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ORIGINAL ARTICLE

Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma

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ABSTRACT

BACKGROUND

Rituximab plus chemotherapy has been shown to be effective in patients with advanced-stage, previously untreated follicular lymphoma; nevertheless, most patients will have a relapse. Combination immunotherapy with lenalidomide and rituximab is an immunomodulatory regimen that has shown promising activity in patients with indolent B-cell non-Hodgkin's lymphoma.

METHODS

We conducted this multicenter, international, phase 3 superiority trial to evaluate rituximab plus lenalidomide, as compared with rituximab plus chemotherapy, in patients with previously untreated follicular lymphoma. Patients were randomly assigned to receive one of the two regimens, followed by maintenance monotherapy with rituximab. Treatment with rituximab plus lenalidomide consisted of 18 cycles of the two drugs, followed by rituximab maintenance therapy every 8 weeks for 12 cycles (six additional doses). Treatment with rituximab plus chemotherapy consisted of the investigator's choice of one of three rituximab-based regimens, followed by maintenance monotherapy with rituximab every 8 weeks for 12 cycles. The primary end points were complete response (confirmed or unconfirmed) at 120 weeks and progression-free survival.

RESULTS

A total of 1030 patients were randomly assigned to receive rituximab plus lenalidomide (513 patients) or rituximab plus chemotherapy (517 patients). The rate of confirmed or unconfirmed complete response at 120 weeks was similar in the two groups: 48% (95% confidence interval [CI], 44 to 53) in the rituximab–lenalidomide group and 53% (95% CI, 49 to 57) in the rituximab–chemotherapy group (P=0.13). The interim 3-year rate of progression-free survival was 77% (95% CI, 72 to 80) and 78% (95% CI, 74 to 82), respectively. A higher percentage of patients in the rituximab–chemotherapy group had grade 3 or 4 neutropenia (32% vs. 50%) and febrile neutropenia of any grade (2% vs. 7%), and a higher percentage of patients in the rituximab–lenalidomide group had grade 3 or 4 cutaneous reactions (7% vs. 1%).

CONCLUSIONS

Among patients with previously untreated follicular lymphoma, efficacy results were similar with rituximab plus lenalidomide and rituximab plus chemotherapy (with both regimens followed by rituximab maintenance therapy). The safety profile differed in the two groups. (Funded by Celgene; RELEVANCE ClinicalTrials.gov numbers, NCT01476787 and NCT01650701, and EudraCT number, 2011-002792-42.)

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

Drs. Morschhauser and Fowler contributed equally to this article.

RITUXIMAB PLUS CHEMOTHERAPY FOLlowed by maintenance therapy with rituximab has been shown to be effective in patients with advanced follicular lymphoma for whom treatment is indicated, with median progression-free survival reaching approximately 6 to 10 years and with a 3-year overall survival rate of greater than 90%.[1-3] However, cytotoxic chemotherapy is associated with well-known side effects, including myelosuppression and immunosuppression, gastrointestinal and cardiac toxic effects, and neuropathy, and with the development of second primary cancers.[1,4,5] In addition, follicular lymphoma is characterized by a defective immune microenvironment that suppresses normal T-cell and natural-killer (NK)–cell activity and a long natural history of disease with repeated relapses in most patients.[6,7] Follicular lymphomas may also acquire additional genetic lesions and progress to clinically aggressive diffuse large B-cell lymphomas.[8]

Lenalidomide is an immunomodulatory agent that binds the cereblon E3 ubiquitin ligase complex, which results in recruitment, ubiquitination, and degradation of transcription factors Aiolos and Ikaros.[9-11] In malignant lymphoma B cells, this degradation results in up-regulation of interferon-stimulated genes and apoptosis.[11] In T cells, the degradation results in enhanced IL-2 secretion, which leads to T-cell activation, thereby indirectly activating NK cells.[9,10] Combining lenalidomide with rituximab enhances apoptosis and antibody-dependent cell-mediated cytotoxicity of B-cell non-Hodgkin's lymphoma cells more effectively than monotherapy.[12-16] In addition, lenalidomide repairs defective immune synapses between follicular lymphoma cells and T cells.[17] In phase 2 trials involving patients with previously untreated follicular lymphoma, rituximab plus lenalidomide showed promising activity, with high response rates.[18-21]

Here, we report the results of the Rituximab Lenalidomide versus Any Chemotherapy (RELEVANCE) trial, a randomized, phase 3 trial that compared the efficacy and safety of rituximab plus lenalidomide with those of rituximab plus chemotherapy, with both regimens followed by maintenance therapy with rituximab, in patients with previously untreated, advanced follicular lymphoma.

METHODS

PATIENTS

Patients were eligible for inclusion in the trial if they had histologically confirmed, CD20-positive follicular lymphoma (grade 1 to 3a); were assessed as being in need of treatment according to Groupe d'Étude des Lymphomes Folliculaires (GELF) criteria[2,22]; and had received no previous systemic treatment for lymphoma. Additional eligibility criteria, information regarding GELF criteria, and details of the trial methods are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

TRIAL DESIGN AND TREATMENT

The RELEVANCE trial was a multicenter, international, randomized, open-label, phase 3 trial. Patients were randomly assigned, in a 1:1 ratio, to receive rituximab plus lenalidomide (rituximab–lenalidomide group) or rituximab plus chemotherapy (rituximab–chemotherapy group), followed by maintenance therapy with rituximab. Randomization was stratified according to Follicular Lymphoma International Prognostic Index (FLIPI) score (0 or 1 [low risk], 2 [intermediate risk], or 3 to 5 [high risk]; details are provided in the Methods section in the Supplementary Appendix), age (≤60 vs. >60 years), and lesion size (≤6 vs. >6 cm). The trial included three main treatment phases (Fig. S1 in the Supplementary Appendix).

Patients who were randomly assigned to the rituximab–lenalidomide group received lenalidomide at a dose of 20 mg per day on days 2 through 22 of each 28-day cycle for 6 cycles (or at a dose of 10 mg per day if the creatinine clearance was between 30 and 59 ml per minute). Patients who had a confirmed or unconfirmed complete response after 6 cycles then received lenalidomide at a dose of 10 mg per day for 12 cycles. Patients who had a partial response after 6 cycles received lenalidomide at a dose of 20 mg per day for 3 or 6 additional cycles until a confirmed or unconfirmed complete response was observed. All the patients received lenalidomide at a dose of 10 mg per day in the remaining cycles, for a total of 18 cycles. Patients in this group received rituximab at a dose of 375 mg per square meter of body-surface area on days 1, 8, 15, and 22 of cycle 1 and on day 1 of cycles 2 through 6;

patients who had a response continued to receive rituximab every 8 weeks for 12 cycles.

Patients who were randomly assigned to the rituximab–chemotherapy group received the investigator's choice of one of three regimens — rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); rituximab and bendamustine (R-B); or rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) — followed by 12 cycles of maintenance therapy with rituximab (every 8 weeks), which in turn was followed by 2 years of maintenance therapy with rituximab at standard doses (see the Methods section in the Supplementary Appendix). The choice of chemotherapy regimen was made by the investigator for each patient before randomization. The total duration of treatment was 120 weeks for both treatment groups.

Dose reductions and interruptions of lenalidomide were permitted for management of toxic effects associated with the drug (details are provided in the Methods section in the Supplementary Appendix). Dose modifications of chemotherapy were made in accordance with clinical practice at the investigator's institution. Growth factor was not administered prophylactically (except in high-risk patients) in either treatment group; when indicated, it was administered in accordance with the guidelines of the American Society of Clinical Oncology and the European Society of Medical Oncology.[23,24]

TRIAL OVERSIGHT

The trial was designed by the first, second, and last authors in collaboration with the sponsors (Celgene and the Lymphoma Academic Research Organisation [LYSARC]) and was conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. All the patients provided written informed consent before any trial-related procedures were performed. An independent data and safety monitoring committee and an expert advisory group provided oversight throughout the conduct of the trial. Representatives from Celgene and LYSARC ensured that appropriate monitoring procedures were performed before, during, and after the trial in accordance with the trial protocol (available at NEJM.org) and with institutional guidelines. The authors collected patient data, and the data were analyzed by the trial sponsors with input from the authors. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first draft of the manuscript was written by medical writers who were funded by Celgene; subsequent drafts were reviewed and revised by all the authors, who also approved the final version. A total of 20 patients were enrolled in the trial before the trial was registered on ClinicalTrials.gov because of the need to await necessary regulatory documentation that allowed LYSARC to be named as one of the sponsors (details are provided in the Supplementary Appendix).

EFFICACY AND SAFETY ASSESSMENTS

The analyses of the coprimary end points of complete response (confirmed or unconfirmed) at 120 weeks and progression-free survival were performed in the intention-to-treat population, which included all patients who underwent randomization. The safety population included all patients who received at least one dose of the trial treatment.

The determination of efficacy was based on the final analysis of confirmed or unconfirmed complete response at 120 weeks and the first interim analysis of progression-free survival; tumor response was assessed according to the 1999 International Working Group criteria.[25] Confirmed or unconfirmed complete response at 120 weeks was chosen as a coprimary end point because it was a slightly better trial-level surrogate for progression-free survival than complete response at 30 months in the FLASH (Follicular Lymphoma Analysis of Surrogate Hypothesis) analysis.[26] Efficacy response data were assessed by an independent review committee (central review), and investigator-assessed results were used in sensitivity analyses. A bone marrow biopsy was required to confirm a confirmed or unconfirmed complete response; bone marrow that was classified as "normal" was assessed as a confirmed complete response, and bone marrow classified as "indeterminate" was assessed as an unconfirmed complete response. Three analyses were planned to evaluate progression-free survival, including two interim analyses (the first of which is reported in this article) and one final analysis for superiority testing (see the Methods section in the Supplementary Appendix). Other end points were overall survival, the duration of response, and

safety. In addition, the rate of histologic transformation at first disease progression was evaluated as a prespecified exploratory end point.

Adverse events that occurred during the treatment period were coded according to the *Medical Dictionary for Regulatory Activities*, version 20.1. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 (with the exception of tumor flare reaction and skin rash, which were graded according to CTCAE, version 3.0).

STATISTICAL ANALYSIS

We specified that the combination of rituximab plus lenalidomide would be considered to be superior to rituximab plus chemotherapy with respect to the primary end points (confirmed or unconfirmed complete response at 120 weeks and progression-free survival) if the two-sided P value for both comparisons was less than 0.05. Confirmed or unconfirmed complete response at 120 weeks was analyzed with the use of a stratified Cochran–Mantel–Haenszel test. We calculated a sample size that would provide the trial with 90% power to detect a between-group difference of 12 percentage points in the rate of confirmed or unconfirmed complete response at 120 weeks (72% in the rituximab–lenalidomide group vs. 60% in the rituximab–chemotherapy group), at a two-sided alpha level of 0.05. With respect to progression-free survival, we estimated that a sample size that would result in a total of 456 events of disease progression or death from any cause would provide the trial with 80% power to detect a risk of disease progression that was lower by 23% (hazard ratio, 0.77) with rituximab plus lenalidomide than with rituximab plus chemotherapy. We specified that superiority of rituximab plus lenalidomide over rituximab plus chemotherapy with respect to progression-free survival at the first interim analysis (after approximately 50% of the 456 planned events had occurred) would be declared if the two-sided P value by a stratified log-rank test was 0.011 or lower. Hazard ratios and corresponding two-sided 95% confidence intervals were estimated with the use of a Cox proportional-hazards model. Prespecified subgroup analyses of progression-free survival and of confirmed or unconfirmed complete response at 120 weeks were also performed.

RESULTS

PATIENTS AND TRIAL TREATMENT

From December 2011 through November 2014, a total of 1030 patients underwent randomization at 137 centers in Australia, Belgium, Canada, France, Germany, Italy, Japan, Portugal, Spain, and the United States. Patients were randomly assigned, in a 1:1 ratio, to the rituximab–lenalidomide group (513 patients) or the rituximab–chemotherapy group (517 patients) (Fig. S2 in the Supplementary Appendix). Baseline characteristics were similar in the two groups (Table 1, and Table S2 in the Supplementary Appendix). Overall, the median age was 59 years, and 49% of the patients were assessed as being at high risk on the basis of their FLIPI score (Table 1). Among the patients in the rituximab–chemotherapy group, 372 (72%) received R-CHOP, 117 (23%) received R-B, and 28 (5%) received R-CVP.

The median relative dose intensity (the proportion of administered doses relative to planned doses) was 90% for lenalidomide and was greater than 99% for rituximab and for chemotherapy. Vincristine had the lowest median relative dose intensity of all the chemotherapeutic agents. Among the patients who received R-CVP, the relative dose intensity for vincristine was less than 75% in 13% of the patients and was 75% to less than 90% in 17% of the patients. Among the patients who received R-CHOP, the relative dose intensity for vincristine was less than 75% in 16% of the patients and was 75% to less than 90% in 2% of the patients. Although the median relative dose intensity of lenalidomide was 90% over the course of the entire treatment period, the relative dose intensity of lenalidomide in the rituximab–lenalidomide group was less than 75% in 21% of the patients and was 75% to less than 90% in 29% of the patients. A higher percentage of the patients in the rituximab–lenalidomide group than in the rituximab–chemotherapy group had adverse events that led to dose reduction (36% vs. 14%), dose interruption (59% vs. 35%), or early discontinuation of trial treatment (11% vs. 3%), findings that reflected the protocol-specified guidelines on dose modification for the management of toxic effects. Among the patients in the rituximab–lenalidomide group, neutropenia was the most common reason for dose reduction (20% of the patients) and interruption (32%); neutrope-

Table 1. Baseline Demographic and Disease Characteristics (Intention-to-Treat Population).*

Characteristic	Rituximab–Lenalidomide Group (N = 513)	Rituximab–Chemotherapy Group (N = 517)	Total (N = 1030)
Median age (range) — yr	59 (30–89)	59 (23–83)	59 (23–89)
Age >70 yr — no. (%)	80 (16)	78 (15)	158 (15)
Male sex — no. (%)	251 (49)	251 (49)	502 (49)
ECOG performance status — no. (%)†			
0	341 (66)	345 (67)	686 (67)
1	157 (31)	157 (30)	314 (30)
2	13 (3)	14 (3)	27 (3)
Could not be evaluated or data missing	2 (<1)	1 (<1)	3 (<1)
Ann Arbor stage — no. (%)‡			
I or II	30 (6)	40 (8)	70 (7)
III or IV	483 (94)	477 (92)	960 (93)
Bulky disease — no. (%)§	218 (42)	199 (38)	417 (40)
Follicular lymphoma grade — no. (%)			
1 or 2	437 (85)	443 (86)	880 (85)
3a	65 (13)	63 (12)	128 (12)
Unspecified grade or grade other than 1, 2, or 3a	11 (2)	11 (2)	22 (2)
Lactate dehydrogenase >ULN — no. (%)	156 (30)	137 (26)	293 (28)
Beta$_2$-microglobulin >ULN — no. (%)	261 (51)	262 (51)	523 (51)
B symptoms — no. (%)¶	141 (27)	134 (26)	275 (27)
FLIPI score — no. (%)‖			
0 or 1	77 (15)	76 (15)	153 (15)
2	183 (36)	191 (37)	374 (36)
3 to 5	253 (49)	250 (48)	503 (49)

* There were no significant between-group differences in the characteristics evaluated at baseline. ULN denotes the upper limit of the normal range. Percentages may not sum to 100 because of rounding.
† The Eastern Cooperative Oncology Group (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.
¶ B symptoms are systemic symptoms such as weight loss, night sweats, and fever.
‖ A Follicular Lymphoma International Prognostic Index (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 per deciliter, more than four nodal areas (with the exception of spleen), age older than 60 years, a lactate dehydrogenase level above the ULN, and Ann Arbor stage III or IV disease.

nia led to early discontinuation of trial treatment in 1% of the patients. A total of 69% of the patients in the rituximab–lenalidomide group and 71% of the patients in the rituximab–chemotherapy group completed 120 weeks of treatment. In the rituximab–lenalidomide group, 76% of the patients completed all 18 cycles of lenalidomide.

EFFICACY

Primary End Point

After a median follow-up of 37.9 months, the rates of the primary end points of confirmed or unconfirmed complete response at 120 weeks and interim progression-free survival were similar in the two treatment groups (Table 2). The

Table 2. Efficacy (Intention-to-Treat Population).

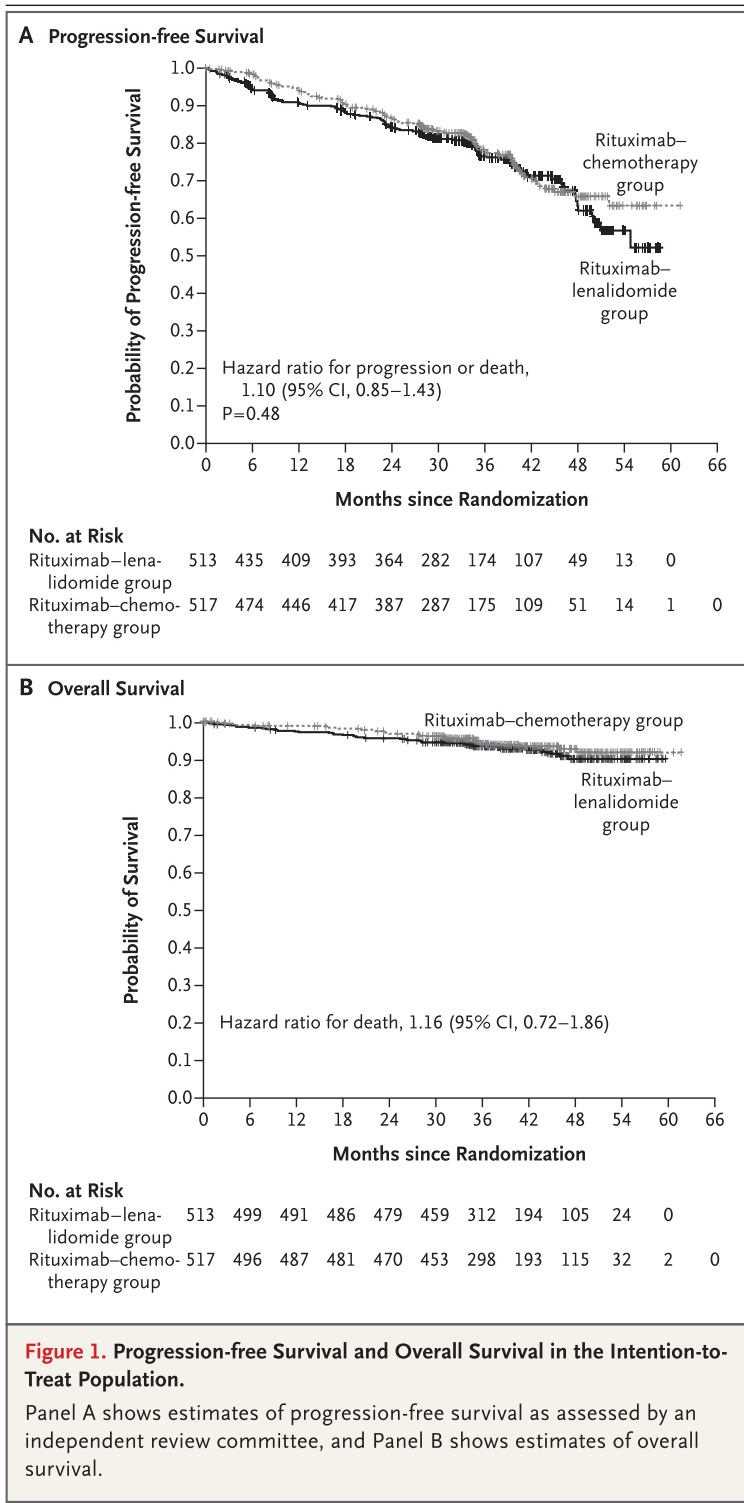| Variable	Rituximab–Lenalidomide Group (N = 513)	Rituximab–Chemotherapy Group (N = 517)	Hazard Ratio (95% CI)	P Value
Response status at 120 weeks, as assessed by independent review committee				
Overall response — no. (% [95% CI])	312 (61 [56–65])	336 (65 [61–69])		
Confirmed or unconfirmed complete response — no. (% [95% CI])	247 (48 [44–53])	274 (53 [49–57])		0.13
Complete response, confirmed — no. (%)	142 (28)	169 (33)		
Complete response, unconfirmed — no. (%)	105 (20)	105 (20)		
Partial response — no. (%)	65 (13)	62 (12)		
Stable disease — no. (%)	2 (<1)	0		
Progressive disease or death — no. (%)*	87 (17)	79 (15)		
Not evaluated or data missing — no. (%)†	112 (22)	102 (20)		
Response status at 120 weeks, as assessed by investigator				
Overall response — no. (% [95% CI])	335 (65 [61–69])	353 (68 [64–72])		
Confirmed or unconfirmed complete response — no. (% [95% CI])	283 (55 [51–60])	299 (58 [53–62])		0.38
Complete response, confirmed — no. (%)	201 (39)	242 (47)		
Complete response, unconfirmed — no. (%)	82 (16)	57 (11)		
Partial response — no. (%)	52 (10)	54 (10)		
Stable disease — no. (%)	0	0		
Progressive disease or death — no. (%)*	90 (18)	94 (18)		
Not evaluated or missing — no. (%)‡	88 (17)	70 (14)		
Progression-free survival at 3 years				
Rate, as assessed by independent review committee — % (95% CI)	77 (72–80)	78 (74–82)	1.10 (0.85–1.43)	0.48
Rate, as assessed by investigator — % (95% CI)	77 (72–80)	78 (74–81)	0.94 (0.73–1.22)	0.63
Overall survival rate at 3 years — % (95% CI)	94 (91–96)	94 (91–96)	1.16 (0.72–1.86)	

* This category includes patients who had disease progression or died at or before 120 weeks.
† Among the 214 patients who were included in this category, 129 patients prematurely discontinued the trial treatment and did not undergo imaging between 110 and 130 weeks, 55 patients started subsequent treatment before 110 weeks, 16 patients had 120-week scans that the independent review committee was unable to assess because of the poor quality of the scans, and 14 patients either had no baseline scan or scans with quality too poor for the independent review committee to assess.
‡ Among the 158 patients who were included in this category, 122 patients prematurely discontinued the trial treatment and did not undergo imaging between 110 and 130 weeks, 35 patients started subsequent treatment before 110 weeks, and 1 patient had no baseline scan.

rate of confirmed or unconfirmed complete response at 120 weeks, as assessed by the independent review committee, was 48% (95% confidence interval [CI], 44 to 53) in the rituximab–lenalidomide group and 53% (95% CI, 49 to 57) in the rituximab–chemotherapy group (P=0.13). The investigator-assessed rate of confirmed or unconfirmed complete response at 120 weeks was 55% (95% CI, 51 to 60) in the rituximab–lenalidomide

group and 58% (95% CI, 53 to 62) in the rituximab–chemotherapy group (P=0.38). The rate of best overall response, which was defined as the best response (confirmed or unconfirmed complete response or partial response) at any time during the trial, as assessed by the independent review committee was 84% (95% CI, 81 to 87) in the rituximab–lenalidomide group and 89% (95% CI, 86 to 91) in the rituximab–chemotherapy

A Progression-free Survival

No. at Risk

Rituximab–lena-lidomide group	513	435	409	393	364	282	174	107	49	13	0
Rituximab–chemo-therapy group	517	474	446	417	387	287	175	109	51	14	1	0

B Overall Survival

No. at Risk

Rituximab–lena-lidomide group	513	499	491	486	479	459	312	194	105	24	0
Rituximab–chemo-therapy group	517	496	487	481	470	453	298	193	115	32	2	0

Figure 1. Progression-free Survival and Overall Survival in the Intention-to-Treat Population.

Panel A shows estimates of progression-free survival as assessed by an independent review committee, and Panel B shows estimates of overall survival.

55 to 64) in the rituximab–lenalidomide group and 67% (95% CI, 63 to 71) in the rituximab–chemotherapy group; the rates as assessed by the investigators were 65% (95% CI, 60 to 69) and 70% (95% CI, 66 to 74), respectively. Responses were similarly durable in both groups.

The probability of a complete response (confirmed or unconfirmed) or partial response lasting for at least 3 years was 77% (95% CI, 71 to 82) in the rituximab–lenalidomide group and 74% (95% CI, 69 to 79) in the rituximab–chemotherapy group as assessed by the independent review committee and 82% (95% CI, 78 to 86) and 77% (95% CI, 72 to 81), respectively, as assessed by the investigators. The probability of a complete response (confirmed or unconfirmed) lasting for at least 3 years was 77% (95% CI, 69 to 83) in the rituximab–lenalidomide group and 81% (95% CI, 75 to 86) in the rituximab–chemotherapy group as assessed by the independent review committee and 86% (95% CI, 81 to 90) and 81% (95% CI, 75 to 86), respectively, as assessed by the investigators (Figs. S3 and S4 in the Supplementary Appendix).

The results of the assessment of progression-free survival appeared to be similar in the two treatment groups as assessed by the independent review committee (hazard ratio for progression or death from any cause, 1.10; 95% CI, 0.85 to 1.43; P=0.48) and as assessed by the investigators (hazard ratio, 0.94; 95% CI, 0.73 to 1.22; P=0.63) (Table 2 and Fig. 1A, and Fig. S5 in the Supplementary Appendix). The 3-year rate of progression-free survival, both as assessed by the independent review committee and as assessed by the investigators, was 77% (95% CI, 72 to 80) in the rituximab–lenalidomide group and 78% (95% CI, 74 to 82) in the rituximab–chemotherapy group. Overall survival results were immature, with 3-year rates of 94% in both treatment groups (Table 2 and Fig. 1B).

Histologic Transformation

The rate of histologic transformation at first disease progression was evaluated as a prespecified exploratory end point. Among the 102 patients who had progression and for whom biopsy and pathology reports were available at the time of progression, a total of 17 patients (10 of 49 patients in the rituximab–lenalidomide group and 7 of 53 patients in the rituximab–chemotherapy group) had histologic transformation according

group; the best overall response rates as assessed by the investigators were 86% (95% CI, 83 to 89) and 92% (95% CI, 89 to 94), respectively. The rate of best confirmed or unconfirmed complete response for the entire trial as assessed by the independent review committee was 59% (95% CI,

to review at a central pathology laboratory (additional details are provided in the Supplementary Appendix). Post hoc analyses showed that most of these transformations occurred soon after randomization. In the rituximab–lenalidomide group, 5 of the 10 patients had transformation within 28 weeks after randomization, and all 10 patients had transformation within 120 weeks. In the rituximab–chemotherapy group, none of the 7 patients had transformation within 28 weeks, and 6 of the 7 patients had transformation within 120 weeks.

Subgroup Analyses

The planned subgroup analyses of progression-free survival and of confirmed or unconfirmed complete response at 120 weeks showed that the efficacy of rituximab plus lenalidomide was independent of conventional prognostic factors, whereas rituximab plus chemotherapy appeared to have more activity in patients who were assessed as being at low risk on the basis of FLIPI score and in patients who had follicular lymphoma of Ann Arbor stage I or II (on a 4-stage scale, with higher stages indicating more extensive disease). The subgroup analysis of progression-free survival is shown in Figure 2A. The subgroup analysis of confirmed or unconfirmed complete response at 120 weeks is presented overall in Figure 2B and according to treatment group in Figure S6 in the Supplementary Appendix. A post hoc analysis of progression-free survival according to specific chemotherapy regimen showed results that were consistent with those of the intention-to-treat analysis (Fig. S7 in the Supplementary Appendix).

SAFETY

The safety population included 507 patients in the rituximab–lenalidomide group and 503 patients in the rituximab–chemotherapy group. Of these, 506 patients in the rituximab–lenalidomide group (99.8%) and 498 in the rituximab–chemotherapy group (99.0%) had at least one adverse event that occurred during the treatment period. Adverse events of any grade that were less common in the rituximab–lenalidomide group than in the rituximab–chemotherapy group included anemia (in 66% vs. 89% of the patients), fatigue (23% vs. 29%), nausea (20% vs. 42%), vomiting (7% vs. 19%), peripheral neuropathy (7% vs. 16%), leukopenia (4% vs. 10%), febrile neutropenia (2% vs. 7%), and alopecia (1% vs. 9%) (Table 3). Conversely, adverse events of any grade that were more common with rituximab plus lenalidomide than with rituximab plus chemotherapy included cutaneous reactions (in 43% vs. 24% of the patients), diarrhea (37% vs. 19%), rash (29% vs. 8%), abdominal pain (15% vs. 9%), myalgia (14% vs. 6%), muscle spasms (13% vs. 4%), and tumor flare reaction (6% vs. <1%). Rates of thromboembolic events of any grade were similar in the two groups (see the Supplementary Appendix).

The percentage of patients who had grade 3 or 4 adverse events during the treatment period was similar in the two groups overall (65% in the rituximab–lenalidomide group and 68% in the rituximab–chemotherapy group) and according to individual chemotherapy regimen (Tables S3 and S4 in the Supplementary Appendix). A higher percentage of the patients in the rituximab–lenalidomide group than in the rituximab–chemotherapy group had grade 3 or 4 cutaneous reactions (7% vs. 1%). Grade 3 or 4 neutropenia was observed in 32% of the patients in the rituximab–lenalidomide group and in 50% of the patients in the rituximab–chemotherapy group. Grade 4 neutropenia was reported in 8% and 31%, respectively; 5 patients in the rituximab–lenalidomide group and 32 patients in the rituximab–chemotherapy group had an absolute neutrophil count that fell below 100 per cubic millimeter. A higher percentage of patients in the rituximab–chemotherapy group than in the rituximab–lenalidomide group had infections of any grade (12% vs. 5%) and grade 3 or 4 infections (4% vs. 2%) that were associated with grade 3 or 4 neutropenia, despite the fact that more patients in the rituximab–chemotherapy group received concomitant antimicrobial agents (Table S5 in the Supplementary Appendix). Hospitalization due to febrile neutropenia was reported in 2% of the patients in the rituximab–lenalidomide group and in 5% of the patients in the rituximab–chemotherapy group. Growth factors were used in 23% of the patients in the rituximab–lenalidomide group and in 68% of the patients in the rituximab–chemotherapy group. Anemia was more common with rituximab plus chemotherapy than with rituximab plus lenalidomide (Fig. S8 in the Supplementary Appendix).

Adverse events that occurred during the treatment period and resulted in death (grade 5 events) were reported in 4 patients (1%) in the rituximab–lenalidomide group and in 5 patients (1%) in the
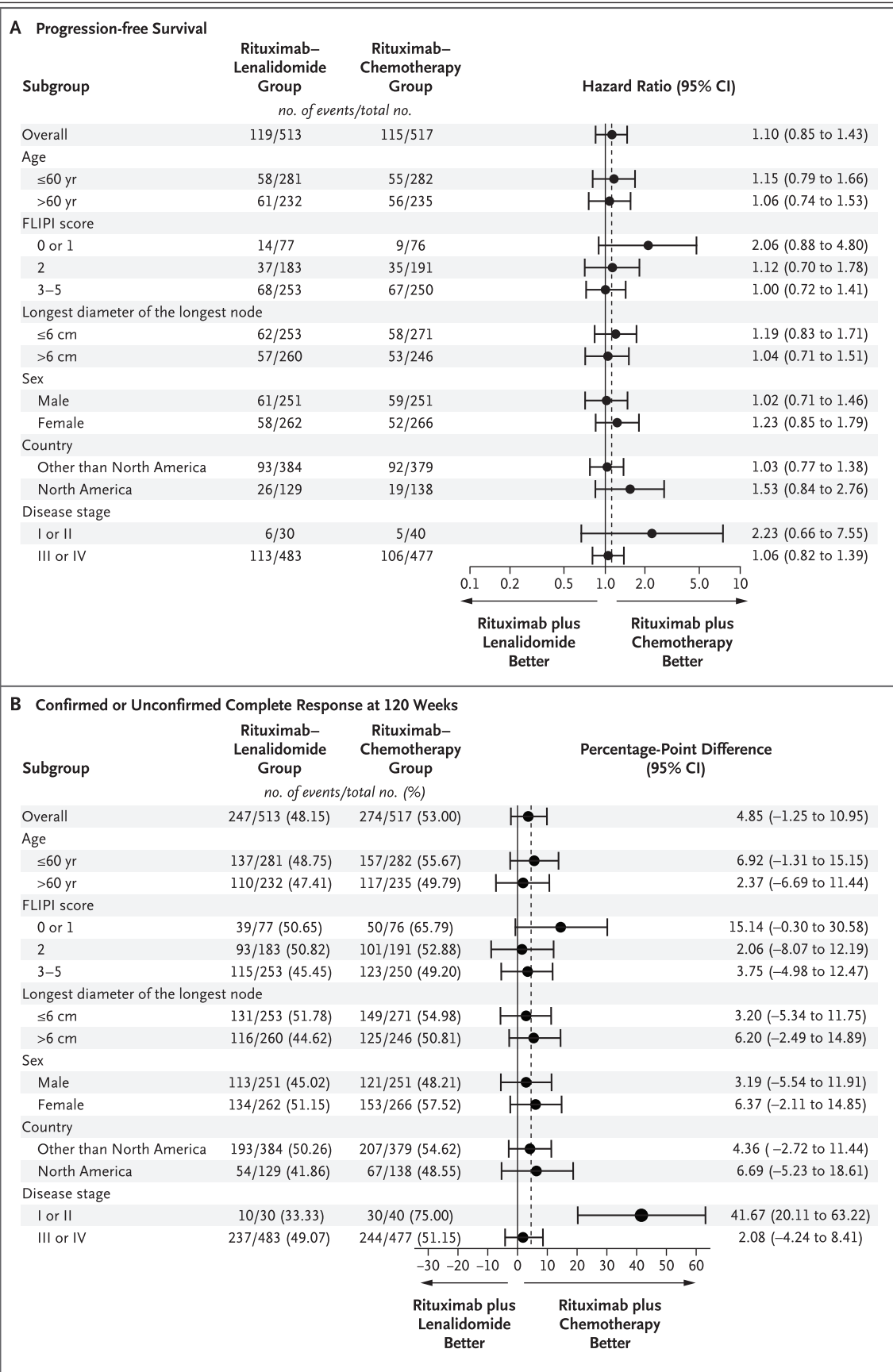
A Progression-free Survival

Subgroup	Rituximab–Lenalidomide Group	Rituximab–Chemotherapy Group	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
	no. of events/total no.			
Overall	119/513	115/517		1.10 (0.85 to 1.43)
Age				
≤60 yr	58/281	55/282		1.15 (0.79 to 1.66)
>60 yr	61/232	56/235		1.06 (0.74 to 1.53)
FLIPI score				
0 or 1	14/77	9/76		2.06 (0.88 to 4.80)
2	37/183	35/191		1.12 (0.70 to 1.78)
3–5	68/253	67/250		1.00 (0.72 to 1.41)
Longest diameter of the longest node				
≤6 cm	62/253	58/271		1.19 (0.83 to 1.71)
>6 cm	57/260	53/246		1.04 (0.71 to 1.51)
Sex				
Male	61/251	59/251		1.02 (0.71 to 1.46)
Female	58/262	52/266		1.23 (0.85 to 1.79)
Country				
Other than North America	93/384	92/379		1.03 (0.77 to 1.38)
North America	26/129	19/138		1.53 (0.84 to 2.76)
Disease stage				
I or II	6/30	5/40		2.23 (0.66 to 7.55)
III or IV	113/483	106/477		1.06 (0.82 to 1.39)

0.1　0.2　0.5　1.0　2.0　5.0　10

← Rituximab plus Lenalidomide Better　　Rituximab plus Chemotherapy Better →

B Confirmed or Unconfirmed Complete Response at 120 Weeks

Subgroup	Rituximab–Lenalidomide Group	Rituximab–Chemotherapy Group	Percentage-Point Difference (95% CI)	Percentage-Point Difference (95% CI)
	no. of events/total no. (%)			
Overall	247/513 (48.15)	274/517 (53.00)		4.85 (−1.25 to 10.95)
Age				
≤60 yr	137/281 (48.75)	157/282 (55.67)		6.92 (−1.31 to 15.15)
>60 yr	110/232 (47.41)	117/235 (49.79)		2.37 (−6.69 to 11.44)
FLIPI score				
0 or 1	39/77 (50.65)	50/76 (65.79)		15.14 (−0.30 to 30.58)
2	93/183 (50.82)	101/191 (52.88)		2.06 (−8.07 to 12.19)
3–5	115/253 (45.45)	123/250 (49.20)		3.75 (−4.98 to 12.47)
Longest diameter of the longest node				
≤6 cm	131/253 (51.78)	149/271 (54.98)		3.20 (−5.34 to 11.75)
>6 cm	116/260 (44.62)	125/246 (50.81)		6.20 (−2.49 to 14.89)
Sex				
Male	113/251 (45.02)	121/251 (48.21)		3.19 (−5.54 to 11.91)
Female	134/262 (51.15)	153/266 (57.52)		6.37 (−2.11 to 14.85)
Country				
Other than North America	193/384 (50.26)	207/379 (54.62)		4.36 (−2.72 to 11.44)
North America	54/129 (41.86)	67/138 (48.55)		6.69 (−5.23 to 18.61)
Disease stage				
I or II	10/30 (33.33)	30/40 (75.00)		41.67 (20.11 to 63.22)
III or IV	237/483 (49.07)	244/477 (51.15)		2.08 (−4.24 to 8.41)

−30　−20　−10　0　10　20　30　40　50　60

← Rituximab plus Lenalidomide Better　　Rituximab plus Chemotherapy Better →

Figure 2 (facing page). Subgroup Analyses of Progression-free Survival and Confirmed or Unconfirmed Complete Response at 120 Weeks.

Panel A shows the results of the prespecified subgroup analysis of progression-free survival. The dashed vertical line indicates a hazard ratio of 1.10, normalized to the overall population. No interaction between treatment group and any of the subgroups was found. Panel B shows the results of the prespecified subgroup analysis of confirmed or unconfirmed complete response at 120 weeks. The vertical line normalizes the plot to the overall difference in the rate of confirmed or unconfirmed complete response at 120 weeks between the rituximab–chemotherapy group and the rituximab–lenalidomide group (4.85%). A Follicular Lymphoma International Prognostic Index (FLIPI) score indicates low (0 or 1), intermediate (2), or high (3 to 5) risk on the basis of a scoring system that assigns one point for each of the following risk factors: a hemoglobin level of less than 12 g per deciliter, more than four nodal areas (with the exception of spleen), age older than 60 years, a lactate dehydrogenase level above the upper limit of the normal range, and Ann Arbor stage III or IV disease. A significant interaction between treatment group and subgroup was found in the subgroup defined according to disease stage (I or II vs. III or IV). The interaction was determined to be quantitative instead of qualitative according to the Gail and Simon (1985) test.[27]

rituximab–chemotherapy group. Among the patients who received at least one dose of trial treatment, 37 deaths were reported in the rituximab–lenalidomide group (with 23 of the deaths attributed by the investigators to lymphoma) as compared with 29 deaths reported in the rituximab–chemotherapy group (with 10 of the deaths attributed by the investigators to lymphoma). The death of 1 patient in each group was assessed as being related to the trial treatment (see the Results section in the Supplementary Appendix).

At the time of the current follow-up, second primary cancers were reported in 38 patients (7%) in the rituximab–lenalidomide group (including 25 patients who had invasive second tumors and 13 who had noninvasive second tumors) and in 48 patients (10%) in the rituximab–chemotherapy group (including 27 patients who had invasive second tumors and 21 who had noninvasive second tumors). Details are provided in Table S6 in the Supplementary Appendix.

DISCUSSION

RELEVANCE was a randomized, phase 3 trial that compared an immunomodulatory regimen, rituximab plus lenalidomide, with the current standard of care, rituximab plus chemotherapy, in previously untreated patients with advanced follicular lymphoma who were in need of treatment according to GELF criteria. Overall, both treatment groups showed good outcomes, and a median has not yet been reached for either progression-free survival or overall survival. Superiority was not shown for either regimen. The RELEVANCE trial was designed as a superiority trial on the basis of results of early phase 2 trials that showed high rates of best confirmed or unconfirmed complete response with rituximab plus lenalidomide in previously untreated patients with indolent lymphoma who did not have to meet GELF criteria before the initiation of treatment.[19,21] At the time that the RELEVANCE trial was designed, the phase 2 trials had short follow-up periods for assessment of confirmed or unconfirmed complete response and immature time-to-event data. However, the efficacy of rituximab plus lenalidomide appeared to be similar to that of rituximab plus chemotherapy, although the safety profile appeared to differ between the two regimens.

Incorporation of rituximab into combination chemotherapy regimens has been shown to significantly improve survival over chemotherapy alone.[28] In the current trial, rituximab in combination with lenalidomide showed results that were similar to those reported with rituximab plus chemotherapy in two randomized phase 3 trials with similar populations.[1,2] In the rituximab–chemotherapy group, the rate of progression-free survival at 3 years was 78% (as assessed by both the independent review committee and the investigators), and the rate of overall survival at 3 years was 94%. These results are consistent with 3-year rates of progression-free survival of 78% (by central assessment) and 73% (by investigator assessment) and an overall survival rate of 92% with rituximab plus chemotherapy in the GALLIUM trial[1] and a 3-year rate of progression-free survival of 75% (by investigator assessment) with rituximab plus chemotherapy in the PRIMA trial.[2,3] The progression-free survival and overall survival results for the rituximab–lenalidomide group were also similar to historical results in two phase 2 trials[19,21]; the 3-year progression-free survival rate of 77% reported here was similar to that reported in the Cancer and Leukemia Group B (CALGB) 50803 trial (81%)[21] and in a trial sponsored by M.D. Anderson Cancer Center (79%).[19] A limita-

Table 3. Adverse Events during the Treatment Period in the Safety Population.

Adverse Event	Rituximab–Lenalidomide Group (N = 507)		Rituximab–Chemotherapy Group (N = 503)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Neutropenia*	381 (75)	160 (32)	386 (77)	252 (50)
Anemia*	333 (66)	0	446 (89)	0
Thrombocytopenia*	268 (53)	11 (2)	266 (53)	8 (2)
Cutaneous reactions†	220 (43)	36 (7)	120 (24)	5 (1)
Diarrhea	187 (37)	10 (2)	95 (19)	6 (1)
Constipation	178 (35)	1 (<1)	167 (33)	5 (1)
Rash	146 (29)	20 (4)	39 (8)	1 (<1)
Fatigue	115 (23)	1 (<1)	147 (29)	4 (<1)
Nausea	100 (20)	0	209 (42)	8 (2)
Abdominal pain	78 (15)	4 (<1)	46 (9)	4 (<1)
Myalgia	73 (14)	0	29 (6)	1 (<1)
Arthralgia	71 (14)	3 (<1)	70 (14)	1 (<1)
Peripheral edema	69 (14)	0	47 (9)	1 (<1)
Muscle spasms	68 (13)	0	21 (4)	0
Infusion-related reaction	66 (13)	7 (1)	56 (11)	1 (<1)
Upper respiratory tract infection	47 (9)	0	55 (11)	0
Vomiting	34 (7)	2 (<1)	94 (19)	7 (1)
Peripheral neuropathy	35 (7)	1 (<1)	79 (16)	3 (<1)
Tumor flare reaction	30 (6)	7 (1)	1 (< 1)	0
Leukopenia	21 (4)	8 (2)	48 (10)	30 (6)
Febrile neutropenia	11 (2)	11 (2)	34 (7)	33 (7)
Tumor lysis syndrome	7 (1)	6 (1)	5 (1)	3 (<1)
Alopecia	5 (1)	0	45 (9)	3 (<1)

* This event was reported as an adverse event on the basis of laboratory test results. All the events of anemia were assessed as grade 1.
† Cutaneous reactions included preferred terms from the system organ classes of skin and subcutaneous tissue disorders, gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, and reproductive system and breast disorders.

tion inherent to the current analysis is the limited follow-up time for time-to-event end points. Longer follow-up with more mature survival data will be needed to assess long-term outcomes.

The number of patients who had confirmed histologic transformation was similar in the rituximab–lenalidomide group and the rituximab–chemotherapy group. The rate of transformation was less than 1% per year in both groups (10 of 513 patients in the rituximab–lenalidomide group and 7 of 517 patients in the rituximab–chemotherapy group over the course of a 37.9-month follow-up

period), which was well within the historical rate of 2 to 3% per year.[29,30]

The trial groups had expected but different safety profiles. Grade 3 or 4 neutropenia was more common in the rituximab–chemotherapy group than in the rituximab–lenalidomide group. Furthermore, a higher percentage of patients in the rituximab–chemotherapy group had febrile neutropenia and infections associated with grade 3 or 4 neutropenia, despite the fact that more patients in that group received concomitant antimicrobial agents. The apparent differences between lenalid-

omide-induced neutropenia and chemotherapy-induced neutropenia may be based on biologic differences in their mechanisms of action. In contrast to chemotherapy-induced direct inhibition of bone marrow precursors, lenalidomide-induced neutropenia is attributable to a reversible maturation arrest of myeloid lineage, subsequent to degradation of the transcription factor Ikaros at the time of cereblon binding by lenalidomide.[31] In addition, unlike chemotherapy, rituximab plus lenalidomide did not suppress hemoglobin levels, which may explain the lower rate of fatigue in the rituximab–lenalidomide group than in the rituximab–chemotherapy group. At the time of the current follow-up, second primary cancers were reported in 38 patients (7%) in the rituximab–lenalidomide group and 48 patients (10%) in the rituximab–chemotherapy group. Although thromboembolic disease has been reported more commonly with lenalidomide in patients with myeloma than in patients with lymphoma, no such trend was apparent in this trial.

In conclusion, the efficacy of rituximab plus lenalidomide was similar to that of rituximab plus chemotherapy; however, differences between the two groups were noted in safety profiles, with a higher incidence of grade 3 or 4 neutropenia and febrile neutropenia of any grade with rituximab plus chemotherapy and a higher incidence of grade 3 or 4 cutaneous reactions with rituximab plus lenalidomide.

APPENDIX

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