

CLL- Inducing a Response and Maintaining Remission

Jornada Chilena en Hematología y Medicina
Transfusional

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First-line treatment of CLL

Historical overview (pre-Rituximab)

- Purine analogue monotherapy, e.g. fludarabine
 - ORRs of 60–80%, CRs of 10-20%¹⁻³
- Purine analogue + alkylating agent
 - Improvements in ORR + PFS, CRs of 20–35%
 - No improvement demonstrated in OS^{2,4}
- Purine analogue + alkylating agent + anthracycline, e.g. FCM
 - ORR of 91%, CR of 50% (including 23% MRD–ve CR)
 - 55% response duration at 36 months⁵

1. Rai KR, *et al. New Engl J Med* 2000; 343:1750–1757.

2. Eichhorst BF, *et al. Blood* 2006; 107:885–891.

3. Keating MJ, *et al. Blood* 1998; 92:1165–1171.

4. Flinn IW, *et al. J Clin Oncol* 2007; 25:793–798.

5. Bosch F, *et al. Clin Cancer Research* 2008;

Rituximab as part of first-line therapy for CLL: Rationale

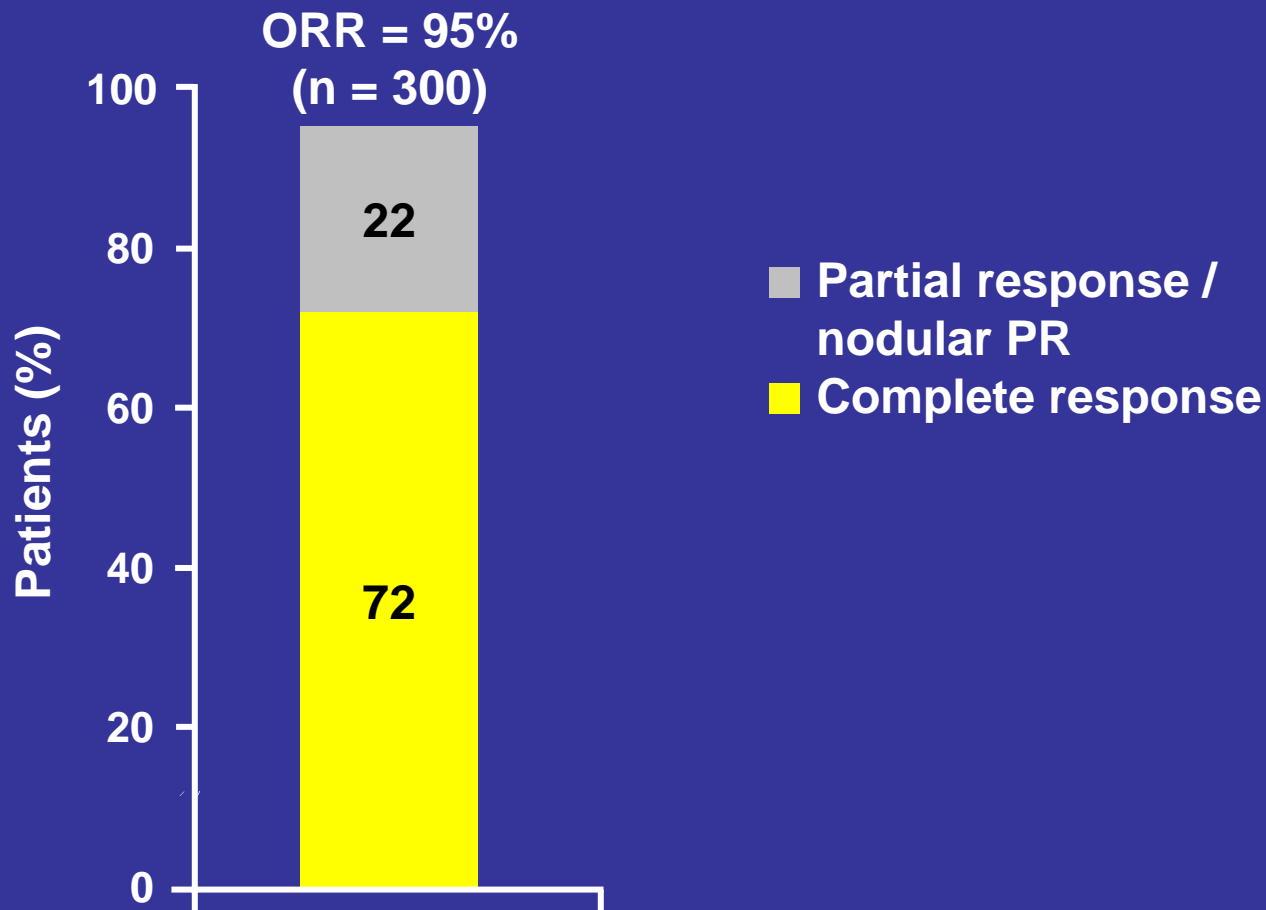
- Rituximab monotherapy is active in CLL
 - Activity is dose dependent (between 500–2250 mg/m²)
O'Brien SM, et al. J Clin Oncol 2001; 19:2165–2170
- Rituximab acts synergistically *in vitro* with other agents
 - Increases fludarabine activity in NHL cell lines¹
 - Increases activity of bendamustine, mitoxantrone and other chemotherapeutic agents in CLL cells²
- Rituximab combination therapies (e.g. FR, FCR, PCR, FCM-R, Bendamustine-R) are now being assessed

1. Alas S, et al. *Clin Cancer Res* 2001; 7:709–723.
2. Chow KU, et al. *Haematologica* 2002; 87:33–43.

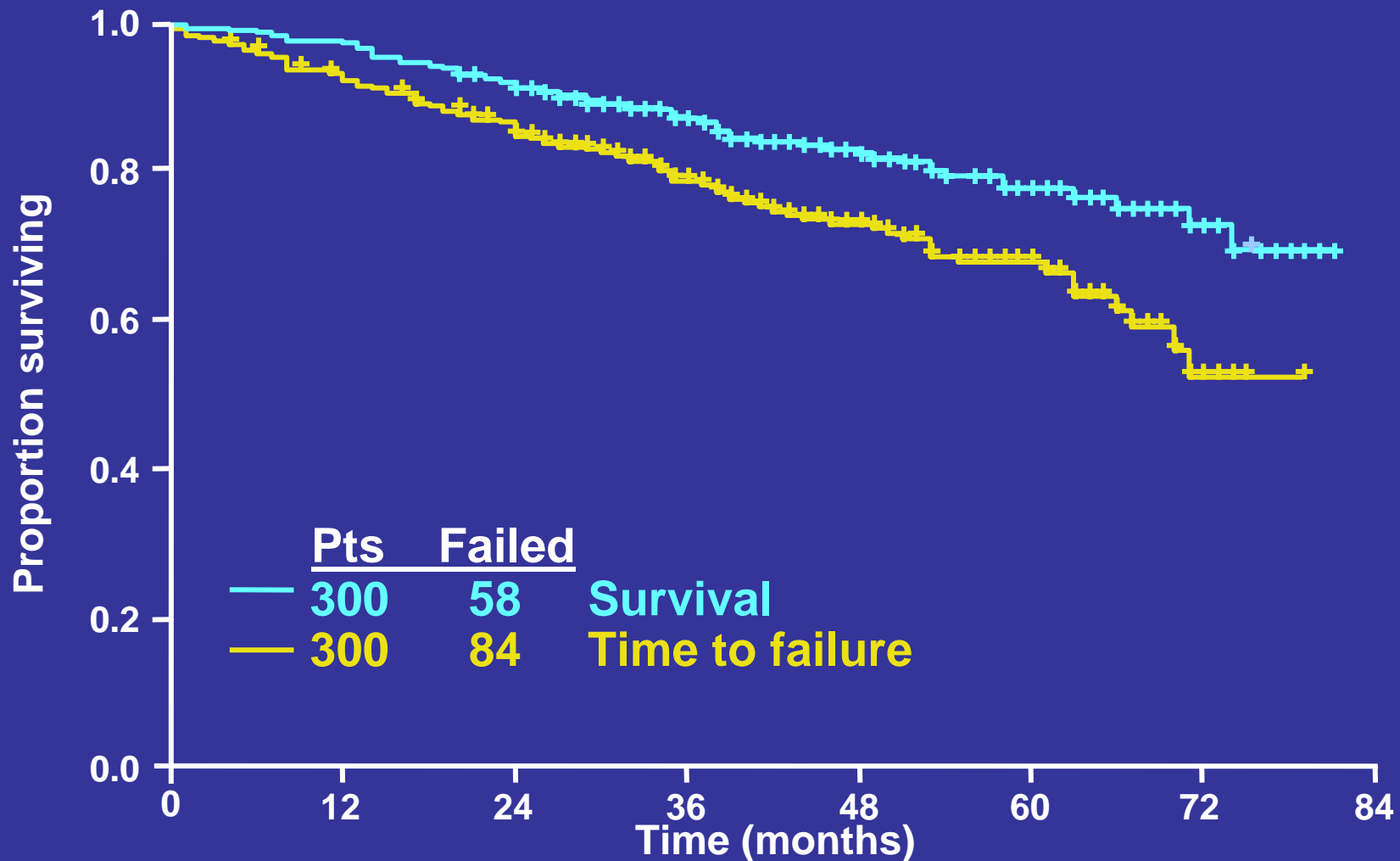
First-line FCR: Dose and schedule

Drug	Dose (mg/m ²)	Days of course	
		Course 1	Courses 2–6
Rituximab	375–500	Day 1 (375 mg/m ²)	Day 1 (500 mg/m ²)
Fludarabine	25	2–4	1–3
Cyclophosphamide	250	2–4	1–3

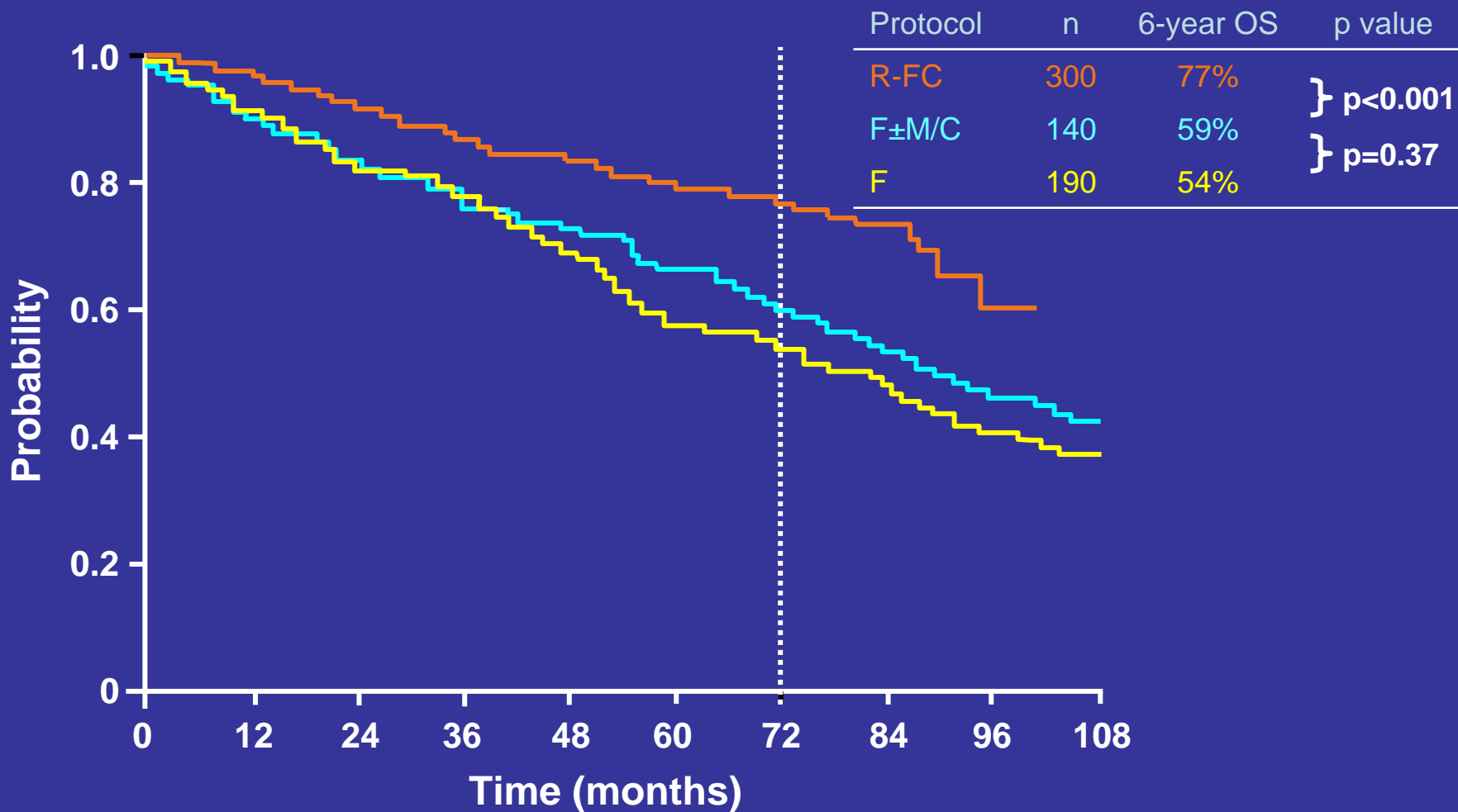
First-line FCR: Almost all patients respond, with a high proportion of CR



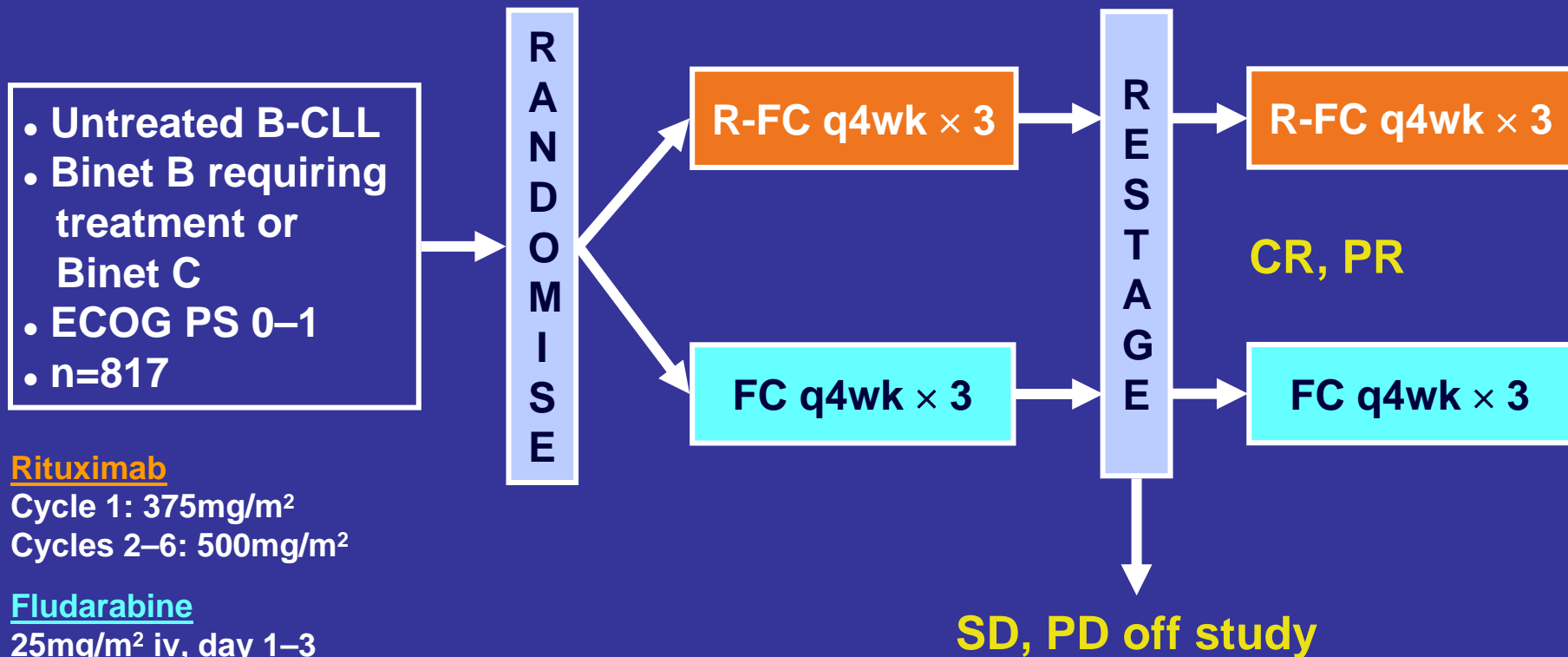
First-line FCR: Survival and time to failure



Improved OS with R-FC in first-line CLL (historical comparison)



The CLL-8 trial: R-FC vs. FC in previously untreated 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

ECOG PS = Eastern Cooperative Oncology
Group performance status; q4wk = every 4 weeks
SD = stable disease; progressive disease

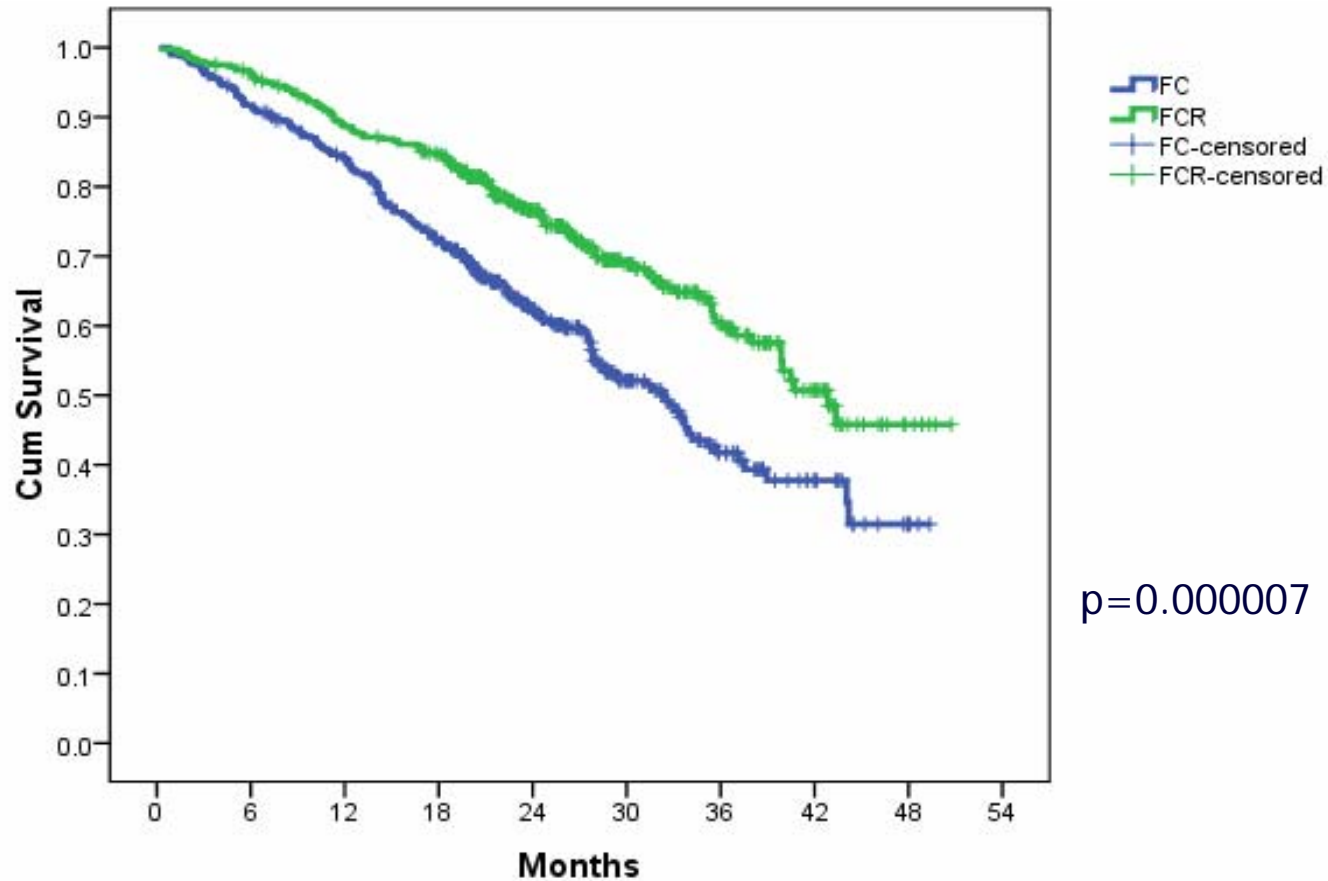
Principal investigators: M Hallek, G Fingerle-Rowson

CLL 8 - German CLL Study Group

	FC	FCR
Evaluable patients	390 (409)	371 (408)*
ORR (%)	84.4	94.9
CR (%)	23.5	44.7
PR (%)	61.7	48.1
PD (%)	8.1	3.3
PFS @ 2 yrs (median)	~32 m.	~ 42 m.
OS @ 2 yrs	88%	91%

(*) between parenthesis total number of patients randomized

Progression free survival: FCR versus FC



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

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

(R)-FCM in CLL

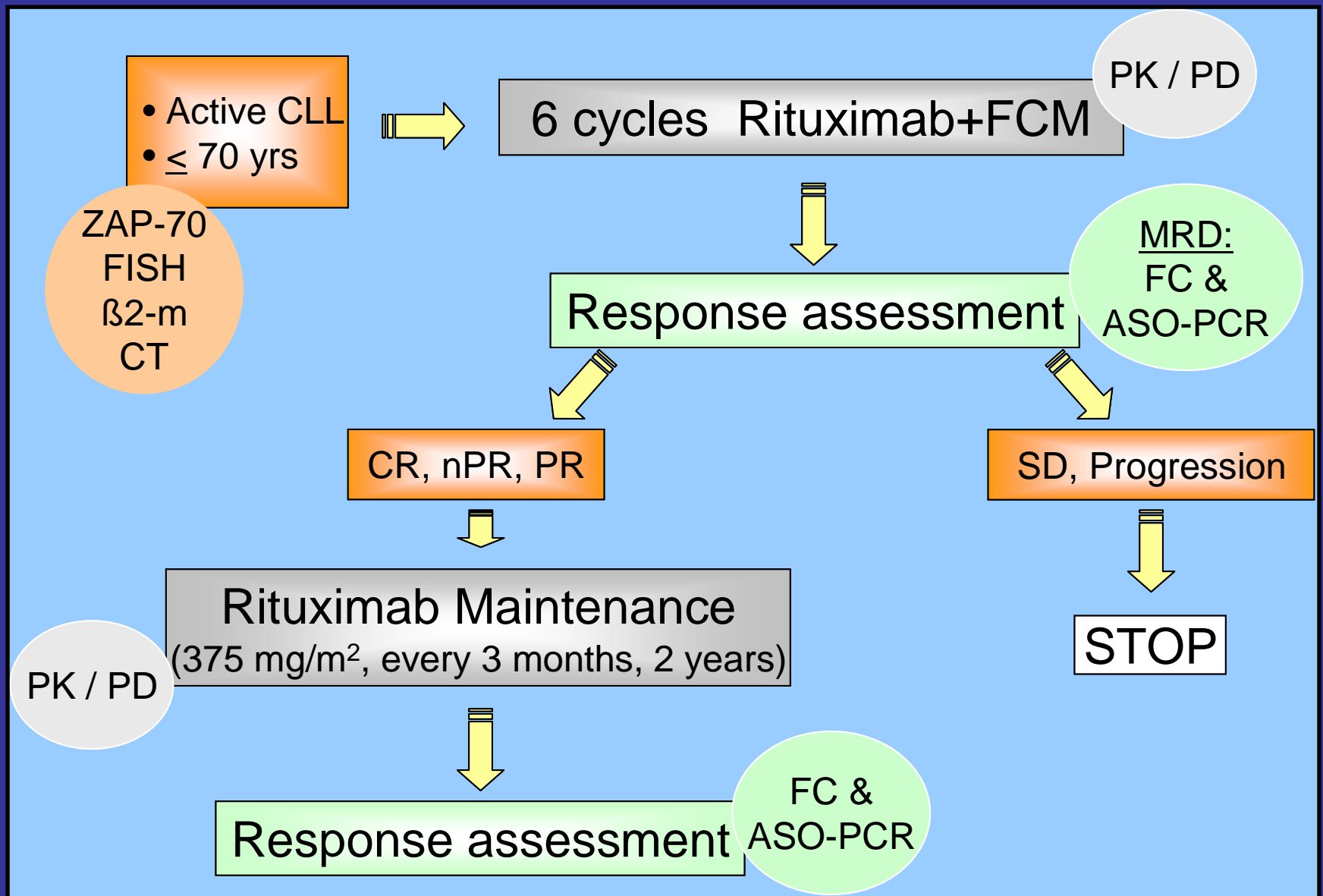
- Synergism of fludarabine with both cyclophosphamide and mitoxantrone ⁽¹⁾
- Treatment with FCM (fludarabine, cyclophosphamide, and mitoxantrone) results in:
 - 60% response rate in relapsed or refractory CLL ⁽²⁾
 - 90% response rate in previously untreated CLL ⁽³⁾

(1) Bellosillo B et al. *Br J Haematol*, 1998; *Blood*, 1999

(2) Bosch F et al. *Br J Haematol*, 2002

(3) Bosch F et al. *Clin Cancer Res*, 2008 (in press)

R-FCM Treatment Schedule



R-FCM regimen

Lymphocyte count
> 30,000

50% dose day 0

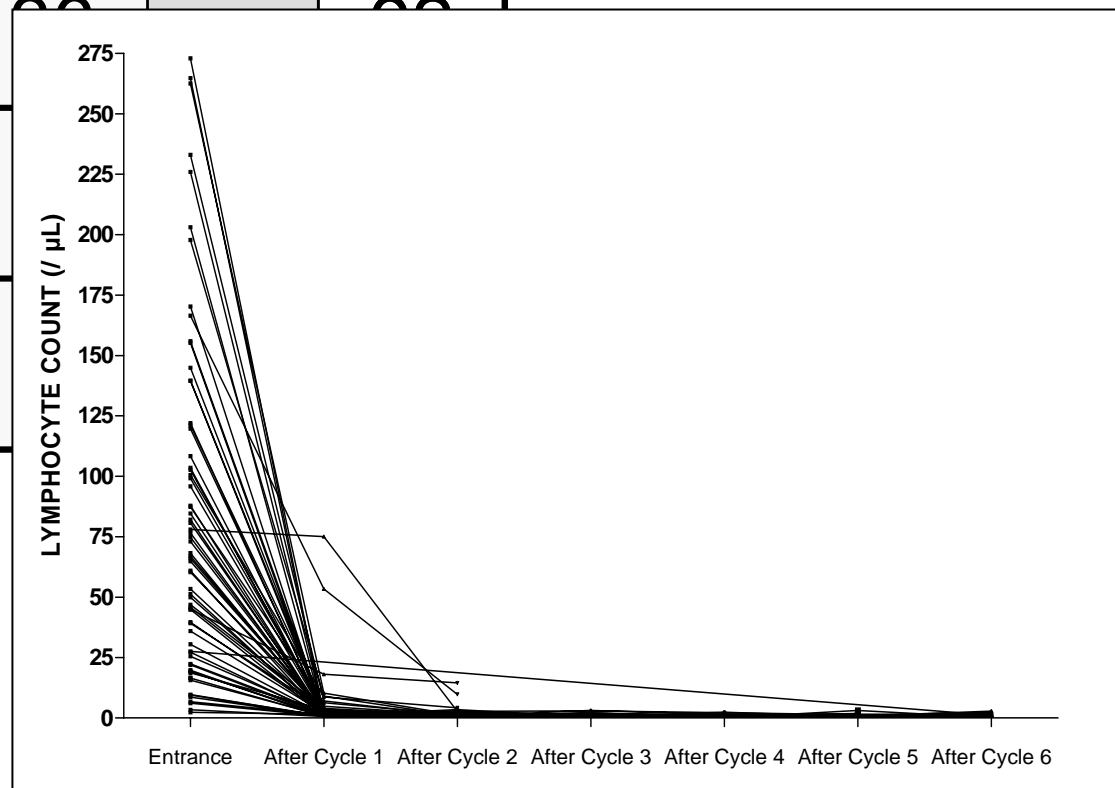
50% dose day 1

	Doses	Days
Rituximab	500 mg/m ² i.v. (375 mg/m ² i.v, 1 st dose)	1
Fludarabine	25 mg/m ² i.v	1-3
Cyclophosphamide	200 mg/m ² i.v.	1-3
Mitoxantrone	6 mg/m ² i.v.	1

Every four weeks, 6 cycles

G-CSF, cotrimoxazole

Response	%		
CR MRD (-)	46	82	
CR MRD(+)	36		36
PR			
Failure			



RFCM: Toxicity

	Grade 1/2	Grade 3/4
Hematological (NCI-WG)		
<i>Anemia</i>	17%	-
<i>Thrombocytopenia</i>	4%	2%
<i>Neutropenia</i>	28%	13%
No Hematological (WHO)		
<i>Infusion reaction</i>	9%	1%
<i>Fever unknown origin</i>	16%	
<i>Infection</i>	8%	5%(*)
<i>Mucositis</i>	10%	-
<i>Liver toxicity</i>	6%	-
<i>Renal toxicity</i>	3%	-
<i>Nausea/vomiting</i>	13%	1%
(*) Aspergillus + CMV that resulted fatal (1 patient)		

FCM vs. R-FCM

VARIABLE	FCM	R-FCM	p=
Grade 3-4 toxicity			
Neutropenia	4	13	< .001
Thrombocytopenia	—	2	< .01
Infection	1	5	< .001
Response			
CR MRD negative	26	46	
CR MRD positive	38	36	.034
PR	26	11	
Failure	10	7	
CR achievement predictors	Clinical stage, spleen size, serum LDH, β 2-microglobulin, BM, del(17p)	Clinical stage, β 2-microglobulin, del(17p)	

What is relapsed / refractory CLL?

- RELAPSE: Evidence of disease progression AFTER a period of 6 months of achieving the criteria of a CR or PR
- REFRACTORY DISEASE: Treatment failure (stable disease, non-response, progressive disease) or disease progression WITHIN 6 months of the last anti-leukemic therapy
 - “HIGH RISK CLL” (for allogeneic transplantation): refractory to a purine-analogue based therapy or to autologous hematopoietic SCT

CLL: Mechanisms of resistance

1. Impaired DNA-damage response genes

- Del17p → P53
- Del11q → ATM

2. Low expression of miR34

Zenz et al, Blood 2008

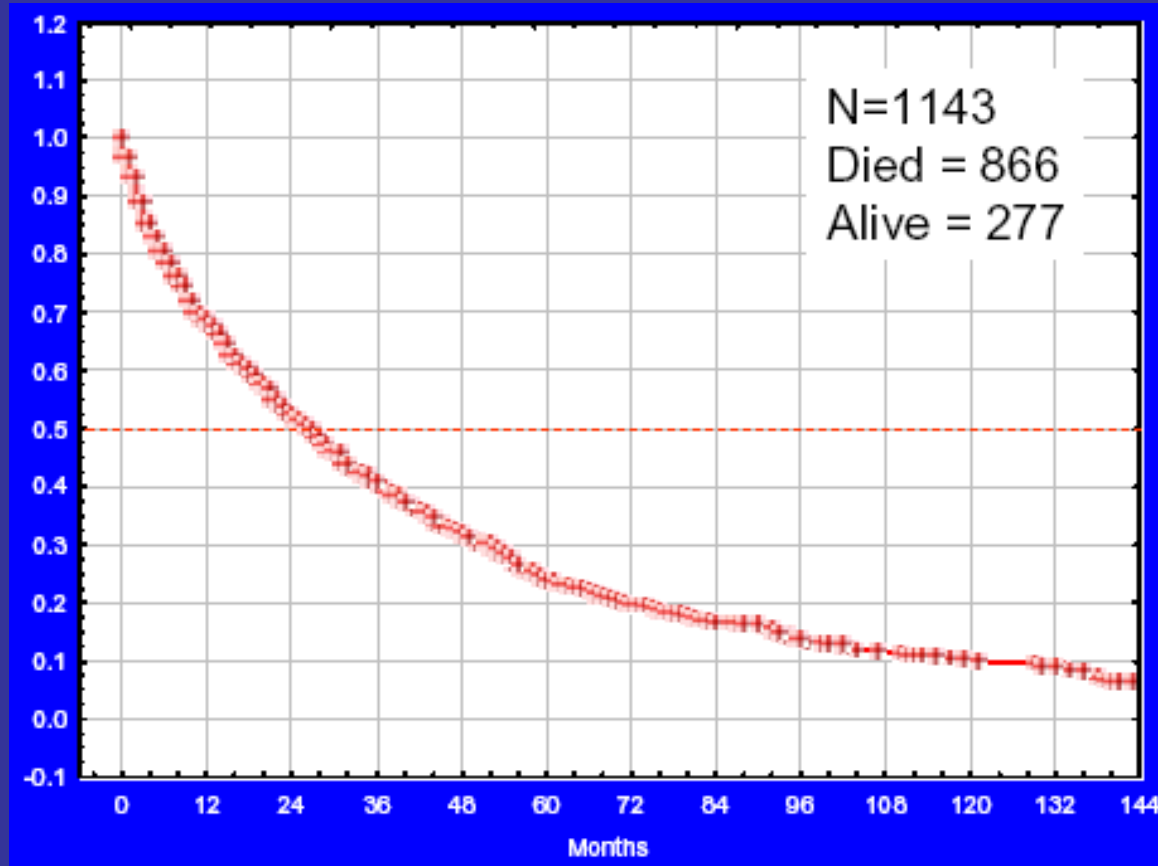
3. Microenvironment

- Lack of response to alemtuzumab in bulky disease

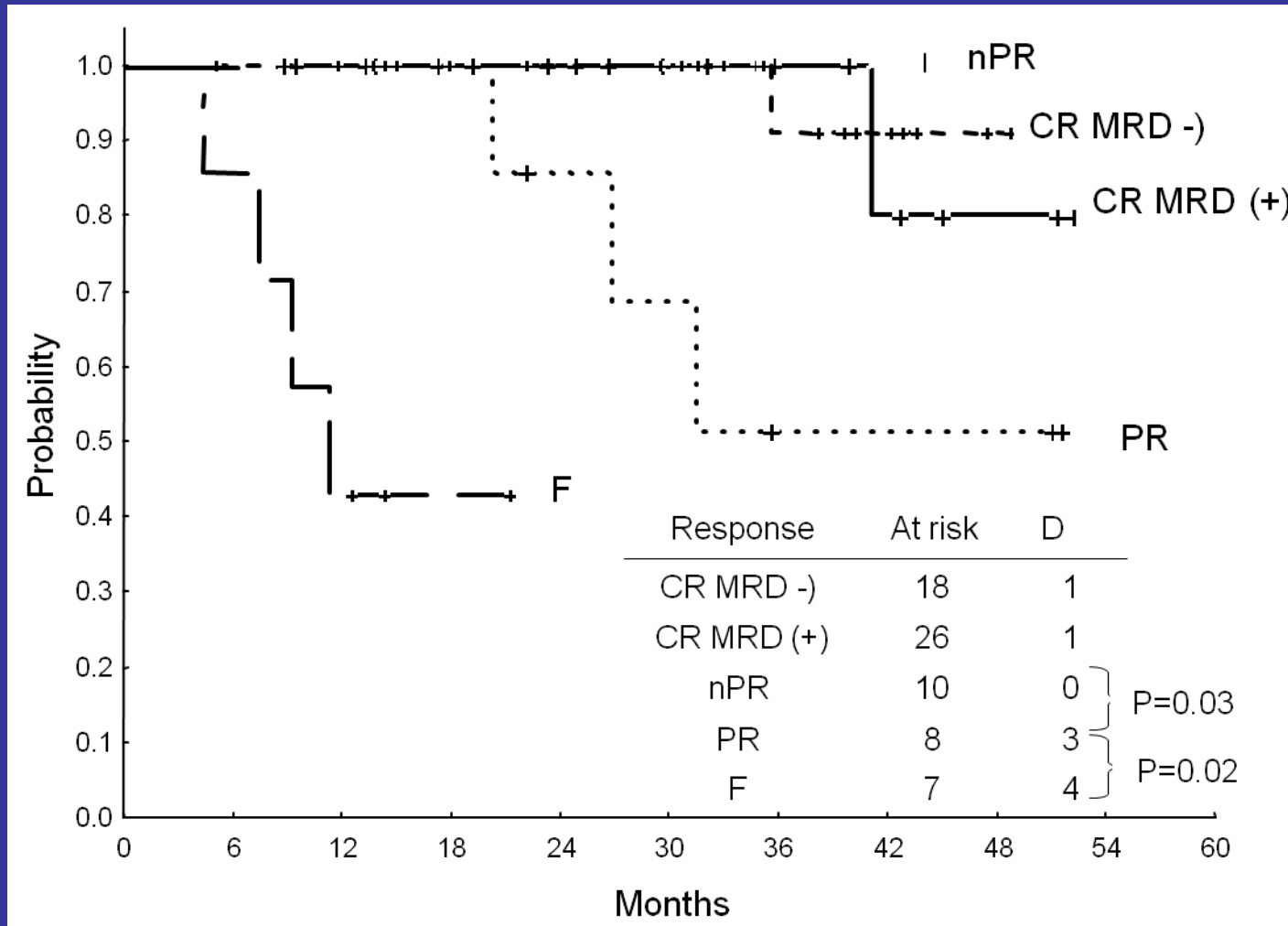
Moreton et al, J Clin Oncol 2005

- Activity of Immunomodulators (Lenalidomide, Thalidomide)

Survival in previously treated CLL from salvage treatment



FCM Frontline: Survival by Response



Relapse work-up

- Prognostic factors
 - ZAP-70, CD38
 - Cytogenetics !!
- Exclude histological transformation
 - Increased LDH
 - B-symptoms
 - “Bulky” disease
 - Increased FDG intake (PET)

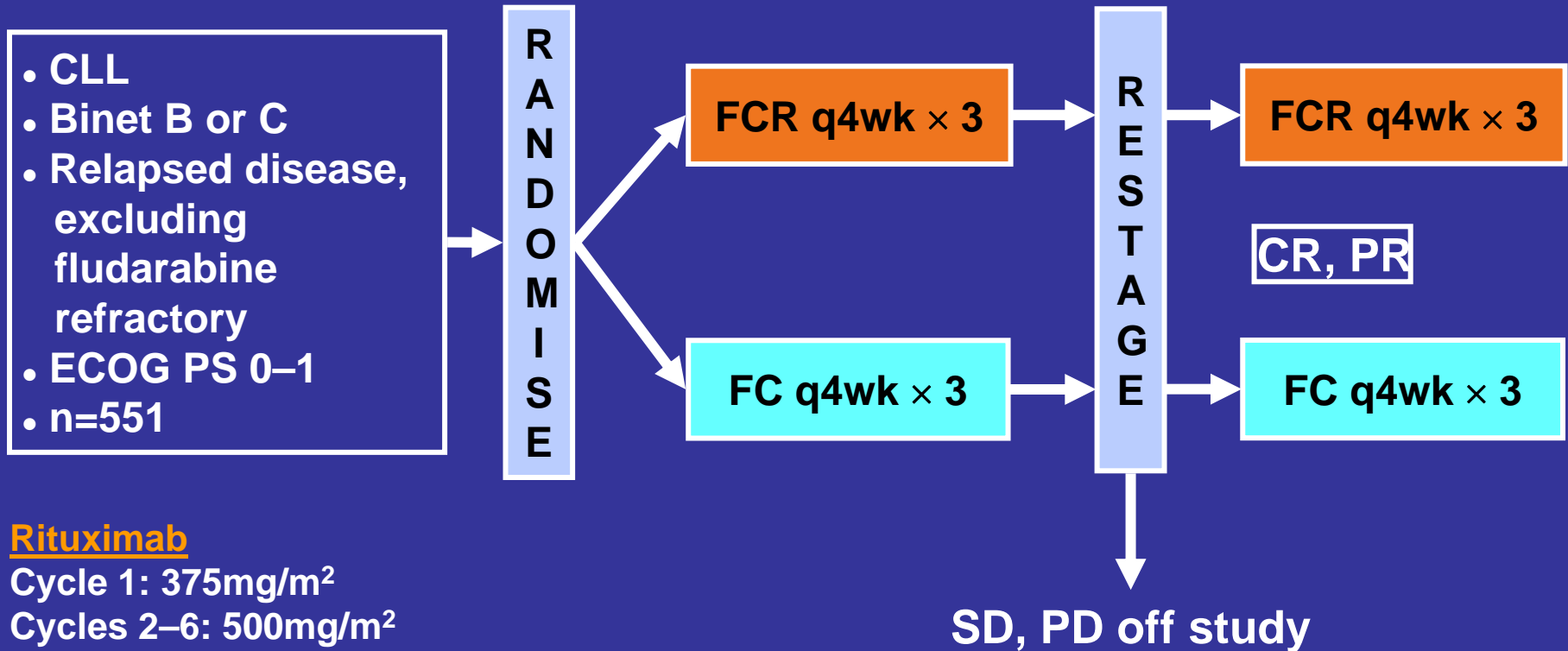
Treatment of relapsed / refractory CLL

- Relapsed disease (e.g. PFS > 24 months) → Treat as newly diagnosed patient
- Refractory disease → Consider:
 - Mechanisms of resistance (p53 dysfunction)
 - Intention of the treatment (palliation vs. “cure”)
 - Previous therapy:
 - 46% of patients failing to chlorambucil respond to fludarabine

*Rai et al, N Engl J Med, 2000; Keating et al, Leuk Lymph, 2002;
Sorensen et al, J Clin Oncol, 1997;*

The REACH trial

FCR vs. FC in relapsed CLL



Rituximab

Cycle 1: 375mg/m²
Cycles 2–6: 500mg/m²

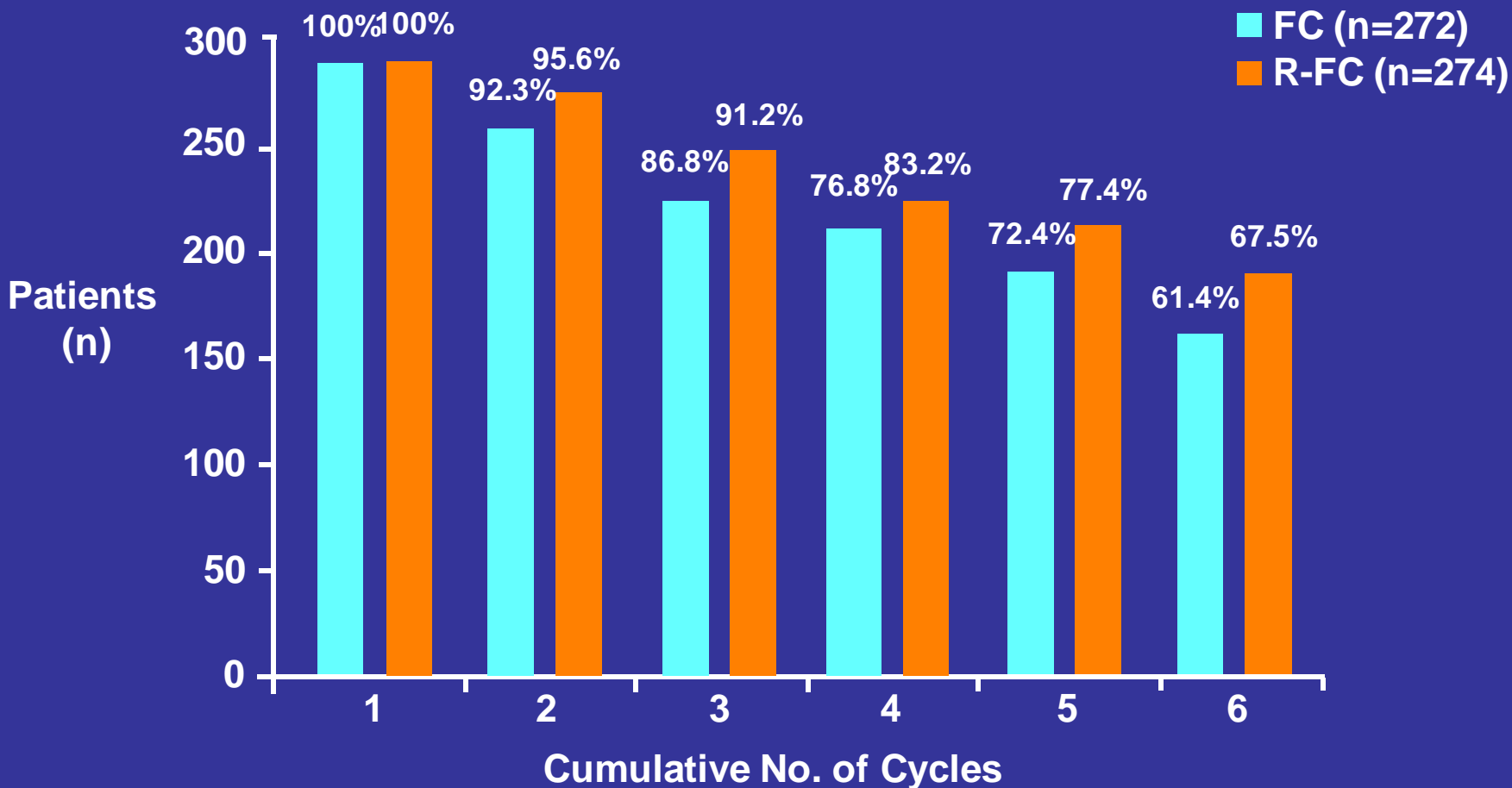
Fludarabine

25mg/m² iv, day 1–3

Cyclophosphamide

250mg/m² iv, day 1–3

REACH: Treatment Cycles Received



REACH: Selected Grade 3/4 CTC Adverse Events

Event type	FC (%) n = 272	R-FC (%) n = 274
All	60	65
Infusion-related	4	6
Tumor Lysis Syndrome	3	2
Neutropenia	40	42
Febrile Neutropenia	12	15
Thrombopenia	9	11
AIHA	12	5
Infections	19	17
Hepatitis B	–	2
Neoplasms	3	7

REACH Trial

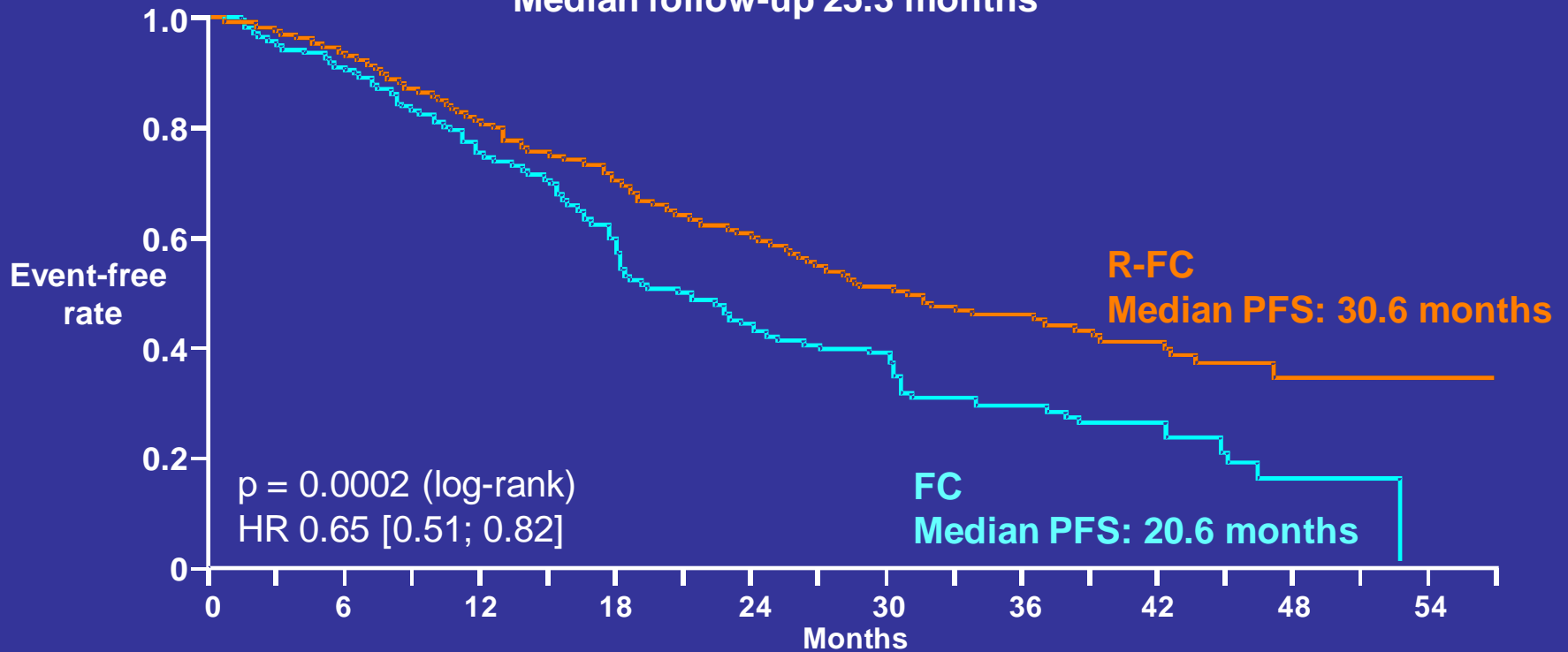
	FC	FCR
N. patients	272	274
Median age	62	62
CR (%)	13	24.3
PR (%)	44.9	45.7
PD (%)	5.4	2.5
TTF (median)	20.6 m.	30.6 m.*
OS (median)	52	NR **
Fatal events	10%	13%

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

Robak et al, ASH 2008

REACH: Primary Endpoint PFS – ITT

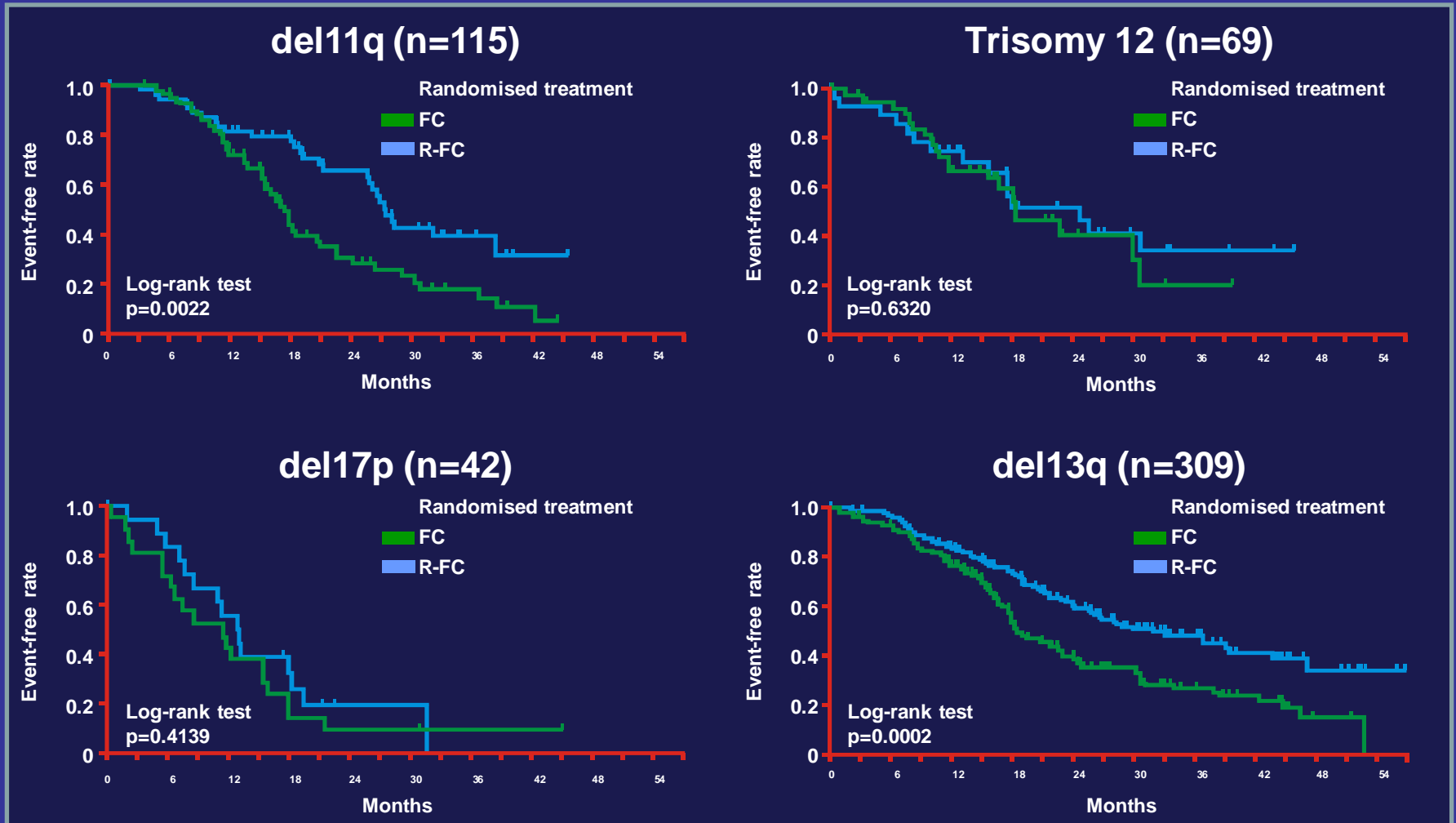
Median follow-up 25.3 months



No. at risk

FC	276	241	228	208	182	162	119	93	77	60	50	37	31	26	20	10	4	3	0	0
R-FC	276	259	246	228	207	181	157	133	119	102	87	72	56	45	32	22	12	9	3	0

REACH: PFS by Cytogenetics – ITT



First-line treatment: Summary

- FCR is the new standard for treatment of previously untreated patients with CLL
- FCR consolidates the concept of chemoimmunotherapy in CLL
- FCR opens the door to future studies aimed at making chemoimmunotherapy:
 - safer
 - applicable to more patients
 - a curative therapy for CLL

Salvage Therapy in CLL: Summary

- Relapsed (prolonged DFI):
 - Treat as a newly diagnosed patient
 - FCR as new standard
- Refractory to alkylating agents or FAMP:
 - Consider purine analogs in combination
- Refractory to immunochemotherapy and/or adverse genetic abnormalities
 - Clinical trials!
 - Consider Allo-SCT in young patients