

ASH up-date:
Changing the Standard of Care for
Patients with
B-cell Chronic Lymphocytic Leukaemia
(or: Who to treat with What When?)

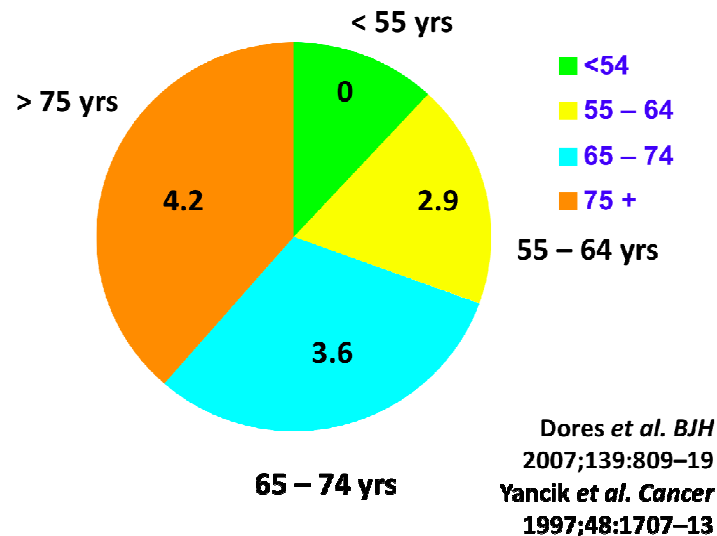
Dr Anna Schuh, MD, PhD, MRCP, FRCPath
Consultant and Senior Lecturer in Hematology
Oxford Radcliffe Hospitals

Age at diagnosis, at death and mean number of co-morbidities for patients with CLL

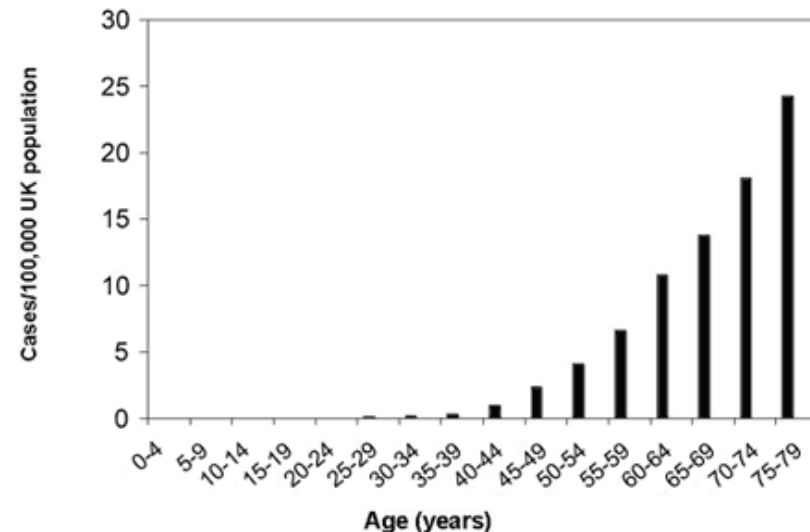
- From 2002-2006, the median age at diagnosis for chronic lymphocytic leukemia was 72 years of age
- From 2002-2006, the median age at death for chronic lymphocytic leukemia was 79 years of age

SEER	<20	20-34	35-44	45-54	55-64	65-74	75-84	>/=85
Incidence %	0	0.2	1.7	9.1	19.3	26.5	30	13.2
Death %	0	0.1	0.5	3.1	10.3	21.6	36.1	28.3

mean no. of co-morbidities

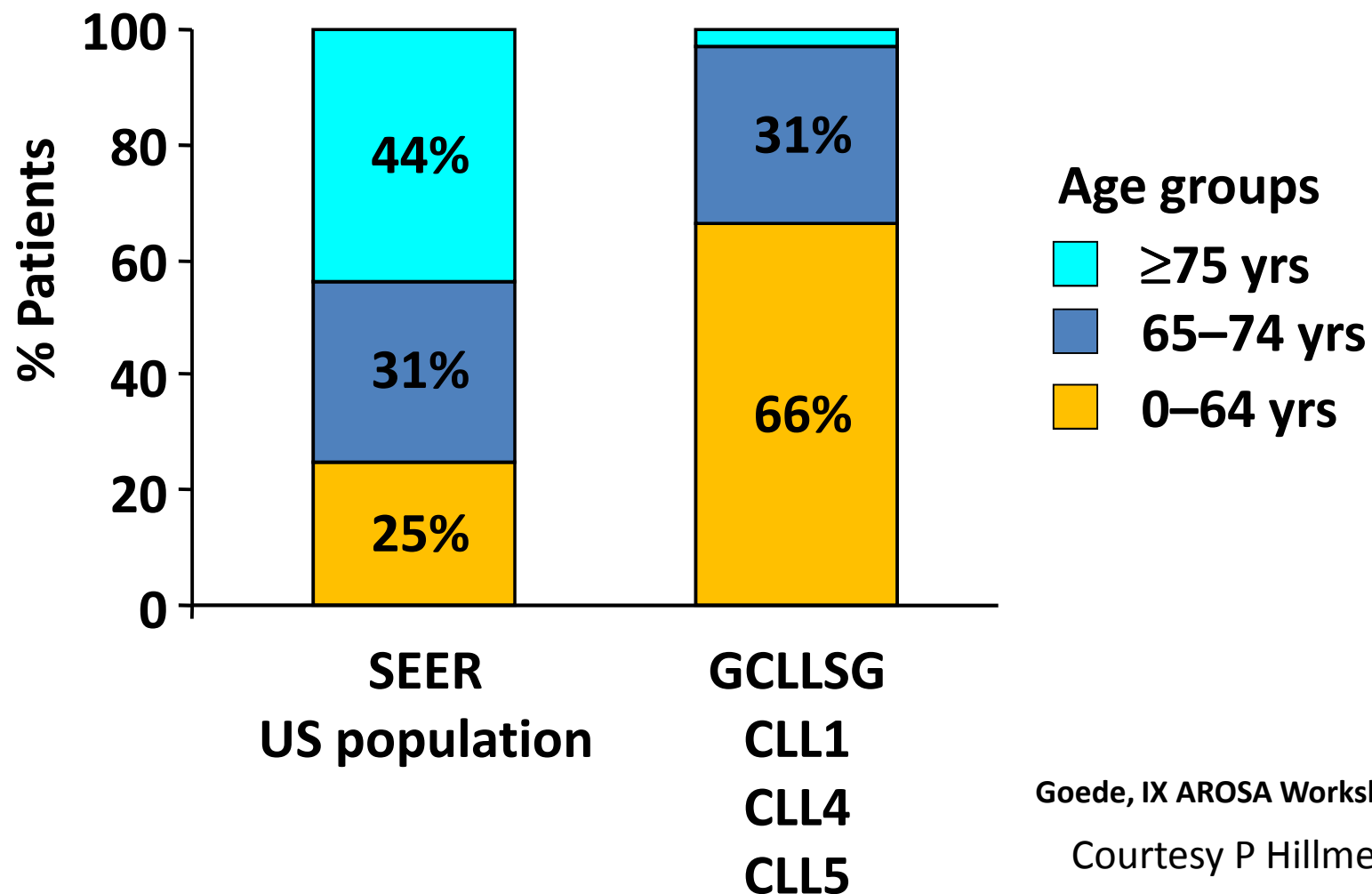


Incidence of Chronic Lymphocytic Leukaemia in the UK



The elderly patient in and out of trials

GCLLSG trials



Go-Go: CIRS score <6
 Slow-Go: CIRS score??
 No-Go: CIRS score?
 Other score??

Fig. 1. Scoring sheet for CIRS(G) displaying 14 organ-system categories

Scoring Sheet
 Cumulative Illness Rating Scale for Geriatrics—CIRS(G)

PATIENT _____ AGE _____

RATER _____ DATE _____

Instructions: Please refer to the CIRS(G) Manual. Write brief descriptions of the medical problem(s) that justified the endorsed score on the line following each item. (Use the reverse side for more writing space.)

Rating Strategy

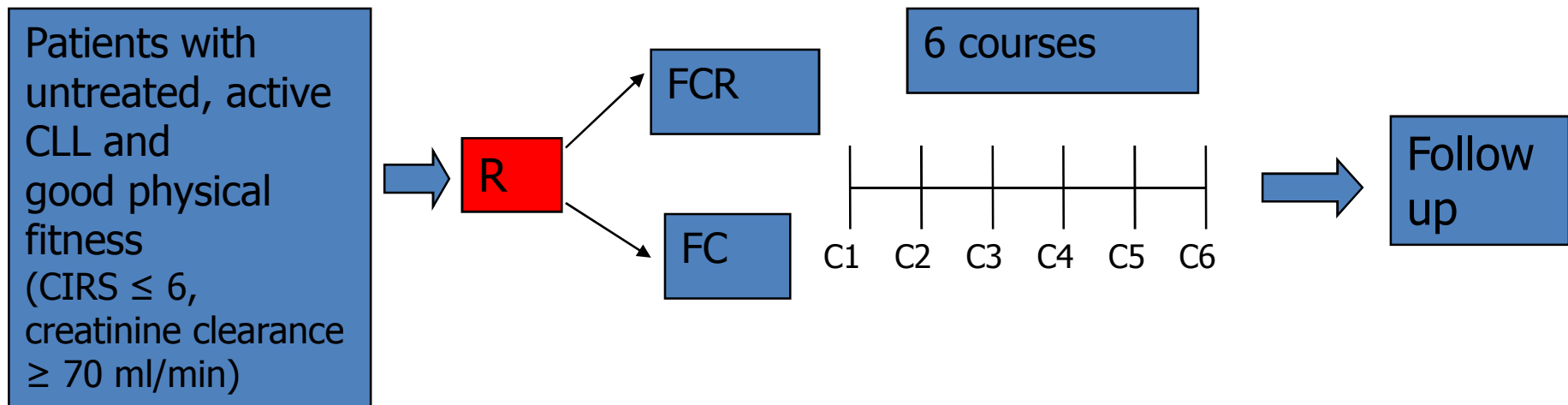
- 0 - No problem
- 1 - Current mild problem or past significant problem
- 2 - Moderate disability or morbidity/requires "first line" therapy
- 3 - Severe/constant significant disability/"uncontrollable" chronic problems
- 4 - Extremely severe/immediate treatment required/end organ failure/severe impairment function

	Score
Heart	_____
Vascular	_____
Hematopoietic	_____
Respiratory	_____
Eyes, ears, nose, throat, and larynx	_____
Upper gastrointestinal tract	_____
Lower gastrointestinal tract	_____
Liver	_____
Renal	_____
Genito-urinary	_____
Musculoskeletal/integument	_____
Neurological	_____
Endocrine/metabolic and breast	_____
Psychiatric illness	_____
<hr/>	
Total Number Categories Endorsed	_____
Total Score	_____
Severity Index: (total score/total number of categories endorsed)	_____
Number of categories at level-3 severity	_____
Number of categories at level-4 severity	_____

Five summary variables are listed at the bottom of the scoring sheet. CIRS(G) = Cumulative Illness Rating Scale, operationalized with a manual of guidelines geared toward the geriatric patient.

Changing the Standard of Care in B-CLL

535 First-Line Treatment with Fludarabine (F), Cyclophosphamide (C), and Rituximab (R) (FCR) Improves Overall Survival (OS) in Previously Untreated Patients (pts) with Advanced Chronic Lymphocytic Leukemia (CLL): Results of a Randomized Phase III Trial On Behalf of An International Group of Investigators and the German CLL Study Group



Updated results of the 2nd analysis. Median observation time 37.7 months.

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)	59.7%	53.8%
Del(11q23)	22.5%	26.8%
Del(17p13)	9.5%	7.0%

*P<0,05

Adverse events CTC grade 3 and 4

	FC	FCR	p
Total number of patients with ≥ 1 grade 3/4 event	248 (62.9%)	309 (76.5%)	< 0.0001
Hematological toxicity	39.6%	55.7 %	< 0.0001
Neutropenia	21.0%	33.7%	< 0.0001
Leukocytopenia	12.1%	24.0%	< 0.0001
Thrombocytopenia	11.1%	7.4%	0.07
Anemia	6.8%	5.4%	0.42
Infection	21.5%	25.5%	0.18
Tumor lysis syndrome	0.5%	0.2%	0.55
Cytokine release syndrome	0.0%	0.2%	0.32

Treatment related mortality 2% for both arms.

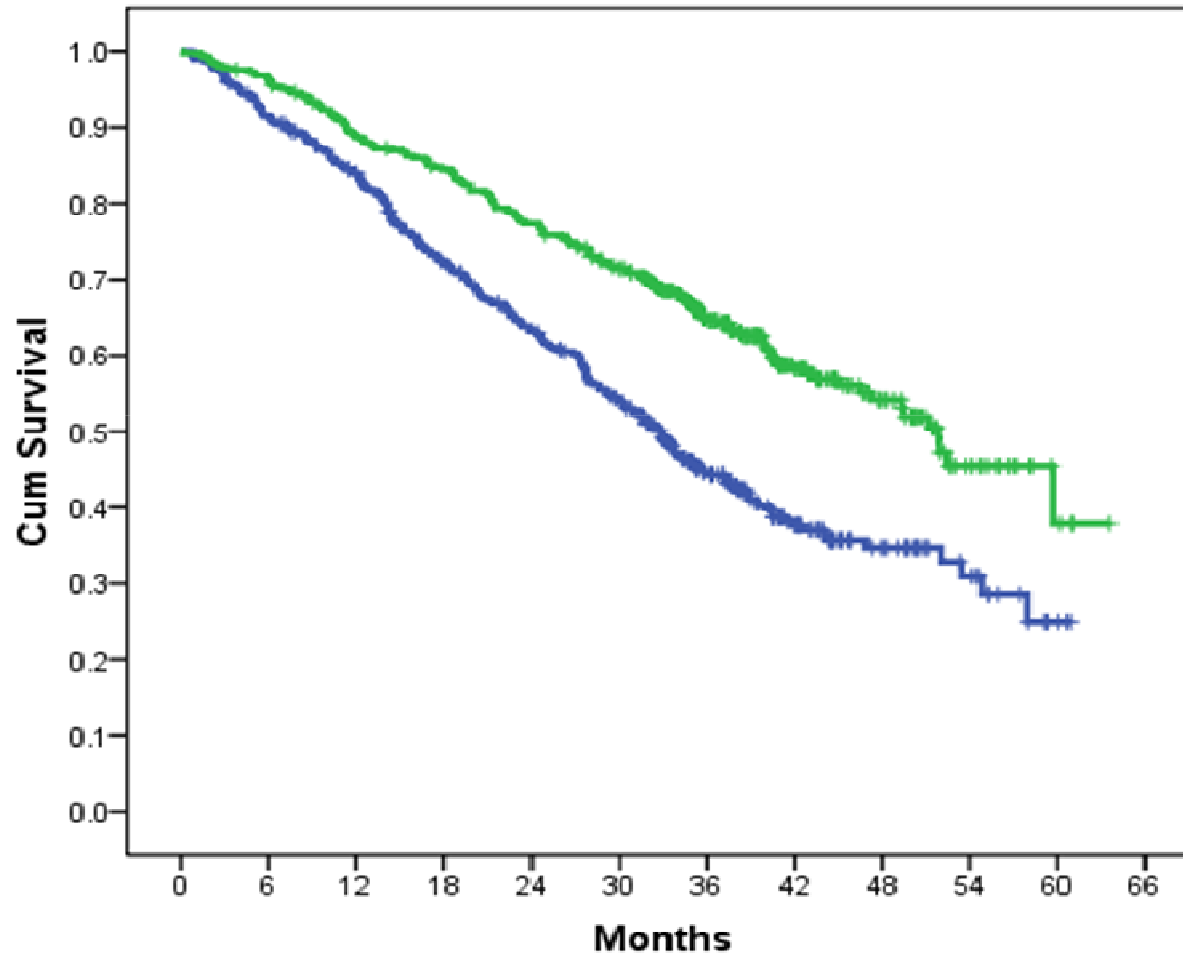
Best response to treatment

		FC	FCR
CR*		21.8%	44.1%
PR		66.6%	51.0%
Overall response rate		88.4%	95.1%
All included in PR	**CR _u	4.6%	3.6%
	**CR _i	1.9%	2.3%
	nPR	5.7%	3.4%
SD		7.8%	3.9%
PD		3.8%	1.0%

*According NCI WG Criteria, confirmatory BM assessment performed up to 6 months after final restaging

P < 0.01

Progression-free survival



Median PFS:

FCR: 51.8 months

FC: 32.8 months

(N=790)

Hazard ratio 0.563,
ranges 0.460-0.689,
 $p < 0.001$)

PFS rate 3 yrs

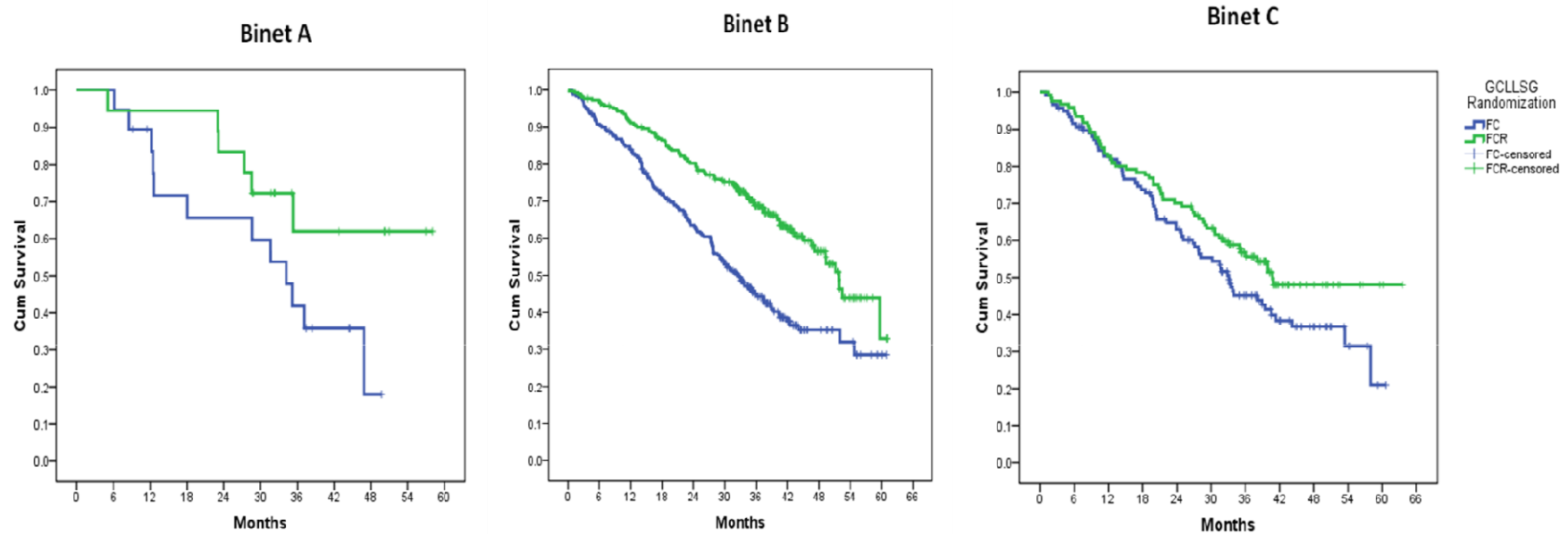
post

randomization:

FCR: 64.9%

FC: 44.7%

Progression-free survival and Binet stage



Binet A	Binet B	Binet C	
37	513	239	n
0.423	0.504	0.732	Hazard ratio
41.8 months	44.9 months	45.2 months	PFS FC at 3 ys post randomization
61.9 months	68.8 months	56.8 months	PFS FCR at 3 ys post randomization

Treatment efficacy in Binet stage C patients

	FC	FCR	<i>p</i> -value
CR (best response)	14.7%	37.4%	< 0.001
MRD– (final restaging, PB)	27.3%	61.9%	< 0.001
Median PFS (months)	45.2	56.8	0.081

Imbalance between treatment arms in Binet stage C patients

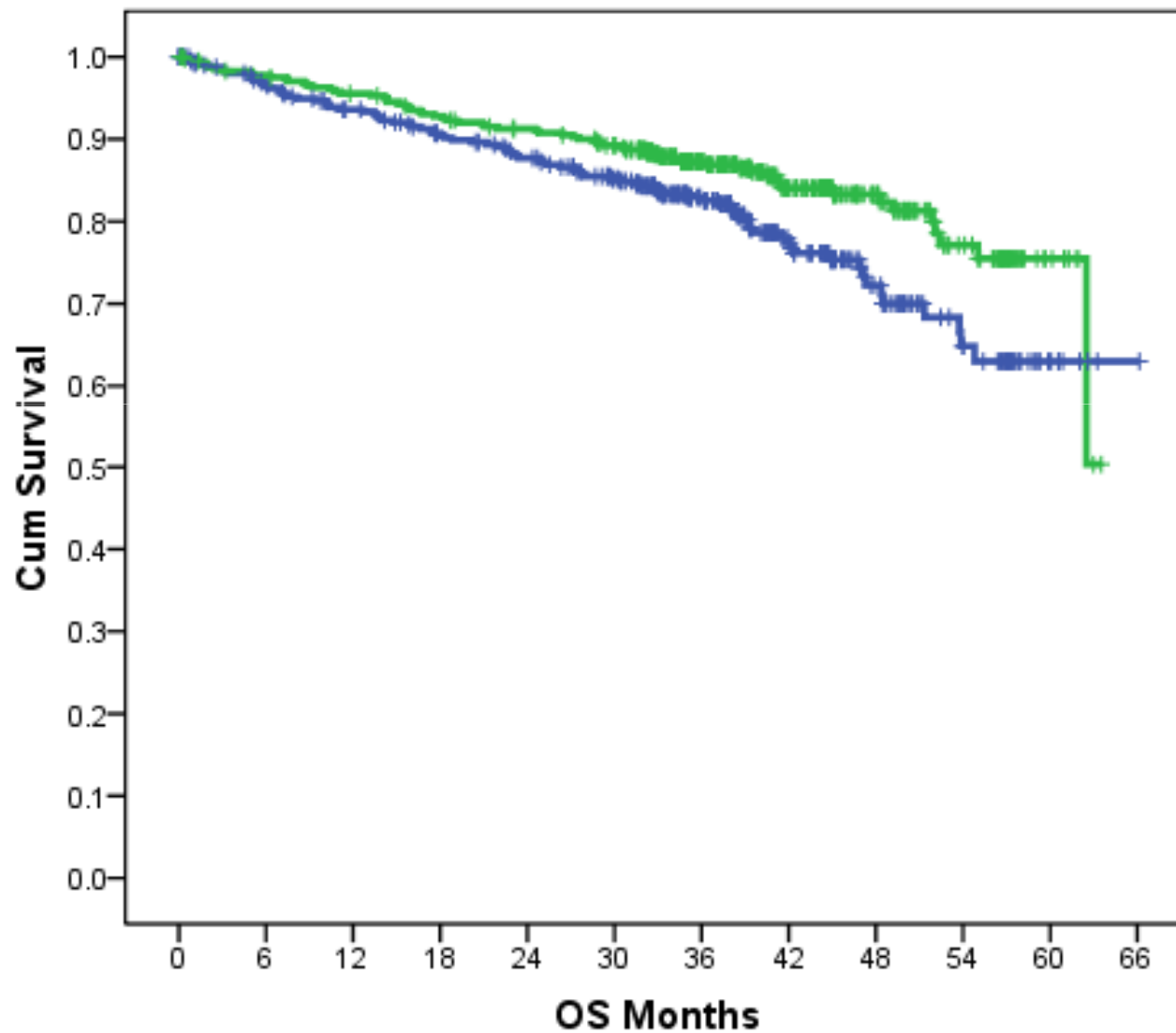
Risk factors (all differences $p > 0.05$)

	FC	FCR
Age \geq 65 yrs	28.6%	34.9%
Time from diagnosis to study (months)	12.6	22.5
Elevated ZAP-70	33.3%	42.2%
IGHV unmutated	48.4%	55.1%
β_2 -m \geq 3.5 mg/dl	44.0%	51.6%

More treatment reductions and delays with FCR ($p < 0.01$)

	FC	FCR
Treatment delays $> 10\%$	22.1%	41.1%
Courses with $> 10\%$ dose reduction	27.9%	49.2%

Overall survival



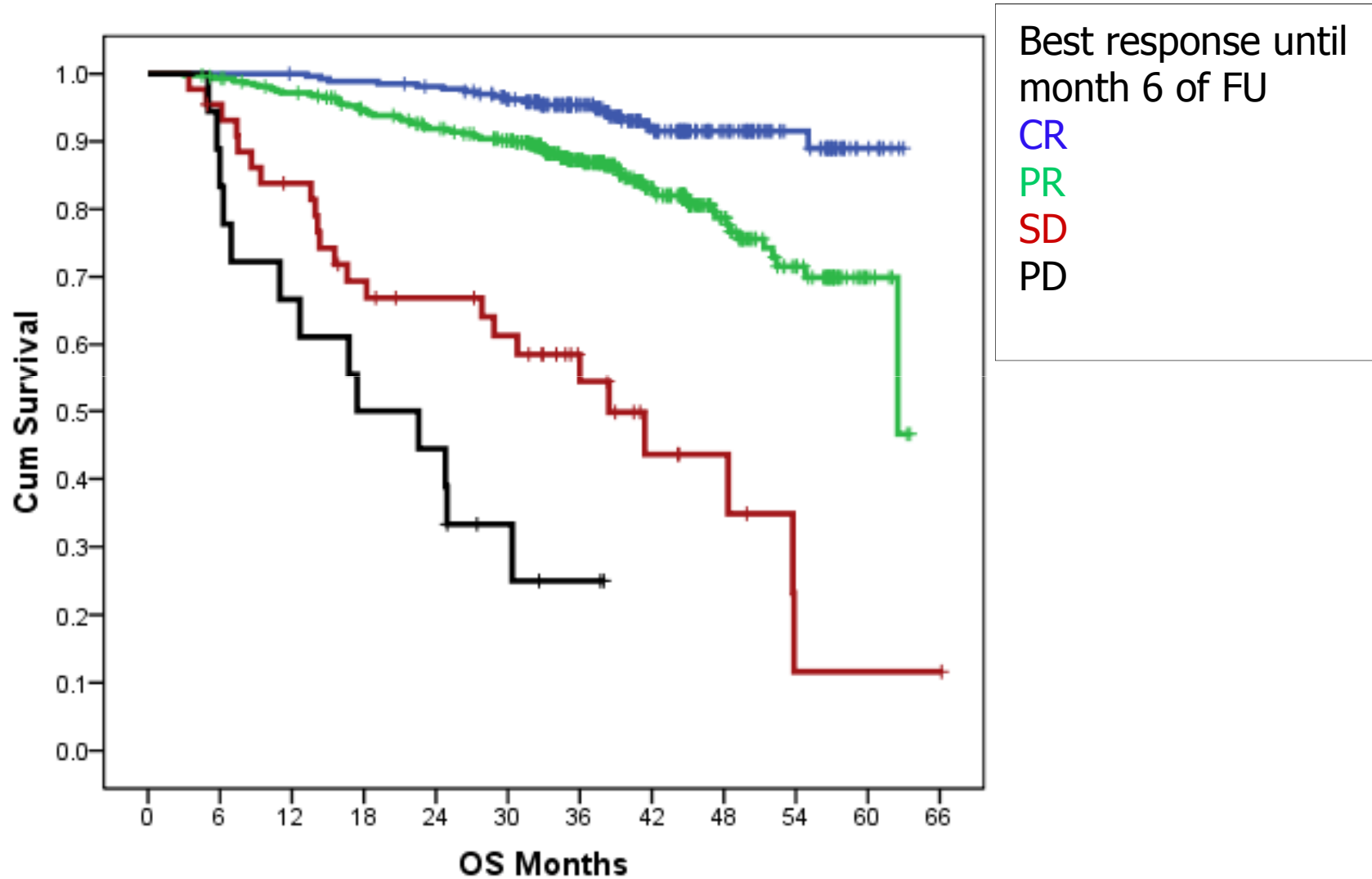
Overall survival 3
years post
randomization:

FCR: 87.2%

FC: 82.5%

n=817, HR 0.664,
p=0.012

Overall survival and type of response



Rate of complete remissions in different genetic subgroups

(S. Stilgenbauer)

	n	CR (%)	FC (%)	FCR (%)	Δ	p
All patients	759	33.2	21.8	44.1	2.0x	< 0.001
13q- single	211	36.5	24.8	49.0	2.0x	<0.001
11q-	135	37.0	15.5	53.2	3.4x	< 0.001
Trisomy 12	56	42.9	21.9	70.8	3.2x	< 0.001

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Trisomy 12	56	42.9	21.9	70.8	3.2x	< 0.001
17p-	43	2.3	0	4.8	n.a.	0.3
None	130	33.8	28.6	37.8	1.3x	0.27

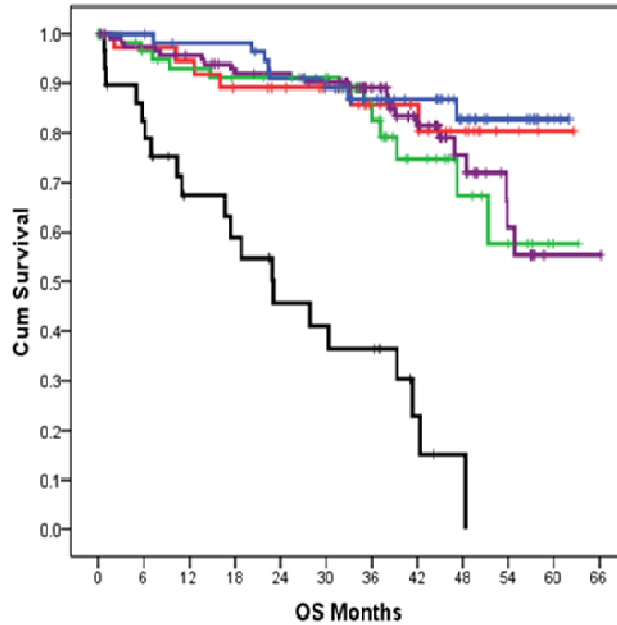
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17p-	43	2.3	0	4.8	n.a.	0.3
None	130	33.8	28.6	37.8	1.3x	0.27
<i>IGHV</i> mut.	206	35.9	19.8	51.4	2.6x	< 0.001
<i>IGHV</i> unmut.	351	32.2	20.4	42.9	2.1x	< 0.001

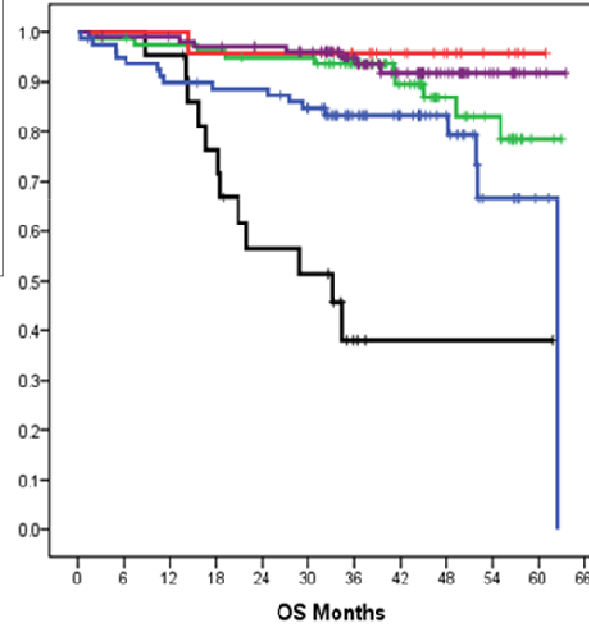
Overall survival and cytogenetic abnormalities according to the hierarchical model

FC



3-yr OS*
None: 86.9%
12q+: 85.8%
11q-: 82.6%
13q-: 89.1%
17p-: 36.5%

FCR



3-yr OS*
None: 83.8%
12q+: 95.8%
11q-: 93.7%
13q-: 94.9%
17p-: 38.1%

Cox regression analysis of prognostic factors

Parameter	PFS (95% CI)		OS (95% CI)	
	Hazard ratio	P-value	Hazard ratio	P-value
FCR treatment	0.479	<0.001	0.581	0.009
$\beta_2m > 3,5$ mg/dl	1.450	0.005	2.287	<0.001
ECOG ≥ 1			1.731	0.009
Del(17p)	7.642	<0.001	9.013	<0.001
IGHV unmut	1.478	0.013		
Age > 60 y	1.339	0.022		
WBC >50 G/L	1.432	0.011		

205 Bendamustine Combined with Rituximab (BR) in First-Line Therapy of Advanced CLL: A Multicenter Phase II Trial of the German CLL Study Group (GCLLSG)

M Hallek

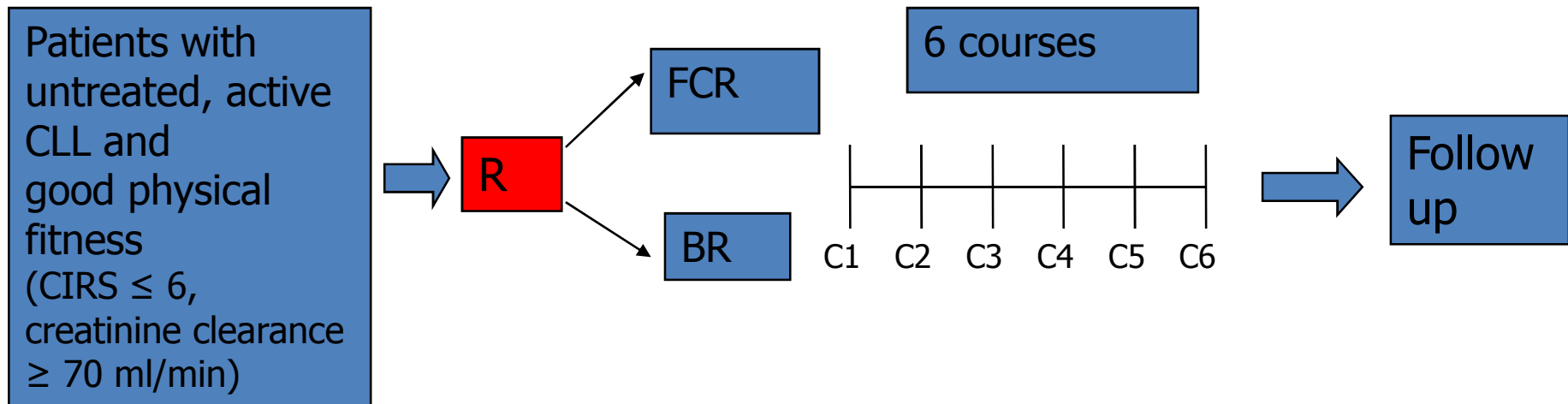
117 patients, median age 64 years

Bendamustine 90mg² D1+2, R 375mg²/500mg²

Toxicity: myelosuppression (6%) and infection \geq CTC grade 3: 5% of cycles

- ORR 90%, clinical CR: 32.7% (44% with FC-R), no patients had progressive disease
- MRD blood: 29/50
- MRD bone marrow: 7/25
- 11qdel: ORR 90.5%
- 17pdel ORR: 42%
- IGH unmutated QRR: 88.9%
- 5% stopped early because of infections, 10% because of other causes

Planned GCLLSG CLL 10: FC-R vs BR



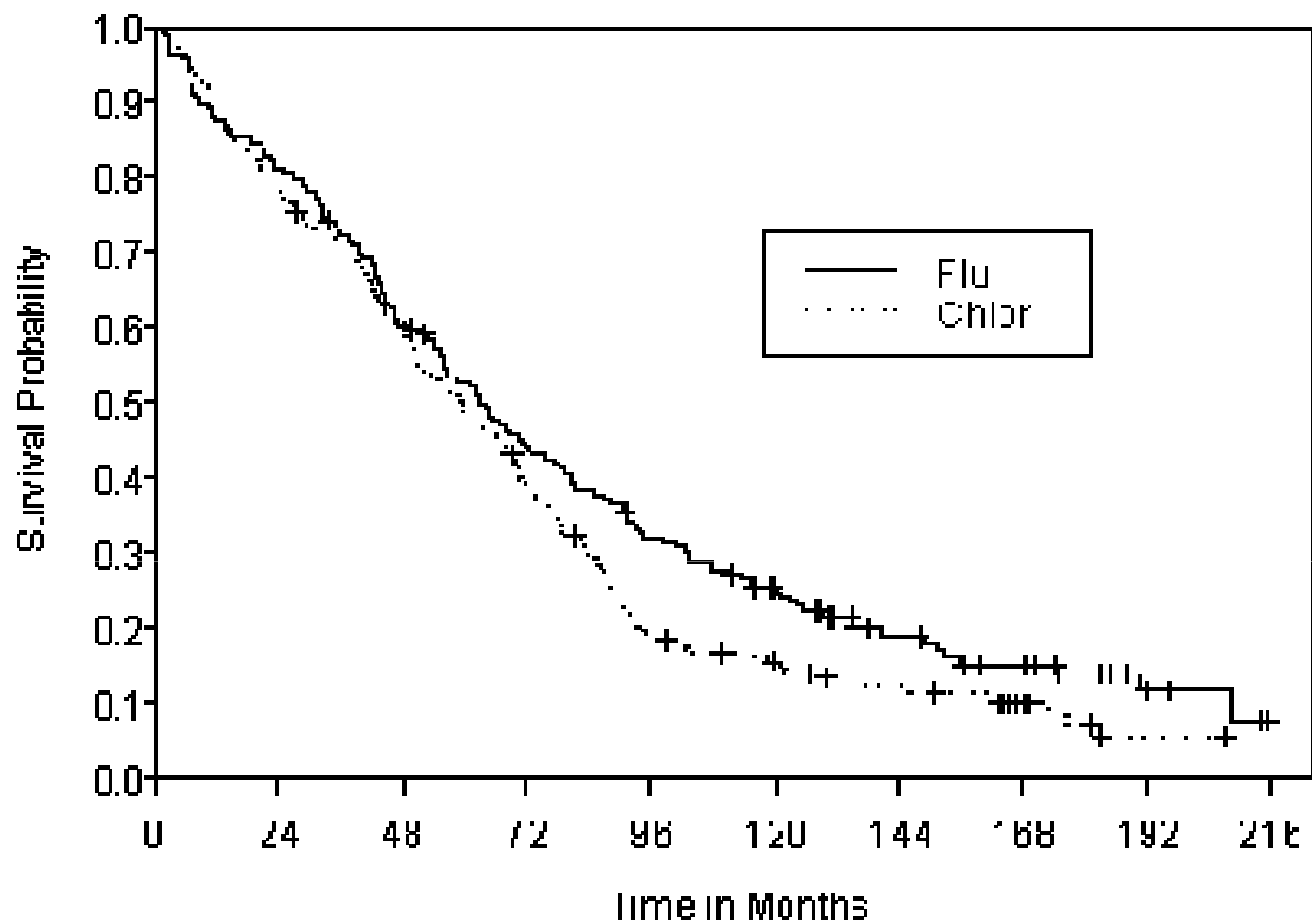
**536 Long-Term Survival Analysis of the North American Intergroup Study
C9011 Comparing Fludarabine (F) and Chlorambucil (C) in Previously
Untreated Patients with Chronic Lymphocytic Leukemia (CLL)
Kanti Rai, New York**

- Period: 10/90 to 12/94
 - Cross-over allowed
 - FC arm closed due to toxicity

 - OS benefit after 5-6 years

 - Second cancers in 17%
 - 27 epithelial cancers
 - 34 Richter's
 - 19 lymphomas
 - 7 myeloid neoplasm
- 6 in FC, 1 in F

	Fludarabine	Chlorambucil	F+C
N	179	193	137
Died N (%)	147 (82)	172 (89)	113 (82)
Median PFS	20 (17-25)	13 (12-17)	
%PFS at 2 yrs	45	26	
%PFS at 3 yrs	31	10	
%PFS at 4 yrs	21	6	
Median OS	63 (55-75)	59 (51-70)	45 (43-64)
%alive at 4 yrs	60	60	54
%alive at 6 yrs	31	10	37
%alive at 8 yrs	31	19	26



Number of Patients at Risk

Flu	179	145	107	76	54	36	21	14	4	0
Chbr	193	152	115	73	35	26	18	9	2	0

540 Minimal Residual Disease Is a Predictor for Progression-Free and Overall Survival in Chronic Lymphocytic Leukemia (CLL) That Is Independent of the Type or Line of Therapy

Peter Hillmen, Leeds

137 patients, different treatments

BM MRD by 4-colour flow according to International Standardization

58 MRD negative: 28 CR, 20 CRi, 3 nPR and 7 PR patients

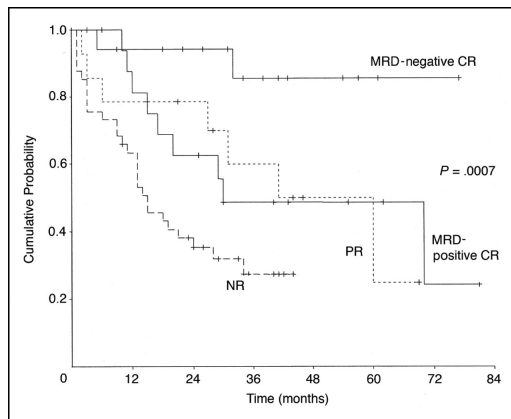
5 year PFS 89% for MRD neg vs 0% for MRD pos patients

	Overall Survival Hazard Ratio (95%CI)
Age	2.2
Hb (>10g/l)	1.03
Plt (<100)	0.81
Prior treatment	2.29
Prior fludarabine	1.85
Type of treatment	
CR vs PR	1.1
MRD	2.4

P value<0.05

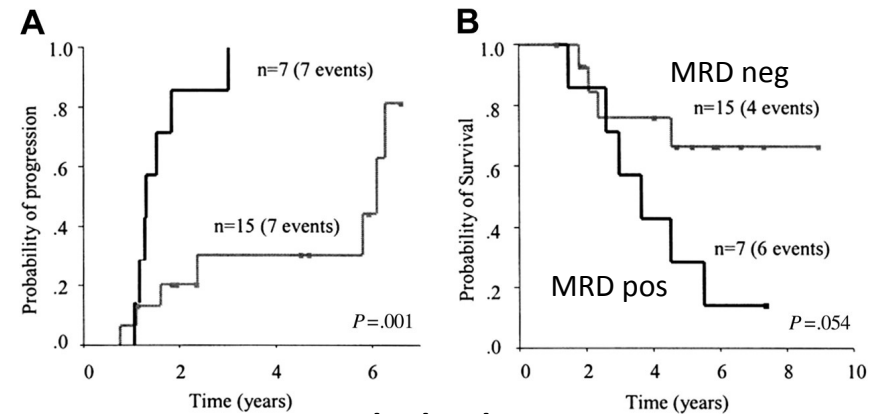
Role of Minimal Residual Disease Monitoring

Overall survival after Campath in refractory/relapsed CLL



Moreton, P. et al. J Clin Oncol; 23:2971-2979 2005

Progression and OS after autologous PBSCT



Moreno, C. et al. Blood 2006;107:4563-4569

Other studies:

FCM Bosch, F. et al. Clin Cancer Res 2008

FC UK CLL4, Lancet 2008

FC-R GCLLSG CLL8, ASH 2008

- International Standardization of MRD measurement by Flowcytometry, Leukemia 2007
- International Standardisation of MRD by qPCR Leukaemia 2003

SLOW-GO PATIENTS

Poster III-177
R-Chlorambucil - CLL208 (MO20927)
Peter Hillmen on behalf of NCRI UK Study Group

1st line Phase II: Chlorambucil +R in patients with co-morbidities
Planned interim analysis of the first 50 patients
Comparison with CLL4 chlorambucil arm
Median age 70.5 years, 52% Stage C
Grade 3-4 neutropenia: 40%

Toxicity

- The most common AEs were gastrointestinal disorders
- 25 serious AEs (SAEs) reported in 17 patients
- Most common SAEs were infections (10 SAEs, in 6 patients)
- Grade 3 or 4 neutropenia was reported in 40% of patients
- Additionally there were 3 cases (in 3 patients) of febrile neutropenia

Courtesy Peter Hillmen

R-chlorambucil - CLL208 vs LRF CLL4

Overall response rate

Overall Response Rate and 95% Confidence Interval

Trial	ORR	SD/PD	Missing	95% CI achieving at least a PR*	Total number of patients
CLL208	84.0%	10.0%	6.0%	[70.9, 92.8]	50
CLL4 (Chlor)	66.7%	30.0%	3.3%	[58.5, 74.1]	150

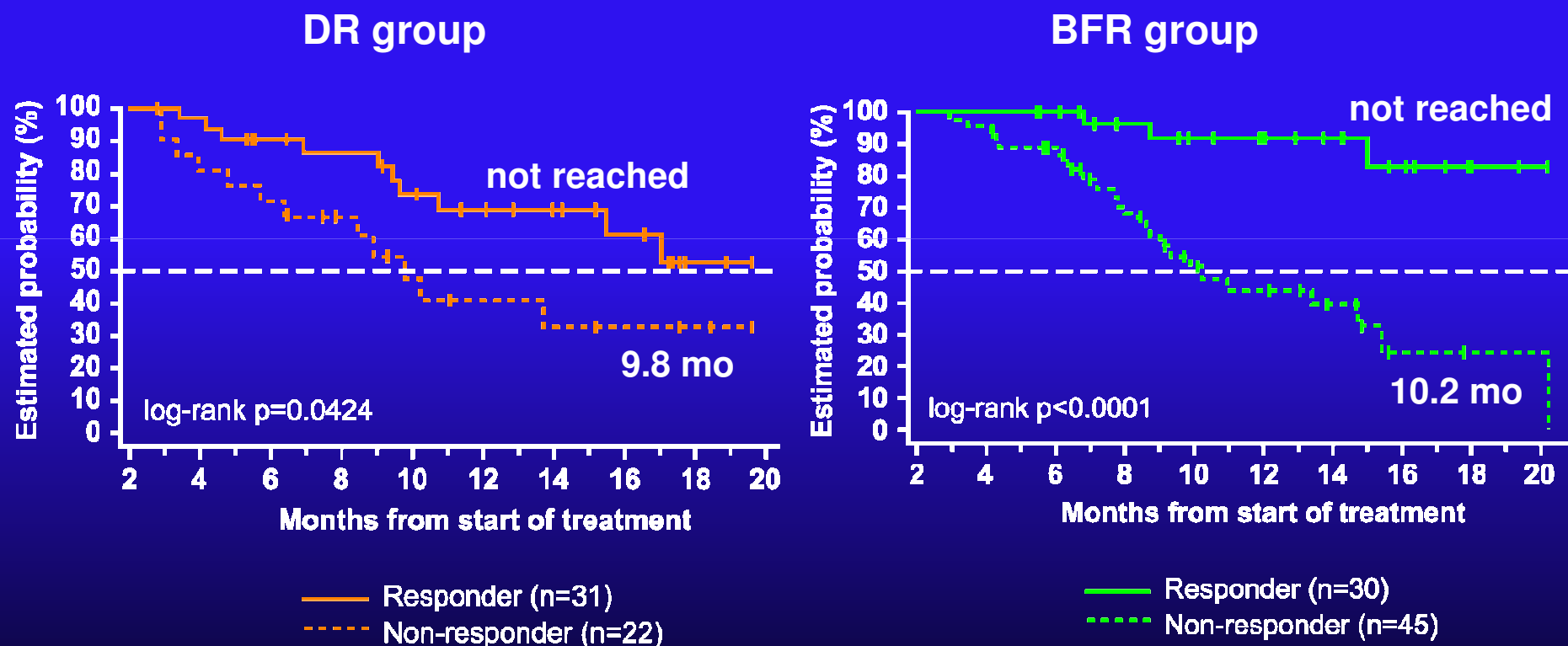
*Confidence intervals are calculated using the Exact method

NB the confidence interval for the two groups is [4.7%, 30.0%] and does not include zero suggesting that the patients in the Chlor-R responded better than those in CLL4

Ofatumumab in refractory CLL

Median overall survival by response

Landmark analysis¹ at Week 12*



1. Anderson et al. *J Clin Oncol* 2008;26: 3913.

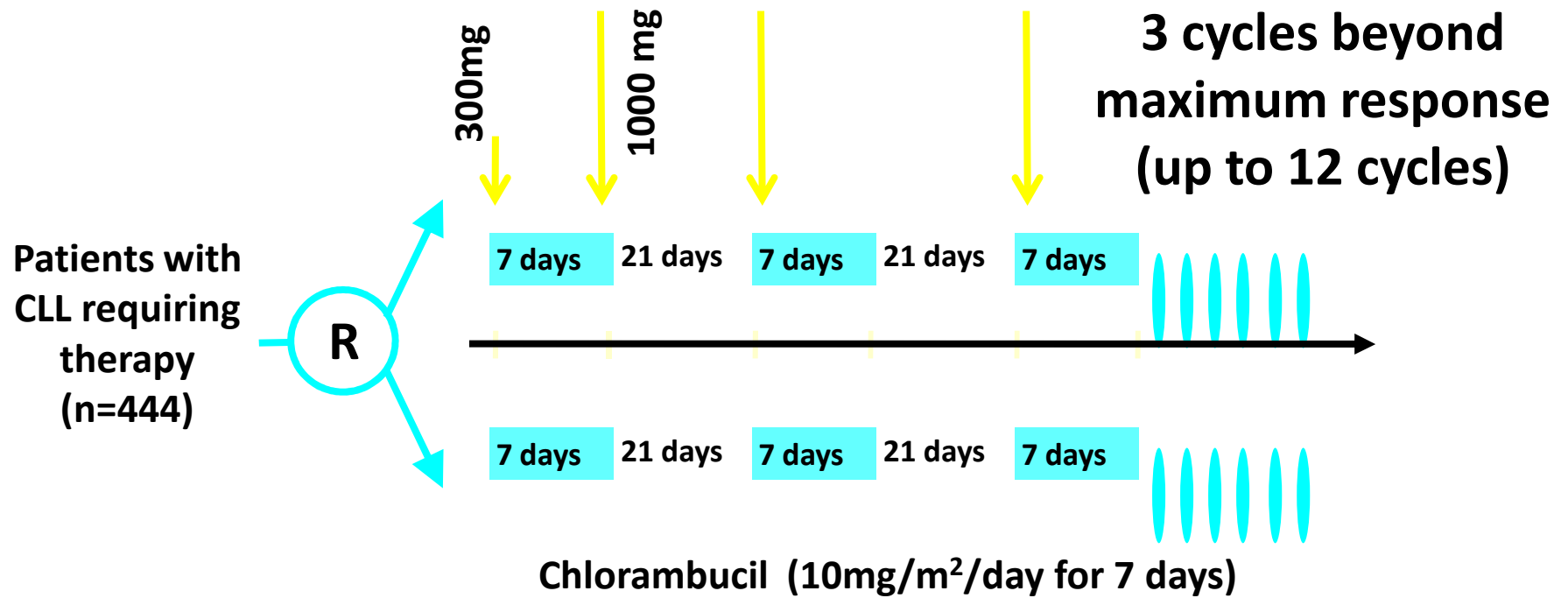
*Analysis included patients who were alive at the Week 12 time point.

884 Phase I Study of RO5072759 (GA101) in
Relapsed/Refractory Chronic Lymphocytic Leukaemia
Morschhauser F et al, France

- Dose escalation study
- 13 patients, relapsed/refractory “last ditch” ?
bulky disease
- Well tolerated, grade 3/4 neutropenia in 9/3
patients, G-CSF supported
- ORR 62%
- PK data awaited

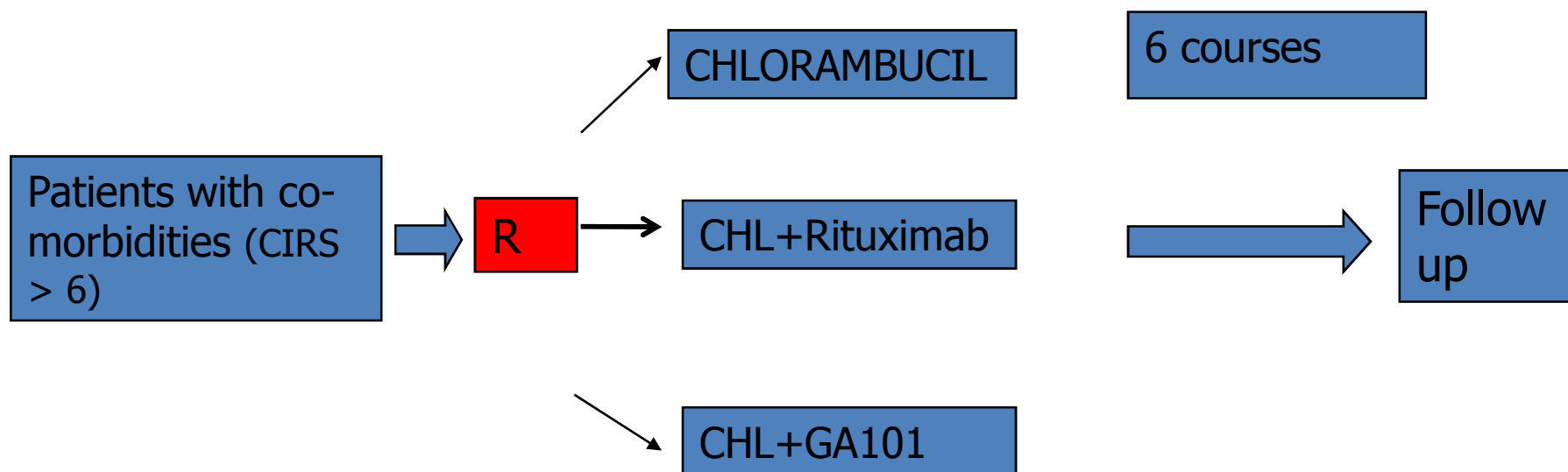
NCRN CLL7: GSK Registration Study for Ofatumumab (OMB110911 Trial) for patients with co-morbidities

Ofatumumab (300mg + 1000mg cycle 1, 1000mg cycles 2–12)
Chlorambucil (10mg/m²/day for 7 days)



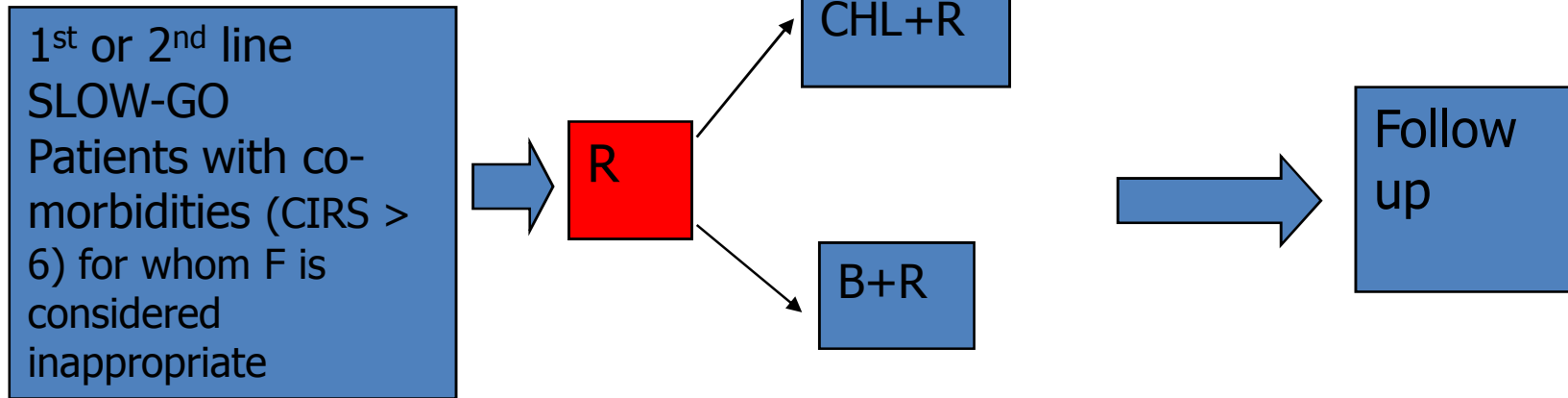
Primary end-point = Progression Free Survival

German CLL11 (10 UK Centres)



GA101, but not Rituximab given weekly for the first 4 weeks

“Ribbecca”



ALEMTUZUMAB

Alemtuzumab Combinations

209 Chemoimmuno-Therapy with Fludarabine, Cyclophosphamide and Alemtuzumab (FC-Cam) in Patients with Relapsed or Genetic High-Risk CLL: Final Analysis of the CLL2L Trial of the German CLL Study Group

- CLL2L: relapsed patients, 15% F refractory
- F25/C200-Cam D1-3, 90mgs/cycle s.c.
- 61 patients, Mean age: 63
- **12 deaths** (5 related to therapy, 3 concomitant disease, 4 progressive disease)
SAEs: CMV (x5), H zoster x1, Aspergillus x2;
study stopped

210 Consolidation Therapy with Subcutaneous (SC) Alemtuzumab After Fludarabine and Rituximab (FR) Induction Therapy Improves the Complete Response (CR) Rate in Chronic Lymphocytic Leukemia (CLL) and Eradicates Minimal Residual Disease (MRD) but Is Associated with Severe Infectious Toxicity: Final Analysis of CALGB Study 10101FR-Alemtuzumab consolidation

- **A maintenance 30mgs 3x/week up to 6 weeks after FRx6**
- After occurrence of 3 deaths in CR, study was changed to: maintenance with A only if not in CR
- **7 deaths** in total, 5 in CR

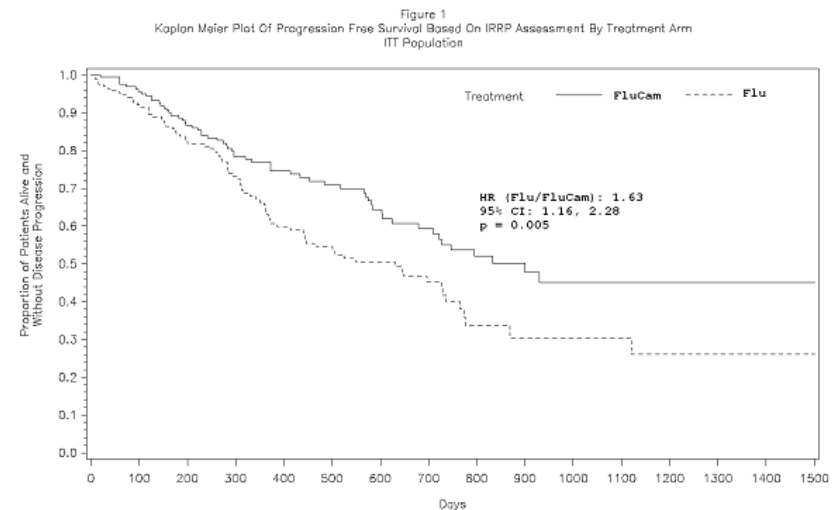
	ORR	CR	MRD neg CR
After FR	90	29	15
After A maintenance	91	56	50

538 Immunochemotherapy with Fludarabine (F), Cyclophosphamide (C), and Rituximab (R) (FCR) Versus Fludarabine (F), Cyclophosphamide (C) and MabCampath (Cam) (FCCam) in Previously Untreated Patients (pts) with Advanced B-Chronic Lymphocytic Leukemia (B-CLL) : Experience On Safety and Efficacy within a Randomised Multicenter Phase III Trial of the french Cooperative Group On CLL and WM (FCGCLL/MW) and the “Groupe Ouest-Est d’Etudes Des Leucémies Aigües Et Autres Maladies Du sang” (GOELAMS) : CLL2007FMP (for fit medically patients)

- FC-R versus FC-A
- 178 patients, CIRS<6, <65 years old
- Trial stopped early due to **excess mortality** in FC-A arm 7 patients vs 0 in FC-R
- Causes of death:
3 of B diffuse large B-cell lymphoma (one of them EBV positive), 1 of mucormycosis, 1 of septic shock due to P.aeruginosae and 2 of heart failure during neutropenia. ORR in the first 100:
96% in the FCR arm vs 85% in the FCCam arm (p=0.086). CR: 78% (FCR arm) versus 58% (FCCam arm) (p=0.072).

537 Improved Progression-Free Survival (PFS) of Alemtuzumab (Campath®, MabCampath®) Plus Fludarabine (Fludara®) Versus Fludarabine Alone as Second-Line Treatment of Patients with B-Cell Chronic Lymphocytic Leukemia: Preliminary Results From a Phase III Randomized Trial

- Randomised controlled trial
- 335 patients
- Relapsed, F refractory excluded
- 20% had received F before, 14% bulky LN
- Fludarabine versus Flu 30mgs iv +Campath 30mgs iv D1-3
- Median age 60
- ORR: 84.8% vs 68 %
- CR: 30% vs 16%
- PR: 54% vs 51%
- PFS: 29% vs 20.7%
- Deaths: 2% in F-Cam vs 5% in F



Conclusions:

- The addition of rituximab to FC first line therapy improves the outcome of patients with advanced, symptomatic CLL with regards to
 - Response rates (CR, ORR, MRD)
 - Progression-free survival
 - Overall survival
 - Del11q and trisomy 12 are no longer poor prognostic factors
 - Del17p requires different treatment approaches
 - The presence of a del(17p), FC (versus FCR) therapy, and an elevated serum β_2 -microglobulin levels are the strongest predictors for treatment failure.
- CLL8 is the first randomized trial to demonstrate that the choice of first line therapy improves the natural course of CLL
- FC-R is the new Standard of Care for GO-GO Patients with B-CLL

Conclusions, cont:

- Long-term follow-up data on B-CLL suggests that sequential treatment does not improve overall survival and probably shortens it
- MRD monitoring becomes the accepted surrogate marker for overall survival
- The next generation of Phase III trials in the UK and Germany will investigate the role of Bendamustine, Rituximab, GA101 and Ofatumumab
- There is currently no role for Alemtuzumab combination therapy Standards of Care for relapsed patients in the post FC-R era and for patients with co-morbidities need to be defined