ORIGINAL ARTICLE

Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia

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ABSTRACT

BACKGROUND

Single-agent ibrutinib has shown substantial activity in patients with relapsed Waldenström's macroglobulinemia, a rare form of B-cell lymphoma. We evaluated the effect of adding ibrutinib to rituximab in patients with this disease, both in those who had not received previous treatment and in those with disease recurrence.

METHODS

We randomly assigned 150 symptomatic patients to receive ibrutinib plus rituximab or placebo plus rituximab. The primary end point was progression-free survival, as assessed by an independent review committee. Key secondary end points were response rates, sustained hematologic improvement from baseline, and safety. The mutational status of *MYD88* and *CXCR4* was assessed in bone marrow samples.

RESULTS

At 30 months, the progression-free survival rate was 82% with ibrutinib–rituximab versus 28% with placebo–rituximab (hazard ratio for progression or death, 0.20; P<0.001). The benefit in the ibrutinib–rituximab group over that in the placebo–rituximab group was independent of the *MYD88* or *CXCR4* genotype. The rate of major response was higher with ibrutinib–rituximab than with placebo–rituximab (72% vs. 32%, P<0.001). More patients had sustained increases in hemoglobin level with ibrutinib–rituximab than with placebo–rituximab (73% vs. 41%, P<0.001). The most common adverse events of any grade with ibrutinib–rituximab included infusion-related reactions, diarrhea, arthralgia, and nausea. Events of grade 3 or higher that occurred more frequently with ibrutinib–rituximab than with placebo–rituximab included atrial fibrillation (12% vs. 1%) and hypertension (13% vs. 4%); those that occurred less frequently included infusion reactions (1% vs. 16%) and any grade of IgM flare (8% vs. 47%). The major hemorrhage rate was the same in the two trial groups (4%).

CONCLUSIONS

Among patients with Waldenström's macroglobulinemia, the use of ibrutinib–rituximab resulted in significantly higher rates of progression-free survival than the use of placebo–rituximab, both among those who had received no previous treatment and among those with disease recurrence. Atrial fibrillation and hypertension were more common with ibrutinib–rituximab, whereas infusion reactions and IgM flare were more common with placebo–rituximab. (Funded by Pharmacyclics and Janssen Research and Development; ClinicalTrials.gov number, NCT02165397.)

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*A complete list of the members of the iNNOVATE Study Group and the European Consortium for Waldenström's Macroglobulinemia is provided in the Supplementary Appendix, available at NEJM.org.

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Waldenström's macroglobulinemia, a rare form of B-cell lymphoma, is characterized by elevated serum levels of IgM and infiltration of the bone marrow and other organs by IgM-producing clonal lymphoplasmacytic cells.[1,2] Treatment is commonly initiated in patients with the disease who have anemia, hyperviscosity, fatigue, or other constitutional symptoms.[1,3,4] With few large studies, defining treatment standards has been challenging.[5-10] Rituximab, which is frequently used as monotherapy to avert chemoimmunotherapy-associated toxic events, has shown considerable activity in patients with Waldenström's macroglobulinemia, both among those who have received no previous treatment and among those with disease recurrence. Rituximab combinations with alkylating agents, proteasome inhibitors, and nucleoside analogues are frequently recommended.[1,3,4,11-14] More recently, single-agent ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor, has also gained acceptance as a treatment for this condition.[1,3,4,11,15]

Interest in ibrutinib for this application was driven by a high prevalence of the *MYD88* L265P mutation and its influence on tumor-cell survival through BTK-triggered activation of nuclear factor κB.[16] A phase 2 study of single-agent ibrutinib showed high rates of durable response among 63 patients with relapsed disease, 40% of whom had disease that was resistant to previous therapy.[15] These results, which led to the approval of ibrutinib for the treatment of Waldenström's macroglobulinemia in the United States and Europe, were confirmed in patients with rituximab-resistant disease; however, outcomes with single-agent ibrutinib showed dependence on *MYD88* and *CXCR4* mutational status.[17]

Given the synergistic activity of the ibrutinib–rituximab combination in preclinical studies,[18] as well as the substantial activity of single-agent ibrutinib and the widespread use of rituximab in patients with Waldenström's macroglobulinemia, we initiated the iNNOVATE trial to evaluate the combination of ibrutinib and rituximab in patients with Waldenström's macroglobulinemia, both among those who had received no previous treatment and among those who had disease recurrence with sensitivity to rituximab.

METHODS

PATIENTS

From July 2014 through January 2016, we enrolled patients at 45 sites in nine countries. Eligible patients had received a centrally confirmed diagnosis of Waldenström's macroglobulinemia that required treatment, according to criteria that have been reported previously.[2,7] Patients could be receiving treatment for the first time or after relapse. Those who had been treated with a rituximab-containing regimen were required to have had a response to the regimen that lasted for at least 12 months. Patients were excluded if they had resistance to the previous rituximab-containing therapy or had received rituximab within 12 months before the administration of the first dose of a trial drug.

TRIAL OVERSIGHT AND CONDUCT

The trial was approved by the institutional review board or independent ethics committee at each institution and was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation. All the patients provided written informed consent.

The trial was sponsored by Pharmacyclics and designed by the sponsor in collaboration with the investigators and Janssen Research and Development; the two companies provided funding for the trial. Janssen representatives had access to the data and were permitted a courtesy review of the manuscript but were otherwise not involved in the trial conduct. All the investigators and their research teams collected data. The sponsor confirmed the accuracy of the data and compiled the data for analysis. All the authors had full access to the data and analyses. The first author, the last author, and two authors who were employed by the sponsor wrote the first draft of the manuscript. Editorial support was provided by a professional medical writer who was funded by the sponsor. All the authors reviewed the manuscript and made the decision to submit it for publication and vouch for the accuracy and completeness of the data and analyses and for the adherence of the trial to the protocol (available with the full text of this article at NEJM.org). An independent review committee

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evaluated the response and disease progression in a blinded manner.

RANDOMIZATION AND TREATMENT

The patients were randomly assigned in a 1:1 ratio to receive either oral ibrutinib (420 mg once daily) or placebo until disease progression or unacceptable toxic effects. The two groups also received extended intravenous rituximab (375 mg per square meter of body-surface area, with infusions at weeks 1 to 4 and 17 to 20), a regimen that was consistent with current treatment guidance and data for rituximab in patients with Waldenström's macroglobulinemia.[19,20] Patients were stratified according to the score on the International Prognostic Scoring System for Waldenström's Macroglobulinemia at screening (low vs. intermediate vs. high) (Table S1 in the Supplementary Appendix, available at NEJM.org), the number of prior regimens (0 vs. 1 or 2 vs. ≥3), and Eastern Cooperative Oncology Group performance-status score (0 or 1 vs. 2; scores range from 0 to 5, with higher scores indicating greater disability; a score of 5 indicates death). Patients in the placebo group were allowed to cross over to receive ibrutinib after disease progression, as confirmed by an independent review committee.

END POINTS

The primary end point was progression-free survival, as assessed by the independent review committee. Key secondary end points were the time until the next treatment, overall survival, response rates, sustained hematologic improvement from baseline (as measured by testing of hemoglobin levels), quality of life, and safety. (Details regarding the trial end points are provided in the Methods section in the Supplementary Appendix.) Responses were based on modified consensus criteria from the sixth International Workshop on Waldenström's Macroglobulinemia (Table S2 in the Supplementary Appendix). The mutational status of *MYD88* and *CXCR4* was assessed in bone marrow samples obtained from the patients before the initiation of treatment.

STATISTICAL ANALYSIS

In calculating the size of enrollment, we assumed a target hazard ratio for progression or death of 0.50, with 71 events providing a power of approximately 80% on the basis of a two-sided log-rank test at an alpha level of 0.05. An interim analysis was planned after approximately 50 events of progression or death had occurred. The results that are presented here are based on this prespecified interim analysis. Details regarding the statistical analysis plan are provided in the Supplementary Appendix.

RESULTS

PATIENTS

A total of 150 patients were randomly assigned to receive ibrutinib–rituximab (75 patients) or placebo–rituximab (75 patients) (Fig. S1 in the Supplementary Appendix). The characteristics of the patients at baseline were generally well balanced (Table 1). The median age was 69 years, and 33% of the patients were 75 years of age or older; 45% of the patients had received no previous treatment. Patients with relapsed disease had received a median of two prior therapies (range, one to six); of these patients, 85% had been previously treated with rituximab. Extramedullary disease was reported in 79% of the patients at baseline. Of the 136 patients for whom baseline mutational data were available, *MYD88* L265P and *CXCR4* WHIM genotypes were found in 85% and 36%, respectively. The most common reasons for initiating therapy were fatigue, anemia, and constitutional symptoms (Table S3 in the Supplementary Appendix).

All the patients received rituximab, and 93% of the patients in the ibrutinib–rituximab group completed rituximab treatment, as compared with 71% of the patients in the placebo–rituximab group (Fig. S1 in the Supplementary Appendix). At a median follow-up of 26.5 months, 75% of the patients in the ibrutinib–rituximab group were continuing treatment. Overall, 95% of the patients in the ibrutinib–rituximab group and 92% of those in the placebo–rituximab group were alive at the time of this analysis.

PROGRESSION-FREE SURVIVAL

The 30-month progression-free survival rate was 82% in the ibrutinib–rituximab group and 28% in the placebo–rituximab group (median, not reached vs. 20.3 months), for an 80% lower risk of progression or death in the ibrutinib–rituximab group (hazard ratio for progression or

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Ibrutinib–Rituximab (N=75)	Placebo–Rituximab (N=75)
Age		
Median (range) — yr	70 (36–89)	68 (39–85)
≥75 yr — no. (%)	30 (40)	20 (27)
Male sex — no. (%)	45 (60)	54 (72)
Median time from diagnosis (range) — mo	50 (1–257)	56 (1–247)
ECOG performance-status score — no. (%)†		
0	39 (52)	37 (49)
1	32 (43)	32 (43)
2	4 (5)	6 (8)
Prognostic score — no. (%)‡		
Low	15 (20)	17 (23)
Intermediate	33 (44)	28 (37)
High	27 (36)	30 (40)
Genotype — no./total no. (%)		
*MYD88*WT/*CXCR4* WT	11/69 (16)	9/67 (13)
MYD88 L265P/*CXCR4* WT	32/69 (46)	35/67 (52)
MYD88 L265P/*CXCR4* WHIM	26/69 (38)	23/67 (34)
Cytopenia at baseline — no. (%)		
Hemoglobin of ≤11 g/dl	44 (59)	50 (67)
Platelet count of ≤100,000/mm^3	4 (5)	7 (9)
Absolute neutrophil count of ≤1500/mm^3	4 (5)	1 (1)
Median hemoglobin (range) — g/dl	10.5 (6.9–15.5)	10.0 (6.6–16.1)
Bone marrow infiltration		
Median cellularity (range) — %	80 (25–100)	80 (2–100)
Median intertrabecular space (range) — %	36 (2–95)	40 (1–95)
Serum IgM		
Median (range) — g/liter	32.9 (6.2–77.6)	31.8 (5.9–83.3)
>70 g/liter — no. (%)	2 (3)	4 (5)
Median β_2 microglobulin (range) — mg/liter	3.4 (1.4–27.9)	3.9 (1.5–11.6)
Extramedullary disease — no. (%)	59 (79)	60 (80)
Adenopathy§	56 (75)	58 (77)
Splenomegaly¶	9 (12)	18 (24)
No. of previous systemic therapies — no. (%)		
0	34 (45)	34 (45)
1 or 2	34 (45)	36 (48)
≥3	7 (9)	5 (7)
Previous rituximab-containing regimen — no./total no. (%)	36/41 (88)	34/41 (83)

* There was no significant difference between the groups at baseline. Percentages may not total 100 because of rounding. WT denotes wild type.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability; a score of 5 indicates death.
‡ Scores on the International Prognostic Scoring System for Waldenström's Macroglobulinemia range from 0 to 5, with higher scores indicating a greater risk of death.
§ Adenopathy was defined as the presence of lymph nodes with a long axis of more than 1.5 cm or a short axis of more than 1.0 cm.
¶ Splenomegaly was defined as a spleen depth (cranial to caudal) of more than 13 cm.

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death, 0.20; 95% confidence interval [CI], 0.11 to 0.38; P<0.001) (Fig. 1A). These results were consistent with investigator-assessed rates of 30-month progression-free survival of 80% with ibrutinib–rituximab and 39% with placebo–rituximab (hazard ratio, 0.22; 95% CI, 0.12 to 0.40). A low rate of histologic transformation to diffuse large B-cell lymphoma was observed (in two patients in the ibrutinib–rituximab group and no patients in the placebo–rituximab group).

In subgroup analyses, higher rates of progression-free survival were observed with ibrutinib–rituximab than with placebo–rituximab across prespecified subgroups, including patients who had received no previous treatment (hazard ratio, 0.34; 95% CI, 0.12 to 0.95) and those with relapsed disease (hazard ratio, 0.17; 95% CI, 0.08 to 0.36) (Fig. 1B). At 24 months, the progression-free survival rate among patients who had received no previous treatment was 84% with ibrutinib–rituximab and 59% with placebo–rituximab (Fig. S2A in the Supplementary Appendix). Since patients who had received no previous treatment were enrolled after a protocol amendment, 30-month progression-free survival rates could not be estimated among these patients. In patients with disease recurrence, the 24-month progression-free survival rate was 80% with ibrutinib–rituximab and 37% with placebo–rituximab; the rates were 80% and 22%, respectively, at the 30-month landmark (Fig. S2B in the Supplementary Appendix).

An analysis that was based on the mutational status showed similarly higher rates of progression-free survival with ibrutinib–rituximab than with placebo–rituximab across different *MYD88* and *CXCR4* genotypes. The 30-month progression-free survival rates were 86% versus 33% among patients with the *MYD88* L265P/*CXCR4* WT genotype, 80% versus 29% among those with the *MYD88* L265P/*CXCR4* WHIM genotype, and 80% versus 21% among those with the *MYD88* WT/*CXCR4* WT genotype (Fig. S2C in the Supplementary Appendix). Higher rates of 30-month progression-free survival with ibrutinib–rituximab than with placebo–rituximab were also consistent among the patients who had risk scores on the International Prognostic Scoring System for Waldenström's Macroglobulinemia that were high (93% vs. 22%), intermediate (70% vs. 28%), and low (86% vs. 42%) (Fig. S2D in the Supplementary Appendix).

OVERALL SURVIVAL

The 30-month overall survival rate was 94% with ibrutinib–rituximab and 92% with placebo–rituximab. The median duration of overall survival was not reached in either group (Fig. 2). Of note, 30 patients in the placebo–rituximab group crossed over to receive ibrutinib after disease progression had been confirmed by the independent review committee; 3 patients received ibrutinib outside the trial. During a median follow-up of 26.5 months, there were 4 deaths in the ibrutinib–rituximab group (all of which occurred during long-term follow-up) and 6 deaths in the placebo–rituximab group (3 of which occurred during active treatment and resulted from adverse events) (Table S4 in the Supplementary Appendix).

MAJOR AND OVERALL RESPONSE RATES

As assessed by the independent review committee, ibrutinib–rituximab was associated with significantly higher response rates than placebo–rituximab with respect to a major response (i.e., a complete response, very good partial response, or partial response) (72% vs. 32%, P<0.001) and an overall response (92% vs. 47%, P<0.001) before the initiation of subsequent antineoplastic therapy, disease progression, death, or the date of the interim analysis, whichever was earliest (Fig. 3A). Patients in the ibrutinib–rituximab group had a rate of very good partial response of 23%, as compared with 4% in the placebo–rituximab group, findings that are consistent with the investigator-assessed responses. Robust responses to ibrutinib–rituximab were observed in patients with either the *MYD88* L265P/*CXCR4* WT genotype or the *MYD88* L265P/*CXCR4* WHIM genotype (Fig. S3 in the Supplementary Appendix), although patients in the placebo–rituximab group with the latter genotype had a numerically higher rate of major response than those with other genotypes.

Among the patients who had at least a partial response to ibrutinib–rituximab treatment, the response was ongoing in 92% at 24 months, as compared with 41% in the placebo–rituximab group. The median duration of response was not reached (range, 1.9 to 36.4 months) among the 54 patients who had at least a partial response in the ibrutinib–rituximab group and was 21.2 months (range, 4.6 to 25.8) among the 24 patients with at least a partial response in the placebo–rituximab group.

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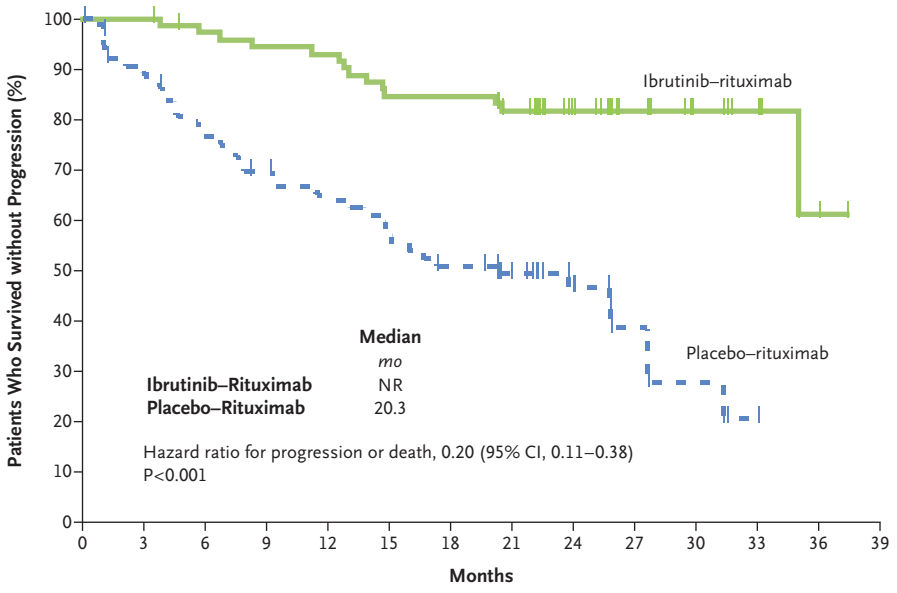
A Progression-free Survival

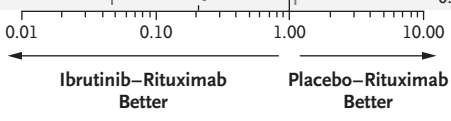


No. at Risk

Ibrutinib–rituximab	75	73	69	67	66	60	60	54	40	24	14	9	2	0
Placebo–rituximab	75	65	55	49	44	40	34	27	16	7	4	1	0	0

B Progression-free Survival, According to Subgroup

Subgroup	No. of Patients	Hazard Ratio (95% CI)
All patients	150	0.21 (0.11–0.39)
Age		
<65 yr	58	0.29 (0.11–0.76)
≥65 yr	92	0.17 (0.07–0.39)
Sex		
Male	99	0.23 (0.11–0.49)
Female	51	0.20 (0.06–0.63)
Previous treatment		
No	68	0.34 (0.12–0.95)
Yes	82	0.17 (0.08–0.36)
Baseline IgM		
<40 g/liter	94	0.08 (0.02–0.25)
≥40 g/liter	56	0.44 (0.19–1.00)
Baseline hemoglobin		
≤11 g/dl	94	0.24 (0.11–0.50)
>11 g/dl	54	0.18 (0.06–0.56)
Baseline β2-microglobulin		
≤3 mg/liter	42	0.40 (0.15–1.11)
>3 mg/liter	108	0.15 (0.07–0.34)
Prognostic score		
Low	32	0.16 (0.03–0.76)
Intermediate	61	0.43 (0.19–1.00)
High	57	0.07 (0.02–0.31)
Genotype		
MYD88 L265P/*CXCR4* WT	67	0.17 (0.06–0.49)
MYD88 L265P/*CXCR4* WHIM	49	0.24 (0.09–0.66)
MYD88 WT/*CXCR4* WT	20	0.21 (0.04–1.08)



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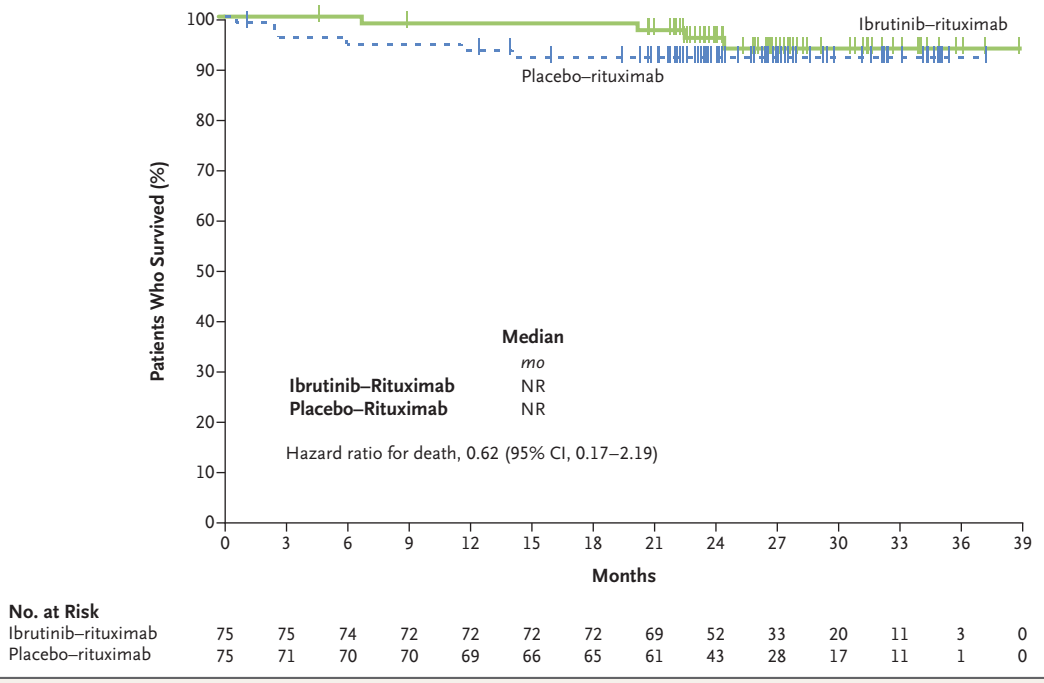

Figure 2. Overall Survival.

Shown are the results of the secondary analysis of overall survival, comparing a combination of ibrutinib plus rituximab with placebo plus rituximab. The tick marks indicate censoring of data.

IgM and Hemoglobin Levels

The median IgM level declined more rapidly and to a greater extent with ibrutinib–rituximab than with placebo–rituximab. After 4 weeks of treatment, the median IgM level was reduced from baseline by 56% with ibrutinib–rituximab as compared with an increase of 6% with placebo–rituximab (Fig. 3B). Changes in mean IgM levels over time in patients with critical IgM levels of more than 50 g per liter at baseline are shown in Figure S4 in the Supplementary Appendix. Transient increases in IgM levels (i.e., IgM flare) were reported less frequently with ibrutinib–rituximab than with placebo–rituximab (8% vs. 47%), and no patient underwent plasmapheresis in the ibrutinib–rituximab group, as compared with 12 patients in the placebo–rituximab group.

The rate of sustained increase in hemoglobin levels was significantly higher with ibrutinib–rituximab than with placebo–rituximab in the overall population (73% vs. 41%, P<0.001), as well as in patients with anemia at baseline (95% vs. 56%, P<0.001). A corresponding clinically meaningful improvement from baseline in the total score on the Functional Assessment of Cancer Therapy–Anemia evaluation[21] was reported in a greater percentage of patients in the ibrutinib–rituximab group than in the placebo–rituximab group (73% vs. 59%, P=0.06); similar results were observed for the anemia subscale score (64% vs. 48%, P=0.05).

Figure 1 (facing page). Progression-free Survival among All Patients and According to Subgroup.

Shown are the results of the primary analysis of progression-free survival, as assessed by the independent review committee in the overall population (Panel A) and according to subgroup (Panel B). The tick marks indicate censoring of data. NR denotes not reached. In Panel B, the hazard ratios are for disease progression or death. The sizes of the circles are proportional to the sizes of the subgroups. The dashed vertical line represents the overall treatment effect in all patients. The prognostic score was measured on the International Prognostic Scoring System for Waldenström's Macroglobulinemia, which ranges from 0 to 5, with higher scores indicating a greater risk of death.

Safety

Patients continued to receive ibrutinib for a median of 25.8 months (range, 1.0 to 37.2) and placebo for a median of 15.5 months (range, 0.4 to 34.3), so the collection period for safety data was longer in the ibrutinib–rituximab group.

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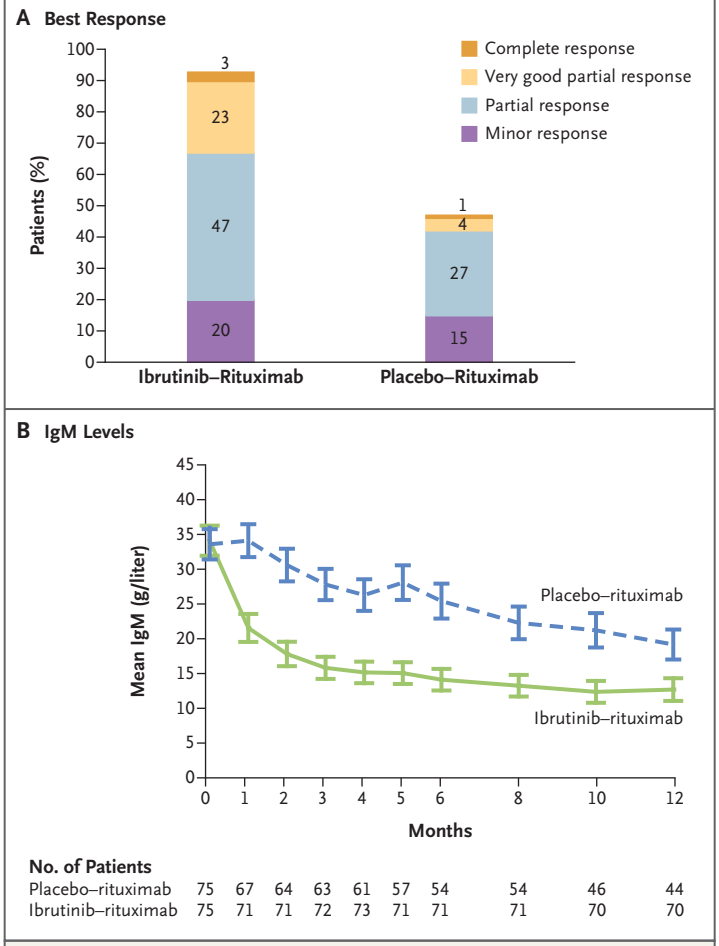

Figure 3. Best Response Rates and a Comparison of IgM Levels.

Panel A shows the best response to treatment, as assessed by the independent review committee, in the ibrutinib–rituximab group versus the placebo–rituximab group before the initiation of subsequent antineoplastic therapy, disease progression, death, or the date of the interim analysis, whichever was earliest. Categories for response assessments included complete response, very good partial response, partial response, and minor response. Data were unknown, missing, or could not be evaluated for 4 patients in the ibrutinib–rituximab group and for 2 patients in the placebo–rituximab group. The percentages of patients in each category of response may not total the overall proportion with a response because of rounding. Panel B shows the mean IgM levels over time among all the patients in the intention-to-treat population in each treatment group. The I bars represent the standard error.

(Rituximab infusions were completed at week 20, and ibrutinib or placebo was continued until disease progression or unacceptable toxic events.) Adverse events of any grade that were substantially more frequent with ibrutinib–rituximab than with placebo–rituximab were diarrhea, arthralgia, and nausea, and those that were less frequent were IgM flare, infusion-related reactions, fatigue, asthenia, anemia, and headache (Table 2).

Overall, approximately 60% of the patients in each group had at least one adverse event of grade 3 or higher. The most common such adverse events that occurred more frequently with ibrutinib–rituximab than with placebo–rituximab included hypertension (13% vs. 4%) and atrial fibrillation (12% vs. 1%), and those that occurred less frequently included anemia (11% vs. 17%) and infusion-related reactions (1% vs. 16%). Serious adverse events occurred more frequently with ibrutinib–rituximab than with placebo–rituximab (43% vs. 33%); the most common serious adverse events in the ibrutinib–rituximab group included pneumonia (8%), atrial fibrillation (7%), and respiratory tract infection (4%). Fatal adverse events occurred in no patients in the ibrutinib–rituximab group and in three patients in the placebo–rituximab group.

The rate of discontinuation of treatment because of adverse events was 5% for ibrutinib and 4% for placebo (Table S4 in the Supplementary Appendix). Adverse events led to a dose reduction of ibrutinib in 13 patients (Table S5 in the Supplementary Appendix). The most common reasons for ibrutinib dose reductions were neutropenia (in 3 patients), atrial fibrillation (in 2 patients), and muscle spasms (in 2 patients).

Atrial fibrillation of any grade occurred in 15% of the patients in the ibrutinib–rituximab group and in 3% of those in the placebo–rituximab group. Among these patients, there was a history of atrial fibrillation in 27% of those in the ibrutinib–rituximab group and in none of those in the placebo–rituximab group. The treatment course in patients with atrial fibrillation is shown in Figure S5 in the Supplementary Appendix. Bleeding events occurred more frequently in patients treated with ibrutinib–rituximab than in those treated with placebo–rituximab (51% vs. 21%); grade 1 or 2 events occurred in 92% versus 81% of these patients, respectively. Major hemorrhage occurred in 3 patients (4%) in each treatment group (Table S6 in the Supplementary Appendix), whereas the use of anticoagulant or antiplatelet medications was more common with ibrutinib–rituximab than with placebo–rituximab (43% vs. 36%). One patient in the placebo–rituximab group had a fatal intracranial hemorrhage.

DISCUSSION

Ibrutinib has shown substantial single-agent activity in patients with Waldenström's macroglobulinemia.[15,17] In long-term follow-up of a pivotal

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Table 2. Adverse Events and Duration of Treatment.

Variable	Ibrutinib–Rituximab (N=75)	Placebo–Rituximab (N=75)
Median duration of treatment (range) — mo	25.8 (1.0–37.2)	15.5 (0.4–34.3)
Most common adverse events of any grade — no. of patients (%)*		
Infusion-related reaction	32 (43)	44 (59)
Diarrhea	21 (28)	11 (15)
Arthralgia	18 (24)	8 (11)
Nausea	16 (21)	9 (12)
Anemia	14 (19)	22 (29)
Asthenia	12 (16)	19 (25)
Fatigue	10 (13)	20 (27)
Headache	10 (13)	17 (23)
IgM flare	6 (8)	35 (47)
Adverse event of grade ≥3 — no. of patients (%)†	45 (60)	46 (61)
Hypertension	10 (13)	3 (4)
Atrial fibrillation	9 (12)	1 (1)
Anemia	8 (11)	13 (17)
Neutropenia	7 (9)	2 (3)
Pneumonia	7 (9)	2 (3)
Hyponatremia	4 (5)	2 (3)
Infusion-related reaction	1 (1)	12 (16)
Thrombocytopenia	0	4 (5)
Serious adverse event — no. of patients (%)‡	32 (43)	25 (33)
Pneumonia	6 (8)	2 (3)
Atrial fibrillation	5 (7)	1 (1)
Respiratory tract infection	3 (4)	0
Anemia	2 (3)	0
Congestive cardiac failure	2 (3)	0
Fall	2 (3)	0
Gastroenteritis	2 (3)	0
Myocardial ischemia	2 (3)	0
Arthralgia	2 (3)	0

* Listed are adverse events of any grade that occurred in at least 20% of the patients in either treatment group and for which the frequency differed between treatment groups by at least 5 percentage points. Data regarding major hemorrhage (which occurred in 4% of the patients in each group) are not listed because the incidence did not meet the criteria for reporting here.
† Listed are adverse events of grade 3 or higher that occurred in at least 5% of the patients in either treatment group.
‡ Listed are serious adverse events that occurred in at least 2% of the patients in either treatment group.

trial of ibrutinib in patients with advanced Waldenström's macroglobulinemia, the duration of progression-free survival had not been reached at a median follow-up of 47 months.[22] The durable responses, taken together with the established long-term safety profile of ibrutinib in various B-cell cancers,[22-24] made ibrutinib an attractive option for the treatment of Waldenström's macroglobulinemia. However, questions remain about the efficacy of ibrutinib among patients who have not received previous treatment and about the influence of *MYD88* and *CXCR4* mutations on response, which may affect the course of the disease, as well as the efficacy of a dual-targeting combination to overcome the potential effects of *MYD88* and *CXCR4* genotypes on the response to ibrutinib.[10,16] We conducted a placebo-controlled trial to evaluate the effect of adding ibrutinib to rituximab.

In the iNNOVATE trial, we found that the combination of ibrutinib plus rituximab resulted in significantly better efficacy over rituximab

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alone in producing rapid and durable responses, with substantially longer durations of progression-free survival, both among patients who had received previous treatment and among those with recurrent disease. The rapid reduction in IgM levels, especially in patients with high IgM levels at baseline, indicated that the addition of ibrutinib to rituximab can prevent IgM flare. Sustained increases in hemoglobin levels also allowed for amelioration of anemia and fatigue, which are among the most common reasons for initiating treatment.

We observed that traditional prognostic factors did not have a meaningful effect on the outcome of patients who were treated with ibrutinib–rituximab. Although risk scores on the International Prognostic Scoring System for Waldenström's Macroglobulinemia were developed to predict overall survival,[25] increased durations of progression-free survival with ibrutinib–rituximab were observed across all risk scores. In previous studies, mutations in *MYD88* and *CXCR4* had prognostic value among patients with Waldenström's macroglobulinemia[16] and may have affected the clinical response to single-agent ibrutinib.[15] In the iNNOVATE trial, we prospectively analyzed the predictive value of these mutations in a large patient population. Response rates with ibrutinib–rituximab were similar across different *CXCR4* genotypes but were slightly lower among patients who did not have the activating *MYD88* L265P mutation, which triggers the growth of malignant cells through BTK and hematopoietic-cell kinase, both of which are targeted by ibrutinib.[15,16] These minor differences in response rates with regard to the *MYD88*/*CXCR4* genotypes did not affect the progression-free survival benefit observed with ibrutinib–rituximab, although the mechanistic rationale for these interactions is as yet unknown. These data must be interpreted with caution because of the small numbers of patients. A final assessment of the effect of prognostic factors on outcomes requires longer follow-up.

The observed safety profile of ibrutinib–rituximab was similar to the known safety profiles of each agent used individually, and no unexpected toxic effects were identified. A higher incidence of atrial fibrillation was observed with ibrutinib–rituximab than with placebo–rituximab after a median treatment duration of 26 months; these rates were similar to those reported for single-agent ibrutinib with prolonged follow-up.[22,23] Atrial fibrillation was generally treated with dose modifications and supportive medications and led to treatment discontinuation in 4% of the patients in the ibrutinib–rituximab group. Ibrutinib was associated with the occurrence of low-grade bleeding events; major hemorrhage occurred in 4% of the patients in each treatment group. No unexpected safety findings were seen with extended rituximab therapy, although frequencies of IgM flare (47%) and infusion-related reactions (59%) were higher than those in the ibrutinib–rituximab group (8% and 43%, respectively). The addition of ibrutinib appeared to lower the occurrence of these key toxic effects associated with rituximab, which could potentially result from ibrutinib-mediated inhibition of cytokine secretion.[26,27] Additional analyses after longer-term follow-up will help to determine the risk of lymphoproliferative disorders with this regimen.

Rituximab monotherapy is still widely used in patients with either newly diagnosed or relapsed Waldenström's macroglobulinemia.[28,29] In the iNNOVATE trial, the extended use of rituximab resulted in a 24-month progression-free survival rate of 59% among patients who had received no previous treatment, whereas the median duration of progression-free survival among the patients with disease recurrence (many of whom had received previous treatment with rituximab) was 14.8 months. Although these outcomes are consistent with the previously reported efficacy of rituximab in Waldenström's macroglobulinemia, they are inferior to outcomes with single-agent ibrutinib in patients with relapsed disease, in whom the duration of progression-free survival with ibrutinib exceeded the median follow-up of 47 months[22] and an 18-month progression-free survival rate of 86% was noted among patients who had resistance to previous rituximab therapy.[17]

We conclude that the addition of ibrutinib to rituximab represents a viable treatment approach for patients with Waldenström's macroglobulinemia, both among those who have received no previous therapy and among those with disease recurrence, regardless of prognostic or genotypic factors.

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APPENDIX

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