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# IELSG38: phase II trial of front-line chlorambucil plus subcutaneous rituximab induction and maintenance in mucosa-associated lymphoid tissue lymphoma

*Anastasios Stathis*[*1,2], Maria Cristina Pirosa*[*1,3], Lorella Orsucci[4], Pierre Feugier[5], Monica Tani[6], Hervé Ghesquières[7], Gerardo Musuraca[8], Francesca Gaia Rossi[9], Francesco Merli[10], Romain Guièze[11], Emmanuel Gyan[12], Guido Gini[13], Dario Marino[14], Remy Gressin[15], Franck Morschhauser[16], Federica Cavallo[17], Francesca Palombi[18], Annarita Conconi[19], Benoît Tessoulin[20], Hervé Tilly[21], Manuela Zanni[22], Maria Giuseppina Cabras[23], Enrico Capochiani[24], Catello Califano[25], Melania Celli[26], Alessandro Pulsoni[27], Francesco Angrilli[28], Ubaldo Occhini[29], René-Olivier Casasnovas[30], Guillaume Cartron[31], Liliana Devizzi[32], Corinne Haioun[33], Anna Marina Liberati[34], Roch Houot[35], Michele Merli[36], Giuseppe Pietrantuono[37], Francesca Re[38], Michele Spina[39], Francesco Landi[1] , Franco Cavalli[3], Francesco Bertoni[1,2,3], Davide Rossi[1,2,3], Nicoletta Ielmini[3] , Elena Borgo[40], Stefano Luminari[#10,41], Emanuele Zucca[#1,2,3,42], Catherine Thieblemont[#43].*

1. Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland
2. Università della Svizzera Italiana, Faculty of Biomedical Sciences, Lugano, Switzerland
3. Institute of Oncology Research, Bellinzona, Switzerland
4. S.C. Ematologia, AOU Città della Salute e della Scienza di Torino, Turin, Italy
5. Department of Clinical Hematology, Nancy University Hospital, INSERM 1256, Nancy, France
6. U.O. Ematologia, Dipartimento Oncologia e Ematologia, Ospedale Santa Maria delle Croci, Ravenna, Italy
7. Hematology Department, Hospices Civils de Lyon, CHU Lyon-Sud, Pierre-Bénite, France
8. Hematology Unit, IRCCS Istituto Scientifico Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy
9. Hematology-BMT Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milano, Italy
10. AUSL-IRCCS of Reggio Emilia, Reggio Emilia, Italy
11. Service d'Hématologie Clinique et de Thérapie Cellulaire, CHU Estaing, Clermont-Ferrand, France.
12. Hématologie et thérapie cellulaire, CIC Inserm U1415, Centre Hospitalier Universitaire de Tours, Tours, France.
13. Hematology, Department of Clinical and Molecular Sciences, Marche Polytechnic University, Ancona, Italy
14. Oncology 1 Unit, Istituto Oncologico Veneto IOV-IRCCS, Padova, Italy
15. Institute for Advanced Biosciences, INSERM U1209/CNRS UMR 5309/Grenoble Alpes University, Grenoble, France
16. Université de Lille, CHU Lille, Department of Hematology, Lille, France
17. Division of Hematology, Department of Molecular Biotechnologies and Health Sciences, University of Torino/AOU Città della Salute e della Scienza di Torino, Turin, Italy
18. Hematology and Stem Cell Transplant Unit, IRCCS. National Cancer Institute, Istituto Regina Elena, Rome Italy
19. Division of Hematology, Ospedale degli Infermi, Biella, Italy
20. Hématologie Clinique, CHU de Nantes, INSERM CRCINA Nantes-Angers, NeXT Université de Nantes, Nantes, France
21. Department of Hematology and U1245, Centre Henri Becquerel, Rouen, France
22. Hematology Unit, Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy

23. Ospedale Oncologico, Ematologia e CTMO, Cagliari, Italy
24. Hematology Unit, Azienda USL Toscana NordOvest, Center for Translational Medicine, Livorno, Italy
25. Hematology Unit, P.O. A. Tortora, Pagani, Italy
26. Hematology Unit, Ospedale degli Infermi, Rimini, Italy
27. Department of Translational and Precision Medicine, Sapienza University, Rome, Italy
28. Unità Operativa Semplice Dipartimentale Centro Diagnosi e Terapia Linfomi, Presidio Ospedaliero, Pescara, Italy
29. Unità Operativa di Ematologia, Ospedale San Donato, AUSL Toscana Sud-Est, Arezzo, Italy
30. Department of Hematology, University Hospital F Mitterrand and INSERM 1231, Dijon, France
31. Hématologie Clinique, CHU Montpellier, UMR 5535 Montpellier, France
32. Hematology Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy
33. Lymphoid Malignancies Unit, Hôpital Henri Mondor, AP-HP, Créteil, France
34. SC Oncoematologia, Azienda Ospedaliera Santa Maria, Università degli studi di Perugia, Terni, Italy
35. Department of Clinical Hematology, University Hospital of Rennes, Rennes, France
36. Division of Hematology, University Hospital Ospedale di Circolo e Fondazione Macchi ASST Sette Laghi, University of Insubria, Varese, Italy
37. Hematology Unit, Centro di Riferimento Oncologico della Basilicata IRCCS Rionero in Vulture, Italy
38. Hematology and BMT Center, Azienda Ospedaliera Universitaria, Parma, Italy
39. Division of Medical Oncology, Centro di Riferimento Oncologico IRCCS, Aviano, Italy
40. FIL, Fondazione Italiana Linfomi ONLUS, Alessandria, Italy
41. CHIMOMO Department, University of Modena and Reggio Emilia, Reggio Emilia, Italy
42. Medical Oncology, University Hospital and University of Bern, Switzerland
43. APHP - Service d'Hématologie-Oncologie, Hôpital Saint Louis, Université de Paris - Diderot, Paris, France.

*AS and MCP contributed equally as co-first authors;
[#] SL, EZ and CT contributed equally as co-senior authors.

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**Authors' contributions**

AS and EZ designed the trial and wrote the study protocol. AS, MCP, SL, EZ and CT analyzed the data and wrote the manuscript. AS, MCP, and EZ accessed and verified the trial data. NI, EB and BP coordinated regulatory activities and collection, assembly and management of the data. The remaining authors registered and treated patients or provided follow-up data. All authors provided critical review of the manuscript and approved the definitive version and its submission.

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***Correspondence***

Dr. Anastasios Stathis, IOSI, Ospedale San Giovanni, CH-6500 Bellinzona, Switzerland.

Telephone: +41 91 811 89 31. E-mail: anastasios.stathis@eoc.ch

## Abstract

The IELSG38 trial was conducted to investigate the effects of subcutaneous (SC) rituximab on the complete remission (CR) rate and the benefits of SC maintenance in patients with extranodal marginal zone lymphoma (MZL) who received frontline treatment with chlorambucil plus rituximab.

Study treatment comprised an induction phase with chlorambucil 6 mg/m$^2$/day orally on weeks 1-6, 9-10, 13-14, 17-18, and 21-22, and rituximab 375 mg/m$^2$ intravenously on day 1 of weeks 1-4, and 1400 mg SC on weeks 9, 13, 17, and 21. Then, a maintenance phase followed with rituximab administered at 1400 mg SC every two months for two years.

Of the 112 patients enrolled, 109 were evaluated for efficacy. The CR rates increased from 52% at the end of the induction phase to 70% upon completion of the maintenance phase. With a median follow-up of 5.8 years, the 5-year event-free, progression-free, and overall survival rates were 87% (95% CI, 78-92), 84% (95% CI, 75-89), and 93% (95% CI, 86-96), respectively. The most common grade ≥3 toxicities were neutropenia (33%) and lymphocytopenia (16%). Six patients experienced treatment-related serious adverse events, including fever of unknown origin, sepsis, pneumonia, respiratory failure, severe cerebellar ataxia, and fatal acute myeloid leukemia.

The trial showed that subcutaneous rituximab did not improve the complete remission rate at the conclusion of the induction phase, which was the main endpoint. Nevertheless, SC maintenance might have facilitated long-term disease control, potentially contributing to enhanced event-free and progression-free survival.

## Introduction

Extranodal marginal zone B-cell lymphoma (MZL) of mucosa-associated lymphoid tissue (MALT lymphoma) accounts for approximately 8% of lymphomas. The stomach is the most frequent site of localization, but MALT lymphomas can occur at any extranodal site [1, 2]. The clinical course is usually indolent, with median survival exceeding 10 years[1]. However, patients with high-risk baseline features[3, 4] and those with relapse or progression within 2 years from the initiation of the first systemic treatment have a significantly shorter survival[5-7]. Rituximab combinations with chemotherapy (chlorambucil or bendamustine)[8-10] are generally considered valid front-line treatment options[11]. In particular, a 6-month combination regimen of rituximab and chlorambucil was evaluated in the largest phase 3 randomized study ever conducted in patients with MALT lymphoma (IELSG19 trial), showing the superiority of the combination over either agent alone in terms of response rates, event-free survival (EFS) and progression-free (PFS) survival[8]. Following these results, we designed the IELSG38 phase 2 trial, to investigate whether the activity of a 6-month combination of intravenous (IV) rituximab with oral chlorambucil could be retained using the subcutaneous (SC) administration of rituximab and potentially enhanced by adding a 2-year maintenance treatment. Here we present the results of this trial.

## Methods

### *Study design and eligibility criteria*

IELSG38 was a single-arm, open-label, multicenter phase 2 clinical trial sponsored by the International Extranodal Lymphoma Study Group (IELSG) and conducted in collaboration with the Fondazione Italiana Linfomi (FIL) and the Lymphoma Study Association (LYSA).

Patients with MALT lymphoma either de novo, or relapsed following local therapy (i.e., surgery and/or radiotherapy) were eligible. Patients with primary *H. pylori*-positive gastric

MALT lymphoma treated with antibiotics were also eligible if they had endoscopic and histologic evidence of disease progression at any time after *H. pylori* eradication or stable disease with persistent lymphoma at ≥ 1 year after eradication or had relapsed without reinfection after a prior remission.

Other inclusion criteria included measurable or evaluable disease, according to the revised response criteria for malignant lymphoma[12]. The main exclusion criteria were evidence of histologic transformation, prior chemotherapy or anti-CD20 monoclonal antibody, CNS involvement, active HCV or HBV infection, and history of HIV infection.

The study procedures were in accordance with the principles of the Declaration of Helsinki. The Ethics Committee of the participating centers approved the study and all patients provided written informed consent.

Patients were staged with computed tomography (CT); positron emission tomography (PET) was allowed in addition to CT scans. Bone marrow biopsy was recommended but not mandatory. Esophagogastroduodenoscopy and/or colonoscopy with multiple mucosal biopsies were carried out in case of gastrointestinal involvement. ECG and standard laboratory exams (including viral serologies) were performed at the screening. Antibiotic and antiviral prophylaxis were administered as per local guidelines.

Treatment consisted of an induction (analogous to the regimen previously used in the IELSG19 trial[8]) and a maintenance phase with SC rituximab. During induction, patients received chlorambucil 6 mg/m$^2$ daily PO for 42 consecutive days (weeks 1-6) and rituximab 375 mg/m$^2$ IV on days 1, 8, 15 and 22. After restaging (weeks 7-8), patients with complete remission (CR), partial remission (PR) or stable disease (SD) received daily chlorambucil 6 mg/m$^2$ PO for 14 consecutive days (d1-14) every 28 days (one cycle) for up to four cycles in combination with rituximab 1400 mg SC on day 1 every 28 days for 4 cycles. After the induction phase, patients were restaged and those with at least SD

underwent maintenance treatment with rituximab 1400 mg SC every two months for two years (see Data Supplement, Figure S1).

*Study endpoints and clinical assessment*

The study endpoints were defined according to the revised response criteria for malignant lymphoma[12]. Primary end point was investigator-assessed CR rate at the end of induction. Secondary endpoints included investigator-assessed overall response rate (ORR), duration of response, progression-free-survival (PFS), event-free-survival (EFS), and overall survival (OS), for all patients[12].

Toxicity analysis was carried out using NCI Common Terminology Criteria for Adverse Events (CTCAE v4.03)[13].

Disease restaging for efficacy assessment was performed during weeks 7-8 and at the end of induction (weeks 25-26), then every year during maintenance. Following the revised response criteria for malignant lymphoma[12], responses at radiologically measurable lesions were assessed by CT; PET uptake was not used for response definition. In case of intestinal involvement response had to be confirmed by absence of lymphoma in posttreatment endoscopic biopsy. The histological response of gastric lymphomas was evaluated according to the GELA scoring system[14]. Cutaneous involvement was assessed by clinical examination, biopsy of normal appearing skin was not required to assign a complete response. At the completion of trial therapy, patients were followed every 4 months during the first 2 years, then every 6 months for 3 years and annually up to 10 years from study entry.

All patients who received at least one dose of therapy were included in the safety analysis, while the efficacy analysis comprised only patients without any major protocol violation that could affect the assessment of the study regimen activity.

*Sample size calculation and statistical considerations*

Sample size estimation was based on the primary endpoint (CR rate at the end of induction). The number of required patients was calculated, with alpha=0.05 (one-sided test) and power 90%, to show a CR rate higher than that in the chlorambucil alone arm of the previous IELSG19 study (H0=65%) and at least as high as in the chlorambucil plus IV rituximab arm (H1=78%) of the same study. Moreover, the required sample size had to retain the 90% power (with alpha=0.05, two-sided) to detect clinically relevant improvements of 15% in 5-year EFS and PFS in comparison with those observed in the IELSG19 trial (68% and 72%, respectively)[8].

In a post-hoc analysis, the impact of early relapse was estimated on OS calculated from disease progression, in patients with progression of disease within 24 months of treatment initiation (POD24), and from 24 months after start of treatment, in those without, using the same methodology adopted in a prior analysis of the IELSG19 study cohort[5].

The median follow-up was computed by the reverse Kaplan-Meier method[15]. Survival curves were estimated by the Kaplan-Meier method,[16] and differences were evaluated by using the log-rank test[17]. Binomial exact 95% confidence intervals (95%CI) were calculated for proportions. Associations were analyzed by using the chi-square or the Fisher's exact test, as appropriate. Cox proportional hazard models were used for multivariable analysis and the estimation of hazard ratios (HRs). Statistical analysis was performed by using the Stata/SE 17.0 software package (StataCorp, College Station, TX).

## Results

Between January 2014 and March 2016, 112 patients were enrolled in 38 sites (in Switzerland, Italy, and France). A central histology review was not planned. The clinical cut-off date for the primary analysis was November 15, 2021.

Median age at diagnosis was 66 years (range 32-86), 53% were males. An ECOG performance status score PS=0 was registered in 80% of patients. Over half of patients (56%) had stage III-IV disease. According to the MALT IPI, 30% of patients had low risk, 40% intermediate and 30% high-risk. Primary lymphoma localization was non-gastric in 68% and gastric in 32% of treated patients. The most frequent sites of involvement were stomach in 36 patients (32%), 16 each for lung and orbit (14%), salivary glands in 12 (11%), bowel in 8 (7%), skin in 7 (6%), upper airways in 4 (4%), peritoneum in 3 (3%), 2 each for thyroid and liver (2%) and one each for prostate, kidney, and vagina (1%). Additionally, three patients with splenic MZL were also included. Twenty-seven patients received prior therapy; among them 22 (20%) antibiotics, 4 (4%) surgery while one patient had received prior radiotherapy. Baseline patients' and disease characteristics are summarized in **Table 1**.

Eighty-eight patients (79%) completed the study treatment according to the protocol. Fifteen discontinued before starting maintenance, 4 of them due to drug-related (DR) adverse events (AEs), 3 due to non-DR AEs, 2 due to high-grade transformation, and 2 due to withdrawal of consent. One patient each discontinued due to progressive disease (PD), a second tumor, protocol deviation, and investigator decision. Nine patients withdrew treatment during the maintenance phase (3 for DR AEs, 2 for PD, 2 due to other malignancies, 1 for patient decision and 1 for a protocol deviation).

*Efficacy*

Albeit ineligible, three patients with primary splenic MZL were enrolled. These patients achieved an early complete remission and then received the entire study treatment. They have not relapsed, but according to the protocol they were excluded from the efficacy analysis, which was performed on the eligible and evaluable subjects (efficacy population, N=109). Fifty-seven of 109 patients (52%; 95%CI, 43-62) attained a CR at the end of

induction (primary endpoint) and 37 patients had a PR, resulting in ORR of 86% (95%CI, 78-92) (**Table 2**). Six patients had an early progression of disease (POD24). Five of them, were re-biopsied at progression and 2 had a histologically confirmed transformation into high grade lymphoma.

CR rate increased over the time, being documented in 66 patients (61%; 95%CI, 51-70) after 1 year of maintenance and in 76 (70%; 95%CI, 61-78) at the end of the second year. Five additional patients converted from PR to CR during the post-maintenance follow-up (**Table 2**). Overall, 90 patients (83%; 95%CI, 74-89) achieved a CR as their best response any time during the study duration. Median time to response (either CR or PR) was 2.8 months (interquartile range of 1.7-8.2 months). Responses were durable, with 93% (95%CI, 86-97) of patients who achieved either PR or CR still in continuous remission at 5 years from the response attainment. The Kaplan-Meier estimate of response duration for patients achieving a CR is depicted in **Figure 1.**

With a median follow-up of 70 months (interquartile range of 65-76 months) the estimated 5-year PFS, EFS, and OS rates in the efficacy population were 87% (95% CI, 78-92), 84% (95% CI, 75-89), and 93% (95% CI, 86-96), respectively (**Figure 2**). Outcome analysis in the whole cohort of 112 patients is summarized in the Data Supplement **(TableS1).**

The patients who achieved a CR as their best response, compared to those achieving a PR, showed superior 5-year PFS rates: 93% (95%CI, 85-97) versus 70% (95%CI, 33-89) respectively (P=0.0422). Similarly, EFS rates were significantly higher in those attaining CR: 92% (95%CI, 84-96) compared to 58% (95%CI, 27-80) for those achieving PR (P=0.009).

According to the primary lymphoma localization, CR rate at the end of induction was significantly higher (P<0.001) for gastric MZL (84%; 95%CI, 67-95) compared to non-gastric localizations (46%; 95%CI, 34-59), while ORR was 100% and 96%, respectively.

However, the difference in terms of best response, with CR rate of 92% (95%CI, 77-98) for gastric and 78% (95%CI, 67-87) for non-gastric MZL, was not statistically significant (P=0.079). Moreover, no significant difference was seen between gastric and non -gastric MZL also in terms of PFS (P=0.300), EFS (P=0.279), and OS (P=0.612). At univariable analysis age>70 years, elevated beta-2 microglobulin, hemoglobin <120 g/L and the MALT-IPI score (trend test) were individually associated with significantly shorter PFS, EFS and OS. In the cohort of 105 patients evaluable for early progression, the 6 patients with POD24 had a significantly shorter OS. At multivariable analysis, only anemia maintained a significant impact on PFS, while both anemia and elevated beta-2 microglobulin levels were associated with shorter EFS and shorter OS. POD24, when added to the OS Cox model retained its significant impact.

The Data Supplement shows remission rates and survival outcomes at each primary anatomic site of lymphoma involvement (**Table S2)**, as well as the univariable (**Tables S3**) and multivariable analysis (**Table S4)** of the prognostic impact of the main clinical features.

*Safety*

All patients received at least one dose of treatment and all experienced adverse events of any grade. Seventy-two DR grade ≥3 hematologic AEs were reported in 46 patients (41%); among them, neutropenia was the most frequently observed in 37 patients (33%) (**Table 3**). Non-hematological AEs were almost exclusively of grade 1–2, with asthenia, nausea and infusion-related reactions being the most frequently observed adverse events. Only eight patients experienced grade ≥3 non-hematologic AEs (**Table 4**).

A total of 45 Serious Adverse Events (SAEs) occurred involving 35 patients; six of them had a therapy-related SAE, two (fever of unknow origin, respiratory failure) occurred during the induction phase and 3 (sepsis, pneumonia, and encephalopathy with severe autoimmune cerebellar ataxia resulting in permanent total disability) during maintenance.

One drug related SAE of acute myeloid leukemia was reported during the follow up. This patient had discontinued the study treatment after 5 months due to a non-drug-related transient ischemic attack, while the diagnosis of AML, attributed to chlorambucil, occurred 2 years later. It is worth noting that a baseline bone marrow evaluation was conducted during the screening, revealing no evidence of lymphoma or any underlying myelodysplastic syndrome prior to the initiation of the study treatment.

A second case of encephalopathy with severe cerebellar ataxia, which eventually resulted in patient death, was reported, too, and defined by the treating investigator as paraneoplastic, not related to the study treatment. Notably, in both patients with cerebellar ataxia the presence of JC virus was actively searched and ruled out.

Among SAEs, in addition to the above mentioned acute myeloid leukemia 15 other malignancies were diagnosed during the study but considered not related to the study treatment (3 cutaneous basal cell carcinoma, 3 breast cancer, 3 lung cancer, 2 hepatocellular carcinoma, 1 pancreatic carcinoma, 1 melanoma in situ, 1 prostate cancer, 1 Hodgkin lymphoma). Histological transformation into large cell lymphoma was reported in 3 patients.

Eleven deaths were observed but only one was related to study treatment (i.e., acute myeloid leukemia). Among non-drug related deaths, two patients died due to progressive disease, two after histologic transformation into DLBCL, two due to lung carcinoma, one for a progressive encephalopathy associated with the above-mentioned cerebellar ataxia and one for SARS-COV2 infection. In two patients the cause of death remained unknown.

## Discussion

The IELSG38 trial was designed on the backbone of the combination arm of the IELSG19 study[8] and it is the first prospective clinical trial which specifically assessed in MALT lymphomas whether the use of SC rituximab results in similar rate of CR as previously

observed at the end of induction in the IELSG19 trial and whether maintenance with SC rituximab is of any benefit. While no unexpected safety signals emerged, the primary endpoint was not met. This primary endpoint (CR rate at 6 months) was chosen to allow a rapid evaluation of the clinical activity of the SC route. However, this choice represents a major weakness in a study assessing the role of maintenance. Indeed, CR rates continuously increased over time and rituximab maintenance allowed long-term disease control, with improvement of both EFS and PFS. In this context, there are differences between this trial and the IELSG19 that impact the observed outcomes. Despite identical inclusion criteria, slightly more patients with advanced stage (56% vs 45%), extragastric localization (68% vs 60%), elevated LDH (13% vs 10%), elevated beta-2 microglobulin (34% vs 27%) and high-risk MALT-IPI score (30 vs 18%) entered the IELSG38 trial compared with the IELSG19 combination arm[8]. The main distinction, however, lies in the utilization of updated response definitions in the current study[12], while the IELSG19 adopted older definitions[18].

Moreover, in the current trial, the CRs raised from 52% at 6 months to 70% at the end maintenance. Maintenance might have also contributed to a reduction of patients with POD24 (6% in the current study and 13% in the IELSG19[5]). Regarding time-related secondary endpoints, the 5-year PFS (87%; 95% CI, 78-92) and EFS (83%;95% CI, 75-89), were both superior to those of 72% (95%CI, 63-79) and 68% (95%CI, 60-76) respectively observed without maintenance in the combination arm of the IELSG19 study[8]. The duration of response (93%; 95%CI, 86-97%) was also better than the one observed without maintenance in the prior study (79%; 95%CI, 71-85) study[8].

The need of rituximab maintenance in non-follicular indolent lymphomas is controversial, with no evidence of OS benefit[19-23]. In the MALT2008-01 response-adapted prospective phase 2 trial of the front-line combination of bendamustine and rituximab in extranodal MZL, patients received no maintenance and achieved a 7-year EFS of 88%[9]. Nowadays,

rituximab maintenance is not recommended or is considered optional in front line treatment of MALT lymphoma[11, 24, 25]. Indeed, there are only few published data in the specific setting of patients with MZL and MALT lymphoma in particular[23, 26]. The ECOG E4402 study, which compared maintenance rituximab vs retreatment in indolent lymphomas, enrolled 71 MZL patients (29 with MALT lymphoma) who had responded to prior single-agent rituximab. The 5-year treatment failure-free survival was significantly better in the maintenance arm (45% vs 20%; P =0.012) for patients with small lymphocytic lymphoma and MZL but specific data on the different histologic subsets were not reported[21]. Results of the STIL NHL7-2008 MAINTAIN TRIAL, thus far published only as abstract, showed an improvement of PFS in patients with splenic MZL and nodal MZL treated with rituximab maintenance in comparison to observation after rituximab plus bendamustine; the study did not enroll MALT lymphoma patients [23]. On the other hand, an exploratory analysis of the randomized Gallium trial, which evaluated the efficacy and safety of obinutuzumab or rituximab-based chemotherapy followed by obinutuzumab or rituximab maintenance in patients with previously untreated MZL, including MALT lymphomas, did not demonstrate a difference in terms of PFS between the two arms, but the obinutuzumab arm had more adverse events[27]. A Korean group reported results of a phase 2 trial which evaluated 2-year rituximab-maintenance in patients with advanced MZL responding to first-line therapy with the R-CVP (rituximab, cyclophosphamide, vincristine, and prednisolone) regimen. This study enrolled 47 patients, 30 of whom had an extranodal MZL. Forty-five patients (96%) received rituximab maintenance. The 3-year PFS rate was 81%[26]. Finally, in a retrospective international survey of 237 patients with extranodal MZL treated with front-line rituximab plus bendamustine, with or without maintenance, the 5-year PFS was 81% in the entire group and 94% in the subset of 48 patients (20%) who had rituximab maintenance, however, maintenance had no impact on OS[25].

Our results show a potential benefit from maintenance with SC rituximab on response quality and duration, as well as on EFS and PFS. Noteworthy, considering the different rates of CR at end of induction and CR as best response in gastric and non-gastric patients, maintenance may be particularly useful in patients with non-gastric lymphoma. Nevertheless, it is important to consider that the response assessment for gastric lymphoma was based on endoscopic biopsies and not on imaging. This may have affected the observed differences in response rates. Indeed, no significant difference was seen between gastric and non-gastric MZL in terms of PFS, EFS and OS, but the study is underpowered for this analysis. Hence, the maintenance benefit should be confirmed in a randomized setting before recommending prolonged treatment in patients with MALT lymphoma.

This benefit should, however, be confirmed in a randomized setting before recommending a prolonged treatment in patients with MALT lymphoma. As also indicated by the MALT2008-01 study mentioned before[9], patients achieving a rapid CR may not need additional treatments. In our study and similar to all other indolent lymphomas, maintenance had no effect on OS and, the recent COVID pandemic has made us more alert to the risk of infectious complications after cancer treatments that induce prolonged immunodeficiency[28]. Moreover, albeit acceptable (less than 10% of the patients in the IELSG38 discontinued treatment due to adverse events), toxicity may be increased by maintenance, particularly hematological side effects and (opportunistic) infections.

The incidence of other malignancies (15%) diagnosed during and after treatment is similar to the incidences reported in other studies and most likely related to the older median age of patients[29-31]. Two patients developed cerebellar ataxia, with a different evaluation of causality. Notable, despite extremely rare, this paraneoplastic syndrome has been reported in patients with marginal zone lymphoma[32, 33].

In conclusion, subcutaneous rituximab did not improve remission rates at the end of induction, which was the main endpoint. However, the CR rate increased over time and subcutaneous rituximab maintenance might have allowed for long-term disease control and a potential improvement in event-free and progression-free survival**.**

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## Tables

**Table 1. Patients' characteristics (N=112)**

| **Patients' Characteristics** | N | percent |
|---|---|---|
| *Age* | | |
| Median, 66 years (range, 32-86) | | |
| >70 years | 37 | 33% |
| *Sex* | | |
| Male: | 59 | 53% |
| Female | 53 | 47% |
| *Stage* | | |
| I-II | 49 | 44% |
| III-IV | 63 | 56% |
| *Performance status* | | |
| ECOG 0 | 90 | 80% |
| ECOG 1 | 22 | 20% |
| *Anemia* | | |
| Hemoglobin ≥120 g/L | 95 | 85% |
| Hemoglobin <120 g/L | 17 | 15% |
| *B-symptoms* | | |
| absent | 105 | 94% |
| present | 7 | 6% |
| *Serum LDH* | | |
| normal | 97 | 87% |
| elevated | 15 | 13% |
| *Serum beta-2 microglobulin (n=96)* | | |
| normal | 63 | 64% |
| elevated | 36 | 36% |
| *MALT IPI* | | |
| Low risk | 33 | 29% |
| Intermediate risk | 45 | 40% |
| High risk | 34 | 30% |
| *Previous treatment* (n=27) | | |
| Antibiotic | 22 | 20% |
| Surgery | 4 | 4% |
| Radiotherapy | 1 | 1% |
| *Number of extranodal sites* | | |
| ≤1* | 77 | 69% |
| >1 | 35 | 31% |
| *Primary site* | | |
| Stomach | 36 | 32% |
| Lung | 16 | 14% |
| Orbit | 16 | 14% |
| Salivary glands | 12 | 11% |
| Bowel | 8 | 7% |
| Skin | 7 | 6% |
| Upper airways | 4 | 4% |
| Peritoneum | 3 | 3% |
| Genitourinary tract | 3 | 3% |
| Spleen | 3 | 3% |
| Thyroid | 2 | 2% |
| Liver | 2 | 2% |

* Primary splenic involvement (n=3 patients) was not considered extranodal
Percentages may not total 100 due to rounding.

**Table 2. Response rate at the planned restaging timepoints after 6 months of induction immunochemotherapy (primary endpoint) and after 12 and 24 months of rituximab maintenance in the efficacy population (n=109)**

| Response | Planned Restaging Timepoints | | | | | | Additional Restaging | |
|---|---|---|---|---|---|---|---|---|
| | After Induction (month 6) | | **After 1 year of maintenance** (month 18) | | **After 2 years of Maintenance** (month 30) | | **During Follow-up** (up to month 60) | |
| | N | percent | N | percent | N | percent | N | percent |
| CR | 57 | 52% | 66 | 61% | 76 | 70% | 81 | 74% |
| PR | 37 | 34% | 21 | 19% | 8 | 7% | 8 | 7% |
| SD | 3 | 3% | 2 | 2% | 1 | 1% | 2 | 2% |
| PD | 2 | 2% | 2 | 2% | 1 | 1% | 6 | 5% |
| NA | 10 | 9% | 18 | 17% | 23 | 21% | 12 | 11% |

CR, complete remission; PR, partial remission; SD, stable disease; PD, Progressive disease (including those progressing between the scheduled restaging timepoint); NA, not assessed.
Percentages may not total 100 due to rounding.

**Table 3. Hematological toxicity observed in ≥5% of patients (safety population n=112)**

| **Adverse event** | **Any grade N(%)** | | | **Grade ≥3 N(%)** | | |
|---|---|---|---|---|---|---|
| | All | Induction phase | Maintenance phase | All | Induction phase | Maintenance phase |
| Neutropenia | 50 (45%) | 29 (26%) | 21 (19%) | 37 (33%) | 22 (20%) | 15 (13%) |
| Leukopenia | 29 (26%) | 20 (18%) | 9 (8%) | 16 (14%) | 11 (10%) | 5 (4%) |
| Lymphocytopenia | 23 (21%) | 12 (11%) | 11 (10%) | 18 (16%) | 16 (14%) | 2 (2%) |
| Thrombocytopenia | 14 (13%) | 12 (11%) | 2 (2%) | 1 (1%) | 1 (1%) | --- |
| Anemia | 7 (6%) | 6 (5%) | 1 (1%) | --- | --- | --- |

Percentages may not total 100 due to rounding.

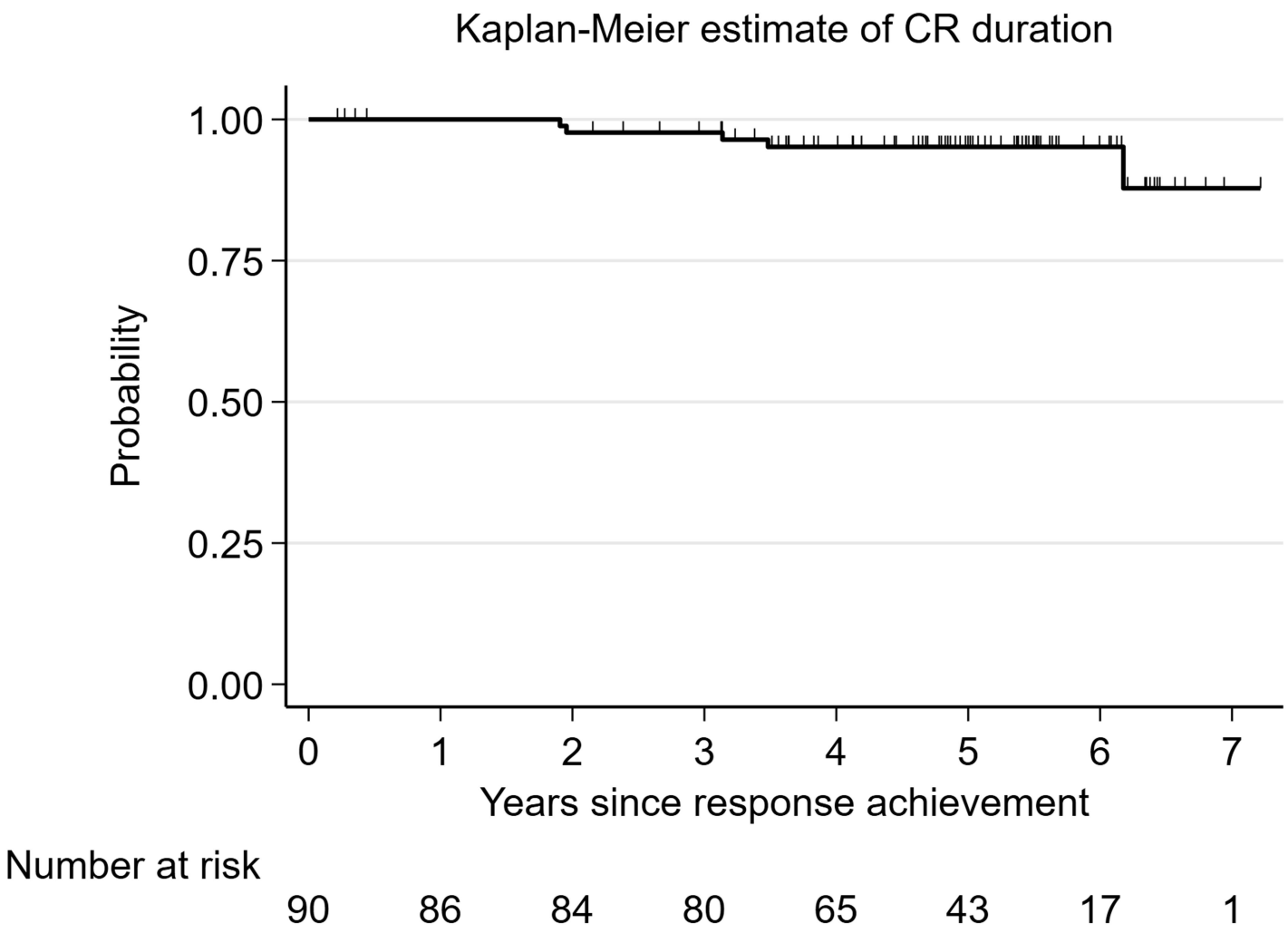
**Table 4. Non hematological toxicity observed in ≥5% of patients (safety population n=112)**
Percentages may not total 100 due to rounding.

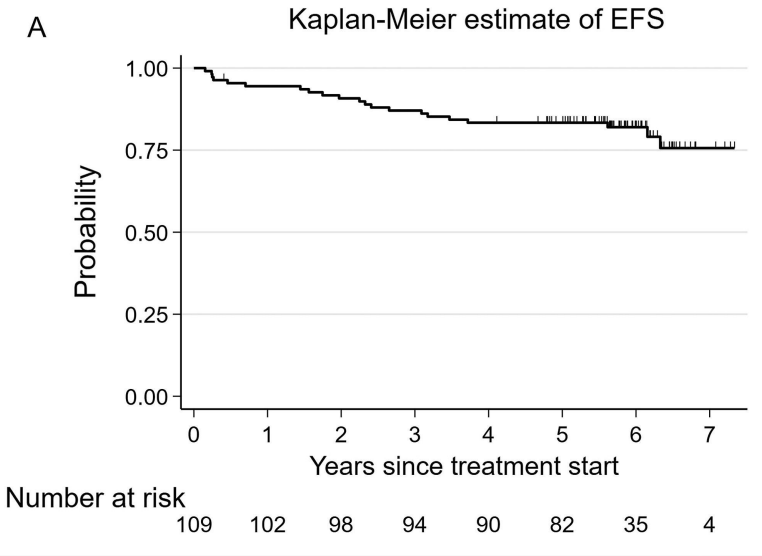
| Adverse event | **Any grade N(%)** | | | **Grade ≥3 N(%)** | | |
|---|---|---|---|---|---|---|
| | All | Induction phase | Maintenance phase | All | Induction phase | Maintenance phase |
| Asthenia | 28 (25%) | 24 (21%) | 4 (4%) | 3 (3%) | 3 (3%) | --- |
| Nausea | 19 (17%) | 19 (17%) | --- | --- | --- | --- |
| Infusion reaction | 14 (13%) | 12 (11%) | 2 (2%) | 1 (1%) | 1 (1%) | --- |
| Gastrointestinal pain | 12 (11%) | 11 (10%) | 1 (1%) | --- | --- | --- |
| Skin rash | 9 (8%) | 9 (8%) | --- | 1 (1%) | 1 (1%) | --- |
| Constipation | 8 (5%) | 8 (5%) | --- | --- | --- | --- |
| Herpes infection | 7 (6%) | 4 (3%) | 3 (3%) | 1 (1%) | --- | 1 (1%) |
| Vomiting | 6 (5%) | 6 (5%) | --- | 1 (1%) | 1 (1%) | --- |
| Headache | 6 (5%) | 6 (5%) | --- | 1 (1%) | 1 (1%) | --- |

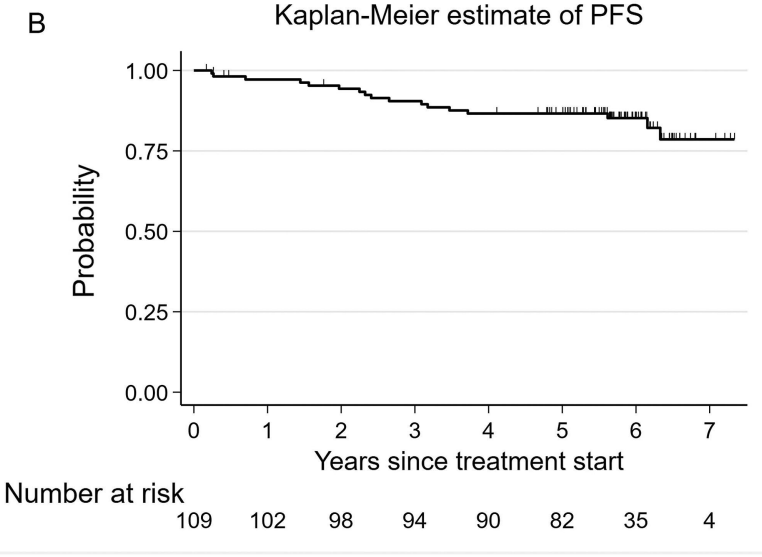
## Figure Legends

**Figure 1. Kaplan-Meier estimate of the duration of complete response.** Of 90 patients with complete remission, 95% (95%CI, 87-98%) remained in CR at 5 years from response attainment.

**Figure 2. Kaplan-Meier survival estimates**. (A) event-free survival, (B) progression-free survival and (C) overall survival in the efficacy population (n=109)


Kaplan-Meier estimate of CR duration
1.00
0.75
0.50
0.25
0.00
Probability
0
1
2
3
4
5
6
7
Years since response achievement
Number at risk
90
86
84
80
65
43
17
1


A
Kaplan-Meier estimate of EFS
Probability
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
6
7
Years since treatment start
Number at risk
109 102 98 94 90 82 35 4


B
Kaplan-Meier estimate of PFS
Probability
1.00
0.75
0.50
0.25
0.00
0
1
2
3
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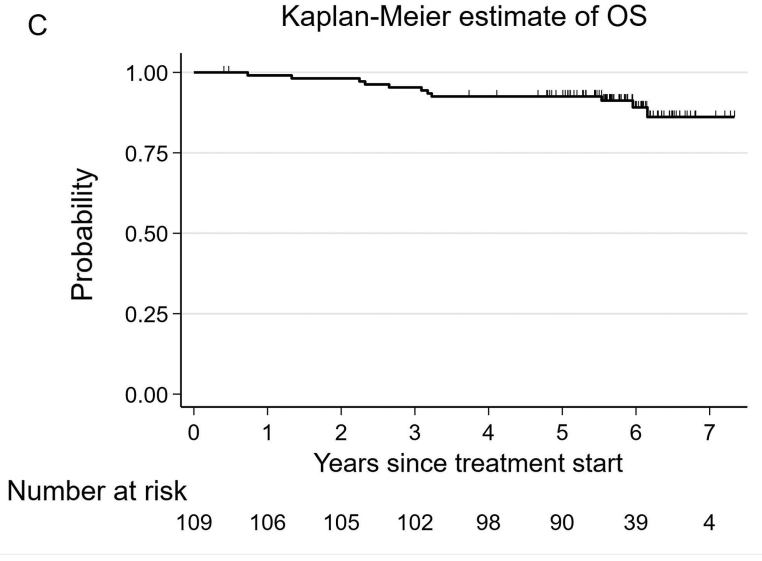
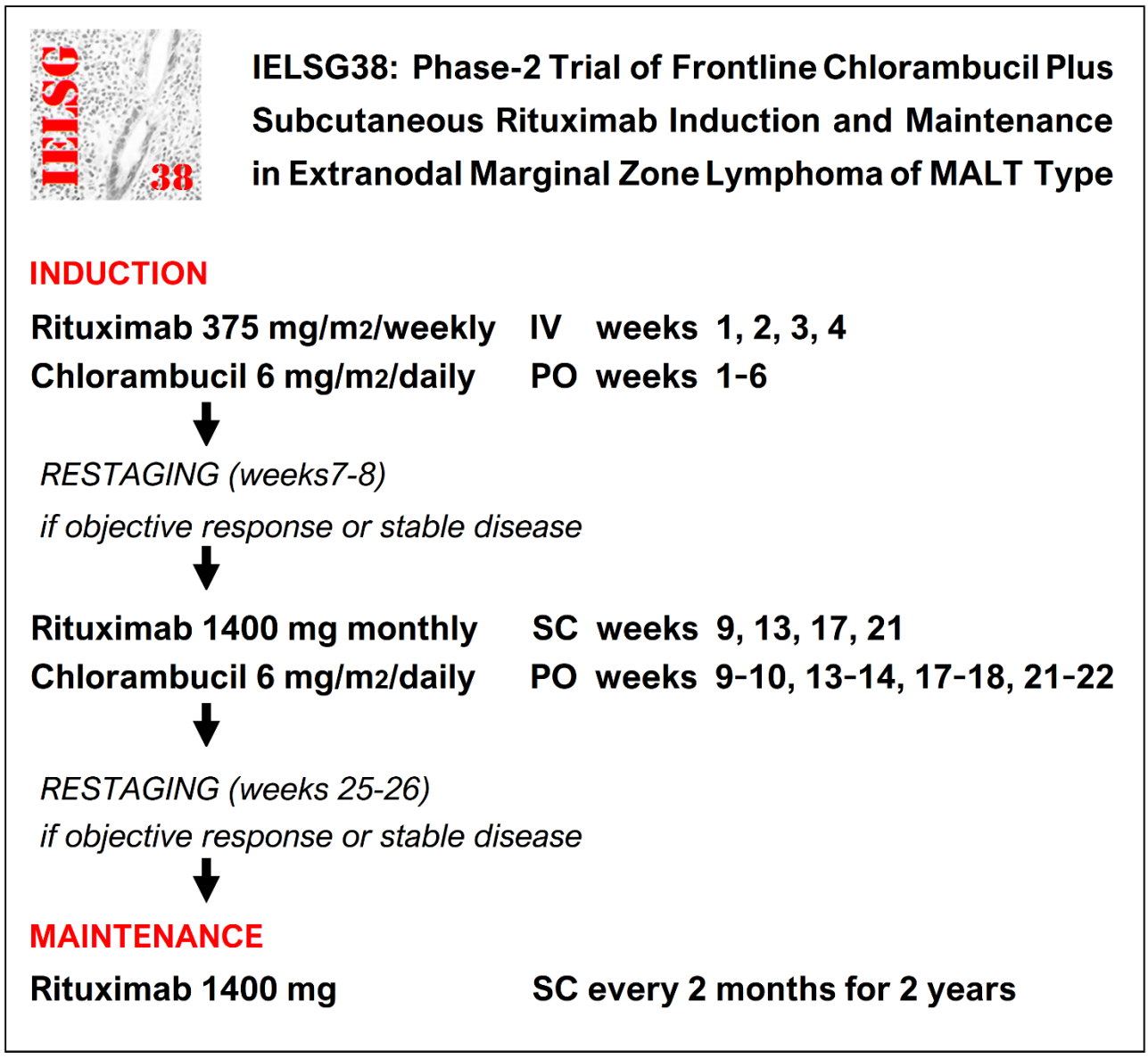
5
6
7
Years since treatment start
Number at risk
109 102 98 94 90 82 35 4


C
Kaplan-Meier estimate of OS
Probability
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
6
7
Years since treatment start
Number at risk
109 106 105 102 98 90 39 4

# DATA SUPPLEMENT

## Figure S1. Study design



## Table S1. Outcome analysis in the entire cohort of 112 enrolled patients

| | A. Response (at different time points from study entry) | | | | | |
|---|---|---|---|---|---|---|
| | **2 months N *(%)*** | **6 months N *(%)*** | **18 months N *(%)*** | **30 months N *(%)*** | **later N *(%)*** | **best ever N *(%)*** |
| **CR** | 41 (37) | 60 (54) | 69 (62) | 79 (71) | 84 (75) | 93 (83) |
| **PR** | 56 (50) | 37 (33) | 21 (19) | 8 (7) | 8 (7) | 12 (11) |
| **SD** | 3 (3) | 3 (3) | 2 (2) | 1 (1) | 2 (2) | 5 (2) |
| **PD** | 2 (2) | 2 (2) | 2 (2) | 1 (1) | 6 (5) | 2 (2) |
| **NA** | 10 (9) | 10 (9) | 18 (16) | 23 (21) | 12 (11) | 0 |
| | | | | | | |
| | **B. Survival rates** | | | | | |
| | **PFS % (95%CI)** | **EFS % (95%CI)** | **CSS % (95%CI)** | **OS % (95%CI)** | **DOR % (95%CI)** | **CRDUR % (95%CI)** |
| **2-year rate** | 94 (88-97) | 90 (83-94) | 98 (93-100) | 99 (93-100) | 96 (90-98) | 98 (91-99) |
| **5-year rate** | 87 (79-92) | 83 (74-89) | 96 (90-99) | 93 (86-96) | 94 (86-97) | 95 (88-98) |
| | | | | | | |

CR, complete remission; PR, partial remission; SD, stable disease; PD, Progressive disease (including those progressing between the scheduled restaging timepoint); NA, not assessed; PFS, progression-free survival; EFS, event-free survival; CSS, Cause-specific survival; OS. Overall survival. DOR, Duration of response (PR+CR). CRDUR, duration of CR.
Percentages may not total 100 due to rounding.

## Table S2. Patient outcome by the primary site of marginal zone lymphoma involvement

| Anatomic site | N (%) | Best response (95%CI) | | Survival rates (95%CI) | | |
|---|---|---|---|---|---|---|
| | | CR | PR | 5-year PFS | 5-year EFS | 5-year OS |
| Stomach | 36 (32) | 92% (77-98) | 6% (<1-19) | 91% (75-97) | 88% (72-96) | 91% (76-97) |
| Intestine* | 11 (10) | 73% (39-94) | 18% (2-52) | 70% 833-89) | 63% (30-84) | 100% |
| Lung | 16 (14) | 81% (54-96) | 0 | 80% (50-93) | 75% (46-90) | 88% (59-97) |
| Ocular Adnexa | 16 (14) | 75% (48-93) | 19% (4-46) | 88% (59-97) | 88% (59-97) | 94% (63-99) |
| Salivary Glands | 12 (11) | 83% (52-98) | 17% (2-48) | 100% | 100% | 100% |
| Upper Airways | 4 (4) | 75% (19-99) | 25% (<1-81) | 75% (13-96) | 75% (13-96) | 75% (13-96) |
| Thyroid | 2 (2) | 100% (15-100)** | 0 | 100% | 100% | 100% |
| Genitourinary Tract | 3 (3) | 67% (9-99) | 33% (<1-90) | 100% | 67% (54-94) | 100% |
| Liver | 2 (2) | 100% (15-100)** | 0 | 100% | 100% | 100% |
| Skin | 7 (6) | 71% (29-96) | 14% (<1-58) | 71% (26-92) | 71% (26-92) | 86% (33-98) |
| Spleen | 3 (3) | 100% (29-100)** | 0 | 100% | 67% (54-94) | 100% |
| All non-gastric | 76 (68) | 78% (67-87) | 14% (7-24) | 84% (74-94) | 81% (70-88) | 93% (84-97) |

N, number of patients; CI, confidence interval; CR, complete response; PR, partial response; PFS, progression-free survival; EFS, event-free survival; OS, overall survival.

*The subgroup includes three patients with peritoneal involvement.

**One-sided 97.5%CI

**Table S3. Univariable analysis of clinical prognostic factors in the efficacy cohort (N=109)**

| Clinical features | 5-y PFS (95%CI) | P-value (log-rank) | 5-yr EFS (95%CI) | P-value (log-rank) | 5-yr OS (95%CI) | P-value (log-rank) |
|---|---|---|---|---|---|---|
| *Age* | | | | | | |
| <70 years | 92 (82-96) | | 90 (79-94) | | 96 (88-99) | |
| >70 years | 77 (59-88) | **0.0120** | 72 (55-84) | **0.0105** | 86 (69-94) | **0.0026** |
| *Sex* | | | | | | |
| Male: | 87 (75-94) | | 83 (70-90) | | 93 (82-97) | |
| Female | 86 (72-93) | 0.3463 | 84 (71-92) | 0.6335 | 98 (80-97) | 0.6204 |
| *Stage* | | | | | | |
| I-II | 91 (78-97) | | 89 (76-95) | | 96 (84-99) | |
| III-IV | 83 (71-90) | 0.6172 | 79 (66-87) | 0.5531 | 90 (79-95)( | 0.2186 |
| *Performance status* | | | | | | |
| ECOG 0 | 87 (78-92) | | 85 (75-90) | | 94 (87-98) | |
| ECOG 1 | 84 (59-95) | 0.9165 | 80 (55-92) | 0.9775 | 85 (60-95) | 0.4433 |
| *Anemia* | | | | | | |
| Hb≥120 g/L | 88(79-93) | | 85 (76-91) | | 94 (86-97) | |
| Hb<120 g/L | 75 (45-92) | **0.0230** | 72 (41-88) | **0.0195** | 85 (53-96) | **0.0156** |
| *B-symptoms* | | | | | | |
| Absent | 88 (79-93) | | 84 (75-90) | | 93 (86-97) | |
| Present | 78 (45-92) | 0.3047 | 71 (26-92) | 0.4965 | 86 (33-98) | 0.6495 |
| *Serum LDH* | | | | | | |
| Normal | 88(79-93) | | 85 (76-91) | | 94 (86-97) | |
| Elevated | 75 (45-92) | 0.4857 | 71 (41-88) | 0.3393 | 86 (54-96) | 0.5049 |
| *Serum β2-MG* | | | | | | |
| Normal | 92 (82-97) | | 91 (80-96) | | 97 (88-99) | |
| Elevated | 79 (60-90) | **0.0252** | 72 (53-84) | **0.0052** | 87 (69-95) | **0.0022** |
| *MALT IPI* | | | | | | |
| Low risk | 97 (80-100) | | 97 (80-100) | | 100 | |
| Intermediate risk | 86 (71-93) | | 81 (66-90) | | 91 (77-96) | |
| High risk | 77 (59-89) | **0.0378** | 73 (54-85) | **0.0151** | 87 (70-95) | **0.0135** |
| *Primary site* | | | | | | |
| Gastric | 91 (75-97) | | 89 (72-96) | | 91 (76-97) | |
| non-Gastric | 84 (73-91) | 0.3003 | 81 (70-88) | 0.2788 | 93 (84-97) | 0.6117 |
| *POD24* | | | | | | |
| *No* | Not applicable | | Not applicable | | 88 (73-95) | |
| *Yes* | | | | | 48 ( 9-79) | **0.0007** |

EFS, event-free survival; PFS, progression-free survival; OS. Overall survival:

At univariable analysis (Log-rank test), among the patient characteristics at study entry, age>70 years, elevated beta-2 microglobulin, hemoglobin <120 g/L, and the MALT-IPI score (trend test) were individually associated with significantly shorter PFS, EFS and OS. In the cohort of 105 patients evaluable for early progression, the 6 patients with POD24 had a significantly shorter OS.

**Table S4. Multivariable analysis**

| **A. Cox models for PFS, EFS, OS** | | | | | |
|---|---|---|---|---|---|
| **Endpoint** | **Risk factor** | **HR** | **SE** | **P-value.** | **95% CI** |
| **PFS** | Hemoglobin <120 g/L | 4.51 | 2.53 | 0.007 | 1.50-13.56 |
| **EFS** | β2-Microglobulin >ULN | 3.20 | 1.57 | 0.018 | 1.22-8.38 |
| | Hemoglobin <120 g/L | 3.31 | 1.68 | 0.018 | 1.22-8.97 |
| **OS** | β2-Microglobulin | 6.63 | 5.38 | 0.020 | 1.35-32.53 |
| | Hemoglobin <120 g/L | 4.31 | 2.93 | 0.032 | 1.14-16.34 |
| **B. Cox model for OS including the POD24 status** | | | | | |
| **Endpoint** | **Risk factor** | **HR** | **SE** | **P-value.** | **95% CI** |
| **OS** | β2-Microglobulin | 7.14 | 5.78 | 0.015 | 1.46-34.84 |
| | Hemoglobin <120 g/L | 4.84 | 3.33 | 0.022 | 1.26-18.62 |
| | POD<24 months | 8.55 | 7.28 | 0.012 | 1.61-45.42 |

PFS, progression-free survival; EFS, event-free survival; OS. overall survival; HR, hazard ratio; SE, standard error, 95%CI, 95% confidence interval; ULN, upper limit of normal; POD, progression of disease.

At multivariable analysis (stepwise backward Cox model including the features with a significant impact at univariable analysis), only anemia maintained a significant impact on PFS, while both, hemoglobin below 120 g/L and beta-2 microglobulin higher than normal were associated with shorter EFS and shorter OS.
When POD24 was added to the stepwise backward Cox model for the overall survival analysis, its significant impact on survival was also confirmed (together with anemia and beta-2 microglobulin).