

Final Results of the IELSG-19 Randomized Trial of Mucosa-Associated Lymphoid Tissue Lymphoma: Improved Event-Free and Progression-Free Survival With Rituximab Plus Chlorambucil Versus Either Chlorambucil or Rituximab Monotherapy

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Published at jco.org on March 29, 2017.

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Clinical trial information: NCT00210353.

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0732-183X/17/3517w-1905w/\$20.00

A B S T R A C T

Purpose

There is no consensus on the optimal systemic treatment of patients with extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue. The IELSG-19 phase III study, to our knowledge, was the first such study to address the question of first-line treatment in a randomized trial.

Patients and Methods

Eligible patients were initially randomly assigned (1:1 ratio) to receive either chlorambucil monotherapy (6 mg/m²/d orally on weeks 1 to 6, 9 to 10, 13 to 14, 17 to 18, and 21 to 22) or a combination of chlorambucil (same schedule as above) and rituximab (375 mg/m² intravenously on day 1 of weeks 1, 2, 3, 4, 9, 13, 17, and 21). After the planned enrollment of 252 patients, the protocol was amended to continue with a three-arm design (1:1:6 ratio), with a new arm that included rituximab alone (same schedule as the combination arm) and with a final sample size of 454 patients. The main end point was event-free survival (EFS). Analysis of chlorambucil versus the combination arm was performed and reported separately before any analysis of the third arm.

Results


At a median follow-up of 7.4 years, addition of rituximab to chlorambucil led to significantly better EFS (hazard ratio, 0.54; 95% CI, 0.38 to 0.77). EFS at 5 years was 51% (95% CI, 42 to 60) with chlorambucil alone, 50% (95% CI, 42 to 59) with rituximab alone, and 68% (95% CI, 60 to 76) with the combination ($P = .0009$). Progression-free survival was also significantly better with the combination ($P = .0119$). Five-year overall survival was approximately 90% in each arm. All treatments were well tolerated. No unexpected toxicities were recorded.


Conclusion


Rituximab in combination with chlorambucil demonstrated superior efficacy in mucosa-associated lymphoid tissue lymphoma; however, improvements in EFS and progression-free survival did not translate into longer overall survival.

J Clin Oncol 35:1905-1912. © 2017 by American Society of Clinical Oncology

ASSOCIATED CONTENT

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DOI: <https://doi.org/10.1200/JCO.2016.70.6994>

 Data Supplement
DOI: <https://doi.org/10.1200/JCO.2016.70.6994>

DOI: <https://doi.org/10.1200/JCO.2016.70.6994>

INTRODUCTION

Extranodal marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) constitutes 8% of all non-Hodgkin lymphomas.^{1,2}

Apart from the eradication of *Helicobacter pylori* as an initial treatment of early-stage gastric

MALT lymphoma,³ there is no consensus regarding optimal treatment of patients with gastric involvement who experience failure with antibiotics who have extensive disease or primary extragastric localization.^{1,4-7} Radiotherapy can result in long-term local control for localized lymphoma,⁸⁻¹⁰ but it is not always feasible. Up to one third of patients present with disseminated disease that involves multiple extranodal sites.¹¹⁻¹⁴

Few single agents or combination chemotherapy regimens have been tested specifically in patients with MALT lymphomas, and most of the available data come from small, phase II studies with short follow-up that have generally tested compounds and regimens used for treating other indolent lymphomas.¹⁵⁻¹⁷ Rituximab has proven active in phase II studies^{18,19} and a study of combined bendamustine and rituximab has shown promising activity in first-line treatment.²⁰ More intensive combination regimens are usually limited to patients with histologic transformation or those with high tumor burden.^{2,21,22}

The International Extranodal Lymphoma Study Group 19 (IELSG-19) study is the first randomized trial to investigate systemic treatment of MALT lymphoma. The study was initially designed to compare chlorambucil alone and in combination with rituximab. After the planned enrollment, the study protocol was amended to add a third arm of treatment with rituximab alone.²³ Preliminary results of the first two-arm portion of the study—rituximab plus chlorambucil versus chlorambucil—were previously published.²³ Here, we report the final results of the entire three-arm study.

PATIENTS AND METHODS

Study Design

The IELSG-19 study, an open-label, randomized phase III trial, was conducted at 78 centers in six countries according to the principles of the Declaration of Helsinki and after approval by local institutional review boards and/or ethics committees. All patients provided written informed consent. The study was initially designed to randomly compare in a 1:1 ratio chlorambucil alone (arm A, standard treatment) with combination chlorambucil plus rituximab (arm B, study treatment). After enrollment of the planned 252 patients, the protocol was amended and continued with a three-arm design. The new arm included rituximab alone (arm C, study treatment), and the random assignment ratio was changed to 1:1:6 for a final total sample size of 454 patients. Following the amended protocol, analysis of chlorambucil versus chlorambucil plus rituximab was performed before any analysis of the third arm and reported previously.²³ Random assignment was stratified by primary tumor site (gastric *v* nongastric), nodal involvement (presence *v* absence), prior local therapy (surgery, radiation, or antibiotics *v* nonpretreated), and International Prognostic Index (IPI) score (low and low-intermediate risk *v* intermediate-high and high risk).

Patient Population

Patients with MALT lymphoma—either newly diagnosed or those who experienced relapse after prior local therapy—were eligible. Central pathology review was performed. Patients with primary gastric *H. pylori*-positive MALT lymphomas were eligible for inclusion in cases of endoscopic and histologic evidence of disease progression at any time post-*H. pylori* eradication or for stable disease with persistent lymphoma > 1 year after *H. pylori* eradication. Apart from *H. pylori* eradication, no prior systemic therapy was allowed. In all cases, measurable or evaluable disease, according to the National Cancer Institute International Workshop criteria,²⁴ was required.

Treatments

Patients who were assigned to arm A received induction treatment with daily chlorambucil of 6 mg/m² orally for 42 consecutive days (weeks 1 to 6). After restaging, patients with stable disease or an objective response then received chlorambucil 6 mg/m² per day for 2 weeks every 4 weeks (one cycle) for up to four cycles (weeks 9 to 10, 13 to 14, 17 to 18, and 21 to 22).

For patients who were assigned to arm B, chlorambucil was administered as in arm A. Rituximab 375 mg/m² was administered intravenously according to manufacturer instructions on days 1, 8, 15, and 22 during the induction phase. After restaging, rituximab was administered on day 1 of each of the subsequent chlorambucil cycles (weeks 9, 13, 17, and 21). Patients in arm C received rituximab alone with the same schedule used in arm B. Rituximab was provided by F Hoffmann-La Roche (Basel, Switzerland).

Outcome Measures

Primary end point was event-free survival (EFS), calculated from the date of trial registration to experience of treatment failure—including disease progression, early discontinuation of protocol treatment for any reason, or initiation of new treatment without documented progression—death as a result of any cause, or last follow-up.²⁴ Secondary end points were complete response rate (CR), overall response rate (ORR), response duration, progression-free survival (PFS), overall survival (OS), and toxicity.

Response was assessed after the first 6 weeks of therapy and at the end of treatment. Further assessments were scheduled every 4 months for 2 years, every 6 months for the next 3 years, and then annually for at least 5 years and included physical examination, routine laboratory tests, chest x-ray, and abdominal ultrasound. Additional imaging and/or endoscopic studies to evaluate all initial disease sites were planned as appropriate.

Additional methodology details, including statistical analysis, sample size calculation, and toxicity assessment, were previously published.²³

RESULTS

Patient Characteristics and Treatment

Figure 1 shows the patient flow through the trial. Four hundred fifty-four patients were enrolled and randomly assigned: 151 to chlorambucil, 152 to chlorambucil plus rituximab, and 151 to rituximab. Forty-two patients—16 in arm A, 19 in B, and seven in C—were shown to be ineligible and were excluded after pathology review gave other diagnoses. Eleven additional patients were not evaluable—six were never treated and five because of major protocol violations. Therefore, the analyzed population included 401 patients (131 in arm A, 132 in B, and 138 in C). Baseline characteristics are listed in Table 1. With the exception of a lower frequency of B symptoms in patients who were enrolled in the chlorambucil arm, there were no significant differences in the distribution of known risk factors. Details on the distribution of the anatomic sites across the three study arms are listed in Appendix Table A1 (online only).

Three hundred eighteen patients (79%) completed the treatment program according to the protocol. Thirty-eight patients required at least one chlorambucil dose reduction, but no rituximab dose reduction was permitted. Treatment discontinuation was recorded in 61 patients; 17 patients in arm B concomitantly discontinued both drugs, 25 discontinued chlorambucil only (18 patients in arm A and seven in arm B), and 19 discontinued rituximab only (three in arm B and 16 in arm C). This was usually a result of toxicity, disease progression, or patient preference, and withdrawal rates were not statistically different between arms. Median duration of treatment with chlorambucil was 14 weeks in arms A (range, 5 to 14 weeks) and B (range, 3 to 14 weeks). Median number of delivered rituximab doses was eight in arms B and C (range, 1 to 8 doses in both arms).

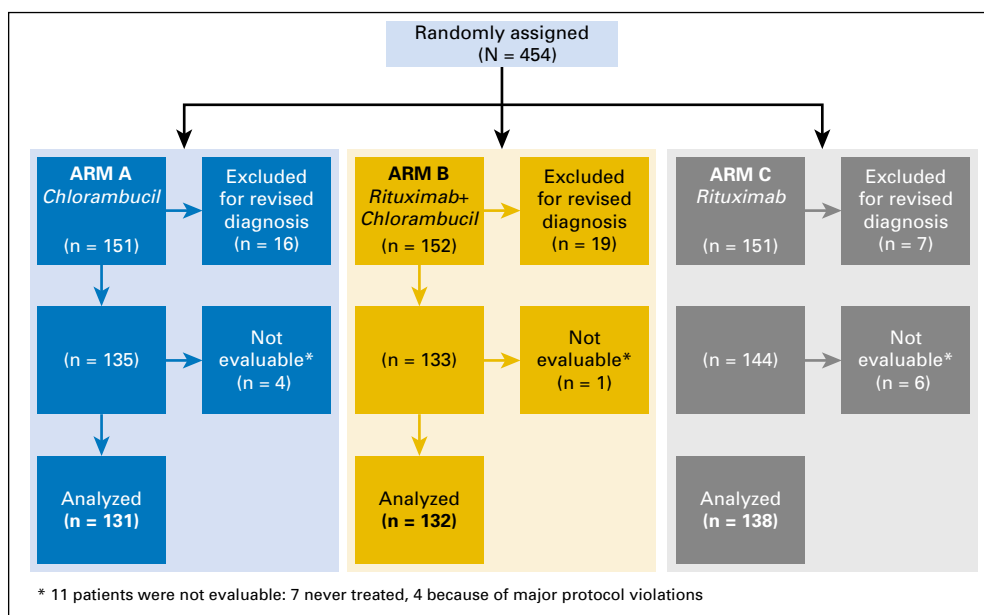


Fig 1. CONSORT diagram of study profile and patient flow. Forty-two patients were excluded after revised diagnosis, had diffuse large B-cell lymphoma (12 patients), follicular lymphoma (four patients), mantle-cell lymphoma (10 patients), primary splenic marginal-zone B-cell lymphoma (nine patients), primary nodal marginal-zone B-cell lymphoma (two patients), small lymphocytic lymphoma (one patient), non-mucosa-associated lymphoid tissue (MALT) indolent lymphoma, not otherwise classifiable (two patients), and no evidence of lymphoma tissue (two patients, one with chronic gastritis and one with Crohn's disease). (*) Eleven patients were not evaluable: seven were never treated and four had major protocol violations.

Treatment

Five (1%) of 401 patients who were treated according to protocol were never evaluated for response. One patient who was assigned to arm B withdrew consent and was lost to follow-up, one patient assigned to arm A experienced a fatal ischemic stroke during treatment, one patient in arm B died of disease progression after histologic transformation during treatment, and two patients in arm C withdrew after experiencing allergic reaction to the first or second rituximab administration.

Three hundred forty-five patients (86%; 95% CI, 82 to 89) achieved an objective response, with 264 CR (66%) and 81 partial response (20%). Treatment with the combination of

chlorambucil plus rituximab produced better responses with significantly higher ORR and CR rates than either drug administered alone. Results of response assessment—best response according to treatment arm—are listed in Table 2. Median time to best response was 3.8 months in the whole cohort (interquartile range, 2.0 to 6.4 months) with no difference among the three arms ($P = .367$). There was a trend toward longer remission duration in the combination arm, with 79% (95% CI, 71 to 85) of patients who achieved response in continuous remission at 5 years compared with 70% (95% CI, 60 to 78) and 66% (95% CI, 56 to 74) in the chlorambucil and rituximab arms, respectively; however, these differences did not reach a statistical significance (Fig 2).

Table 1. Baseline Patient Characteristics

Characteristic	All Patients (N = 401)	Arm A Chlorambucil (n = 131)	Arm B Chlorambucil Plus Rituximab (n = 132)	Arm C Rituximab (n = 138)	P*
Median age (range), years	61 (26-81)	60 (26-80)	59.5 (26-79)	62.5 (27-81)	.349
Male sex	197 (49.1)	69 (52.7)	64 (48.5)	64 (46.4)	.578
Ann Arbor stage I	170 (42.4)	52 (39.7)	60 (45.4)	58 (42.0)	.636
Ann Arbor stage III and IV	175 (43.6)	53 (40.6)	59 (44.7)	63 (45.6)	.662
ECOG PS \geq 2	6 (1.5)	4 (3.0)	1 (0.7)	1 (0.7)	.293
Presence of B-symptoms	42 (10.5)	6 (4.6)	20 (15.1)	16 (11.6)	.017
Elevated serum LDH (n = 400)	42 (10.5)	11 (8.5)	10 (7.6)	21 (15.3)	.076
Extranodal sites \geq 2	123 (30.7)	44 (33.6)	44 (33.3)	35 (25.4)	.247
Nodal involvement	142 (35.4)	45 (34.3)	49 (37.2)	48 (34.8)	.879
Bone marrow involvement	71 (17.7)	22 (16.8)	30 (22.7)	19 (13.8)	.148
Prior local therapy†	32 (8.0)	14 (10.7)	10 (7.6)	8 (5.8)	.328
Primary gastric site‡	171 (42.6)	57 (43.5)	53 (40.1)	61 (44.2)	.774
IPI risk (n = 400)					.795
Low	229 (57.2)	79 (60.8)	74 (56.1)	76 (55.1)	
Low-intermediate	94 (23.5)	25 (19.2)	34 (25.8)	35 (25.4)	
Intermediate-high	68 (17.0)	23 (17.7)	20 (15.1)	25 (18.1)	
High	9 (2.3)	3 (2.3)	4 (3.0)	2 (1.4)	

NOTE. Data are given as No. (%) unless otherwise indicated.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PS, performance status.

*P values refer to comparison of frequencies (χ^2 or Fisher's exact test as appropriate) or medians (nonparametric k-sample test) in the three arms.

†Includes previous surgery, antibiotic therapy, and/or radiation therapy.

‡Includes 10 patients with other extranodal localizations.

Table 2. Response to Treatment

Response	All Patients (N = 401)		Arm A Chlorambucil (n = 131)		Arm B Chlorambucil Plus Rituximab (n = 132)		Arm C Rituximab (n = 138)	
	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)
Complete remission*	264	65.8 (61.0 to 70.5)	83	63.4 (54.5 to 71.6)	104	78.8 (70.1 to 85.4)	77	55.8 (47.0 to 64.2)
Partial remission	81	20.2 (16.4 to 24.5)	29	22.1 (15.3 to 30.2)	21	15.9 (10.1 to 23.3)	31	22.5 (15.8 to 30.3)
Stable disease	28	7.0 (4.7 to 9.9)	11	8.4 (4.3 to 14.5)	1	0.8 (0.02 to 4.1)	16	11.6 (6.8 to 18.1)
Progressive disease	23	5.7 (3.7 to 8.5)	7	5.3 (2.2 to 10.7)	4	3.0 (0.8 to 7.6)	12	8.7 (3.0 to 12.0)
Not assessed	5	1.3 (0.4 to 2.9)	1	0.8 (0.02 to 4.2)	2	1.5 (0.2 to 5.4)	2	1.5 (0.2 to 5.1)
Overall response rate *	345	86.0 (82.2 to 89.3)	112	85.5 (78.3 to 91.0)	125	94.7 (89.4 to 97.8)	108	78.3 (70.4 to 84.8)

* $P < .001$.

Time-Related End Point Analysis

Median follow-up of the entire study cohort (N = 401) was 7.4 years (interquartile range, 5.6 to 9.7 years) and, as a result of the later addition of the third arm, it was longer in arms A and B (9.3 years; interquartile range, 6.8 to 10.3 years) than in arm C (5.7 years; interquartile range, 4.8 to 6.5 years).

Median EFS, the main end point of the study, was 8.6 years in the whole cohort, but was significantly shorter for patients who were treated with chlorambucil alone (5.1 years) or with rituximab alone (5.6 years) compared with those who received rituximab plus chlorambucil (median EFS not reached; $P = .0009$). Compared with chlorambucil alone, addition of rituximab resulted in significant reduction of the risk of EFS events (hazard ratio [HR], 0.54; 95% CI, 0.38 to 0.77), whereas rituximab alone showed a nearly identical risk (HR, 0.97; 95% CI, 0.69 to 1.35). The 5-year EFS in patients who were treated with combination therapy was 68% (95% CI, 60 to 76), 51% in those who received chlorambucil alone (95% CI, 42 to 60), and 50% in those who were treated with rituximab alone (95% CI, 42 to 59; Fig 3A).

Median PFS was significantly better ($P = .0119$) in patients who were treated with combination therapy: median not reached versus 8.3 years and 6.9 years for chlorambucil and rituximab alone, respectively. HR for the combination arm was 0.62 (95% CI,

0.42 to 0.93), whereas rituximab alone produced an outcome (HR, 1.10; 95% CI, 0.76 to 1.59) that was similar to chlorambucil alone (Fig 3B). The 5-year PFS in patients who were treated with combination therapy was also superior (72%; 95% CI, 63 to 79) to that after chlorambucil (59%; 95% CI, 50 to 68) or rituximab (57%; 95% CI, 48 to 65).

Overall, 58 patients—20 in arm A, 25 in arm B, and 13 in arm C—have died. Causes of death are described in Table 3. There was no significant difference in OS ($P = .464$) between treatment arms (Fig 3C). The 5-year OS rate was 90% (95% CI, 83 to 94) in patients who were treated with combination therapy, 89% after chlorambucil alone (95% CI, 82 to 93), and 92% after rituximab (95% CI, 86 to 96).

Histologic transformation during the trial was reported in 10 patients (two in arm A, six in arm B, and two in arm C), and six have died (four of six patients as a result of disease progression of aggressive lymphoma). Second primary malignancies were reported in 34 patients (14 in arm A, nine in arm B, and 11 in arm C; $P = .512$): 27 solid tumors, four second B-cell neoplasms (one acute lymphoblastic leukemia, one chronic lymphocytic leukemia, and one mantle cell lymphoma), and three myeloid neoplasms.

Impact of Patient Characteristics on Outcome

In univariate analysis, IPI score and the presence of lymph node involvement demonstrated a statistically significant effect on EFS, PFS, and OS in the whole cohort, whereas primary gastric origin had an impact only on EFS and PFS. Conversely, there was no impact for prior local treatment (Appendix Table A2, online only). In multivariate analysis of EFS and PFS (Cox proportional hazards regression model that included treatment in arm B and the stratification factors that had statistical significance at univariate analysis), the type of treatment remained significantly associated with EFS and PFS after controlling for nodal involvement, IPI group, and primary site (Appendix Table A3, online only). In a similar Cox proportional hazards regression model for OS—excluding primary anatomic site—only the IPI group retained a significant impact (Appendix Table A3).

In addition to better EFS and PFS, the CR rate was also significantly ($P = .015$) higher in gastric (72%; 95% CI, 65 to 79) versus primary nongastric lymphomas (61%; 95% CI, 54 to 67); however, the gastric lymphoma group had a significantly higher rate of patients with localized disease (stage I disease in 60% v 30%; $P < .001$), whereas the nongastric group comprised a variety of

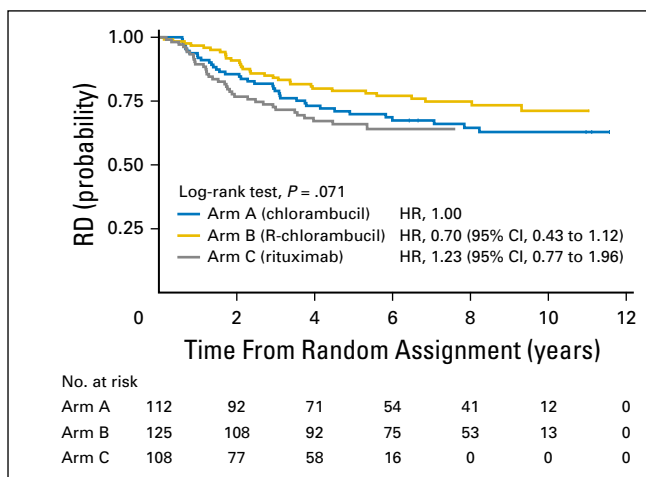


Fig 2. Kaplan-Meier estimates of response duration (RD) according to treatment arm in the 345 patients who achieved a response (partial response, n = 81; complete response, n = 264). HR, hazard ratio.

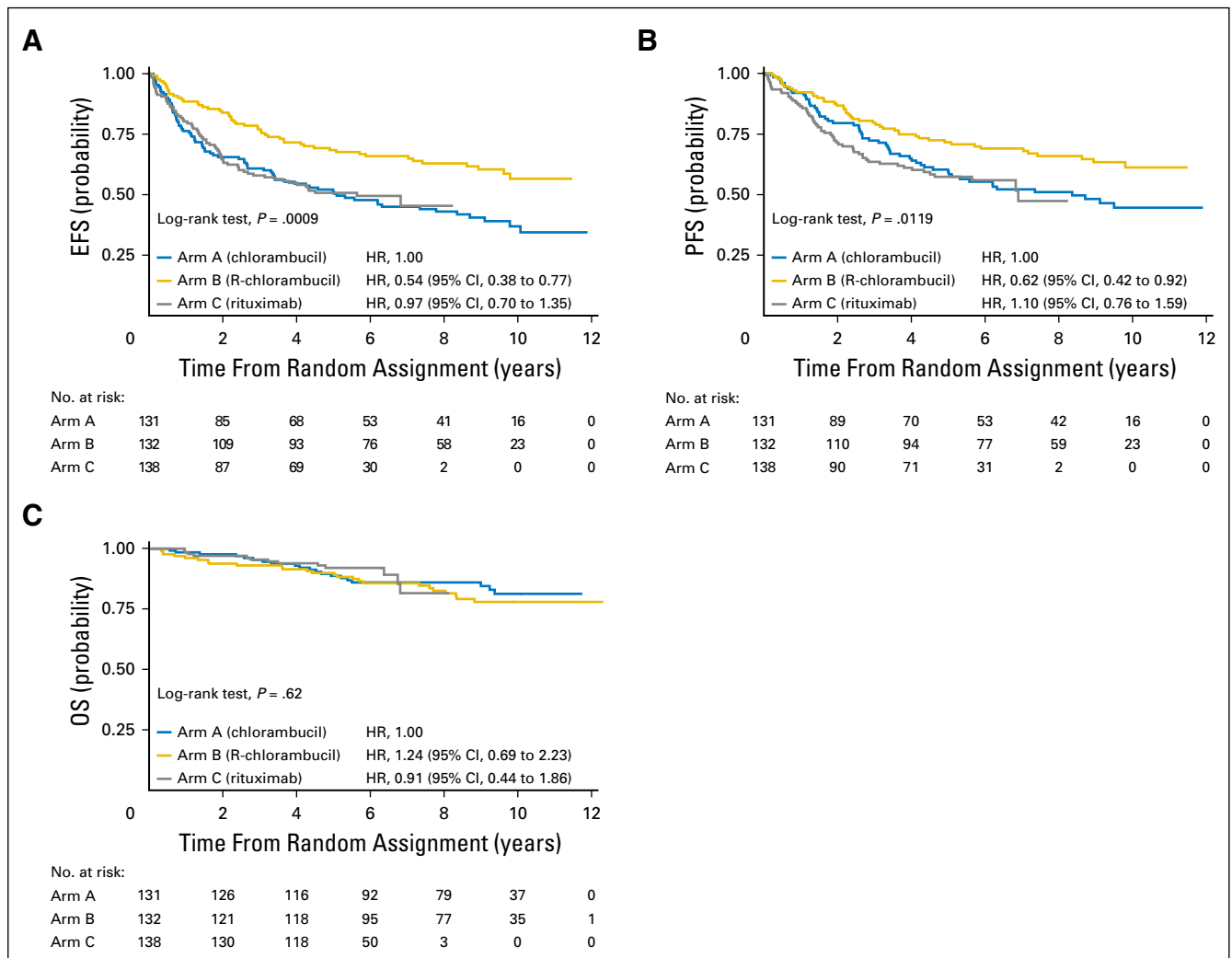


Fig 3. Kaplan-Meier survival curves according to treatment received for (A) event-free survival (EFS), (B) progression-free survival (PFS), and (C) overall survival (OS). HR, hazard ratio.

anatomic primary localizations (Appendix Table A1) with diverse outcomes (Appendix Fig A1, online only). Nevertheless, a significantly higher CR rate was achieved with combination therapy in

both primary gastric (91% v 61% after chlorambucil and 67% after rituximab; $P = .001$) and primary nongastric MALT lymphomas (72% v 62% after chlorambucil and 48% after rituximab; $P = .008$).

Table 3. Causes of Death

Cause of Death	All Patients (58 of 401; 14.5%)	Arm B Chlorambucil Plus Rituximab (25 of 132; 18.9%)		
		Chlorambucil (20 of 131; 15.3%)	Rituximab (13 of 138; 9.4%)*	Arm C Rituximab (13 of 138; 9.4%)*
Lymphoma progression	14 (24.1)	6 (30.0)	5 (20.0)	3 (23.1)
Second tumor	17 (29.3)	7 (35.0)	5 (20.0)	5 (38.4)
Transformed lymphoma	4 (6.9)	0 (0)	4 (16.0)	0 (0)
Infection	4 (6.9)	1 (5.0)	2 (8.0)	1 (7.7)
Respiratory failure	4 (6.9)	1 (5.0)	2 (8.0)	1 (7.7)
Stroke	4 (6.9)	1 (5.0)	1 (4.0)	2 (15.4)
Trauma	1 (1.72)	0 (0)	1 (4.0)	0 (0)
Deep venous thrombosis	1 (1.72)	1 (5.0)	0 (0)	0 (0)
Unknown	9 (15.5)	3 (15.0)	5 (20.0)	1 (7.7)
Total deaths	58 (100)	20 (34.5)	25 (43.1)	13 (22.4)

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

*The reduced death rate in arm C may simply reflect the significantly shorter follow-up time and was not statistically significant ($P = .080$).

With respect to the primary end point of the study, a significantly longer EFS in patients who were treated with the combination of rituximab and chlorambucil was evident in both gastric ($P = .002$) and nongastric ($P = .022$) patients as well as in those with ($P = .0054$) or without ($P = .0094$) lymph node involvement and those with low and low-intermediate IPI ($P = .0005$) but not in those with unfavorable IPI scores (Appendix Table A4, online only). As expected, patients with stage I disease had significantly better treatment outcome (Appendix Table A5, online only).

Safety

The safety population comprised all 401 patients who were treated according to protocol. Hematologic toxicity, as expected, was more frequent in the combination arm (Table 4); however, all treatments were well tolerated. A low number of adverse events was reported, with no unexpected differences between treatment arms. Nonhematologic adverse effects that occurred in more than five patients are also listed in Table 4, and a complete list of recorded nonhematologic toxicities is given in Appendix Table A6 (online only).

DISCUSSION

This study is the final report of the first randomized trial on the systemic treatment of MALT lymphoma. In a previous article, we reported the initial results of patients who were randomly assigned between chlorambucil and chlorambucil plus rituximab. The present analysis concerns the final results of the entire study population and includes the third study arm (rituximab alone). At the time of conception, chlorambucil alone was considered an acceptable comparator arm for a study that was aimed at evaluating

the clinical benefit of adding rituximab to chemotherapy.¹⁵ Although rituximab as single agent was known to carry significant antitumor activity in MALT lymphomas,¹⁸ the efficacy of chemoimmunotherapy had never been formally tested in this disease.

Sample size was calculated on a 20% difference in EFS, assuming that OS would likely not be affected in an indolent disease and that the required benefit in terms of EFS must be substantial to justify the additional cost that is associated with use of rituximab.²³

In this study, addition of rituximab to chlorambucil resulted in improved remission quality—measured by ORR and CR rate—and led to significantly prolonged EFS and PFS. As expected, differences in EFS, PFS, and response rate have not yet translated into improved OS, likely as a result of effective second treatment options in indolent disease (Appendix Tables A7-A8, online only). Synergism in anticancer drug combinations can be formally assessed only in preclinical studies; however, it is worth noting that this is the only controlled clinical trial to date that compared chemotherapy alone with the combination of rituximab and chemotherapy or rituximab alone. With respect to the main study end point, observed improvement in EFS (46% reduction in HR, with 95% CI ranging from 23% to 62%) suggests that clinical synergy of the drug combination may be present. This benefit was confirmed in multivariate analysis of EFS and PFS, which also showed that IPI and the presence of lymph node involvement are associated with outcome (Appendix Table A3).

As the only randomized study that has specifically addressed MALT lymphoma, these results can be considered a benchmark for future trials in this entity. Lack of OS difference between arms has also provided evidence for the use of rituximab alone as initial therapy to delay or avoid the long-term risks of chemotherapy and radiotherapy.

Table 4. Hematologic Toxicity and Nonhematologic Adverse Events Experienced by At Least Five Patients

Adverse Event	Arm A Chlorambucil (n = 131)				Arm B Chlorambucil Plus Rituximab (n = 132)				Arm C Rituximab (n = 138)			
	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4
Hematologic toxicity												
Leukopenia	4	5	2	—	2	9	5	—	—	—	1	—
Neutropenia	3	3	—	2	4	3	10	9	—	—	2	—
Lymphocytopenia	—	2	2	—	—	1	1	2	—	—	—	—
Anemia	4	—	1	—	2	1	—	—	1	—	0	—
Thrombocytopenia	2	3	1	—	2	2	2	—	1	—	—	—
Febrile neutropenia	—	—	—	—	—	—	3	—	—	—	—	—
Nonhematologic												
Fatigue	12	4	—	—	11	2	—	—	12	4	—	—
Fever	1	—	—	—	4	2	—	—	5	3	—	1
Diarrhea	1	1	—	—	5	1	—	—	3	—	—	—
Dyspepsia	2	1	—	—	2	—	3	—	1	—	—	—
Nausea	6	1	—	—	17	1	—	—	6	1	—	—
Stomatitis	1	1	—	—	3	—	—	—	1	—	—	—
Skin rash	5	2	—	—	4	2	1	—	3	1	—	—
Infections	3	11	2	1	1	8	4	—	4	6	4	—
Cough	2	—	—	—	—	—	—	—	4	2	—	—
Transaminase increase	—	—	2	1	—	2	—	1	1	—	3	—
Gastric pain	6	2	1	—	6	4	1	—	3	4	—	—
Headaches	2	—	—	—	2	2	—	—	3	2	—	—
IR symptoms	—	—	—	—	15	4	1	1	10	8	2	—

Abbreviations: G, toxicity grade (according to Common Terminology Criteria for Adverse Events version 3); IR, infusion related (including: bronchospasm, chills, fever, rash, arthralgias, pruritus).

In this study, patients with primary gastric localization, a stratification criterion, achieved better CR rate and EFS than did those with nongastric lymphoma. The value of unplanned analysis of patient subsets is debatable, and this finding does not necessarily indicate that gastric MALT lymphoma represents a distinct disease. The patients with gastric lymphoma who were enrolled in the study, compared with those with extragastric localizations, had a significantly higher rate of stage I disease, which may explain the different results. Moreover, extragastric sites comprise different anatomic primary localizations that may have different clinical outcomes, which has also been pointed out by a study of the SEER database.²⁵ The current study is underpowered to address the clinical relevance of any individual anatomic localizations. Nevertheless, the benefit of combination therapy on the main study end point—EFS—was statistically significant in both gastric and nongastric MALT lymphomas.

All treatments were well tolerated and no unexpected adverse effects were recorded. To date, no clinically significant differences in acute and long-term toxicity have been observed between arms, despite the expected occurrence of infusion-related symptoms in the rituximab-containing arms, as well as increased the number of patients with grade 3 and 4 neutropenia in the combination arm (Table 4). This latter result did not cause a significant increase in neutropenic fever and infection rates.

A phase II study of the Spanish GELTAMO group has shown promising activity with the combination of bendamustine and rituximab for first-line systemic treatment²⁰ of MALT lymphoma. This single-arm, phase II trial evaluated 57 patients. After a median follow-up of 43 months, EFS at 4 years was 88% (95% CI, 74 to 95). These results seemed to be extremely good, although CIs overlap those of the IELSG-19 study. Moreover, in arm B of the IELSG-19 trial, several unfavorable clinical features were more common than in the GELTAMO study, including B symptoms and involvement of multiple extranodal sites, lymph nodes, and bone marrow. Hence, given the long natural history of this disease and the different size and design of the studies, direct comparison of these results with those of the randomized trial, which has approximately three times longer follow up, should be taken with caution.²⁶

In conclusion, we have shown the superior efficacy of rituximab in combination with chlorambucil in treatment of MALT lymphoma. Improved EFS and PFS with little added toxicity justifies the first-line use of this regimen, and the results of this controlled clinical study may define a standard regimen for treatment of patients MALT lymphoma who are in need of systemic therapy. The lack of OS benefit, however, leaves room to consider the use of chlorambucil alone when treatment cost is a relevant issue, but also provides evidence for the use of single-agent rituximab to avoid the toxicity of chemotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Support

Supported in part by a grant from Oncosuisse (ICP OCS-01356-03-2003) and by an unrestricted grant from Roche.

Prior Presentation

Presented in part at the 12th International Conference on Malignant Lymphoma, Lugano, Switzerland, June 19-22, 2013.



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Final Results of the IELSG-19 Randomized Trial of Mucosa-Associated Lymphoid Tissue Lymphoma: Improved Event-Free and Progression-Free Survival With Rituximab Plus Chlorambucil Versus Either Chlorambucil or Rituximab Monotherapy

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Acknowledgment

This study would have not been possible without the commitment of major cooperative trial groups (Fondazione Italiana Linfomi, Groupe d'Etude des Lymphomes de l'Adulte, United Kingdom National Cancer Research Institute, and the Grup per l'Estudi dels Limfomes de Catalunya i Balears). We acknowledge all the study investigators as well as the nursing and medical staff who looked after patients at each center. In addition, we thank Elena Porro, Cristina Morinini, Nicoletta Ielmini, Monica Bellei, Marina Cesaretti, Christelle Da Cruz, Pascale Godard, Marie-Christine Pinail, Kelly Cozens, Carol J. Tyas, Ira Jakupovic, Louisa Little, Joanne Simon, and Rita Gianascio Gianocca for the data management and secretarial assistance. We also thank the members of the Data and Safety Monitoring Board (Silvia Marsoni, Walter Mingrone, and Maria Grazia Valsecchi). We appreciated the conceptual contributions from Bruno Oesterwalder, Myriam Mendila, and Michael Wenger of F. Hoffmann-La Roche.

Appendix

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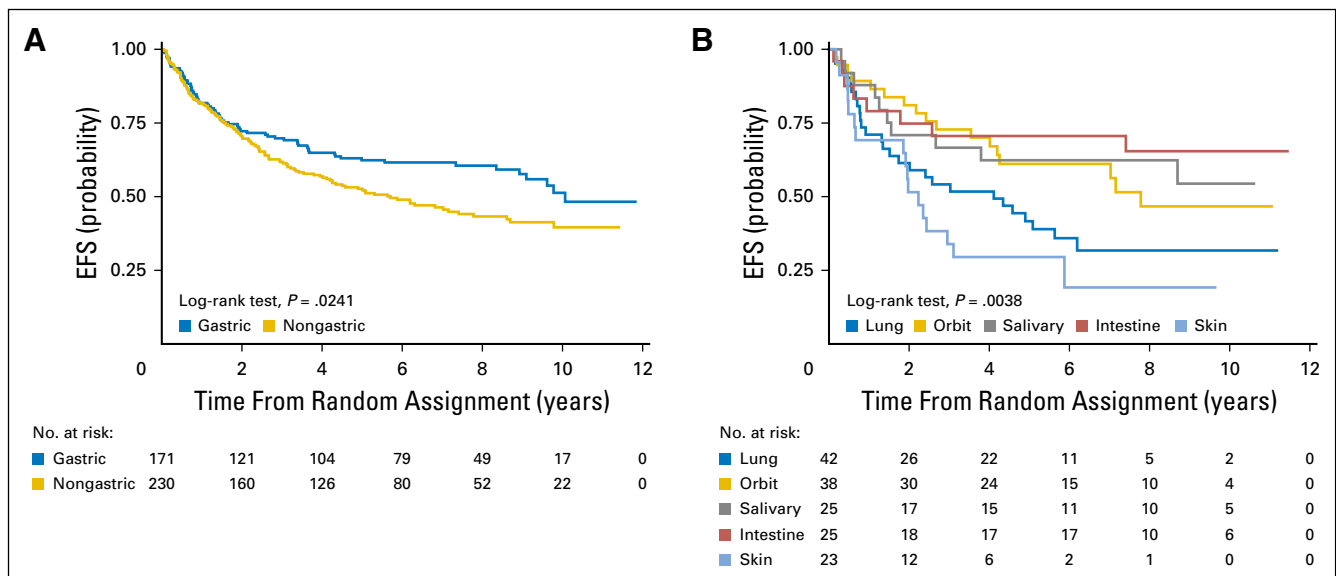


Fig A1. Kaplan-Meier event-free survival (EFS) curves by the primary localization of mucosa-associated lymphoid tissue (MALT) lymphoma in (A) gastric versus extragastric disease and in (B) the most frequent primary extragastric localizations.

Final Results of the MALT Lymphoma Randomized Trial IELSG-19

Table A1. Patient Distribution According to Primary Site, Regardless of Stage

Site of Localization	All Patients (N = 401)	Arm A Chlorambucil (n = 131)	Arm B Chlorambucil Plus Rituximab (n = 132)	Arm C Rituximab (n = 138)
Stomach	156 (38.9)	50 (38.2)	49 (37.1)	57 (41.3)
Lung	42 (10.5)	19 (14.5)	10 (7.6)	13 (9.4)
Orbit	38 (9.5)	9 (6.9)	11 (8.3)	18 (13.0)
Salivary glands	25 (6.2)	11 (8.4)	10 (7.6)	4 (2.9)
Skin	23 (5.7)	6 (4.6)	10 (7.6)	7 (5.1)
Upper airways	13 (3.2)	2 (1.5)	6 (4.5)	5 (3.6)
Colon	14 (3.5)	3 (2.3)	7 (5.3)	4 (2.9)
Small bowel	11 (2.7)	2 (1.5)	5 (3.8)	4 (2.9)
Genitourinary tract	5 (1.2)	2 (1.5)	0 (0)	3 (2.2)
Other individual sites*	14 (3.5)	3 (2.3)	7 (5.3)	4 (2.9)
Multiple sites†	60 (15.0)	24 (18.3)	17 (12.9)	19 (13.8)

NOTE. Data are given as No. (%). Differences in site distribution among arms were not statistically significant.

*Either gastric or extragastric primary presentation with additional MALT sites involved.

†Including breast, liver, thyroid, bone, soft tissues, pleura, and pancreas, each comprising fewer than five patients.

Table A2. Univariate Analysis of the Impact of Patient Characteristics Used for Stratification on Survival End Points

	EFS			PFS			OS		
	5-Year EFS % (95% CI)	Median (years)	P (log-rank)	5-Year PFS % (95% CI)	Median (years)	P (log-rank)	5-Year OS % (95% CI)	Median (years)	P (log-rank)
Lymph node involvement			.0001			< .0001			.0385
No	63 (56 to 68)	n.r.		69 (63 to 75)	n.r.		93 (89 to 96)	n.r.	
Yes	46 (37 to 54)	3.4		51 (42 to 59)	5.6		85 (78 to 90)	n.r.	
IPI			< .0001			< .0001			< .0001
Low to low-intermediate	61 (55 to 66)	9.8		68 (62 to 73)	n.r.		93 (90 to 95)	n.r.	
High-intermediate to high	39 (28 to 49)	2.7		42 (31 to 53)	3.3		78 (67 to 86)	n.r.	
Primary site			.0241			.0013			.0729
Gastric	62 (54 to 69)	5.7		71 (63 to 77)	n.r.		93 (88 to 96)	n.r.	
Extragastric	53 (46 to 59)	10.1		57 (50 to 63)	7.0		88 (83 to 92)	n.r.	
Prior local therapy*			.6200			.5523			.3886
No	57 (51 to 62)	8.7		63 (58 to 68)	n.r.		90 (86 to 93)	n.r.	
Yes	58 (38 to 73)	6.3		62 (41 to 77)	7.0		93 (41 to 77)	n.r.	

Abbreviations: EFS, event-free survival; IPI, International Prognostic Index; n.r., not reached; OS, overall survival; PFS, progression-free survival.

*Including previous surgery, antibiotic therapy, and/or radiation therapy.

Table A3. Cox Models Studying the Effect of Treatment Arm on Survival End Points After Controlling for Stratification Factors With a Significant Impact on Univariate Analysis

	Event-Free Survival		Progression-Free Survival		Overall Survival	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Nodal involvement	1.66 (1.24 to 2.22)	.001	1.78 (1.29 to 2.45)	< .001	1.37 (0.81 to 2.34)	.242
High-intermediate to high IPI	1.65 (1.19 to 2.28)	.003	1.77 (1.25 to 2.51)	.001	3.19 (1.86 to 5.45)	< .001
Primary extragastric site	1.24 (0.92 to 1.67)	.156	1.50 (1.07 to 2.10)	.019	n.a.	n.a.
Combination arm	0.53 (0.38 to 0.73)	< .001	0.57 (0.41 to 0.82)	.002	1.30 (0.77 to 2.20)	.329

NOTE. All models included all patients (N = 401) and were statistically significant (P > .001).

Abbreviations: HR, hazard ratio; IPI, international prognostic index; n.a., not applicable.

Table A4. Impact of Patient Characteristics Used for Stratification on Complete Remission and Event-Free Survival Rates Across Study Arms

	Arm A Chlorambucil		Arm B Chlorambucil Plus Rituximab		Arm C Rituximab		<i>P</i> (univariate analysis)	
	CR Rate (%)	5-Year EFS % (95% CI)	CR Rate (%)	5-Year EFS % (95% CI)	CR Rate (%)	5-Year EFS % (95% CI)	χ^2 Test for CR	Log-Rank Test for EFS
Lymph node involvement								
No	62	54 (43 to 64)	82	73 (62 to 81)	63	61 (50 to 70)	.007	.0094
Yes	62	45 (30 to 59)	75	60 (45 to 73)	44	31 (118 to 44)	.006	.0054
IPI								
Low to low-intermediate	67	57 (47 to 66)	84	74 (64 to 81)	56	52 (42 to 61)	< .001	.0005
High-intermediate to high	40	29 (14 to 47)	58	44 (23 to 62)	59	44 (25 to 61)	.351	.774
Primary site								
Gastric	61	51 (37 to 63)	91	77 (63 to 86)	67	60 (46 to 72)	.001	.0018
Extragastric	62	52 (40 to 63)	72	63 (51 to 72)	48	43 (31 to 54)	.008	.0218

Abbreviations: CR, complete remission; EFS, event-free survival; IPI, International Prognostic Index.

Table A5. Treatment Outcome According to Stage

End Point	Stage I (n = 170)	Stage II and IV (n = 231)	<i>P</i> *
	% (95% CI)	% (95% CI)	
CR	75 (67 to 81)	59 (53 to 66)	.001
ORR	88 (82 to 93)	84 (79 to 89)	.275
In first remission at 5 years	85 (77 to 90)	62 (54 to 69)	< .0001
5-year EFS	72 (65 to 79)	47 (40 to 53)	< .0001
5-year PFS	78 (70 to 84)	52 (45 to 58)	< .0001

Abbreviations: CR, complete remission; EFS, event-free survival; ORR, overall response rate; PFS, progression-free survival.

* χ^2 or log-rank test, as appropriate.

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Table A6. Nonhematologic Adverse Events													
Adverse Event	Arm A Chlorambucil (n = 131)				Arm B Chlorambucil Plus Rituximab (n = 132)				Arm C Rituximab (n = 138)				
	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4	
Constitutional symptoms													
Fatigue	12	4	—	—	11	2	—	—	12	4	—	—	
Fever	1	—	—	—	4	2	—	—	5	3	—	1	
Sweating	—	—	—	—	1	—	—	—	1	1	—	—	
GI													
Diarrhea	1	1	—	—	5	1	—	—	3	—	—	—	
Dyspepsia	2	1	—	—	2	—	3	—	1	—	—	—	
Nausea	6	1	—	—	17	1	—	—	6	1	—	—	
Vomiting	—	2	—	—	—	2	—	—	—	—	—	—	
Dysphagia	—	—	—	—	—	—	—	1	—	—	—	—	
Anorexia	—	—	—	—	—	—	1	—	1	1	—	—	
Constipation	2	—	—	—	2	—	—	—	—	—	—	—	
Stomatitis	1	1	—	—	3	—	—	—	1	—	—	—	
Dermatology/skin													
Skin rash	5	2	—	—	4	2	1	—	3	1	—	—	
Pruritus/itching	1	1	—	—	—	—	1	—	—	—	—	—	
Infection													
Febrile neutropenia	—	—	—	—	—	—	3	—	—	—	—	—	
Infection other	3	11	2	1	1	8	4	—	4	6	4	—	
Renal/genitourinary													
Polyuria	1	—	—	—	—	—	—	—	—	—	—	—	
Ocular/visual													
Tearing, watery eye (epiphora, tearing)	—	—	—	—	1	—	—	—	—	—	—	—	
Pulmonary/upper respiratory													
Dyspnea	—	—	—	—	—	—	—	—	1	1	—	—	
Cough	2	—	—	—	—	—	—	—	4	2	—	—	
Cardiac arrhythmia													
Palpitations	—	—	—	—	1	—	—	—	—	—	—	—	
Atrial fibrillation	—	—	—	—	—	—	—	1	—	—	—	—	
Cardiac general													
Pericardial effusion	—	—	—	—	1	—	—	—	—	—	—	—	
Hypertension	—	—	—	—	—	1	—	—	—	—	—	—	
Neurology													
Dizziness	—	—	—	—	1	—	—	—	1	—	1	—	
Mood alteration, anxiety	1	1	—	—	—	—	—	—	—	—	—	—	
Syncope	—	—	1	—	—	—	—	—	—	—	—	—	
Paresthesia	—	—	—	—	1	—	—	—	2	2	—	—	
Insomnia	1	—	—	—	2	1	—	—	—	—	—	—	
Metabolic/laboratory													
Transaminase	—	—	2	1	—	2	—	1	1	—	3	—	
Hypophosphatemia	—	—	—	—	—	—	1	—	—	—	—	—	
GGT	—	1	—	—	—	1	—	—	—	—	—	—	
ALP	—	—	—	—	1	—	—	—	—	—	—	—	
Hypoalbuminemia	—	—	—	—	—	—	—	—	1	—	—	—	
Vascular													
Hemorrhage	1	—	—	—	1	—	—	—	1	—	1	—	
Pulmonary embolism (vascular)	—	—	1	—	—	—	—	—	—	—	—	—	
Auditory/ear													
Tinnitus	—	—	—	—	1	—	—	—	—	—	—	—	
Pain													
Arthralgia (pain)	—	2	—	—	—	—	—	—	—	—	—	—	
Bone/muscle pain	—	—	—	—	1	—	—	—	2	2	—	—	
Eye pain/blurred vision	—	—	—	—	—	—	—	—	1	—	—	—	
Gastric pain	6	2	1	—	6	4	1	—	3	4	—	—	
Headaches	2	—	—	—	2	2	—	—	3	2	—	—	
Pancreatitis	—	—	—	—	—	—	—	—	—	—	1	—	
IR symptoms	—	—	—	—	15	4	1	1	10	8	2	—	

Abbreviations: ALP, alkaline phosphatase; G, toxicity grade (according to Common Terminology Criteria for Adverse Events version 3); GGT, gamma glutamyl transpeptidase; IR, infusion related (including: bronchospasm, chills, fever, rash, arthralgias, pruritus).

Table A7. Second-Line Treatment

	All Patients	Arm A Chlorambucil	Arm B Chlorambucil Plus Rituximab	Arm C Rituximab
Treatment type*, No. (%)	134	46	36	52
None	14 (10.4)	6 (13.0)	3 (8.3)	5 (9.6)
R alone	10 (7.5)	6 (13.0)	3 (8.3)	1 (1.9)
Alkylating based	12 (8.9)	2 (4.4)	3 (8.3)	7 (13.4)
Purine analog based	5 (3.7)	1 (2.2)	2 (5.6)	2 (3.8)
R-bendamustine	8 (6.0)	1 (2.2)	3 (8.3)	4 (7.7)
R and anthracycline based	16 (12.0)	11 (23.9)	3 (8.3)	2 (3.9)
R and alkylating based	26 (19.4)	7 (15.2)	3 (8.3)	16 (30.8)
Fludarabine/cyclophosphamide-R	2 (1.5)	0 (0.0)	0 (0.0)	2 (3.8)
Others	11 (8.2)	3 (6.5)	4 (11.1)	4 (7.7)
Radiotherapy	15 (11.2)	4 (8.7)	5 (13.9)	6 (11.5)
Unknown	15 (11.2)	5 (10.9)	7 (19.5)	3 (5.8)

Abbreviation: R, rituximab.

*Alkylating-based regimens included single-agent chlorambucil or cyclophosphamide, or cyclophosphamide combined with vincristine and prednisone. Purine analog-based regimens included single-agent cladribine or fludarabine, or fludarabine combination regimens with cyclophosphamide or with mitoxantrone and dexamethasone. Anthracycline-based regimens included CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and CHOP-like. Other treatments included antibiotics, everolimus, bortezomib, and radioimmunotherapy with ibritumomab-tiuxetan.

Table A8. Time to Next Therapy*

	All Patients (n = 83)	Arm A Chlorambucil (n = 26)	Arm B Chlorambucil Plus Rituximab (n = 23)	Arm C Rituximab (n = 34)
Median (years)	2.3	2.7	2.4	1.6
Interquartile range (years)	1.3-3.9	1.3-5.3	2.1-4.3	1.0-2.8

*Information on time to next treatment was not included in the follow-up case report forms of the trial and could only be retrieved for 83 patients. In this small subset, the difference in the time to next therapy among the three arms was statistically significant (Log-rank test, $P = .014$). These results, however, should be interpreted with caution due to the considerable amount of missing information.