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#] and Catherine Thieblemont[43#]

Correspondence: A. Stathis
anastasios.stathis@eoc.ch

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[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, Bern, Switzerland and [43]APHP - Service d'Hématologie-Oncologie, Hôpital Saint Louis, Université de Paris-Diderot, Paris, France

**AS and MCP contributed equally as first authors.*
#SL, EZ and CT contributed equally as senior authors.

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 rituximab maintenance in patients with extranodal marginal zone lymphoma (MZL) who received front-line treatment with chlorambucil plus rituximab. Study treatment was an induction phase with oral chlorambucil 6 mg/m^2/day on weeks 1-6, 9-10, 13-14, 17-18, and 21-22, and intravenous rituximab 375 mg/m^2 on day 1 of weeks 1-4, and 1,400 mg SC on weeks 9, 13, 17, and 21. Then, a maintenance phase followed with rituximab administered at 1,400 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 SC rituximab did not improve the CR rate at the conclusion of the induction phase, which was the main endpoint. Nevertheless, SC rituximab 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 ten years.[1] However, patients with high-risk baseline features[3,4] and those with relapse or progression within two 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 III 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 survival (PFS).[8] Following these results, we designed the IELSG38 phase II 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 II 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, central nervous system (CNS) involvement, active hepatitis C virus (HCV) or hepatitis B virus (HBV) infection, and history of human immunodeficiency virus (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. The study was registered at *clinicaltrials.gov 01808599*.

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. Electrocardiogram 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 oral (PO) chlorambucil 6 mg/m^2 daily for 42 con-

secutive days (weeks 1-6) and intravenous (IV) rituximab 375 mg/m^2 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 4 cycles in combination with SC rituximab 1,400 mg 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 1,400 mg SC every two months for two years (see *Online Supplementary Appendix*, *Online Supplementary 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, PFS, EFS, and 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 post-treatment endoscopic biopsy. The histological response of gastric lymphomas was evaluated according to the scoring system of the Groupe d'Etude des Lymphomes de l'Adulte (GELA).[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 four months during the first two years, then every six months for three years, and annually up to ten 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 α=0.05 (one-sided test) and 90% power, 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 α=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 using the log-rank test.[17] Binomial exact 95% confidence intervals (95%CI) were calculated for proportions. Associations were analyzed by using the χ^2 or the Fisher's exact test, as appropriate. Cox proportional hazard models were used for multivariable analysis and the estimation of hazard ratios (HR). Statistical analysis was performed by using the Stata/SE 17.0 software package (StataCorp, College Station, TX, USA).

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 Eastern Cooperative Oncology Group (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 Mucosa-Associated Lymphoid Tissue International Prognostic Index (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, 3 patients with splenic MZL were also included. Twenty-seven patients received prior therapy; among them, 22 (20%) received antibiotics, 4 (4%) underwent 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 (AE), 3 due to non-DR AE, 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 AE, 2 for PD, 2 due to other malignancies,

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

Patients' characteristics	N	%
Age in years		
Median 66 (range 32-86)		
>70	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 β-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. ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; MALT IPI: Mucosa-Associated Lymphoid Tissue International Prognostic Index.

one for patient decision, and one for a protocol deviation.

Efficacy

Albeit ineligible, 3 patients with primary splenic MZL were enrolled. These patients achieved an early CR 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) obtained 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.

Complete remission rate increased over the time period under study, being documented in 66 patients (61%; 95%CI: 51-70) after one 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, 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 five years from the response attainment. The Kaplan-Meier estimate of response duration for patients achieving a CR is shown in Figure 1.

With a median follow-up of 70 months (interquartile range, 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 *Online Supplementary Table S1*. The patients who achieved a CR as their best response showed superior 5-year PFS rates to those achieving a PR: 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 a 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 β-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 β-2 microglobulin

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	%	N	%	N	%	N	%
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.

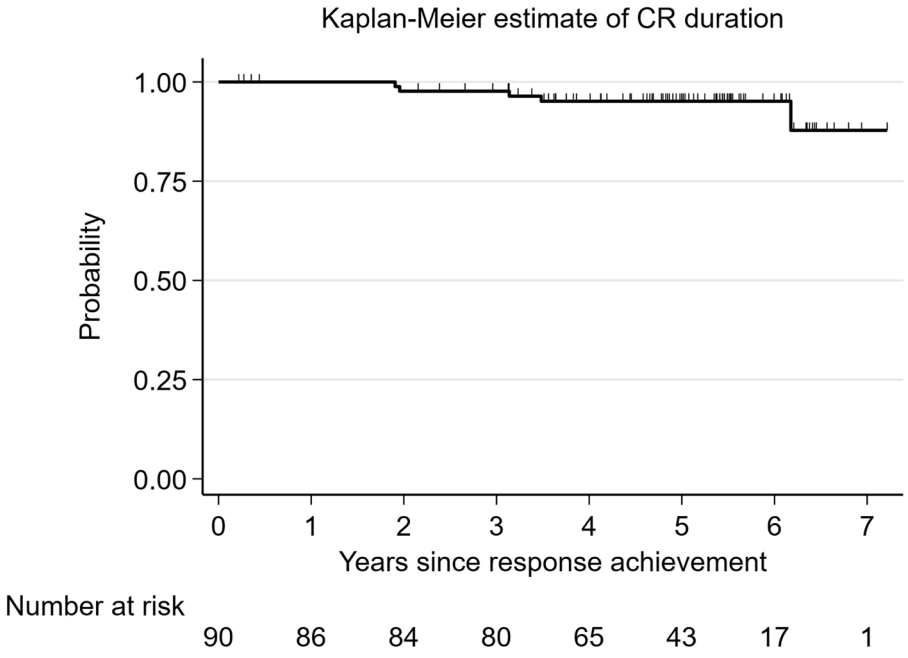

Figure 1. Kaplan-Meier estimate of the duration of complete response. Of 90 patients with complete remission, 95% (95% Confidence Interval [CI]: 87-98%) remained in complete remission (CR) at five years from response attainment.

levels were associated with shorter EFS and shorter OS. POD24, when added to the OS Cox model, retained its significant impact.

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

Safety

All patients received at least one dose of treatment and all experienced AE of any grade. Seventy-two DR grade ≥3 hematologic AE were reported in 46 patients (41%); among them, neutropenia was the most frequently observed (37 patients, 33%) (Table 3). Non-hematologic AE were almost exclusively of grade 1-2, with asthenia, nausea, and infusion-related reactions being the most frequently observed AE. Only 8 patients experienced grade ≥3 non-hematologic AE (Table 4).

A total of 45 serious adverse events (SAE) occurred involving 35 patients; 6 of them had a therapy-related SAE, 2 (fever of unknown 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 (AML) was reported during the follow up. This patient had discontinued the study treatment after five months due to a non-drug-related transient ischemic attack, while the diagnosis of AML, attributed to chlorambucil, occurred two 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 the patient's death, was also reported, and was defined by the treating investigator as paraneoplastic, and not related to the study treatment. Notably, in both patients with cerebellar ataxia, the presence of JC virus was actively searched for and ruled out.

Among SAE, in addition to the above-mentioned AML, 15 other malignancies were diagnosed during the study but considered not to be 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). Histologic transformation into large cell lymphoma was reported in 3 patients.

Eleven deaths were observed, but only one was related to study treatment (i.e., AML). Among non-drug related deaths, 2 patients died due to progressive disease, 2 after histologic transformation into DLBCL, 2 due to lung carcinoma, one for a progressive encephalopathy associated with the above-mentioned cerebellar ataxia, and one for SARS-CoV-2 infection. In 2 patients, the cause of death remained unknown.

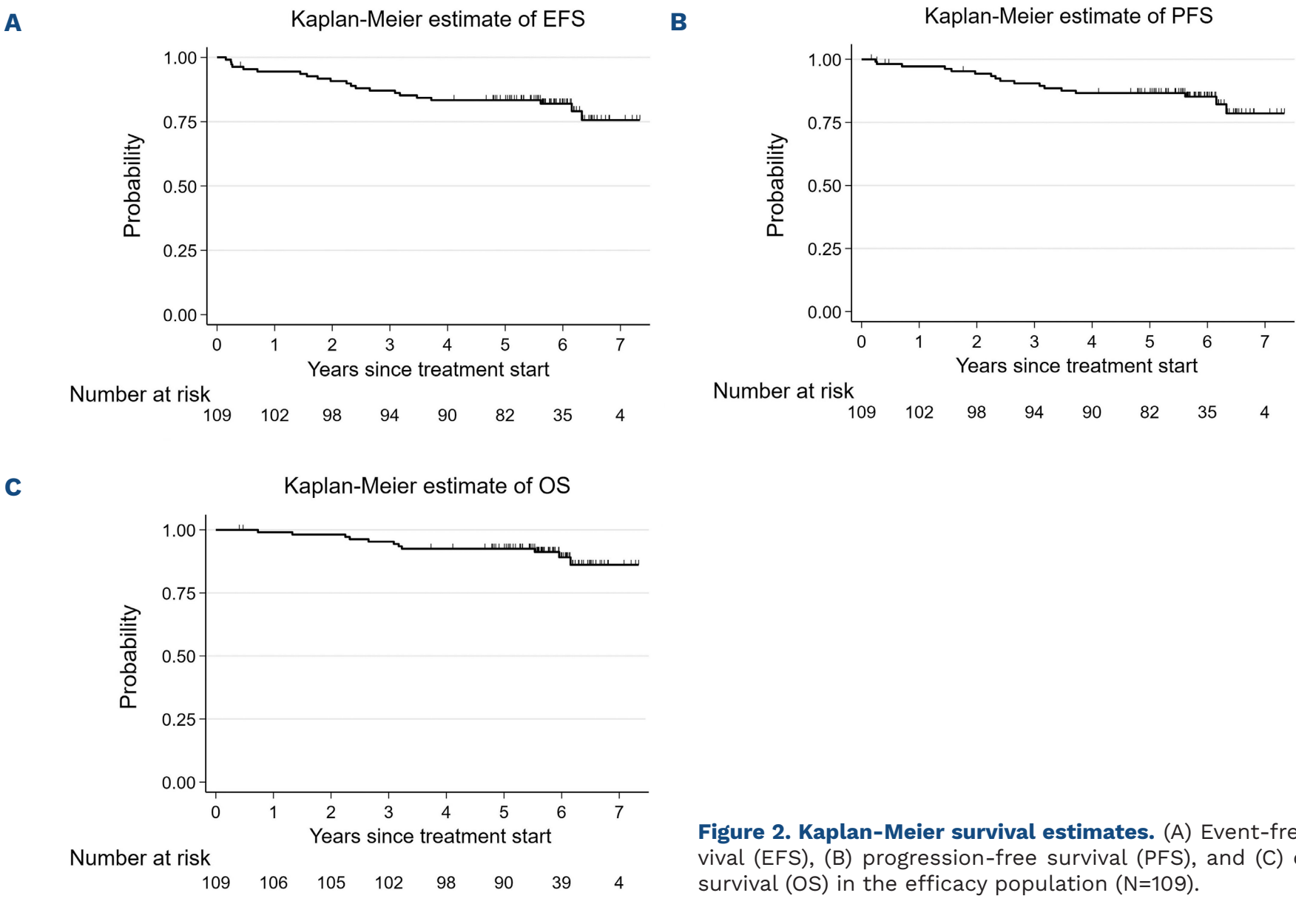

Figure 2. Kaplan-Meier survival estimates. (A) Event-free survival (EFS), (B) progression-free survival (PFS), and (C) overall survival (OS) in the efficacy population (N=109).

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 rates 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 lactate dehydrogenase (13% *vs*. 10%), elevated β-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 number of CR increased from 52% at six months to 70% at the end of maintenance. Maintenance might have also contributed to a reduction of the number 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 longer than that observed without maintenance in the prior study (79%; 95% CI: 71-85).[8] The need for 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 II 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

Table 3. Hematologic 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-hematologic 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
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)	-

Percentages may not total 100 due to rounding.

compared maintenance rituximab *versus* 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, so far published only as an 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 any difference in terms of PFS between the two arms, but the obinutuzumab arm had more AE.[27] A Korean group reported results of a phase II 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. Interestingly, considering the different rates of CR at the 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.

As also indicated by the MALT2008-01 study mentioned above,[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 (<10% of the patients in the IELSG38 discontinued treatment due to AE), toxicity may be increased by maintenance, particularly hematologic 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 is most likely related to the older median age of the patients.[29-31] Two patients developed cerebellar ataxia, with a different evaluation of causality. Notably,, despite being extremely rare, this paraneoplastic syndrome has been reported in patients with MZL.[32,33]

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

Disclosures

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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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Data-sharing statement

The dataset generated and analyzed during the current study is not publicly available due to legal restrictions. De-identified data sharing could be possible for scientific research on reasonable request addressed to the IELSG (ielgs@ior.usi.ch).

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