VOLUME 31 · NUMBER 5 · FEBRUARY 10 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Addition of Rituximab to Chlorambucil Produces Superior Event-Free Survival in the Treatment of Patients With Extranodal Marginal-Zone B-Cell Lymphoma: 5-Year Analysis of the IELSG-19 Randomized Study

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Published online ahead of print at www.jco.org on January 7, 2013.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00210353.

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0732-183X/13/3105-565/$20.00

DOI: 10.1200/JCO.2011.40.6272

## ABSTRACT

### Purpose
Apart from localized gastric disease, there is no consensus on standard initial treatment of mucosa-associated lymphoid tissue lymphoma. The IELSG-19 study (Randomized Trial of Chlorambucil Versus Chlorambucil Plus Rituximab Versus Rituximab in MALT Lymphoma) was launched to compare chlorambucil alone versus chlorambucil plus rituximab in patients not previously given systemic anticancer therapy.

### Patients and Methods
Patients not responding to or not suitable for local therapy were eligible. In arm A, chlorambucil was given daily 6 mg/m$^2$ orally (PO) for 6 weeks. Responding patients and those with stable disease continued to be given daily chlorambucil 6 mg/m$^2$ PO for 14 consecutive days every 28 days for four cycles. In arm B, intravenous rituximab 375 mg/m$^2$ per day was added on days 1, 8, 15, 22, 56, 84, 112, and 140. After completion of the planned accrual, the protocol was amended to introduce a third arm with rituximab alone. We report the planned final analysis of the first two arms (113 patients in arm A and 114 in arm B).

### Results
At a median follow-up of 62 months, the 5-year event-free survival (EFS) was significantly better for the patients treated in arm B (68% *v* 50%; $P = .002$) who, despite similar overall response rates (90% *v* 87%), achieved a higher complete remission rate (78% *v* 65%; $P = .025$). Progression-free survival was also improved but it did not reach statistical significance ($P = .057$). Five-year overall survival (OS) was 89% in both arms. Both treatments were well tolerated without unexpected toxicities.

### Conclusion
Both treatments were active; the better response rate and EFS obtained with the addition of rituximab did not translate into improved OS.

*J Clin Oncol 31:565-572. © 2013 by American Society of Clinical Oncology*

## INTRODUCTION

Extranodal marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) constitutes approximately 8% of non-Hodgkin lymphomas. The stomach is the most frequent site, but MALT lymphomas can arise at any extranodal site.[1,2]

Despite abundant literature on its histologic, clinical, and biologic features and several studies[1,3] showing that eradication of *Helicobacter pylori* can be the sole initial treatment for most patients with localized gastric involvement, there is no consensus on the optimal treatment for patients requiring subsequent treatment or for those with extensive disease. Indeed, radiotherapy can result in long-term local control for localized lymphoma,[4-6] but it is not always feasible.[7-10]

Retrospective series[7-12] that include patients with various sites of MALT lymphoma treated with surgery, radiotherapy, and chemotherapy have shown good disease control and excellent overall survival (OS) in most patients, regardless of the treatment modality. Few single agents or chemotherapy regimens have been tested specifically in MALT lymphomas, and most information comes from

phase II studies with limited numbers of patients and short follow-up. Treatment with oral alkylating agents has been reported to result in a high rate of disease control.[13] Other studies[14] have demonstrated the significant activity of purine analogs and of the combination of chlorambucil, mitoxantrone, and prednisone.[15] The proteasome inhibitor bortezomib has been evaluated as a targeted treatment, but its clinical utility seems limited.[16] More intensive combination regimens such as CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] are likely active but comparatively toxic and should be limited to patients with histologic transformation or with high tumor burden.[2] The anti-CD20 monoclonal antibody rituximab has also been shown to be highly active in phase II studies (with a response rate of approximately 70%) and may represent an additional option for the treatment of systemic disease.[17,18] Here, we report the results of the two-arm portion of the International Extranodal Lymphoma Study Group 19 (IELSG-19) phase III randomized study (Randomized Trial of Chlorambucil Versus Chlorambucil Plus Rituximab Versus Rituximab in MALT Lymphoma), which investigated the addition of rituximab to chlorambucil as initial systemic treatment in patients with MALT lymphoma.

## PATIENTS AND METHODS

### Study Design and End Points

During the first part of this randomized phase III study, conducted from January 2003 to October 2005, patients were randomly assigned in a 1:1 ratio to chlorambucil alone (arm A, standard treatment) or to the combination of chlorambucil plus rituximab (arm B, study treatment). After the enrollment of the planned 252 patients, the study protocol was amended, and in October 2006, the trial was reopened with a three-arm design. The novel third arm included rituximab alone (arm C, study treatment), and the randomization ratio was changed to 1:1:6 for a final total sample size of 450 patients. The amended protocol stated that the analysis of chlorambucil versus chlorambucil plus rituximab should be performed and reported first, before any

**Table 1.** Baseline Patient Characteristics

| Characteristic | All Patients (N = 231) | | Chlorambucil (arm A) (n = 116) | | Chlorambucil Plus Rituximab (arm B) (n = 115) | | |
|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | *P** |
| Male sex | 122 | 53 | 65 | 56 | 57 | 50 | .33 |
| Age, years | | | | | | | |
| Median | 59.8 | | 60.4 | | 59.2 | | .68 |
| Range | 26-81 | | 28-81 | | 26-81 | | |
| Ann Arbor stage > II | 96 | 42 | 44 | 38 | 52 | 45 | .26 |
| ECOG PS ≥ 2 | 4 | 2 | 3 | 3 | 1 | 1 | .62 |
| Presence of "B" symptoms | 21 | 9 | 6 | 5 | 15 | 13 | .037 |
| Increased serum LDH | 17 | 7 | 7 | 6 | 10 | 9 | .44 |
| Two or more extranodal sites | 81 | 35 | 40 | 34 | 41 | 36 | .85 |
| Nodal involvement | 88 | 38 | 44 | 38 | 44 | 38 | .96 |
| Bone marrow involvement | 50 | 22 | 20 | 17 | 30 | 26 | .10 |
| Prior local therapy† | 24 | 10 | 14 | 12 | 10 | 9 | .40 |
| Primary gastric site‡ | 96 | 42 | 50 | 43 | 46 | 40 | .63 |
| IPI risk | | | | | | | .65 |
| Low | 135 | 58 | 71 | 61 | 64 | 56 | |
| Low-intermediate | 49 | 21 | 21 | 18 | 28 | 24 | |
| Intermediate-high | 40 | 17 | 21 | 18 | 19 | 17 | |
| High | 7 | 3 | 3 | 3 | 4 | 3 | |
| Primary extranodal site | | | | | | | |
| Stomach | 86 | 37 | 44 | 38 | 42 | 37 | .83 |
| Pharynx | 4 | 2 | 2 | 2 | 2 | 2 | 1.00 |
| Orbit | 17 | 7 | 7 | 6 | 10 | 9 | .44 |
| Salivary glands | 19 | 8 | 11 | 9 | 8 | 7 | .49 |
| Lung | 21 | 9 | 14 | 12 | 7 | 6 | .11 |
| Skin | 15 | 6 | 5 | 4 | 10 | 9 | .19 |
| Small bowel | 5 | 2 | 1 | 1 | 4 | 3 | .21 |
| Colon | 9 | 4 | 3 | 3 | 6 | 5 | .33 |
| Breast | 2 | 1 | 2 | 2 | — | — | .50 |
| Liver | 3 | 1 | — | — | 3 | 3 | .12 |
| Genital tract | 2 | 1 | 2 | 2 | — | — | .50 |
| Waldeyer's ring | 3 | 1 | 1 | 1 | 2 | 2 | .62 |
| Others | 6 | 3 | 2 | 2 | 4 | 4 | .45 |
| Multiple sites | 39 | 17 | 23 | 20 | 16 | 14 | .23 |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PS, performance status.
*$P$ values referring to the comparison of frequencies between the two arms ($\chi^2$ or Fisher's exact test, as appropriate).
†Including previous surgery, antibiotic therapy, and radiation therapy.
‡Including 10 patients with other extranodal localizations

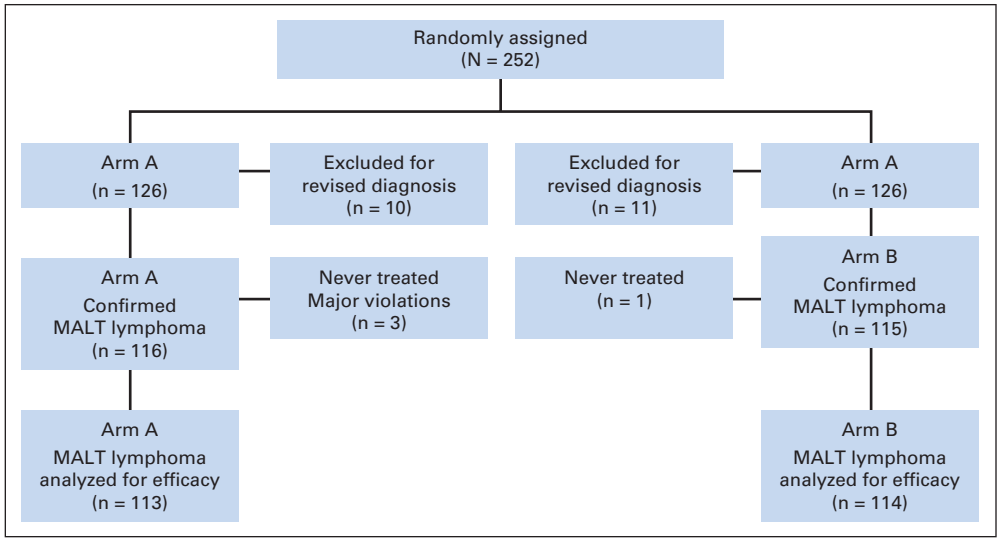


**Fig 1.** CONSORT diagram of study profile and patient flow. MALT, mucosa-associated lymphoid tissue.



analysis of the third arm. Planned interim analysis was performed after the enrollment of 80 and 330 patients, and an independent data and safety monitoring board recommended continuation of the study.

Randomization was stratified by tumor site (gastric *v* nongastric primary site), nodal involvement (presence *v* absence), prior "local" therapy (either previous surgical, radiation, or antibiotic treatment for gastric lymphomas *v* nonpretreated disease), and International Prognostic Index (IPI) score (low/low-intermediate risk *v* intermediate-high/high risk). The inclusion of nodal involvement and IPI among stratification criteria was based on the results of a previous IELSG study.[8] On disease progression or relapse, further treatment was at the treating physician's discretion.

The 252 patients enrolled onto the initial two-arm portion of study, before the introduction of the amendment, represent the patients in this analysis. The primary end point was event-free survival (EFS). Secondary end points were overall response rate, response duration, progression-free survival (PFS), OS, and acute and long-term toxicity. The sample size was based on the primary end point. The number of patients required was calculated to show a 20% improvement with 80% power at an overall 5% significance level, on the assumption that 5-year EFS for patients treated with chlorambucil would be 50%.

### Study Sites

The trial was conducted at 78 centers in six countries with the cooperation of major collaborative trial groups (Fondazione Italiana Linfomi [FIL], Groupe d'Etude des Lymphomes de l'Adulte [GELA], United Kingdom National Cancer Research Institute [CR United Kingdom], Grup per l'Estudi dels Limfomes de Catalunya i Balears [GELCAB]) according to the principles of the Declaration of Helsinki with its current amendments. The study was approved by the institutional review boards/ethics committees of each participating institution. All patients provided written informed consent.

### Patient Population and Pretreatment Evaluation

Patients older than age 18 years with a histologic diagnosis of $CD20^+$ MALT lymphoma arising at any extranodal site were eligible. Patients with disease either newly diagnosed or relapsed after prior local therapy were eligible. Patients with primary gastric *H. pylori*–positive MALT lymphomas were eligible for inclusion in case of clinical (endoscopic) and histologic evidence of disease progression at any time after *H. pylori* eradication or in stable disease with persistent lymphoma more than 1 year after *H. pylori* eradication. Apart from *H. pylori* eradication, no prior systemic therapy was allowed. Measurable or evaluable disease, according to the National Cancer Institute (NCI) International Working Group (IWG) criteria,[19] was required. Patients were not eligible if there was evidence of histologic transformation, CNS involvement, previous or concomitant malignancy, or HIV infection. Patients were staged according to the Ann Arbor criteria, with computed tomography and bone marrow biopsy. Esophagogastroduodenoscopy and/or colonoscopy with multiple mucosal biopsies were carried out in case of gastrointestinal involvement.

### Pathology Review

The diagnostic biopsies were reviewed independently by panels of pathologists coordinated by the national scientific groups participating in the study. A histologic diagnosis of MALT lymphoma was made according to the

**Table 2.** Response to Treatment

| Response | All Patients (N = 227) | | Chlorambucil (arm A) (n = 113) | | Chlorambucil Plus Rituximab (arm B) (n = 114) | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Overall response rate* | 205 | 90 | 98 | 87 | 107 | 94 |
| Complete response† | 162 | 71 | 73 | 65 | 89 | 78 |
| Partial response | 43 | 19 | 25 | 22 | 18 | 16 |
| Stable disease | 8 | 3 | 8 | 7 | — | — |
| Progressive disease | 10 | 5 | 6 | 5 | 4 | 4 |
| Not assessed | 4 | 2 | 1 | 1 | 3 | 3 |

*$\chi^2$ $P$ = .069.
†$\chi^2$ $P$ = .025.

criteria of the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissue.[20]

### Treatments

Patients assigned to arm A received induction treatment with daily chlorambucil 6 mg/m$^2$ orally for 42 consecutive days (weeks 1 through 6). After restaging, patients with stable disease or an objective response then received daily chlorambucil 6 mg/m$^2$ 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).

In arm B, chlorambucil was administered as in arm A, and rituximab 375 mg/m$^2$ was administered intravenously 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).

Rituximab was provided by Roche International (Basel, Switzerland). Treatment was discontinued on withdrawal of the patient's consent, disease progression, or the occurrence of unacceptable toxicity. Hematopoietic growth factors were not routinely administered, but patients who experienced severe neutropenia or developed neutropenic fever could receive growth factors for subsequent cycles at the treating physician's discretion. No specific recommendations were made regarding antimicrobial prophylaxis.

### Assessment of Toxicity

Patients who received at least one dose of therapy were included in the toxicity analysis by using NCI Common Terminology Criteria for Adverse Events (CTCAE v3.0).[21]

### Assessment of Response

Patients were assessed for response after the first 6 weeks of therapy and at the end of the program. Tumor responses were defined according to the NCI standardized response criteria for non-Hodgkin lymphomas. Overall response rate was defined as the sum of complete response (CR) and partial response rates.[19] For primary gastric sites, response was based on endoscopic and histologic findings after extensive sampling of the gastric mucosa and according to the GELA histologic grading system for post-treatment evaluation.[22]

### Follow-Up Evaluations

Patient 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 parameters were planned if clinically indicated.

### Statistical Considerations

Statistical analysis was performed by using the Stata/SE 11.0 software package (StataCorp, College Station, TX). The median follow-up was computed by the reverse Kaplan-Meier method.[23] The definitions of EFS, response duration, PFS, and OS were based on the Revised Criteria for Malignant Lymphoma.[24] Therefore, the primary end point (EFS) was calculated from the date of trial registration to failure of treatment (including any of 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. Survival probabilities were calculated by using the life-table method, survival curves were estimated by using the Kaplan-Meier method,[25] and differences were evaluated by using the log-rank test.[26] Binomial exact 95% CIs were calculated for proportions. Associations were analyzed by using the $\chi^2$ or the Fisher's exact test. Median values were compared by using the Wilcoxon rank sum test. *P* values less than .05 (two-sided test) were considered statistically significant. The Cox proportional hazard model[27] was used for estimation of hazard ratio (HRs) and 95% CIs.

## RESULTS

### Patient Characteristics

Two hundred fifty-two patients were enrolled and randomly assigned: 126 to chlorambucil and 126 to chlorambucil plus rituximab. Twenty-one patients (10 in arm A and 11 in arm B) were shown to be ineligible and were excluded: revised diagnosis of diffuse large cell lymphoma (four patients), follicular lymphoma (one patient), mantle-cell lymphoma (five patients), primary nodal marginal-zone B-cell lymphoma (two patients), and primary splenic marginal-zone B-cell lymphoma (nine patients).

Baseline characteristics of randomly assigned patients with confirmed MALT lymphoma diagnosis (N = 231) are summarized in Table 1. The primary site in 96 patients was the stomach, 135 patients had a primary extragastric site, and 39 patients had multiple mucosal sites. Eighty-one patients had more than one extranodal site, including bone

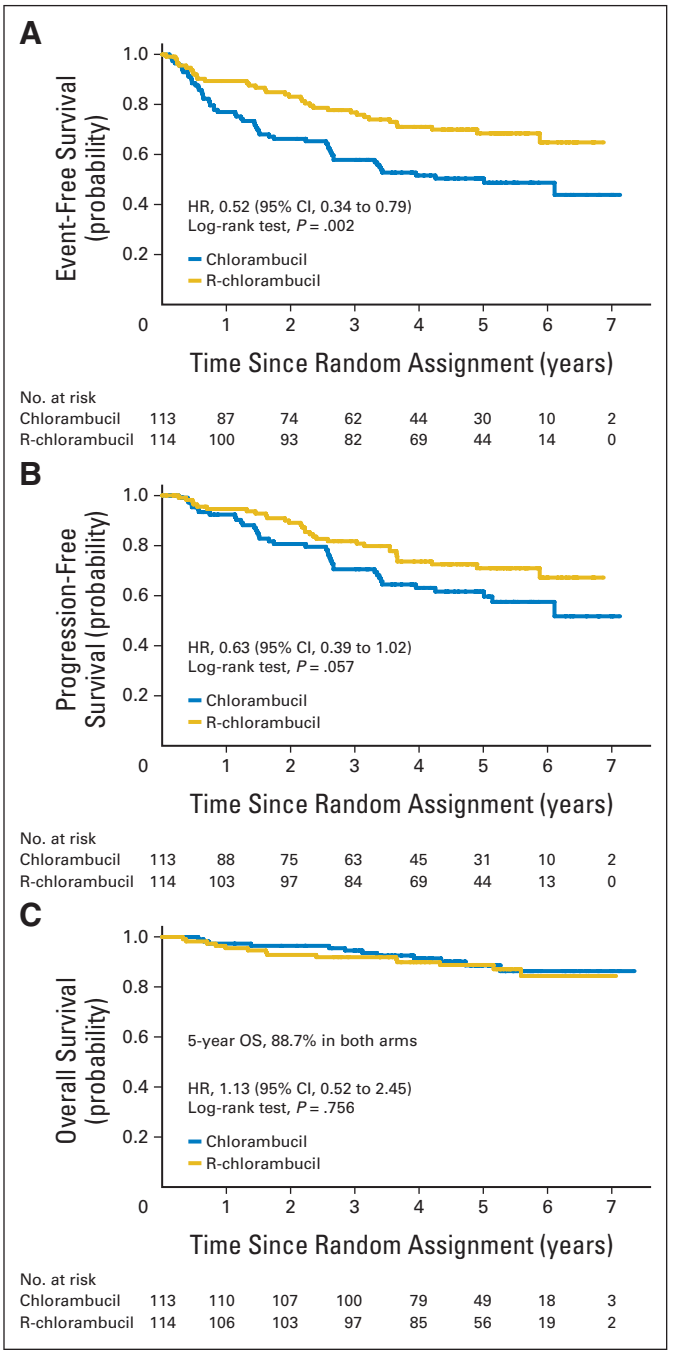


**Fig 2.** Kaplan-Meier survival curves according to treatment received for (A) event-free survival, (B) progression-free survival, and (C) overall survival. HR, hazard ratio; R-Chlorambucil, rituximab plus chlorambucil.

marrow and spleen. With the exception of a higher frequency of "B" symptoms in patients enrolled onto the combination arm, no significant differences in the distribution of known risk factors were evident.

### Treatment

Four of the 231 randomly assigned eligible patients were excluded from the analysis: two patients withdrew their consent before treatment start, and major early violations of the study protocol were documented in two other patients. Therefore, the analyzed population included 227 patients; 113 received chlorambucil and 114 received chlorambucil plus rituximab. Figure 1 shows the patient flow through the trial. One hundred seventy-one patients (75%) completed the treatment program without dose reduction. Fifty-six patients (25%) required at least one dose reduction, 33 patients (15%) discontinued treatment with chlorambucil (12 in arm A and 21 in arm B), 16 patients (14% of the arm B population) discontinued rituximab (14 of whom concomitantly discontinued chlorambucil). Discontinuation of treatment was usually due to toxicity, disease progression, or patients' preferences. The median number of chlorambucil weeks of treatment delivered was 14 (range, 3 to 14 weeks), with no significant difference between the two study arms ($P = .101$). The median number of rituximab doses delivered was eight (range, one to eight).

### Response to Treatment

Four of the eligible patients treated according to protocol were not evaluated for response. One patient assigned to arm B withdrew consent during the first part of the treatment program and was lost to follow-up; one patient assigned to arm A experienced a fatal ischemic stroke during treatment. Two patients in arm B died of disease progression after histologic transformation, which occurred during treatment. Table 2 provides the results of response assessment at the end of the study treatment according to treatment arm. Two hundred five patients (90%; 95% CI, 86% to 94%) had an objective response with no significant difference between the two arms ($P = .069$). However, the rate of CR was significantly higher ($P = .025$) in arm B: 78% (95% CI, 69% to 85%) for 89 patients treated with the combination of chlorambucil plus rituximab compared with 65% (95% CI, 55% to 73%) for 73 patients treated with chlorambucil. The higher CR rate was observed in both primary gastric and nongastric MALT lymphomas. The median time to best response was 6 months in the whole cohort (range, 1 to 46 months) with no difference between the two arms ($P = .366$). Median duration of response has not been reached overall or in either arm: at 2 years, 86% (95% CI, 77% to 92%) of patients in arm A and 95% (95% CI, 88% to 98%) of patients in arm B were in continuous remission ($P = .013$).

### Analysis of Time-Related End Points

After a median follow-up of 62 months (range, 2 to 89 months), the median EFS in the whole cohort (N = 227) had not been reached. The 5-year EFS in patients treated with rituximab plus chlorambucil was significantly better (68%; 95% CI, 59% to 76%) than in those receiving chlorambucil alone (50%; 95% CI, 41% to 60%; Fig 2A). The addition of rituximab resulted in a significant reduction of the risk of EFS events (HR, 0.52; 95% CI, 0.34 to 0.79). Twenty-two patients had an event that was neither progression nor death: one second tumor requiring treatment, six early-treatment discontinuations due to toxicity (n = 4) or patient withdrawal (n = 2), and 15 instances of the initiation of nonprotocol therapy (14 in arm A: nine rituximab alone or in combination with a new chemotherapy regimen, three radiotherapy, one radioimmunotherapy, and one surgery, although only one patient in arm B received radiotherapy). All these patients, except for those with a second tumor, were censored at the time of these events in the PFS analysis. The 5-year PFS in the whole cohort was 67% (95% CI, 59% to 73%): 62% (95% CI, 51% to 71%) for single-agent chlorambucil and 71% (95% CI, 61% to 79%) for the combination, without reaching a statistically significant difference ($P = .057$) between the two arms (Fig 2B). Overall, 26 patients (12 in arm A and 14 in arm B) have died (Table 3). The 5-year OS rate was 89% (95% CI, 83% to 92%). There was no significant difference in OS ($P = .756$) between treatment arms (Fig 2C). Six patients with histologic transformation (five in arm B and one in arm A) were observed and five of the transformations resulted in death. With respect to the stratification factors, at univariate analysis, the IPI score and the presence of lymph node involvement demonstrated a statistically significant effect on EFS, PFS, and OS. Conversely, there was no impact of primary gastric origin and prior local treatment (Table 4). In multivariate analysis (Cox regression model including the stratification criteria [ie, IPI score, nodal involvement, primary extranodal site, previous treatment]), only the IPI remained significantly associated with longer EFS, PFS, and OS (data not shown). When treatment arm was added to the Cox model, both IPI and treatment in arm B predicted a better EFS and PFS, although only IPI retained a significant impact on OS (Table 4).

**Table 3.** Cause of Death (n = 26)

| | All Patients (N = 227) | | Chlorambucil (arm A) (n = 113) | | Chlorambucil Plus Rituximab (arm B) (n = 114) | |
|---|---|---|---|---|---|---|
| Cause of Death | No. | % | No. | % | No. | % |
| Lymphoma progression | 8 | 31 | 5 | 42 | 3 | 21 |
| Second tumor | 7 | 27 | 2 | 17 | 5 | 36 |
| Infection | 2 | 8 | 1 | 8 | 1 | 7 |
| Transformed lymphoma | 5 | 19 | 1 | 8 | 4 | 29 |
| Other* | 3 | 11 | 2 | 17 | 1 | 7 |
| Unknown | 1 | 4 | 1 | 8 | — | — |

*Respiratory failure, two patients; stroke, one patient.

**Table 4.** Univariate and Multivariate Analysis of the Impact of Patient Characteristics on Survival Endpoints

| Characteristic | EFS | | | | PFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Univariate Analysis Log-Rank *P* | Multivariate Analysis | | | Univariate Analysis Log-Rank *P* | Multivariate Analysis | | | Univariate Analysis Log-Rank *P* | Multivariate Analysis | | |
| | | HR | 95% CI | *P* | | HR | 95% CI | *P* | | HR | 95% CI | *P* |
| Not included in the multivariate analysis | | | | | | | | | | | | |
| Sex | .779 | N/A | | N/A | .920 | N/A | | N/A | .498 | N/A | | N/A |
| Age > 60 years | .048 | N/A | | N/A | .109 | N/A | | N/A | < .001 | N/A | | N/A |
| Ann Arbor stage III to IV | < .001 | N/A | | N/A | < .001 | N/A | | N/A | < .001 | N/A | | N/A |
| ECOG PS ≥ 2 | .116 | N/A | | N/A | .213 | N/A | | N/A | .020 | N/A | | N/A |
| Presence of "B" symptoms | .081 | N/A | | N/A | .075 | N/A | | N/A | .003 | N/A | | N/A |
| Elevated serum LDH | .170 | N/A | | N/A | .035 | N/A | | N/A | .085 | N/A | | N/A |
| Two or more extranodal sites | .006 | N/A | | N/A | .002 | N/A | | N/A | < .001 | N/A | | N/A |
| Bone marrow involvement | .017 | N/A | | N/A | .011 | N/A | | N/A | .008 | N/A | | N/A |
| Included in the multivariate analysis | | | | | | | | | | | | |
| Nodal involvement | .020 | 1.4 | 0.9 to 2.1 | .117 | .023 | 1.4 | 0.9 to 2.3 | .158 | .045 | 1.4 | 0.6 to 3.2 | .372 |
| IPI risk (low *v* low-intermediate *v* intermediate-high *v* high) | < .001 | 1.5 | 1.2 to 1.9 | < .001 | < .001 | 1.6 | 1.2 to 2.1 | < .001 | < .001 | 2.5 | 1.7 to 3.7 | < .001 |
| Prior local therapy* | .365 | 0.8 | 0.3 to 1.7 | .504 | .560 | 0.8 | 0.3 to 1.9 | .665 | .691 | 0.8 | 0.2 to 3.7 | .820 |
| Primary nongastric site | .375 | 1.0 | 0.6 to 1.6 | .998 | .124 | 1.2 | 0.7 to 2.0 | .566 | .799 | 0.8 | 0.3 to 1.8 | .557 |
| Study arm | .002 | 0.5 | 0.3 to 0.8 | .002 | .057 | 0.6 | 0.4 to 0.9 | .038 | .756 | 1.1 | 0.5 to 2.4 | .799 |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; HR, hazard ratio; IPI, International Prognostic Index; LDH, lactate dehydrogenase; N/A, not applicable; OS, overall survival; PFS, progression-free survival; PS, performance status.
*Including previous surgery, antibiotic therapy, and radiation therapy.



### *Safety*

The analyzed population comprised 113 patients in arm A and 114 patients in arm B. During follow-up, a low number of reversible grade 1 to 2 events was reported with no clinically significant differences in acute and long-term toxicity observed between the two arms, despite the occurrence of infusion-related symptoms as well as the increased number of patients with grade 3 to 4 neutropenia in the combination arm (Table 5). The latter, however, did not result in a significant increase of neutropenic fever episodes and infection rates. No toxic death was reported.

**Table 5.** Safety Profile

| Event | Chlorambucil (arm A) (n = 113) | | | | Chlorambucil Plus Rituximab (arm B) (n = 114) | | | |
|---|---|---|---|---|---|---|---|---|
| | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| Hematologic AEs | | | | | | | | |
| Leukopenia | 3 | 4 | 2 | — | 1 | 7 | 5 | — |
| Neutropenia | 3 | 3 | — | 2 | 4 | 3 | 8 | 8 |
| Lymphocytopenia | — | 1 | 2 | — | — | 1 | 1 | 1 |
| Anemia | 3 | — | 1 | — | 1 | 1 | — | — |
| Thrombocytopenia | 2 | 3 | 1 | — | 2 | 1 | 2 | — |
| Nonhematologic AEs | | | | | | | | |
| Asthenia | 8 | 4 | — | — | 10 | 1 | — | — |
| Diarrhea | 1 | 1 | — | — | 4 | 1 | — | — |
| Dispepsia | 2 | 1 | — | — | 2 | — | 3 | — |
| Fever | 1 | — | — | — | 2 | 1 | — | — |
| Nausea | 6 | — | — | — | 15 | 1 | — | — |
| Skin rash | 4 | 2 | — | — | 3 | 1 | 1 | — |
| Vomiting | — | 1 | — | — | 1 | 2 | — | — |
| Gastric pain | 4 | 1 | 1 | — | 4 | 3 | 1 | — |
| Headaches | 2 | — | — | — | 3 | 2 | — | — |
| Infection | 3 | 8 | 2 | 1 | — | 6 | 4 | — |
| Neutropenic fever | — | — | — | — | — | — | 3 | — |
| Increased transaminase | 1 | — | 2 | 1 | — | 2 | — | 1 |
| Stomatitis | 1 | 1 | — | — | 3 | — | — | — |
| Infusion-related symptoms* | — | — | — | — | 15 | 3 | 1 | 1 |

Abbreviation: AEs, adverse events; G, grade.
*Including bronchospasm, chills, fever, rash, arthralgias, and pruritus.

## DISCUSSION

This study is, to the best of our knowledge, the first completed randomized trial on the systemic treatment of patients with MALT lymphoma (another randomized study has been published, but it included only gastric lymphomas and was aimed at evaluating the impact of adding chlorambucil to anti-*Helicobacter* therapy[28]).

At the time of conception, chemotherapy for MALT lymphoma was poorly evaluated, with only one published paper that specifically dealt with chemotherapy[13] reporting a 5-year EFS of 50% with single alkylating agents (either cyclophosphamide or chlorambucil). Single alkylating agents or alkylating-based chemotherapy regimens without anthracyclines were considered standard therapy at that time. Chlorambucil alone was therefore considered an acceptable comparator arm for a study aimed at evaluating the clinical benefit of adding rituximab to chemotherapy. In fact, rituximab as a single agent was shown to carry significant antitumor activity in MALT lymphomas[17] but the efficacy of chemoimmunotherapy had not previously been formally tested in this disease entity. A retrospective analysis of 13 patients treated with chemoimmunotherapy has only recently been published[29] and it shows significant activity.

In this two-arm analysis, the addition of rituximab to chlorambucil resulted in improved remission quality (as measured by CR rate) and translated into significantly prolonged EFS, the primary end point of the study.

The 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 important difference in costs and complexity of the two treatments. To date, this study is underpowered to detect a clear benefit on PFS (whose improvement did not reach statistical significance, probably because of the low rate of disease progressions during the observed follow-up in both arms). Of interest, several events defining EFS were the delivery of new treatments without documented progression. The divergence between EFS and PFS is largely due to these new therapies. Nearly all of them were given to patients randomly assigned to chlorambucil only. This observation suggests that stable disease might have been managed differently by the local investigators and highlights an important difficulty in interpretation when individual investigators can decide on the nature of treatment failure in an unblinded study. It may seem that in the "rituximab era," some study investigators have become more eager to initiate rituximab in patients with stable disease. However, it should be noted that stable disease was significantly more frequent in the chlorambucil arm, and this might be a simpler explanation for the observed discrepancy. As expected, the differences in EFS and response rate have not yet translated into improved OS. Both treatments were well tolerated and no unexpected adverse effects were recorded.

In conclusion, the superior efficacy of rituximab in combination with chlorambucil was demonstrated in MALT lymphoma. These data (which will be updated when the third arm follow-up is mature) should be taken as preliminary, given the long natural history of this disease. Nevertheless, the improved EFS (HR, 0.52) and the trend in favor of a longer PFS (HR, 0.63) with little added toxicity justify the front-line use of this regimen. Analysis of the whole study with the inclusion of the rituximab-alone arm is awaited, and further studies will have to be carried out to evaluate the role of rituximab maintenance specifically in the context of MALT lymphoma.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

**Employment or Leadership Position:** None **Consultant or Advisory Role:** Emanuele Zucca, Roche (C); Armando López-Guillermo, Roche (C), Celgene (C); Bertrand Coiffier, Roche (C); Franck Morschhauser, Roche (C); Stefano A. Pileri, Topotarget (C), Takeda-Millennium (C), Celgene (C); Peter Johnson, Roche (C); Franco Cavalli, Roche (C) **Stock Ownership:** None **Honoraria:** Umberto Vitolo, Mundipharma, Roche, Celgene; Franck Morschhauser, Roche; Elias Campo, Roche; Andrew Jack, Roche; Peter Johnson, Roche **Research Funding:** Andrew Jack, Genentech **Expert Testimony:** None **Other Remuneration:** None

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**Manuscript writing:** All authors
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## *SUPPORT*

Supported by Grants No. ICP OCS-01356-03-2003 and No. ICP OCS-02062-03-2007 from Oncosuisse and a grant from Roche International.