Long-term follow up of the FL2000 study comparing CHVP-interferon to CHVP-interferon plus rituximab in follicular lymphoma

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Supplemental data

Clinical investigators

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Supplemental Design and Methods

Patients

Briefly, patients were required to have Ann Arbor stage II, III or IV disease with at least one criterion of high tumor burden among the following: any nodal or extranodal tumor mass with a diameter greater than 7 cm, involvement of three nodal sites with a diameter greater than 3 cm, systemic symptoms, substantial splenic enlargement, any compression syndrome (ureteral, orbital, gastrointestinal) or serous effusion (irrespective of cell content), elevated serum levels of lactic dehydrogenase (LDH) (above upper normal limit) or β2-microglobulin (≥3mg/L) or performance status greater than 1 defined on the Eastern Cooperative Oncology Group (ECOG) scale.

Statistical analysis

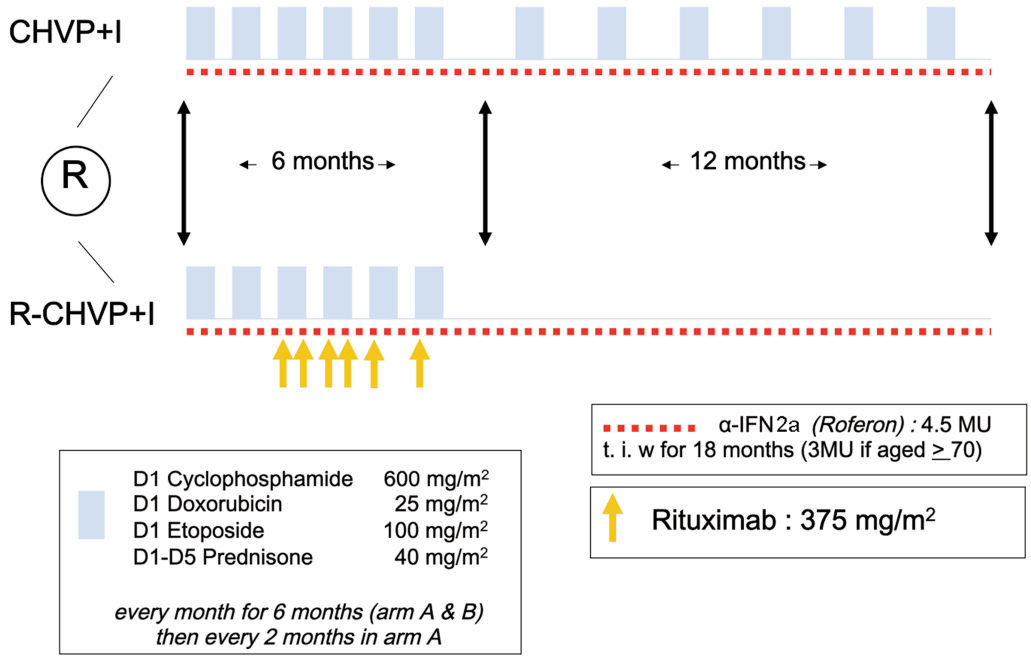
OS was calculated from the date of randomization until the date of death from any cause or the date of last contact. EFS was measured from the date of randomization to the date of death from any cause, relapse, progression, initiation of an alternate treatment or the date of last contact. Response duration (RD) was calculated for patients in complete, complete unconfirmed or partial response from evaluation performed at 18 months to the date of death from any cause, relapse, progression or the date of last contact.

Patients were randomly assigned in a 1:1 ratio to the control or the experimental arm of treatment and the trial was unmasked. Randomization was performed centrally by a data manager at a unique site for the GELA-GOELAMS (Saint Louis Hospital, Paris, France) with the use of a computer-assisted allocation sequence with a fax process without the intervention of investigators. Stratification for group (GOELAMS *vs.* GELA), country (France *vs.* Belgium) and center was performed. No stratification for FLIPI was made since the prognostic score was not published at time of study design. EFS was the primary end-point of the study and the sample size was calculated to detect a 3-year survival improvement of 20% in the experimental arm of treatment with a 90% power and at an overall 5% significance level.

Secondary end-points were OS, response rate and toxicity

The hazard rate was computed as the number of failures per time unit in the respective interval (3-year bandwidth), divided by the average number of surviving cases at the midpoint of the interval. A large enough bandwidth smoothing (i.e. 3-year) was chosen to minimize short time-period variability. Biweight kernel-smoothed estimator of h(t) was used for graphical representation. Of note, a 2-year bandwidth smoothing provided similar conclusion (*data not shown*).

All tests were two-sided and $P < 0.05$ was considered statistically significant. Statistical analyses were realized using SAS software (SAS Institute Inc, Cary, NC, USA) versions 9.0 and 9.2. Comprehensive Meta-Analysis v2 software was used for Forrest plot representation.



Online Supplementary Figure S1. Treatment flowchart.

Online Supplementary Table S1. 3-, 5-, and 8-year event-free survival, relapse-free survival and overall survival for the whole cohort and according to each arm of treatment.

	Event-Free Survival % (95% CI)				Relapse-Free Survival[§] % (95% CI)				Overall Survival % (95% CI)			
	3-yr	5-yr	8-yr	*P*	3-yr	5-yr	8-yr	*P*	3-yr	5-yr	8-yr	*P*
CHVP+I *N*=183	45 (38-52)	37 (30-44)	27 (21-34)		53 (44-61)	43 (34-52)	36 (27-55)		85 (79-89)	78 (71-83)	69 (62-75)	
				0.0004				0.010				0.076
R-CHVP+I *N*=175	67 (59-73)	51 (43-58)	44 (36-51)		64 (55-72)	58 (49-66)	48 (37-58)		92 (87-95)	85 (78-89)	78 (71-84)	
All patients	56 (51-61)	44 (38-49)	35 (30-40)	-	59 (52-64)	51 (45-57)	42 (35-49)	-	88 (85-91)	81 (77-85)	74 (69-78)	-

[§]For Relapse-Free Survival, 258 responders at 18 months out of 358 patients were considered.

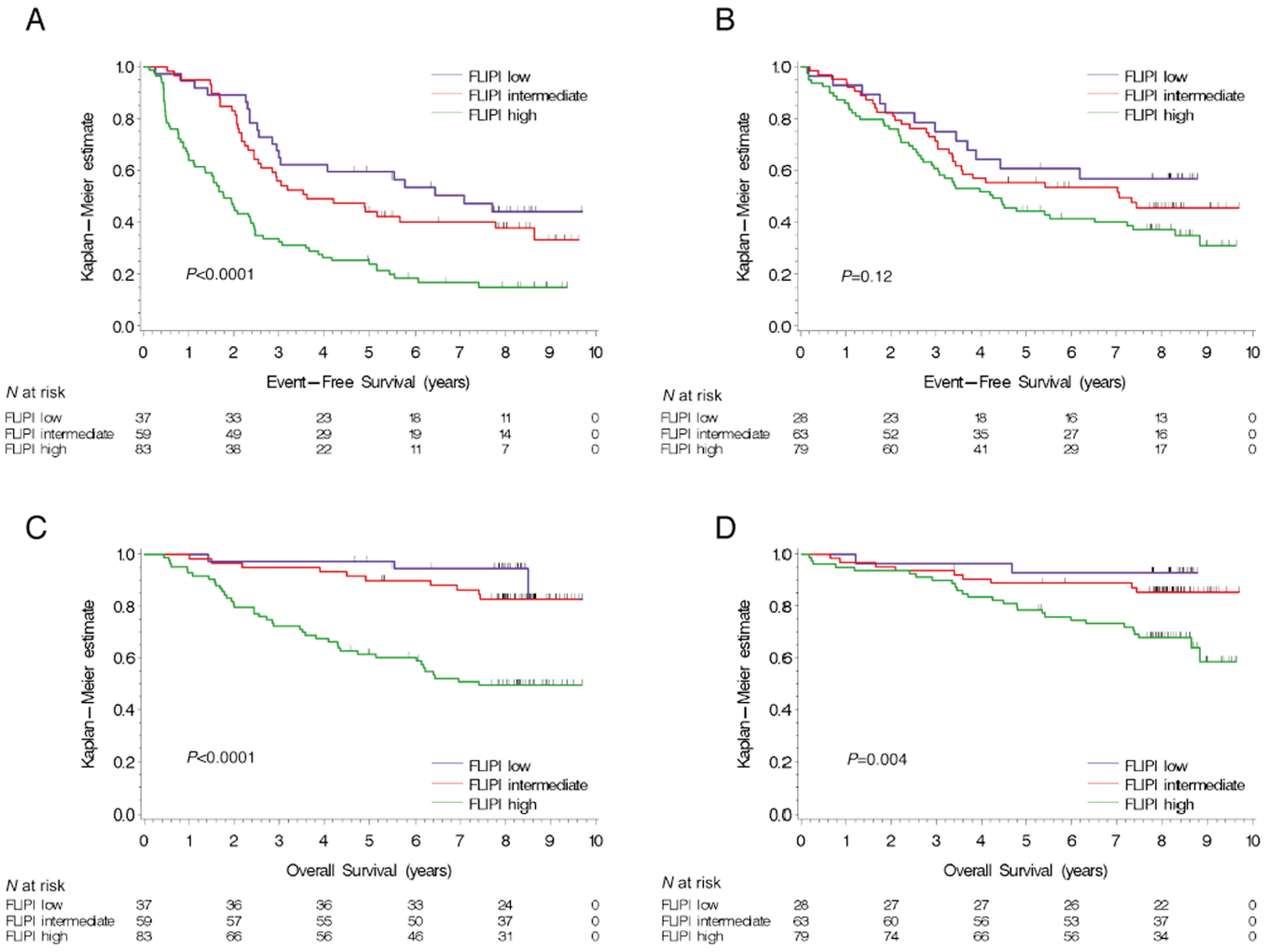
Abbreviations: CHVP, cyclophosphamide-adriamycin-vincristine-prednisone; I, alpha-interferon; R, rituximab; CI, confidence interval.

Online Supplementary Table S2. Univariate analysis of prognostic factors.

	Univariate analysis					
	EFS			OS		
	HR	95% CI	P^	HR	95% CI	P^
Age, yrs						
>60 (*v* <60)	0.984	0.758-1.277	0.900	2.511	1.603-3.933	**<0.0001**
Sex						
Male (*v* female)	1.165	0.898-1.510	0.250	1.213	0.808-1.820	0.351
ECOG						
>1 (*v* ≤1)	2.002	1.277-3.140	**0.002**	2.015	1.074-3.782	**0.029**
B symptoms						
Yes (*v* no)	1.494	1.118-1.996	**0.006**	1.326	0.852-2.064	0.210
Stage						
III-IV (*v* II)	1.973	1.203-3.237	**0.007**	1.668	0.772-3.603	0.193
Nodal sites involvement, n						
>4 (*v* ≤4)	1.873	1.440-2.436	**<0.0001**	1.889	1.249-2.855	**0.002**
Bone marrow involvement						
Yes (*v* no)	1.578	1.180-2.110	**0.002**	0.987	0.645-1.509	0.950
Extranodal sites involvement, n						
>1 (*v* ≤1)	1.592	1.223-2.073	**0.0005**	1.374	0.912-2.069	0.128
LDH						
>UNL (*v* ≤UNL)	1.515	1.160-1.978	**0.002**	2.266	1.508-3.406	**<0.0001**
Hemoglobin, g/dL						
<12 (*v* ≥12)	1.342	0.971-1.855	0.075	2.294	1.472-3.574	**0.0002**
ß2-microglobulin, mg/L						
>3 (*v* ≤3)	1.510	1.146-1.991	**0.003**	2.150	1.418-3.259	**0.0003**
FLIPI						
High (*v* low)	1.454	1.195-1.768	**0.0002**	2.570	1.631-4.049	**<0.0001**
High (*v* intermediate)	1.674	1.246-2.249	**0.0004**	3.235	1.944-5.383	**<0.0001**

^Bold font indicates statistical significance

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, Lactate Dehydrogenase; UNL, upper normal limit; FLIPI, Follicular Lymphoma International Prognostic Index; EFS, event-free survival; OS, overall survival; HR, hazard ratio.



Online Supplementary Figure S2. (A) Kaplan-Meier estimates of event-free survival (EFS) according to FLIPI category in the CHVP+I arm of treatment. (B) EFS according to FLIPI in the R-CHVP+I arm of treatment. (C) Overall survival (OS) according to FLIPI in the CHVP+I arm of treatment. (D) OS according to FLIPI in the R-CHVP+I arm of treatment. FLIPI, Follicular Lymphoma International Prognostic Index; CHVP, cyclophosphamide-adriamycin-vincristine-prednisone; I, alpha-interferon; R, rituximab.

Online Supplementary Table S3. Multivariate analysis of baseline characteristics using FLIPI factors (if significantly associated with outcome in univariate analysis) instead of FLIPI composite score.

Multivariate analysis (using FLIPI factors instead of FLIPI composite score)						
	EFS			OS		
	HR	95% CI	P^{∞}	HR	95% CI	P^{∞}
Age, yrs						
>60 (*v* <60)	-	-	-	2.726	1.700-4.371	**<0.0001**
ECOG						
>1 (*v* ≤1)	1.577	0.975-2.552	0.063	1.031	0.517-2.054	0.930
B symptoms						
Yes (*v* no)	1.344	0.979-1.845	0.067	-	-	-
Stage						
III-IV (*v* II)	1.270	0.672-2.399	0.461	-	-	-
Nodal sites involvement, n						
>4 (*v* ≤4)	1.440	1.066-1.944	**0.017**	1.742	1.091-2.781	**0.020**
Bone marrow involvement						
Yes (*v* no)	1.304	0.906-1.875	0.153	-	-	-
Extranodal sites involvement, n						
>1 (*v* ≤1)	1.312	0.968-1.780	0.080	-	-	-
LDH						
>UNL (*v* ≤UNL)	1.519	1.138-2.026	**0.004**	2.151	1.392-3.325	**0.0006**
Hemoglobin, g/dL						
<12 (*v* ≥12)	-	-	-	1.793	1.100-2.924	**0.019**
ß2-microglobulin, mg/L						
>3 (*v* ≤3)	1.143	0.850-1.537	0.375	1.425	0.899-2.256	0.131

$^{\infty}$Bold font indicates statistical significance.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, Lactate Dehydrogenase; UNL, upper normal limit; FLIPI, Follicular Lymphoma International Prognostic Index; CHVP, cyclophosphamide-adriamycin-vincristine-prednisone; I, alpha-interferon; R, rituximab.