIC) study. Blood 2013;122:1645. abstract.
27. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol 2013;31:88-94.
28. Farooqui M, Lozier J, Valdez J, et al. Ibrutinib (PCI 32765) rapidly improves platelet counts in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) patients and has minimal effects on platelet aggregation. Blood 2014; https://ash.confex.com/ash/2012/webprogram/Paper50250.html. abstract.