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

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DATA SUPPLEMENT

Figure S1. Study design

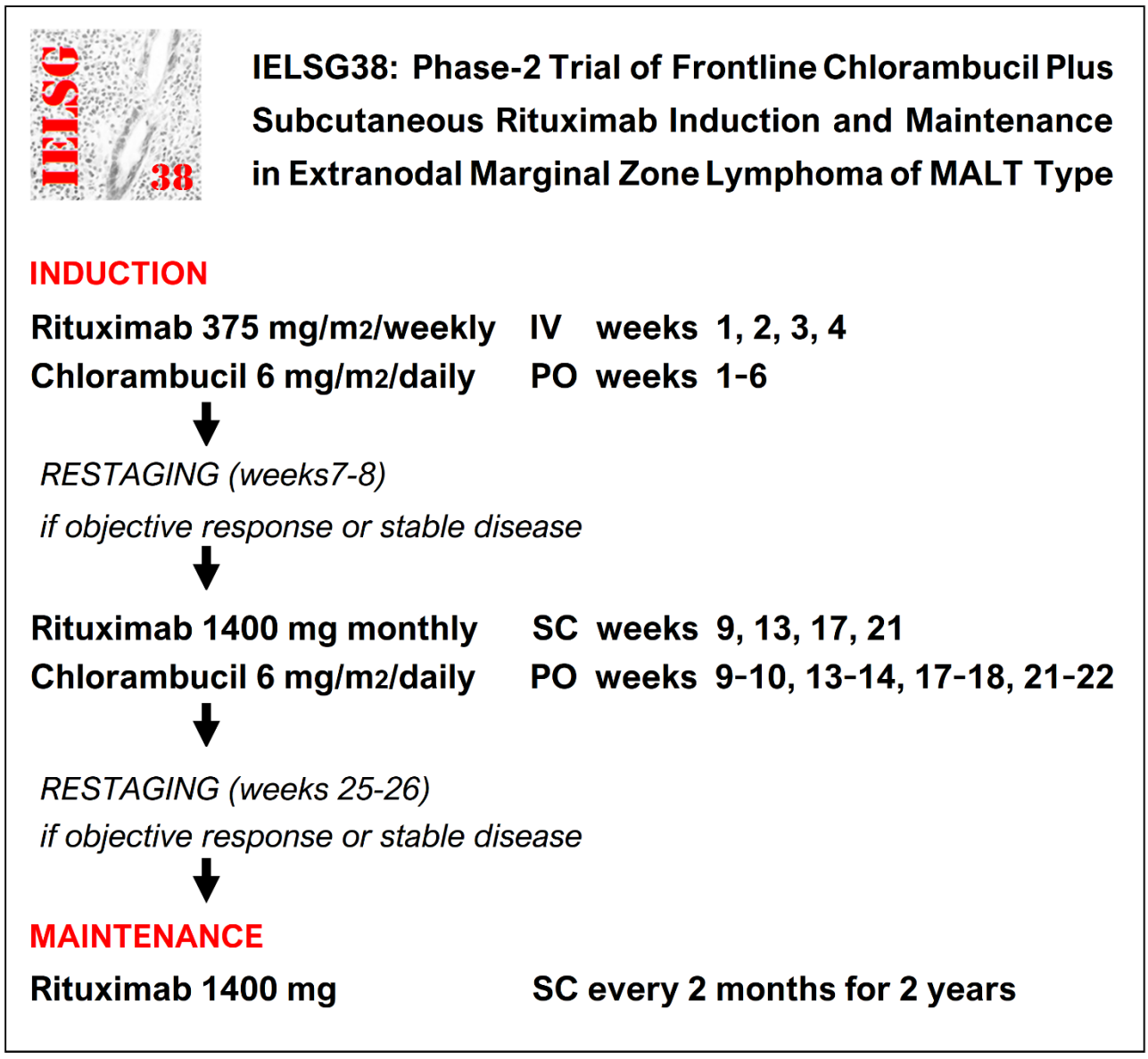

Table S1. Outcome analysis in the entire cohort of 112 enrolled patients

	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).