THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Hillmen P, Robak T, Janssens A, et al, for the COMPLEMENT 1 Study Investigators. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. *Lancet* 2015; published online April 14. http://dx.doi.org/10.1016/S0140-6736(15)60027-7.

Supplementary Appendix

Sample Size Assumption
Data reported before initiation of the study indicated a median PFS for chlorambucil monotherapy with the 10 mg/m^2 day 1-7 regimen of approximately 20 months, albeit in a patient population not restricted to the unfit[1]. The assumption was that in the COMPLEMENT1 trial with a less fit population, the chlorambucil monotherapy group would achieve a lower mPFS of 18 months.

Study Centres and Patients
109 centres in 16 countries: Europe: Belgium (5 centres), Czech Republic (3), Germany (11), Greece (3), Ireland (6), Italy (12), Netherlands (2), Poland (6), Spain (6), Sweden (3), Russia (5), and UK (19); North America: Canada (1), United States (18); Rest of World: Brazil (3) and India (6).

Table S1: Baseline Prognostic Factors by Binet Stage

	Binet A			Binet B			Binet C		
	Chl	O+Chl	TOTAL	Chl	O+Chl	TOTAL	Chl	O+Chl	TOTAL
	N=70	N=77	N=147	N=87	N=74	N=161	N=69	N=70	N=139
β2m >3500 μg/L	n=69	n=75	n=144	n=83	n=73	n=156	n=65	n=66	n=131
	45 (65%)	40 (53%)	85 (59%)	65 (78%)	55 (75%)	120(77%)	59 (91%)	58 (88%)	117(89%)
IgV_H unmutated	n=64	n=72	n=136	n=76	n=68	n=144	n=63	n=61	n=124
	33 (52%)	43 (60%)	76 (56%)	46 (61%)	44 (65%)	90 (63%)	34 (54%)	27 (44%)	61 (49%)
Chromosomal Aberration	n=67	n=74	n=141	n= 82	n= 73	n=155	n=67	n=63	n=130
17p-	2 (3%)	4 (5%)	6 (4%)	9 (11%)	3 (4%)	12 (8%)	6 (9%)	3 (5%)	9 (7%)
11q-*	9 (12%)	15 (20%)	24 (17%)	11 (13%)	15 (21%)	26 (17%)	4 (7%)	9 (14%)	13 (10%)
+12q, 13q-, or 6q-†	40 (52%)	40 (54%)	80 (57%)	33 (40%)	36 (49%)	69 (45%)	38 (67%)	43 (68%)	81 (62%)
ZAP70	n=63	n=73	n=136	n=83	n=71	n=154	n=67	n=64	n=131
B-cell positive	28 (44%)	33 (45%)	61 (45%)	49 (59%)	40 (56%)	89 (58%)	33 (49%)	27 (42%)	60 (46%)
B:Tcell ratio positive	36 (57%)	43 (59%)	79 (58%)	53 (64%)	48 (68%)	101(66%)	46 (69%)	46 (72%)	92 (70%)

* Absence of 17p-. †Absence of 17p- or 11q-.

PFS Subgroup Analysis
The 17p- subgroup had the shortest mPFS with Chl (3·7 months) that improved to 9·3 months with O+Chl, but due to the small number of patients (N=27), the confidence interval included the value '1' (Figure 3). Patients with Binet stage A showed a higher gain in PFS with O+Chl (HR 0·37 [95% CI 0·24, 0·57]) compared to patients with Binet stage B and C as a result of higher performing O+Chl group but similar mPFS in the Chl group. Overall, Patients with Binet stage B or C showed a higher number of risk factors compared to patients with Binet stage A (Table S1). In addition, patients in the O+Chl groups with Binet B and Binet C had a lower percentage of 17p deletion compared to their respective control group.

Sensitivity and Secondary Time to Event Analysis
Investigator-assessed mPFS was 1 month longer for O+Chl (23.4 months [95% CI: 21.0, 26.0]) and 1.7 months longer for Chl (14.8 months [95% CI: 13.6, 16.8]) compared to the IRC- assessed mPFS, with a similar hazard ratio to the IRC results (HR 0.58 [95% CI 0.46, 0.73]; p<0.001). PFS assessment by IRC, where palpated measurements of lymph nodes and organs were replaced with CT scan measurements resulted in slightly longer mPFS similar to the investigator-assessed mPFS (O+Chl: 23.4 months, Chl: 14.5 months; HR 0.54 [95% CI 0.41,0.69], p<0.001). Discrepancy between investigator- and a centralised IRC-assessed PFS was not unexpected and has been observed previously[2].

EFS is defined by considering alternate CLL therapy prior to progression as an event in addition to PD and death. Median EFS, as per IRC assessment was 0·5 month shorter than mPFS in the O+Chl group (21·9 months [95% CI: 17·7, 23·8] and 2·4 months shorter than mPFS in the Chl group (10·7 months [95% CI: 8·9, 12·8]). The treatment comparison for EFS was significant (HR 0.52 [95% CI 0·42, 0·65]; p<0·001; Table S2; Figure S1). Having mEFS and mPFS of similar duration in the O+Chl group, but mEFS shorter than mPFS in the Chl group suggests that alternative treatment was initiated prior to documented progression for a higher proportion of patients in the Chl group. While the open-label nature of the study may have partially contributed to this

effect, this also demonstrates that in the absence of true progression, lack of response requiring initiation of alternative therapy is important in the clinical setting. EFS should therefore be considered as a meaningful secondary endpoint.

Table S2: Secondary Time to Event Analysis

Primary and Secondary Efficacy Endpoint	Chl (N=226)	O+Chl (N=221)
PFS, IRC-Assessed, median (95% CI), months	13·1 (10·6, 13·8)	22·4 (19·0, 25·2)
HR (95% CI), stratified, log-rank p-value	0·57 (0·45, 0·72), <0·001	
PFS, Investigator-Assessed, median (95% CI), months	14·8 (13·6, 16·8)	23·4 (21·0, 26·0)
HR (95% CI), stratified, log-rank p-value	0.58 (0.46, 0.73), <0·001	
EFS, IRC-assessed, median PFS (95% CI), months	10·7 (8·9, 12·8)	21·9 (17·7, 23·8)
HR (95% CI), stratified, log-rank p-value	0·52 (0·42, 0·65), <0·001	
Time to Progression, median (95% CI), months	13·6 (11·2, 14·6)	23·1 (21·2, 25·8)
HR (95% CI), stratified, log-rank p-value	0·54 (0·42, 0·69), <0·001	
Time to Next Therapy, median (95% CI), months	24·7 (22·6,29·1)	39·8 (34·7,48·8)
HR (95% CI), stratified, log-rank p-value	0·49 (0·36, 0·67), <0·001	
Time to Response*	N=154	N=182
median (95% CI) , months	1·9 (1·2, 1·9)	1·2 (1·0, 1·9)
HR (95% CI), stratified, log-rank p-value	0.85 (0.68, 1.06), 0.084	
Duration of Response*	N=154	N=182
median (95% CI) , months	13·2 (10·8, 16·4)	22·1 (19·1, 24·6)
HR (95% CI), stratified, log-rank p-value	0·56 (0·43, 0·74), <0·001	

*Responders (CR, CRi, nPR, PR) only; CI=confidence interval CR=complete response, EFS=event-free survival, HR=hazard ratio, IRC= Independent Review Committee; n/a = not available; Confidence intervals were obtained using the Brookmeyer-Crowley method. Hazard ratios (HRs) were obtained using the Pike estimator.

Figure S1: IRC-Assessed Event-Free Survival

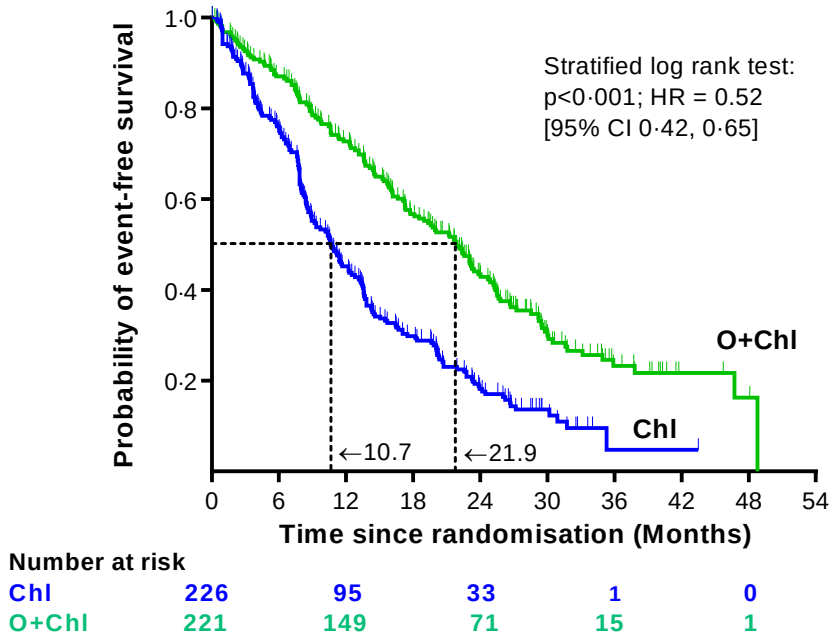
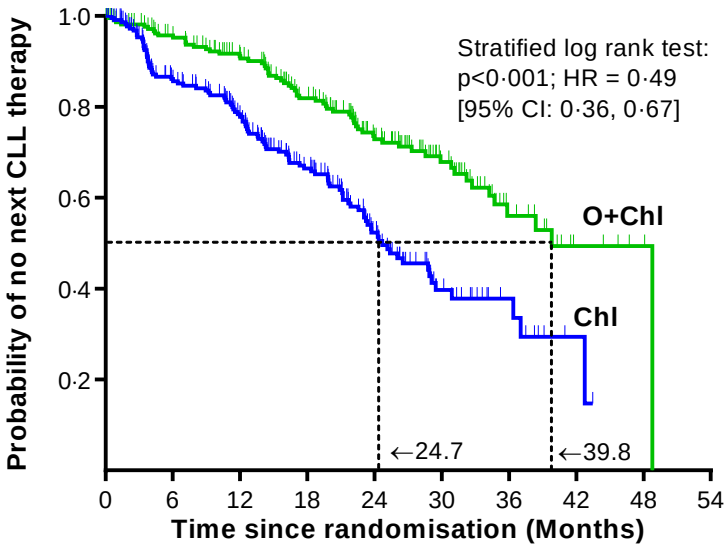


Figure S2: Time to Next Therapy



Number at risk

Chl	226	145	59	9	0
O+Chl	221	171	95	20	2

Secondary Overall Response Analysis

Overall response as assessed by the investigator was similar for O+Chl but higher for Chl compared to the IRC-assessed response (O+Chl: 88% [195/221, 95% CI: 83·2, 92·2]; Chl: 81% [182/226, 95% CI: 74·8, 85.5]). Investigator-assessed CR rate was higher, specifically in the Chl group compared to the IRC-assessed CRs rate, but the CR rate was similar for the O+Chl group (O+Chl: 49% [108/221]; Chl: 21% [48/226]). Over both treatment groups, n=114 patients were considered to have a CR by the investigator but not by the IRC. The discrepancy between the CR assessments of the investigator compared with the IRC was predominantly due to incomplete or missing bone marrow samples (O+Chl n=29; Chl n=10), preventing the IRC from confirming a CR. Furthermore, investigators assigned a response of CR despite a bone marrow invasion of >30% (O+Chl n=29; Chl n=25) or presence of nodules (O+Chl n=8; Chl n=4). Although there was an 85% concordance between investigator and IRC overall response rate, assignment of CR was much lower for the IRC. Again, IRC versus investigator response assessment discordance for has been reported previously[3]. With 9% of bone marrow samples unavailable for the IRC to confirm an investigator-assigned CR, the real CR rate is likely to lie somewhere in between the IRC- and the investigator-assigned rates.

Table S3: Response to Treatment in Prognostic Subgroups

	Chl		O+Chl	
	ORR N (%)	**CR N (%)**	**ORR N (%)**	**CR N (%)**
All Patients [95% CI]	**155 (69)** [62.1, 74.6]	**3 (1)**	**182 (82)** [76.7, 87.1]	**32 (14)**
Male (n=282)	95 (68)	1 (<1)	112 (79)	13 (9)
Female (n=165)	60 (70)	2 (2)	70 (89)	19 (24)
Age 45-55 (n=46)	20 (77)	0	18 (90)	5 (25)
Age 56-65 (n=91)	25 (63)	1 (3)	44 (86)	9 (18)
Age <65 (n= 140)	51 (72)	1 (1)	62 (90)	15 (22)
Age ≥65 (n=307)	104 (67)	2 (1)	120 (79)	17 (11)
Age <70 (n=226)	76 (70)	2 (2)	100 (85)	18 (15)
Age ≥70 (n=221)	79 (68)	1 (<1)	82 (79)	14 (13)
Age <75 (n=328)	109 (67)	2 (1)	137 (83)	27 (16)
Age ≥75 (n=119)	46 (73)	1 (2)	45 (80)	5 (9)
Binet – A (n=147)	56 (80)	0	72 (94)	18 (23)
Binet – B (n=161)	61 (70)	3 (3)	62 (84)	7 (9)
Binet – C (n=139)	38 (55)	0	48 (69)	7 (10)
Comorbidities – 0 or 1 (n=126)	42 (63)	1 (1)	53 (90)	11 (179)
Comorbidities – 2 or more (n=321)	113 (71)	2 (1)	129 (80)	21 (13)
β2m ≤3500 µg/L (n=109)	37 (77)	1 (2)	56 (92)	16 (26)
β2m >3500 µg/L (n=322)	114 (67)	2 (1)	122 (80)	16 (10)
IGHV mutated (n=177)	71 (79)	1 (1)	76 (87)	15 (17)
IGHV unmutated (n=227)	67 (59)	2 (2)	91 (80)	15 (13)
17p del (n=27)	1 (6)	0	6 (60)	1 (10)
11q del (n=63)	14 (58)	0	34 (87)	5 (13)
17p del or 11q del (n=90)	15 (37)	0	40 (82)	6 (12)
13q del or +12 or 6q del (n=230)	84 (76)	2 (2)	99 (83)	19 (16)
No aberration (n=105)	50 (78)	1 (2)	35 (85)	7 (17)
B-cell ZAP70 positive (n=210)	72 (65)	1 (<1)	83 (83)	11 (11)
B-cell ZAP70 negative (n=211)	75 (73)	2 (2)	92 (85)	21 (19)
B:T-cell ZAP70 ratio positive (n=272)	86 (64)	1 (<1)	115 (84)	20 (15)
B:T -cell ZAP70 ratio negative (n=149)	61 (78)	2 (3)	60 (85)	12 (17)
B-cell ZAP70 & B:T ZAP70 ratio positive (n=161)	49 (61)	0	67 (83)	9 (11)
B-cell ZAP70 or B:T ZAP70 ratio positive (intermediate) (n=160)	60 (71)	2 (2)	64 (85)	13 (17)
B-cell ZAP70 & B:T ZAP70 ratio negative (n=100)	38 (79)	1 (2)	44 (85)	10 (19)

CR=complete response (includes CR and CRi). ORR=overall response rate (includes CR, CRi, PR, nPR). NE=not evaluable.

References

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3 Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. *J Clin Oncol* 2009; **27:** 4378–84.