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Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study

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PURPOSE The double-blind, randomized, placebo-controlled phase III iNNOVATE study showed sustained efficacy of ibrutinib-rituximab in Waldenström's macroglobulinemia (WM). Here, we present the final analysis from iNNOVATE.

METHODS Patients had confirmed symptomatic WM, either previously untreated or previously treated; patients with prior rituximab had at least a minor response to their last rituximab-based regimen. Patients were randomly assigned to once-daily ibrutinib 420 mg plus rituximab or placebo plus rituximab (n = 75 per arm). The primary end point was progression-free survival (PFS). Secondary end points included response rate, time to next treatment, hemoglobin improvement, overall survival, and safety.

RESULTS With a median follow-up of 50 (range, 0.5-63) months, median (95% CI) PFS was not reached (57.7 months to not evaluable) with ibrutinib-rituximab versus 20.3 months (13.0 to 27.6) with placebo-rituximab (hazard ratio, 0.250; *P* < .0001). PFS benefit was regardless of prior treatment status, *MYD88* and *CXCR4* mutation status, or key patient characteristics. Higher response rates (partial response or better) were observed with ibrutinib-rituximab (76% *v* 31% with placebo-rituximab; *P* < .0001) and were sustained over time. Median time to next treatment was not reached with ibrutinib-rituximab versus 18 months with placebo-rituximab. More patients receiving ibrutinib-rituximab versus placebo-rituximab had sustained hemoglobin improvement (77% *v* 43%; *P* < .0001). Median overall survival was not reached in either arm. Ibrutinib-rituximab maintained a manageable safety profile; the prevalence of grade ≥ 3 adverse events of clinical interest generally decreased over time.

CONCLUSION In the final analysis of iNNOVATE with a median follow-up of 50 months, ibrutinib-rituximab showed ongoing superiority across clinical outcomes in patients with WM regardless of *MYD88* or *CXCR4* mutation status, prior treatment, and key patient characteristics.

INTRODUCTION

Ibrutinib, a once-daily Bruton tyrosine kinase (BTK) inhibitor, is indicated as either a single-agent therapy or in combination with rituximab, a commonly used nonchemotherapy-based treatment, for patients with Waldenström's macroglobulinemia (WM) across all lines of therapy[1] and is the only BTK inhibitor approved for the treatment of WM. Ibrutinib with or without rituximab has demonstrated high overall response rates (ORRs) in patients with WM,[2-4] is an International Workshop for Waldenström's Macroglobulinemia (IWWM) preferred treatment option in the first line and for patients with

relapsed or refractory disease, and is the only category-1–preferred regimen for primary therapy and previously treated WM recommended by the National Comprehensive Cancer Network (NCCN).[5,6]

Mutations in *MYD88* and *CXCR4* are highly prevalent in patients with WM[7] and drive constitutive activation of key BTK-dependent signaling pathways involved in clonal WM cell survival and proliferation,[7,8] making the BTK pathway a favorable therapeutic target.[9] A pivotal phase II study demonstrated high response rates in relapsed patients with WM who were treated with single-agent ibrutinib.[10] In this study, lower response

CONTEXT

Key Objective
To present the final analysis of iNNOVATE, to our knowledge the first phase III study conducted in patients with Waldenström's macroglobulinemia (WM). This randomized study evaluated the efficacy and safety of ibrutinib plus rituximab versus placebo plus rituximab in patients with WM. The final analysis reports results after a median 50-month follow-up, building upon the 30-month median follow-up results from the primary analysis.

Knowledge Generated
Ibrutinib plus rituximab maintained a manageable safety profile, provided sustained efficacy, and significantly reduced the risk of disease progression or death compared with rituximab alone, regardless of patient genotype or prior treatment status. Additionally, time to response was shorter and time to next treatment was substantially longer with ibrutinib plus rituximab compared with rituximab alone.

Relevance *(S. Lentzsch)*
Long-term follow-up showed that ibrutinib plus rituximab had ongoing superiority across clinical outcomes compared to rituximab alone in patients with WM regardless of prior treatment status or *MYD88/CXCR4* genotype, confirming its role as a standard of care for WM.*

*Relevance section written by *JCO* Associate Editor Suzanne Lentzsch, MD, PhD.

rates were observed in patients without *MYD88* mutations and in those with concurrent *MYD88* and *CXCR4* mutations compared with patients with *MYD88*, but without *CXCR4*, mutations.

The phase III randomized iNNOVATE study (PCYC-1127; NCT02165397) evaluated the efficacy and safety of ibrutinib in combination with rituximab in both previously untreated and previously treated patients.[2] At the primary analysis (median follow-up, 26.5 months), ibrutinib-rituximab demonstrated superior progression-free survival (PFS) and higher ORR versus single-agent rituximab, independent of patient genotype.[2] Here, we present the final analysis from the randomized arms of the iNNOVATE study after a median follow-up of 50 (range, 0.5-63) months.

METHODS

Study Design

iNNOVATE (PCYC-1127) was a double-blind, randomized, placebo-controlled, multicenter, international, phase III study designed to assess the efficacy and safety of ibrutinib-rituximab versus placebo-rituximab in patients with WM. Study design details have been previously published.[2] Patients age $\geq$ 18 years with centrally confirmed WM were eligible. Patients could have been previously untreated or previously treated and not refractory (ie, achieved at least a minor response [MR]) to the last rituximab-based therapy and had not received rituximab < 12 months before the study. Patients were randomly assigned 1:1 to ibrutinib-rituximab or placebo-rituximab (stratification factors: International Prognostic Scoring System for WM score, number of prior regimens, and Eastern Cooperative Oncology Group performance

status). Patients received oral once-daily ibrutinib 420 mg or placebo until unacceptable toxicity or progressive disease (PD) and intravenous rituximab 375 mg/m^{2} on day 1 of weeks 1-4 and 17-20. Patients in the placebo-rituximab arm could cross over and receive single-agent ibrutinib after Independent Review Committee (IRC)–confirmed PD. The Protocol (online only) was approved by institutional review boards or independent ethics committees at participating institutions. The study was conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines from the International Conference on Harmonization. All patients provided written informed consent before screening.

End Points and Assessments

The primary end point was PFS per IRC. Secondary end points included ORR (MR or better) per IRC, hematologic improvement per change in serum hemoglobin (Hgb) levels, time to next treatment (TTNT), overall survival (OS), and safety.[2] Patient-reported outcomes (PROs) were an exploratory end point. Major response rates (partial response or better) per IRC and changes in immunoglobulin M (IgM) levels were also assessed. Responses were assessed according to the modified consensus criteria from the Sixth International Workshop on WM.[11]

Genotype Analysis

MYD88 and *CXCR4* mutational status was centrally assessed using the Personalis ACE Extended Cancer Panel (Menlo Park, CA) with > 500 × mean coverage depth. Calls of somatic variants for *MYD88* and *CXCR4* used the Personalis Cancer Panel DNA pipeline operating in the tumor-only mode with no matched normal samples and a 2% limit of detection.

PROs

PROs and disease-related symptoms were measured according to the Functional Assessment of Cancer Therapy-Anemia (FACT-An) and EuroQoL 5-Dimension 5-Level Questionnaire (EQ-5D-5L; copyright EuroQol Research Foundation. EQ-5D is a trademark of the EuroQol Research Foundation); additional methods are provided in the Data Supplement (online only).

Statistical Analysis

Efficacy was analyzed in the intent-to-treat population, which included all randomly assigned patients. Safety was assessed in the safety population, which included all patients who received ≥ 1 dose of any study drug.

This study was powered to evaluate the effect of treatment on the PFS end point, defined as the duration from date of random assignment to date of PD or death. Sample size and power calculations were based on a two-sided log-rank test for PFS, assuming a target hazard ratio (HR) of 0.5, minimum 80% power, and two-sided overall significance level of $P = .05$.

TTNT was measured as time from random assignment to start date of any subsequent WM treatment. Investigators could switch a patient to a second therapy if their disease was worsening or per investigator's decision after study unblinding per Data Monitoring Committee recommendation, even if the

patient did not meet the criteria for PD. Sustained hematologic improvement was defined as improvement in Hgb of ≥ 2 g/dL (intent-to-treat population) or an increase to > 11 g/dL with an improvement of ≥ 0.5 g/dL (patients with baseline Hgb ≤ 11 g/dL) for ≥ 56 days.

Median PFS, OS, and TTNT were estimated using the Kaplan-Meier method. Treatment differences were analyzed using the stratified log-rank test. For patients who crossed over to single-agent ibrutinib, OS sensitivity analysis was performed using the two-stage Accelerated Failure Time model to adjust treatment effect as a result of crossover.[12]

Adverse events (AEs) were graded by the investigator according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. SAS version 9.3 (SAS Institute Inc, Cary, NC) was used to perform all statistical analyses.

RESULTS

Patient Demographics and Characteristics

A total of 150 patients (n = 75 per randomized arm) were enrolled. Baseline demographics and disease characteristics were generally well-balanced between arms (Table 1 and Data Supplement). In patients treated with ibrutinib-rituximab, the median age was 70 years; 55% had received ≥ 1 prior systemic treatment for WM, with a

TABLE 1. Demographics and Clinical Characteristics of Patients at Baseline

Characteristic	Ibrutinib-Rituximab (n = 75)	Placebo-Rituximab (n = 75)
Median age, years (range)	70 (36-89)	68 (39-85)
Male, No. (%)	45 (60)	54 (72)
IPSSWM, No. (%)		
Low	15 (20)	17 (23)
Intermediate	33 (44)	28 (37)
High	27 (36)	30 (40)
Median Hgb, g/dL (range)	10.5 (6.9-15.5)	10.0 (6.6-16.1)
Baseline Hgb ≤ 11.0 g/dL, No. (%)	44 (59)	50 (67)
Median serum IgM, g/L (range)	33 (6-78)	32 (6-83)
No. of prior systemic therapies, No. (%)		
0	34 (45)	34 (45)
1-2	34 (45)	36 (48)
≥ 3	7 (9)	5 (7)
Genotype, No. (%)		
$MYD88^{L265P}/CXCR4^{WT}$	32 (43)	35 (47)
$MYD88^{L265P}/CXCR4^{WHIM}$	26 (35)	23 (31)
$MYD88^{WT}/CXCR4^{WT}$	11 (15)	9 (12)
Unknown[a]	6 (8)	8 (11)
Bone marrow infiltration: percentage of cellularity, median (range)	80 (25-100)	80 (2-100)

Abbreviations: Hgb, hemoglobin; IgM, immunoglobulin M; IPSSWM, International Prognostic Scoring System for Waldenström's Macroglobulinemia.
[a]Genetic subtype was unevaluable because of poor sample quality: 12 of 14 patients had low tumor cell count and 2 of 14 had low library yield.

median number of one (range, 0-5) prior treatment; the median baseline Hgb level was 10.5 g/dL (range, 6.9-15.5 g/dL); 59% of patients had a baseline Hgb level ≤ 11.0 g/dL. Mutational data were available for 91% of patients (n = 136) overall and for 92% (n = 69) in the ibrutinib-rituximab arm; of those in this arm, 46% (n = 32) had the $MYD88^{L265P}$/$CXCR4^{WT}$ genotype, 38% (n = 26) the $MYD88^{L265P}$/$CXCR4^{WHIM}$ genotype, and 16% (n = 11) the $MYD88^{WT}$/$CXCR4^{WT}$ genotype.

Patient Disposition

The final analysis was performed upon study closure; the median follow-up was 50 (range, 0.5-63) months. The most common reasons for discontinuing ibrutinib or placebo were PD (ibrutinib-rituximab, n = 7 [9%]; placebo-rituximab, n = 34 [45%]) and investigator decision (ibrutinib-rituximab, n = 3 [4%]; placebo-rituximab, n = 29 [39%]) (Table 2; Data Supplement [Fig S1, Table S2]). The majority of patients (24 of 29 [83%]) in the placebo-rituximab arm who discontinued because of investigator decision did so because of study unblinding per Data Monitoring Committee recommendation. During the study, 35 patients (47%) in the placebo-rituximab arm crossed over to receive single-agent ibrutinib; in addition to those 35 patients, three additional patients from that arm received ibrutinib off-study, for a total of 38 patients (51%) who received ibrutinib as next-line therapy. Sixty-eight patients (45%) continued to receive ibrutinib in a commercial setting (n = 36) or through a treatment extension program (n = 32) after study closure.

PFS

At the final analysis, median PFS was significantly longer in the ibrutinib-rituximab arm (median not reached; 95% CI, 58 to not evaluable [NE]) compared with the placebo-rituximab arm (median 20 months; 95% CI, 13 to 28) (Fig 1A), indicating a 75% reduction in risk of disease progression or death with ibrutinib-rituximab (HR, 0.25; 95% CI, 0.15 to 0.42; $P < .0001$). Survival benefits per standard Kaplan-Meier methodology were similar at timepoints of clinical significance relative to the median 50-month (range, 0.5-

63 months) follow-up: the estimated 54-month PFS rate for ibrutinib-rituximab versus placebo-rituximab was 68% (95% CI, 55 to 78) versus 25% (95% CI, 15 to 37) compared with estimated 48-month PFS rates of 71% (95% CI, 58 to 80) versus 25% (95% CI, 15 to 37).

PFS benefit with ibrutinib-rituximab was observed regardless of genotype (Fig 1B). In patients with the $MYD88^{WT}$/$CXCR4^{WT}$ genotype, the 54-month PFS rate was 70% with ibrutinib-rituximab versus 30% with placebo-rituximab. In patients with the $MYD88^{L265P}$/$CXCR4^{WT}$ genotype, the 54-month PFS rate was 72% with ibrutinib-rituximab versus 25% with placebo-rituximab. In patients with the $MYD88^{L265P}$/$CXCR4^{WHIM}$ genotype, the 54-month PFS rate was 63% with ibrutinib-rituximab versus 21% with placebo-rituximab. For all genotypes, estimated rates at 54 months were similar to those estimated at 48 months; in the ibrutinib-rituximab and placebo-rituximab arms, 48-month PFS rates were 79% and 25% in patients with the $MYD88^{L265P}$/$CXCR4^{WT}$ genotype, 63% and 21% in patients with the $MYD88^{L265P}$/$CXCR4^{WHIM}$ genotype, and 70% and 30% in patients with the $MYD88^{WT}$/$CXCR4^{WT}$ genotype, respectively.

Likewise, PFS benefit with ibrutinib-rituximab was observed regardless of prior treatment status (Fig 1C). In previously untreated patients, the 54-month PFS rate was not evaluable in either the ibrutinib-rituximab or placebo-rituximab arm; the 48-month PFS rate in these subgroups was 70% and 32%, respectively. In previously treated patients, the 54-month PFS rate was 68% with ibrutinib-rituximab versus 20% with placebo-rituximab, with similar 48-month PFS rates of 71% and 20%, respectively. When analyzed by key patient characteristics, treatment with ibrutinib-rituximab significantly reduced risk of progression or death versus placebo-rituximab across all prespecified subgroups within the previously treated population, including by serum IgM level, Hgb, International Prognostic Scoring System for WM score, and $MYD88$ mutational status, and within most of these subgroups in the previously untreated population (Data Supplement [Fig S2]).

TABLE 2. Patient Disposition and Treatment Exposure

Disposition	Ibrutinib-Rituximab (n = 75)	Placebo-Rituximab (n = 75)
Median duration of ibrutinib, months (range)	48 (1-59)	NA
Discontinued ibrutinib/placebo, No. (%)		
PD	7 (9)	34 (45)
AE	8 (11)	5 (7)
Withdrawal by patient	10 (13)	7 (9)
Investigator decision	3 (4)	29 (39)[a]
Patients receiving subsequent treatment, No. (%)	9 (12)	47 (63)

Abbreviations: AE, adverse event; NA, not applicable; PD, progressive disease.

[a]Of the 29 patients in the placebo-rituximab arm who discontinued treatment because of investigator decision, 24 patients discontinued because of study unblinding per Data Monitoring Committee recommendation.
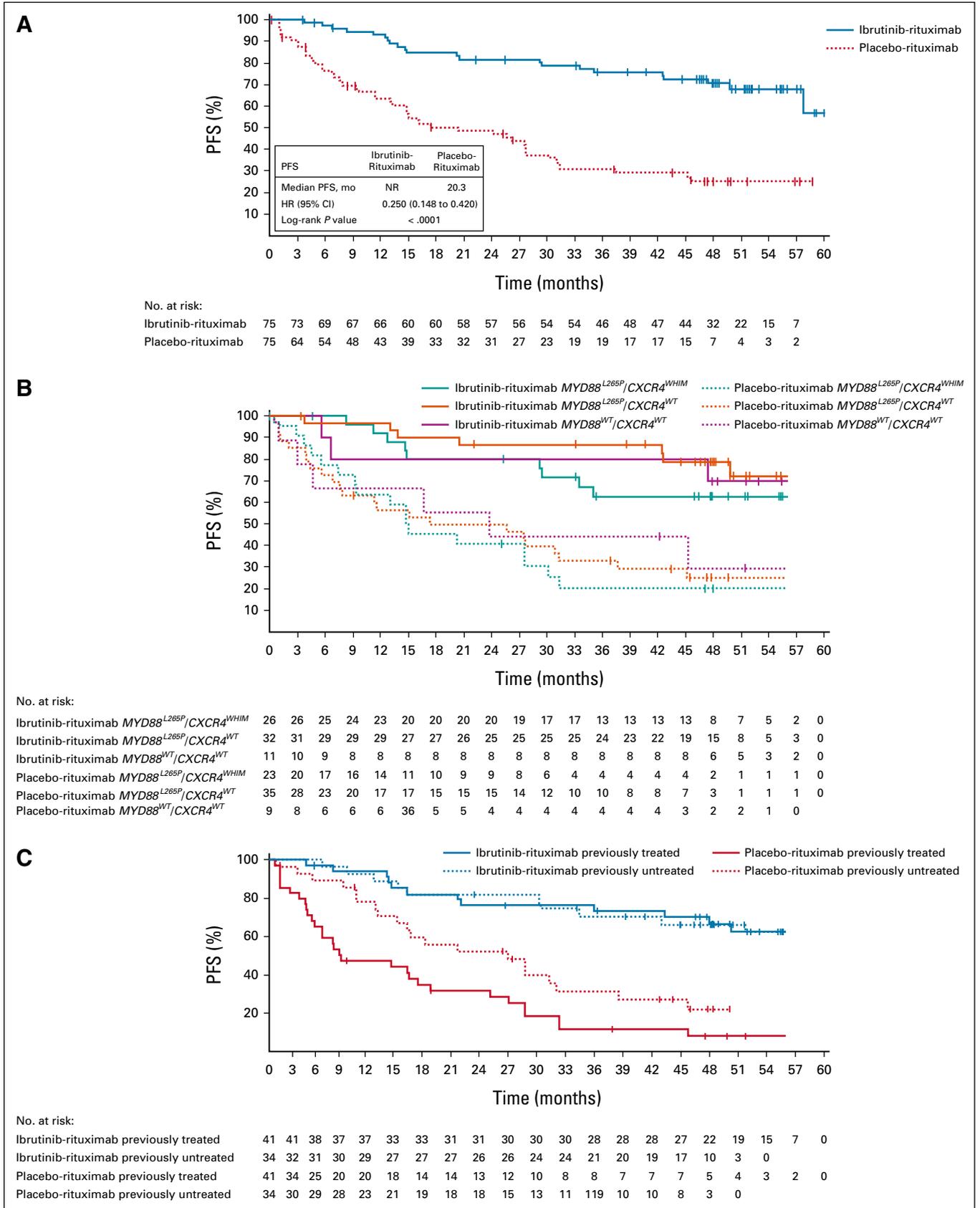
FIG 1. PFS (A) in the intention-to-treat population, (B) by genotype, and (C) by prior treatment status. For PFS by genotype and prior treatment status, Kaplan-Meier curves are shown for time points with ≥ 10 patients. HR, hazard ratio; NR, not reported; PFS, progression-free survival.
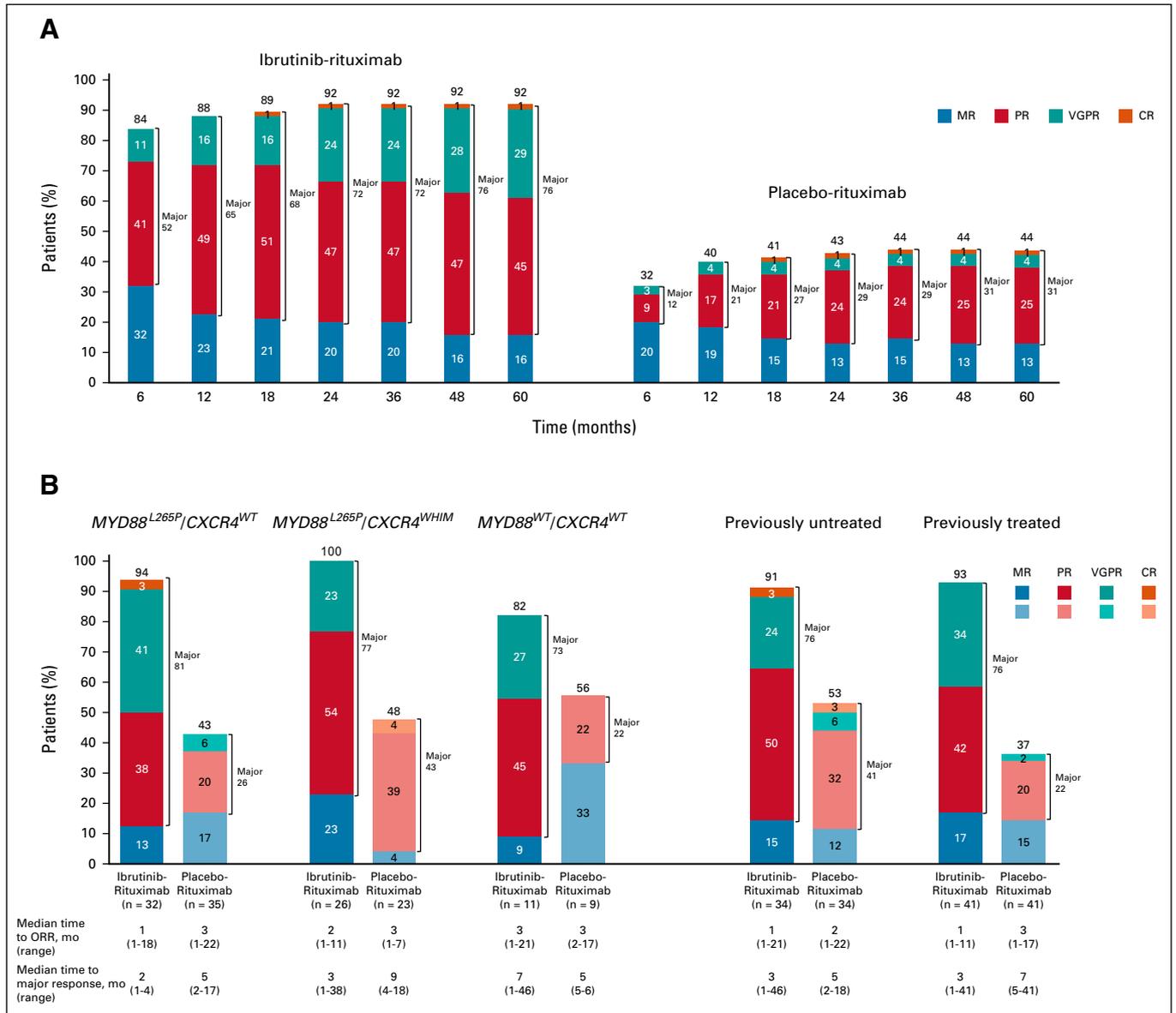
FIG 2. Overall response rates and major response rates in (A) the intention-to-treat population over time (n = 75 for each treatment arm at each timepoint) and (B) by genotype[a] and prior treatment status. [a]Response rates exclude six patients in the ibrutinib-rituximab arm and eight patients in the placebo-rituximab arm who had unknown genotype. NOTE. Values over 100% are due to rounding. CR, complete response; MR, minor response; ORR, overall response rate; PR, partial response; VGPR, very good partial response.

Response

At final analysis, ORR per IRC was significantly higher with ibrutinib-rituximab versus placebo-rituximab (92% v 44%) and time to overall response (MR or better) was faster (median 1 month [range, 1-21 months] v median 3 months [range, 1-22 months]). Major response rates (partial response or better) were also significantly higher with ibrutinib-rituximab versus placebo-rituximab (76% v 31%; P < .0001; Fig 2A). The depth of response to ibrutinib-rituximab increased over time, with major responses increasing from 72% at month 24 to 76% at month 60. One complete response occurred in each arm; both were achieved by month 18. The higher response rates and

faster time to response with ibrutinib-rituximab versus placebo-rituximab were observed regardless of genotype and prior treatment status (Fig 2B). Among patients with the $MYD88^{WT}/CXCR4^{WT}$ genotype, ORR was 82% with ibrutinib-rituximab versus 56% with placebo-rituximab. Similar results were observed among patients with the $MYD88^{L265P}/CXCR4^{WHIM}$ and $MYD88^{L265P}/CXCR4^{WT}$ genotypes, where ORRs with ibrutinib-rituximab were 100% and 94% versus 48% and 43% with placebo-rituximab, respectively.

Improvements in Hgb and IgM Levels

Significantly higher sustained Hgb levels were observed with ibrutinib-rituximab versus placebo-rituximab. At
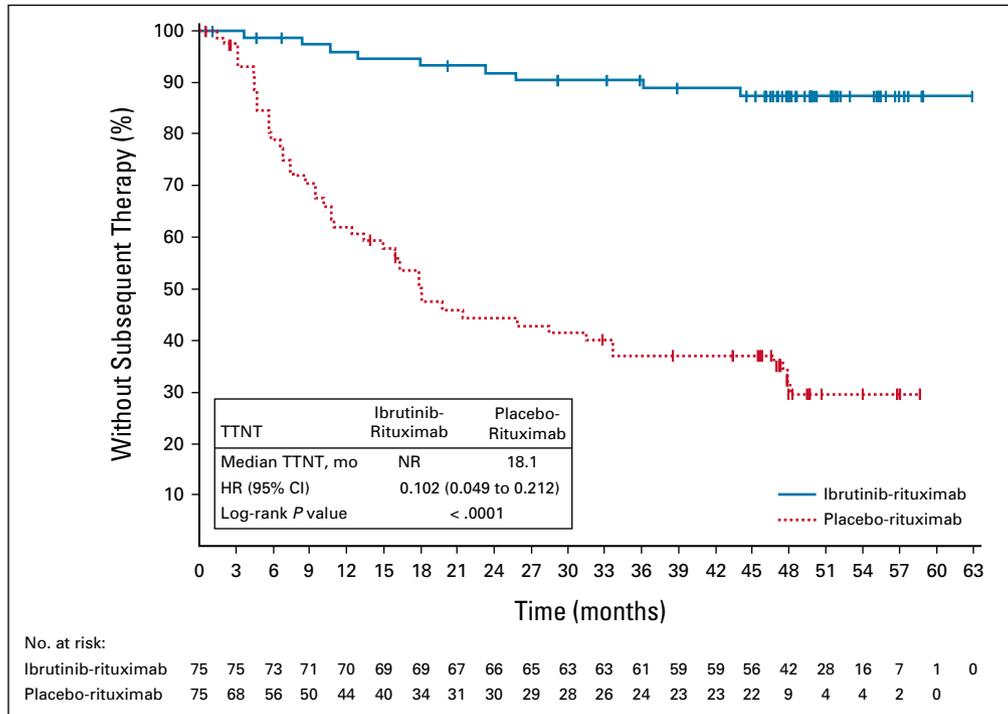
FIG 3. TTNT. HR, hazard ratio; NR, not reported; TTNT, time to next treatment.

baseline, median Hgb was 10.5 g/dL with ibrutinib-rituximab and 10.0 g/dL with placebo-rituximab. At the final analysis, a greater proportion of patients receiving ibrutinib-rituximab versus placebo-rituximab had sustained Hgb improvement (77% [58 of 75] v 43% [32 of 75]; $P < .0001$), including in the subset of patients (n = 94) with Hgb $\leq$ 11.0 g/dL at baseline (95% [42 of 44] v 56% [28 of 50]; $P < .0001$).

Patients receiving ibrutinib-rituximab experienced rapid and sustained reductions in serum IgM levels. Baseline median serum IgM levels were similar between the treatment arms (ibrutinib-rituximab, 32.9 g/L; placebo-rituximab, 31.8 g/L). IgM decreased rapidly during the first year of treatment with ibrutinib-rituximab and reached a maximum median change of –33.5 g/L at 56 months. Initial decreases in IgM were not as pronounced in the placebo-rituximab arm and reached a maximum median change of –26.9 g/L at 57 months (Data Supplement [Fig S3]).

OS

Median OS was not reached in either treatment arm (HR, 0.81; 95% CI, 0.33 to 1.99; $P = .6430$). Estimated 54-month OS rates were similar with ibrutinib-rituximab and placebo-rituximab (86% [95% CI, 74 to 93] v 84% [95% CI, 71 to 92], respectively) (Data Supplement [Fig S4]) and consistent with the estimated 48-month OS rates of 90% [95% CI, 79 to 95] in the ibrutinib-rituximab arm and 88% [95% CI, 77 to 93] in the placebo-rituximab arm. At the final analysis, nine patients (12%) on ibrutinib-rituximab and 10

patients (13%) on placebo-rituximab had died. When adjusted for crossover using a two-stage Accelerated Failure Time model,[12] OS remained consistent with the original analysis, with an improved HR of 0.64 (95% CI, 0.26 to 1.62) (Data Supplement [Fig S4]). In patients who crossed over to single-agent ibrutinib after PD on placebo-rituximab, median OS was not reached (95% CI, 47 months to NE) and the 54-month OS rate was not evaluable.

TTNT

Nine patients (12%) in the ibrutinib-rituximab arm and 47 (63%) patients in the placebo-rituximab arm received subsequent treatment. Median TTNT was significantly longer with ibrutinib-rituximab (not reached [95% CI, NE to NE]) versus placebo-rituximab (18 months [95% CI, 11 to 33]; $P < .0001$) (Fig 3), with substantially more patients (87% v 29%) without subsequent treatment at the 54-month landmark timepoint.

Safety

At the final analysis, the median treatment duration for ibrutinib was 48 (range, 1-59) months. Patients had a mean relative ibrutinib dose intensity of 93%, with 59 patients (79%) having a relative dose intensity $\geq$ 90%. The median treatment duration for placebo-rituximab was 16 (range, 0.4-37) months; safety data for that arm were previously reported.[2,13]

Ibrutinib-rituximab was tolerable regardless of common concomitant medications, including acid-reducing agents (49%), antiplatelet agents (41%), anticoagulants (24%),

TABLE 3. Safety Summary

	Ibrutinib-Rituximab, No. (%)					
	Prevalence by Year					
AE	Year 0-1 (n = 75)	Year 1-2 (n = 69)	Year 2-3 (n = 58)	Year 3-4 (n = 54)	Year 4-5 (n = 40)	Overall (n = 75)
AE leading to ibrutinib dose reduction	7 (9)	10 (15)	7 (12)	6 (11)	2 (5)	17 (23)
AE leading to ibrutinib discontinuation	1 (1)	2 (3)	2 (3)	2 (4)	1 (1)	8 (11)
Death as a result of TEAE	0	0	0	0	1 (3)[a]	1 (3)[a]
Major hemorrhage	2 (3)	0	3 (5)	0	0	5 (7)
Any grade atrial fibrillation	8 (11)	6 (9)	3 (5)	3 (6)	3 (8)	14 (19)

	Prevalence by Year, No. (%)					Overall (n = 75), No. (%)
Grade ≥ 3 TEAEs of Clinical Interest[b]	Year 0-1 (n = 75)	Year 1-2 (n = 69)	Year 2-3 (n = 58)	Year 3-4 (n = 54)	Year 4-5 (n = 40)	
Infections and infestations	13 (17)	4 (6)	4 (7)	7 (13)	2 (5)	22 (29)
Atrial fibrillation	6 (8)	5 (7)	1 (2)	2 (4)	1 (3)	12 (16)
Hypertension	5 (7)	7 (10)	6 (10)	3 (6)	1 (3)	11 (15)
Neutropenia	6 (8)	2 (3)	2 (3)	2 (4)	0	10 (13)
Anemia	10 (13)	0	0	1 (2)	0	9 (12)
Pneumonia	5 (7)	1 (1)	1 (2)	1 (2)	1 (3)	8 (11)
Arthralgia	0	2 (3)	0	1 (2)	0	3 (4)
Fatigue	2 (3)	2 (3)	0	1 (2)	1 (3)	3 (4)
Thrombocytopenia	0	0	0	1 (2)	1 (3)	1 (1)

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

[a]One patient in the ibrutinib-rituximab arm died as a result of pneumonia; this AE was not considered related to study drug.

[b]Listed in descending order of overall frequency.

and antihypertensives (40%) (Data Supplement [Table S3]). The most common grade ≥ 3 treatment-emergent adverse events of clinical interest that occurred with ibrutinib-rituximab were infections and infestations, anemia, atrial fibrillation, and hypertension; the prevalence of these grade ≥ 3 AEs generally decreased over time (Table 3). In total, 19 patients (25%) experienced any grade hypertension (grade 3 or 4, n = 11 [15%]) and 14 patients (19%) experienced any grade atrial fibrillation (grade 3 or 4, n = 12 [16%]). Grade ≥ 3 hypertension events (shown as prevalence) occurred primarily in the first 3 years of treatment, with only one event documented in year 5 (years 0-1, n = 5; years 1-2, n = 7; years 2-3, n = 6; years 3-4, n = 3; and years 4-5, n = 1). Similarly, the prevalence of atrial fibrillation events stabilized after the first 2 years of treatment (years 0-1, n = 6; years 1-2, n = 5) and remained infrequent (n ≤ 2) in years 3-5. Of 12 patients with grade 3 or 4 atrial fibrillation, nine (75%) remained on treatment. No major hemorrhage events were reported in the last 24 months of treatment. One death as a result of an AE of pneumonia occurred during year 4 and was deemed unrelated to study drug. Four patients discontinued treatment because of AEs (pneumonia, atrial fibrillation,

small-cell lung cancer, and metastatic breast cancer) in the ibrutinib-rituximab arm during the last 24 months of treatment, for a total of eight patients overall who discontinued ibrutinib because of an AE (Table 3 and the Data Supplement [Table S2]). Overall, 17 patients had ≥ 1 AE leading to dose reduction (Data Supplement [Table S4]); 11 patients (15%) reduced their dose to 280 mg, and six (8%) reduced their dose to 140 mg. Following dose reduction, 92% of the AEs resolved.

PROs

Patients in both arms reported clinically meaningful improvements in quality-of-life measures. EQ-5D-5L visual analog scale score, FACT-An score, and anemia subscale score improved from baseline. The proportion of patients reporting a clinically meaningful improvement in EQ-5D-5L visual analog scale score (51% in the ibrutinib-rituximab arm v 55% in the placebo-rituximab arm; P = .652) and utility score (47% v 36%; P = .168) was not significantly different between treatment arms. Overall, 56 patients (75%) in the ibrutinib-rituximab arm reported clinically meaningful improvement in total FACT-An score versus 44 (59%) in the placebo-rituximab arm (P = .039). A greater

proportion of patients in the ibrutinib-rituximab arm versus the placebo-rituximab arm also experienced an improvement in anemia subscale score (67% v 48%; P = .025).

DISCUSSION

Consistent with the primary analysis of iNNOVATE,[2] the results from the final analysis confirmed the durable efficacy of ibrutinib-rituximab in patients with WM, regardless of genotype or prior treatment status. With a median follow-up of 50 (range, 0.5-63) months, ibrutinib-rituximab showed ongoing superiority across clinical outcomes versus placebo-rituximab. Median PFS was not reached with ibrutinib-rituximab versus 20 months with placebo-rituximab; risk of disease progression or death was reduced by 75% with ibrutinib-rituximab. Major response rates were high (76% with ibrutinib-rituximab v 31% with placebo-rituximab), and because of increases in very good partial response rates (from 24% at month 24 to 29% at month 60), continued to deepen over time in the ibrutinib-rituximab arm. Furthermore, time to response was shorter and TTNT was substantially longer with ibrutinib-rituximab versus placebo-rituximab. Rapid and sustained Hgb improvements were observed with ibrutinib-rituximab, including in 95% of patients with anemia at baseline. As noted in the primary analysis, infusion-related reactions (43% v 59%) and IgM flare (8% v 47%) were less frequent with ibrutinib-rituximab versus placebo-rituximab[2] and serum IgM levels remained low with extended follow-up.

No new safety signals emerged in this study with a median follow-up of 50 months. Consistent with observations from other studies, AEs were generally most common during the first year of treatment and decreased over time.[14-17] Here, the prevalence of grade ≥ 3 hypertension was relatively stable from years 0-3, with no new events after year 3. The majority of patients with grade 3 or 4 atrial fibrillation were able to remain on treatment (9 of 12; 75%); no other ibrutinib discontinuations because of common grade 3 or 4 AEs occurred. As reported previously, 10 of 75 patients in the placebo-rituximab arm discontinued treatment because of an AE (70% from infusion-related reactions).[2] In contrast, no patient receiving ibrutinib-rituximab discontinued because of an infusion-related reaction; a low rate of discontinuations because of AEs was maintained after a median of 48 months on treatment. Most AEs leading to an ibrutinib dose reduction resolved following dose reduction, suggesting that AEs can be managed effectively with dose modification, allowing patients to stay on therapy and maintain disease control.

MYD88 and CXCR4 mutational status can negatively affect treatment outcomes.[18,19] The higher risk of transformation and death in patients expressing wild-type MYD88 may be due to activating mutations in the NFκB pathway that overlap with those observed in diffuse large B-cell lymphoma and are

further downstream of BTK. Patients with wild-type MYD88 exhibit a more aggressive disease course and have a lower probability of response to single-agent ibrutinib.[18,20] Additionally, certain CXCR4 mutations, which occur in up to 40% of patients with WM, may affect response to ibrutinib.[20] For example, a previous nonrandomized study in 63 patients treated with single-agent ibrutinib reported fewer major and very good partial responses and shorter PFS in patients with a CXCR4 mutation.[10] Results from the open-label substudy of iNNOVATE demonstrate that single-agent ibrutinib is effective in patients with rituximab-refractory WM, with a high proportion of heavily pretreated patients achieving an overall response (87% [27 of 31]), including 86% (6 of 7) of patients with CXCR4 mutations.[21] Notably, median PFS was shorter in patients with the MYD88^{L265P}/CXCR4^{WHIM} genotype versus those with the MYD88^{L265P}/CXCR4^{WT} genotype (18 months v not reached). In this final analysis from the iNNOVATE study, clinical benefit with ibrutinib-rituximab versus placebo-rituximab was independent of mutational status, with high overall (100%) and major response rates (77%) achieved in patients with CXCR4 mutations.

Although this study does not include a single-agent ibrutinib comparator arm, outcomes with single-agent ibrutinib suggest a potential benefit of adding rituximab to ibrutinib in those patients who are not refractory to rituximab.[10] In contrast to outcomes reported with single-agent ibrutinib, response rates and PFS with ibrutinib-rituximab were independent of genotype; this is particularly important for patients with CXCR4 mutations and MYD88 wild-type patients who have a lower probability of response to single-agent ibrutinib[10] and may also impact treatment decisions in the absence of genomic testing. Additionally, in the current study, there was a shorter time to major response with ibrutinib-rituximab (3 months) in patients with CXCR4 mutations than that reported in another study with single-agent ibrutinib in previously untreated (7.3 months)[4] and previously treated (4.7 months)[10] patients with WM and CXCR4 mutations. Although the results from the open-label substudy of iNNOVATE demonstrate that single-agent ibrutinib is effective in patients with rituximab-refractory disease,[21] our results suggest a clinical benefit of combining ibrutinib and rituximab across all lines of therapy, particularly for patients with CXCR4 or wild-type genotypes.

Ibrutinib in combination with rituximab provided sustained efficacy and significantly reduced the risk of disease progression or death compared with rituximab alone, regardless of genotype and prior treatment. With a 24-month additional treatment follow-up since the previous analysis, ibrutinib-rituximab maintained a manageable safety profile. In conclusion, with a median follow-up of 50 (range, 0.5-63) months, ibrutinib-rituximab remains an efficacious and well-tolerated chemotherapy-free regimen for patients with WM regardless of prior treatment or MYD88 and CXCR4 mutational status.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study

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