

Prognostic factors identified three risk groups in the LRF CLL4 trial, independent of treatment allocation

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Online Supplementary Table S1. Progression-free survival and overall survival for prognostic factors (excluding biomarkers and beta 2 microglobulin).

	N. of patients	Overall Survival (OS)			Progression-Free survival (PFS)		
		Death	O/E	P value*	Progression/Death	O/E	P value*
Sex							
Male	573	302	1.07	0.02	501	1.05	0.03
Female	204	86	0.80		169	0.87	
Age (years)							
<60	255	88	0.58	<0.00005	217	0.95	0.3
60-69	288	143	0.99		251	1.01	
≥70	234	157	1.69		202	1.05	
Binet stage							
A-progressive	191	84	0.82	0.0002	165	0.98	0.3
B	352	167	0.90		305	0.96	
C	234	137	1.35		200	1.09	
Treatment allocation							
Chlorambucil	387	188	0.96	0.7	349	1.25	<0.00005
Fludarabine	194	98	1.03		174	1.12	
FC	196	102	1.05		147	0.63	
Hemoglobin (g/dL)							
<10.5	188	116	1.47	<0.00005	166	1.17	0.001
10.5-	196	97	1.00		174	1.11	
12.3-	197	92	0.92		166	0.92	
13.7-	196	83	0.74		164	0.86	
Absolute lymphocyte count (x10 ⁹ /L)							
<35	185	83	0.86	0.4	147	0.80	<0.00005
35-	196	113	1.18		170	0.99	
85-	187	87	0.89		164	1.01	
135-	183	94	1.09		167	1.28	
Platelet count (x10 ⁹ /L)							
<100	147	83	1.29	0.9	126	1.11	0.5
100-	234	100	0.79		203	0.97	
150-	198	98	0.98		172	0.97	
200-	198	107	1.10		169	1.00	
Lactate dehydrogenase (U/L)							
<300	163	85	1.01	0.06	140	0.93	0.008
300-	162	67	0.78		129	0.85	
400-	158	73	0.94		136	1.01	
500-	217	126	1.22		196	1.19	

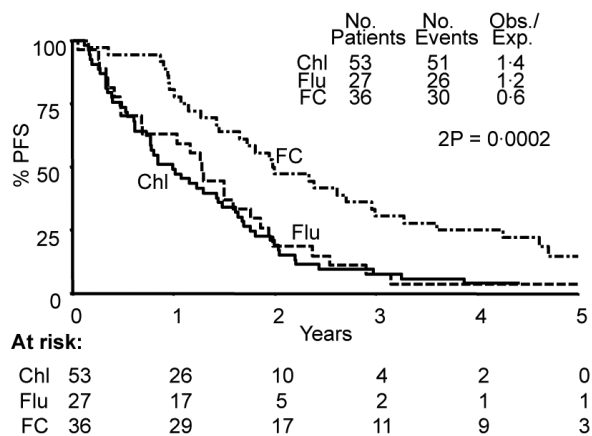
*P value for trend, except for treatment allocation (heterogeneity). FC: fludarabine+cyclophosphamide.

Online Supplementary Table S2. Progression-free survival, overall survival and response for biomarkers and beta-2 microglobulin.

	Overall survival (OS)			Progression-Free survival (PFS)			N. of patients with response data	Response		Good response (CR/NPR)	P value*	
	N. of patients	Death	O/E	P value*	Progression/Death	O/E		P value*	Any response (CR/NPR/PR)			
Beta-2 microglobulin (mg/L)												
<3	168	55	0.57	<0.00005	135	0.82	0.0001	159	140 (88%)	<0.0001	77 (48%)	0.01
3-	142	67	0.94		117	0.89		135	109 (81%)		52 (39%)	
4-	94	55	1.44		86	1.26		87	63 (72%)		33 (38%)	
5-	153	94	1.46		139	1.24		143	101 (71%)		48 (34%)	
FISH (Dohner hierarchical model)												
TP53 del (10%)	33	30	5.11	<0.00005	33	4.39	<0.00005	31	9 (29%)	<0.0001	2 (6%)	0.0007
11q- (5%)	112	66	1.35		103	1.45		104	75 (72%)		30 (29%)	
tris12 (3%)	69	38	1.18		59	1.00		65	52 (80%)		30 (46%)	
6q- (5%)	20	15	1.54		18	0.92		20	17 (85%)		9 (45%)	
normal	83	49	0.96		76	0.92		79	69 (87%)		36 (46%)	
13q- (5%)	224	84	0.62		184	0.79		210	177 (84%)		89 (42%)	
IGHV mutation												
<97%	160	45	0.50	<0.00005	113	0.63	<0.00005	146	126 (86%)	0.0008	69 (47%)	0.02
97%	46	22	0.89		41	0.98		45	36 (80%)		19 (42%)	
98-99%	95	65	1.47		88	1.15		88	75 (85%)		33 (38%)	
100%	232	133	1.25		215	1.34		222	158 (71%)		78 (35%)	
IGHV3-21 use												
IGHV mutated, no V3-21	187	59	0.56	<0.00005	139	0.68	<0.00005	173	146 (84%)	0.03	84 (49%)	0.01
IGHV3-21	40	24	1.33		34	1.15		39	33 (85%)		14 (36%)	
IGHV unmutated, no V3-21	306	182	1.29		284	1.28		289	216 (75%)		101 (35%)	
CD38 expression												
≤7%	201	68	0.60	<0.00005	155	0.75	<0.00005	188	154 (82%)	0.07	77 (41%)	0.4
8-20%	72	43	1.42		65	1.37		68	50 (74%)		25 (37%)	
20-30%	32	18	1.09		28	1.01		31	26 (84%)		12 (39%)	
>30%	230	134	1.30		210	1.20		219	161 (74%)		80 (37%)	
ZAP-70												
≤10%	242	106	0.88	0.07	193	0.83	<0.00005	220	187 (85%)	0.008	98 (45%)	0.09
>10%	236	127	1.12		214	1.24		227	170 (75%)		83 (37%)	

*P values for trend, except for 13q groupings and IGHV3-21 use. O/E: observed/expected; CR: complete response; NPR: nodular partial response; PR: partial response.

Online Supplementary Figure S1. Progression-free survival by randomized treatment arm in patients with >5% 11q loss.



Chl: chlorambucil; Flu: fludarabine; FC: fludarabine+cyclophosphamide.

Online Supplementary Table S3. Associations with IGHV mutational status and other prognostic factors.

Variable	N. of patients	IGHV mutated	IGHV unmutated	P value
Sex				
Male	394	139 (35%)	255 (65%)	0.007
Female	139	67 (48%)	72 (52%)	
Age (years)				
<60	164	71 (43%)	93 (57%)	0.3 *
60-69	207	73 (35%)	134 (65%)	
≥70	162	62 (38%)	100 (62%)	
Binet Stage				
A-progressive	132	56 (42%)	76 (58%)	0.6 *
B	238	78 (33%)	160 (67%)	
C	163	72 (44%)	91 (56%)	
Treatment Allocation				
Chlorambucil	260	102 (39%)	158 (61%)	0.5
Fludarabine	130	54 (42%)	76 (58%)	
Fludarabine+cyclophosphamide	143	50 (35%)	93 (65%)	
FISH (Dohner's hierarchical model)				
TP53 del (10%)	29	7 (24%)	22 (76%)	<0.0001 *
11q- (5%)	106	23 (22%)	83 (78%)	
tris12 (3%)	61	14 (23%)	47 (77%)	
6q- (5%)	14	2 (14%)	12 (86%)	
normal	69	21 (30%)	48 (70%)	
13q- (5%)	177	107 (60%)	70 (40%)	
TP53 deletion				
≤10%	458	179 (39%)	279 (61%)	0.1
>10%	29	7 (24%)	22 (76%)	
11q-				
≤5%	380	161 (42%)	219 (58%)	0.0002
>5%	110	25 (23%)	85 (77%)	
tris12				
≤3%	411	169 (41%)	242 (59%)	0.001
>3%	79	17 (22%)	62 (78%)	
6q-				
≤5%	303	116 (38%)	187 (62%)	0.1
>5%	26	6 (23%)	20 (77%)	
13q-				
≤5%	208	50 (24%)	158 (76%)	<0.0001
>5%	282	136 (48%)	146 (52%)	
CD38				
≤7%	161	104 (65%)	57 (35%)	<0.0001
>7%	286	72 (25%)	214 (75%)	
ZAP-70				
≤10%	232	144 (62%)	88 (38%)	<0.0001
>10%	232	34 (15%)	198 (85%)	

*P value for trend.

Online Supplementary Table S4. Progression-free survival (PFS), overall survival (OS) and response by risk group, within treatment arm.

	Good	Risk Group Intermediate	Poor	P value*
Fludarabine+cyclophosphamide				
Any response, n (%)	25 (100%)	94 (97%)	2 (25%)	<0.0001
5-year PFS (95% CI)	56% (37%-76%)	26% (17%-34%)	0%	<0.00005
5-year OS (95% CI)	83% (68%-98%)	47% (37%-57%)	0%	<0.00005
Fludarabine				
Any response, n (%)	22 (88%)	62 (74%)	3 (38%)	0.009
5-year PFS (95% CI)	33% (15%-51%)	13% (6%-20%)	0%	<0.00005
5-year OS (95% CI)	70% (53%-87%)	50% (39%-61%)	0%	<0.00005
Chlorambucil				
Any response, n (%)	42 (81%)	127 (72%)	4 (27%)	0.001
5-year PFS (95% CI)	25% (14%-36%)	6% (2%-10%)	0%	<0.00005
5-year OS (95% CI)	81% (71%-91%)	58% (51%-65%)	20% (0%-40%)	<0.00005

*P values for trend.