CLL- Inducing a Response and Maintaining Remission

Jornada Chilena en Hematología y Medicina Transfusional

Francesc Bosch
Department of Hematology
Hospital Universitari Vall d'Hebron
Universitat Autonoma of Barcelona

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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 months[5]

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 lines[1]
  - Increases activity of bendamustine, mitoxantrone and other chemotherapeutic agents in CLL cells[2]
- 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.

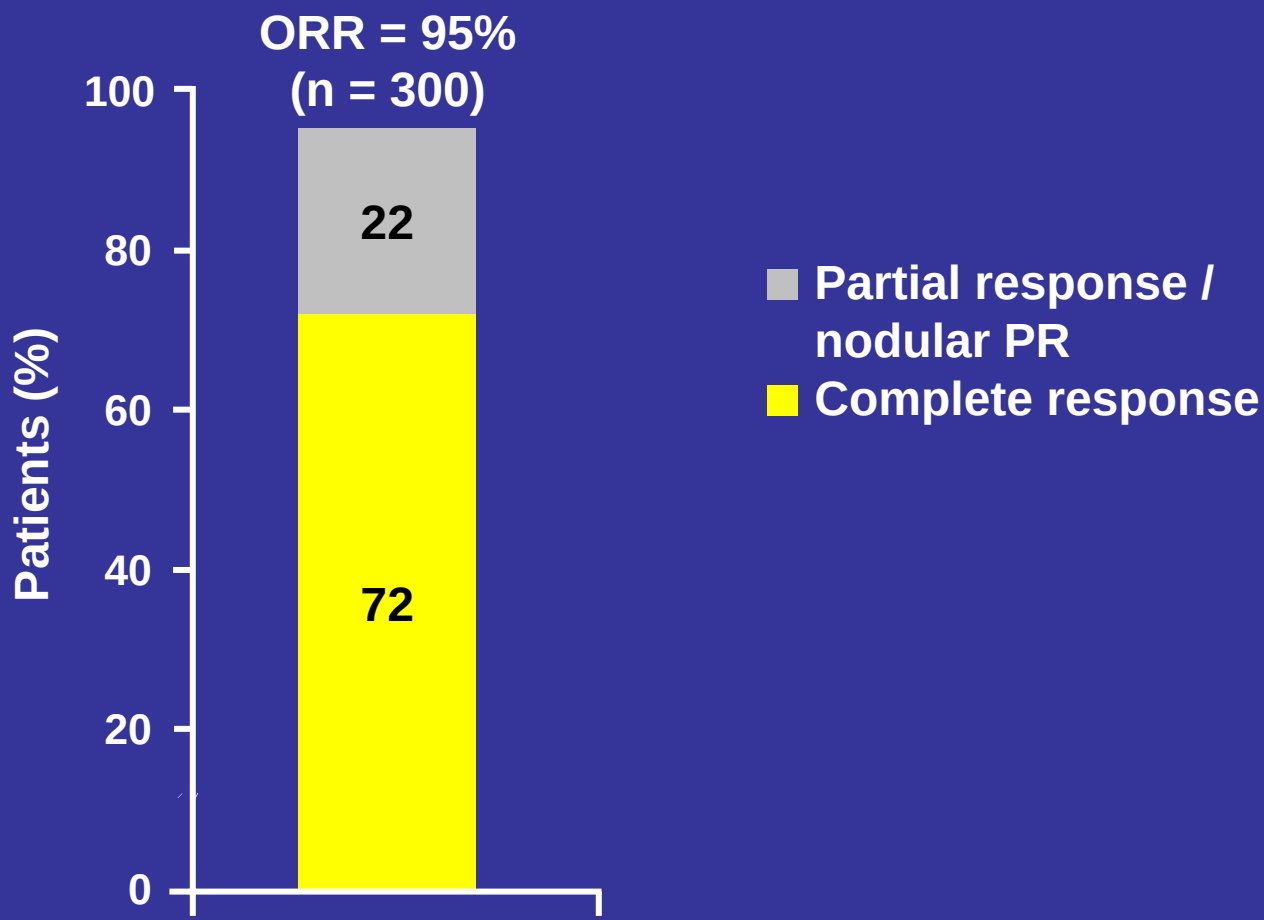
First-line FCR: Dose and schedule

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

Allopurinol 300 mg/day

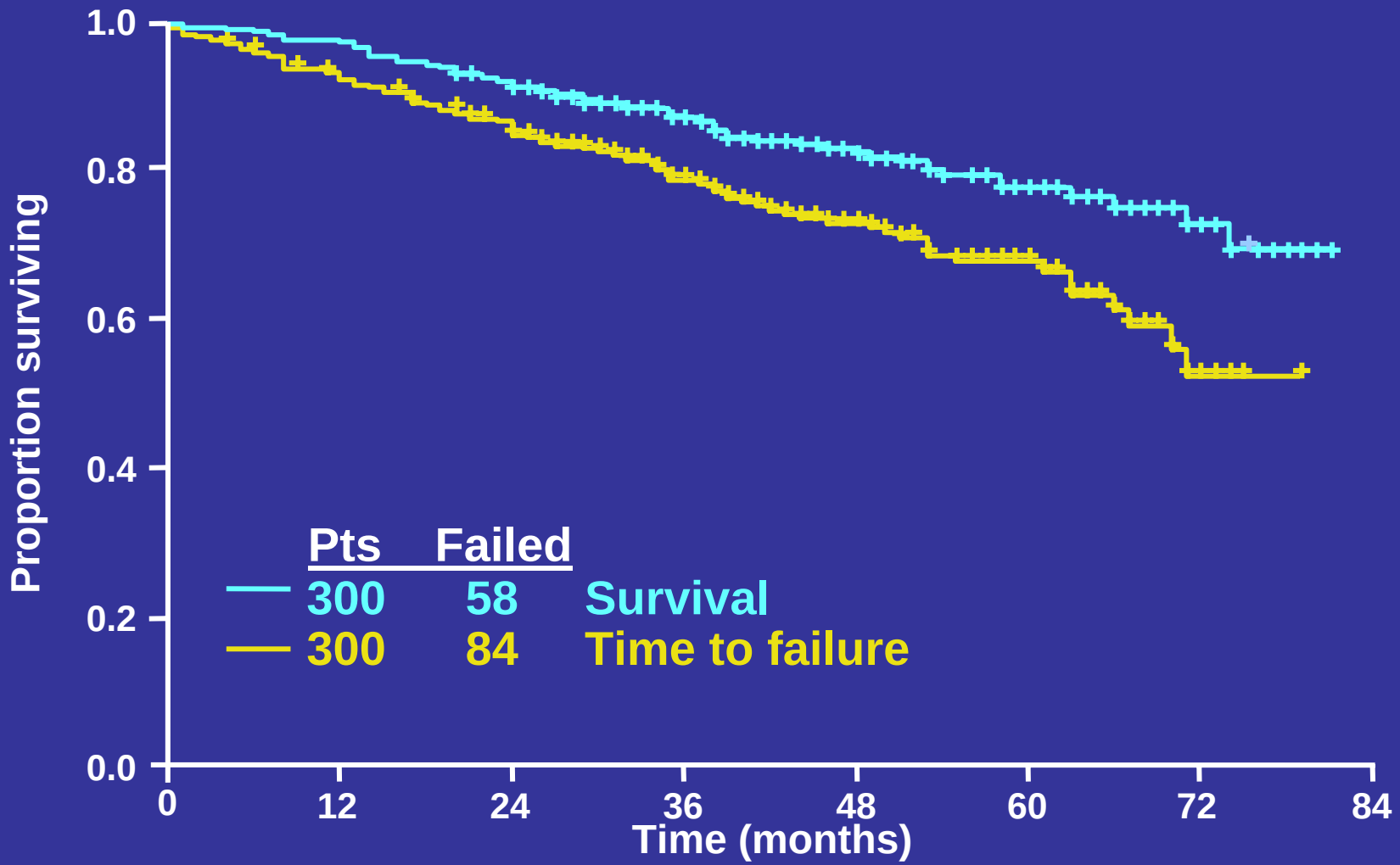
Tam CS, *et al*. *Blood* 2008; 112: 975-980

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



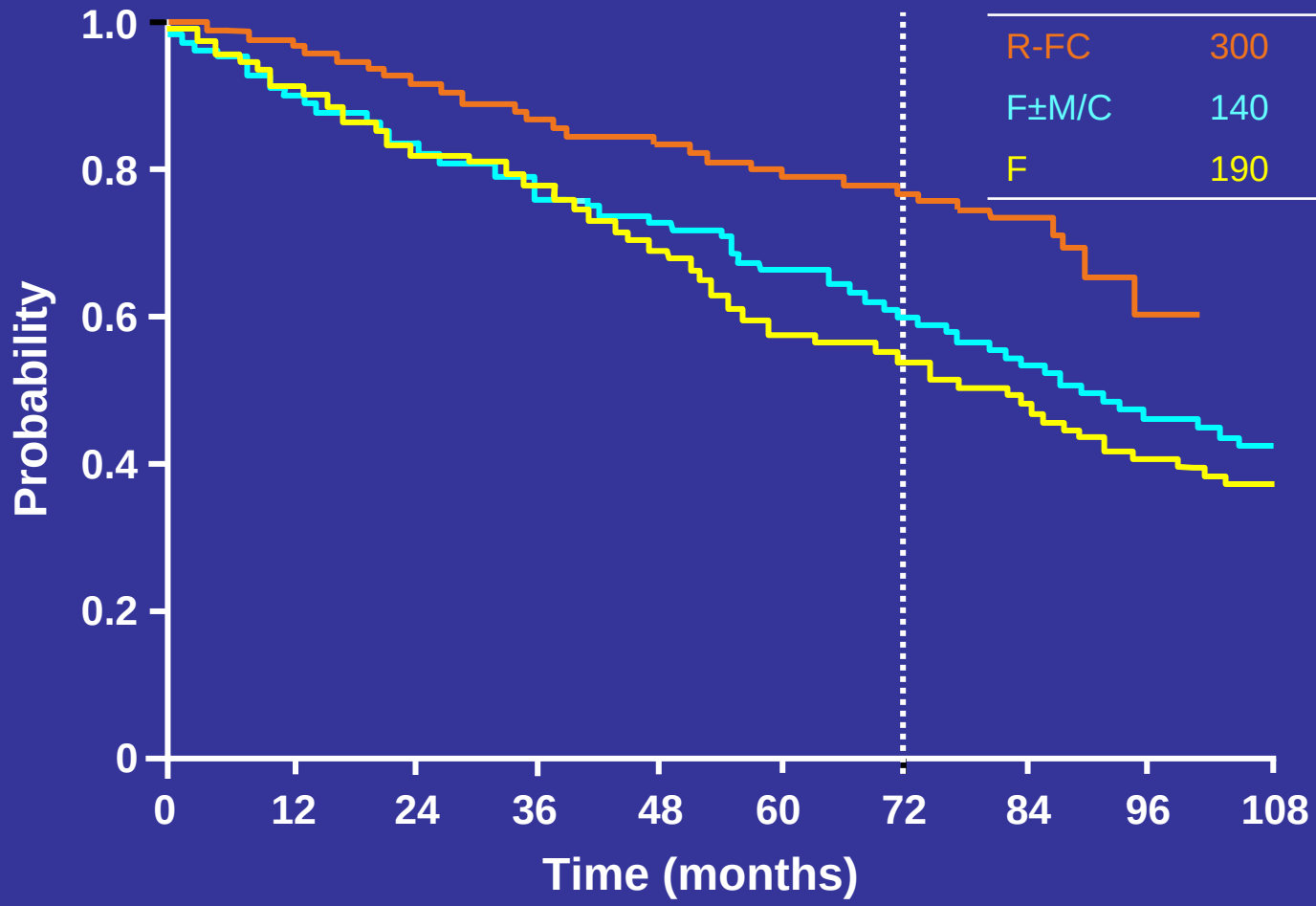
Tam CS, *et al*. *Blood* 2008; 112: 975-980

First-line FCR: Survival and time to failure



Tam CS, *et al*. *Blood* 2008; 112: 975-980

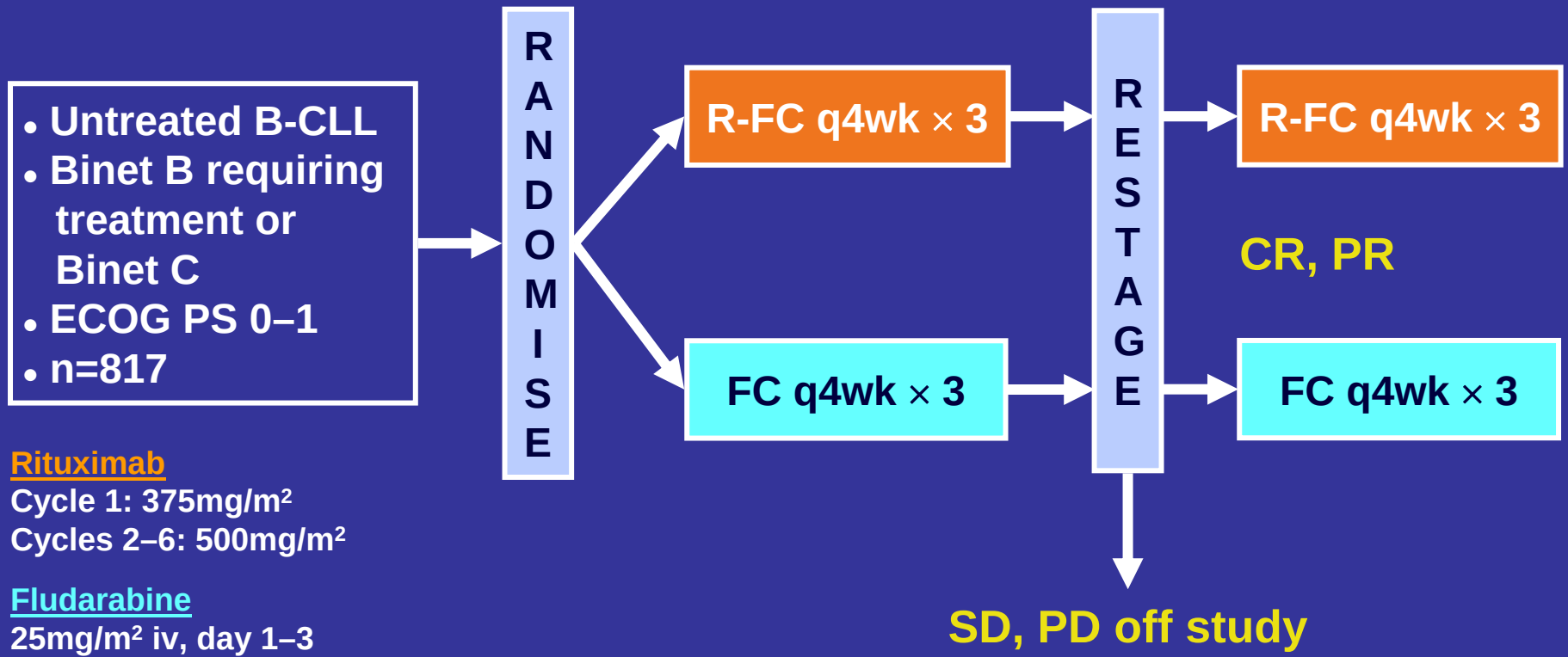
Improved OS with R-FC in first-line CLL (historical comparison)



Protocol	n	6-year OS	p value
R-FC	300	77%	} p<0.001
F±M/C	140	59%	} p=0.37
F	190	54%	

Tam CS, *et al*. *Blood* 2008; 112: 975-980

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

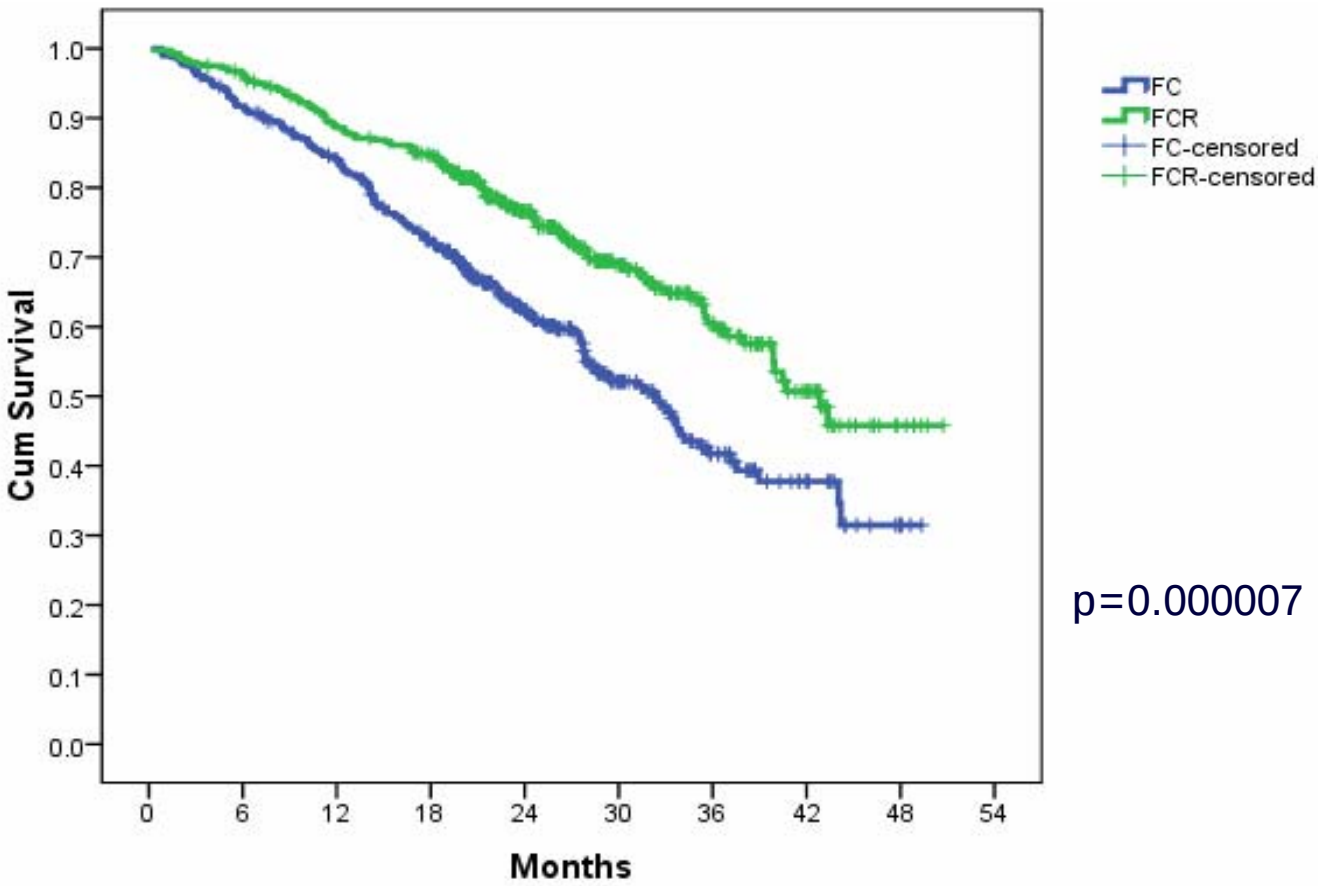
Principal investigators: M Hallek, G Fingerle-Rowson

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



p=0.000007

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

Courtesy M. Hallek

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

Courtesy by M. Hallek

(R)-FCM in CLL

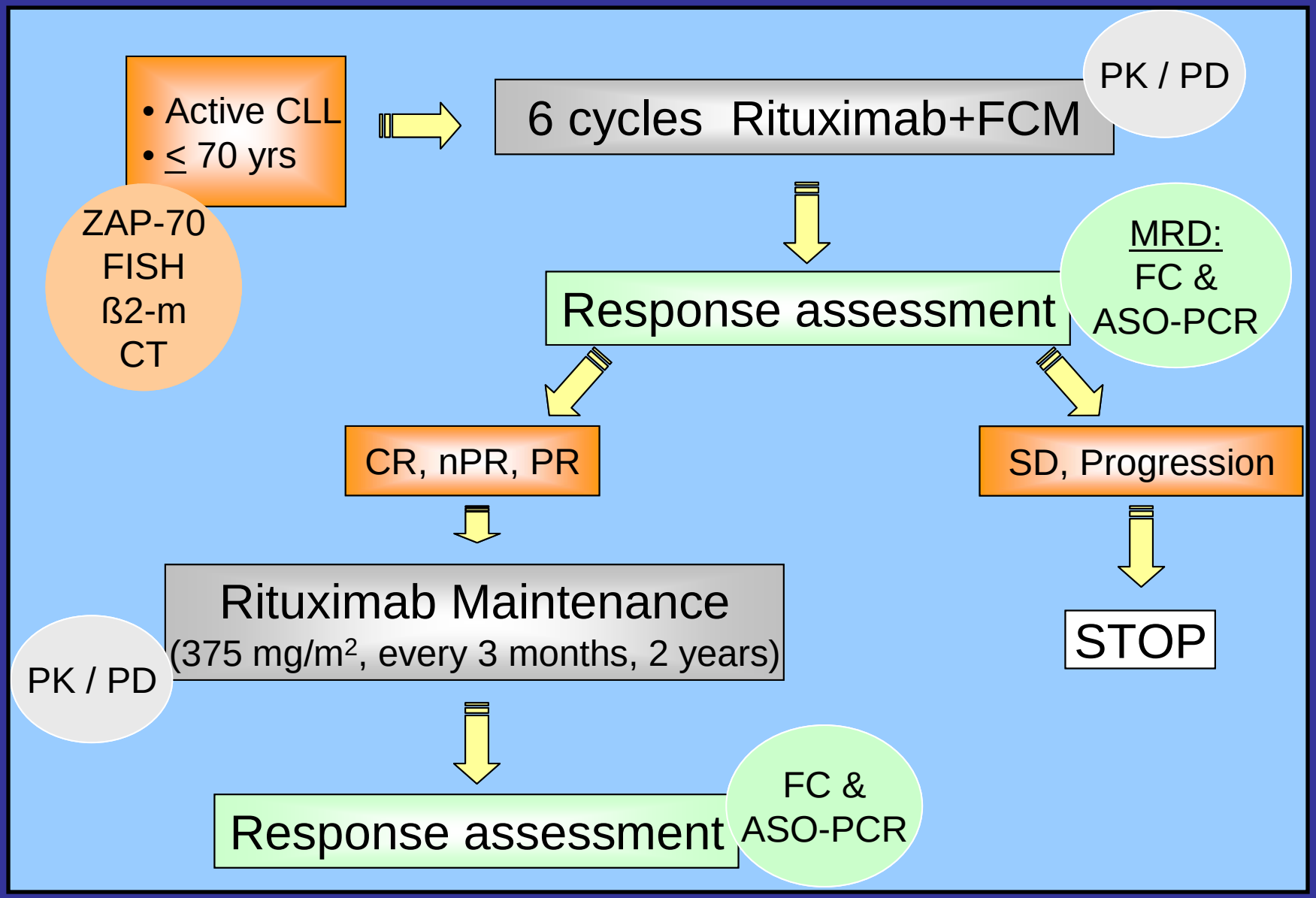
- Synergism of fludarabine with both cyclophosphamide and mitoxantrone [1]
- Treatment with FCM (fludarabine, cyclophosphamide, and mitoxantrone) results in:
  - 60% response rate in relapsed or refractory CLL[2]
  - 90% response rate in previously untreated CLL [3]

(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

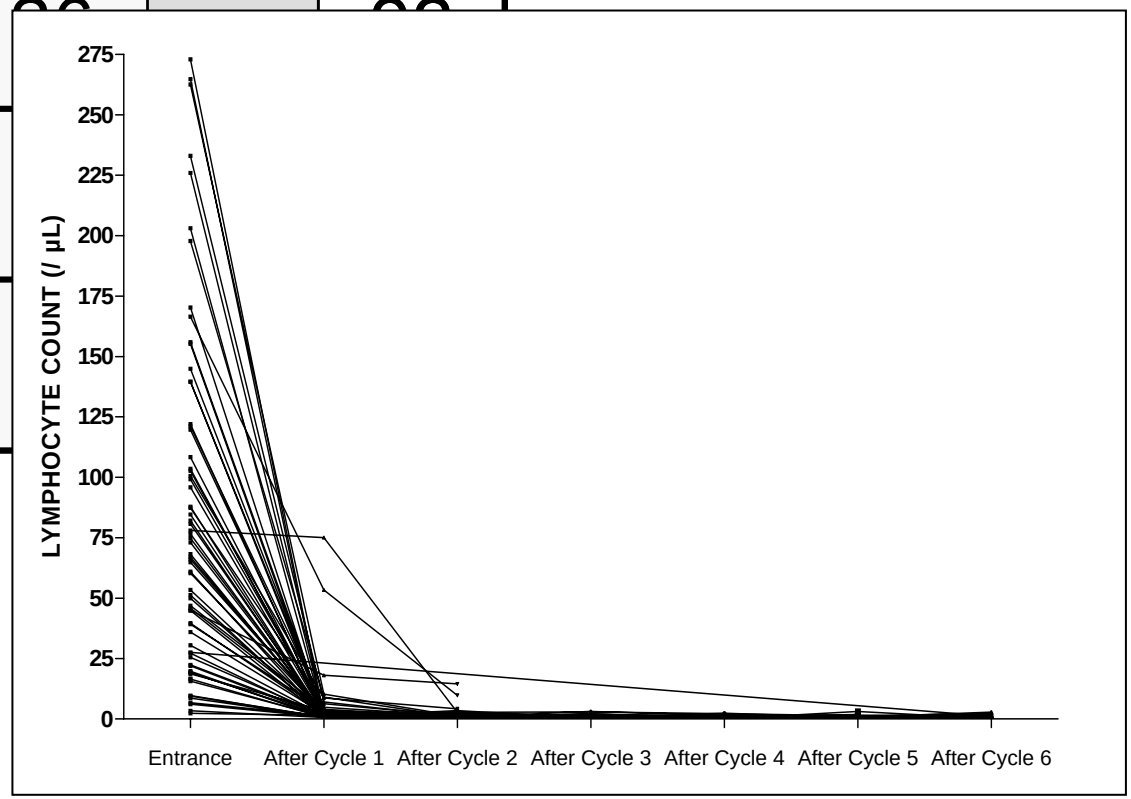


R-FCM regimen

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, 1st 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(+)			
PR			
Failure			



Bosch et al, J Clin Oncol 2009 (in press)

RFCM: Toxicity

	Grade 1/2	Grade 3/4
Hematological (NCI-WG)		
Anemia	17%	-
Thrombocytopenia	4%	2%
Neutropenia	28%	13%
No Hematological (WHO)		
Infusion reaction	9%	1%
Fever unknown origin	16%	
Infection	8%	5%(*)
Mucositis	10%	-
Liver toxicity	6%	-
Renal toxicity	3%	-
Nausea/vomiting	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, ß2-microglobulin, BM, del(17p)	Clinical stage, ß2-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

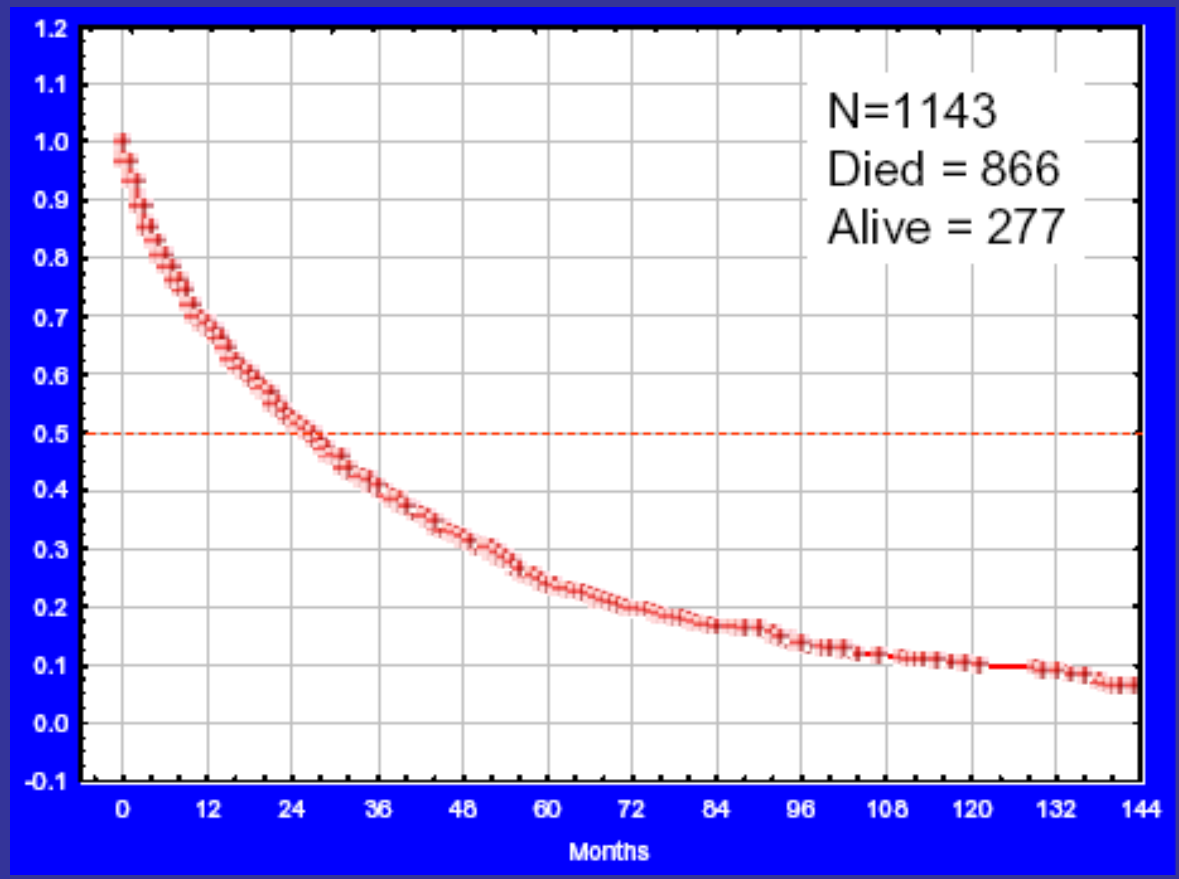
Zenz et al, Blood 2008

3. Microenviroment
   - Lack of response to alemtuzumab in bulky disease

Moreton et al, J Clin Oncol 2005

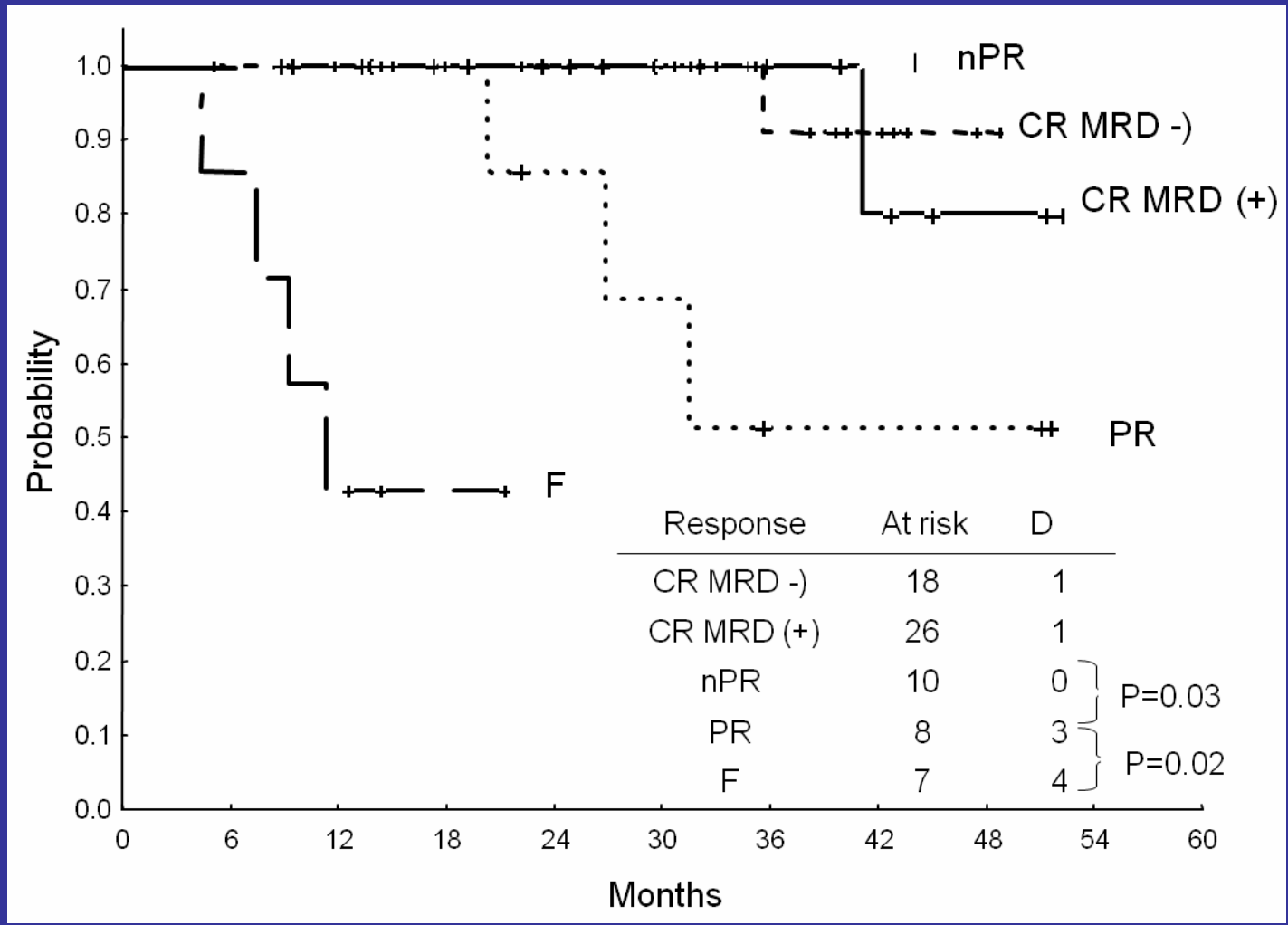
   - Activity of Immunomodulators (Lenalinomide, Thalidomide)

Survival in previously treated CLL from salvage treatment



MDACC, 2007

FCM Frontline: Survival by Response



F. Bosch et al, Clinical Cancer Research 2008

Relapse work-up

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

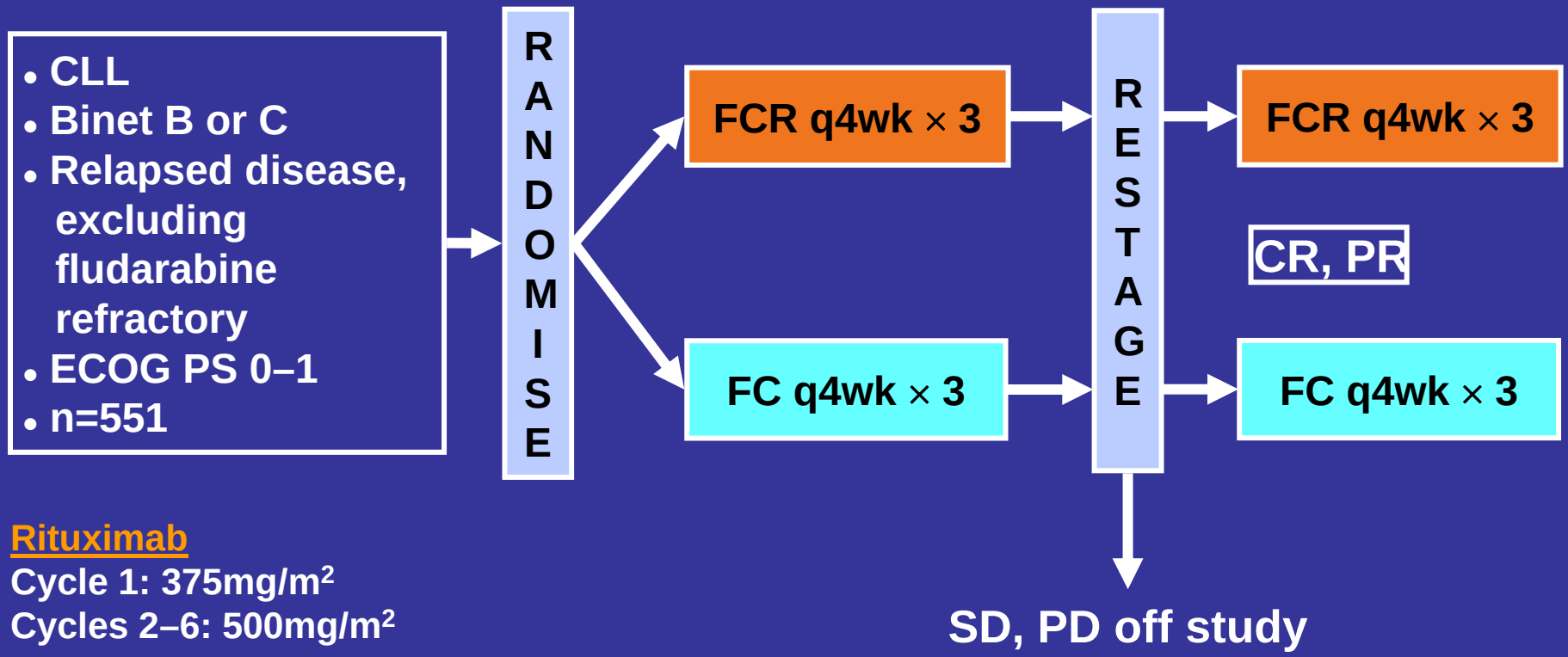
Treatment of relapsed / refractory CLL

- Relapsed disease (e.g. PFS > 24 months) → Treat as newly diagnosed patient

- Refractory disease → Consider:
  - Mechanisms of resistance (p53 disfunction)
  - 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



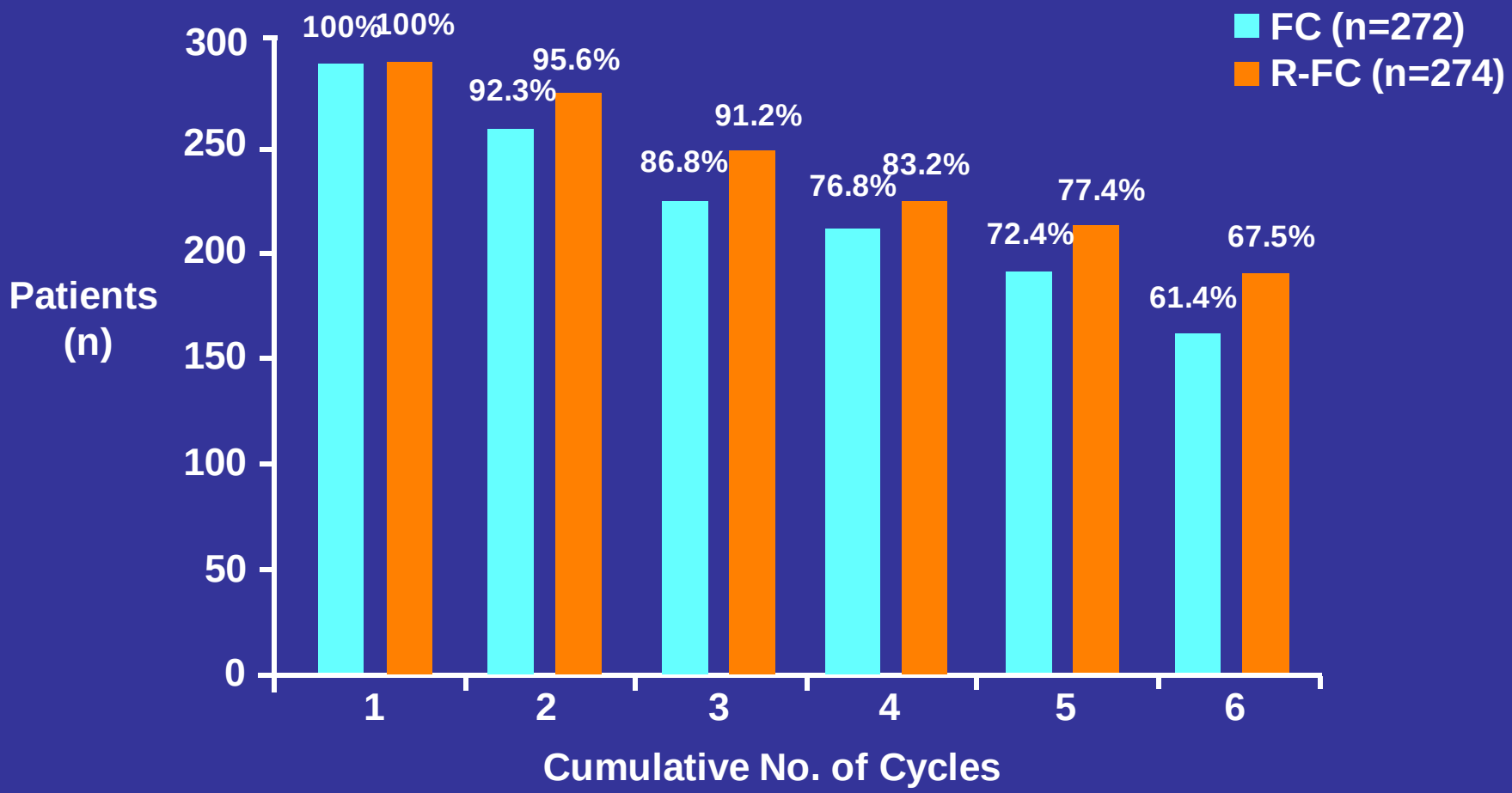
Rituximab
Cycle 1: 375mg/m^2
Cycles 2–6: 500mg/m^2

Fludarabine
25mg/m^2 iv, day 1–3

Cyclophosphamide
250mg/m^2 iv, day 1–3

Robak et al, ASH 2008

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

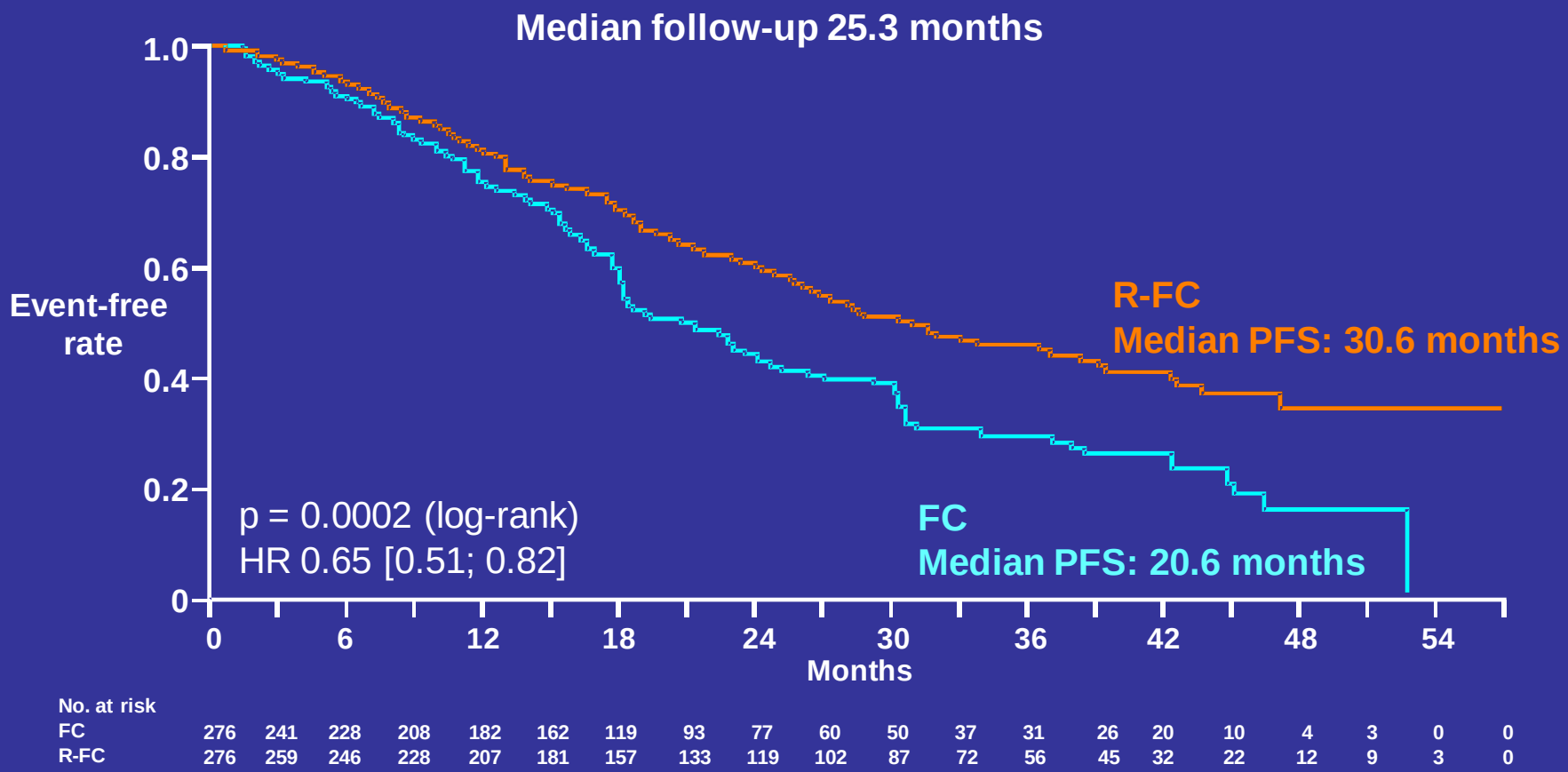
REACH Trial

	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%

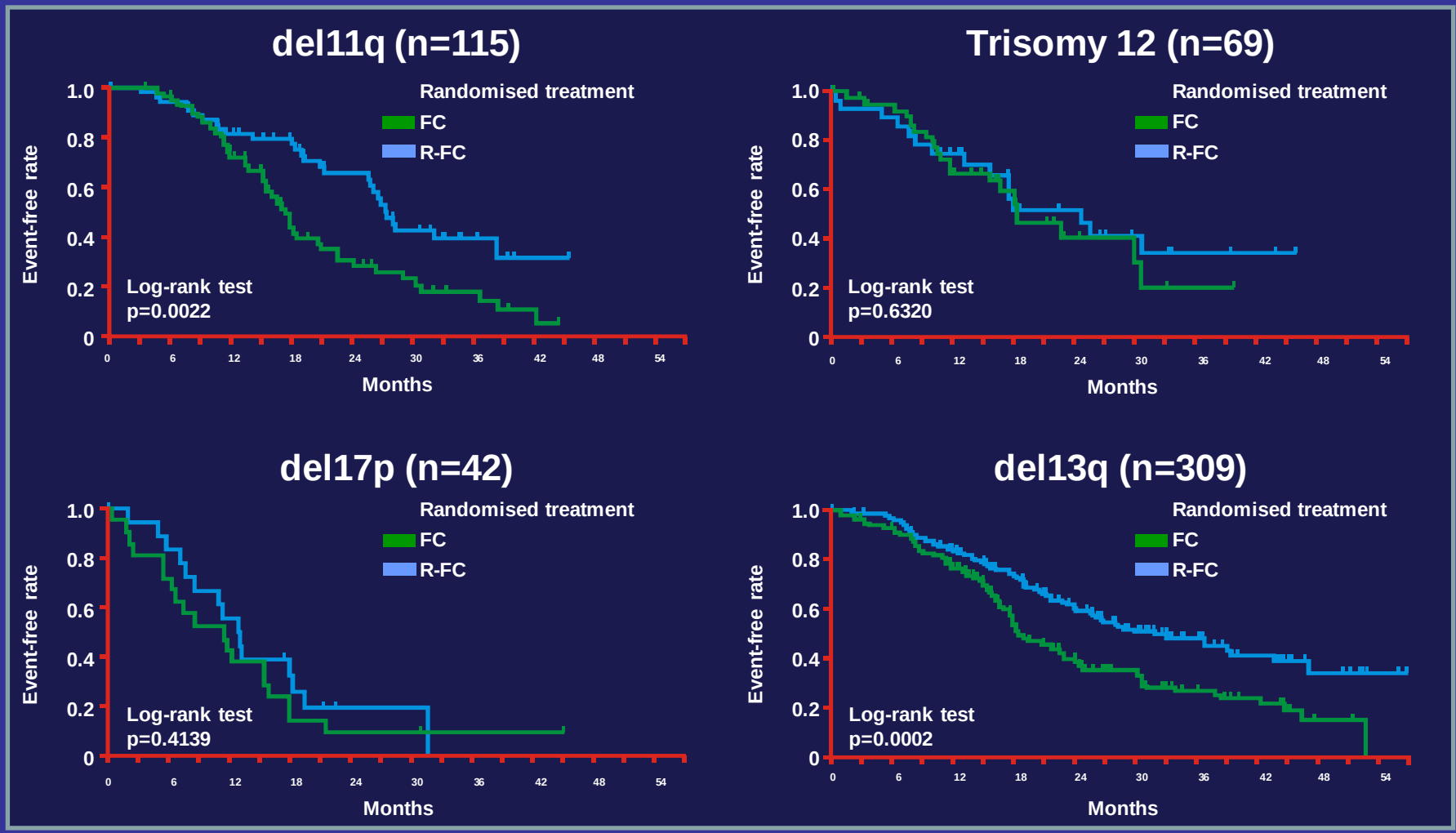
(*) p <0.05 // (**) NS

Robak et al, ASH 2008

REACH: Primary Endpoint PFS – ITT



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