

Chronic Lymphocytic Leukemia: Advances in Research and Treatment

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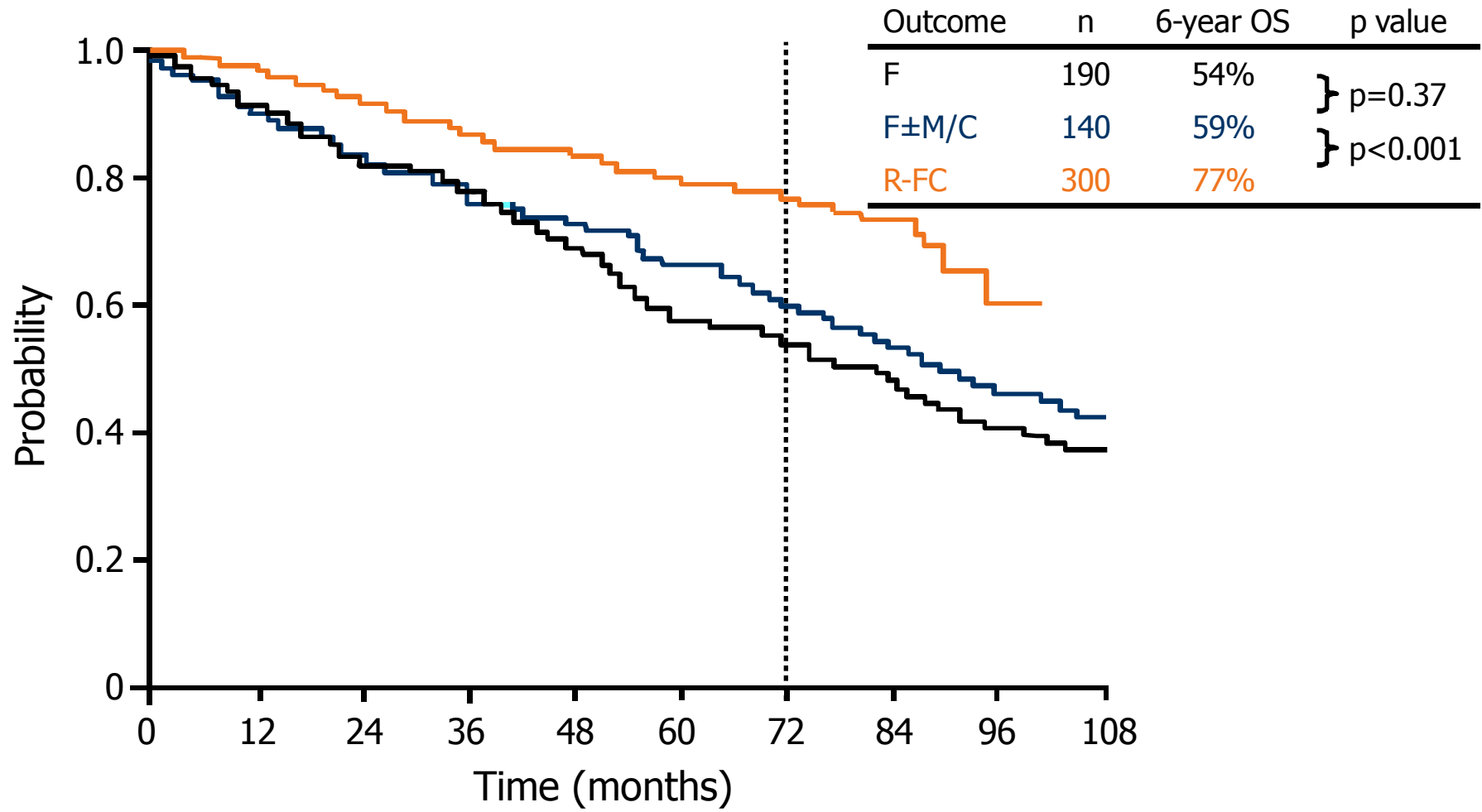


Fludarabine (F) + cyclophosphamide (C) is superior to F in Previously Untreated CLL

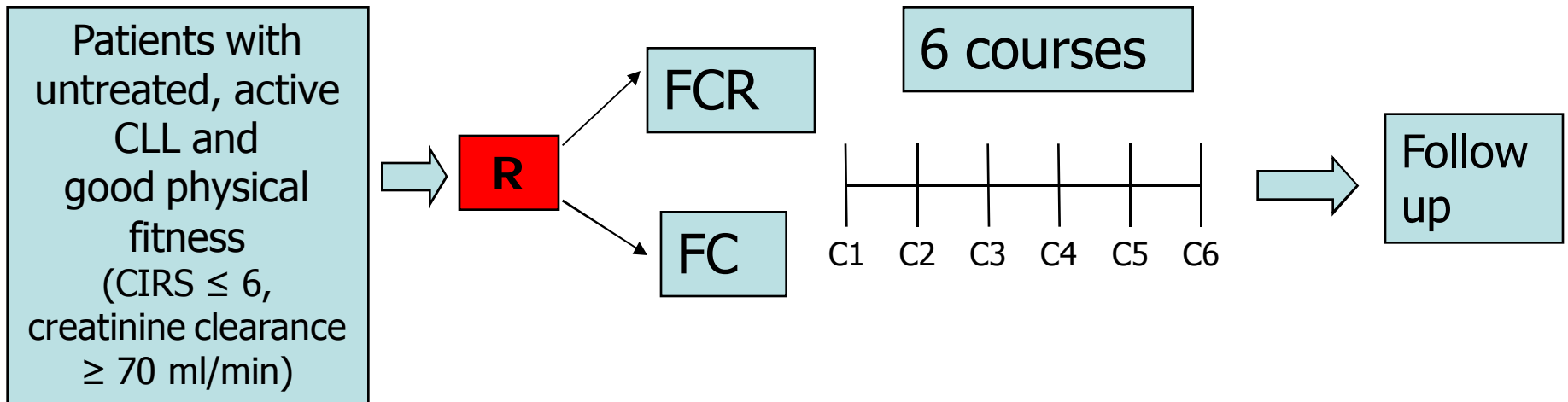
Regimen	Chl	F	FC	F	FC	F	FC
N	387	194	196	137	141	182	180
Med age	65	64	65	61	61	59	58
Rai Stage III- IV, Binet C, %	31	29	30	42	44	41	39
Grade 3 / 4 ↓ ANC, %	28	41	56	63	69	26	56
% CR	7	15	38	5	23	7	24
% OR	72	80	94	59	74	83	95
Med PFS, months	20	23	43	19.2	31.6	20	48

Catovsky D, et al. *Lancet*. 2007;370(9583):230-239. Flinn IW, et al. *J Clin Oncol*. 2007;25(7):793-798; Eichhorst BF, et al. *Blood*. 2006;107(3):885-891.

Improved efficacy by combining FC chemotherapy with rituximab (MD Anderson, historical comparison)



CLL8 Study Design



Primary endpoint

-Progression-free survival (PFS)

Secondary endpoints

- Overall survival
- Rates of molecular, complete and partial remission
- Rates of treatment-related adverse effects

Patients: ITT population (n=817) of the CLL8 protocol

	FC (n = 409)	FCR (n = 408)
Female	105 (26%)	105 (26%)
Male	304 (74%)	303 (74%)
Median age	61 (range 36-81)	61 (range 30-80)
Binet A	22 (5.4%)	18 (4.4%)
Binet B	259 (63.6%)	263 (64.6%)
Binet C	126 (31%)	126 (31%)
B symptoms*	197 (48%)	167 (41%)
Median cumulative illness rating scale (CIRS)	1 (range 0-8)	1 (range 0-7)
Trisomy 12	14.4%	9.6%
Del(13q)	59.9%	53.7%
Del(11q23)	22.5%	26.7%
Del(17p13)	9.5%	7.0%

All adverse events of CTC grade 3 and 4

	FC	FCR	p
Total number of patients with ≥ 1 grade 3/4 event	248 (62.6%)	309 (77.5%)	< 0.0001
Hematological toxicity	39.4%	55.7 %	< 0.0001
Neutropenia	21.0%	33.7%	< 0.0001
Leukocytopenia	12.1%	24.0%	< 0.0001
Thrombocytopenia	10.9%	7.4%	0.09
Anemia	6.8%	5.4%	0.42
Infection	14.9%	18.8%	0.14
Tumor lysis syndrome	0.5%	0.2%	0.55
Cytokine release syndrome	0.0%	0.25	0.32

Infectious adverse events, grade 3 and 4

	FC	FCR	p
Infections, total	14.9%	18.8%	0.14
Infections, if specified	9.3%	13.6%	0.06
Bacterial	1.3%	2.2%	0.30
Viral	4.0%	4.2%	0.90
Fungal	0.3%	0.7%	0.33
Parasitic	0.0%	0.2%	0.32

Differences not statistically significant

Treatment related mortality: 2.0% in the FCR and 1.5% in the FC arm

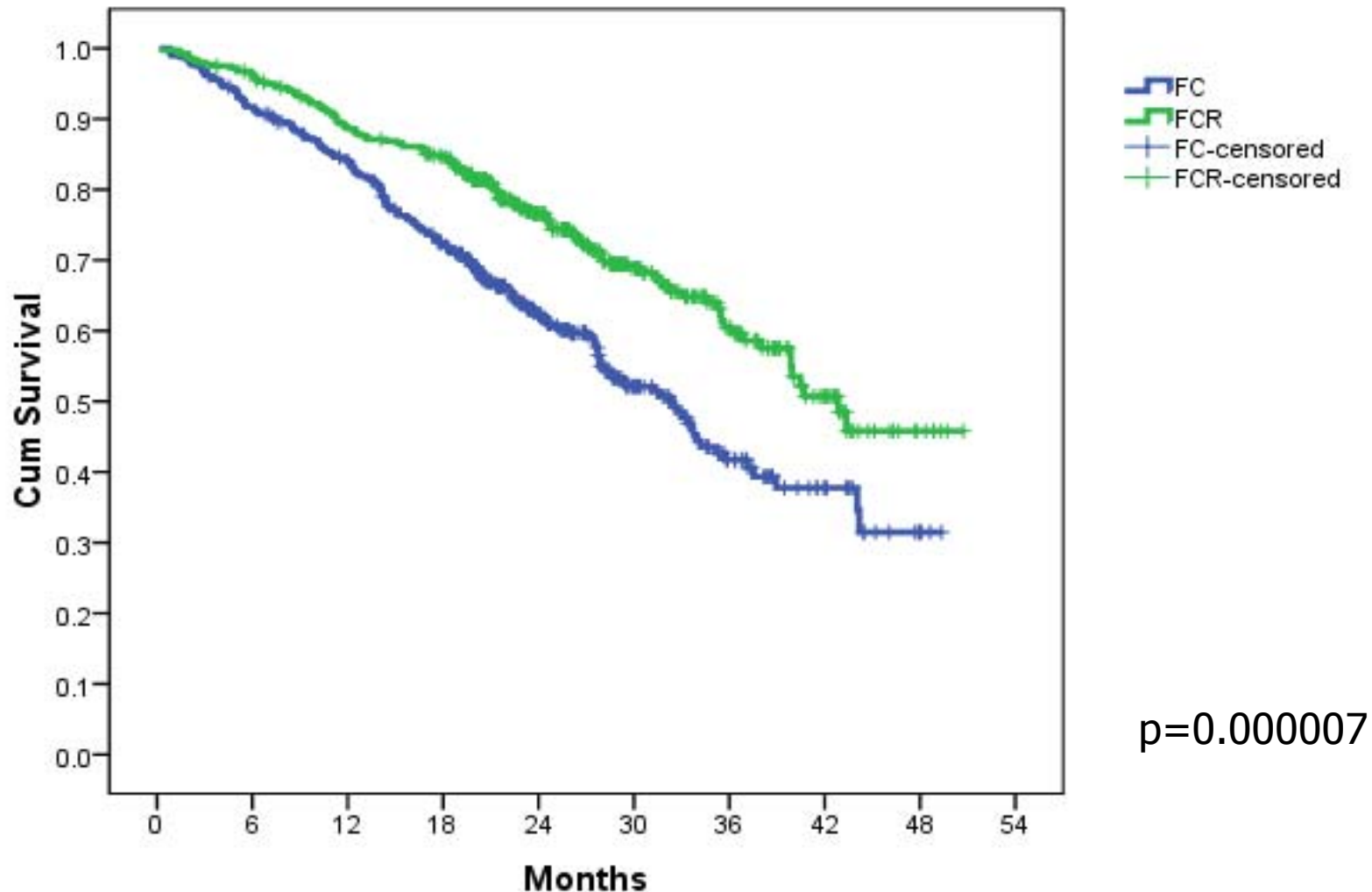
Hallek M, et al. *Blood*. 2008;112: Abstract 325.

Response to treatment

	FC	FCR	p
CR	22.9%	44.5%	<0.01
CR _u	5.1%	3.3%	0.22
CR _i	1.9%	2.6%	0.52
nPR	4.9%	2.8%	0.15
PR	50.4%	39.6%	<0.01
SD	6.7%	3.9%	0.08
PD	8.1%	3.3%	<0.01

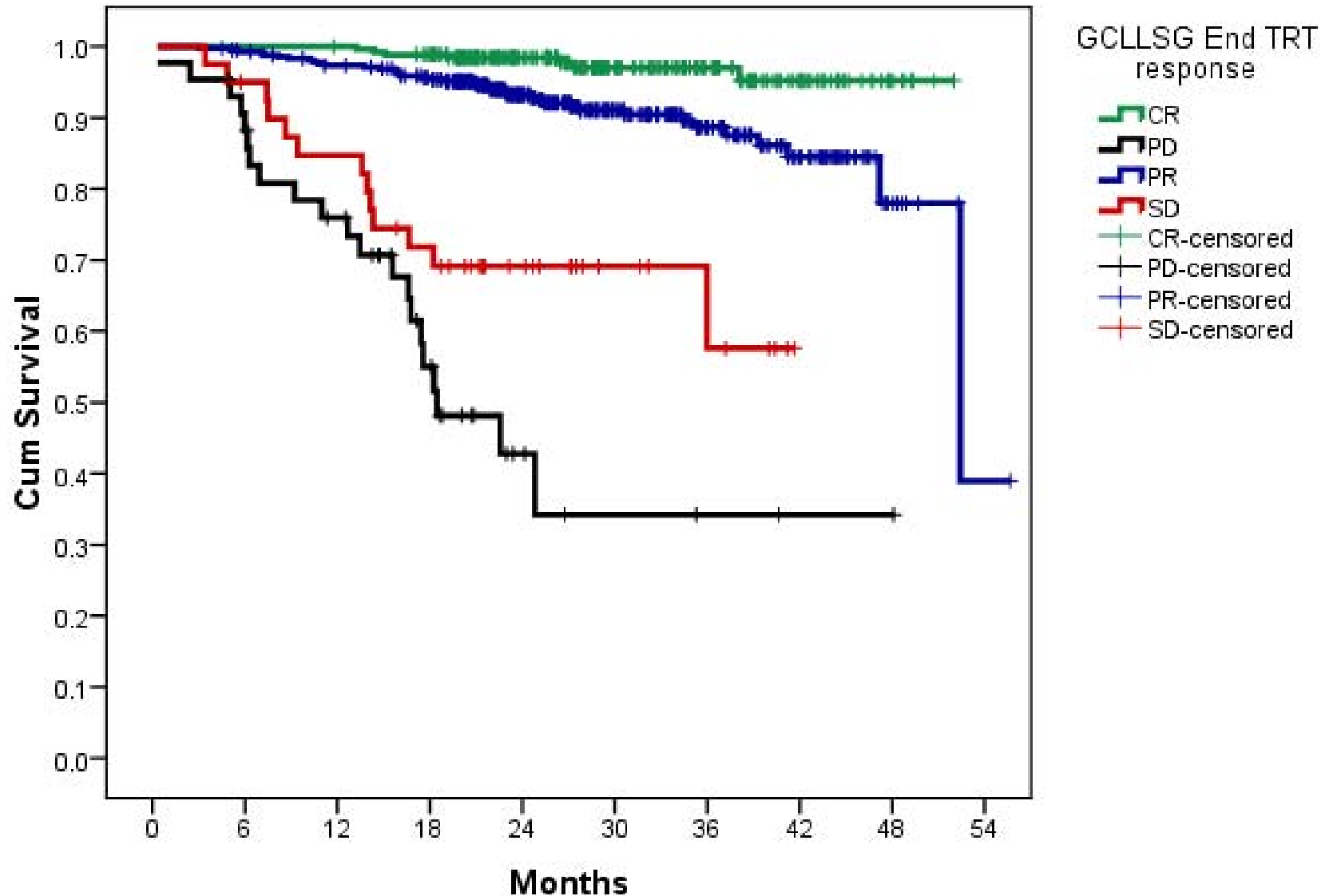
Progression free survival: FCR versus FC

Median observation time 25.5 months



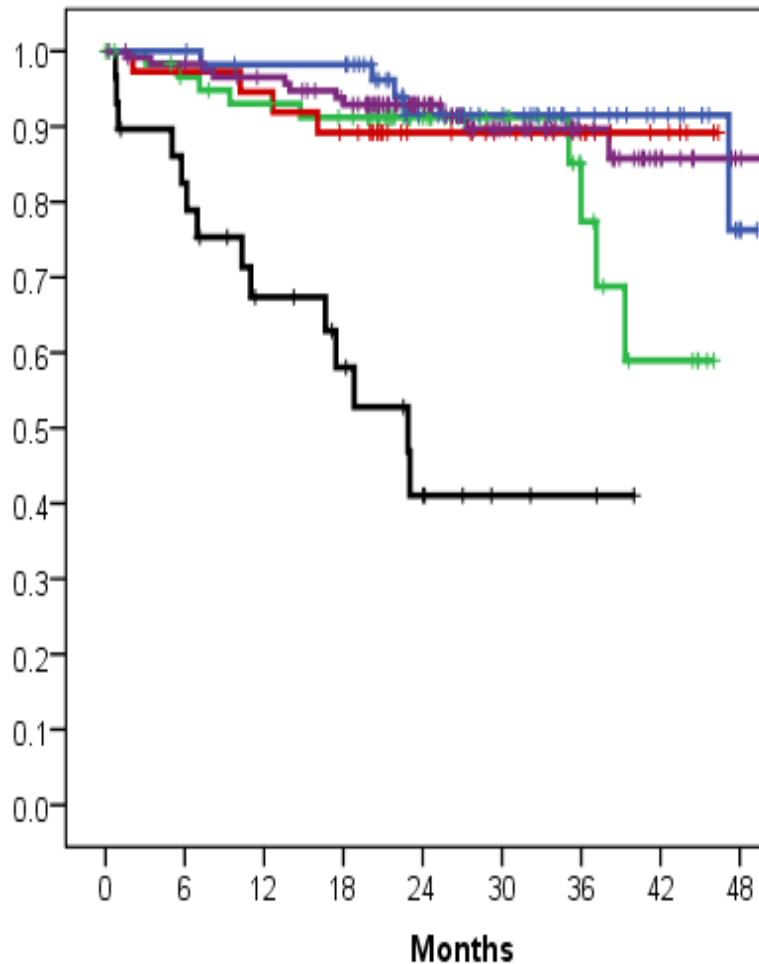
Median PFS: 32.3 months for FC vs 42.8 months for FCR

Overall survival and type of response

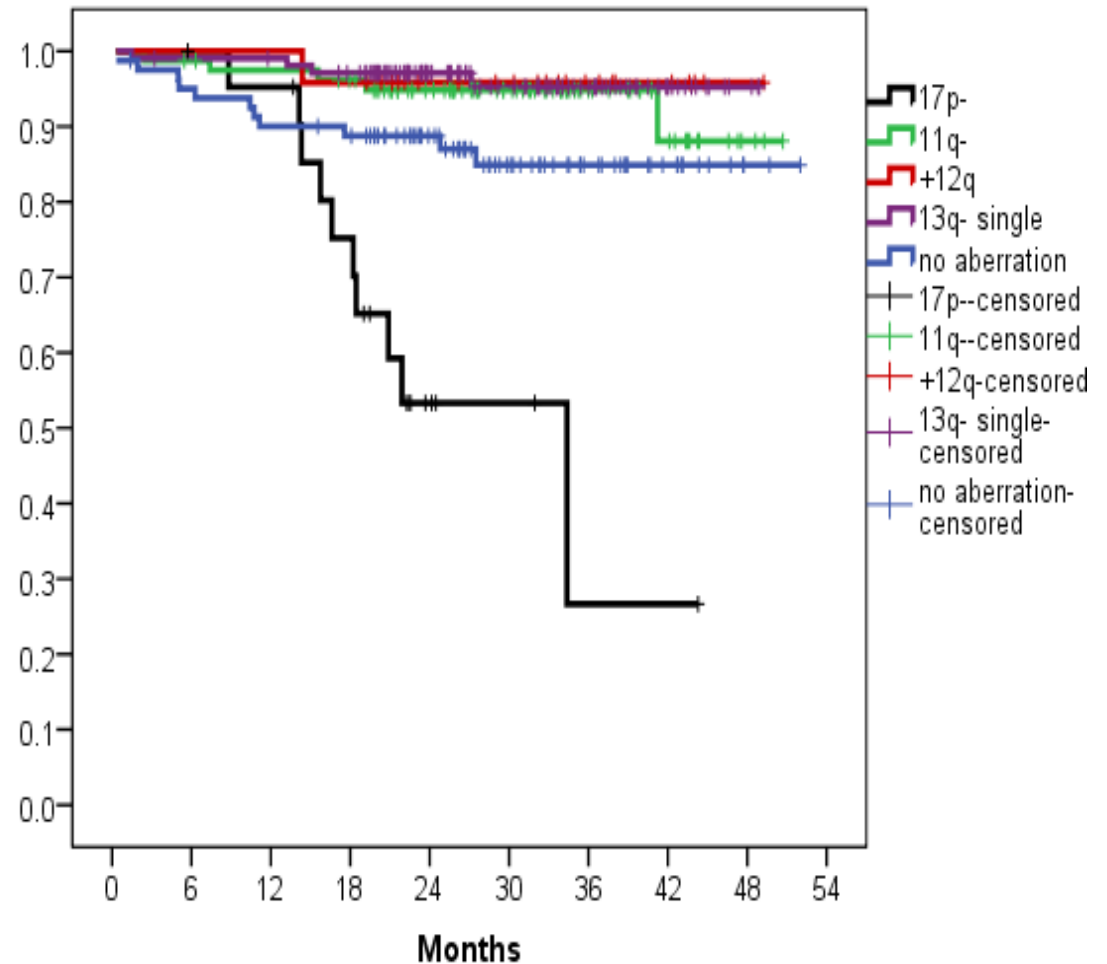


CLL8 Genetic Analyses: OS

FC



FCR



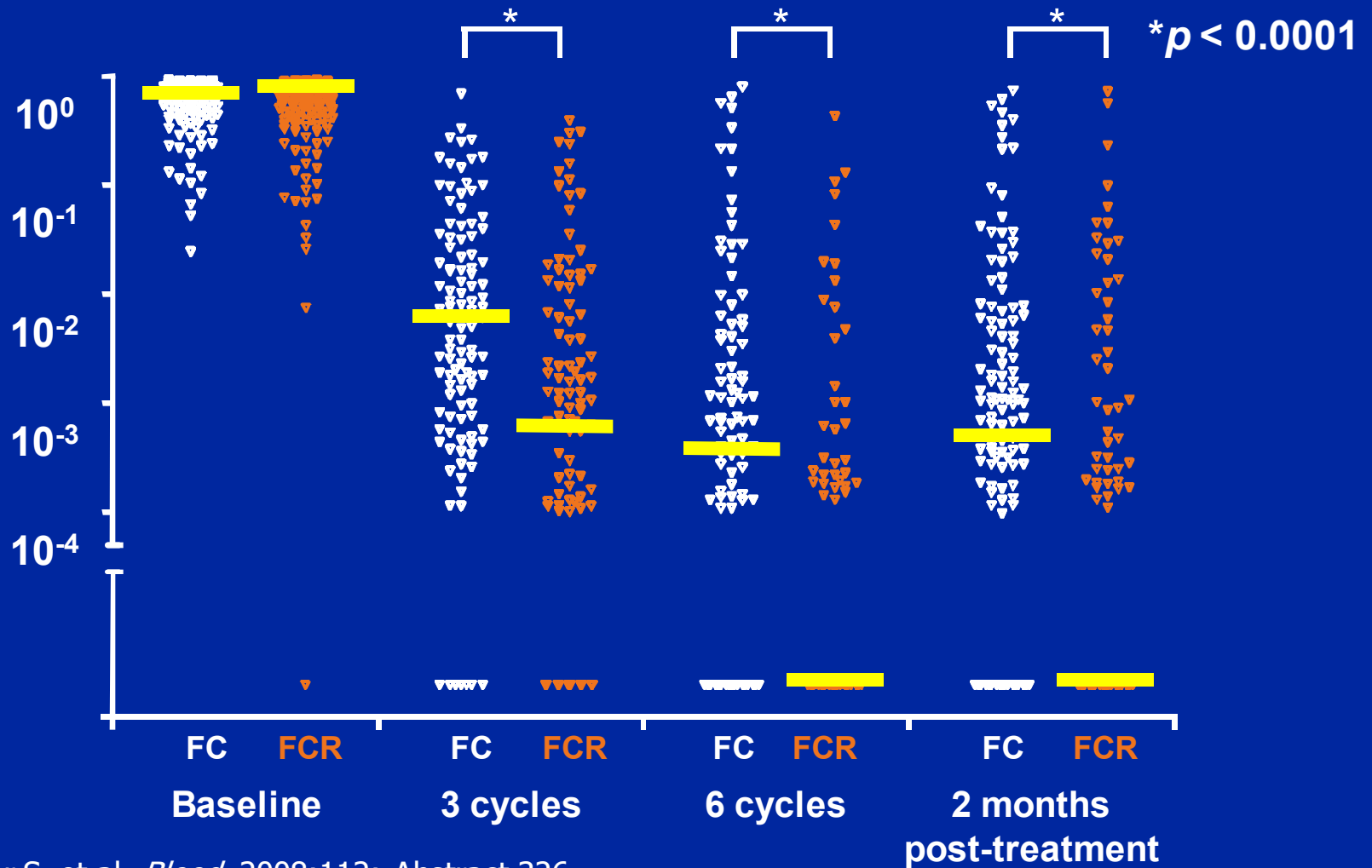
CLL8 Genetics: Multivariate Analyses

Included parameters:

Treatment arm, age, sex, stage, creatinine-clearance, WBC, TK, β 2-MG, genomic aberrations, VH status

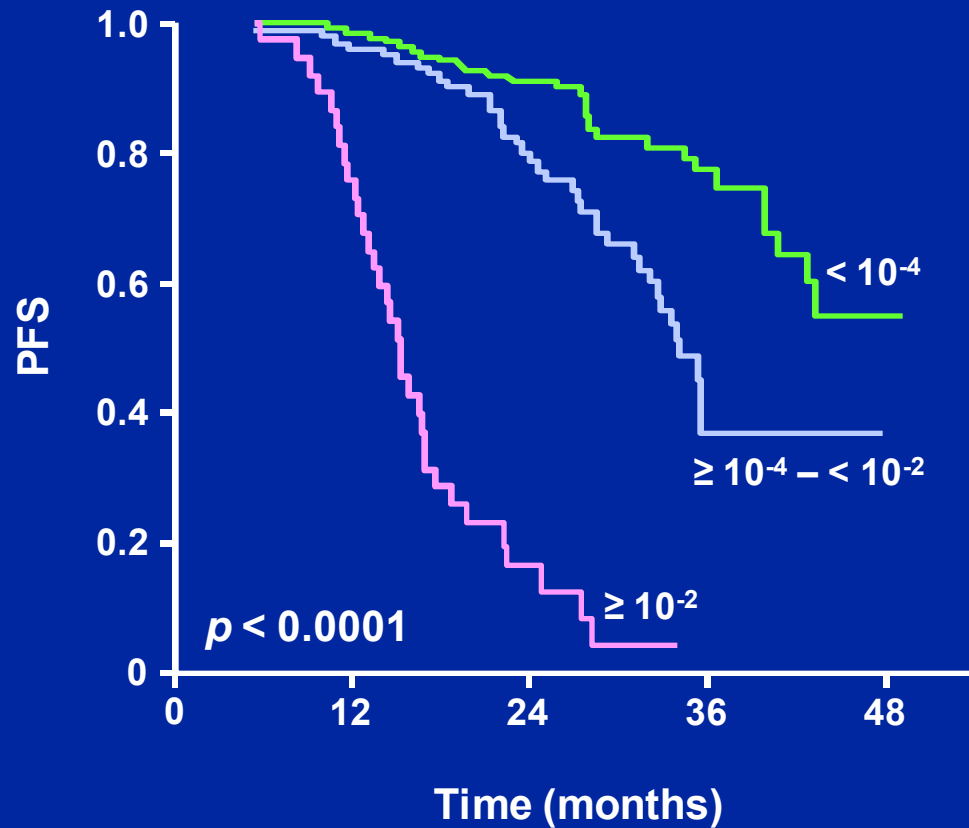
<u>Parameter:</u>	<u>PFS:</u>		<u>OS:</u>	
	<u>HR:</u>	<u>p-value:</u>	<u>HR:</u>	<u>p-value:</u>
FCR	.511	<.001	.584	.046
Age > 60	1.512	.006	-	-
Male	1.471	.036	-	-
WBC > 50	1.504	.014	-	-
β 2-MG > 3.5	1.474	.012	2.130	.006
TK > 10	-	-	2.441	.047
VH unmut.	1.913	<.001	-	-
17p-	8.535	<.001	8.709	<.001

Median MRD levels in peripheral blood: FC vs FCR



MRD in peripheral blood predicts PFS: All patients

– 2 months post-treatment –



Cut-off	n	Events
$< 10^{-4}$	139	29
$\ge 10^{-4} - < 10^{-2}$	103	38
$\ge 10^{-2}$	38	33

Summary: FCR in 1st line treatment

- FCR is superior to FC in most cytogenetic subgroups with regard to:
 - Response rates (CR, OR, MRD).
 - Progression-free survival.
- FCR and FC inefficient in del(17p)
- Low MRD level associated with improved PFS
 - Regardless of therapy, sample material, sampling time point
- FCR is safe:
 - FCR causes more neutropenias
 - FCR does not cause more infections or other severe side.
 - FCR is well tolerated in physically fit patients > 65 or 70 years.
- FCR is the new standard treatment for physically fit CLL patients

Recommendation for prognostic factors in CLL management

(Hallek et al., *Blood* 111, 5446, 2008)

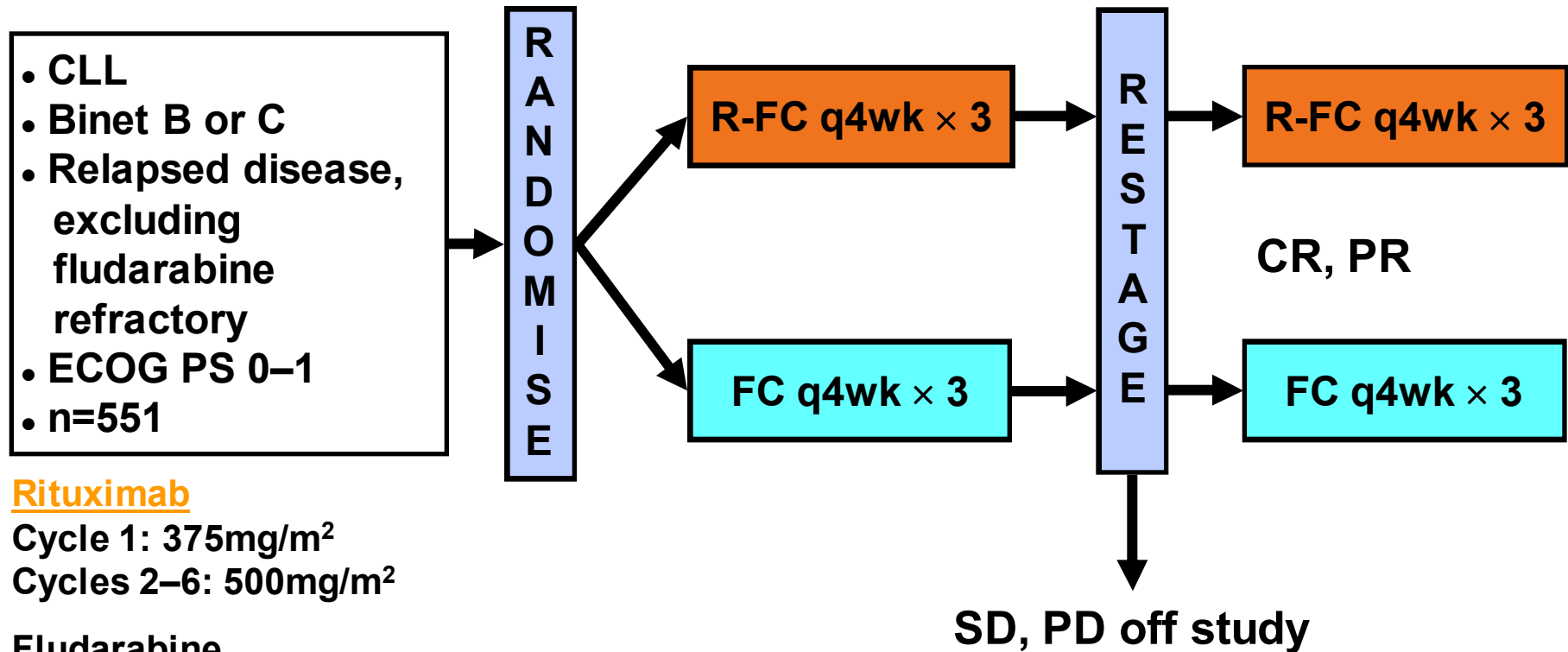
- Recommend 4 parameters:
 - Staging
 - Response to treatment
 - Molecular cytogenetics (FISH) **prior to therapy**
 - Physical fitness
- Other new biologic variables (ZAP70, IgVH, TK, β_2 -microglobulin, CD38)
 - may help to predict the individual course in early stage patients,
 - have little value in guiding treatment decisions,
 - need further evaluation in clinical trials.

Prognosis of advanced, relapsed CLL

Survival

Responsive to both alkylating agents and fludarabine	2-3 years
Alkylator refractory	1-2 years
Fludarabine refractory (17p-)	< 1 year

The REACH trial: R-FC vs. FC in relapsed CLL



Rituximab

Cycle 1: 375mg/m²

Cycles 2-6: 500mg/m²

Fludarabine

25mg/m² iv, day 1-3

Cyclophosphamide

250mg/m² iv, day 1-3

REACH Trial

	FC	FCR
N. patients	272	274
Median age	62	62
CR (%)	13	24.3
PR (%)	44.9	45.7
PD (%)	5.4	2.5
TTF (median)	20.6 m.	30.6 m.*
OS (median)	52	NR **
Fatal events	10%	13%

(*) p <0.05 // (**) NS

CLL2M Study

Protocol amendment 1

Second to fourth-line therapy

81 patients

6 cycles BR

Bendamustine 70mg/m² day 1-2
q4wks, cycle 1-6

Rituximab 375 mg/m² day 0, cycle 1
500 mg/m² cycle 2-6

First-line therapy

119 patients

6 cycles BR

Bendamustine 90mg/m² day 1-2
q4wks, cycle 1-6

Rituximab 375 mg/m² day 0,
cycle 1 500 mg/m² cycle 2-6

Comparison BR GCLLSG – FCR MD Anderson

	BR CLL2M GCLLSG			FCR Wierda et al., JCO 2005		
	% of patients			% of patients		
Patients characteristics						
Number of patients	62			177		
Median number of pretreatment	2 (1-3)			2 (1-10)		
Efficacy						
ORR	77.4%			73%		
CR	14.5%			25%		
nPR	1.6%			16%		
PR	61.3%			32%		
TTP/OS				28 months/42 months		
Response by pretreatment						
	Pts (N)	ORR (%)	CR	Pts (N)	ORR (%)	CR(%)
Fludarabine sensitive	41	70.7%		108	76%	
Fludarabine refractory	9	77.8%	-	37	59%	5%

Fischer K, et al. *Blood*. 2008;112: Abstract 330.

Wierda W, et al. *J Clin Oncol*. 2005;23(18):4070-4078.

Comparison BR GCLLSG – FCR MD Anderson

	BR CLL2M GCLLSG	FCR Wierda et al., JCO 2005
Safety		
	% of all cycles	% of all cycles
N cycles	328	529/539/745
Neutropenia CTC 3+4	12.2%	62 %
Thrombocytopenia CTC 3+4	9.1%	17%
Major infection	5.2%	5%
Anemia	6.1% (of all cycles)	24% (of all pts)
PCP prophylaxis applied	none by routine	none by routine
Antiviral prophylaxis applied	none by routine	none by routine
Growth factors applied	none by routine	none by routine

Fischer K, et al. *Blood*. 2008;112: Abstract 330.

Wierda W, et al. *J Clin Oncol*. 2005;23(18):4070-4078.

Responses to lenalidomide in heavily pretreated CLL (prior treatments: median 5)

Ferrajoli et al, *Blood* 111: 5291-5297, 2008

Response	No. of patients	%
OR	14	32
CR	3	7
Nodular PR	1	2
PR	10	23
SD	11	25
PD	19	43

Flavopiridol in CLL

(30 min IV bolus → 4-h infusion weekly for 4 weeks, repeat after 6 weeks)
Phelps, *Blood*, Prepublished online Nov 3, 2008

Table 4. Clinical Response by Cytogenetic Risk Group. Partial responses (PR), the PR rate, and median progression-free survival (PFS) are shown for all patients as well as for individual cytogenetic risk groups.

	All Patients (n=52)	Flu Refractory (n=43)	Not Flu Refractory (n=9)	Complex Karyotype (n=25)	Deletion of 17p13 (n=18)	Deletion of 11q22 (n=21)
Partial Response	21	17	4	8	7	15
% PR	40%	40%	44%	38%	39%	74%
Median PFS	12.0 months	12.4 months	8.3 months	8.4 months	14.5 months	11.7 months

EBMT Consensus: indications for allogeneic stem cell transplantation in CLL

(Dreger et al. *Leukemia*, 2007)

- Non-response or early progression (12 months) after purine analog therapy
- Early progression after purine analog based combination therapy or autologous transplantation (24 months)
- Mutation of p53 or del(17p) plus indication for therapy
- Within clinical trials

NRM of RIC alloSCT for CLL

Study	Seattle	GCTSG	DFCI	CLL3X
n	82	30	46	90
NRM	23% (5y)	15% (4y)	17% (2y)	23% (3y)
OS	50% (5y)	69% (4y)	54% (2y)	66% (3y)
REL	38% (5y)	30% (4y)	48% (2y)	42% (3y)
REL >2y	2	4	0	3
F/U (mo)	60	44	20	28

Sorrer *JCO* 2005, ASH 2007; Schetelig *JCO* 2003, *Leukemia* 2007;
Brown *BBMT* 2006; GCLLSG 2008

Sorrer ML, et al. *J Clin Oncol.* 2005;23(16):3819-3829. Sorror ML, et al. *Blood.* 2007;110: Abstract 1662. Schetelig J, et al. *J Clin Oncol.* 2003;21(14):2747-2753. Dreger P, et al. *Leukemia.* 2007;21(1):12-17. Brown JR, et al. *Biol Blood Marrow Transplant.* 2006;12(10):1056-1064. Dreger P, et al. *Blood.* 2008;112: Abstract 565.

Summary: CLL Treatment 2009

Binet Stage	Fitness	First line treatment	GCLLSG trial
A, asymptomatic B	Irrelevant	<u>None</u>	CLL7
C, symptomatic B	Go Go	<u>FCR</u> (BR, FR, FCA) Del(17p): FCA → AlloTx	CLL10
	Slow Go	<u>CLB</u> , Bendamustine F (+C? +R?, reduced dose)	CLL11
Relapse	Fitness	Second line	GCLLSG trial
Early (< 1 year) = refractory disease	Go Go	<u>Alemtuzumab, FC-A</u> → <u>Allo Tx</u>	CLLX2
	Slow Go	<u>Alemtuzumab</u> (17p-), Bendamustine (+R), R- CHOP, lenalidomide, flavopiridol	CLL2G, CLL2M
Late (> 1 year)	Go Go & Slow Go	Repeat first line	