Systematic review of purine analog treatment for chronic lymphocytic leukemia: lessons for future trials

CLL Trialists' Collaborative Group (CLLTCG)*

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Statistical methods

Risk ratios (RR) were calculated for responses and pooled using Mantel-Haenszel methods. The I^2 statistic[1] was calculated to indicate the degree of heterogeneity between trials. PFS and survival were analyzed as time-to-event and observed minus expected (o-e) number of events, and its variance (v) were calculated; these o-e values were then added over all trials to produce a total (T), with variance (V) equal to the sum of the separate variances. These were used to calculate an overall odds ratio (OR), or ratio of event rates, and its 95% confidence interval (CI) equal to $\exp(T/V \pm 1.96/\sqrt{V})$. Results are presented as forest plots with a square representing the point estimate of the OR and a horizontal line showing the 99% confidence interval for each trial. The size of the square is proportional to the amount of information available, with larger squares representing trials or subgroups with a larger number of events. Overall estimates are shown by a diamond with the width representing the 95% confidence interval. All *P* values given are two-sided. Heterogeneity between the effects in different trials or subgroups was tested with $\mathbf{X}^2_{n-1}$ equal to $S\text{-}T^2/V$, where S is the sum of $(o\text{-}e)^2/v$ from each of n trials or n subgroups[2]. Reasons for heterogeneity were explored by examining differences between trial protocols and response recording.

T and V obtained by summing o-e and v from log rank analyses restricted to each one year time period were used to estimate the log OR, b, for each year. The estimated overall event rate in each time period, r, equals the number of events divided by the number of person years, and the probability of surviving event free during that year is exp(-r). Descriptive survival curves were drawn from the separate probability estimates $p+0.5p(p-1)b$ for one treatment group, and $p-0.5p(p-1)b$ for the other treatment group[2].

Results

Online Supplementary Table S2 describes methods of randomization, definitions of response and progression used. Most trials issued the treatment allocation from a central office by phone or fax. One trial used envelopes in the treating centers and in two cases the location is unknown. No trials used blinding.

There was variability in the rules applied for response assessment (*Online Supplementary Table S5*). The proportion of patients excluded from response analyses in the IPD trials with unknown or unassessable response varied from 0 in CLB 9011 to 22% in the CLL 101 trial. There were clearly differences between trials in the definition of whether a patient was eligible for response assessment. For example, of those with response not recorded, the proportion who died within six months varied between trials from 0 in PALG CLL1 to 57% in CLL 101.

The median timing of response assessments matched the protocol timings varying from two months (EORTC 06916) to seven months (FRE-CLL-90, LRF CLL4). The ranges indicated that some trials were more restrictive than others, presumably with responses recorded outside a narrow time range excluded. One trial (PALG CLL1) did not record the date of response.

Adverse effect data were obtained from reports. It was only possible to combine results for hemolytic anemia, infections and neutropenia (*Online Supplementary Table S6*).

a) Single agent PA versus *alkylating agent based treatment*

Infections and neutropenia were increased with fludarabine. Reported effects on the rate of hemolytic anemia varied between trials (P=0.09; I^2=50%), but the overall estimate was a possible increase (RR=1.35; 95% CI=0.91-2.02).

b) Addition of cyclophosphamide to PA

There was no evidence of an increase in hemolytic anemia or infections, but a likely increase in neutropenia (RR=1.29; 95% CI=1.13-1.47; P=0.0002), although the size of the effect varied between trials (I^2=57%; P=0.1).

c) PA plus cyclophosphamide versus *alkylating agent based*

Only LRF CLL4 reported adverse effects, with neutropenia increased (P<0.0001) but hemolytic anemia reduced (P=0.005) with FC.

d) Addition of chlorambucil to PA

No data were available.

e) Addition of epirubicin to PA

No data were available.

f) Addition of mitozantrone to PA

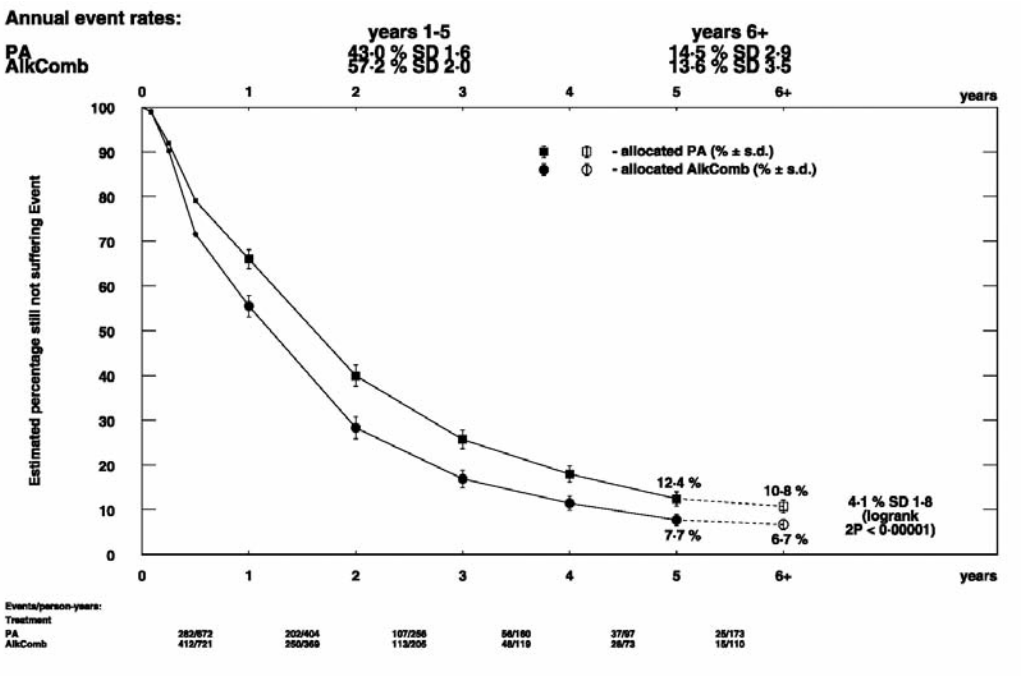
There was no significant increase in reported infections or neutropenia.

g) Cladribine versus *fludarabine*

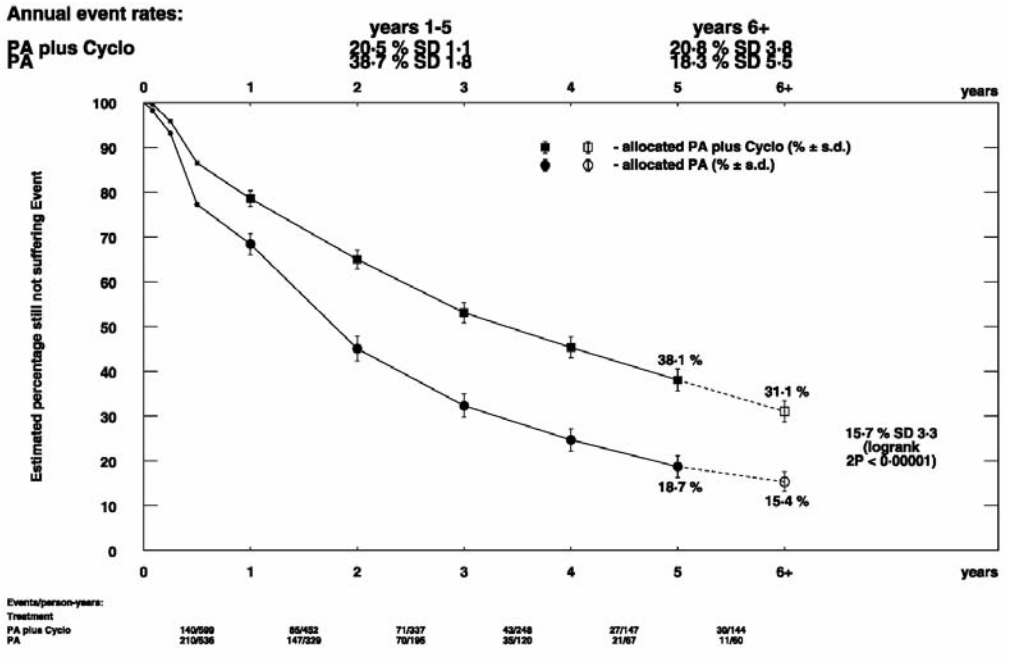
There were no significant differences in hemolytic anemia, infections or neutropenia, although there were differences between the trials in the relative risk of neutropenia (I^2=76; P=0.04).

References

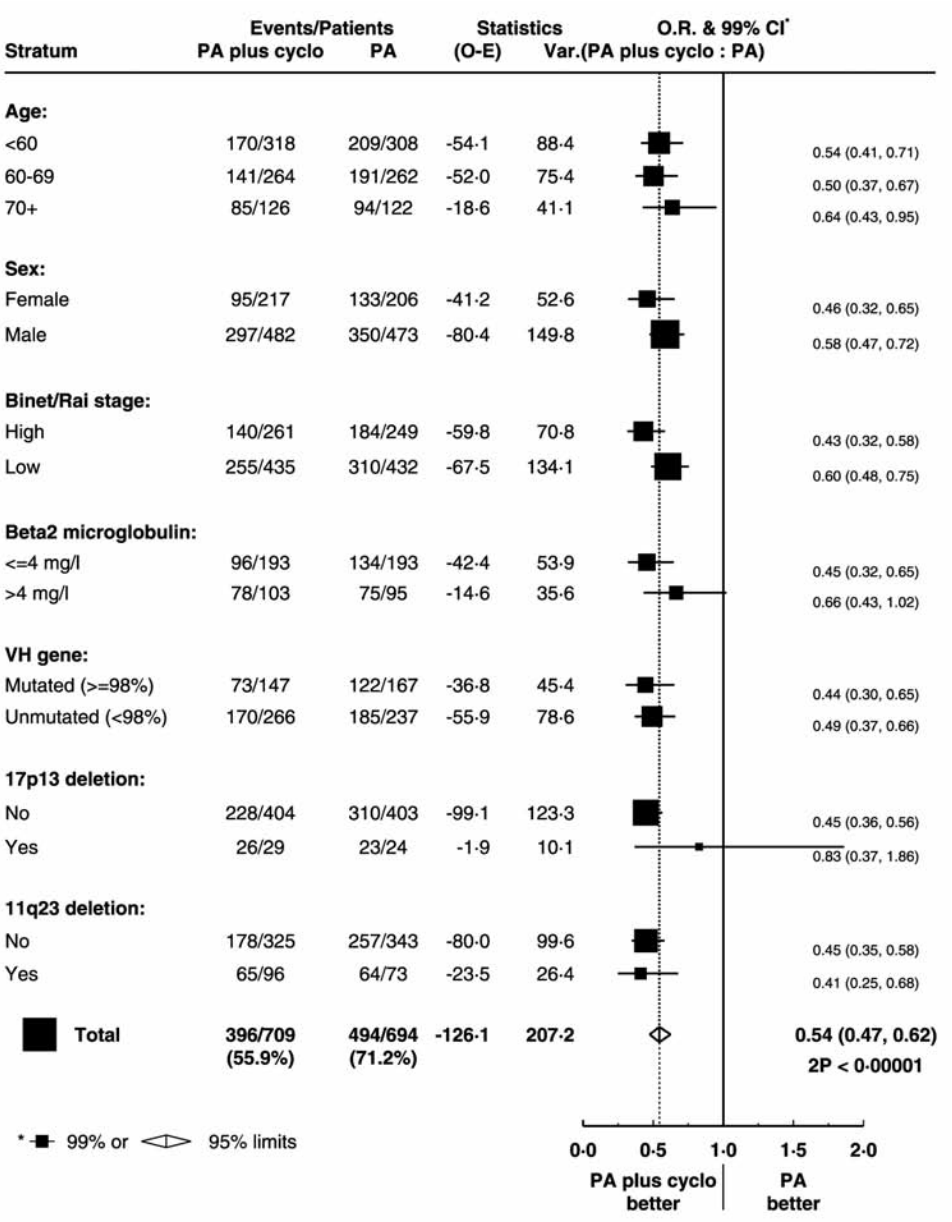
1. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-60.
2. Early Breast Cancer Trialists' Collaborative Group. Treatment of Early Breast Cancer. Volume 1: Worldwide Evidence 1985-1990. Oxford, Oxford University Press, 1990;1-207.



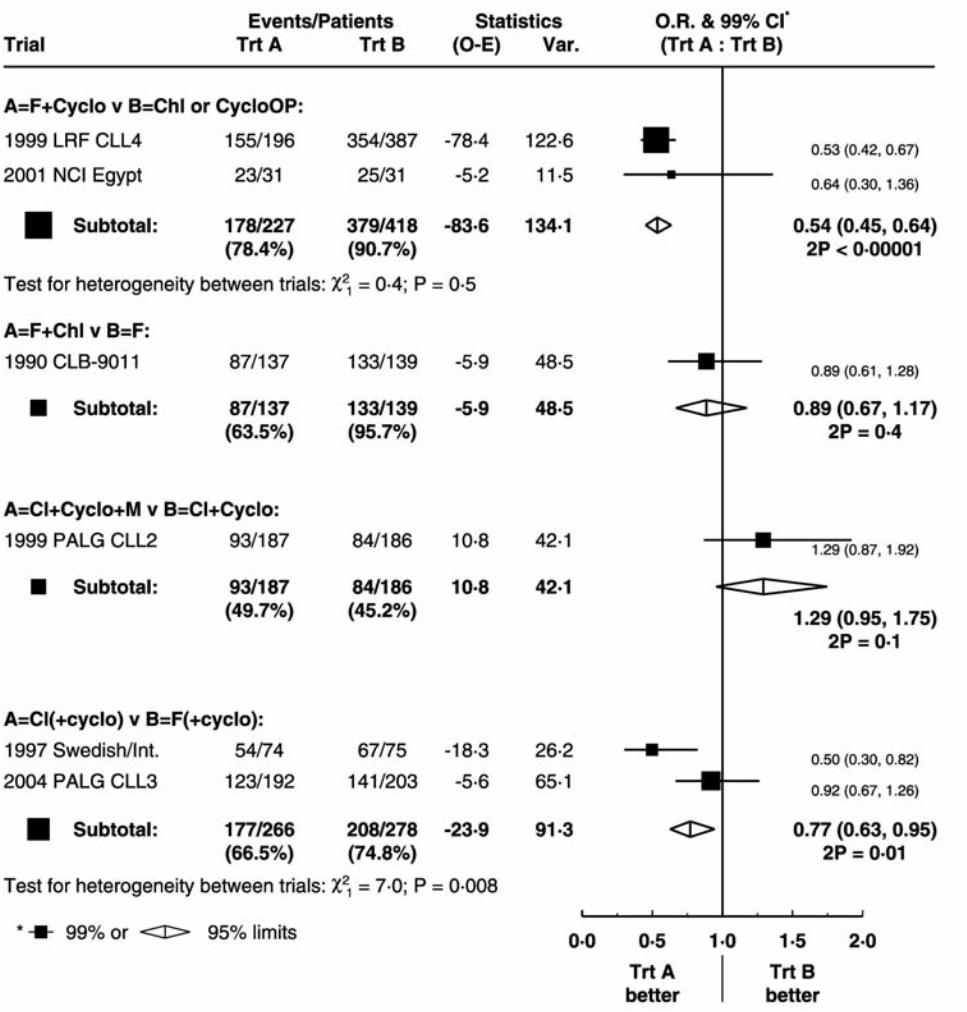
Online Supplementary Figure S1. Descriptive progression free survival curves for purine analog *versus* alkylating agent based treatment.



Online Supplementary Figure S2. Descriptive progression free survival curves for the addition of cyclophosphamide to a purine analog.



Online Supplementary Figure S3. Effect of the addition of cyclophosphamide to a purine analog on progression free survival within subgroups.



Online Supplementary Figure S4. Other comparisons: effects on progression free survival.

Online Supplementary Table S1. Data request.

DATA FORMAT

Please include data on all patients randomised into the trial whether or not they actually received their allocated treatment.

Length	Item *(code)*
12	Patient identifier
1	Sex *(1=male, 2=female)*
8 or 2	Date of birth (DDMMYYYY) or age at entry *(in columns 14-15)*
	Pre-randomisation characteristics:
3	Initial haemoglobin (g/dl) x10 *(multiply by 10 to avoid use of decimal point)*
5	Initial platelet count *[x10^9/l]*
3	Serum beta-2 microglobulin (mg/l) x10 *(multiply by 10 to avoid use of decimal point)*
1	Binet stage (A/B/C) and/or
1	Rai stage (0=0, 1=I, 2=II, 3=III, 4=IV)
	Any enlargement of:
1	Lymph nodes in neck (N=no, Y=yes)
1	" " " axillae (N=no, Y=yes)
1	" " " groin (N=no, Y=yes)
1	Spleen (N=no, Y=yes)
1	Liver (N=no, Y=yes)
	Randomisation:
8	Date of randomisation (DDMMYYYY)
1	Allocated treatment *(Please define codes used)*
	Initial outcome:
1	Response (1=complete response, 2=nodular partial response, 3=partial response, 4=no response, 5=progressive disease, 6=not assessable, 9=unknown) (*Please send us the definitions used in this trial)*
8	Date at which response was determined (DDMMYYYY)
8	Date of first progression (DDMMYYYY) (NK = progressed but date unknown, blank = no progression) *(Please send us the definition of progression used)*
	Second line treatment and outcome:
1	Second line treatment (*Please define codes used*)
8	Date second line treatment started (DDMMYYYY)
1	Response to second line treatment (1,2,3,4,5,6,9 – as above)
8	Date of response to second line treatment (DDMMYYYY)
	Final outcome:
1	Status when last traced *(1 = alive, 2 = dead, 3 = lost to follow-up)*
8	Date died or last traced (DDMMYYYY)
2	If patient died, cause of death *(please specify coding system used)*
	Additional genetic data (if available; if sending these data would cause delay, please send main data first and send any available genetic data separately):
3	VH gene homology (percentage x10) or whether mutated (M=mutated, U=unmutated)
1	V3-21 usage (Y=yes, N=no)
3	ZAP-70 (percentage x10)
3	17p13 deletion (p53 locus) (percentage x10)
3	Trisomy 12 (percentage x10)
3	11q23 deletion (percentage x10)
3	6q21 deletion (percentage x10)
3	13q14 deletion (percentage x10)
3	CD38 expression (percentage x10)

This data format is our preferred format but if it will be easier for you to supply data in a different format, please do so and we will re-format it. Please specify precisely what each item is and what the codes for each item are if you use a format different to this one.

Online Supplementary Table S2. Randomization methods and response/progression definitions used.

Trial name	Random-isation location	Random-isation method	Response definition used	Response timing	Treatment duration	Progression definition used	Progression free survival used in published report
CLL 101	Several centers, phone or fax	Balanced by institution and stratified for prior therapy/not, stage, age (<70,≥70)	NCI 1988 (1)	6 months	6 courses with up to 4 additional courses in case of incomplete but continuing response. Patients unresponsive or who had PD after at least 2 courses were withdrawn.	Change from Binet stage A to stage B or C, or from stage B to C. Progressive disease defined as: Lymphocyte count >10,000/μL & >25% increase above remission values OR >50% increase in marrow infiltration OR corresponding enlargement of lymph nodes, liver or spleen	End of treatment to progression or death in responders only.
FRE-CLL-90	Central, phone	Stratified by stage	NCI 1996 (2)	6 months.	6 monthly courses. Patients on FAMP or CAP arms with SD/PD after 3 courses were switched to CAP or FAMP respectively. If SD/PD after 6 courses on ChOP then switched to FAMP.	NCI 1996	Remission to progression or death in responders only.
CLB 9011	Central	Stratified by risk group and time from diagnosis to study entry	NCI 1988.	Monthly.	Maximum of 12 (monthly) cycles until CR, response that plateaued over 2 mo of treatment or disease progression. Patients on F+Chl with no response or relapse <6 mo after stopping therapy were removed from study. Patients in F and Chl groups without PR or with disease progression could cross over to the other drug.	Progressive disease defined as: Increase of >50% in size of lymph nodes, spleen or liver if they were previously enlarged, or detection of enlargement if not previously enlarged, or increase of >50% in number of peripheral-blood lymphocytes	Randomisation to disease progression or death (all pts included). If died ≤6 months after last date known unprogressed then counted as event at death in PFS analyses; if >6 months, then censored.
EORTC 06916	Central, phone	Minimisation on center, age, total tumour mass	Based on TTM, organomegaly, lymphocytes, Hb & platelets	Weeks 9 & 18	18 weeks	No response, including stopping treatment due to toxicity or sustained increase in TTM after 2 months in CR/PR	**Not applicable**
Italian Multicenter	Central	Simple	NCI 1996	6 cycles.	6 cycles then a further 2 if CR,3 if PR. If PD or SD after 3 and 6 courses respectively then treatment discontinued.	NCI 1996	**Not applicable**
PALG CLL1	Central, phone	Simple	NCI 1988	3 or 6 courses.	3 courses then assess response. If CR then stop, if PR then up to 3 more courses, if NR/PD or relapse <12 mo then switch to alternative arm	At least one of: increase in ALC>10x10^9/L, >50% lymphocytes on marrow differential analysis, >50% increase in sum of sizes of at least 2 lymph nodes, appearance of new lymph nodes, >50% increase in liver or spleen span below costal margin, new appearance of palpable hepatosplenomegaly, development of aggressive lymphoma	End of first line therapy to disease progression or death in responders only.

Trial name	Random-isation location	Random-isation method	Response definition used	Response timing	Treatment duration	Progression definition used	Progression free survival used in published report
Scand/ Aust	Central (2 centers), fax	Stratified by stage, age, region (Scandinavia/ Australia) Blocks of 6 in each category	**Not known**	At least one month after final chemotherapy.	3 cycles then assess. PR or better, then 3 more courses. Less than PR, initially randomized between remaining options but subsequently free second line.	Progressive lymphocytosis/lymphadenopathy.	From inclusion to progression. Also from inclusion to start of second line treatment.
SHG	**Not known**	**Not known**	**Not known**	**Not known**	Maximum of 6 (monthly) cycles	**Not known**	**Not known**
LRF CLL4	Central, phone	Minimisation on stage, age, sex	Modified NCI 1996.	3 to 6 months for FDR & FC arms, 6 to 12 months for Chl.	To max. response, up to 6 courses for FDR & FC, 12 courses for Chl.	One of: persistent rise in lymphocyte count with doubling time <12 months, downward trend in Hb or platelets, ≥50% increase in liver, spleen or lymph nodes, symptoms.	Randomization to progression or death. Non-responders counted as event on date of response assessment.
Intergroup E2997	Central	Permuted block. Stratified on Rai stage (0-2 v 3-4)	NCI 1996.	1-2 monthly, with confirmation by BM aspirate and biopsy 2 mths after.	1-6 cycles.	One of (i) 50% increase in the sum of the products of at least 2 lymph nodes on 2 consecutive examinations 2 weeks apart (at least 1 node must be 2 cm). New lymph nodes. (ii) 50% increase in the size of liver and/or spleen as determined by measurement below the respective costal margin; new hepatomegaly or splenomegaly, (iii) 50% increase in number of circulating lymphocytes, (iv) presence of> 2 gm/dl decrease in hemoglobin, or > 50% decrease in platelets or absolute granulocyte count will not exclude a patient from continuing on study. (v) Transformation to a more aggressive histology (e.g., Richter's)	Randomization to progression or death. Not assessable censored at day zero.
PALG CLL2	Central, phone, fax or email	Simple	NCI 1996.	After 3 courses. If PR again after additional courses.	3 courses. If PR up to 3 additional courses given. If NR/PD after 3 courses treatment discontinued.	At least one of: increase in ALC>10x10^9/L, >50% increase in new lymph nodes, >50% increase in liver or spleen below costal margin, new appearance of palpable hepatosplenomegaly, development of aggressive lymphoma	End of first-line therapy to disease progression or death in responders only.
GCLLSG CLL4	Central, phone	Stratified by center.	NCI 1996.	After 3rd & 6th courses.	6 courses.	At least 50% enlargement of lymph nodes, splenomegaly or hepatomegaly, appearance of new lymph nodes or more than 50% increase of lymphocytes on 2 time points at least 4 weeks apart, as well as transformation to more aggressive histology. Also higher Binet stage. (NCI 1996)	Randomization to disease progression or death. Not assessable for response excluded.

Trial name	Random-isation location	Random-isation method	Response definition used	Response timing	Treatment duration	Progression definition used	Progression free survival used in published report
GCLLSG CLL5	Central, phone	Stratified by center	NCI 1996	Flu: After 3 & 6 courses Chl: After 3,6,9 and 12 months	Flu arm: up to 6 courses Chl arm: up to 12 months Stopped if no remission after 3 months.	At least 50% enlargement of lymph nodes, splenomegaly or hepatomegaly, appearance of new lymph nodes or more than 50% increase of lymphocytes on 2 time points at least 4 weeks apart, as well as transformation to more aggressive histology. Also higher Binet stage. (NCI 1996)	Randomization to disease progression or death.
Tirana	**Not known**	**Not known**	**Not known**	**Not known**	**Not known**	**Not known**	**Not applicable**
NCI Egypt	Envelope	Simple	NCI 1996.	After 3rd & 6th cycles.	3-6 cycles unless evidence of progression or major toxicity.	NCI 1996	First response to disease progression. Non-responders & not assessable excluded.
PALG CLL3	Central (envelope), phone or fax	Not stratified	NCI 1996 guidelines.	NCI-SWOG guidelines.	6 courses		Randomization to progression or death.

Online Supplementary Table S3. Trial size, median follow up and patients' characteristics.

Trial name	N	Median follow-up (years)	Gender		Age group			Stage (Low = Binet A/B, or Rai 0-II, High = C or III-IV)		Beta-2 microglobulin (mg/l)		IGHV mutation status		17p13 deletion		11q deletion	
			Male	Female	<60	60-69	≥70	Low	High	≤4	>4	U	M	No	Yes	No	Yes
CLL 101	105	4	70 67%	35 33%	38 36%	50 48%	17 16%	67 64%	38 36%								
FRE-CLL-90	937	7	640 71%	267 29%	360 39%	404 44%	160 17%	650 69%	287 31%								
CLB 9011	509	12[1] (PFS:2)	347 68%	162 32%	197 39%	197 39%	115 23%	307 60%	202 40%								
EORTC 06916	88	7	56 64%	32 36%	42 48%	33 37%	13 15%	61 73%	23 27%	15 65%	8 35%						
PALG CLL1	229	2	166 66%	84 34%	105 43%	88 36%	49 20%	147 59%	103 41%								
Scand/ Aust	227	5	165 73%	62 27%	81 36%	104 46%	42 18%	124 55%	101 45%			74 64%	41 36%	56 98%	1 2%	42 75%	14 25%
LRF CLL4	777	7	573 74%	204 26%	255 33%	288 37%	234 30%	543 70%	234 30%	323 58%	234 42%	327 61%	206 39%	538 94%	33 6%	434 82%	112 18%
Intergroup E2997	278	4	195 70%	83 30%	124 45%	104 37%	50 18%	155 56%	123 44%			113 55%	91 45%	225 92%	19 8%	197 82%	47 18%
PALG CLL2	547	2	342 63%	205 37%	243 45%	191 35%	107 20%	307 57%	231 43%								
GCLLSG CLL4	375	4	256 73%	94 27%	218 58%	157 42%	0 0%	232 66%	121 34%	220 75%	75 25%	221 65%	119 35%	309 95%	16 5%	257 80%	66 20%
GCLLSG CLL5	193	3	122 65%	67 35%	0 0%	89 46%	104 54%	119 63%	70 37%	74 50%	75 50%	55 62%	33 37%	152 94%	10 6%	139 86%	22 14%
NCI Egypt	62	3	42 68%	20 32%	46 74%	16 26%	0 0%	20 32%	42 68%	48 77%	14 23%						
PALG CLL3	395	3	260 66%	135 34%	210 55%	113 29%	62 16%	267 68%	128 32%	206 69%	94 31%			190 86%	31 14%	169 80%	43 20%

1. Follow-up for progression was less than for survival: median 8 years in the F/Chl arms, and 1 year in the F+Chl arm

Online Supplementary Table S4. Treatment effects on response rates. Full details of patient and event numbers, weight contributed by each trial, and relative risks.

	Total patients		Good response		Weight[1] (%)	Relative risk (99% or 95% CI[3])	p	Any response		Weight (%)	Relative risk (99% or 95% CI[3])	p
Purine analog (PA) versus alkylating agent based (Alkb)[4]												
Fludarabine v Chlorambucil												
	PA	Alkb	PA	Alkb				PA	Alkb			
CLB-9011	179	193	33	7	7.0/3.0	5.08 (1.80-14.35)		105	66	17.3/8.0	1.72 (1.27-2.32)	
EORTC 06916	45	36	15	17	19.5/8.5	0.71 (1.42-2.10)		38	34	10.3/4.7	0.89 (0.74-1.09)	
Scand/Aust[2]	72	71	5	6	6.2/(3.6)	0.82 (0.18-3.68)		48	42	11.5/(5.3)	1.13 (0.81-1.57)	
LRF CLL4	181	367	76	98	66.8/29.0	1.57 (1.15-2.16)		145	266	47.9/22.1	1.10 (0.97-1.25)	
GCLLSG-5	78	87	6	0	0.5/0.2	14.49 (0.34-621.88)		67	51	13.1/6.0	1.47 (1.13-1.90)	
Subtotal	555	754	135	128	100	1.66 (1.35-2.05)	<0.0001	403	459	100	1.24 (1.15-1.34)	<0.0001
Fludarabine v Cyclophosphamide+doxorubicin+prednisolone+/-vincristine												
CLL101	41	41	12	8	7.1/3.6	1.50 (0.54-4.20)		37	30	9.3/3.8	1.23 (0.93-1.63)	
FRE-CLL90	330	577	138	143	92.9/46.7	1.69 (1.31-2.17)		247	402	90.7/36.7	1.07 (0.96-1.20)	
Subtotal	371	618	150	151	100	1.67 (1.39-2.02)	<0.0001	284	432	100	1.09 (1.01-1.18)	0.003
Cladribine+/-prednisolone v Chlorambucil+/-prednisolone												
PALG CLL1	126	103	58	11	67.2/5.4	4.31 (1.99-9.36)		106	59	61.1/8.1	1.47 (1.15-1.87)	
Scand/Aust[2]	69	71	8	6	32.8/(3.6)	1.37 (0.37-5.14)		48	42	38.9/(5.2)	1.18 (0.85-1.63)	
Subtotal	195	174	66	17	100	3.35 (2.04-5.50)	<0.0001	154	101	100	1.35 (1.17-1.57)	<0.0001
Total	**1121**	**1475**	**351**	**290**	**100**	**1.81 (1.59-2.08)**	**<0.0001**	**841**	**950**	**100**	**1.20 (1.13-1.26)**	**<0.0001**
Addition of Cyclophosphamide to single agent purine analog[5]												
	PAC	PA	PAC	PA				PAC	PA			
PA=Fludarabine												
LRF-CLL4	182	181	110	76	83.3/58.3	1.44 (1.10-1.89)		171	145	39.8/30.2	1.17 (1.05-1.31)	
E2997	132	119	35	6	6.9/4.8	5.26 (1.77-15.65)		104	79	22.7/17.2	1.19 (0.97-1.46)	
G-CLL4	165	165	29	9	9.8/6.9	3.22 (1.26-8.26)		156	137	37.5/28.4	1.14 (1.03-1.26)	
Subtotal	479	465	174	91	100/70.0	1.88 (1.54-2.30)	<0.0001	431	361	100/75.9	1.16 (1.10-1.23)	<0.0001
PA=Cladribine												
P-CLL2	165	147	45	37	100/30.0	1.08 (0.66-1.77)		137	110	100/24.1	1.11 (0.95-1.29)	
Total	**644**	**612**	**219**	**128**	**100**	**1.64 (1.37-1.96)**	**<0.0001**	**568**	**471**	**100**	**1.15 (1.09-1.21)**	**<0.0001**
Fludarabine +cyclophosphamide(PAC) versus alkylating agents(Alk)												
	PAC	Alk	PAC	Alk				PAC	Alk			
LRF CLL4	182	367	110	98	91.7	2.26 (1.73-2.97)		171	266	92.3	1.29 (1.17-1.42)	
NCI Egypt	27	28	15	6	8.3	2.59 (0.92-7.28)		20	15	7.7	1.38 (0.81-2.37)	
Total	**209**	**395**	**125**	**104**	**100**	**2.29 (1.87-2.80)**	**<0.0001**	**191**	**281**		**1.30 (1.21-1.40)**	**<0.0001**
Addition of Chlorambucil to single agent purine analog												
	PAChl	PA	PAChl	PA				PAChl	PA			
CLB9011	137	139	22	29	100	0.77 (0.40-1.49)	0.3	76	82	100	0.94 (0.72-1.23)	0.6
Addition of Mitoxantrone to cladribine plus cyclophosphamide												
	PACM	PAC	PACM	PAC				PACM	PAC			
P-CLL2	155	165	59	45	100	1.40 (0.92-2.13)	0.04	121	137	100	0.94 (0.82-1.08)	0.3
Cladribine versus fludarabine												
	Clad	Flud	Clad	Flud				Clad	Flud			
Scand/Aust	69	72	8	5	5.0	1.67 (0.41-6.79)		48	48	22.0	1.04 (0.78-1.40)	
P-CLL3	191	193	90	94	95.0	0.97 (0.74-1.27)		169	167	78.0	1.02 (0.93-1.13)	
Total	**260**	**265**	**98**	**99**	**100**	**1.00 (0.82-1.23)**	**1.0**	**217**	**215**	**100**	**1.03 (0.95-1.11)**	**0.5**

1. Weight shows the contribution of each trial to subtotals/totals.
2. The Scand/Aust trial contributes only once to the PA versus Alkb total using fludarabine + cladribine arms versus chlorambucil.
3. 99% confidence intervals for individual trials, 95% for subtotals and totals.

Heterogeneity between trials:

4. p=0.00004 (good response), p<0.00001 (any response)
5. p=0.0006 (good response)

Online Supplementary Table S5. Variability of response recording in data.

Trial name	Months to response CR, nPR or PR: Median Q1,Q3 Range	Response unavailable/ unknown (% of total)	Died within 6 months (% of those with unknown response)
CLL 101	6 6,6 5-8	23 (22%)	13 (57%)
FRE-CLL-90	7 6,8 3-45	30 (3%)	14 (47%)
CLB 9011	4 3,6 1-22	0 (0%)	0
EORTC 06916	2 2,3 1-4	7 (8%)	2 (29%)
PALG CLL1	Not available	21 (8%)	0 (0%)
Scand/Aust	4 3,6 2-14	15 (7%)	1 (7%)
LRF CLL4	7 6,9 1-20	47 (6%)	20 (43%)
Intergroup E2997	2 2,4 0.3-18	27 (10%)	4 (15%)
PALG CLL2	3 3,5 0.4-18	80 (15%)	5 (6%)
GCLLSG CLL4	3 3,5 2-11	45 (12%)	7 (16%)
GCLLSG CLL5	4 3,5 1-24	28 (15%)	10 (36%)
NCI Egypt	6 4,6 4-18	7 (11%)	4 (57%)
PALG CLL3	4 3,7 1-46	7 (2%)	6 (86%)

Online Supplementary Table S6. Adverse effects of treatments (from published reports).

	Total patients		Haem anaemia		Relative risk (95% CI)	Infections grade 3-4		Relative risk (95% CI)	Neutropenia grade 3-4		Relative risk (95% CI)
Purine analog (PA) versus alkylating agent based (Alkb)											
	PA	Alkb	PA	Alkb		PA	Alkb		PA	Alkb	
CLB9011	170	178	-	-		27	16	1.77(0.82,3.79)	46	34	1.42(0.85,2.37)
Scand/Aust	145	76	-	-		44	13	1.77(0.86,3.67)	66	27	1.28(0.81,2.03)
LRF CLL4	191	380	21	47	0.89(0.47,1.68)	-	-		78	105	1.48(1.08,2.01)
GCLLSG-5	87	96	7	2	3.86(0.51,29.40)	4	7	0.63(0.13,3.03)	12	11	1.20(0.44,3.29)
CLL101	53	52	2	0	4.91(0.09,257.18)	4	4	0.98(0.17,5.65)	21	19	1.08(0.57,2.06)
FRE-CLL90	341	597	6	3	3.50(0.57,21.46)	23	28	1.44(0.71,2.91)	122	202	1.06(0.83,1.34)
PALG CLL1	126	103	7	2	2.86(0.37,21.93)	25	5	4.09(1.21,13.77)	11	4	2.25(0.52,9.72)
Total					1.35(0.91, 2.02)$	127	73	1.70(1.28,2.26)*			1.23(1.10,1.39)*
Addition of Cyclophosphamide to single agent purine analog											
	PAC	PA	PAC	PA		PAC	PA		PAC	PA	
LRF-CLL4	196	191	9	21	0.42(0.15,1.13)	-	-		109	78	1.36(1.03,1.80)
E2997	136	132	-	-		24	19	1.23(0.59,2.53)	94	83	1.10(0.88,1.38)
GCLLSG-4	173	173	4	6	0.67(0.13,3.44)	15	15	1.00(0.41,2.46)	-	-	
PALG CLL2	162	166	-	-		55	45	1.25(0.81,1.93)	50	32	1.60(0.96,2.66)
Total					0.47(0.25,0.90)			1.20(0.92,1.56)			1.29(1.13,1.47)*$
Fludarabine +cyclophosphamide(PAC) versus alkylating agents(Alk)											
	PAC	Alk	PAC	Alk		PAC	Alk		PAC	Alk	
LRF CLL4	196	380	9	47	0.37(0.15,0.92)	-	-		109	105	2.01(1.54,2.64)*
Addition of mitozantrone to Cladribine plus Cyclophosphamide											
	PACM	PAC	PACM	PAC		PACM	PAC		PACM	PAC	
PALG CLL2	151	162	-	-		60	55	1.17(0.80,1.72)	57	50	1.22(0.82,1.83)

	Total patients		Haem anaemia		Relative risk (95% CI)	Infections grade 3-4		Relative risk (95% CI)	Neutropenia grade 3-4		Relative risk (95% CI)
Cladribine (plus cyclo) versus fludarabine (plus cyclo)											
	Cl	Fl	Cl	Fl		Cl	Fl		Cl	Fl	
Scand/Aust	72	73	-	-		26	18	1.46(0.75,2.84)	41	25	1.66(1.01,2.73)
PALG CLL3	192	203	19	14	1.43(0.60,3.42)	53	54	1.04(0.68,1.59)	39	43	0.96(0.58,1.59)
Total								1.15(0.87,1.50)			1.22(0.93,1.60)$

* Treatment difference p<0.0001; $ Evidence of heterogeneity between trials (I^2 > 50%)

Leukaemia Meta-analysis Protocol

All leukaemia meta-analyses using individual patient data use the same methodology as in the breast cancer meta-analyses, as laid out in the following web page.

http://www.ctsu.ox.ac.uk/reports/ebctcg-1990/index_html

CLL overview
Questions to be addressed, endpoints and subgroups in particular leukaemias are particular to the type of disease and are given below.

CLL Overview Analysis Plan

Detailed searches for all randomised trials in CLL are being updated and a complete trial list will be produced for the 2007 meeting.

The main purpose of the overview is to compare the effects of different treatments. So all analyses will be comparisons by treatment, overall or for particular subgroups or time periods.

All analyses will be stratified by trial so that patients from one trial will never be compared with those in another, who might differ in characteristics, non-trial treatments, etc. Results will be presented as 'forest plots' showing the result for each trial or subgroup and overall. Descriptive survival curves will be used to display the estimated treatment effects over time.

Primary analyses will be of overall survival.
Secondary analyses will be of progression free survival, disease free survival, CLL related death, non-CLL related death, and response.

Subgroup analyses will be done, with tests for heterogeneity of treatment effect between subgroups, for

1. Sex (males, females)
2. Age (<60, 60-69, 70+)
3. Binet stage (A,B,C)
4. Rai stage (0,1,2,3,4)
5. Year since randomisation
6. VH genes (unmutated, mutated)
7. p53 deletion

If sufficient data are available, further analyses will be performed

1. with respect to a small number of other genetic/cytogenetic subgroups.
2. of response and survival by second line treatment.

Descriptive tables will be produced giving information by trial on protocol treatment details, eligibility criteria, randomisation methods, patient characteristics, length of follow-up, and second line treatments used.

Trials will be grouped according to the comparisons they address. This will initially be decided by the secretariat but will be finalised only after discussion by the group. The main comparisons initially will be

1. Single agent purine analogue versus alkylating agents
2. Purine analogue plus cyclophosphamide versus alkylating agents
3. Addition of alkylating agents to purine analogue.

Results will be presented at the meeting for other treatment comparisons where data are available.

Future plans

The aim is an ongoing collaboration, with meetings every few years, so that future comparisons could look at monoclonal antibodies and other new treatments.

It is our intention that publications resulting from the overview analyses will be published under group authorship, with a listing of one or two representatives from all those trial groups contributing data included in the paper, along with the CLL Triallists Collaborative Group secretariat. Draft manuscripts will be circulated to the trial groups for checking and comment and all comments will be taken into account before submission for publication.