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Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

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ABSTRACT

BACKGROUND

Bruton's tyrosine kinase (BTK) is a mediator of the B-cell–receptor signaling pathway implicated in the pathogenesis of B-cell cancers. In a phase 1 study, ibrutinib, a BTK inhibitor, showed antitumor activity in several types of non-Hodgkin's lymphoma, including mantle-cell lymphoma.

METHODS

In this phase 2 study, we investigated oral ibrutinib, at a daily dose of 560 mg, in 111 patients with relapsed or refractory mantle-cell lymphoma. Patients were enrolled into two groups: those who had previously received at least 2 cycles of bortezomib therapy and those who had received less than 2 complete cycles of bortezomib or had received no prior bortezomib therapy. The primary end point was the overall response rate. Secondary end points were duration of response, progression-free survival, overall survival, and safety.

RESULTS

The median age was 68 years, and 86% of patients had intermediate-risk or high-risk mantle-cell lymphoma according to clinical prognostic factors. Patients had received a median of three prior therapies. The most common treatment-related adverse events were mild or moderate diarrhea, fatigue, and nausea. Grade 3 or higher hematologic events were infrequent and included neutropenia (in 16% of patients), thrombocytopenia (in 11%), and anemia (in 10%). A response rate of 68% (75 patients) was observed, with a complete response rate of 21% and a partial response rate of 47%; prior treatment with bortezomib had no effect on the response rate. With an estimated median follow-up of 15.3 months, the estimated median response duration was 17.5 months (95% confidence interval [CI], 15.8 to not reached), the estimated median progression-free survival was 13.9 months (95% CI, 7.0 to not reached), and the median overall survival was not reached. The estimated rate of overall survival was 58% at 18 months.

CONCLUSIONS

Ibrutinib shows durable single-agent efficacy in relapsed or refractory mantle-cell lymphoma. (Funded by Pharmacyclics and others; ClinicalTrials.gov number, NCT01236391.)

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Mantle-cell lymphoma is a distinct subtype of non-Hodgkin's lymphoma that has an aggressive clinical course and a poor prognosis.[1] Current frontline combination chemotherapies[2] and intensive chemoimmunotherapy followed by stem-cell transplantation have improved the outcome for patients with this disease.[3,4] Although these regimens have high initial response rates, most patients eventually have a relapse and die from mantle-cell lymphoma. More effective agents are needed.

Constitutive activation of B-cell receptor signaling appears to be essential for the survival and proliferation of malignant B cells, an observation that has led to the design of inhibitors of B-cell receptor–associated kinases.[3-5] Bruton's tyrosine kinase (BTK) has been identified as an essential component of the B-cell–receptor signaling pathway.[6-9] An antigen-driven origin of mantle-cell lymphoma has been suggested,[10] and genomic and expression profiling of samples from patients with mantle-cell lymphoma has identified proteins upstream of BTK, such as the spleen tyrosine kinase Syk, as important contributors to the growth and survival of mantle-cell lymphoma cells.[11]

Ibrutinib (PCI-32765) is an oral covalent inhibitor of BTK that significantly reduced the tumor burden in a rodent treatment and prevention model of mantle-cell lymphoma.[12] In early-stage clinical trials, ibrutinib has shown antitumor activity in B-cell cancers.[13-15] In a phase 1 study, ibrutinib induced a response in seven of nine patients with relapsed or refractory mantle-cell lymphoma; investigation of the side effects and efficacy at various doses in this study established 560 mg as the phase 2 dose.[14] On the basis of these results, we conducted a phase 2, open-label trial to assess the efficacy and safety of ibrutinib at a daily dose of 560 mg in patients with relapsed or refractory mantle-cell lymphoma.

Methods

Patients

Eligible patients had a confirmed diagnosis of mantle-cell lymphoma with cyclin D1 overexpression or translocation breakpoints at t(11;14) and measurable disease (lymph-node diameter, ≥2 cm). Patients had received at least one but no more than five previous lines of treatment, with no partial or better response to the most recent treatment regimen or with disease progression after the most recent regimen.

Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less (scores range from 0 to 5, with 0 indicating asymptomatic and higher numbers indicating increasing disability) and adequate organ function. An absolute neutrophil count of at least 0.75×10^9 per liter and a platelet count of at least 50×10^9 per liter were required unless the patient had bone marrow involvement by lymphoma.

Study Design and Treatment

This international open-label, phase 2 study was conducted at 18 sites. Patients with mantle-cell lymphoma were enrolled without randomization and were classified as either having received treatment with bortezomib (≥2 cycles) or not having received such treatment (<2 complete cycles or no prior bortezomib therapy). Single-agent bortezomib is a treatment approved by the Food and Drug Administration for patients with mantle-cell lymphoma that has progressed after at least one initial treatment. Therefore, a defined cohort of patients with prior bortezomib treatment was included in this study, and the combination of the two cohorts was representative of a broad population of patients with relapsed or refractory mantle-cell lymphoma. Patients received single-agent ibrutinib administered orally at a daily dose of 560 mg until progression of disease or until unacceptable levels of adverse events occurred. All the patients provided written informed consent.

The institutional review board at each site approved the study protocol, which was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. The protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org.

Study Oversight

The academic authors were responsible for designing the study protocol and statistical analysis plan together with the sponsor, Pharmacyclics. The investigators and their respective research teams collected all the data, and the sponsor confirmed the accuracy of the data and compiled them for summation and analysis. Statistical analyses were performed by the biometrics group at Janssen Research and Development and were independently confirmed and validated by a separate statistical group at Pharmacyclics. The investigators had full access to the data and analyses

for the compilation of this report. Manuscript drafts were prepared by all the authors, with editorial assistance from a professional medical writer paid by the sponsor. All the authors vouch for the accuracy and completeness of the data reported and for the adherence of the study to the protocol, and all the authors made the decision to submit the manuscript for publication.

ASSESSMENTS

The primary end point was the rate of overall response, defined as either a partial response or a complete response according to the Revised International Working Group Criteria for non-Hodgkin's lymphoma.[16] In addition, a response evaluation based on computed tomographic (CT) and positron-emission tomographic (PET) scans, bone marrow–biopsy specimens, gastrointestinal biopsy specimens (if a gastrointestinal biopsy was performed), and clinical data was conducted by an independent central review vendor (BioClinica). Tumor assessment was performed during screening with the use of CT scans of the chest, abdomen, pelvis, and any other disease sites (e.g., neck); PET scans; and bone marrow biopsy. CT scanning was repeated at cycles 3, 5, and 7 and then every three cycles until disease progression. A PET scan was mandatory for confirmation of a complete response.

The secondary end points included response duration, measured from the time when the criteria for a response were met until the first date on which recurrent or progressive disease was objectively documented; progression-free survival, measured as the time from the first administration of the study drug until lymphoma progression or death from any cause; overall survival, measured from the time of the first administration of the study drug until the date of death; and safety. Safety was assessed on the basis of the frequency and severity of adverse events. Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.[17] The safety assessment was based on reported adverse events, clinical laboratory tests (hematologic testing, serum chemical testing, and urinalysis), measurements of weight and vital signs, physical examinations, and ECOG performance status.

PERIPHERAL-BLOOD LYMPHOCYTE COUNTS

In chronic lymphocytic leukemia, ibrutinib causes a transient increase in blood lymphocytes that is concurrent with a reduction in lymph-node size.[15] Whether a similar phenomenon occurs in patients with mantle-cell lymphoma was investigated by counting and characterizing peripheral-blood lymphocytes after treatment with ibrutinib (see the Supplementary Appendix, available at NEJM.org). The effect of ibrutinib on cytokine expression was also evaluated in a subset of patients (see the Supplementary Appendix).

STATISTICAL ANALYSIS

The sample for this study was 115 patients; we planned to include 65 patients with no prior treatment with bortezomib and 50 with prior bortezomib treatment. With the use of Simon's two-stage design[18] (see the study protocol), the study was designed to check the efficacy of the drug in a small group of patients before enrolling the entire planned study population. If an appropriate number of patients had a response in the first stage (see below), then we would continue enrollment; if the level of response did not meet our success criteria for clinical benefit, the study would be terminated for that group.

For the cohort of patients without prior treatment with bortezomib, a two-stage design was planned to test the null hypothesis that the response rate would be 20% or less (i.e., before the investigators could proceed to stage 2 of the study, at least 6 of 25 patients had to have a response). We calculated that a sample of 65 patients would provide 91% power to test a difference in the response rate of 20% versus 40% at a one-sided alpha level of 0.01. For the cohort of patients with prior bortezomib treatment, a two-stage design was planned to test the null hypothesis that the response rate would be 15% or less (i.e., before the investigators could proceed to stage 2 of the study, at least 5 of 25 patients had to have a response). We calculated that a sample of 50 patients would provide 80% power to test a difference in the response rate of 15% versus 35% at a one-sided alpha level of 0.01.

In each cohort, an interim analysis for futility was conducted on the basis of the stopping rules for Simon's two-stage design.[18] On the basis of this interim analysis, enrollment in both study cohorts was allowed to continue, per protocol.

The final analysis was planned to be performed approximately 8 months after the last patient was enrolled in the study. Frequency tables were used to summarize categorical vari-

ables. The distribution of time-to-event end points, including response duration, progression-free survival, and overall survival, were estimated with the use of the Kaplan–Meier method.[19] All statistical tests were based on a two-sided alpha level of 0.05.

RESULTS

PATIENTS AND TREATMENT

From February 15, 2011, through March 21, 2012, a total of 115 patients with relapsed or refractory mantle-cell lymphoma were enrolled without ran-

Table 1. Demographic and Baseline Clinical Characteristics.*

Characteristic	No Prior Treatment with Bortezomib (N=63)	Prior Treatment with Bortezomib (N=48)	All Patients (N=111)†
Age — yr			
Median	66	69	68
Range	46–83	40–84	40–84
Sex — no. (%)			
Male	46 (73)	39 (81)	85 (77)
Female	17 (27)	9 (19)	26 (23)
ECOG performance status — no. (%)‡			
0 or 1	53 (84)	46 (96)	99 (89)
2	9 (14)	2 (4)	11 (10)
>2	1 (2)	0	1 (1)
No. of prior regimens			
Median	2	3	3
Range	1–5	1–5	1–5
≥3 — no. (%)	31 (49)	30 (62)	61 (55)
Previous therapy — no. (%)			
Hyper-CVAD	18 (29)	15 (31)	33 (30)
Stem-cell transplantation	8 (13)	4 (8)	12 (11)
Lenalidomide	9 (14)	18 (38)	27 (24)
Rituximab or rituximab-containing regimen	56 (89)	43 (90)	99 (89)
Simplified MIPI — no. (%)§			
Low risk	9 (14)	6 (12)	15 (14)
Intermediate risk	24 (38)	18 (38)	42 (38)
High risk	30 (48)	24 (50)	54 (49)
Bulky mass — no. (%)¶	6 (10)	3 (6)	9 (8)
At least one node ≥5 cm — no. (%)	26 (41)	17 (35)	43 (39)
Refractory disease — no. (%)‖	27 (43)	23 (48)	50 (45)
Advanced disease — no. (%)**	49 (78)	31 (65)	80 (72)

* Percentages may not add up to 100% because of rounding. Hyper-CVAD denotes hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone.

† Four patients who were enrolled in the study did not receive ibrutinib treatment owing to the investigator's decision.

‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating asymptomatic, 1 symptomatic but ambulatory, and 2 symptomatic and in bed less than half the day; a score of more than 2 indicates only limited self-care and in bed more than half the day (3), completely disabled and confined to bed or chair (4), or dead (5).

§ The simplified Mantle-Cell Lymphoma International Prognostic Index (MIPI) score was derived with the use of the four prognostic factors of age, ECOG score, lactate dehydrogenase level, and white-cell count at baseline, and its range depends on the range of these characteristics. The index classifies patients as having low-, intermediate-, or high-risk disease, as defined by scores of 0 to 3, 4 or 5, and 6 to 11, respectively.

¶ Bulky mass was defined as a tumor with a diameter of at least 10 cm.

‖ Refractory disease was defined as a lack of at least a partial response to the last therapy before study entry.

** Advanced disease was defined as involvement of bone marrow, extranodal sites, or both.

domization. We classified patients into two groups: patients with prior bortezomib treatment (50 patients) or no prior bortezomib treatment (65 patients, including 58 who had never received bortezomib and 7 who had received fewer than two cycles). The baseline characteristics of the patients in the two groups are provided in Table 1.

Of the 115 enrolled patients, 3 (2 patients with prior bortezomib treatment and 1 without prior treatment) did not receive the study drug owing to rapid disease progression, and 1 was not treated for administrative reasons. A total of 111 patients received at least one dose of ibrutinib, and the median number of cycles administered in the overall study population was 9 (range, 1 to 24).

With an estimated median follow-up of 15.3 months (range, 1.9 to 22.3), 46 patients were still receiving treatment, and 65 had discontinued therapy. Reasons for treatment discontinuation included progression of disease in 50 patients (including 2 patients who discontinued treatment within 30 days after the first dose and 1 with unconfirmed progression of disease), patient or investigator decision for 7 patients (including 1 patient who proceeded to stem-cell transplantation), and adverse events in 8 patients (including 2 patients with subdural hematomas, and 1 each with pneumonia, an elevated bilirubin level, sepsis, metastatic adenocarcinoma, respiratory failure, and cardiac arrest) (Table S1 in the Supplementary Appendix).

SAFETY

With continuous ibrutinib treatment, the majority of the adverse events observed were grade 1 or 2. The most common nonhematologic adverse events occurring in more than 20% of patients were diarrhea (in 50% of patients), fatigue (in 41%), nausea (in 31%), peripheral edema (in 28%), dyspnea (in 27%), constipation (in 25%), upper respiratory tract infection (in 23%), vomiting (in 23%), and decreased appetite (in 21%) (Table 2). The most common infection of grade 3, 4, or 5 was pneumonia (in 6% of patients) (Table S2 in the Supplementary Appendix). Serum IgM, IgG, and IgA levels did not change during treatment (data not shown). A decrease in neutrophils, platelets, or hemoglobin level was reported in less than 19% of patients.

Table 2. Adverse Events.*

Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Overall
			no. of patients with event (%)			
Hematologic event						
Neutropenia	1 (1)	1 (1)	7 (6)	11 (10)	0	20 (18)
Thrombocytopenia	4 (4)	4 (4)	8 (7)	4 (4)	0	20 (18)
Nonhematologic event						
Diarrhea	36 (32)	13 (12)	7 (6)	0	0	56 (50)
Fatigue	22 (20)	19 (17)	5 (5)	0	0	46 (41)
Nausea	26 (23)	8 (7)	0	0	0	34 (31)
Peripheral edema	21 (19)	8 (7)	1 (1)	1 (1)	0	31 (28)
Dyspnea	14 (13)	11 (10)	4 (4)	0	1 (1)	30 (27)
Constipation	20 (18)	8 (7)	0	0	0	28 (25)
Upper respiratory tract infection	6 (5)	20 (18)	0	0	0	26 (23)
Vomiting	19 (17)	6 (5)	0	0	0	25 (23)
Decreased appetite	11 (10)	10 (9)	2 (2)	0	0	23 (21)
Cough	13 (12)	7 (6)	0	0	0	20 (18)
Pyrexia	14 (13)	5 (5)	1 (1)	0	0	20 (18)
Abdominal pain	10 (9)	3 (3)	6 (5)	0	0	19 (17)
Contusion	17 (15)	2 (2)	0	0	0	19 (17)
Rash	11 (10)	4 (4)	2 (2)	0	0	17 (15)

* Data are for adverse events reported during treatment in the 111 patients included in the study. Listed events occurred in at least 15% of patients on or before the data-cutoff date of December 26, 2012. For four events (one event each of diarrhea, depression, asthenia, and hypersomnia), the grade was not available; these four events are included in the grade 3 category.

Grade 3 and 4 hematologic adverse events included neutropenia (in 16% of patients), thrombocytopenia (in 11%), and anemia (in 10%). Grade 3 bleeding events occurred in five patients, with no grade 4 or 5 hemorrhagic events (Table S2 in the Supplementary Appendix). Four patients had subdural hematomas (grade 1 in one patient, grade 2 in one, and grade 3 in two); all were associated with falls, head trauma, or both. In addition, all four patients were receiving either aspirin or warfarin within 2 days before or on the date of occurrence of these events.

An adverse event leading to discontinuation of therapy occurred in 8 patients (7%) (Table S1 in the Supplementary Appendix). A total of 16 patients (14%) died during the trial, with 12 deaths due to disease progression and 4 due to an adverse event (2 deaths from pneumonia, 1 from sepsis, and 1 from a cardiac arrest that was deemed not to be drug-related).

EFFICACY

In the 111 patients who had received ibrutinib, the estimated median follow-up was 15.3 months (range, 1.9 to 22.3). The response rate for all patients was 68%, with 47% of patients having a partial response and 21% having a complete response (Table 3). The response to ibrutinib did not vary on the basis of baseline characteristics or the presence of risk factors associated with treatment failure with chemotherapy (Fig. 1). Of 43 patients with lymph nodes that were at least 5 cm in diameter, 27 (63%) had a response to treatment (Fig. S1 in the Supplementary Appendix). Response rates were similar in the two cohorts, and 17 of 27 patients (63%) previously treated with lenalidomide had a response to ibrutinib. The overall response rate and the complete response rate also improved over time with continued therapy.

For the 75 patients who had a response at the time of data analysis, the estimated median response duration was 17.5 months (range, 0.0 to 19.6; 95% confidence interval [CI], 15.8 to not reached) (Fig. 2A and Table 3). The median time to a response was 1.9 months (range, 1.4 to 13.7), and the median time to a complete response was 5.5 months (range, 1.7 to 11.5). The estimated median progression-free survival among all treated patients was 13.9 months (range, 0.7 to 21.4; 95% CI, 7.0 to not reached) (Fig. 2B and Table 3). The median progression-free survival for patients who had a partial response as the best response was 17.5 months, and the median progression-free survival for those who had a complete response was not reached. The median overall survival for this study was also not reached (estimated overall survival rate of 58% at 18 months) (Fig. 2C and Table 3).

The efficacy data, which were further evaluated by an independent review committee, showed a response rate of 69%, with a complete response rate of 21% and a partial response rate of 48%. For 95% of patients with an investigator-assessed response, the response was confirmed by the independent review committee. The median response duration estimated by the independent review committee was 19.6 months.

Table 3. Best Response to Therapy.*

Variable	No Prior Treatment with Bortezomib (N=63)	Prior Treatment with Bortezomib (N=48)	All Patients (N=111)
Response — no. (%)			
Overall	43 (68)	32 (67)	75 (68)
Complete	12 (19)	11 (23)	23 (21)
Partial	31 (49)	21 (44)	52 (47)
None†	20 (32)	15 (31)	35 (32)
Response duration — mo			
Median	15.8	NR	17.5
95% CI	5.6–NR	NR–NR	15.8–NR
Progression-free survival — mo			
Median	7.4	16.6	13.9
95% CI	5.3–19.2	8.3–NR	7.0–NR
Overall survival — mo			
Median	NR	NR	NR
95% CI	10.0–NR	11.9–NR	13.2–NR

* Response data included only those patients who received ibrutinib and had at least one postbaseline efficacy assessment. CI denotes confidence interval, and NR not reached.
† No response was defined as stable or progressive disease.

MANTLE-CELL LYMPHOMA CELLS IN PERIPHERAL BLOOD

Ibrutinib has been shown to inhibit the adhesion of chronic lymphocytic leukemia cells[20] and mantle-cell lymphoma cells[21] in vitro, suggesting the potential to mobilize cells from tissues to the peripheral blood. The findings in a mouse model bearing human mantle-cell lymphoma cells engrafted in subcutaneously implanted human fetal

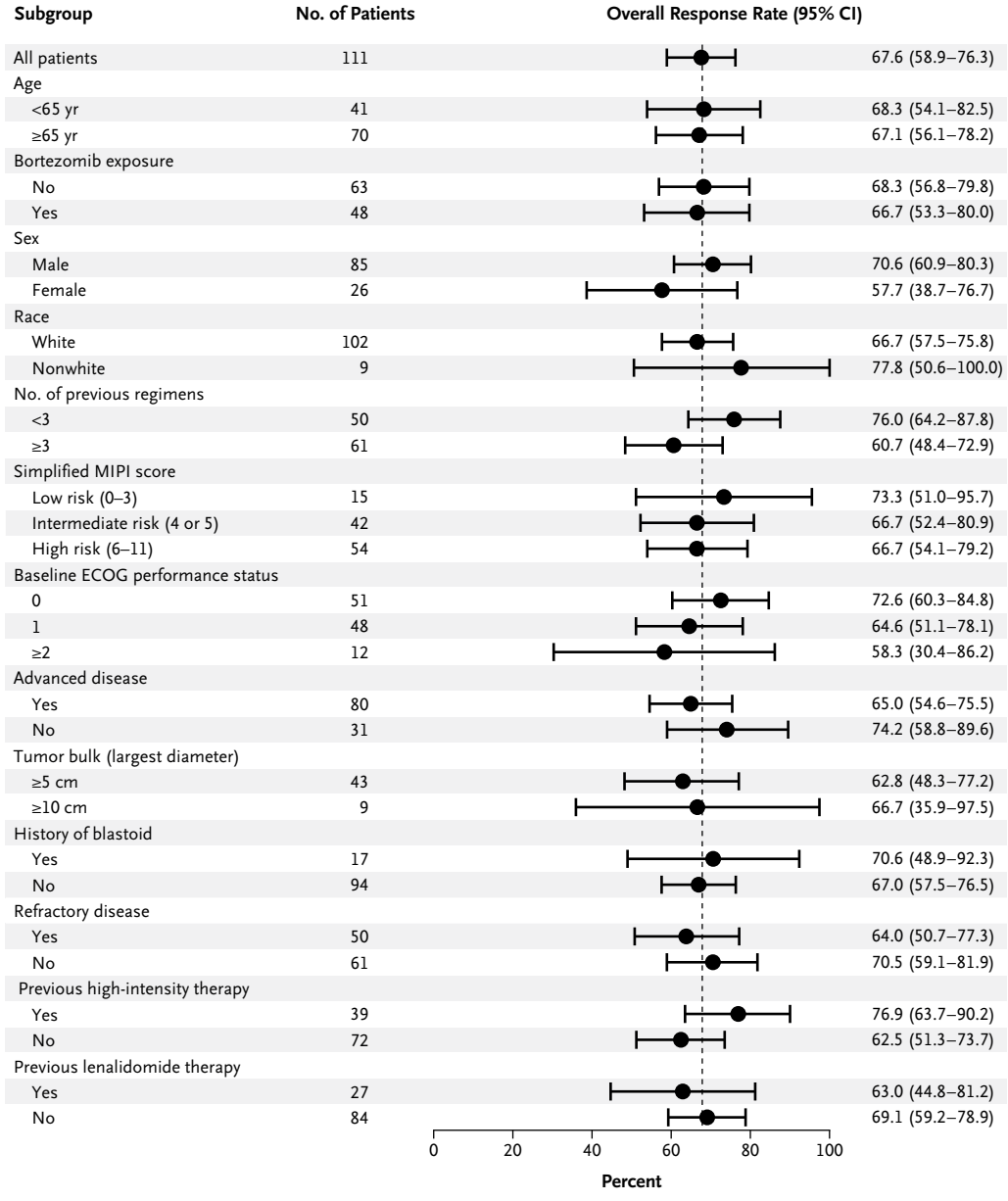

Figure 1. Overall Response Rates According to Subgroup.

This forest plot of data for all treated patients shows the overall response rate according to demographic and clinical characteristics and risk factors. The 95% confidence intervals (CIs) are based on normal approximation to the binomial distribution. The simplified Mantle-Cell Lymphoma International Prognostic Index (MIPI) score ranges from 0 to 11 and was derived with the use of the four prognostic factors of age, Eastern Cooperative Oncology Group (ECOG) performance-status score, lactate dehydrogenase level, and white-cell count at baseline. The index classifies patients as having low-, intermediate-, or high-risk disease, as defined by scores of 0 to 3, 4 or 5, and 6 to 11, respectively. ECOG performance-status scores range from 0 to 5, with 0 indicating asymptomatic, 1 symptomatic but ambulatory, and 2 symptomatic and in bed less than half the day; a score of more than 2 indicates only limited self-care and in bed more than half the day (3), completely disabled and confined to bed or chair (4), or dead (5). Advanced disease was defined as involvement of bone marrow, extranodal sites, or both; and refractory disease as a lack of at least a partial response to the last therapy before study entry. High-intensity therapy was defined as stem-cell transplantation; treatment with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD); or treatment with a hyper-CVAD–like regimen.

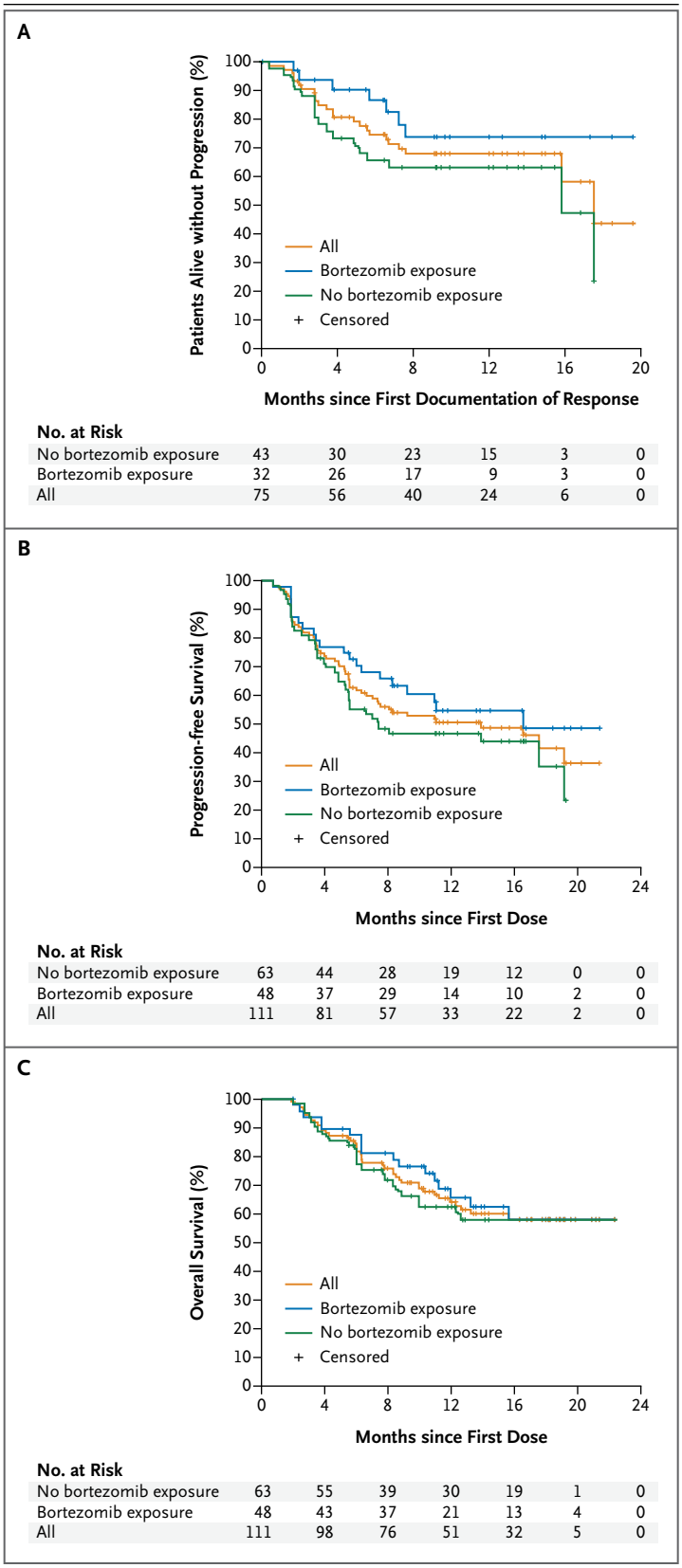

Figure 2. Duration of Response, Progression-free Survival, and Overall Survival.

Panel A shows the duration of the response (shown as the percentage of patients alive without progression of disease) for the 75 patients who had a response; the estimated median duration was 17.5 months. For the 43 patients in the cohort without prior bortezomib treatment who had a response, the estimated median duration was 15.8 months. For the 32 patients in the cohort with prior bortezomib treatment who had a response, the median duration was not reached. Panel B shows progression-free survival for all 111 treated patients, according to cohort. In this analysis, data from the 1 patient who received subsequent anticancer therapy before progression of disease were censored at the time of the start of that therapy. For all patients, the estimated median progression-free survival was 13.9 months; for the 63 patients without prior bortezomib treatment and for the 48 with prior bortezomib treatment, the estimated median progression-free survival was 7.4 and 16.6 months, respectively. Panel C shows the results of the overall-survival analysis performed at the time of the primary analysis of progression-free survival, when 70 patients (63%) were alive. The median overall survival was not reached.

bone[22] were consistent with these observations, revealing a substantial increase in mantle-cell lymphoma cells in the peripheral blood 10 days after ibrutinib treatment, followed by a decrease to near baseline by day 28 (data not shown). A total of 34% of patients had a transient increase in the absolute lymphocyte count (≥50% increase from baseline and >5000 cells per cubic millimeter) during the course of ibrutinib treatment, with the peak count occurring at a median of 4 weeks after the initiation of treatment (Fig. S2 in the Supplementary Appendix). Toward the end of the second cycle, the elevated lymphocyte levels decreased substantially and tapered off during cycle 4 or 5.

Peripheral-blood mononuclear cells obtained from patients before treatment and 1 week after treatment were subjected to triple staining for CD19, CD5, and CD3 and analyzed by means of flow cytometry. The increase in peripheral-blood lymphocytes included primarily CD19+CD5+CD3− lymphocytes (data not shown). The peripheral-blood CD19+CD5+CD3− cells showed a pattern of light-chain restriction, which was consistent with the presence of mantle-cell lymphoma cells in the peripheral blood, after 1 week of ibrutinib therapy. Ibrutinib treatment also led to a decrease in the secretion of macrophage inflammatory proteins 1α (CCL3) and 1β (CCL4), macrophage-derived che-

mokine (CCL22), and tumor necrosis factor α in most of the patients who were evaluated (Fig. S2 in the Supplementary Appendix).

DISCUSSION

This study shows the therapeutic activity of the oral BTK inhibitor ibrutinib in patients with relapsed or refractory mantle-cell lymphoma. Single-agent ibrutinib induced a high response rate (68%) and durable responses, given the relatively short period of follow-up (estimated median duration of response, 17.5 months) and the fact that patients who had a response included those who had risk factors for a poor outcome.

Safety data showed that grade 3 and 4 adverse events were uncommon with ibrutinib therapy (Table S3 in the Supplementary Appendix). Four patients had subdural hematomas during the study. The risk of subdural hematoma is known to increase with age, head trauma, falls, anticoagulant and antiplatelet therapies, and cardiovascular disease.[23] Multiple factors contributing to subdural hematoma were identified in all four patients. Only one of the four had a low platelet count that required platelet transfusions. Subsequent studies have excluded the use of warfarin in clinical trials of ibrutinib; however, other anticoagulant agents are permitted. Randomized trials are required to determine whether bleeding associated with ibrutinib is increased in this patient population.

With respect to efficacy, a response rate of 68% and a complete response rate of 21% (complete response rate of 37% among the 51 patients who had been receiving treatment the longest) are high response rates for a single agent in this patient population. Previously, such a high rate of complete response in this population with substantial previous treatment has been achieved only with intensive chemotherapy regimens, such as ESHAP (etoposide, methylprednisolone sodium succinate, cytarabine, and cisplatin),[24] MINE (mesna, ifosfamide, mitoxantrone [Novantrone], and etoposide),[25] hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone),[26] and R-ICE (rituximab, ifosfamide, carboplatin, and etoposide),[27] all of which are myelotoxic. In contrast, conventional-dose salvage regimens achieve only modest response rates and short remissions.[28,29]

In conclusion, the BTK inhibitor ibrutinib is a highly active new agent showing durable single-agent activity in relapsed and refractory mantle-cell lymphoma. The favorable toxicity profile suggests that ibrutinib provides the opportunity for treatment with less intensive and more effective regimens than those currently available.

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APPENDIX

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REFERENCES

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma: the Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-18.
2. Romaguera JE, Fayad LE, Feng L, et al. Ten-year follow-up after intense chemoimmunotherapy with rituximab-hyperCVAD alternating with rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. Br J Haematol 2010;150:200-8. [Erratum, Br J Haematol 2010;151:111.]
3. Wiestner A. Targeting B-cell receptor signaling for anticancer therapy: the Bruton's tyrosine kinase inhibitor ibrutinib induces impressive responses in B-cell malignancies. J Clin Oncol 2013;31:128-30.
4. Davis RE, Ngo VN, Lenz G, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. Nature 2010;463:88-92.
5. Kenkre VP, Kahl BS. The future of B-cell lymphoma therapy: the B-cell receptor and its downstream pathways. Curr Hematol Malig Rep 2012;7:216-20.
6. Buggy JJ, Elias L. Bruton tyrosine kinase (BTK) and its role in B-cell malignancy. Int Rev Immunol 2012;31:119-32. [Erratum, Int Rev Immunol 2012;31:428.]
7. Rushworth SA, Bowles KM, Barrera LN, Murray MY, Zaitseva L, MacEwan DJ. BTK inhibitor ibrutinib is cytotoxic to myeloma and potently enhances bortezomib and lenalidomide activities through NF-κB. Cell Signal 2013;25:106-12.
8. Harrison C. Trial watch: BTK inhibitor shows positive results in B cell malignancies. Nat Rev Drug Discov 2012;11:96.
9. Alinari L, Christian B, Baiocchi RA. Novel targeted therapies for mantle cell lymphoma. Oncotarget 2012;3:203-11.
10. Hadzidimitriou A, Agathangelidis A, Darzentas N, et al. Is there a role for antigen selection in mantle cell lymphoma? Immunogenetic support from a series of 807 cases. Blood 2011;118:3088-95.
11. Rinaldi A, Kwee I, Taborelli M, et al. Genomic and expression profiling identifies the B-cell associated tyrosine kinase Syk as a possible therapeutic target in mantle cell lymphoma. Br J Haematol 2006;132:303-16.
12. Chang BY, Francesco M, Steggerda S, et al. Ibrutinib inhibits malignant cell adhesion and migration and reduces tumor burden in lymph node and bone marrow in a murine model of mantle cell dissemination and progression. Presented at the American Association for Cancer Research Annual Meeting 2013, Washington, DC, April 6–10, 2013. abstract.
13. Herman SE, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. Blood 2011;117:6287-96.
14. 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.
15. 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.
16. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-86.
17. Cancer Therapy Evaluation Program CTCfAE, version 4.0. May 28, 2009 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_30).
18. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989;10:1-10.
19. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
20. de Rooij MF, Kuil A, Geest CR, et al. The clinically active BTK inhibitor PCI-32765 targets B-cell receptor- and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. Blood 2012;119:2590-4.
21. Chang BY, Francesco M, Magadala P, et al. Egress of CD19$^+$CD5$^+$ cells into peripheral blood following treatment with the Bruton tyrosine kinase inhibitor, PCI-32765, in mantle cell lymphoma patients. Blood 2011;118:436. abstract.
22. Wang M, Zhang L, Han X, et al. A severe combined immunodeficient-hu in vivo mouse model of human primary mantle cell lymphoma. Clin Cancer Res 2008;14:2154-60.
23. Aspegren OP, Åstrand R, Lundgren MI, Romner B. Anticoagulation therapy a risk factor for the development of chronic subdural hematoma. Clin Neurol Neurosurg 2012 November 2 (Epub ahead of print).
24. Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP — an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol 1994;12:1169-76.
25. Rodriguez MA, Cabanillas FC, Velasquez W, et al. Results of a salvage treatment program for relapsing lymphoma: MINE consolidated with ESHAP. J Clin Oncol 1995;13:1734-41.
26. Wang M, Fayad L, Cabanillas F, et al. Phase 2 trial of rituximab plus hyper-CVAD alternating with rituximab plus methotrexate-cytarabine for relapsed or refractory aggressive mantle cell lymphoma. Cancer 2008;113:2734-41.
27. Vose J, Sneller V. Outpatient regimen rituximab plus ifosfamide, carboplatin and etoposide (R-ICE) for relapsed non-Hodgkin's lymphoma. Ann Oncol 2003;14:Suppl 1:i17-i20. [Erratum, Ann Oncol 2004;15:541.]
28. Hess G, Herbrecht R, Romaguera J, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. J Clin Oncol 2009;27:3822-9.
29. Fisher RI, Bernstein SH, Kahl BS, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol 2006;24:4867-74.