

ORIGINAL ARTICLE

Ibrutinib plus Bendamustine and Rituximab in Untreated Mantle-Cell Lymphoma

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ABSTRACT

BACKGROUND

Ibrutinib, a Bruton's tyrosine kinase inhibitor, may have clinical benefit when administered in combination with bendamustine and rituximab and followed by rituximab maintenance therapy in older patients with untreated mantle-cell lymphoma.

METHODS

We randomly assigned patients 65 years of age or older to receive ibrutinib (560 mg, administered orally once daily until disease progression or unacceptable toxic effects) or placebo, plus six cycles of bendamustine (90 mg per square meter of body-surface area) and rituximab (375 mg per square meter). Patients with an objective response (complete or partial response) received rituximab maintenance therapy, administered every 8 weeks for up to 12 additional doses. The primary end point was progression-free survival as assessed by the investigators. Overall survival and safety were also assessed.

RESULTS

Among 523 patients, 261 were randomly assigned to receive ibrutinib and 262 to receive placebo. At a median follow-up of 84.7 months, the median progression-free survival was 80.6 months in the ibrutinib group and 52.9 months in the placebo group (hazard ratio for disease progression or death, 0.75; 95% confidence interval, 0.59 to 0.96; $P=0.01$). The percentage of patients with a complete response was 65.5% in the ibrutinib group and 57.6% in the placebo group ($P=0.06$). Overall survival was similar in the two groups. The incidence of grade 3 or 4 adverse events during treatment was 81.5% in the ibrutinib group and 77.3% in the placebo group.

CONCLUSIONS

Ibrutinib treatment in combination with standard chemoimmunotherapy significantly prolonged progression-free survival. The safety profile of the combined therapy was consistent with the known profiles of the individual drugs. (Funded by Janssen Research and Development and Pharmacyclis; SHINE ClinicalTrials.gov number, NCT01776840.)

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*A complete list of the SHINE trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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MANTLE-CELL LYMPHOMA IS A SUBTYPE of B-cell non-Hodgkin's lymphoma and is considered to be incurable.¹ Most patients with mantle-cell lymphoma are older and are unsuitable candidates for aggressive treatment or autologous stem-cell transplantation, a situation that results in unsatisfactory clinical outcomes.²⁻⁵ Current guidelines recommend less-aggressive first-line therapy in older patients, such as bendamustine plus rituximab, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), or VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone).⁶⁻⁸ Combination therapy with bendamustine and rituximab has become one of the most-used first-line regimens for mantle-cell lymphoma,⁹ given evidence showing longer progression-free survival with this combination than with R-CHOP (35.4 vs. 22.1 months)¹⁰ and a better safety profile.^{10,11} Two independent observational studies^{9,12} showed significantly prolonged progression-free survival or overall survival with the addition of rituximab maintenance therapy after induction therapy with bendamustine and rituximab, in contrast to the results of a prospective randomized trial.¹³ The findings of these observational studies are aligned with the benefits that have been observed with rituximab maintenance therapy after R-CHOP.¹⁴

Single-agent ibrutinib, an oral Bruton's tyrosine kinase (BTK) inhibitor, has transformed the care of patients with relapsed or refractory mantle-cell lymphoma with its durable activity, particularly when it is used at first relapse.¹⁵⁻¹⁷ A phase 1b study involving 17 patients with untreated, relapsed, or refractory mantle-cell lymphoma showed that the addition of ibrutinib to bendamustine and rituximab therapy was safe and efficacious; 76% of the patients had a complete response.¹⁸ Here, we report the primary results of the international, randomized, double-blind, phase 3 SHINE trial, in which we evaluated the combination of ibrutinib with bendamustine plus rituximab and rituximab maintenance therapy, as compared with placebo with bendamustine plus rituximab and rituximab maintenance therapy, in older patients with untreated mantle-cell lymphoma.

METHODS

PATIENTS

We enrolled eligible patients 65 years of age or older who had a centrally confirmed diagnosis

of mantle-cell lymphoma with cyclin C1 overexpression or translocation breakpoints at t(11;14); previously untreated, documented stage II to IV disease; at least one measurable site of disease that was at least 1.5 cm in the longest diameter; an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a scale ranging from 0 to 5, with higher numbers indicating greater disability); and adequate organ function. Patients were excluded if stem-cell transplantation was planned or if they had known central nervous system involvement, had a history of stroke or intracranial hemorrhage within 6 months before randomization, were receiving anticoagulation with warfarin or equivalent vitamin K antagonists or treatment with strong CYP3A inhibitors, or had had clinically significant cardiovascular disease within 6 months before screening. Complete eligibility criteria are provided in the trial protocol, which is available with the full text of this article at NEJM.org.

TRIAL DESIGN AND TREATMENTS

Randomization was stratified according to the simplified Mantle Cell Lymphoma International Prognostic Index (MIPI) score category (low risk [score, 0 to 3], intermediate risk [4 or 5], or high risk [6 to 11]).¹⁹ Patients were randomly assigned in a 1:1 ratio to receive either ibrutinib, at a dose of 560 mg administered orally once daily, or matching placebo. Ibrutinib or placebo was administered in combination with bendamustine, at a dose of 90 mg per square meter of body-surface area (on days 1 and 2 of each cycle, which was defined as 28 days), and rituximab, at a dose of 375 mg per square meter (on day 1 of each cycle), which were administered every 4 weeks for six cycles. After induction treatment, patients with an objective response (defined as a complete or partial response) continued to receive ibrutinib or placebo daily plus rituximab maintenance therapy at a dose of 375 mg per square meter, administered every 8 weeks for up to 12 additional doses. Patients with a best response of stable disease after induction treatment could continue to receive ibrutinib or placebo only. Ibrutinib or placebo was administered until the occurrence of progressive disease or unacceptable toxic effects. Supportive care, including the use of prophylactic anti-infective agents, was given at the discretion of the investigator.



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END POINTS AND ASSESSMENTS

The primary end point, progression-free survival as assessed by the investigators, was defined as the time from randomization to disease progression or death, whichever occurred first. Disease progression was assessed according to the 2007 Revised Response Criteria for Malignant Lymphoma.²⁰

Secondary end points included complete response, the time to next treatment, overall survival, objective response, undetectable minimal residual disease (<5 in 10^4 cells as assessed by flow cytometry in patients with a complete response), and the time to worsening as assessed with the Lymphoma subscale of the Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) instrument, which measures disease-related symptoms and concerns.²¹ Safety was also evaluated.

Efficacy was assessed by means of computed tomographic scans of the neck, chest, abdomen, pelvis, and any other location where disease was present or by means of magnetic resonance imaging if the sites of disease could not be adequately imaged by computed tomography. Radiologic assessments were performed at screening, every 12 weeks during the first 12 months after the initiation of ibrutinib or placebo, and then every 16 weeks until disease progression. A positron-emission tomographic scan was required for the confirmation of a complete response. In addition, patients with bone marrow involvement at baseline were required to undergo a repeat bone marrow evaluation at the time of complete response, and an endoscopy was required in order to confirm a complete response in patients with known gastrointestinal involvement at baseline. Safety was assessed throughout the trial and up to 30 days after the last dose of ibrutinib or placebo. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.03.

TRIAL OVERSIGHT

The trial was designed by representatives of Janssen Research and Development in collaboration with the academic investigators and Pharmacyclics; both companies funded the trial. The trial protocol and all amendments were approved by the appropriate ethics committees at each trial site. The trial was conducted in accordance with the Guidelines on Good Clinical Practice from the International Conference on

Harmonisation, the principles of the Declaration of Helsinki, and all other applicable regulations. Before enrollment, all the patients provided written informed consent to participate in the trial.

All the investigators were responsible for the collection of data, which were analyzed by Janssen Research and Development. An independent data and safety monitoring committee performed regular assessments of the efficacy and safety data. The authors had full access to the data, vouch for the accuracy and completeness of the data, and attest that the trial was conducted in accordance with the protocol and all amendments. All the authors contributed to the writing of the manuscript, representatives of Pharmacyclics reviewed the manuscript, and medical writing assistance was funded by Janssen Research and Development.

STATISTICAL ANALYSIS

We calculated the sample size on the basis of the primary end point, progression-free survival. We estimated that the enrollment of approximately 520 patients would be necessary to observe 265 events of disease progression or death, which would provide the trial with approximately 77% power to detect a 30% lower risk of progression or death in the ibrutinib group than in the placebo group at a one-sided significance level of 0.025. The O'Brien–Fleming boundaries were used for a superiority test of efficacy in two interim analyses and one primary analysis. The significance boundary for superiority in the primary analysis was a *P* value of less than 0.023. Progression-free survival was estimated with the use of the Kaplan–Meier method. The hazard ratio and associated two-sided 95% confidence interval were calculated by a stratified Cox proportional-hazards model. If the primary end point reached statistical significance, tests of secondary end points were to be performed at a two-sided significance level of 0.05 in a sequential hierarchical manner on the basis of a closed testing procedure.

Overall survival and the time to next treatment were estimated with the use of the Kaplan–Meier method, and a stratified log-rank test was used to compare the trial groups. For the percentages of patients with a complete response, undetectable minimal residual disease, and an objective response, the between-group differences were assessed with the use of the Cochran–Mantel–Haenszel test.

All the efficacy end points were analyzed in the intention-to-treat population (defined as all the patients who had undergone randomization), and safety was assessed in all the patients who received at least one dose of ibrutinib or placebo. The full statistical analysis plan is available with the protocol.

RESULTS

PATIENTS AND TREATMENT

From May 2013 through November 2014, a total of 523 patients from 183 trial sites in North America, South America, Europe, and the Asia-Pacific region underwent randomization (261 patients in the ibrutinib group and 262 in the placebo group), and 519 patients received at least one dose of ibrutinib or placebo (Fig. S1 in the Supplementary Appendix). The median age of the patients was 71 years (range, 65 to 87). The characteristics of the patients at baseline were well balanced in the two groups (Table 1). Although the trial participants were generally representative of the global population of patients with newly diagnosed mantle-cell lymphoma, Black patients were underrepresented in this trial in the United States (2% of the U.S. patients in this trial vs. a published incidence of 4%) (Table S1).

At the data-cutoff date for the primary analysis (June 30, 2021), the median follow-up among all the patients was 84.7 months (7.1 years; range, 0.1 to 97.5 months). In the ibrutinib group, 209 patients (80.7%) received all six cycles of induction therapy with bendamustine and rituximab, and 206 patients (78.9%) received at least one cycle of rituximab maintenance therapy. In the placebo group, 215 patients (82.7%) received all six cycles of induction therapy with bendamustine and rituximab, and 210 patients (80.2%) received at least one cycle of rituximab maintenance therapy. The median duration of the treatment period was 24.1 months (range, 0.2 to 95.2) with ibrutinib and 34.1 months (range, 0.0 to 97.5) with placebo, with a median relative dose intensity of 95% (range, 20 to 100) and 98% (range, 11 to 100), respectively. A total of 54% of the patients received prophylactic anti-infective agents.

As of the data-cutoff date, 220 patients (84.3%) in the ibrutinib group and 201 (76.7%) in the placebo group had discontinued all trial treatments. The most common reasons for dis-

continuation were an adverse event (in 39.5% of the patients in the ibrutinib group and in 24.0% of those in the placebo group), progressive disease or relapse (in 10.7% and 34.7%, respectively), withdrawal of consent (in 13.0% and 8.0%), and death (in 10.0% and 5.7%).

EFFICACY

A total of 116 patients (44.4%) in the ibrutinib group and 152 (58.0%) in the placebo group had disease progression or died as of the data-cutoff date. The median progression-free survival as assessed by the investigators was 80.6 months (95% confidence interval [CI], 61.9 to not evaluable) in the ibrutinib group, as compared with 52.9 months (95% CI, 43.7 to 71.0) in the placebo group (stratified hazard ratio for disease progression or death, 0.75; 95% CI, 0.59 to 0.96; $P=0.01$) (Fig. 1A). The progression-free survival benefit with ibrutinib was observed across most, but not all, prespecified subgroups (Figs. 2 and S2). In particular, patients with a simplified MIPI score category indicating high risk and those with *TP53* mutations did not have a clear benefit.

A complete response, as assessed by the investigators, was observed in 171 patients (65.5%) in the ibrutinib group and in 151 (57.6%) in the placebo group ($P=0.06$) (Table S2). The percentage of patients with an objective response was similar in the two groups (89.7% in the ibrutinib group and 88.5% in the placebo group). Undetectable minimal residual disease in peripheral blood or bone marrow was observed in 162 of 261 patients (62.1%) in the ibrutinib group and in 148 of 262 patients (56.5%) in the placebo group.

As of the data-cutoff date, 104 patients (39.8%) in the ibrutinib group and 107 (40.8%) in the placebo group had died. Overall survival was similar in the two groups (hazard ratio for death, 1.07; 95% CI, 0.81 to 1.40) (Fig. 1B). Overall survival at 7 years was 55.0% in the ibrutinib group and 56.8% in the placebo group. Causes of death throughout the entire trial period are listed in Table S3. Death due to disease progression occurred in 30 patients (11.5%) in the ibrutinib group and in 54 (20.6%) in the placebo group. Death due to progression or to adverse events during the treatment period was reported in 58 patients (22.2%) in the ibrutinib group and in 70 (26.7%) in the placebo group. During the post-treatment follow-up period, 46 patients

Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Ibrutinib Group (N = 261)	Placebo Group (N = 262)
Age		
Median (range) — yr	71 (65–86)	71 (65–87)
≥70 yr — no. (%)	162 (62.1)	154 (58.8)
≥75 yr — no. (%)	74 (28.4)	82 (31.3)
Male sex — no. (%)	178 (68.2)	186 (71.0)
Race — no. (%)†		
White	199 (76.2)	206 (78.6)
Black	2 (0.8)	1 (0.4)
Asian	47 (18.0)	42 (16.0)
Other or multiple	3 (1.1)	4 (1.5)
Not reported	10 (3.8)	9 (3.4)
Median time from initial diagnosis to randomization (range) — mo	1.4 (0.2–116.1)	1.5 (0.1–66.1)
ECOG performance-status score — no. (%)‡		
0	134 (51.3)	141 (53.8)
1 or 2	127 (48.7)	121 (46.2)
Disease stage — no. (%)		
II	9 (3.4)	14 (5.3)
III	19 (7.3)	22 (8.4)
IV	233 (89.3)	226 (86.3)
Simplified MIPI score category — no. (%)		
Low risk	44 (16.9)	46 (17.6)
Intermediate risk	124 (47.5)	129 (49.2)
High risk	93 (35.6)	87 (33.2)
Bone marrow involvement — no. (%)		
Yes	198 (75.9)	200 (76.3)
No	63 (24.1)	62 (23.7)
Histologic features — no. (%)		
Blastoid or pleomorphic	19 (7.3)	26 (9.9)
Nonblastoid or nonpleomorphic	211 (80.8)	201 (76.7)
Unknown	31 (11.9)	35 (13.4)
Extranodal disease — no. (%)		
Yes	234 (89.7)	226 (86.3)
No	27 (10.3)	36 (13.7)
Tumor bulk — no. (%)		
<5 cm in largest diameter	165 (63.2)	163 (62.2)
≥5 cm in largest diameter	95 (36.4)	98 (37.4)
Unknown	1 (0.4)	1 (0.4)
TP53 status — no. (%)		
Nonmutated	114 (43.7)	105 (40.1)
Mutated	26 (10.0)	24 (9.2)
Unknown	121 (46.4)	133 (50.8)

Table 1. (Continued.)

* The intention-to-treat population included all the patients who underwent randomization. All patients in the trial also received bendamustine and rituximab. Randomization was stratified according to the simplified Mantle Cell Lymphoma International Prognostic Index (MIPI) score (low vs. intermediate vs. high risk).¹⁹ Scores range from 0 to 11, with a score of 0 to 3 indicating low risk, a score of 4 or 5 indicating intermediate risk, and a score of 6 or higher indicating high risk. Percentages may not total 100 because of rounding.

† Race was determined by the investigators.

‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers indicating greater disability. A score of 0 indicates that the patient is fully active and able to carry on all predisease performance without restriction, a score of 1 that the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, and a score of 2 that the patient is ambulatory and capable of all self-care but is unable to carry out any work activities. Three patients in the placebo group had an ECOG performance-status score of 2 (which was outside the protocol specification). In one case, there was a randomization error and the patient was not treated in the trial. Two patients had a score of 1 at randomization but had a score of 2 on day 1 of the first cycle (baseline).

(17.6%) in the ibrutinib group and 37 (14.1%) in the placebo group died. A post hoc analysis of cause-specific survival that included only deaths due to disease progression or adverse events during treatment showed a hazard ratio of 0.88 (95% CI, 0.62 to 1.24) (Fig. S3).

Second-line anticancer therapy was received by 52 patients (19.9%) in the ibrutinib group and by 106 (40.5%) in the placebo group; 6 of the 52 patients (12%) in the ibrutinib group received second-line ibrutinib and 41 of the 106 (39%) in the placebo group received a second-line BTK inhibitor (34 patients were treated with ibrutinib, 4 with acalabrutinib, and 3 with zanubrutinib) (Table S4). Data on the time to the next treatment are reported in Figure S4.

SAFETY

Adverse events of grade 3 or 4 during the treatment period occurred in 81.5% of the patients in the ibrutinib group and in 77.3% of those in the placebo group. The most common grade 3 or 4 adverse events (defined as those that occurred in $\geq 10\%$ of the patients in either group) were neutropenia (in 47.1% of the patients in the ibrutinib group and in 48.1% of those in the placebo group), pneumonia (in 20.1% and 14.2%, respectively), lymphopenia (in 16.2% and 11.9%), anemia (in 15.4% and 8.8%), thrombocytopenia (in 12.7% and 13.1%), rash (in 12.0% and 1.9%), and leukopenia (in 10.0% and 11.2%) (Table 2). Adverse events that occurred during the first 6 months (induction period) and from 6 months onward (maintenance period) are listed in Table S5.

Of the adverse events of clinical interest for BTK inhibitors, atrial fibrillation was reported in 13.9% of the patients in the ibrutinib group and in 6.5% of those in the placebo group; hyperten-

sion in 13.5% and 11.2%, respectively; diarrhea in 46.3% and 36.9%; major hemorrhage in 5.8% and 4.2%; and arthralgia in 17.4% and 16.9%. Pneumocystis pneumonia was noted in 1 patient in each group, and aspergillus infection was diagnosed in 4 patients in the ibrutinib group and in 1 patient in the placebo group.

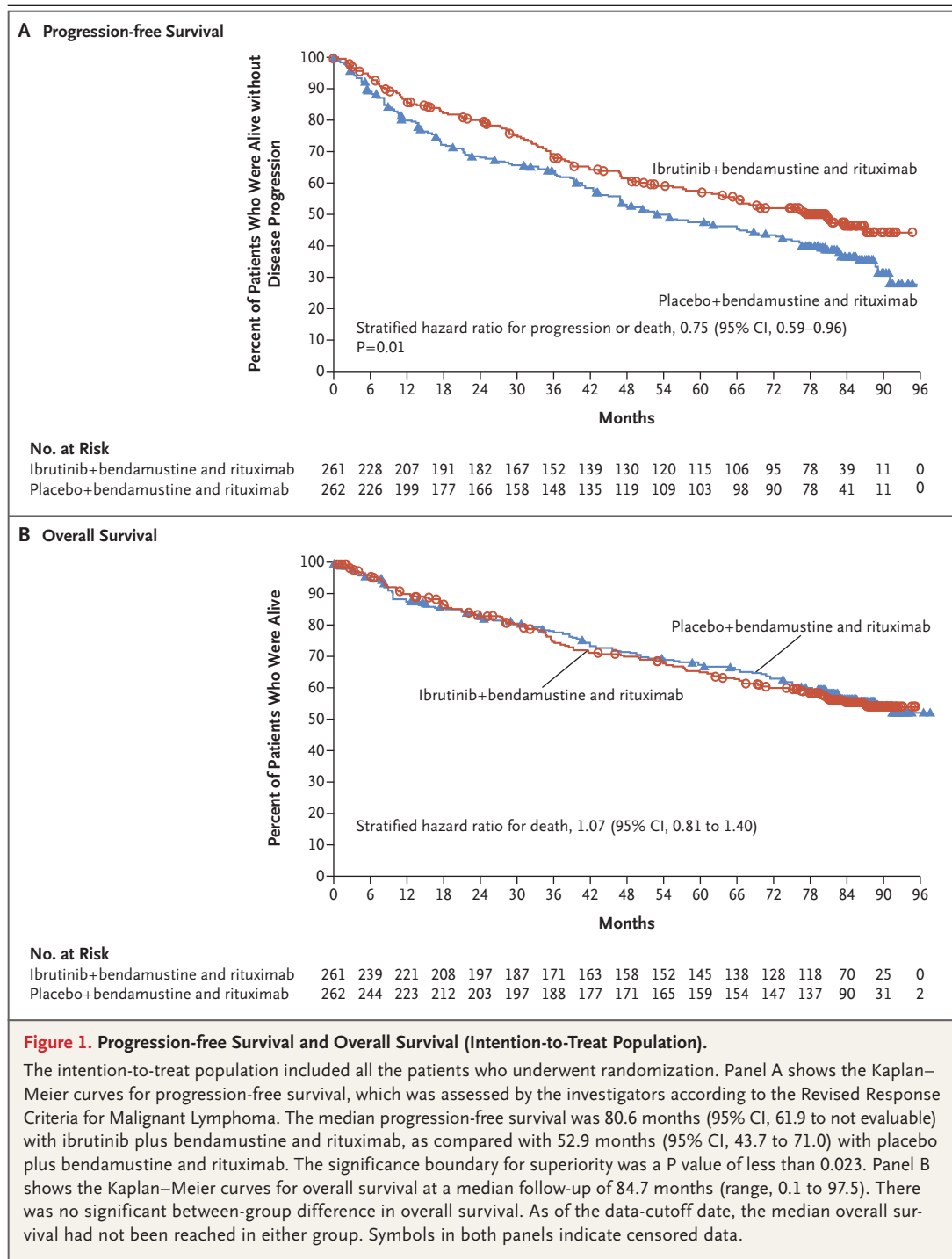
Adverse events during the treatment period were the primary cause of death in 28 patients (10.7%) in the ibrutinib group and in 16 (6.1%) in the placebo group (Table 3). Among these events, death due to cardiac disorders occurred in 3 patients in the ibrutinib group and in 5 in the placebo group. During the entire trial period, second primary cancers were observed in 20.8% of the patients in the ibrutinib group and in 18.8% of those in the placebo group; myelodysplastic syndrome or acute myeloid leukemia was observed in 2 patients in the ibrutinib group and in 3 in the placebo group. There were 5 deaths due to coronavirus disease 2019; of these deaths, 3 in the ibrutinib group occurred during the treatment period, and 2 in the placebo group occurred after the treatment period.

PATIENT-REPORTED OUTCOMES

No significant between-group difference was observed in the time to worsening as assessed on the Lymphoma subscale of the FACT-Lym instrument (hazard ratio, 1.02; 95% CI, 0.83 to 1.26). Details are provided in Figure S5.

DISCUSSION

In the SHINE trial, the addition of once-daily ibrutinib treatment to bendamustine plus rituximab and rituximab maintenance therapy led to a significant prolongation of 2.3 years in the



median progression-free survival (6.7 years, vs. 4.4 years in the placebo group) among older patients with previously untreated mantle-cell lymphoma. This result was longer than published data with the commonly used regimens of R-CHOP, VR-CAP, or bendamustine plus ritux-

imab alone, for which the median progression-free survival was 1.5 to 3.5 years.^{9,10,22-24} The separation of the progression-free survival curves occurred within the first year after the initiation of treatment, and the benefit was durable throughout the median follow-up of 7 years.

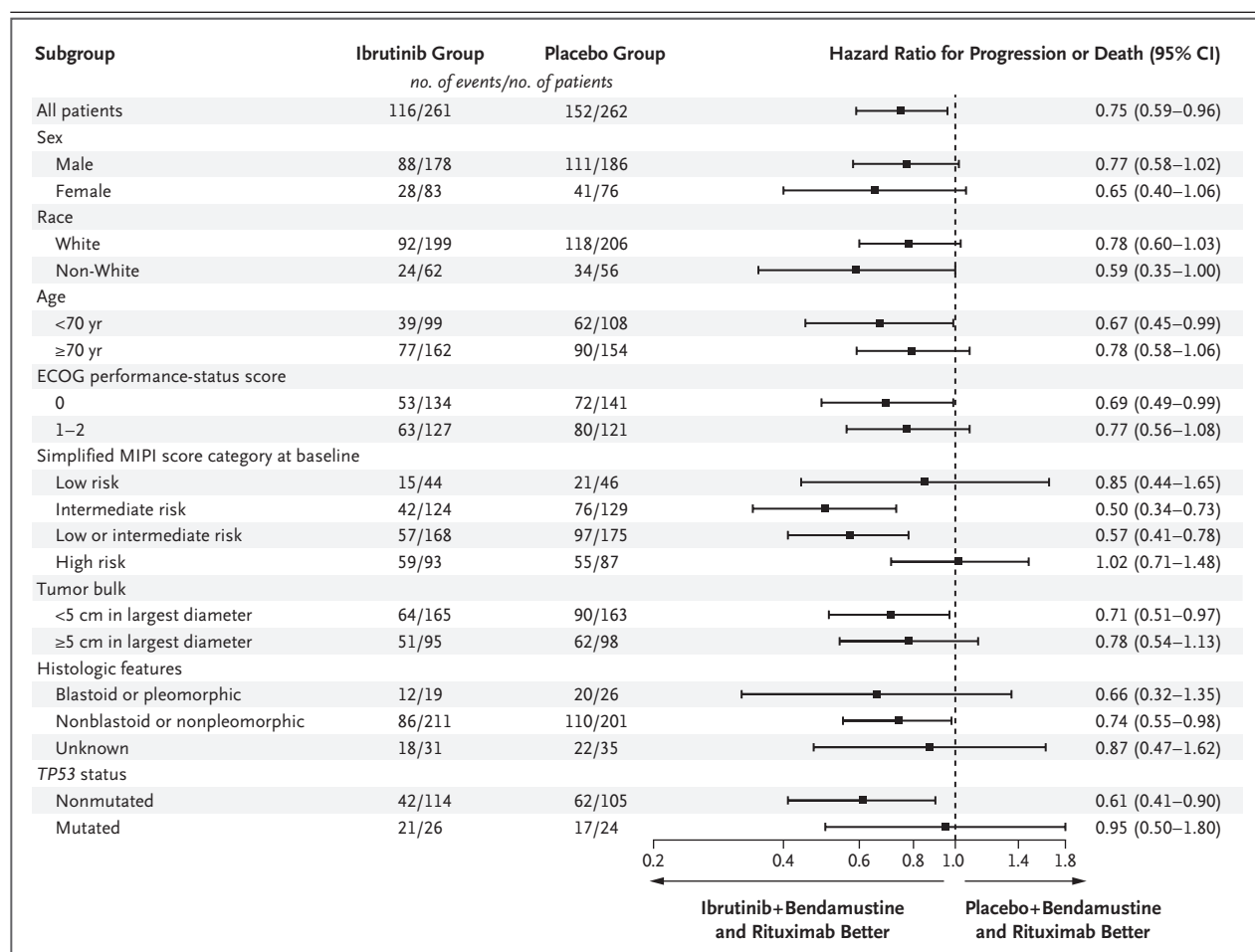


Figure 2. Subgroup Analysis of Progression-free Survival (Intention-to-Treat Population).

Progression-free survival was assessed by the investigators according to the Revised Response Criteria for Malignant Lymphoma. Race was determined by the investigators. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers indicating greater disability. A score of 0 indicates that the patient is fully active and able to carry on all predisease performance without restriction, a score of 1 that the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, and a score of 2 that the patient is ambulatory and capable of all self-care but is unable to carry out any work activities. Scores on the simplified Mantle Cell Lymphoma International Prognostic Index (MIPI) range from 0 to 11, with a score of 0 to 3 indicating low risk, a score of 4 or 5 indicating intermediate risk, and a score of 6 or higher indicating high risk. Tumor bulk was assessed on the largest diameter.

Patients with a simplified MIPI score category indicating high risk did not have a clear benefit in the ibrutinib group as compared with the placebo group. Blastoid or pleomorphic histologic features or TP53 mutation were poor risk factors in both trial groups. These observations will need to be assessed further because the present trial was not powered to compare progression-free survival in these subgroups.

Among the secondary end points, the higher percentage of patients with a complete response (65.5%) that was observed in the ibrutinib group

was not significant. The duration of response was longer in the ibrutinib group than in the placebo group, probably owing to disease control with ongoing ibrutinib treatment after the induction period. Overall survival was similar in the two trial groups, with the total percentage of deaths due to progressive disease or adverse events being slightly lower in the ibrutinib group (22.2% of patients) than in the placebo group (26.7%). Specifically, more deaths were due to adverse events in the ibrutinib group than in the placebo group (in 10.7% vs. 6.1% of the pa-

Table 2. Adverse Events during Treatment That Occurred in at Least 10% of the Patients in Either Group (Safety Population).*

System Organ Class and Preferred Term	Ibrutinib Group (N = 259)		Placebo Group (N = 260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	<i>number of patients (percent)</i>			
Any adverse event	259 (100)	211 (81.5)	257 (98.8)	201 (77.3)
Infection or infestation				
Pneumonia	87 (33.6)	52 (20.1)	61 (23.5)	37 (14.2)
Upper respiratory tract infection	71 (27.4)	4 (1.5)	68 (26.2)	4 (1.5)
Bronchitis	38 (14.7)	6 (2.3)	38 (14.6)	6 (2.3)
Urinary tract infection	38 (14.7)	11 (4.2)	33 (12.7)	6 (2.3)
Sinusitis	28 (10.8)	2 (0.8)	34 (13.1)	3 (1.2)
Conjunctivitis	26 (10.0)	0	6 (2.3)	0
Nasopharyngitis	24 (9.3)	0	28 (10.8)	0
Herpes zoster infection	15 (5.8)	2 (0.8)	28 (10.8)	10 (3.8)
Gastrointestinal disorder				
Diarrhea	120 (46.3)	18 (6.9)	96 (36.9)	10 (3.8)
Nausea	107 (41.3)	6 (2.3)	107 (41.2)	3 (1.2)
Vomiting	58 (22.4)	7 (2.7)	48 (18.5)	0
Constipation	51 (19.7)	0	68 (26.2)	1 (0.4)
Abdominal pain	26 (10.0)	6 (2.3)	30 (11.5)	2 (0.8)
General disorder or administration-site condition				
Pyrexia	95 (36.7)	5 (1.9)	83 (31.9)	5 (1.9)
Fatigue	79 (30.5)	8 (3.1)	77 (29.6)	6 (2.3)
Peripheral edema	51 (19.7)	3 (1.2)	42 (16.2)	0
Asthenia	30 (11.6)	2 (0.8)	25 (9.6)	3 (1.2)
Chills	18 (6.9)	1 (0.4)	39 (15.0)	1 (0.4)
Blood or lymphatic system disorder†				
Neutropenia	133 (51.4)	122 (47.1)	136 (52.3)	125 (48.1)
Anemia	87 (33.6)	40 (15.4)	64 (24.6)	23 (8.8)
Thrombocytopenia	93 (35.9)	33 (12.7)	69 (26.5)	34 (13.1)
Leukopenia	47 (18.1)	26 (10.0)	44 (16.9)	29 (11.2)
Lymphopenia	47 (18.1)	42 (16.2)	35 (13.5)	31 (11.9)
Skin or subcutaneous tissue disorder				
Rash	98 (37.8)	31 (12.0)	57 (21.9)	5 (1.9)
Pruritus	46 (17.8)	6 (2.3)	56 (21.5)	1 (0.4)
Maculopapular rash	26 (10.0)	12 (4.6)	10 (3.8)	3 (1.2)
Respiratory, thoracic, or mediastinal disorder				
Cough	77 (29.7)	1 (0.4)	85 (32.7)	2 (0.8)
Epistaxis	31 (12.0)	0	12 (4.6)	0
Dyspnea	26 (10.0)	2 (0.8)	46 (17.7)	5 (1.9)

Table 2. (Continued.)

System Organ Class and Preferred Term	Ibrutinib Group (N=259)		Placebo Group (N=260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	<i>number of patients (percent)</i>			
Metabolism or nutrition disorder				
Decreased appetite	56 (21.6)	4 (1.5)	36 (13.8)	3 (1.2)
Hypokalemia	39 (15.1)	19 (7.3)	31 (11.9)	14 (5.4)
Musculoskeletal or connective-tissue disorder				
Arthralgia	45 (17.4)	3 (1.2)	44 (16.9)	0
Back pain	36 (13.9)	2 (0.8)	37 (14.2)	1 (0.4)
Myalgia	31 (12.0)	0	30 (11.5)	3 (1.2)
Nervous system disorder: headache	33 (12.7)	0	40 (15.4)	1 (0.4)
Vascular disorder: hypertension	35 (13.5)	22 (8.5)	29 (11.2)	15 (5.8)
Injury, poisoning, or procedural complication: infusion-related reaction	21 (8.1)	2 (0.8)	30 (11.5)	5 (1.9)
Cardiac disorder: atrial fibrillation	36 (13.9)	10 (3.9)	17 (6.5)	2 (0.8)
Psychiatric disorder: insomnia	29 (11.2)	0	28 (10.8)	0
Investigations: decreased weight	26 (10.0)	3 (1.2)	20 (7.7)	1 (0.4)

* An adverse event during treatment was defined as any event that occurred after the first dose of ibrutinib or placebo, through the treatment phase, or during the 30 days after the last dose of ibrutinib or placebo or until subsequent anti-cancer therapy, whichever occurred first; or as any event that was considered by the investigators to be related to ibrutinib or placebo regardless of the start date of the event; or as any event that was present at baseline but that worsened in severity or was subsequently considered by the investigator to be related to ibrutinib or placebo. The safety population included all the patients who received at least one dose of ibrutinib or placebo.

† Preferred terms that were reported by the investigators were combined as follows: neutropenia ("neutropenia" and "neutrophil count decreased"), anemia ("anemia" and "hemoglobin decreased"), thrombocytopenia ("thrombocytopenia" and "platelet count decreased"), leukopenia ("leukopenia" and "white-cell count decreased"), and lymphopenia ("lymphopenia" and "lymphocyte count decreased").

tients), and more deaths were due to progressive mantle-cell lymphoma in the placebo group (11.5% of the patients in the ibrutinib group vs. 20.6% of those in the placebo group). The incidence of death from competing risks that occurred during the post-treatment follow-up period was slightly higher in the ibrutinib group than in the placebo group (17.6% and 14.1%, respectively). No clear patterns were noted among the causes of death in either trial group in this older population of patients with a median age of 71 years. The findings in the analysis of overall survival may also have been influenced by the use of subsequent antilymphoma therapies.

This trial was not designed to answer the question of whether first-line combination therapy with ibrutinib, bendamustine, and rituximab would be superior to the receipt of ibrutinib

therapy after bendamustine and rituximab treatment. Given the shorter progression-free survival with current standard-care chemoimmunotherapy options, a prolongation of progression-free survival in response to primary therapy may provide patients with an improved opportunity for durable disease control in order to prevent or delay relapse.

The improved efficacy with the addition of ibrutinib was accompanied by additional toxic effects. The adverse events were consistent with the known profiles of single-agent ibrutinib, bendamustine, and rituximab.^{10,16} The incidence of infections, particularly pneumonia, was similar in the two trial groups during the first 6 months but was higher in the ibrutinib group than in the placebo group during the maintenance period. In rare cases, infections were fatal, which sug-

Table 3. Causes of Death Due to Adverse Events during Treatment.*

Cause	Ibrutinib Group (N=261)	Placebo Group (N=262)
Adverse event during treatment — no. (%)	28 (10.7)	16 (6.1)
Infection or infestation, excluding Covid-19 — no.†	9	5
Covid-19–related event — no.	3	0
Unknown cause — no.	3	0
Cardiac disorder — no.‡	3	5
Sudden death — no.	2	0
Multiple organ dysfunction syndrome — no.	2	0
Respiratory disorder — no.	1	2
General physical health deterioration — no.	1	0
Traumatic intracranial hemorrhage — no.	1	0
Tumor lysis syndrome — no.	1	1
Cancer — no.§	1	2
Ischemic stroke — no.	1	0
Hemorrhagic stroke — no.	0	1

* An adverse event during treatment was defined as any event that occurred after the first dose of ibrutinib or placebo, through the treatment phase, or during the 30 days after the last dose of ibrutinib or placebo or until subsequent anticancer therapy, whichever occurred first; or as any event that was considered by the investigator to be related to ibrutinib or placebo regardless of the start date of the event; or as any event that was present at baseline but that worsened in severity or was subsequently considered by the investigator to be related to ibrutinib or placebo. Covid-19 denotes coronavirus disease 2019.

† Grade 5 events of infections and infestations in the ibrutinib group included pneumonia (in two patients) and bronchopulmonary aspergillosis, hepatitis B virus infection, nosocomial infection, *Pneumocystis jirovecii* pneumonia, fungal pneumonia, viral pneumonia, and sepsis (in one patient each); events in the placebo group included pneumonia, pulmonary sepsis, sepsis, septic shock, and pseudomembranous colitis (in one patient each).

‡ Grade 5 events of cardiac disorders in the ibrutinib group included cardiac arrest (in two patients) and cardiorespiratory arrest (in one); events in the placebo group included cardiopulmonary failure (in two patients) and cardiac arrest and myocardial infarction (in one patient each).

§ Grade 5 events of cancer occurred in one patient in the ibrutinib group (acute myeloid leukemia) and in two in the placebo group (acute myeloid leukemia and myelodysplastic syndrome).

gests the continued need for vigilance in identifying and managing these adverse events. Strategies may include early detection of and therapy for infections, adequate prophylaxis, and monitoring of immunoglobulin levels during both induction and maintenance therapy. The omission of chemotherapy in ibrutinib combinations may also reduce the risk of serious infections.

The incidence of atrial fibrillation, an expected adverse event with BTK inhibitors, was

higher in the ibrutinib group (13.9%) than in the placebo group (6.5%). Hypertension, arthralgia, and major hemorrhage were observed at similar incidences in the two trial groups over the prolonged follow-up. Overall, despite more adverse events and related discontinuations in the ibrutinib group than in the placebo group, the finding that patient-reported outcomes were similar in the two groups supports an acceptable safety profile of the trial combination. Given that the significant progression-free survival benefit at a median of 6.7 years was observed at a median of 2 years of ibrutinib treatment, continuous treatment with ibrutinib may not be necessary. One hypothesis for further exploration could be the time-limited use of ibrutinib to retain efficacy but avoid ongoing toxic effects and costs associated with continuous treatment.

Two other covalent BTK inhibitors (acalabrutinib and zanubrutinib) have been approved for the treatment of relapsed mantle-cell lymphoma on the basis of single-group studies in several countries; however, data comparing these agents in patients with mantle-cell lymphoma are limited. Two ongoing trials, ECHO (ClinicalTrials.gov number, NCT02972840) and MANGROVE (NCT04002297), are evaluating the clinical profile of these drugs when they are used continuously as first-line treatment. Several other randomized trials are ongoing and have the potential to address additional questions regarding the first-line use of BTK inhibitors, including the evaluation of a chemotherapy-free combination of ibrutinib and rituximab in older patients (ENRICH; Cancer Research U.K. trial number, CRUK/14/026); time-limited combination therapy with ibrutinib, venetoclax, and rituximab (OASIS-2; NCT04802590); and BTK inhibitor combinations in younger patients (TRIANGLE [NCT02858258] and EA4181 [NCT04115631]).

The phase 3 SHINE trial showed that ibrutinib in combination with bendamustine plus rituximab and rituximab maintenance therapy was an effective first-line treatment in patients with mantle-cell lymphoma who were 65 years of age or older and were considered to be unsuitable candidates for autologous stem-cell transplantation.

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APPENDIX

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