original report

AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma

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abstract

PURPOSE Patients with indolent non-Hodgkin lymphoma typically respond well to first-line immunochemotherapy. At relapse, single-agent rituximab is commonly administered. Data suggest the immunomodulatory agent lenalidomide could increase the activity of rituximab.

METHODS A phase III, multicenter, randomized trial of lenalidomide plus rituximab versus placebo plus rituximab was conducted in patients with relapsed and/or refractory follicular or marginal zone lymphoma. Patients received lenalidomide or placebo for 12 cycles plus rituximab once per week for 4 weeks in cycle 1 and day 1 of cycles 2 through 5. The primary end point was progression-free survival per independent radiology review.

RESULTS A total of 358 patients were randomly assigned to lenalidomide plus rituximab (n = 178) or placebo plus rituximab (n = 180). Infections (63% *v* 49%), neutropenia (58% *v* 23%), and cutaneous reactions (32% *v* 12%) were more common with lenalidomide plus rituximab. Grade 3 or 4 neutropenia (50% *v* 13%) and leukopenia (7% *v* 2%) were higher with lenalidomide plus rituximab; no other grade 3 or 4 adverse event differed by 5% or more between groups. Progression-free survival was significantly improved for lenalidomide plus rituximab versus placebo plus rituximab, with a hazard ratio of 0.46 (95% CI, 0.34 to 0.62; $P < .001$) and median duration of 39.4 months (95% CI, 22.9 months to not reached) versus 14.1 months (95% CI, 11.4 to 16.7 months), respectively.

CONCLUSION Lenalidomide improved efficacy of rituximab in patients with recurrent indolent lymphoma, with an acceptable safety profile.

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ASSOCIATED CONTENT

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Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Non-Hodgkin lymphomas (NHLs) are mostly of B-cell origin[1] and include low-grade, indolent histologies that usually respond to initial therapy but typically relapse.[1-4] The most common indolent NHL types, follicular lymphoma (FL) and marginal zone lymphoma (MZL), account for 22% and 7% of adult NHL, respectively.[5,6] Despite being distinct entities, recurrent FL and MZL are treated similarly.[7,8] Single-agent rituximab is approved by the US Food and Drug Administration and is commonly used as treatment of these patients.

Lenalidomide is an immunomodulatory (IMiD) drug that binds to the cereblon E3 ubiquitin ligase complex, resulting in ubiquitination of the transcription factors Aiolos and Ikaros, leading to antilymphoma effects.[9,10] Preclinically, lenalidomide restored the response of tumor-infiltrating lymphocytes in autologous T-cell conjugates[11] and increased natural killer cell count and function in peripheral blood and natural killer cell lines.[12,13] Adding lenalidomide to rituximab enhanced antibody-dependent cell-mediated cytotoxicity, immune synapse formation, monocyte-mediated killing, and direct cytotoxicity against FL cells.[11,14-16]

There are several treatment options, none considered curative, for patients with relapsed/refractory FL and MZL, including chemotherapy plus anti-CD20 monoclonal antibodies and targeted agents such as phosphatidylinositol 3-kinase inhibitors. Treatment choice is often based on duration of response to prior therapies, types of prior therapies, and patient comorbidities.[3,17] Rituximab monotherapy is a treatment option in patients who had previously responded to rituximab, on the basis of observations that frequent responses can occur with rituximab retreatment.[18,19] Rituximab monotherapy was commonly used in the second-line treatment of FL (25% to 47% of patients) according to studies in the United States and Europe.[20-22] Lenalidomide plus rituximab combination showed clinical activity in patients with previously treated indolent NHL in a key phase II study[23] and others[24,25] demonstrating overall response rates of

65% to 77%, complete response (CR) rates of 35% to 41%, and median progression-free survival (PFS)/time to progression of 1 to 2 years. Recently, the lenalidomide plus rituximab combination also showed clinical activity in a phase III study of advanced untreated FL.[26] The AUGMENT trial (ClinicalTrials.gov identifier: NCT01938001) prospectively compared efficacy and safety of lenalidomide plus rituximab to placebo plus rituximab (a standard of care, among several) in patients with relapsed or refractory indolent NHL who are appropriate for rituximab monotherapy (Appendix Table A1, online only).

METHODS

Patients

Eligible patients had MZL or FL (grades 1 to 3a) requiring treatment per investigator assessment; at least one prior chemotherapy, immunotherapy, or chemoimmunotherapy and two or more previous doses of rituximab; and relapsed, refractory, or progressive disease and not rituximab-refractory disease. Patients with neuropathy grade greater than one were excluded. Additional eligibility criteria are in the Appendix (online only).

Trial Design and Treatment

Patients were randomly assigned (1:1 ratio) to lenalidomide plus rituximab (lenalidomide plus rituximab group) or placebo plus rituximab (placebo plus rituximab group). Random assignment was stratified according to previous rituximab treatment (yes or no), time since last therapy (≤ 2 years $v > 2$ years), and histology (FL *v* MZL). Prior induction and maintenance treatment were considered one treatment line.

Treatment continued for 12 cycles or relapse, progressive disease, withdrawal of consent, or unacceptable toxicity. Lenalidomide plus rituximab dosing included oral lenalidomide 20 mg daily (10 mg for creatinine clearance 30 to 59 mL/min) on days 1 to 21 plus intravenous rituximab 375 mg/m^2 days 1, 8, 15, and 22 of cycle 1 and day 1 of cycles 2 to 5 every 28 days. Placebo plus rituximab was administered similarly. The rituximab regimen was selected using efficacy and statistical assumptions from the LYM-3001 trial (ClinicalTrials.gov identifier: NCT00312845) in similar patients.[18] Rationale for lenalidomide and rituximab dosing schedules are detailed in the Appendix. On treatment completion or discontinuation, patients were observed for progression, subsequent therapies, response to next therapies, and second malignancies for up to 5 years after the last patient was randomly assigned (Appendix).

Dose adjustments of lenalidomide were planned to manage toxicity (Appendix). In patients with thromboembolism risk, prophylactic anticoagulation or antiplatelet therapy at investigator discretion was recommended. Rituximab dose was not reduced, but if discontinued for toxicity, lenalidomide plus placebo continued per protocol (Data Supplement). Growth factor use was allowed per ASCO/European Society for Medical Oncology guidelines.[27,28]

This study was performed following Good Clinical Practice per International Conference on Harmonization Guideline E6 requirements under ethical principles in the Declaration of Helsinki. Study conduct followed guidance of each site's institutional review board, independent ethics committee, and regulatory authorities. All patients provided written informed consent before trial enrollment.

Efficacy and Safety Assessments

Primary efficacy analyses were conducted in the intention-to-treat population, defined as all patients randomly assigned, regardless of receiving trial treatment. The primary end point was PFS assessed by the independent review committee (IRC) per 2007 International Working Group criteria,[29] without positron emission tomographic imaging. Secondary end points included overall response rate, CR, duration of response, overall survival (OS), event-free survival, and time to next antilymphoma treatment. Time to next chemotherapy treatment and histologic transformation were exploratory end points.

Response and progression outcomes were assessed by a blinded, independent central review using 2007 International Working Group criteria on the basis of computed axial tomography/magnetic resonance imaging scans. Patients with gastric mucosa–associated lymphoid tissue lymphoma underwent endoscopy for response evaluation. Bone marrow biopsy was required to confirm CR.

The safety analysis population included all patients receiving at least one dose of study medication. Adverse event classification used National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, except for tumor flare (graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0) and tumor lysis (assessed per Cairo-Bishop Criteria).[30]

Statistical Analyses

The primary objective was to compare efficacy in the lenalidomide plus rituximab group versus the placebo plus rituximab group on the basis of the primary end point of PFS at one-sided $\alpha = 0.025$ level. We hypothesized that median PFS for lenalidomide plus rituximab would be 17.6 months, and 11 months for placebo plus rituximab, on the basis of previous results of rituximab monotherapy (Appendix).[18] For 90% power to detect this difference with one-sided $\alpha = 0.025$ and one interim analysis for the futility at 50% information time, a total of 193 PFS events were required.

The distribution for PFS and other time-to-event data were estimated using the Kaplan-Meier procedure.[31] A hazard ratio (HR) with a two-sided 95% CI was estimated using the stratified Cox proportional hazard regression model. For binary types of secondary efficacy end points, the number and percentage of patients were tabulated by treatment group, a stratified Cochran-Mantel-Haenszel test adjusting

for possible confounding effects of the stratification factors was performed, and a *P* value was provided. Prespecified subgroup analysis of PFS was also performed and HR estimated from Cox proportional hazard regression model; *P* value was generated using Fisher's exact *t* test for binary end points and log-rank test for time to event end points.

RESULTS

Patients and Trial Treatment

From February 13, 2014 through January 26, 2017, 358 patients enrolled from 97 centers in 15 countries were randomly assigned 1:1 to lenalidomide plus rituximab (n = 178) or placebo plus rituximab (n = 180; Fig 1). Baseline characteristics were similar (Table 1). Median age was 63 years (range, 26 to 88 years); 295 patients (82%) had FL, and 63 (18%) had MZL. Overall, 51% had high tumor burden per Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria. The median number of prior therapies was one (range, one to 12), and 86 patients (24%) had three or more prior systemic treatments. Relapse or progression within 2 years of initial diagnosis had occurred in 117 patients (33%), and 56 (16%) were refractory to their last regimen. Four patients had been lost to follow-up.

In the safety population, the full treatment course was completed in 71% of patients with lenalidomide plus rituximab and 61% with placebo plus rituximab. Adverse events leading to dose interruptions were more common with lenalidomide plus rituximab than lenalidomide plus placebo (64% *v* 26%), reductions (26% *v* 3%), and discontinuations (9% *v* 5%). Neutropenia was the most common adverse event leading to reduction (18%) and interruption (39%) of lenalidomide. Dose modifications successfully addressed neutropenia, with only five patients (3%) discontinuing lenalidomide because of neutropenia. Disease progression led to treatment discontinuations in 21 patients (12%) and 54 patients (30%) in the lenalidomide plus rituximab and placebo plus rituximab groups, respectively. Type 1 error was not controlled for secondary and exploratory end points, and *P* values were descriptive in nature.

Efficacy

Primary end point. At the final analysis, median follow-up was 28.3 months, and 185 events total (progression or death) were assessed by IRC (200 events per investigator assessment) before censoring. The primary end point of PFS assessed by IRC was significantly superior in the lenalidomide plus rituximab group (HR, 0.46; 95% CI, 0.34 to 0.62; $P < .0001$; Fig 2A; Table 2). Median PFS assessed by IRC was 39.4 months (95% CI, 22.9 months to not reached) with lenalidomide plus rituximab versus 14.1 months (95% CI, 11.4 to 16.7 months) with placebo plus rituximab. PFS assessed by investigator also showed superiority with lenalidomide plus rituximab versus placebo plus rituximab (HR, 0.51; 95% CI, 0.38 to 0.69; $P < .0001$;

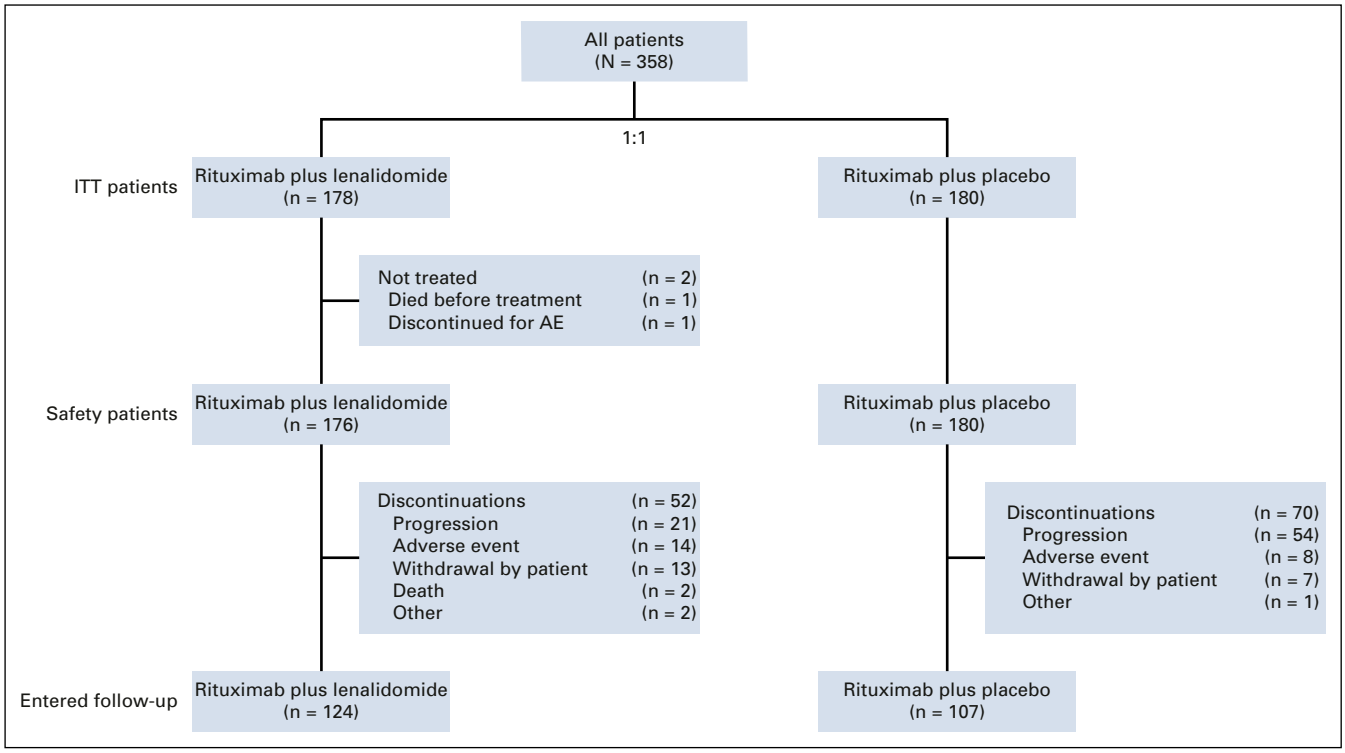

FIG 1. Lenalidomide plus rituximab and placebo plus rituximab group CONSORT diagram (flow of patients from enrollment to analysis). AE, adverse event; ITT, intention to treat.

TABLE 1. Baseline Demographic and Disease Characteristics (ITT Population)*

Characteristic	Lenalidomide + Rituximab (n = 178)	Placebo + Rituximab (n = 180)	Total (N = 358)
Median age, years (range)	64 (26-86)	62 (35-88)	63 (26-88)
Age ≥ 65 years	82 (46)	73 (41)	155 (43)
Male sex	75 (42)	97 (54)	172 (48)
ECOG performance status*			
0	116 (65)	128 (71)	244 (68)
1	60 (34)	50 (28)	110 (31)
2	2 (1)	2 (1)	4 (1)
Positive bone marrow involvement			
Yes	33 (19)	31 (17)	64 (18)
Biopsy not performed	72 (40)	69 (38)	141 (39)
Ann Arbor stage†			
I or II	41 (23)	56 (31)	97 (27)
III or IV	137 (77)	124 (69)	261 (73)
Bulky disease‡	45 (25)	49 (27)	94 (26)
High tumor burden per GELF criteria	97 (54)	86 (48)	183 (51)
Histology			
FL grade	147 (83)	148 (82)	295 (82)
1 or 2	125 (70)	123 (68)	248 (69)
3a	22 (12)	25 (14)	47 (13)
MZL	31 (17)	32 (18)	63 (18)
Extranodal MZL of mucosa-associated lymphoid tissue	14 (8)	16 (9)	30 (8)
Nodal	8 (4)	10 (6)	18 (5)
Splenic	9 (5)	6 (3)	15 (4)
Lactate dehydrogenase > ULN	43 (24)	39 (22)	82 (23)
B symptoms§	16 (9)	12 (7)	28 (8)
FLIPI score‖			
0 or 1	52 (29)	67 (37)	119 (33)
2	55 (31)	58 (32)	113 (32)
3-5	69 (39)	54 (30)	123 (34)
Missing	2 (1)	1 (1)	3 (1)
No. of prior systemic antilymphoma regimens			
1	102 (57)	97 (54)	199 (56)
2	31 (17)	42 (23)	73 (20)
3	25 (14)	19 (11)	44 (12)
≥ 4	20 (11)	22 (12)	42 (12)
Prior rituximab treatment	152 (85)	150 (83)	302 (84)
Prior rituximab-containing chemotherapy regimen	130 (73)	129 (72)	259 (72)
Time since last antilymphoma therapy			
≤ 2 years	89 (50)	92 (51)	181 (51)
> 2 years	89 (50)	88 (49)	177 (49)

(continued on following page)

TABLE 1. Baseline Demographic and Disease Characteristics (ITT Population)* (continued)

Characteristic	Lenalidomide + Rituximab (n = 178)	Placebo + Rituximab (n = 180)	Total (N = 358)
Relapse/progression ≤ 2 years of initial diagnosis	56 (31)	61 (34)	117 (33)
Refractory to last regimen	30 (17)	26 (14)	56 (16)

NOTE. All data are No. (%) unless otherwise stated. There were no significant between-group differences in the characteristics evaluated at baseline. Percentages may not sum to 100 because of rounding.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI; Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; ITT, intention to treat; MZL, marginal zone lymphoma; ULN, upper limit of normal.

*The ECOG performance status scale ranges from 0 to 5, with higher scores indicating greater disability; a score of 0 indicates no symptoms, 1 indicates mild symptoms, and 2 indicates moderate symptoms.

†Stages range from I to IV, with higher stages indicating more extensive disease.

‡Bulky disease was defined as a tumor that was 7 cm or larger in the greatest dimension or at least three lesions 3 cm or larger in the longest diameter, as measured by the investigator.

§B symptoms are systemic symptoms such as weight loss, night sweats, and fever.

‖A FLIPI score indicates low (0 or 1), intermediate (2), or high (3 to 5) risk on the basis of a scoring system that gives one point for each of the following risk factors: a hemoglobin level of less than 12 g/dL, more than four nodal areas (with the exception of spleen), age older than 60 years, a lactate dehydrogenase level greater than the ULN, and Ann Arbor stage III or IV disease.

the median PFS was 25.3 months; 95% CI, 21.2 months to not reached *v* 14.3 months; 95% CI, 12.4 to 17.7 months; Appendix Fig A1, online only; Table 2). PFS probability at 2 years also favored lenalidomide plus rituximab (Table 2). Post hoc subgroup analyses for PFS on the basis of prior rituximab plus bendamustine or plus cyclophosphamide, doxorubicin, vincristine, and prednisone showed results consistent with those of the overall population (Appendix Table A2, online only).

Secondary and exploratory end points. Among patients in the lenalidomide plus rituximab versus placebo plus rituximab groups, the rate of best overall response assessed by IRC was 78% (95% CI, 71% to 83%) versus 53% (95% CI, 46% to 61%; $P < .0001$), with 34% (95% CI, 27% to 41%) versus 18% (95% CI, 13% to 25%) of patients achieving CR ($P = .001$; Table 2), with similar investigator-assessed results. Other secondary and exploratory time-to-event end points assessed by IRC also showed superior results with lenalidomide plus rituximab—response duration (Appendix Fig A2, online only; Table 2), event-free survival (Appendix Fig A3, online only; Table 2), time to next antilymphoma treatment (Appendix Fig A4, online only; Table 2), time to next chemotherapy treatment (Appendix Fig A5, online only; Table 2), and PFS on next antilymphoma treatment (Appendix Fig A6, online only; Table 2).

Overall survival results are maturing, with an HR of 0.61 (95% CI, 0.33 to 1.13; Fig 2B; Table 2). Numerically fewer deaths in treated patients have been observed with lenalidomide plus rituximab versus placebo plus rituximab (15 *v* 26), although the trial was not powered to detect OS differences. Estimated 2-year survival in the lenalidomide plus rituximab group was 93% (95% CI, 87% to 96%) versus 87% (95% CI, 81% to 92%) in the placebo plus rituximab group. Survival for FL and MZL subgroups are shown in Appendix Figures A7 and A8 (online only). In patients with FL, OS results favored lenalidomide plus rituximab (HR, 0.45; 95% CI, 0.22 to 0.92; $P = .02$; Appendix Table A3, online only), with 11 deaths with lenalidomide plus rituximab versus 24 with placebo plus rituximab. No difference was seen between groups in patients with MZL (HR, 2.89; 95% CI, 0.56 to 14.92), but with few events—five with lenalidomide plus rituximab versus two with placebo plus rituximab (Appendix Table A4, online only). Two patients with MZL in the lenalidomide plus rituximab arm died early after random assignment (3 days [did not receive any study treatment] and 13 days). Estimated 2-year survival probability in FL was 95% (95% CI, 90% to 98%) with lenalidomide plus rituximab and 86% (95% CI, 79% to 91%) with placebo plus rituximab (Appendix Table A3). Estimated 2-year survival in MZL was 82% (95% CI, 61% to 92%) with lenalidomide plus rituximab and 94% (95% CI, 77% to 98%) with placebo plus rituximab (Appendix Table A4).

Histologic transformation occurred in two patients (incidence per 100 person-years: 0.5%) with lenalidomide plus rituximab and 10 patients (incidence per 100 person-years: 2.5%) with placebo plus rituximab (Table 3). After transformation, one patient in the lenalidomide plus rituximab group and six in the placebo plus rituximab group died.

Subgroup analyses. PFS improvements were consistent with those of the overall population in all prespecified subgroups except the MZL subgroup (Fig 3). In this subset (n = 63), PFS was not significantly different between the two groups, with an unstratified HR of 1.00 (95% CI, 0.47 to 2.13), and the wide confidence intervals imply the data are uninformative. PFS results in the MZL subgroup are difficult to interpret because of the small sample size and imbalance in baseline prognostic factors (Appendix Table A5, online only).

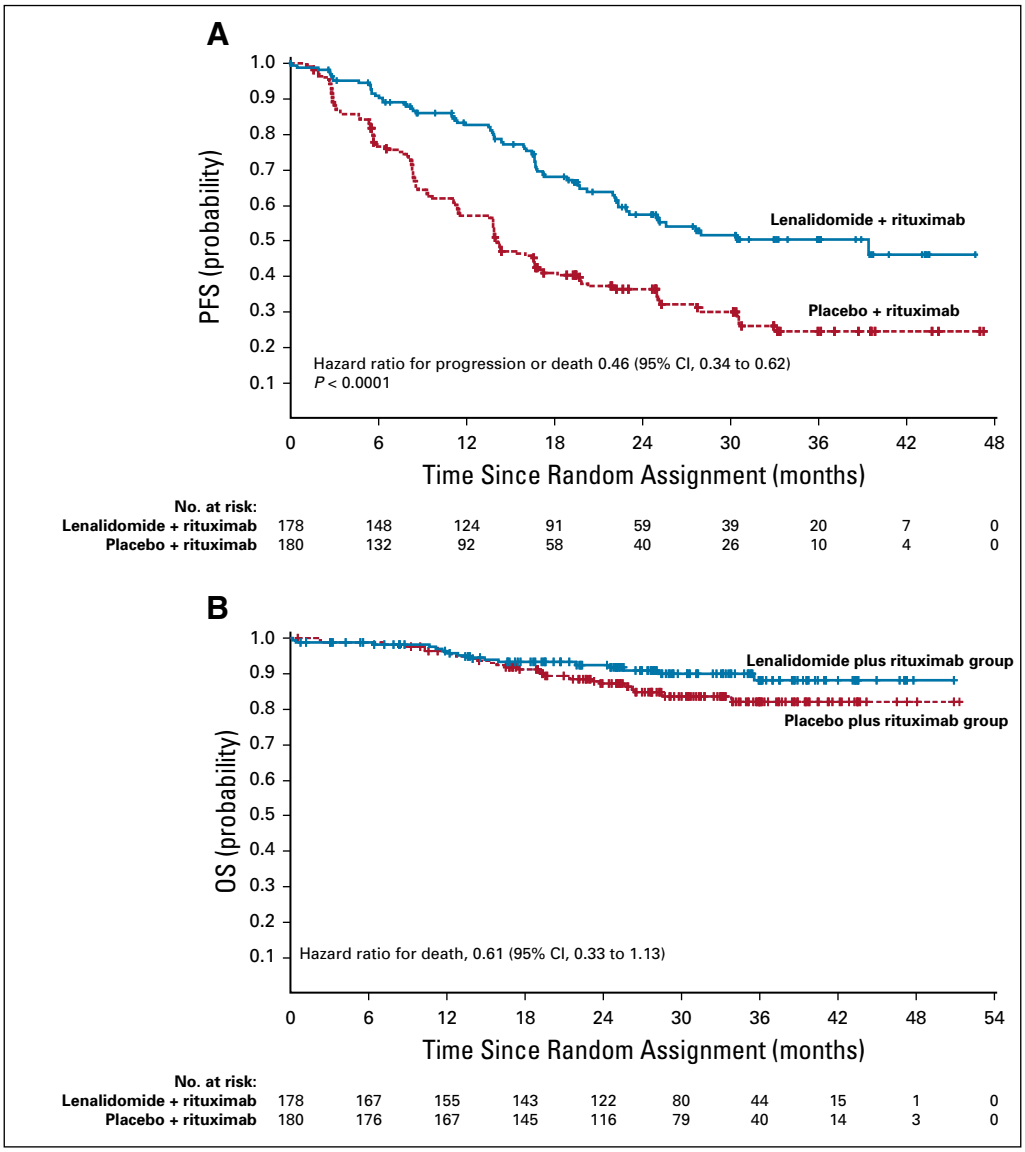

FIG 2. Progression-free survival (PFS) and overall survival (OS) as assessed by independent review committee in the intention-to-treat population: (A) progression-free survival; (B) overall survival.

Safety

The safety population included 176 patients who received lenalidomide plus rituximab and 180 patients who received placebo plus rituximab. Of these, 174 patients who received lenalidomide plus rituximab (99%) and 173 who received placebo plus rituximab (96%) had any-grade adverse events within 28 days after last dose. Most common adverse events are in Table 3. Adverse events of any grade that occurred more frequently (≥ 10% difference) with lenalidomide plus rituximab versus placebo plus rituximab included neutropenia (58% *v* 22%), constipation (26% *v* 14%), leukopenia (20% *v* 9%), anemia (16% *v* 4%), thrombocytopenia (15% *v* 4%), and tumor flare (11% *v* 1%), respectively. More patients who received lenalidomide plus rituximab (69%) had at least one grade 3 or 4 adverse event compared with placebo plus rituximab (32%). The increased rates of grade 3 or 4 adverse events with lenalidomide plus rituximab were attributable primarily to increased grade 3 or 4 neutropenia (50% *v* 13%) and leukopenia (7% *v* 2%). No other grade 3 or 4 adverse events occurred in 5% or more patients in either group. Febrile neutropenia occurred in 3% of patients with lenalidomide plus rituximab versus 1% with placebo plus rituximab. Growth factors were administered to 36% of the lenalidomide plus rituximab group versus 12% in the placebo plus rituximab group. Neutropenia was primarily managed through dose interruptions and/or reductions and growth-factor support. Only five patients had neutropenia leading to lenalidomide discontinuation. All incidences of grade 3 or 4 neutropenia in the lenalidomide plus rituximab group recovered to grade 1 or less, with a median time of 9.0 days. Efficacy was similar regardless of occurrence of grade 3 or 4 neutropenia in the lenalidomide plus rituximab group on the basis of post hoc analysis (Appendix Table A6, online only).

TABLE 2. Efficacy Outcomes (ITT Population)

Variable	Lenalidomide + Rituximab (n = 178)	Placebo + Rituximab (n = 180)	Hazard Ratio (95% CI)	*P*
Median PFS, months (95% CI)				
As assessed by IRC	39.4 (22.9 to NR)	14.1 (11.4 to 16.7)	0.46 (0.34 to 0.62)	< .0001
As assessed by investigator	25.3 (21.2 to NR)	14.3 (12.4 to 17.7)	0.51 (0.38 to 0.69)	< .0001
PFS probability at 2 years, % (95% CI)				
As assessed by IRC	58 (49 to 65)	36 (29 to 44)		
As assessed by investigator	53 (45 to 61)	34 (27 to 41)		
Best response, as assessed by IRC				
ORR, No. (% [95% CI])	138 (78 [71 to 83])	96 (53 [46 to 61])		< .0001
CR, No. (% [95% CI])	60 (34 [27 to 41])	33 (18 [13 to 25])		.0010
PR, No. (%)	78 (44)	63 (35)		
SD, No. (%)	20 (11)	55 (31)		
PD/death, No. (%)	7 (4)	23 (13)		
Not done/missing/no evidence of disease at baseline, No. (%)	13 (7)	6 (3)		
Best response, as assessed by investigator				
ORR, No. (% [95% CI])	141 (79 [73 to 85])	107 (59 [52 to 67])		< .0001
CR, No. (% [95% CI])	57 (32 [25 to 39])	37 (21 [15 to 27])		.0119
PR, No. (%)	84 (47)	70 (39)		
SD, No. (%)	22 (12)	56 (31)		
PD/death, No. (%)	6 (3)	15 (8)		
Not done/missing, No. (%)	9 (5)	2 (1)		
Median DOR as assessed by IRC, months (95% CI)	36.6 (22.9 to NR)	21.7 (12.8 to 27.6)	0.53 (0.36 to 0.79)	.0015
Median EFS as assessed by IRC, months (95% CI)	27.6 (22.1 to NR)	13.9 (11.4 to 16.7)	0.51 (0.38 to 0.67)	< .0001
Median TTNLT, months (95% CI)	NR (NR to NR)	32.2 (23.2 to NR)	0.54 (0.38 to 0.78)	.0007
Median TTNCT, months (95% CI)	NR (NR to NR)	NR (NR to NR)	0.50 (0.32 to 0.78)	.0017
Median PFS on next antilymphoma treatment, months (95% CI)	NR (NR to NR)	NR (NR to NR)	0.52 (0.32 to 0.82)	.0046
Median OS, months (95% CI)	NR (NR to NR)	NR (NR to NR)	0.61 (0.33 to 1.13)	
OS probability at 2 years, % (95% CI)	93 (87 to 96)	87 (81 to 92)		
Histologic transformation, No. (%)	2 (1)	10 (6)		

Abbreviations: CR; complete response; DOR, duration of response; EFS, event-free survival; IRC, independent review committee; ITT, intent to treat; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TTNCT, time to next antilymphoma chemotherapy treatment; TTNLT, time to next antilymphoma treatment.

Fatal adverse events (grade 5) occurred in four patients (1%), two in each group (lenalidomide plus rituximab: arrhythmia and cardiopulmonary failure; placebo plus rituximab: general physical health deterioration and pneumonia). Among treated patients, 15 deaths (9%) occurred in the lenalidomide plus rituximab group (five deaths attributed to lymphoma) versus 26 (14%) with placebo plus rituximab (18 deaths attributed to lymphoma).

With lenalidomide plus rituximab, 45 patients (26%) had at least one serious adverse event versus 25 (14%) with placebo plus rituximab (Appendix Table A7, online only). Pneumonia was the most common serious adverse event, occurring in five patients (3%) in each group. Deep vein thrombosis occurred in three patients (2%) in the lenalidomide plus rituximab and one patient (1%) in the placebo plus rituximab groups; only one incidence (lenalidomide plus rituximab group) was a serious adverse event. Antiplatelet and anticoagulant medication use is listed in Appendix Table A8 (online only). Second primary cancers were reported in six patients (3%) in the lenalidomide plus rituximab group and 10 patients (6%) with placebo plus rituximab (Appendix Table A9, online only). Two patients died of second primary cancers (both placebo plus rituximab arm).

TABLE 3. Treatment-Emergent Adverse Events in the Safety Population (≥ 10% of patients)

	Lenalidomide + Rituximab (n = 176)		Placebo + Rituximab (n = 180)	
Adverse Event	**All Grades**	**Grade 3 or 4**	**All Grades**	**Grade 3 or 4**
Neutropenia*	102 (58)	88 (50)	40 (22)	23 (13)
Diarrhea	55 (31)	5 (3)	41 (23)	0
Constipation	46 (26)	0	25 (14)	0
Cough	40 (23)	1 (1)	31 (17)	0
Fatigue	38 (22)	2 (1)	33 (18)	1 (1)
Pyrexia	37 (21)	1 (1)	27 (15)	3 (2)
Leukopenia	36 (20)	12 (7)	17 (9)	3 (2)
Upper respiratory tract infection	32 (18)	2 (1)	23 (13)	4 (2)
Anemia	28 (16)	8 (5)	8 (4)	1 (1)
Headache	26 (15)	1 (1)	17 (9)	0
Infusion-related reaction	26 (15)	4 (2)	24 (13)	0
Thrombocytopenia	26 (15)	4 (2)	8 (4)	2 (1)
Asthenia	24 (14)	2 (1)	19 (11)	1 (1)
Decreased appetite	23 (13)	2 (1)	11 (6)	0
Muscle spasms	23 (13)	1 (1)	9 (5)	1 (1)
Peripheral edema	23 (13)	0	16 (9)	0
Abdominal pain	22 (13)	2 (1)	16 (9)	0
Pruritus	21 (12)	2 (1)	7 (4)	0
Nausea	20 (11)	0	23 (13)	1 (1)
Dyspnea	19 (11)	2 (1)	8 (4)	1 (1)
Rash	19 (11)	2 (1)	7 (4)	1 (1)
Tumor flare	19 (11)	1 (1)	1 (1)	0
Alanine aminotransferase increased	18 (10)	3 (2)	15 (8)	1 (1)
Influenza	17 (10)	1 (1)	8 (4)	0
Vomiting	17 (10)	0	13 (7)	0
Back pain	14 (8)	0	18 (10)	0
Nasopharyngitis	13 (7)	0	18 (10)	0

NOTE. Data are given as No. (%).

*Febrile neutropenia occurred in five patients (3%) and one patient (1%) in the lenalidomide plus rituximab and placebo plus rituximab groups, respectively; all occurrences were grade 3 or 4.

DISCUSSION

The AUGMENT study met its primary end point; lenalidomide plus rituximab demonstrated statistically significant and clinically relevant superiority in PFS over placebo plus rituximab in patients with relapsed or refractory indolent FL/MZL who are considered appropriate for rituximab monotherapy. Lenalidomide plus rituximab, administered over 1 year, reduced risk of progression by 54% (HR, 0.46; 95% CI, 0.34 to 0.62; $P < .0001$) and increased median PFS by more than 2 years compared with rituximab monotherapy. Efficacy of the combination was also reflected by improvements in secondary and exploratory end points—response rates, response duration, time to next treatment, and time to next chemotherapy. Furthermore, PFS improved in all prespecified subgroups (prior rituximab, age, time since last therapy, sex, race, region, number of prior antilymphoma regimens, stage, refractory to last regimen, high tumor burden, chemoresistant, and unfit for chemotherapy [defined as age ≥ 70 years, or age 60 to 69 years and creatinine clearance < 60 mL/min or Eastern Cooperative Oncology Group performance status ≥ 2]) except for the MZL subgroup. No difference in PFS was observed between treatment groups in the MZL subgroup. Although this could relate to lack of effect in this subset, the small number of patients and imbalance in prognostic factors between arms limit interpretation for this histology.

One limitation of this study was the differences in median PFS seen when assessed by IRC (39.4 months) compared with investigator assessment (25.3 months); however, HRs and *P* values were similar between assessments, indicating

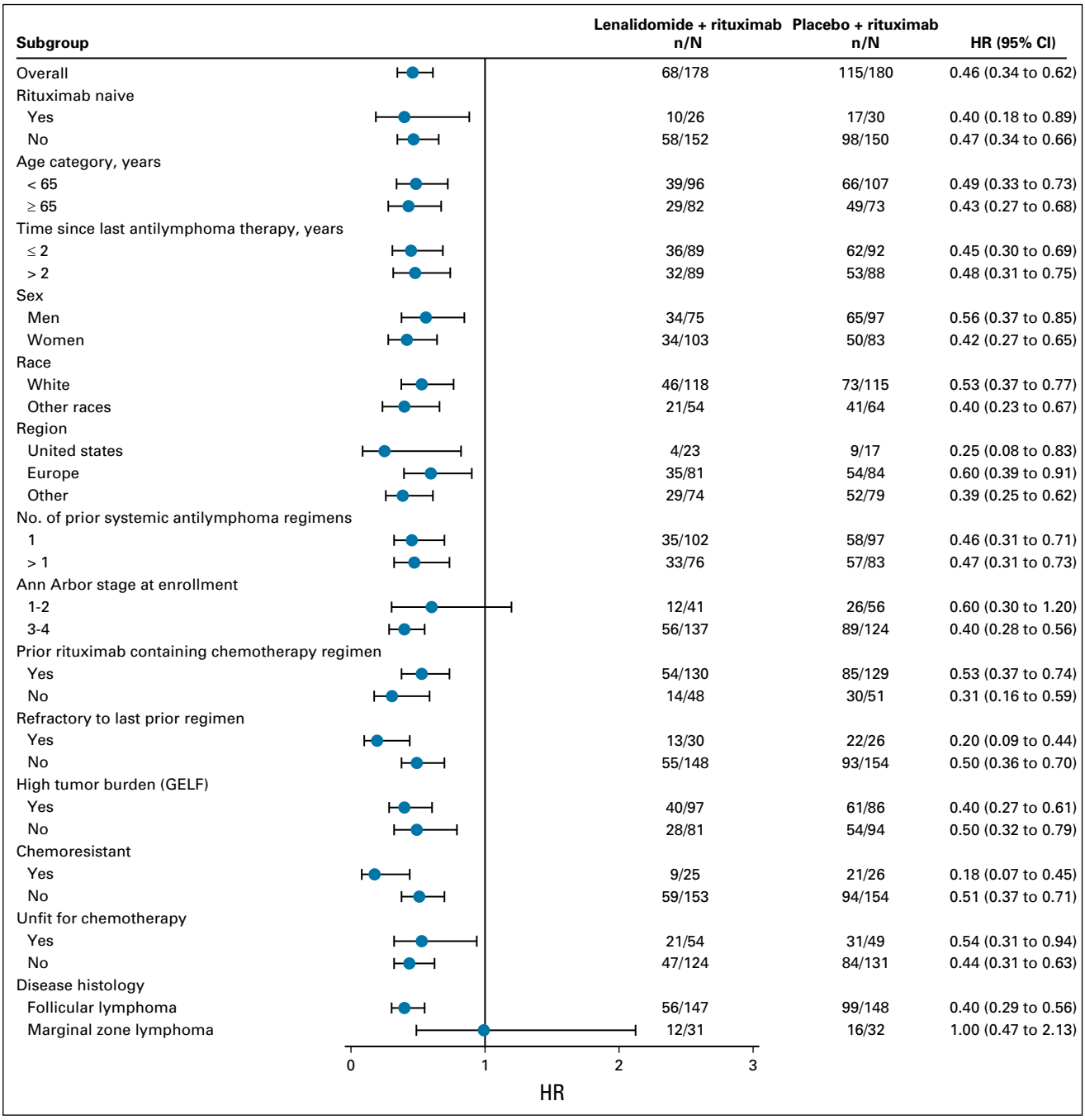

FIG 3. Forest plot: subgroup analyses of progression-free survival. GELF, Groupe d'Etude des Lymphomes Folliculaires; HR, hazard ratio.

consistency in PFS results between IRC and investigator assessments. Another limitation was that longer treatment duration occurred in the lenalidomide plus rituximab group; however, this likely did not influence efficacy results. Notably, separation of PFS Kaplan-Meier curves began early, and PFS benefits and durability of responses persisted beyond 1 year of study treatment duration and were consistently observed throughout the study follow-up period. In addition, schedule of rituximab (eight doses given over 5- to 28-day cycles) is not likely to have influenced results; several studies showed benefit of extended treatment with rituximab (ie, beyond standard 4 weekly infusions) in a manner that is independent of the number or schedule of extended rituximab dosing (ie, four or more doses every 1, 2, 3, or 6 months).[18,32-35] Importantly, the control group performed as expected on the basis of historical rituximab data, with results similar to the 11-month estimate used in the statistical plan.[18,19,36]

Current treatment options for recurrent FL include rituximab monotherapy, bendamustine, or other chemotherapy alone or with obinutuzumab[37] or rituximab.[38] In addition, the phosphatidylinositol 3-kinase inhibitors idelalisib[39] and copanlisib are approved for patients who are more heavily pretreated than the patients in the AUGMENT study.[40] For many patients, the efficacy/toxicity tradeoffs of rituximab versus chemotherapy-based or kinase inhibitor regimens are major issues. There is clear rationale for adding lenalidomide to rituximab in relapsed patients with FL,[26] and in a previous study in recurrent FL, lenalidomide plus rituximab was superior to lenalidomide alone.[23] Our data demonstrate that lenalidomide plus rituximab offers clinically meaningful efficacy advantages over single-agent rituximab in the context of the safety profile. Adverse events were more common in the lenalidomide plus rituximab group, largely due to higher rates of grade 3 or 4 neutropenia, which was successfully managed in most patients through dose modifications and growth factors. Neutropenia was predictable and manageable; the modest increase in infections and cutaneous reactions must be considered in light of the significantly greater efficacy of the lenalidomide plus rituximab combination. In fact, more patients in the lenalidomide plus rituximab group completed therapy than those in the placebo plus rituximab group (71% *v* 61%) because of a lower rate of progression. The magnitude of efficacy differences between the two treatments is clinically meaningful and suggests that lenalidomide plus rituximab should replace rituximab monotherapy as a standard of care for patients with relapsed or refractory indolent NHL.

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AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma

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APPENDIX

Methods

The hypothesized median progression-free survival (PFS) for lenalidomide plus rituximab was 17.6 months, on the basis of a reasonable risk reduction (hazard ratio [HR] = 0.0625) from a median PFS expected of rituximab monotherapy (11 months). In single-arm studies of lenalidomide plus rituximab in previously treated settings, the median PFS has ranged from approximately 12 months to 24 months, making 17.6 months a reasonable assumption. We hypothesized that median PFS for placebo plus rituximab would be 11 months, on the basis of previous results of rituximab monotherapy.

The choice of the rituximab schedule took into consideration studies showing that extended dosing of rituximab with four additional infusions (total eight infusions) further improves efficacy with acceptable toxicity, which has led to the approval of four or eight doses of rituximab in certain countries, including the United States. The totality of published studies showed that extended dosing (ie, additional doses of rituximab beyond standard four weekly infusions) further improves benefit in a manner that is independent of the number or schedule of extended rituximab dosing (ie, four or more doses; every 1, 2, 3, or 6 months; Hainsworth JD, et al: J Clin Oncol 23:1088-1095, 2005; Piro LD, et al: Ann Oncol 10:655-661, 1999).[18,32,33] Lenalidomide 20 mg was chosen based on published studies indicating that the combination of lenalidomide 20 mg with rituximab is well tolerated and active in relapsed/refractory indolent non-Hodgkin lymphoma.[23,35] In a previous study, 25 mg lenalidomide in combination with rituximab was not tolerated because of grade 3 tumor lysis syndrome in two out of four patients.[23]

Key inclusion criteria included: age $\geq$ 18 years; histologically confirmed marginal zone lymphoma or grade 1, 2, or 3a follicular lymphoma (FL; $CD20^+$; histology was retrospectively reviewed by an independent panel of expert hematopathologists); previous treatment with one or more prior systemic chemotherapy, immunotherapy, or chemoimmunotherapy and two or more previous doses of rituximab; documented relapsed, refractory, or progressive disease after prior systemic therapy, and not rituximab refractory (refractory defined as no response or PD $<$ 6 months after last rituximab dose); Eastern Cooperative Oncology Group performance status less than or equal to 2; and bidimensionally measurable disease with at least one nodal lesion greater than 1.5 cm in diameter or at least one extranodal lesion greater than 1.0 cm in both long and short diameters. Key exclusion criteria included: histology other than FL or marginal zone lymphoma or clinical evidence of transformed lymphoma, grade 3b FL, systemic therapy within 28 days before cycle 1 day 1 dosing, prior use of lenalidomide, neuropathy grade greater than one, presence or history of CNS involvement by lymphoma, or unwillingness to take venous thromboembolism prophylaxis if considered at risk for a thromboembolic event.

Dose reductions and interruptions of lenalidomide were planned for management of toxic effects associated with the drug. No more than one dose reduction from one cycle to the next was permitted, and no dose escalation was permitted at any time unless as specified. If lenalidomide or placebo was discontinued, rituximab treatment could continue as per protocol. The dose of rituximab could not be reduced; if rituximab was discontinued because of toxicity, lenalidomide or placebo was continued as per protocol. Lenalidomide was held and restarted at the next lower dose (5-mg increments) if the event resolved to a lower grade or discontinued as specified in the protocol. For all grade 4 neutropenia or grade 3 neutropenia that was sustained for 7 or more days or associated with fever (38.5°C), complete blood counts were monitored every 7 days, growth factor use was permitted, and lenalidomide was restarted if resolved to grade 2 or less. For thrombocytopenia grade 3 or greater (platelets $<$ 50,000 cells/mm^3), complete blood counts were monitored every 7 days, and lenalidomide was restarted if resolved to grade 2 or less. For grade 3 nondesquamating or nonblistering rash, lenalidomide was restarted if resolved to grade 1 or less. For grade 4 rash or any-grade desquamating rash, lenalidomide was discontinued. For grade 3 or greater tumor flare reaction, investigators could initiate therapy with nonsteroidal anti-inflammatory drugs, limited-duration corticosteroids, and/or narcotic therapy, and lenalidomide was restarted if resolved to grade 1 or less. For grade 2 allergic reaction or hypersensitivity, lenalidomide was restarted if resolved to grade 1 or less. For grade 3 or greater allergic reaction or hypersensitivity, lenalidomide was discontinued. For grade 3 or greater constipation, lenalidomide was restarted if resolved to grade 2 or less. For grade 3 or greater vascular access complication, anticoagulation was started and lenalidomide was restarted at investigator's discretion. For grade 3 peripheral neuropathy, lenalidomide was restarted if resolved to grade 1 or less. For grade 4 peripheral neuropathy, lenalidomide was discontinued. For incidences of ALT or AST elevation to grade 3 or greater ($>$ 5 $\times$ upper limit of normal) or total bilirubin grade 2 or greater ($>$ 1.5 $\times$ upper limit of normal), ALT, AST, and total bilirubin were monitored weekly, and lenalidomide was resumed at the same dose if levels returned to baseline in 14 days or less or resumed at next lower dose when returned to baseline if recovery was at greater than 14 days. In the instance of clinical tumor lysis syndrome grade 2 or greater, lenalidomide was held and restarted when resolved to grade 0.

Frequency of follow-up visits was based on disease status. For patients who completed treatment or discontinued treatment for reasons other than PD or relapse, overall survival and second malignancies were assessed every 6 months, and follow-up computed tomography or magnetic resonance imaging scans occurred every year. For patients who discontinued treatment because of PD or relapse, overall survival, subsequent antilymphoma therapies, and second malignancies were assessed every 6 months.

An interim futility analysis was planned when approximately 96 patients had developed PD per independent review committee (IRC) assessment or died (ie, PFS) during the study. The purpose of the interim analysis was to stop the trial in case of futility.

At the time of the interim analysis (data cutoff of March 20, 2017), approximately 96 IRC-assessed events were expected. However, after the IRC had completed review, 137 events were identified. The futility boundary was adjusted based on the actual number of events.

A data monitoring committee (DMC) meeting was held on May 30, 2017, in which DMC members reviewed unblinded efficacy and safety data. The DMC concluded that the results from the primary end points, PFS per IRC assessment under US Food and Drug Administration censoring rule, remained within the protocol-directed futility boundaries, and the adverse event profile did not raise any unexpected safety concerns. Therefore, the DMC recommended that the AUGMENT study continue as planned.

Results

The primary analysis of PFS was based on a total of 183 events assessed by IRC after censoring per rule suggested in US Food and Drug Administration guidance (185 events before censoring; 200 events were assessed by investigator, 199 events after censoring). The proportional hazards assumption was checked by introducing a constructed time-dependent variable, that is, add to the model interaction term for treatment and time. The effect of interaction term is not significant (data not shown). This suggests that the assumption of proportional hazards is not violated. Prior systemic anticancer therapies by regimen for both arms are listed in Appendix Table A10 (online only).

Duration of response was superior for lenalidomide plus rituximab (HR, 0.53; 95% CI, 0.36 to 0.79; P = .015). Median duration of response was 36.6 months (95% CI, 22.9 months to not reached) versus 21.7 months (95% CI, 12.8 to 27.6 months; Appendix Fig A2, online only). Event-free survival was significantly improved for lenalidomide plus rituximab compared with placebo plus rituximab, with HR of 0.51 (95% CI, 0.38 to 0.67; P $<$ .0001). Median event-free survival was 27.6 months (95% CI, 22.1 months to not reached) versus 13.9 months (Appendix Fig A3, online only). Time to next lymphoma treatment was significantly improved for lenalidomide plus rituximab compared with placebo plus rituximab, with HR of 0.54 (95% CI, 0.38

to 0.78; $P = .0007$). Median time to next lymphoma treatment was not reached versus 32.2 months (95% CI, 23.2 months to not reached; $P = .0007$; Appendix Fig A4, online only). Time to next antilymphoma chemotherapy treatment was significantly improved for lenalidomide plus rituximab compared with placebo plus rituximab, with HR of 0.50 (95% CI, 0.32 to 0.78; $P < .0017$). Median time to next antilymphoma chemotherapy treatment was not reached in either group (Appendix Fig A5, online only). PFS on next antilymphoma treatment (PFS2) was significantly improved for lenalidomide plus rituximab compared with placebo plus rituximab, with HR of 0.52 (95% CI, 0.32 to 0.82; $P < .0046$). Post hoc analysis has shown that response to subsequent treatment was better with lenalidomide plus rituximab compared with placebo plus rituximab (Appendix Table A11, online only). Median PFS2 was not reached in either group (Appendix Fig A6, online only).

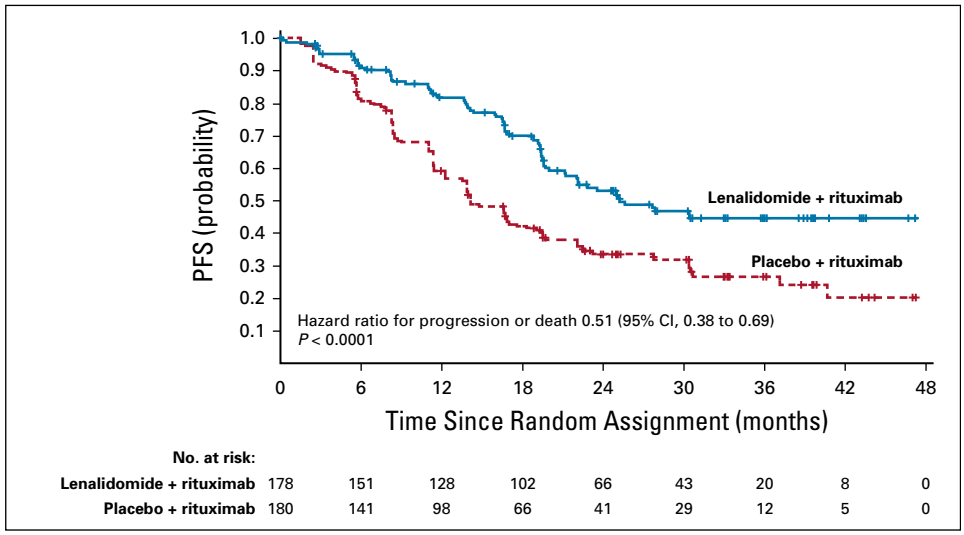

FIG A1. Progression-free survival (PFS) as assessed by investigator in the intention-to-treat population.

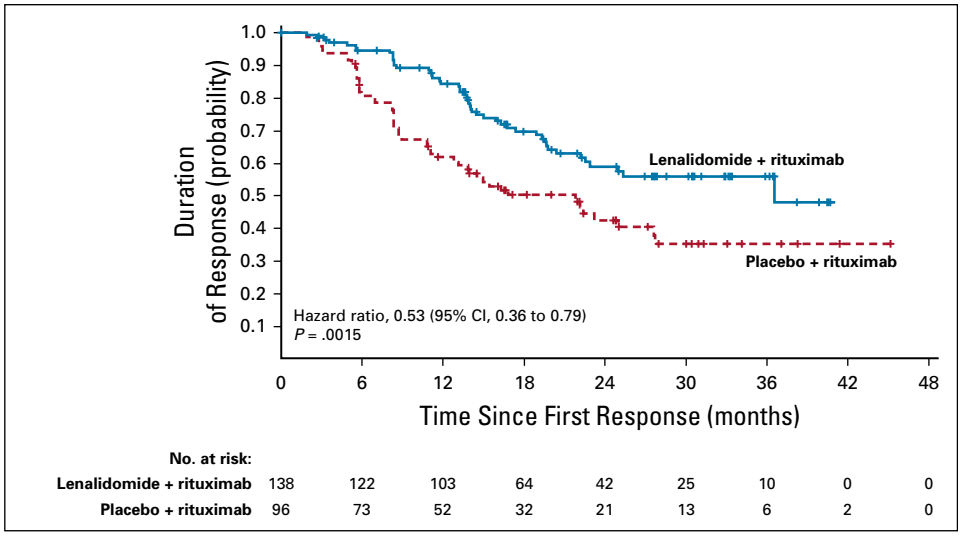

FIG A2. Duration of response as assessed by independent review committee in the intention-to-treat population.

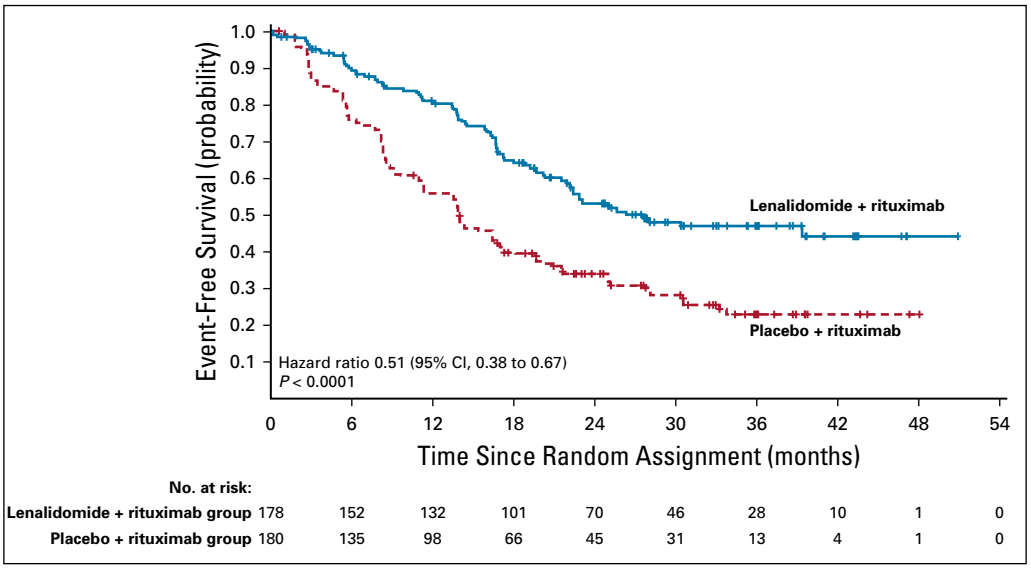

FIG A3. Event-free survival as assessed by independent review committee in the intention-to-treat population.

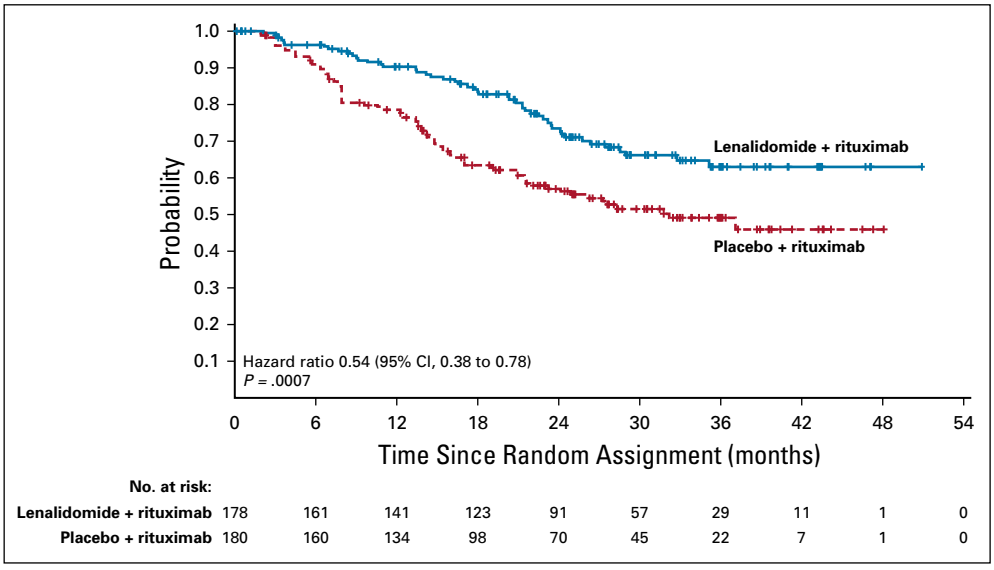

FIG A4. Time to next antilymphoma treatment in the intention-to-treat population.

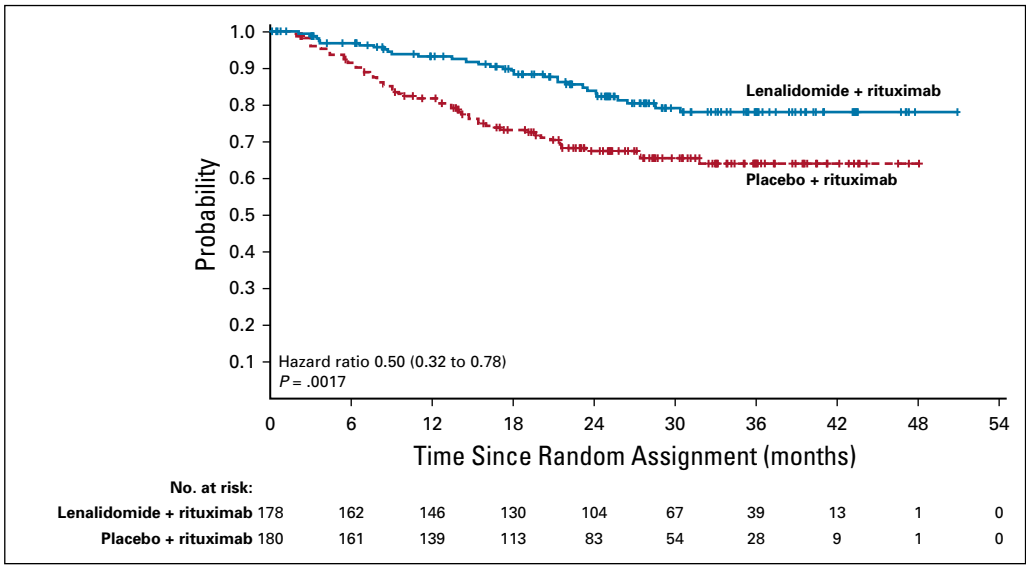

FIG A5. Time to next antilymphoma chemotherapy in the intention-to-treat population.

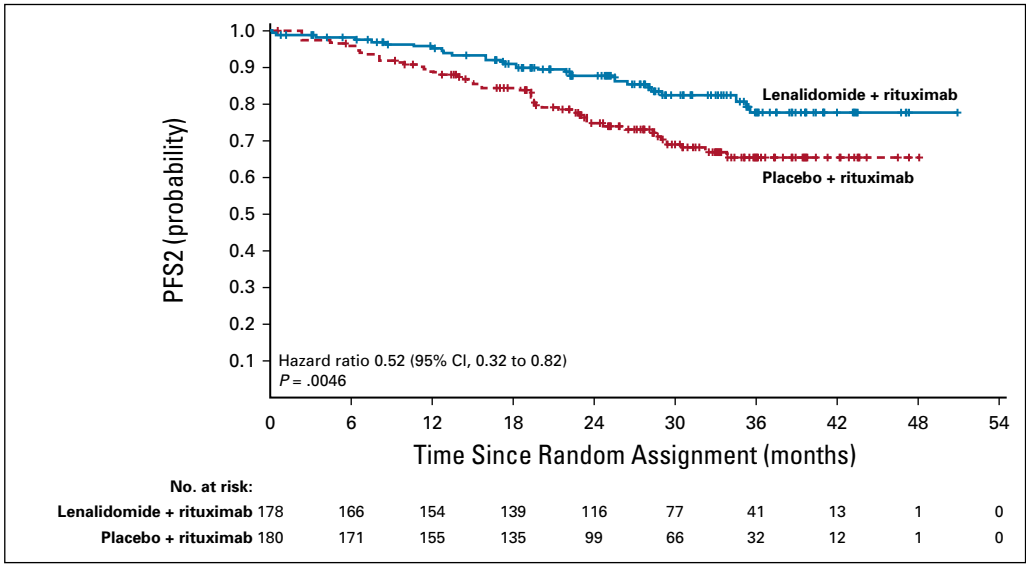

FIG A6. Progression-free survival incorporating next antilymphoma treatment (PFS2) in the intention-to-treat population.

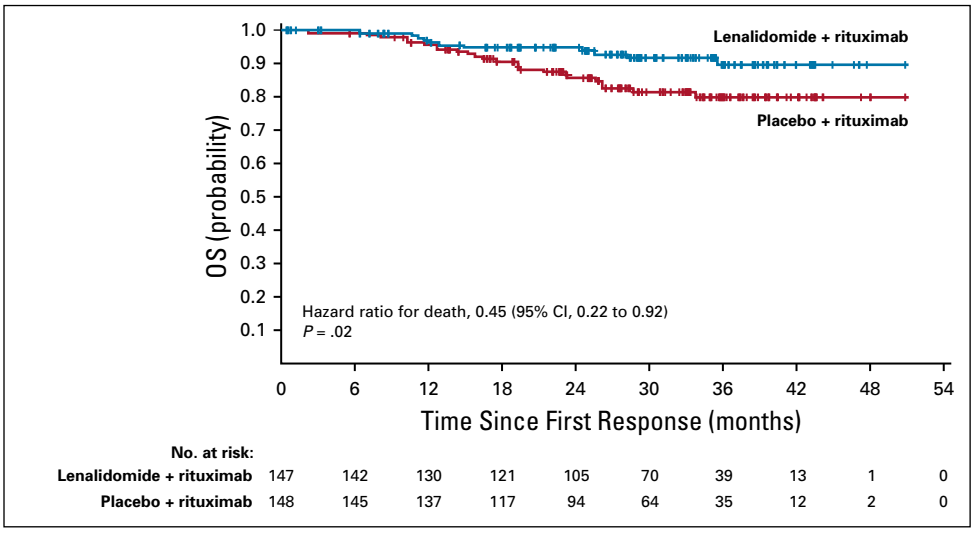

FIG A7. Overall survival (OS) in patients with follicular lymphoma in the intention-to-treat population.

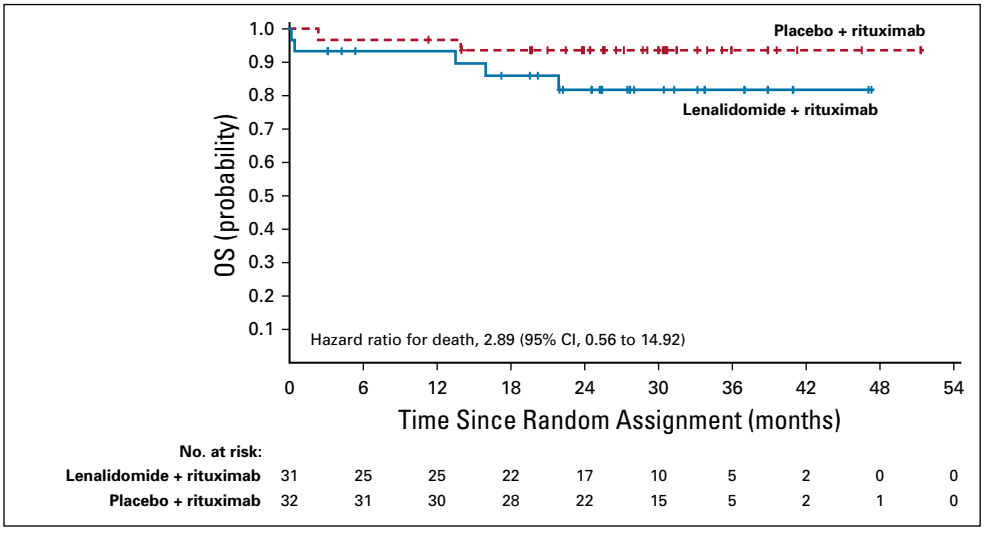

FIG A8. Overall survival (OS) in patients with marginal zone lymphoma in the intention-to-treat population.

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TABLE A1. List of AUGMENT Trial Investigators (continued)

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TABLE A2. Post hoc Subgroup Analyses for Progression-Free Survival on the Basis of Prior Treatment as Assessed by IRC

Group	Lenalidomide + Rituximab PFS (months), Median (95% CI)	Placebo + Rituximab PFS (months), Median (95% CI)	HR (95% CI)
Total ITT population	(n = 178) 39.4 (22.9 to NR)	(n = 180) 14.1 (11.4 to 16.7)	0.46 (0.34 to 0.62)
Prior exposure to rituximab + bendamustine	(n = 19) NR (20.2 to NR)	(n = 14) 11.1 (3.0 to 30.6)	0.23 (0.06 to 0.85)
Prior exposure to rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisolone	(n = 66) 39.4 (22.1 to NR)	(n = 69) 13.9 (8.7 to 28.0)	0.50 (0.30 to 0.82)

Abbreviations: HR, hazard ratio; IRC, independent review committee; ITT, intention-to-treat; NR, not reached; PFS, progression-free survival.

TABLE A3. Efficacy in Patients with Follicular Lymphoma

Variable	Lenalidomide + Rituximab (n = 147)	Placebo + Rituximab (n = 148)	HR (95% CI)*	P*
Best response, as assessed by IRC				
ORR, No. (% [95% CI])	118 (80 [73 to 86])	82 (55 [47 to 64])		< .0001
CR, No. (% [95% CI])	51 (35 [27 to 43])	29 (20 [14 to 27])		.0040
PR, No. (%)	67 (46)	53 (36)		
SD, No. (%)	14 (10)	44 (30)		
PD/death, No. (%)	7 (5)	19 (13)		
Not done/missing/no evidence of disease at baseline, No. (%)	8 (5)	3 (2)		
Median PFS, as assessed by IRC, months (95% CI)	39.4 (23.1 to NR)	13.9 (11.2 to 16.0)	0.40 (0.29 to 0.56)	< .0001
Median PFS, as assessed by investigator, months (95% CI)	27.8 (22.1 to NR)	13.9 (11.4 to 16.8)	0.46 (0.34 to 0.63)	< .0001
Median EFS as assessed by IRC, months (95% CI)	39.4 (22.3 to NR)	13.8 (11.0 to 16.0)	0.42 (0.31 to 0.58)	< .0001
Median DOR, as assessed by IRC, months (95% CI)	36.6 (24.9 to NR)	15.5 (11.2 to 25.0)	0.44 (0.29 to 0.68)	.0001
Median TTNLT, months (95% CI)	NR (NR to NR)	28.2 (20.8 to NR)	0.43 (0.29 to 0.65)	< .0001
OS probability at 2 years, % (95% CI)	95 (90 to 98)	86 (79 to 91)	0.45 (0.22 to 0.92)	.02
Deaths, No. (%)	11 (7)	24 (16)		

Abbreviations: CR; complete response; DOR, duration of response; EFS, event-free survival; HR, hazard ratio; IRC, independent review committee; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TTNLT, time to next antilymphoma treatment.

*In subpopulation analyses, HR was estimated from Cox proportional hazard regression model, *P* value was obtained from Fisher exact *t* test for binary end points and log-rank test for time-to-event end points.

TABLE A4. Efficacy in Patients With Marginal Zone Lymphoma

Variable	Lenalidomide + Rituximab (n = 31)	Placebo + Rituximab (n = 32)	HR (95% CI)*	P*
Best response, as assessed by IRC				
ORR, No. (% [95% CI])	20 (65 [45 to 81])	14 (44 [26 to 62])		.1313
CR, No. (% [95% CI])	9 (29 [14 to 48])	4 (13 [4 to 29])		.1289
PR, No. (%)	11 (35)	10 (31)		
SD, No. (%)	6 (19)	11 (34)		
PD/death, No. (%)	0	4 (13)		
Not done/missing/no evidence of disease at baseline, No. (%)	5 (16)	3 (9)		
Median PFS, as assessed by IRC, months (95% CI)	20.2 (16.0 to NR)	25.2 (11.1 to NR)	1.00 (0.47 to 2.13)	.9984
Median PFS, as assessed by investigator, months (95% CI)	19.2 (13.9 to 30.4)	22.1 (8.7 to NR)	1.04 (0.54 to 2.01)	.8918
Median EFS as assessed by IRC, months (95% CI)	20.2 (14.5 to NR)	25.1 (9.2 to NR)	1.18 (0.60 to 2.29)	.6324
Median DOR, as assessed by IRC, months (95% CI)	17.4 (13.2 to NR)	NR (8.4 to NR)	1.81 (0.56 to 5.84)	.3111
Median TTNLT, months (95% CI)	25.8 (17.7 to NR)	NR (21.6 to NR)	1.58 (0.68 to 3.67)	.3057
OS probability at 2 years, % (95% CI)	82 (61 to 92)	94 (77 to 98)	2.89 (0.56 to 14.92)	
Deaths, No. (%)	5 (16)	2 (6)		

Abbreviations: CR; complete response; DOR, duration of response; EFS, event-free survival; HR, hazard ratio; IRC, independent review committee; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TTNLT, time to next antilymphoma treatment.

*In subpopulation analyses, HR was estimated from Cox proportional hazard regression model, *P* value was obtained from Fisher exact *t* test for binary end points and log-rank test for time-to-event end points.

TABLE A5. Baseline Demographic and Disease Characteristics (ITT Population) by Histology

	Marginal Zone Lymphoma		Follicular Lymphoma		Total	
Characteristic	**Rituximab + Lenalidomide (n = 31)**	**Rituximab + Placebo (n = 32)**	**Rituximab Plus Lenalidomide (n = 147)**	**Rituximab + Placebo (n = 148)**	**Rituximab + Lenalidomide (n = 178)**	**Rituximab + Placebo (n = 180)**
Median age, years	68	66	62	61	64	62
≥ 65	68	59	42	36	46	41
≥ 70	42	38	23	22	26	24
Male	45	53	42	54	42	54
Ann Arbor stage IV at enrollment	65	41	30	31	36	33
FLIPI high risk	48	25	37	31	39	30
ECOG 0	55	72	67	71	65	71
ECOG 1-2	45	28	33	29	35	29
B symptoms present	13	3	8	7	9	7
LDH elevated	29	19	23	22	24	22
Refractory to last prior regimen	13	3	18	17	17	14
High tumor burden per GELF (yes)	65	56	52	46	55	48
Chemoresistant	10	6	15	16	14	14
Unfit for chemotherapy*	48	44	27	24	30	27

NOTE. Data given as % unless otherwise noted.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; ITT, intention-to-treat; LDH, lactate dehydrogenase.

*Defined as age ≥ 70 years, or age 60 to 69 years and creatinine clearance less than 60 mL/min or ECOG performance score greater than or equal to 2.

TABLE A6. Efficacy by Occurrence of Grade 3 or 4 Neutropenia in the Safety Population

	Lenalidomide + Rituximab		Placebo + Rituximab	
Outcome	**≥ 1 Grade 3 or 4 Neutropenia (n = 88)**	**No Grade 3 or 4 Neutropenia (n = 88)**	**≥ 1 Grade 3 or 4 Neutropenia (n = 24)**	**No Grade 3 or 4 Neutropenia (n = 156)**
Best response, as assessed by IRC, No. (%)				
ORR	74 (84)	64 (73)	10 (42)	86 (55)
CR	34 (39)	26 (30)	1 (4)	32 (21)
PR	40 (45)	38 (43)	9 (38)	54 (35)
SD	8 (9)	12 (14)	8 (33)	47 (30)
PD/death	3 (3)	4 (5)	6 (25)	17 (11)
Not done/missing/no evidence of disease at baseline	3 (3)	8 (9)	0	6 (4)
Median PFS, as assessed by IRC, months (95% CI)	NR (22.3 to NR)	39.4 (19.7 to NR)	8.3 (5.6 to 16.6)	14.3 (13.6 to 18.2)
PFS probability at 2 years, % (95% CI)	59 (46 to 69)	57 (44 to 68)	26 (11 to 45)	38 (30 to 46)

Abbreviations: CR, complete response; IRC, independent review committee; NR, not reached; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SD, stable disease.

TABLE A7. Serious Adverse Events Occurring in Three or More Patients in Either Group in the Safety Population

Preferred Term	Lenalidomide + Rituximab (n = 176)	Placebo + Rituximab (n = 180)
Patients with ≥ 1 serious TEAE	45 (26)	25 (14)
Pneumonia	5 (3)	5 (3)
Febrile neutropenia	5 (3)	0
Pulmonary embolism	4 (2)	1 (1)
Sepsis	3 (2)	2 (1)
Pyrexia	3 (2)	0
Neutropenia	3 (2)	0
Pleural effusion	1 (1)	3 (2)

NOTE. Data given as No. (%).
Abbreviation: TEAE, treatment-emergent adverse event.

TABLE A8. On-Study Use of Antiplatelet or Anticoagulant Concomitant Medications in the Safety Population

Patients With Use of ≥ 1 Concomitant Medications	Rituximab + Lenalidomide (n = 176)	Rituximab + Placebo (n = 180)
Antiplatelet	98 (56)	106 (59)
Anticoagulant	49 (28)	32 (18)
Antiplatelet and/or anticoagulant	123 (70)	121 (67)

NOTE. Data given as No. (%).

TABLE A9. Second Primary Malignancies in the Safety Population

Second Primary Malignancies, No. (%)	Rituximab + Lenalidomide (n = 176)	Rituximab + Placebo (n = 180)	Overall (N = 356)
All second primary malignancies	6 (3)	10 (6)	16 (4)
Invasive	3 (2)	8 (4)	11 (3)
Hematologic malignancies	1 (1)	2 (1)	3 (1)
Acute myeloid leukemia	1 (1)	2 (1)	3 (1)
Solid tumor	2 (1)	6 (3)	8 (2)
Carcinoid tumor of the GI tract	1 (1)	0	1 (< 1)
Squamous cell carcinoma of lung	1 (1)	0	1 (< 1)
Adenocarcinoma of colon	0	1 (1)	1 (< 1)
Invasive ductal breast carcinoma	0	2 (1)	2 (1)
Malignant melanoma	0	1 (1)	1 (< 1)
Papillary thyroid cancer	0	1 (1)	1 (< 1)
Transitional cell cancer of the renal pelvis and ureter localized	0	1 (1)	1 (< 1)
Noninvasive	3 (2)	3 (2)	6 (2)
Squamous cell carcinoma of skin	2 (1)	1 (1)	3 (1)
Basal cell carcinoma	1 (1)	2 (1)	3 (1)

NOTE. Data given as No. (%).

TABLE A10. Prior Systemic Anticancer Therapies by Regimen

Prior Systemic Anticancer Therapies by Regimen	Rituximab + Lenalidomide (n = 178)	Rituximab + Placebo (n = 180)	Overall (N = 358)
Rituximab monotherapy	37 (21)	42 (23)	79 (22)
R-benda	19 (11)	14 (8)	33 (9)
R-CHOP	66 (37)	69 (38)	135 (38)
R-CVP	31 (17)	26 (14)	57 (16)
Other R-chemotherapy combinations	37 (21)	41 (23)	78 (22)
O-chemotherapy	3 (2)	1 (1)	4 (1)
Single agent chemotherapy	15 (8)	16 (9)	31 (9)
Combination chemotherapy	59 (33)	56 (31)	115 (32)
Single agent targeted therapy	8 (5)	11 (6)	19 (5)
Combination targeted therapies	1 (1)	4 (2)	5 (1)
Other	7 (4)	8 (4)	15 (4)

NOTE. Data given as No. (%).

Abbreviations: O-chemotherapy, obinutuzumab plus chemotherapy; R-benda, rituximab plus bendamustine; R-chemotherapy, rituximab plus chemotherapy; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisone.

TABLE A11. Response to Subsequent Treatment

Response	Rituximab + Lenalidomide (patients with next antilymphoma treatment; n = 49)	Rituximab + Placebo (patients with next antilymphoma treatment; n = 80)	*P*
ORR, No. (%) [95% CI]	28 (57) [42 to 71]	29 (36) [26 to 48]	.0282
CR, No. (%) [95% CI]	15 (31) [18 to 45]	13 (16) [9 to 26]	.0775

Abbreviations: CR, complete response; ORR, overall response rate.