Early progression of disease predicts shorter survival in MALT lymphoma patients receiving systemic treatment

by Annarita Conconi, Catherine Thieblemont, Luciano Cascione, Valter Torri, Barbara Kiesewetter, Gloria Margiotta Casaluci, Gianluca Gaidano, Markus Raderer, Franco Cavalli, Armando Lopez Guillermo, Peter W. Johnson, and Emanuele Zucca

Haematologica 2020 [Epub ahead of print]

Haematologica. 2020; 105:xxx

Publisher's Disclaimer.
E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval; the final version of the manuscript will then appear in print on a regular issue of the journal. All legal disclaimers that apply to the journal also pertain to this production process.
Early progression of disease predicts shorter survival in MALT lymphoma patients receiving systemic treatment.

Annarita Conconi¹, Catherine Thieblemont², Luciano Cascione³, Valter Torri⁴, Barbara Kiesewetter⁵, Gloria Margiotta Casaluci⁶, Gianluca Gaidano⁶, Markus Raderer⁵, Franco Cavalli³, Armando Lopez Guillermo⁷, Peter W. Johnson⁸, Emanuele Zucca³,⁹

1. Division of Hematology, Ospedale degli Infermi, Biella, Italy.
2. Hemato-Oncology Department, Saint Louis Hospital, Paris, France.
3. Institute of Oncology Research, Bellinzona, Switzerland.
4. Clinical Research Methodology Laboratory, IRCCS–Mario Negri Institute, Milan, Italy.
5. Division of Oncology, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria.
6. Division of Hematology, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy.
7. Department of Hematology, Hospital Clinic, Barcelona, Spain.
8. Cancer Research UK Center, Southampton General Hospital, Southampton, United Kingdom.
9. Division of Medical Oncology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland.

This work was partly supported by a grant from Oncosuisse (ICP OC1356-03-2003). The IELSG-19 clinical trial was partly supported by an unrestricted research grant from Roche International, Ltd. The funders had no role in study design, data collection, analysis, and interpretation, or writing of the report.

Corresponding author: Annarita Conconi, MD
Hematology Division, Department of Internal Medicine
Ospedale degli Infermi, via dei Ponderanesi, 2
Ponderano, Biella, Italy
E-mail: annarita.conconi@aslbi.piemonte.it
Phone: +39 015 15157503/Fax: +39 015 15157505

Running head: Early POD in EMZL

Presented in part at the 2019 Annual Meeting of the American Society of Clinical Oncology (ASCO), held in Chicago, IL, May 31 - June 4, 2019 and at the 15th International Conference on Malignant Lymphoma (15-ICML) held in Lugano, Switzerland, June 18-22, 2019.

Manuscript information: 270 abstract words, 1936 text words; 3 figures; 3 tables; 24 references
Early progression of disease (POD) within two years from diagnosis is linked with poor overall survival (OS) in follicular lymphoma but its prognostic role is less clear in extranodal marginal zone B-cell lymphoma (EMZL). We sought to identify prognostic factors associated with early POD and to determine whether is associated with inferior OS.

We analyzed the impact of early POD in the IELSG19 clinical trial dataset (training set of 401 patients randomly assigned to chlorambucil or rituximab or chlorambucil plus rituximab). Reproducibility was examined in a validation set of 287 patients who received systemic rituximab. In both sets, we excluded from the analysis the patients who, within 24 months from treatment start, died without progression or were lost to follow-up without prior progression. OS was calculated from progression in patients with early POD and from 24 months after start of treatment in those without (reference group).

Early POD was observed in 69 of the 384 (18%) evaluable patients of the IELSG19 study. Patients with high-risk MALT-IPI were more likely to have early POD (p=0.006). The 10-year OS rate was 64% in the early POD group and 85% in the reference group (HR= 2.42, 95%CI, 1.35-4.34; log-rank P=0.002). This prognostic impact was confirmed in the validation set, in which early POD was observed in 64 out of 224 (29%) evaluable patients with 10-year OS rate of 48% in the early POD group and 71% in the reference group (HR= 2.15, 95%CI, 1.19-3.90; log-rank P=0.009).

In patients with EMZL who received front-line systemic treatment, early POD is associated with poorer survival and may represent a useful endpoint in future prospective clinical trials.

**Funding.** International Extranodal Lymphoma Study Group; Oncosuisse, (ICP OCS-01356-03-2003); AIRC 5 x 1000 (No. 21198), AIRC, Milan, Italy, AGING Project – Department of Excellence – DIMET, Universita’ del Piemonte Orientale, Novara, Italy. The IELSG-19 clinical trial was supported in part by an unrestricted research grant from Roche International, Ltd.

**Trial registration:** ClinicalTrials.gov Identifier for the IELSG-19 study: NCT00210353
INTRODUCTION

Marginal zone lymphomas (MZL) comprise three separate disease entities, which present individual epidemiologic, molecular and clinical features. Extranodal marginal zone lymphoma (EMZL), also known as mucosa-associated lymphoid tissue (MALT) lymphoma, represents the most common MZL subtype, accounting for approximately 50 to 70% of MZLs and 5% to 8% of all B cell lymphomas(1-3). It may involve virtually any tissue but most often organs that are normally devoid of lymphocytes, where it arises from lymphoid populations associated with chronic inflammatory processes of either infectious or autoimmune origin (4). The clinical presentation is very heterogeneous and EMZL patients are managed with a variety of treatments. The natural course is usually indolent, particularly in gastric lymphomas, and aggressive therapy is rarely required(1, 3, 5). Outcome, however, may be different from organ to organ(2, 6). We recently proposed a prognostic model, the MALT-lymphoma International Prognostic Index (MALT-IPI), which is based on age, stage and LDH at diagnosis. MALT-IPI discriminated between patients with different progression-free survival (PFS) and overall survival (OS), and retained its prognostic utility in both gastric and non-gastric MALT lymphomas(7). In this context, the identification of the minority of patients with shorter survival may become important, especially in the perspective of personalized medicine, and might form the basis for adapting therapeutic approaches.

In follicular lymphoma the early progression of disease (POD), namely, within 24 months after diagnosis, has been reported to be associated with poor outcomes(8). Currently, the clinical significance of early POD in EMZL is uncertain, and the impact of early POD on subsequent survival has not been properly explored yet.

The present study aimed to understand whether time to progression after first-line systemic therapy may be a factor affecting survival outcomes in EMZL. We analyzed data from the IELSG19 clinical trial to determine whether early POD is predictive of inferior OS in this disease, and we validated our findings in an independent cohort.
METHODS

Patients

Details regarding the IELSG19 randomized phase III trial (NCT 00210353) have been published elsewhere(6, 9). All patients provided written informed consent and the study was approved by the institutional review board or ethics committee of each institution. This trial compared chlorambucil alone to rituximab alone and to the combination of rituximab and chlorambucil as front-line therapy in EMZL patients, with event-free survival (EFS) as the primary endpoint(6).

Early POD was defined as in the follicular lymphoma study by Casulo et al(8). Patients enrolled in the IELSG19 study were divided into two groups: those with early POD, that is, progression within 24 months from the start of first-line treatment, and the reference group of those without early POD. An independent validation set, comprising only patients who received front-line systemic treatment (chemotherapy, immunotherapy or both), was derived from the validation cohort of the MALT-IPI study, which included patients from different sources (the databases of the IELSG1 multicenter study and of a retrospective survey conducted at the Oncology Institute of Southern Switzerland, and at the Haematology Division of the University of Eastern Piedmont, in Novara Italy, and a cohort of patients diagnosed at the Medical University of Vienna, Austria) whose details have also been published elsewhere(7).

Statistical Methods

Primary analysis of OS from risk-defining events was performed in both testing and validation sets, commencing the observation for the group with early POD from the time progression occurs onward, and for the reference group from 24 months after the start of front-line therapy.

Statistical analysis was performed using the Stata/SE 11.0 software package (StataCorpLP, College Station, TX). The median follow-up was computed as the median time to censoring or death using the reverse Kaplan–Meier method(10). Survival probabilities were calculated using the life table method and survival curves estimated by the method of Kaplan–Meier; differences between patient groups were evaluated using the log-rank test(11). Binomial exact 95% confidence intervals (CI) were calculated for proportions. The chi-square test or the Fisher's exact test were used as appropriate for comparing proportions. Hazard ratio (HR) and its confidence interval were estimated using a Cox proportional hazard model. Multivariable analysis of clinical prognostic
factors (including the international prognostic scores, IPI(12) and MALT-IPI(7)) for OS was performed by Cox regression(13) with backward stepwise selection. To identify factors associated with early POD, logistic regression was also performed with backwards stepwise selection. P-values <0.05 (two-sided test) were considered statistically significant.

RESULTS

Testing set

The analyzed population included 401 patients enrolled in the IELSG19 study, 131 treated with chlorambucil, 132 with chlorambucil and rituximab and 138 with rituximab; their main clinical features are summarized in Table 1. Estimated hazard curves showed that peak risk of progression occurred within the first 24 months after diagnosis (Figure 1A). Among these 401 patients, 69 (17%) had an early POD relapsing within 24 months of starting treatment; of the remaining 332 patients, 315 (79%) had no relapse or death during the first 24 months and represent the reference group. Relapses were later observed in 64 (20%) patients in the reference group. Nine patients were lost to follow-up and eight patients died without POD within 24 months of starting treatment (Figure 2, left panel).

For the 69 patients with early POD, median age was 62 years (range, 31 to 81 years), 32 (46%) patients were male and 26 patients (38%) had a primary gastric localization (Table 2).

Early POD was most frequent in patients with ECOG performance status >1 (P=0.042) and elevated serum lactate dehydrogenase (LDH) (P=0.002). Patients with early POD were more likely to have high-risk MALT-IPI scores (P=0.005) and high-risk IPI scores (P=0.013) than the reference group. In the contrast, elevated serum beta2-microglobulin, advanced stage (III-IV vs I-II), multiple extranodal sites of involvement, primary site of disease localization (gastric vs extra-gastric), age at diagnosis (with either 60 or 70 years cut-off) were not associated with early POD. An unbalanced distribution of patients with early POD was evident across the treatment arms, with early POD occurring more frequently (34/132, 26%) in the single agent rituximab arm and less frequently in the combination arm (13/125, 10%) when compared with the standard arm of single agent chlorambucil (22/127, 17%) (Chi-square test, P=0.006) (Table 2).

In a stepwise logistic regression (including the above mentioned individual factors predicting early POD at univariate analysis: treatment arm, LDH, PS, high risk IPI score, high risk MALT-IPI score),
only high-risk MALT-IPI score retained statistical significance (P=0.006. Odds ratio, 2.39; 95%CI, 1.29-4.45).

The proportion of early POD was also higher in patients achieving PR after first-line therapy in comparison with complete responders (P<0.0001) and, notably, a transformation into aggressive histology was detected more frequently in patients with early POD than in the reference group (7 of 69 vs. 3 of 315, P<0.0001).

With a median follow-up time of 7.4 years, 18 of 69 patients with early POD died and the OS rates at 5 and 10 years after risk-defining event were 80% (95% CI, 69-88%) and 64% (95%CI, 45-78%), respectively, in the early POD group vs. 91% (95%CI, 87-94%) and 85% (95%CI, 79-90%), respectively, in the reference group (HR=2.42, 95%CI, 1.35-4.35; log-rank P=0.002) (Figure 3A).

Early POD maintained its predictive power on OS (after a risk-defining event) together with a MALT-IPI high-risk score and age (as a continuous variable) in a stepwise Cox model after controlling for treatment arm, LDH, PS, stage, age, B-symptoms, multiple extranodal sites and IPI high-risk groups (Table 3).

**Validation Set**

Table 1 shows the main patient characteristics in the validation cohort, which comprised 287 MALT lymphoma patients who received front-line systemic treatment (chemotherapy, immunotherapy or both). Median age was 63 years (range, 23 to 92 years). Most patients were female (60%).

Estimated hazard curves showed a peak risk of progression approximately at 24 months after diagnosis (Figure 1B). After a median follow-up of 5.7 years, 64 patients (22%) had early POD. Fifty-four patients had a follow-up shorter than two years and nine died without prior disease progression within 2 years of treatment start (Figure 2, right panel). Hence, the reference cohort comprised 160 patients, relapses were later observed in 51 (33%) of them. The early POD rates were similar in the groups of patients receiving different initial therapy (chemotherapy alone, rituximab alone or rituximab combined with different chemotherapeutic or immunomodulatory agents). Similar to the testing cohort, the early POD group was enriched in cases with transformation into aggressive histology (6 of 64 vs 3 of 160 patients in the reference group, P=0.018) and early POD was most frequent in patients with elevated LDH (P<0.001), high-risk
MALT-IPI scores (P=0.001) and high-risk IPI scores (P=0.001) (Table 2). In addition, in the validation cohort, early POD was associated with advanced stage (P=0.004) (Table 2).

Analogous to the IELSG-19 study cohort, the patients in the validation set who experienced early POD after systemic therapy had an increased risk of death (HR=2.15, 95% CI, 1.19 to 3.90; log-rank P=0.009). In the early-POD group, the 5-year OS rate was 70% (95% CI, 54% to 81%), and the 10-year OS rate was 48% (95% CI, 28% to 66%). In comparison, the 5-year OS rate in the reference group was 88% (95% CI, 80% to 93%), and the 10-year OS rate was 71% (95% CI, 58% to 81%) (Figure 3B).

DISCUSSION

The present study provided the first validated evidence that early POD, defined by lymphoma progression within 2 years from the initial treatment, is a powerful tool to predict long-term survival in EMZL.

Early POD is a widely accepted survival predictor in follicular lymphoma(8, 14-18), where many studies showed that 20% of patients relapse within 2 years of treatment regardless of the addition of maintenance rituximab (Casulo). In a heterogeneous population of indolent non follicular B-cell lymphomas, a retrospective study from the Mayo Clinic and University of Iowa reported that EFS at 12 months was associated to better outcome (19). However, in keeping with follicular lymphoma, the IELSG-19 study showed a PFS at 2 years of approximately of 20% (ZUCCA). A large retrospective series from the University of Miami including only EMZL also showed similar PFS rates(20). Therefore, in our EMZL analysis, we decided to maintain the 24-month time-span, already validated in follicular lymphoma. Our choice was further justified by the estimated hazard curves showing that peak risk of progression occurred within 2 years.

A potential prognostic relevance of early POD was suggested by the above-mentioned study from the University of Miami(20). An observational study of non-follicular indolent lymphomas from the Italian Lymphoma Foundation (FIL) has also described a prognostic value of early POD in MZL(21).

However, none of these reports provides a thorough description of the clinical features of the EMZL patients with early POD and they did not include independent validation of their findings.
Compared to these reports, the present study has additional strengths. It analyzed the impact of early POD in a cohort of patients prospectively collected in the largest controlled clinical trial performed so far in EMZL, with histological diagnosis confirmed by central pathology review and with uniformly defined follow-up investigations.

The external validation strengthens our findings. The prognostic impact of early POD in EMZL was confirmed in an independent cohort, obtained by merging three heterogeneous series of EMZL(7), which included patients treated with a variety of conventional chemotherapy regimens and immunomodulatory agents in combination with rituximab or not.

We showed that our results might be applied to both gastric and extra-gastric primary lymphomas, and to patients receiving different initial therapies.

Histological transformation of MZL is a well-recognized risk factor, which affects the clinical course of the disease(22-24). The significant proportion of cases with evidence of transformation into aggressive histologies among patients relapsing early after systemic treatment may contribute to the inferior outcome seen in this study. This observation emphasizes the need for repeated histological evaluations, in particular in the case of early relapse, since transformed histology requires more intensive therapy.

In conclusion, we provide novel evidence that, in patients with EMZL who received front-line systemic treatment, early POD is associated with poor survival and should be further investigated as a potentially useful endpoint in future prospective clinical trials.
ACKNOWLEDGMENTS

The authors thank the IELSG-19 study investigators, data managers, and nursing staff. The authors also thank Ayda Lüönd and Rita Gianascio Gianocca for the excellent secretarial assistance.

CONFLICT-OF-INTEREST DISCLOSURE

The authors declare no competing financial interests with respect to the present manuscript.
REFERENCES


### Table 1. Patient characteristics of the validation and the testing set

<table>
<thead>
<tr>
<th></th>
<th>Testing set (IESG-19)</th>
<th>Validation set</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>401</td>
<td>287</td>
</tr>
<tr>
<td><strong>Years of diagnosis</strong></td>
<td>2003-2010</td>
<td>1983-2014</td>
</tr>
<tr>
<td><strong>Median age at diagnosis [IQR]</strong></td>
<td>61 years (51-69)</td>
<td>63 years (51-72)</td>
</tr>
<tr>
<td><strong>Male/female ratio</strong></td>
<td>197/204</td>
<td>115/172</td>
</tr>
<tr>
<td><strong>Stage III-IV</strong></td>
<td>175 (44%)</td>
<td>140 (49%)</td>
</tr>
<tr>
<td><strong>PS &gt;1</strong></td>
<td>6 (1.5%)</td>
<td>14 (5%)</td>
</tr>
<tr>
<td><strong>LDH&gt;UNL</strong></td>
<td>42 (10.5%)</td>
<td>42 (16%)</td>
</tr>
<tr>
<td><strong>Beta-2 MG &gt;UNL</strong></td>
<td>46 (16%)</td>
<td>73 (43%)</td>
</tr>
<tr>
<td><strong>Primary gastric lymphoma</strong></td>
<td>171 (43%)</td>
<td>125 (44%)</td>
</tr>
<tr>
<td><strong>IPI, High-Intermediate/High Risk</strong></td>
<td>77 (19%)</td>
<td>88 (31%)</td>
</tr>
<tr>
<td><strong>MULTIPI, High Risk</strong></td>
<td>68 (17%)</td>
<td>69 (26%)</td>
</tr>
<tr>
<td><strong>First-line treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>131 (33%)</td>
<td>158 (55%)</td>
</tr>
<tr>
<td>Rituximab and chemotherapy</td>
<td>132 (33%)</td>
<td>64 (22%)</td>
</tr>
<tr>
<td>Doxorubicin-containing regimen</td>
<td>0%</td>
<td>60 (21%)</td>
</tr>
<tr>
<td>Rituximab only</td>
<td>138 (34%)</td>
<td>28 (10%)</td>
</tr>
<tr>
<td>Other ^f</td>
<td>0%</td>
<td>37 (13%)</td>
</tr>
<tr>
<td><strong>Median follow up (IQR)</strong></td>
<td>7.4 years (5.6-9.7)</td>
<td>5.7 years (2.3-9.2)</td>
</tr>
<tr>
<td><strong>Progression-free survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-year PFS rate (95% CI)</td>
<td>62.8% (57.6-67.6)</td>
<td>46.9% (39.8-53.6)</td>
</tr>
<tr>
<td>10-year PFS rate (95% CI)</td>
<td>50.8% (44.5-56.8)</td>
<td>29.7% (21.6-38.2)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>NR (2.6-NR)</td>
<td>4.6 years (1.8-15.1)</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-year OS rate (95% CI)</td>
<td>90.3% (86.9-92.9)</td>
<td>85.7% (80.1-89.9)</td>
</tr>
<tr>
<td>10-year OS rate (95% CI)</td>
<td>80.0% (74.3-84.7)</td>
<td>70.3% (61.3-77.6)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>NR</td>
<td>17 years (8.18-NR)</td>
</tr>
</tbody>
</table>

Abbreviations: OS, overall survival; CI, confidence interval; NR, not reached; PS, performance status (ECOG); LDH, serum lactate dehydrogenase; Beta2-MG, serum beta-2 microglobulin; UNL, upper normal limit; IPI, international prognostic index; IQR, interquartile range. ^a Reported in 282 cases in the validation set. ^b Reported in 264 cases in the validation set. ^c Assessed only in 289 patients in the testing set and 168 in the validation set. ^d Defined in 281 patients in the validation set. ^e Defined in 267 patients in the validation set. ^f Other comprises: lenalidomide in combination with rituximab (15 patients), lenalidomide single agent (12 patients), interferon-alpha (4 patients), bortezomib (3 patients), thalidomide (2 patients), ofatumumab (1 patient).
### Table 2. Patient characteristics distribution according to early POD in the testing and validation set

<table>
<thead>
<tr>
<th></th>
<th>Testing set (IELSG-19)</th>
<th>Validation set</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early POD subset</td>
<td>Reference subset</td>
<td>Early POD subset</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>69</td>
<td>315</td>
<td>64</td>
</tr>
<tr>
<td><strong>Median age at diagnosis (IQR)</strong></td>
<td>62 years (40-78)</td>
<td>60 years (28-80)</td>
<td>0.667</td>
</tr>
<tr>
<td><strong>Male/female ratio</strong></td>
<td>32/37</td>
<td>153/162</td>
<td>0.741</td>
</tr>
<tr>
<td><strong>Stage IIIV</strong></td>
<td>36 (52%)</td>
<td>131 (42%)</td>
<td>0.108</td>
</tr>
<tr>
<td><strong>PS &gt;1</strong></td>
<td>3 (4%)</td>
<td>2 (1%)</td>
<td>0.042</td>
</tr>
<tr>
<td><strong>LDH&gt;UNL</strong></td>
<td>14 (20%)</td>
<td>25 (8%)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Beta2 MG &gt;UNL</strong></td>
<td>36 (16%)</td>
<td>8 (16%)</td>
<td>0.906</td>
</tr>
<tr>
<td><strong>Primary gastric lymphoma</strong></td>
<td>26 (38%)</td>
<td>136 (43%)</td>
<td>0.403</td>
</tr>
<tr>
<td><strong>IPI, High-Intermediate/High Risk</strong></td>
<td>20 (29%)</td>
<td>51 (16%)</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>MALT IPI, High Risk</strong></td>
<td>19 (28%)</td>
<td>43 (14%)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>First-line treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>22 (32%)</td>
<td>105 (33%)</td>
<td>42 (66%)</td>
</tr>
<tr>
<td>Immuno-chemotherapy</td>
<td>13 (19%)</td>
<td>112 (36%)</td>
<td>11 (17%)</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>34 (49%)</td>
<td>98 (31%)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Median follow up (IQR)</strong></td>
<td>6.0 years (5.2-9.4)</td>
<td>8.0 years (5.9-9.9)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Abbreviations: PS, performance status (ECOG); LDH, serum lactate dehydrogenase; Beta2-MG, serum beta-2 microglobulin; UNL, upper normal limit; IPI, international prognostic index; IQR, interquartile range

P-values refer to the comparison of proportions in early POD versus reference subsets by chi-square or the Fisher's exact test, as appropriate.
Table 3. Multivariate analysis for OS in the testing set (stepwise Cox model, 383 patients)

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early POD</td>
<td>1.90</td>
<td>1.03-3.49</td>
<td>0.039</td>
</tr>
<tr>
<td>Age</td>
<td>1.13</td>
<td>1.08-1.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MALT-IPI high risk</td>
<td>2.71</td>
<td>1.43-5.13</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; CI, confidence interval; POD, progression of disease; MALT-IPI, mucosa-associates lymphoid tissue lymphoma international prognostic index.
FIGURE LEGENDS

Figure 1. Risk of progression.
Estimated hazard of progression for the cohort of the IELSG-19 study (A) and for the patients included in the validation set (B).

Figure 2. Patient distribution.
Patient selection and distribution according to timing of disease progression in the testing and validation sets.

Figure 3. Overall survival.
Kaplan-Meier estimates of overall survival and their confidence bands according to the occurrence of early progression of disease in patients enrolled in the IELSG-19 randomized clinical trial (A) and in the validation set of patients who received front-line systemic therapy (B).
A

Testing set

Estimated progression hazard rate

Time (years)

B

Validation set

Estimated progression hazard rate

Time (years)
Testing set n=401

Excluded, n=17
Insufficient follow up time (n=9)
Death within 2 years without POD (n=8)

Early POD n=69
Reference n=315

Validation set n=287

Excluded, n=63
Insufficient follow up time (n=54)
Death within 2 years without POD (n=9)

Early POD n=64
Reference n=160