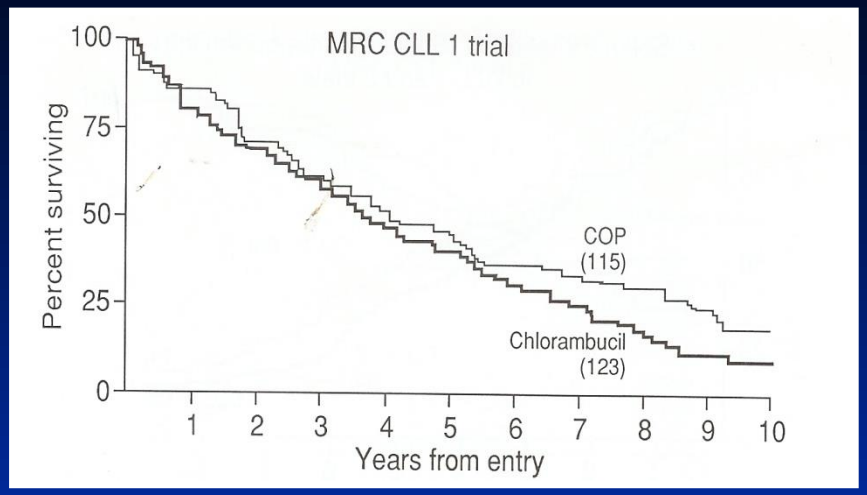
Treating CLL in the Antibody Era

George Ioannidis
Addenbrooke's Hospital, Cambridge


MRC CLL 1 trial
Percent surviving
100
75
50
25
0
COP
(115)
Chlorambucil
(123)
1 2 3 4 5 6 7 8 9 10
Years from entry

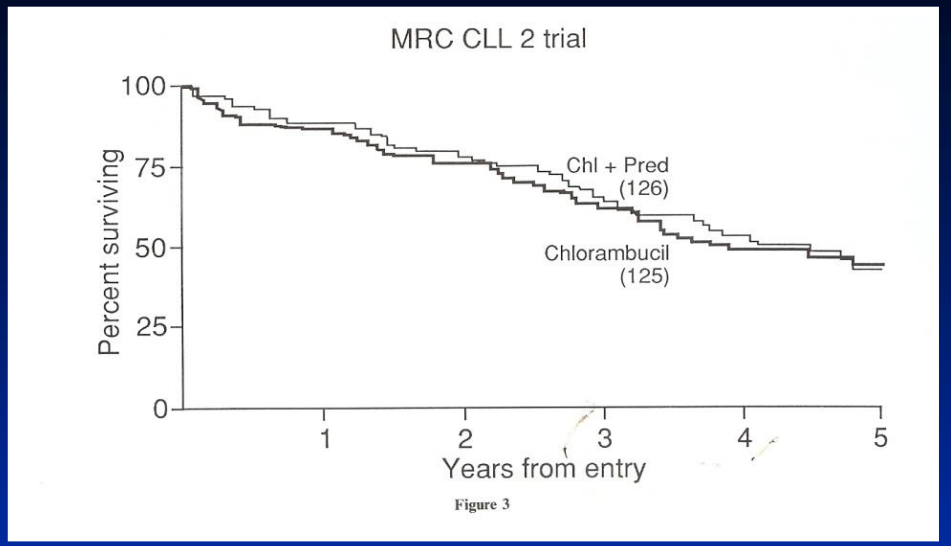
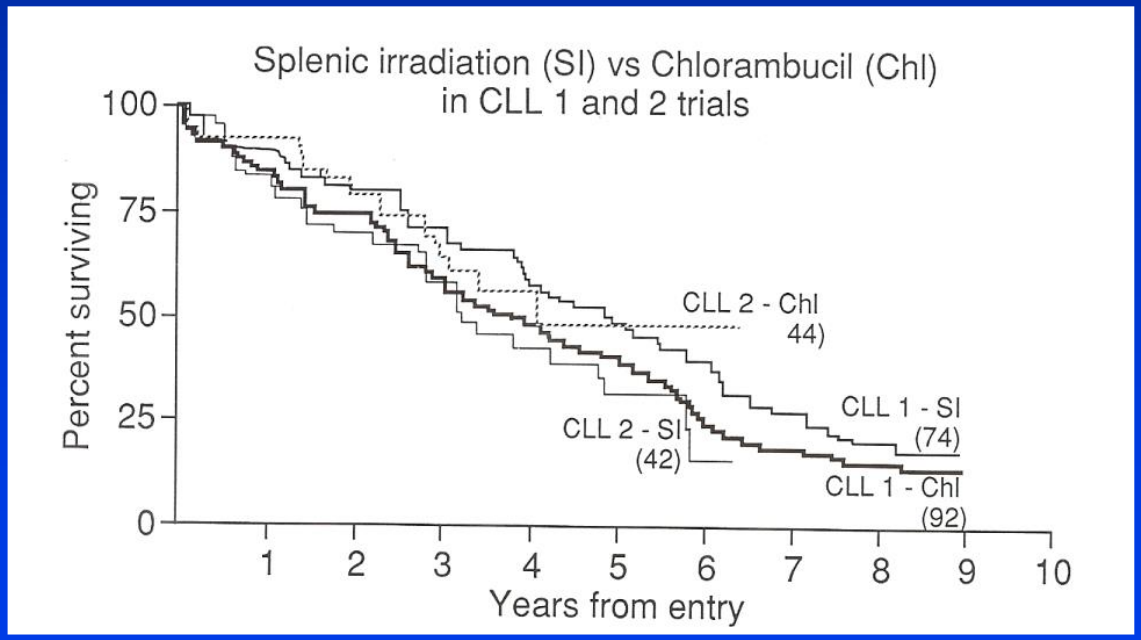
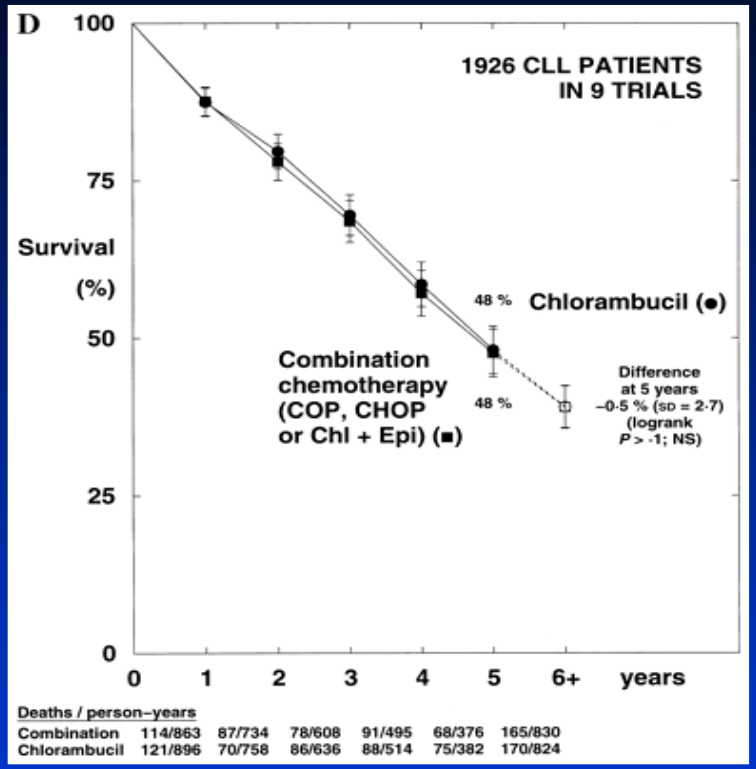
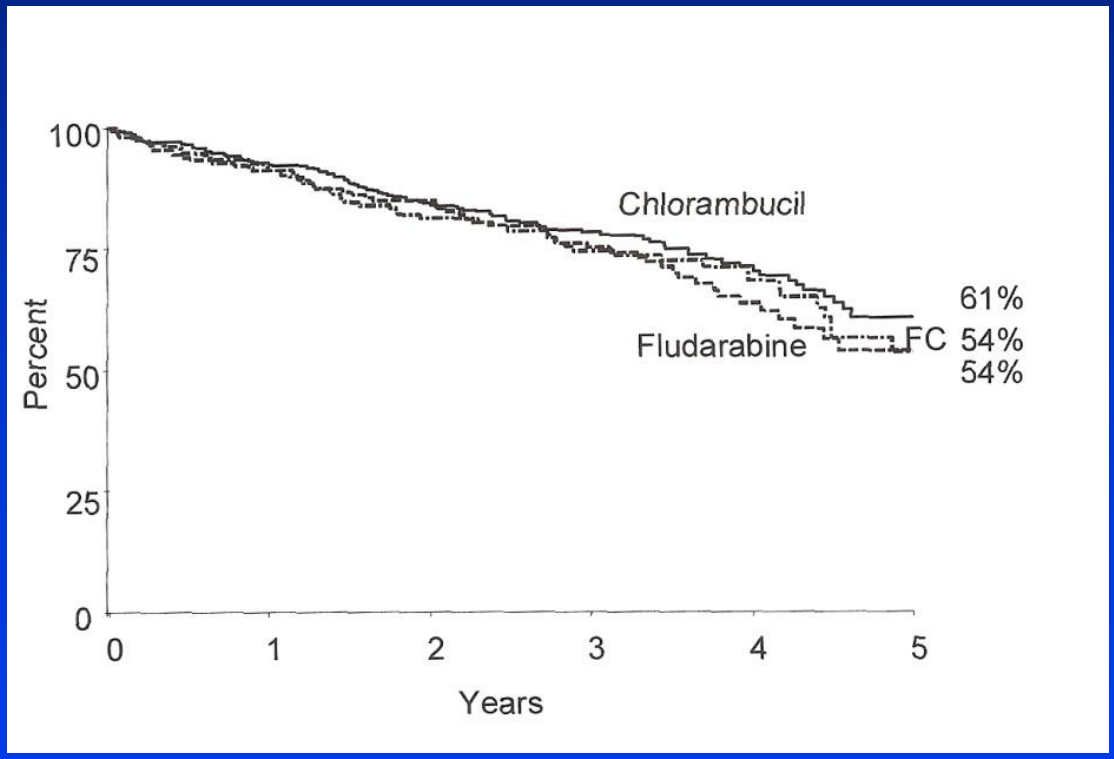

MRC CLL 2 trial
Percent surviving
100
75
50
25
0
Chl + Pred
(126)
Chlorambucil
(125)
1 2 3 4 5
Years from entry

Figure 3


Splenic irradiation (SI) vs Chlorambucil (Chl)
in CLL 1 and 2 trials
Percent surviving
100
75
50
25
0
CLL 2 - Chl
44)
CLL 1 - SI
(74)
CLL 2 - SI
(42)
CLL 1 - Chl
(92)
1 2 3 4 5 6 7 8 9 10
Years from entry


D
100
75
Survival
(%)
50
25
0
1926 CLL PATIENTS
IN 9 TRIALS
48 %
Chlorambucil (●)
Combination
chemotherapy
(COP, CHOP
or Chl + Epi) (■)
48 %
Difference
at 5 years
–0·5 % (SD = 2·7)
(logrank
P > ·1; NS)
0 1 2 3 4 5 6+ years
Deaths / person–years
Combination 114/863 87/734 78/608 91/495 68/376 165/830
Chlorambucil 121/896 70/758 86/636 88/514 75/382 170/824


100
75
50
25
0
Percent
Chlorambucil
Fludarabine
FC
61%
54%
54%
0 1 2 3 4 5
Years

Antibody therapy in CLL

Antibodies with a CLL licence

- Rituximab
- Alemtuzumab
- Ofatumumab (US)

Other antibodies

- Lumiliximab / epratuzumab
- GA101

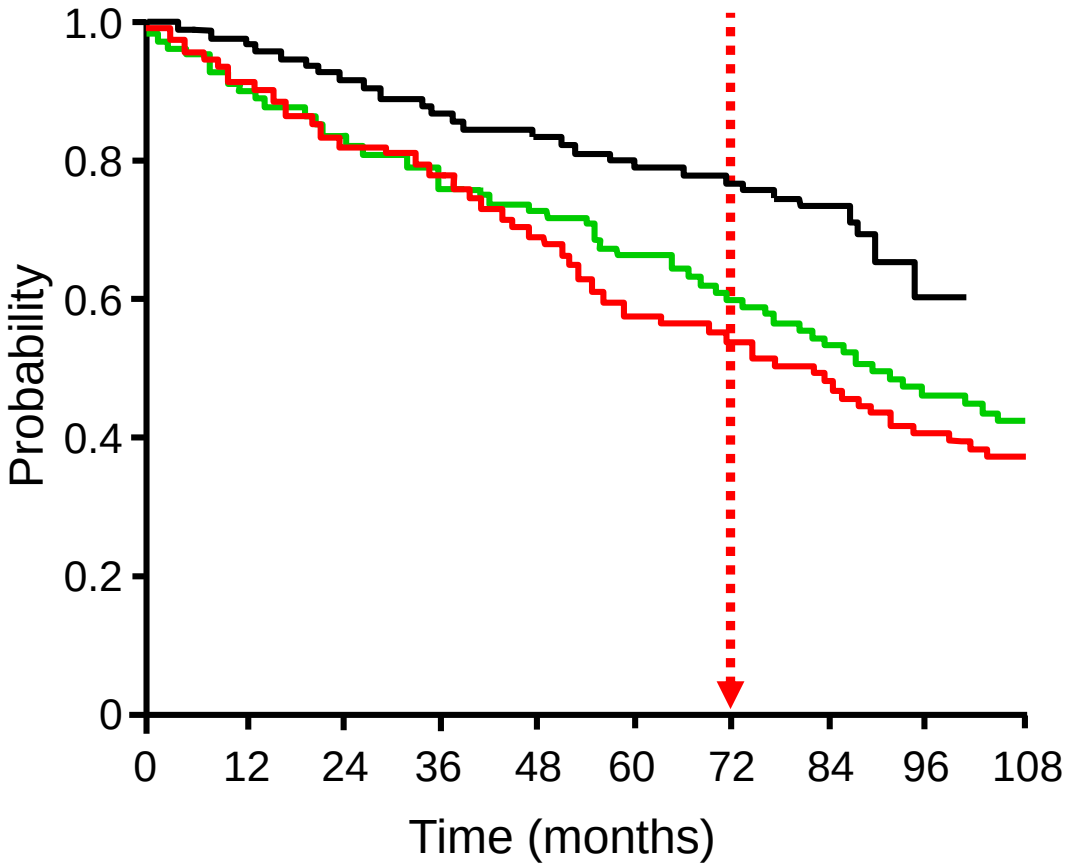
Antibody delivery

- Monotherapy
- Combined with other drugs
  (chemotherapy / steroids)
- Consolidation
- Maintenance

Rituximab in CLL

- Monotherapy
  - Limited efficacy although suggestion of dose-response (O'Brien JCO 2001)
- Combination therapy
  - Multiple drug partners, but largest datasets combined with purine analogues

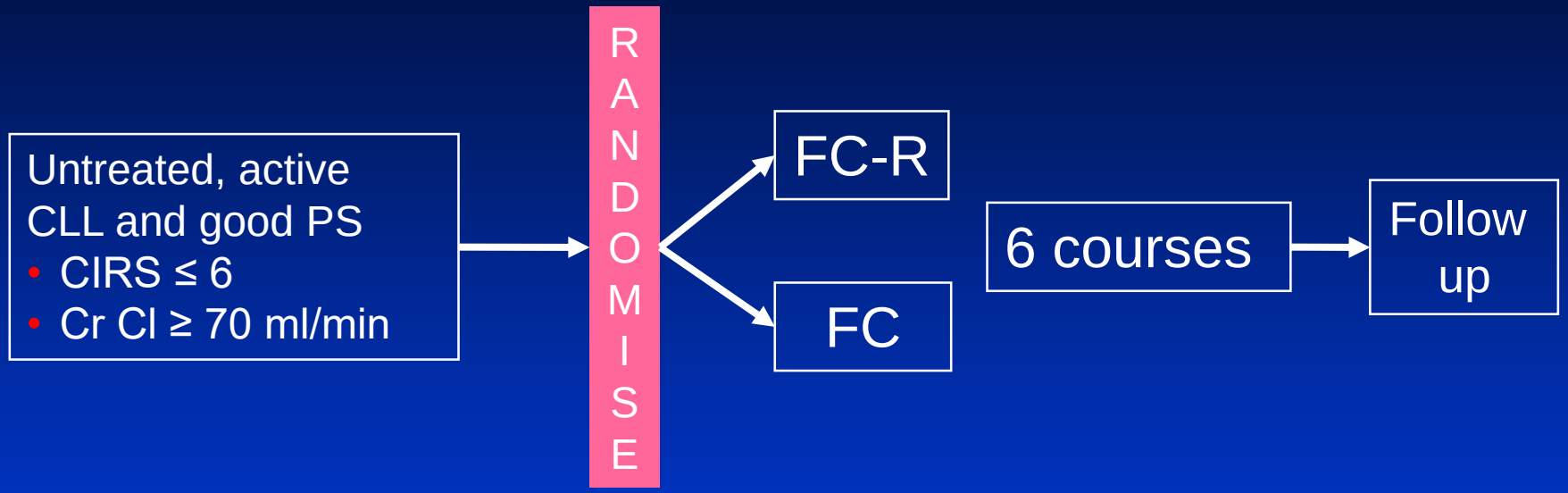
MDACC Phase II FC-R



	n	6-year OS
FC-R	300	77%
F+M/C	140	59%
F	190	54%

Tam CS et al Blood 2008;112:975

GCLLSG CLL8: FC-R vs FC



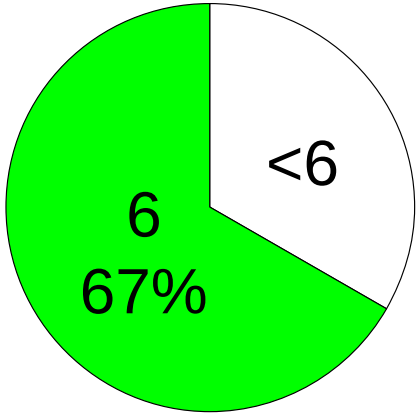
N = 817

- Rituximab = 375 mg/m^2 cycle 1, 500 mg/m^2 subsequent cycles
- F = 25 mg/m^2 iv (d1-3), C = 250 mg/m^2 iv (d1-3)

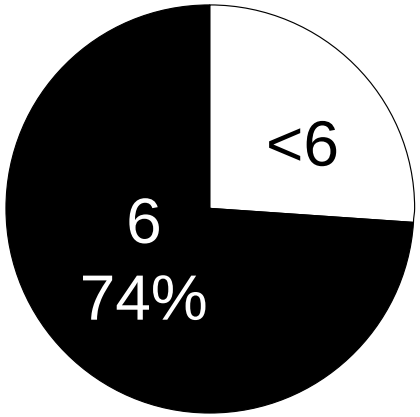
Abstract 325. Session: Chronic Lymphocytic Leukemia – Therapy, Excluding Transplantation
Hallek *et al.* Mon 8 Dec 2008 11:00 AM. Moscone Center, Halls B & C. ASH

CLL8: Dose delivery and toxicity

FC



FC-R

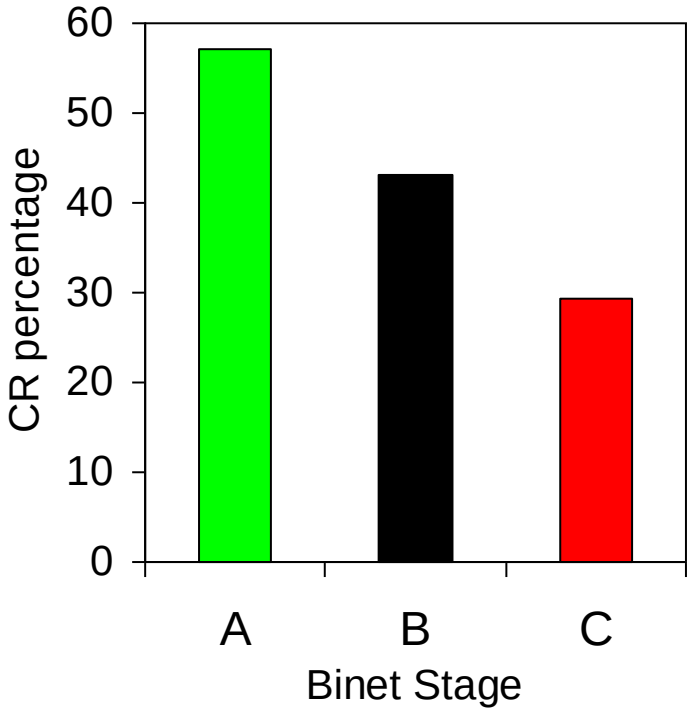


	FC	FC-R	p
≥ 1 grade 3/4 AE	62.6%	77.5%	< 0.0001
Neutropenia	**21.0%**	**33.7%**	**< 0.0001**
Infection	**14.9%**	**18.8%**	**0.14**
Tumor lysis syndrome	0.5%	0.2%	0.55
Cytokine release syndrome	0.0%	0.25%	0.32

Abstract 325. Session: Chronic Lymphocytic Leukemia – Therapy, Excluding Transplantation
Hallek *et al.* Mon 8 Dec 2008 11:00 AM. Moscone Center, Halls B & C. ASH

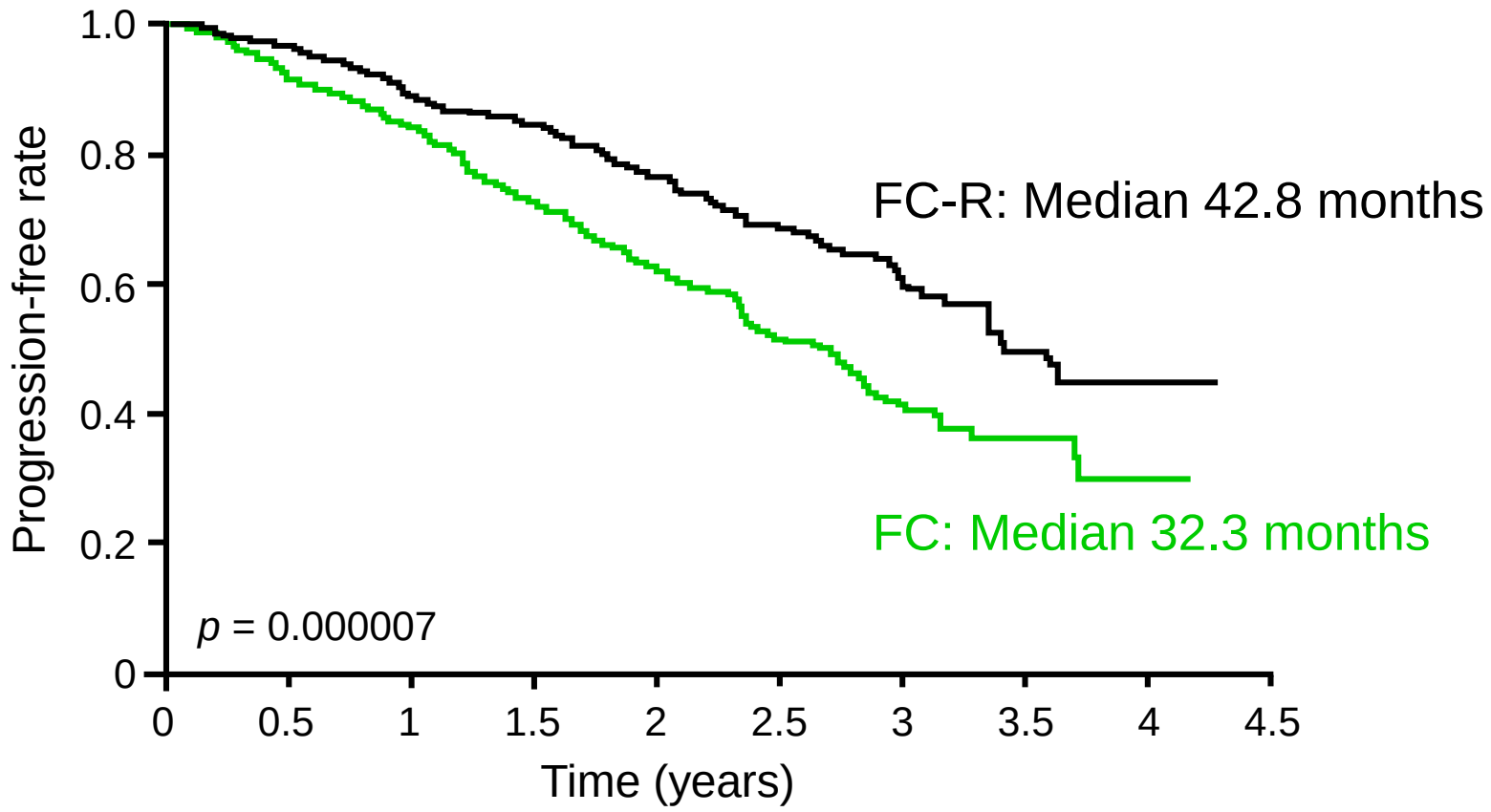
CLL8: Response

	FC	FC-R	p
CR	**22.9%**	**44.5%**	**<0.01**
PR	50.4%	39.6%	<0.01
SD	6.7%	3.9%	0.08
PD	8.1%	3.3%	<0.01



Abstract 325. Session: Chronic Lymphocytic Leukemia – Therapy, Excluding Transplantation
Hallek *et al.* Mon 8 Dec 2008 11:00 AM. Moscone Center, Halls B & C. ASH

CLL8: PFS



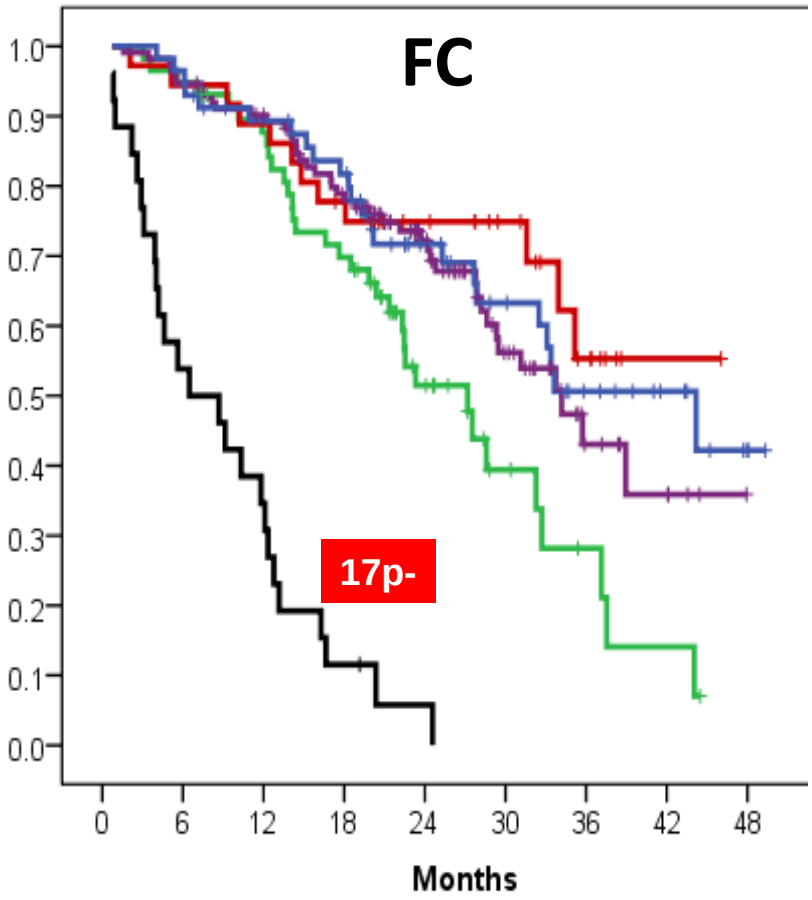
Abstract 325. Session: Chronic Lymphocytic Leukemia – Therapy, Excluding Transplantation
Hallek *et al.* Mon 8 Dec 2008 11:00 AM. Moscone Center, Halls B & C. ASH

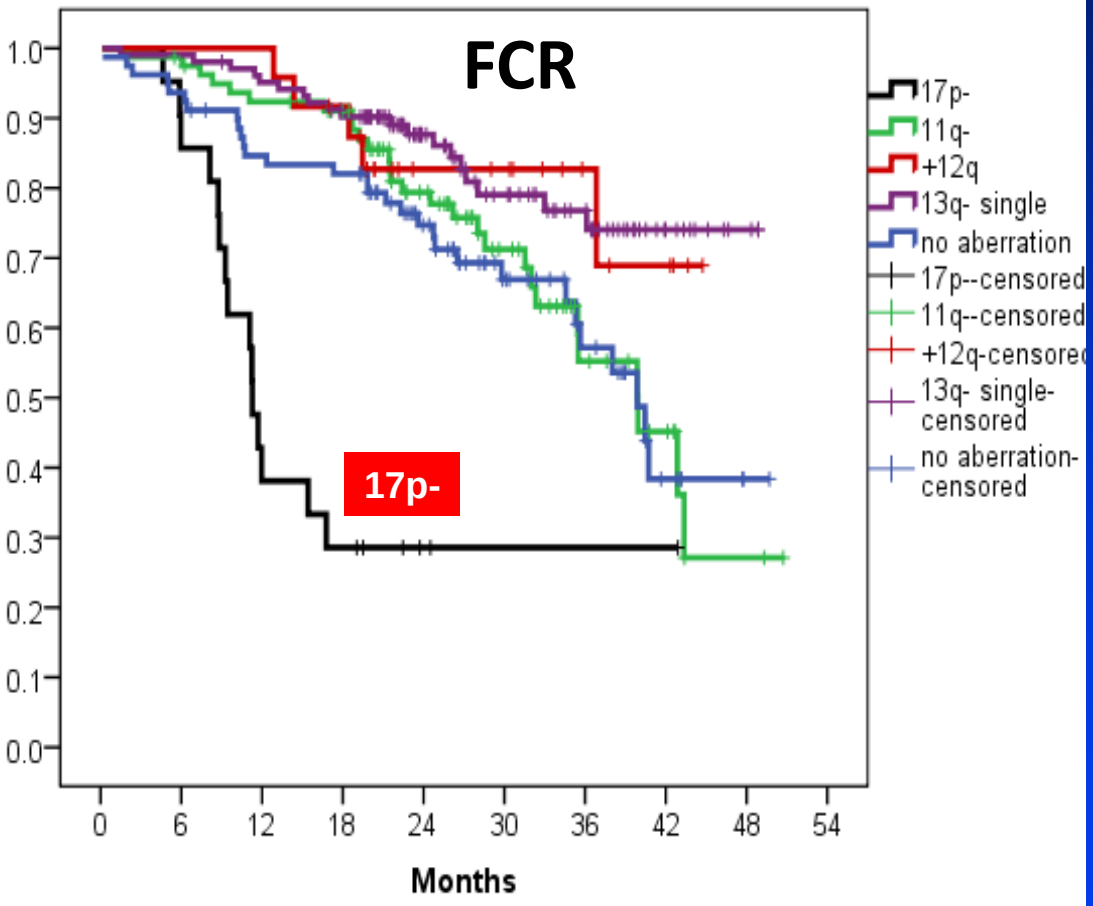
UNIKLINIK KÖLN

CLL8

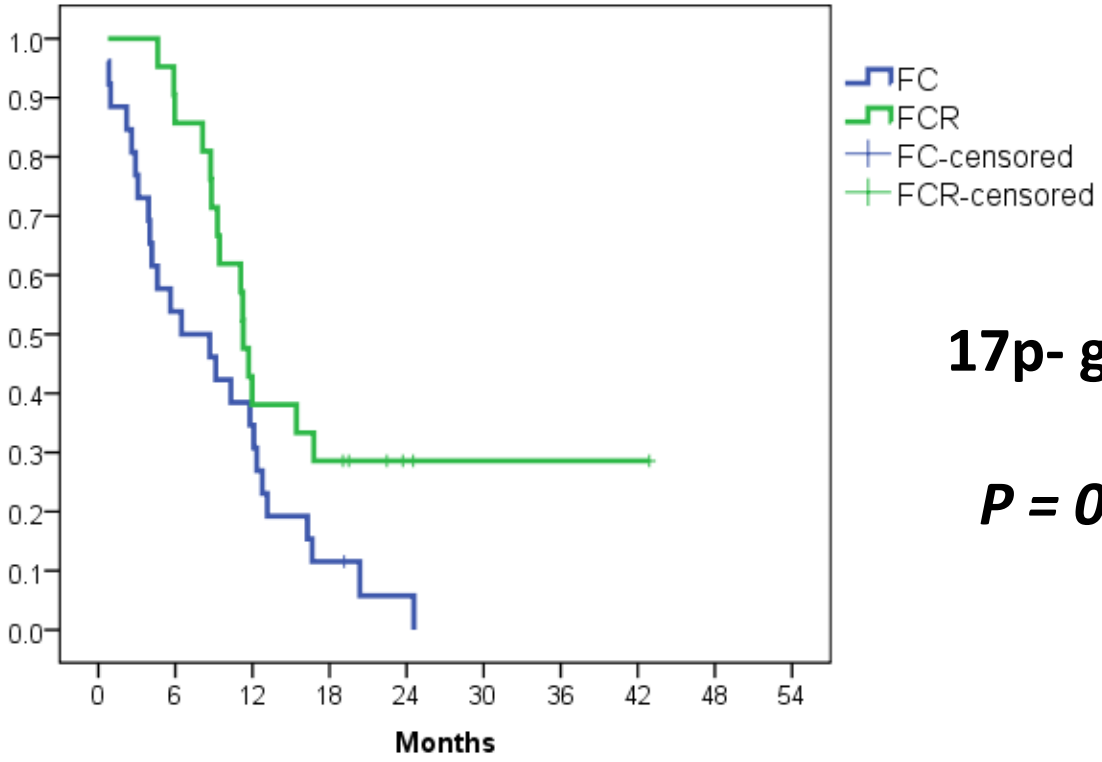
DEUTSCHE CLL STUDIENGRUPPE

CLL8 Genetic Analyses: PFS





Genetic Analyses: PFS Treatment Effect

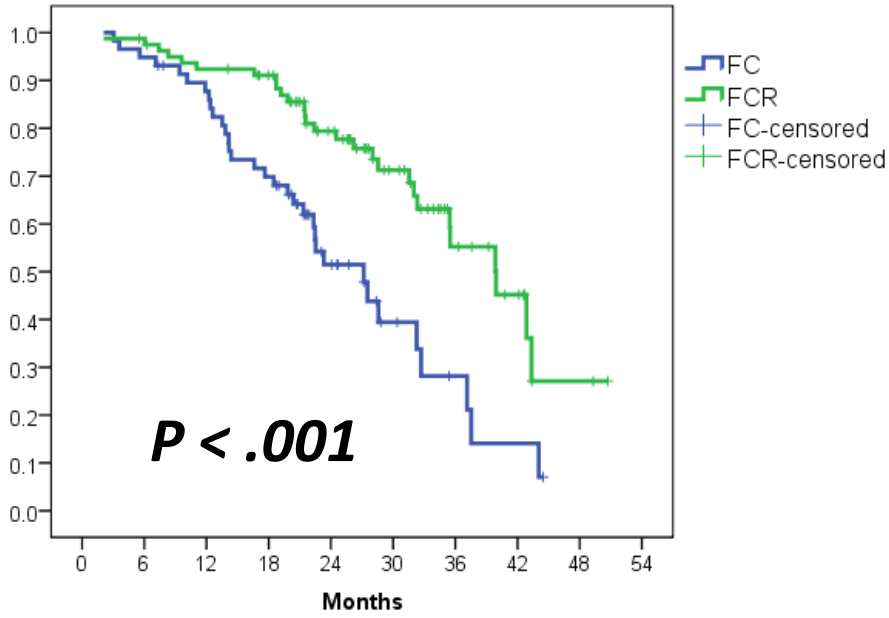


17p- group:

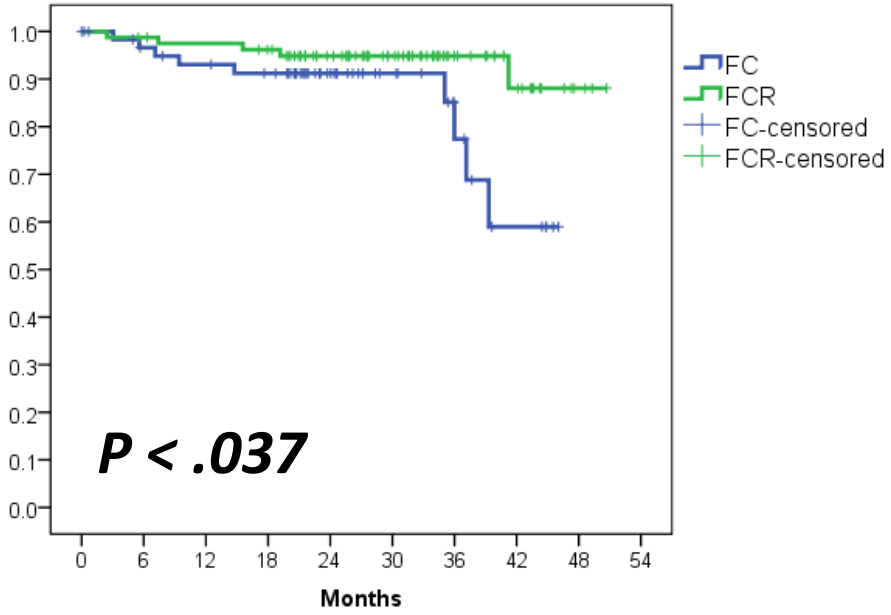
P = 0.029

Genetic Analyses: 11q-

PFS



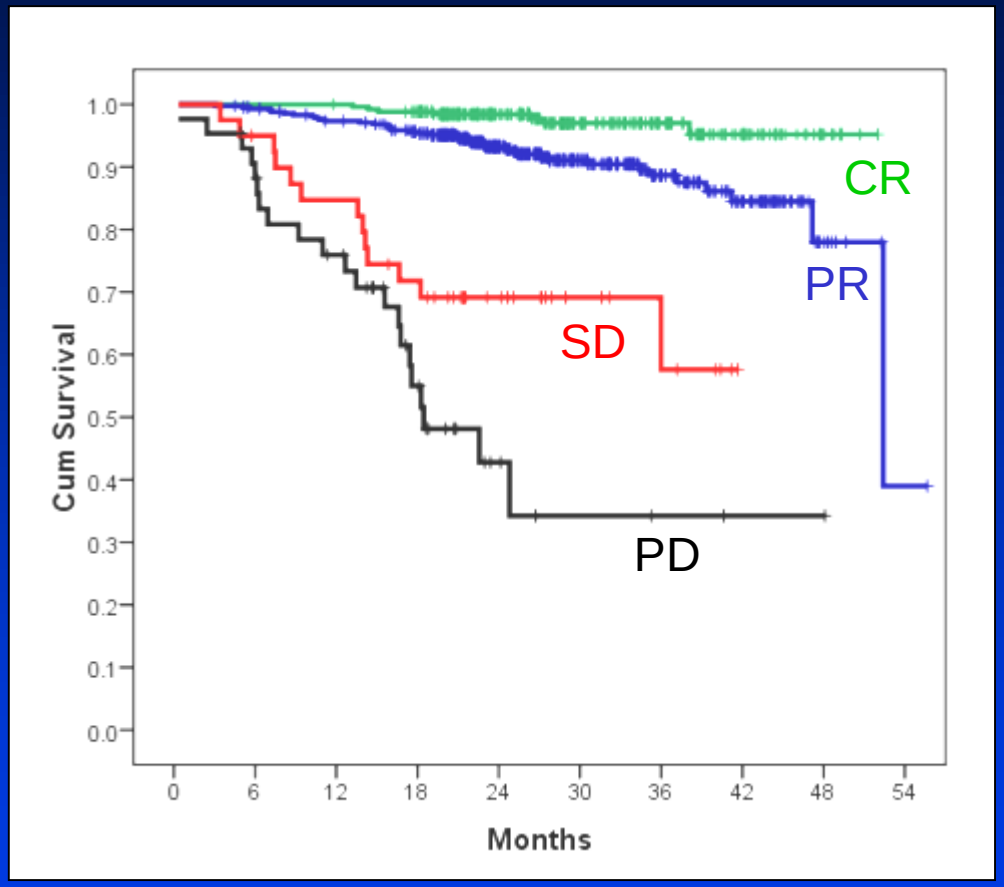
OS



Quality of response predicts PFS and OS

- Traditional criteria for assessment
- MRD assessment

CLL8: Response quality vs outcome



Overall Survival

- Median follow up 25.5 months
- Median OS not reached for either arm.
- FC-R vs FC $p = 0.18$

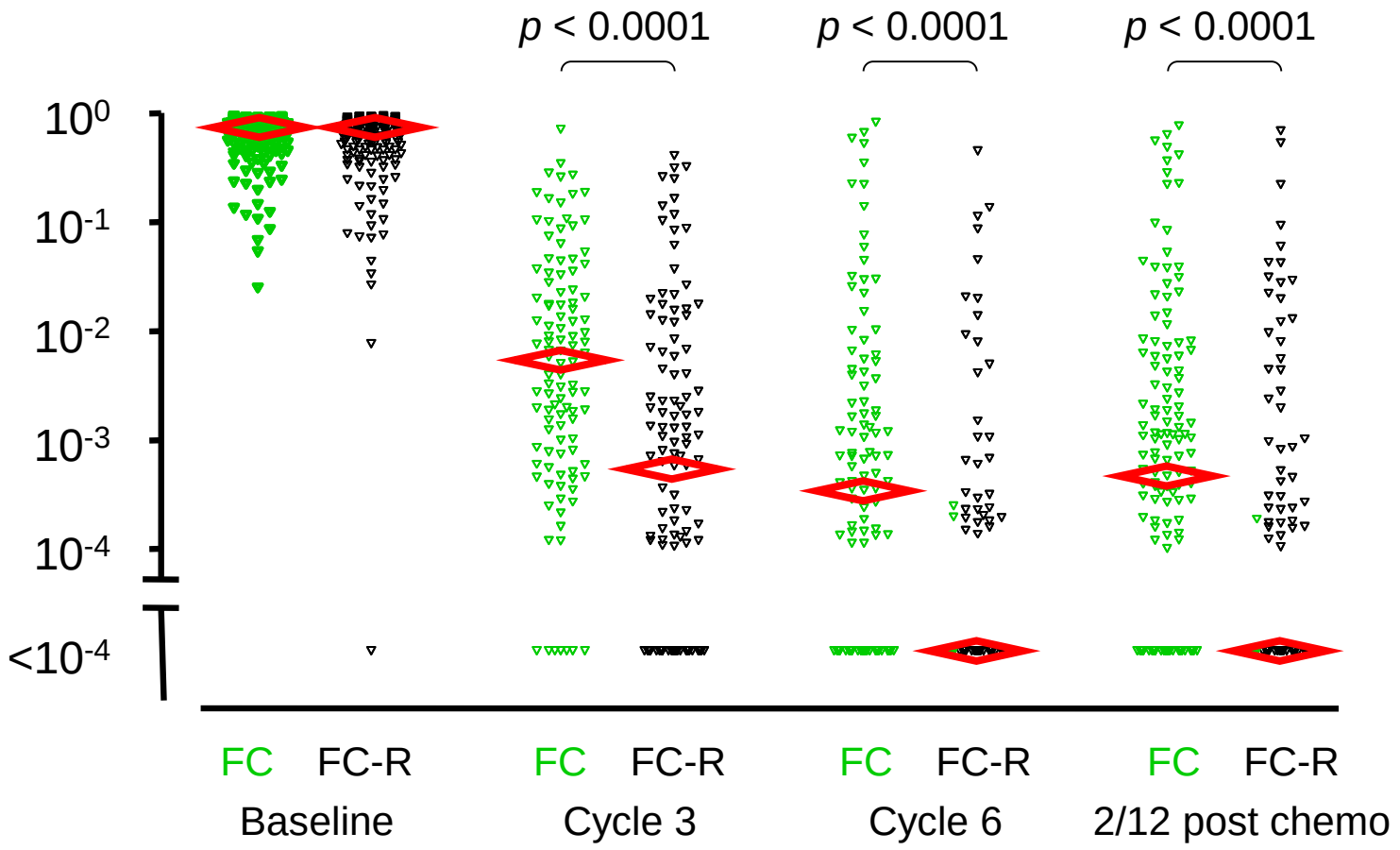
Abstract 325. Session: Chronic Lymphocytic Leukemia – Therapy, Excluding Transplantation
Hallek *et al.* Mon 8 Dec 2008 11:00 AM. Moscone Center, Halls B & C. ASH

CLL8: Response quality vs outcome

MRD	Median PFS
$< 10^{-4}$	Not reached
$\geq 10^{-4} – < 10^{-3}$	35 mo
$\geq 10^{-3} – < 10^{-2}$	33 mo
$\geq 10^{-2} – < 10^{-1}$	16 mo
$\geq 10^{-1}$	12 mo

Abstract 326. Session: Chronic Lymphocytic Leukemia – Therapy, Excluding Transplantation
Böttcher et al. Mon 8 Dec 2008 11:15 AM. Moscone Center, Halls B & C. ASH

CLL8: MRD peripheral blood



Abstract 326. Session: Chronic Lymphocytic Leukemia – Therapy, Excluding Transplantation
Böttcher et al. Mon 8 Dec 2008 11:15 AM. Moscone Center, Halls B & C. ASH

New treatment paradigm in CLL

FCR is the new gold standard in CLL but…

- Is FCR deliverable to all patients?
- Is FCR adequate and appropriate therapy for all patients?
- Is FCR necessary for all patients?
- ? Dose of rituximab
  - Czech data presented at iwCLL 2009 (oral FC + 375mg/m2)
  - UK ARTIC trial

Rituximab and CLL
Other first line combinations

- R + what?
  - F / FC / FCM (dose variations)
    - Note Spannish data JCO August 2009 included R maintenance
    - CR 82% / MRD neg 46%
  - P / PC
  - Bendamustine
    - Current German 1st line trial
  - Chlorambucil

Rituximab with chlorambucil in CLL

- UK 208 Phase II study (now completed recruitment)

Overall Response Rate and 95% Confidence Interval

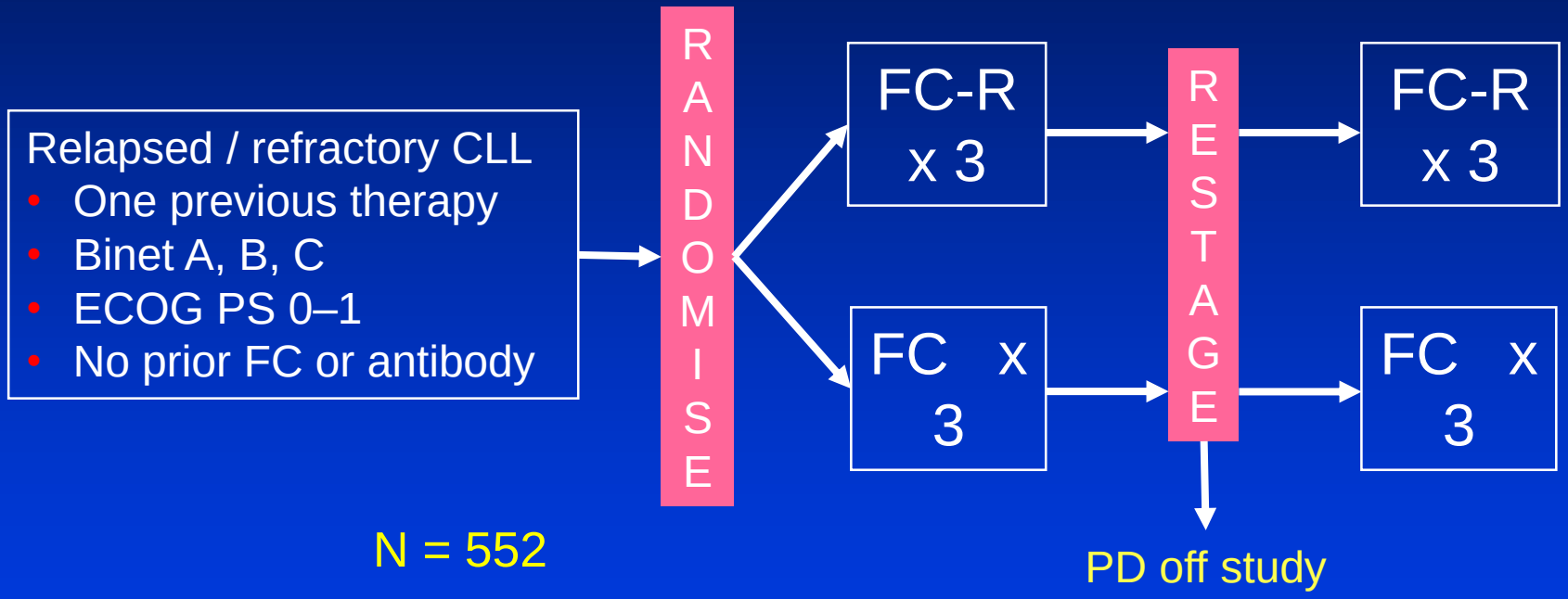
Trial	ORR	SD/PD	Missing	95% CI achieving at least a PR*	Total number of patients
CLL208	84.0%	10.0%	6.0%	[70.9, 92.8]	50
CLL4 (Chlor)	66.7%	30.0%	3.3%	[58.5, 74.1]	150

Rituximab with chlorambucil in CLL

- UK 208 Phase II study (now completed recruitment)
- Italian study in first-line CLL (ongoing)
  - Induction: 8 x rituximab + 10 x chlorambucil
  - Maintenance: 12 x rituximab (q8wk)
- GCLLSG CLL11 study (planned)
  - ‘Slow-go’ patients (CIRS > 6)
  - Binet B/C (or symptomatic A)
  - Chlorambucil vs Clb+rituximab vs Clb+GA-101

Rituximab in relapsed CLL

REACH: FC-R vs FC



N = 552

Chemo regimen identical to CLL8

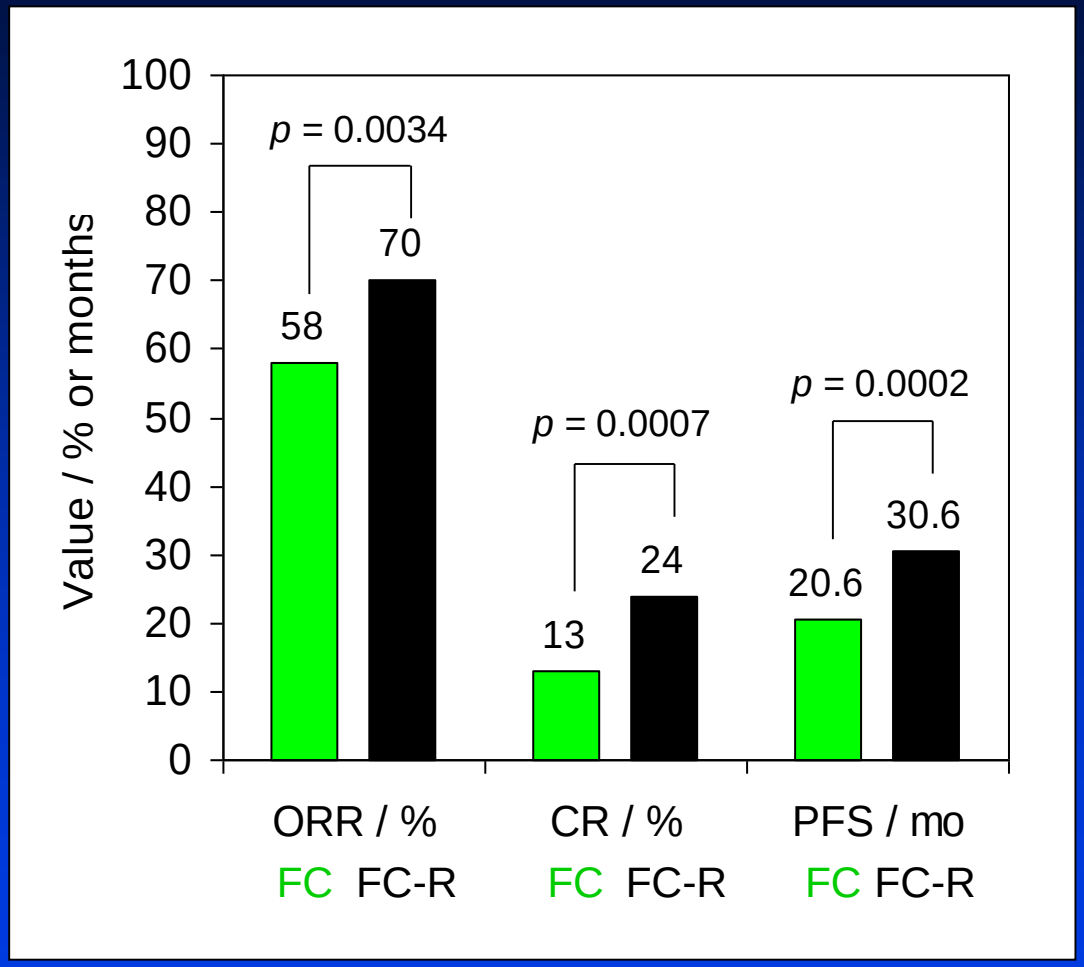
Abstract 15742 (late breaker). Session: Late breaking abstract session
Robak et al. Tue 9 Dec 2008 7:30 AM. Moscone Center, Halls B & C. ASH

REACH: Selected stratification factors

		R-FC n = 276		FC n = 276	
Median time from first diagnosis		3.8 yrs		3.7 yrs	
Median number of prior regimens		1		1	
Prior alkylator	Refractory	27%	**82%**	26%	**82%**
	Sensitive	55%		56%	
Prior purine analogue		16%	**18%**	17%	**18%**
Alkylator → fludarabine		2%		1%	

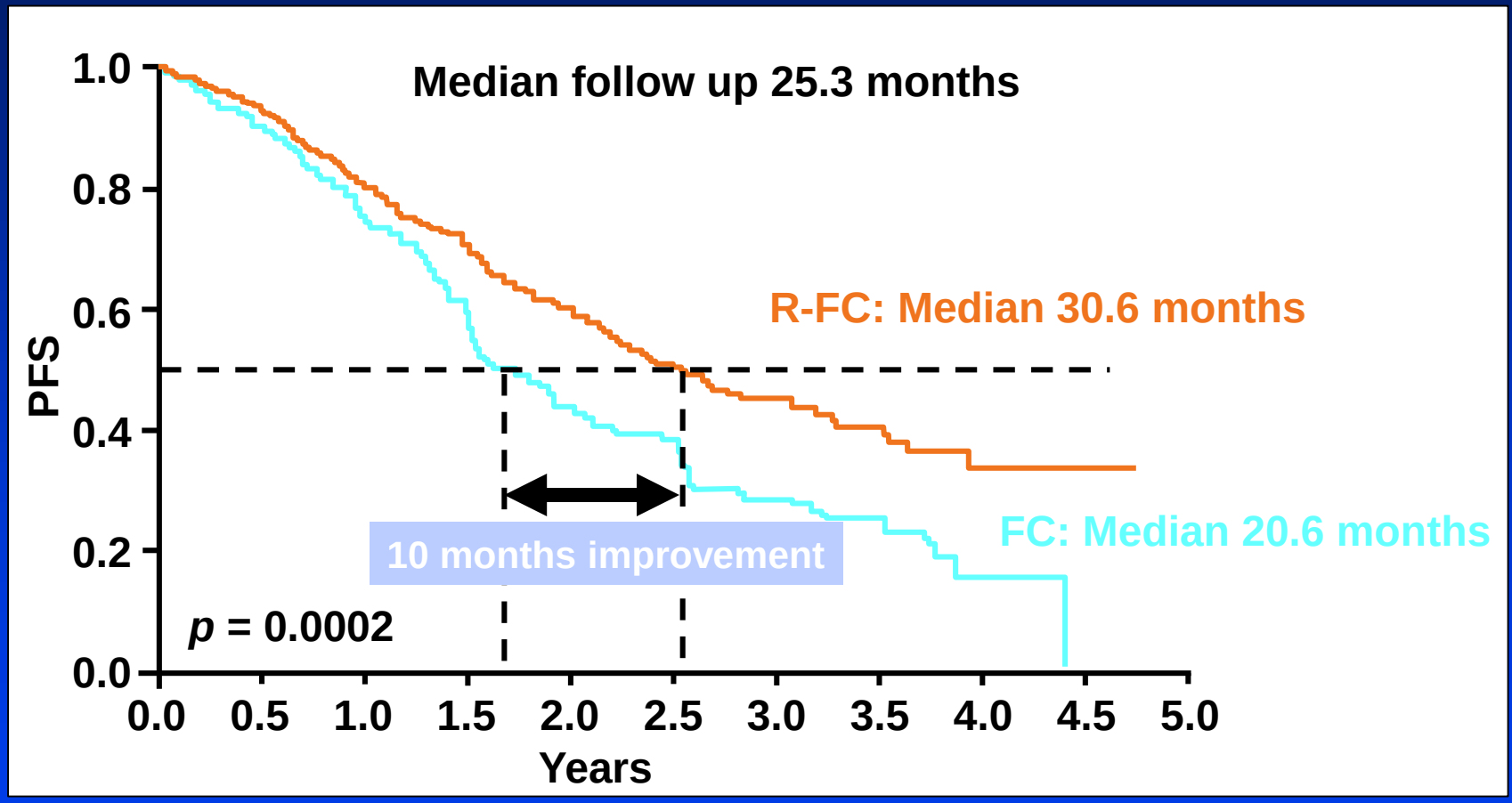
Robak T, *et al. Blood* 2008; 112:Abstract LBA-1.

REACH: Efficacy and Toxicity



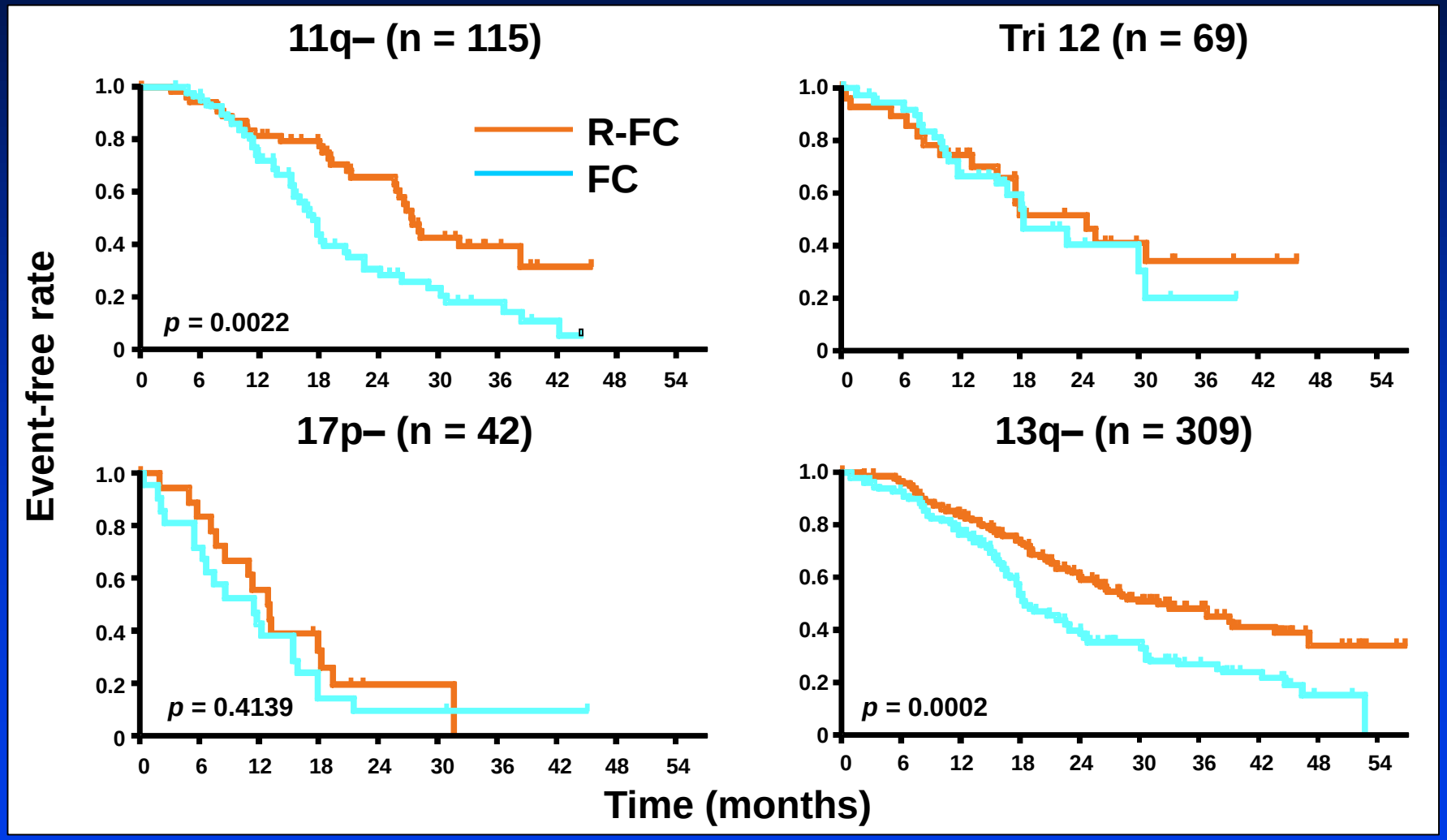
Abstract 15742 (late breaker). Session: Late breaking abstract session
Robak et al. Tue 9 Dec 2008 7:30 AM. Moscone Center, Halls B & C. ASH

REACH: PFS improved by 10 months with R-FC



Robak T, *et al. Blood* 2008; 112:Abstract LBA-1.

REACH: PFS by cytogenetics (ITT)



Robak T, *et al. Blood* 2008; 112:Abstract LBA-1.

REACH: Summary

- R-FC adds 10 months of progression-free time in comparison with FC
- Results were robust and consistent in subgroups and across secondary endpoints, including adverse prognostic groups
  - Binet C
  - 11q–
  - unmutated IgV_H
- R-FC showed a favourable risk-benefit profile with no new or unexpected safety findings

Robak T, *et al. Blood* 2008; 112:Abstract LBA-1.

Rituximab and CLL
Other relapse combinations

- Bendamustine
  - ASH 2008: B+R in relapse CLL (German Phase II)
    81 patients with ORR 77%, CR 14%
    Good responses seen in high risk subgroups
- Steroids (HDMP - Marsden data)
- Lymphoma schedules

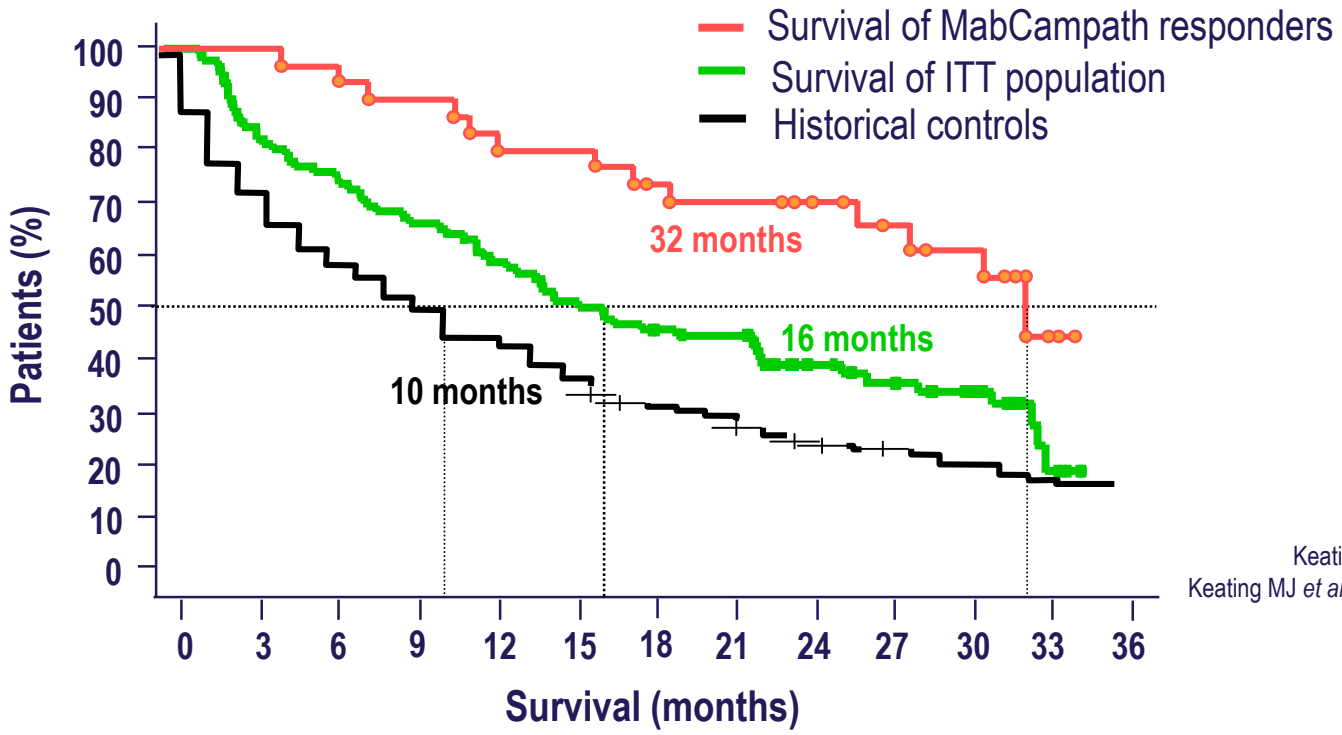
Alemtuzumab

- Monotherapy
  - Refractory disease (CAM 211)
  - First line therapy (CAM307)
  - Consolidation
- Combination therapy

Alemtuzumab – refractory disease

Pivotal trial (CAM 211): overall survival

CLL patients who had failed fludarabine



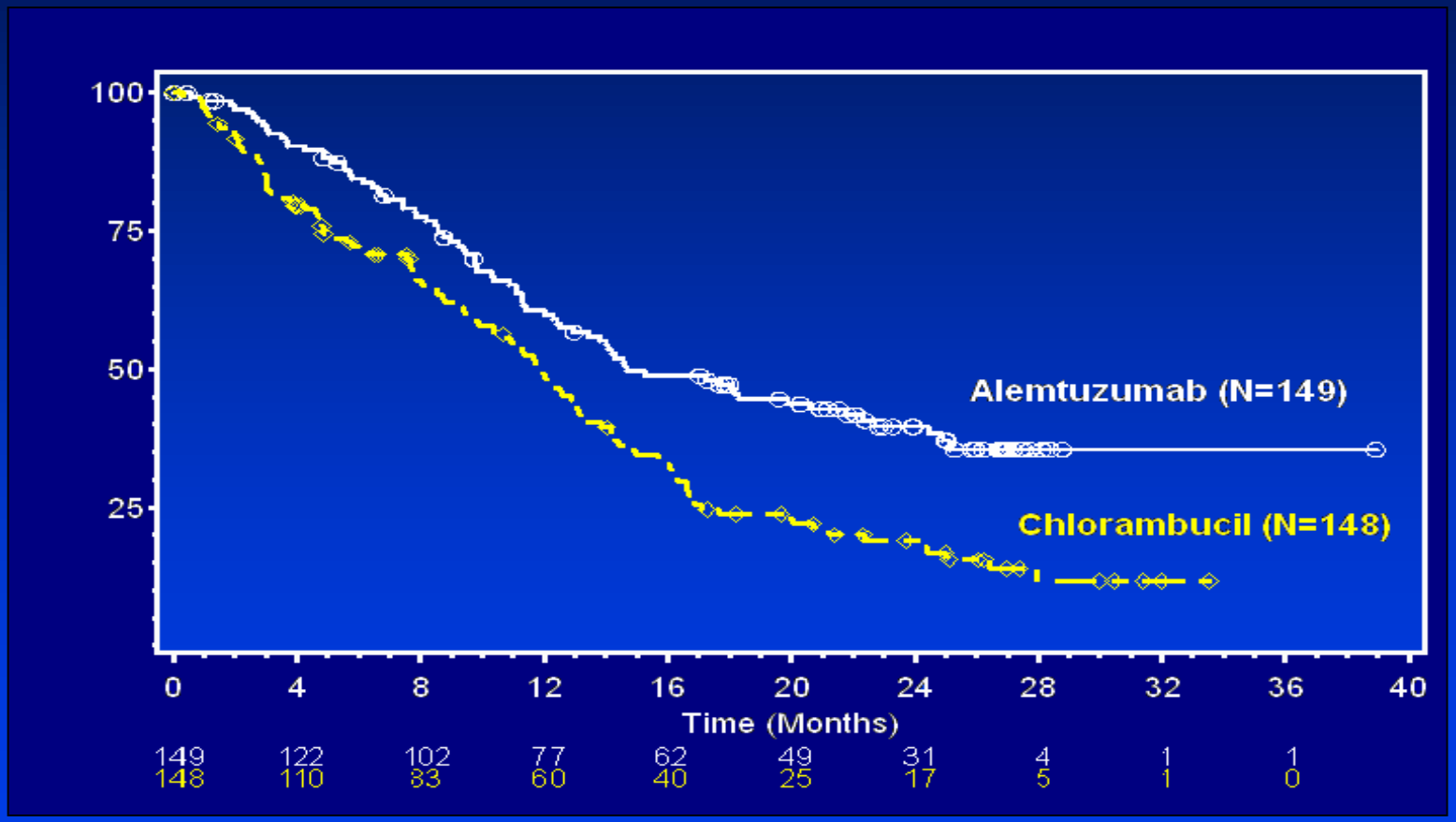
Keating MJ *et al. Blood* 2002;**99**:3554-61
Keating MJ *et al. Leuk Lymphoma* 2002;**43**:1755-62

Non-randomised, non-comparative.

Further investigation was required to satisfy post licensing requirements of the regulatory authorities (EMEA & FDA) following approval of Mabcampath for refractory B-CLL.

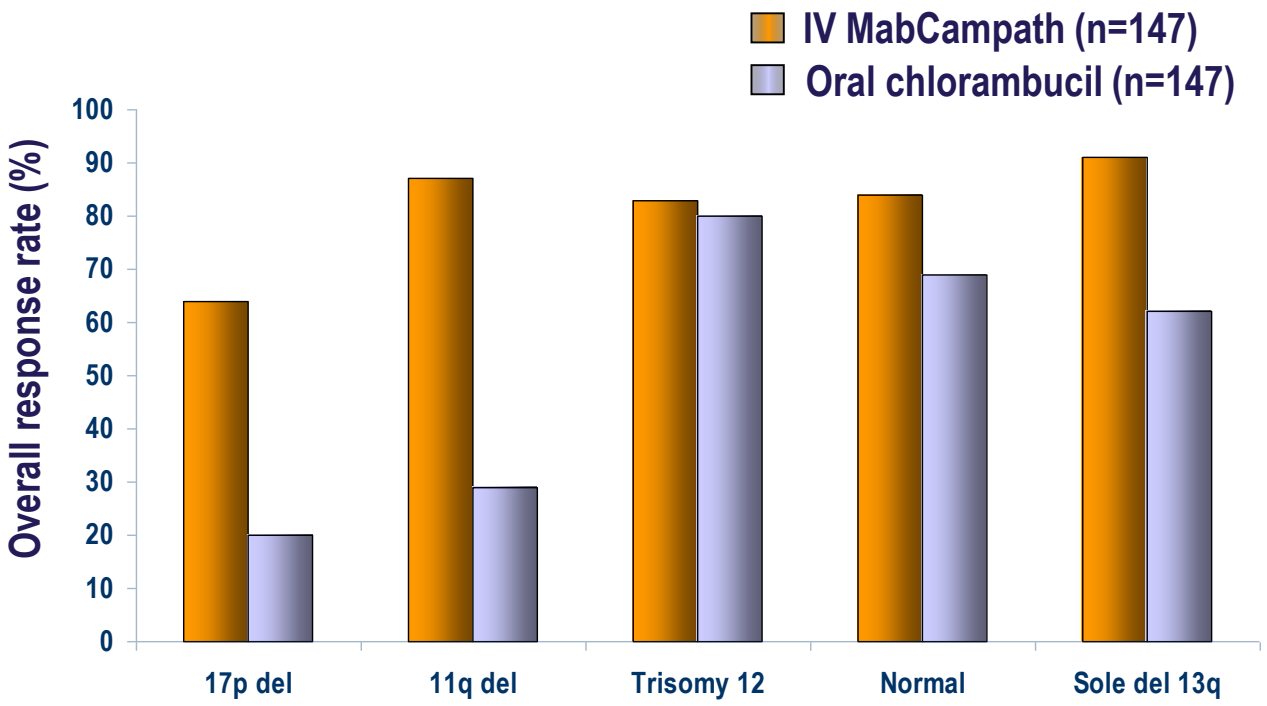
Alemtuzumab – First line therapy

CAM307: Progression-free survival by treatment arm (ITT)



Alemtuzumab – First line therapy

CAM307: ORR according to cytogenetic abnormality



[Data presented according to hierarchical model of Döhner (*NEJM 2000;323:1910-6*)]

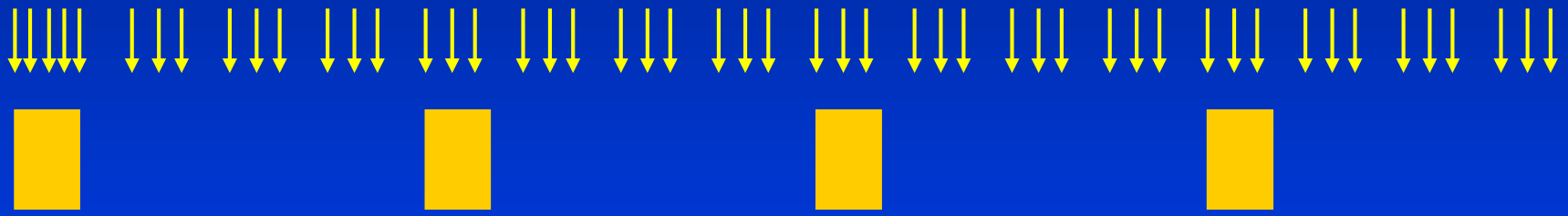
Alemtuzumab – First line therapy

CAM-PRED regimen (Pettitt *et al.*)

(patients requiring therapy and with >20% 17p-deleted cells)

IV alemtuzumab 30 mg thrice weekly

SC alemtuzumab 30 mg thrice weekly from week 5



IV methylprednisolone 1.0 g/m^2 day 1–5 repeated every 28 days

Infection surveillance and prophylaxis!!!

Alemtuzumab – First line therapy

CAMPRED UK206 (Pettit et al EHA 2009)

39 patients

(22 de novo; 17 pre-treated with 1-5 regimens)

Response assessment by IWCLL criteria, 2008

CR/CRi rate: All patients 24%, De novo patients 37%

MRD negative: 3 patients

Toxicity

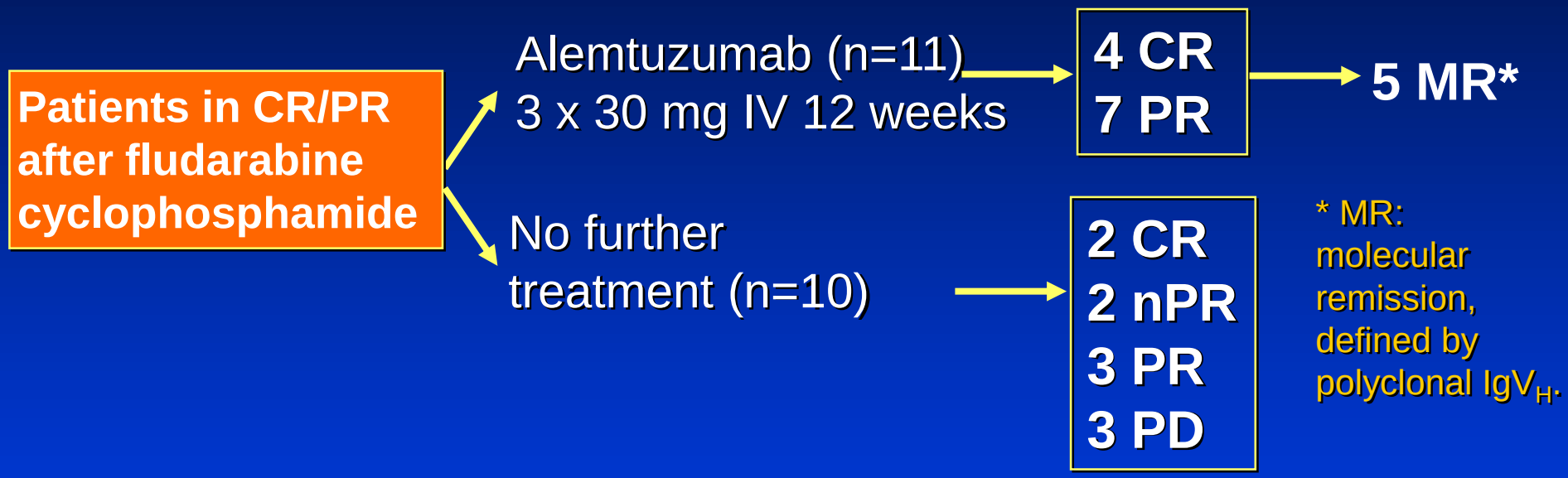
CMV reactivation in 23%

Non-CMV infection in 41%

Steroid-related toxicity in 38%

Alemtuzumab consolidation

German CLL4B study (n=21)

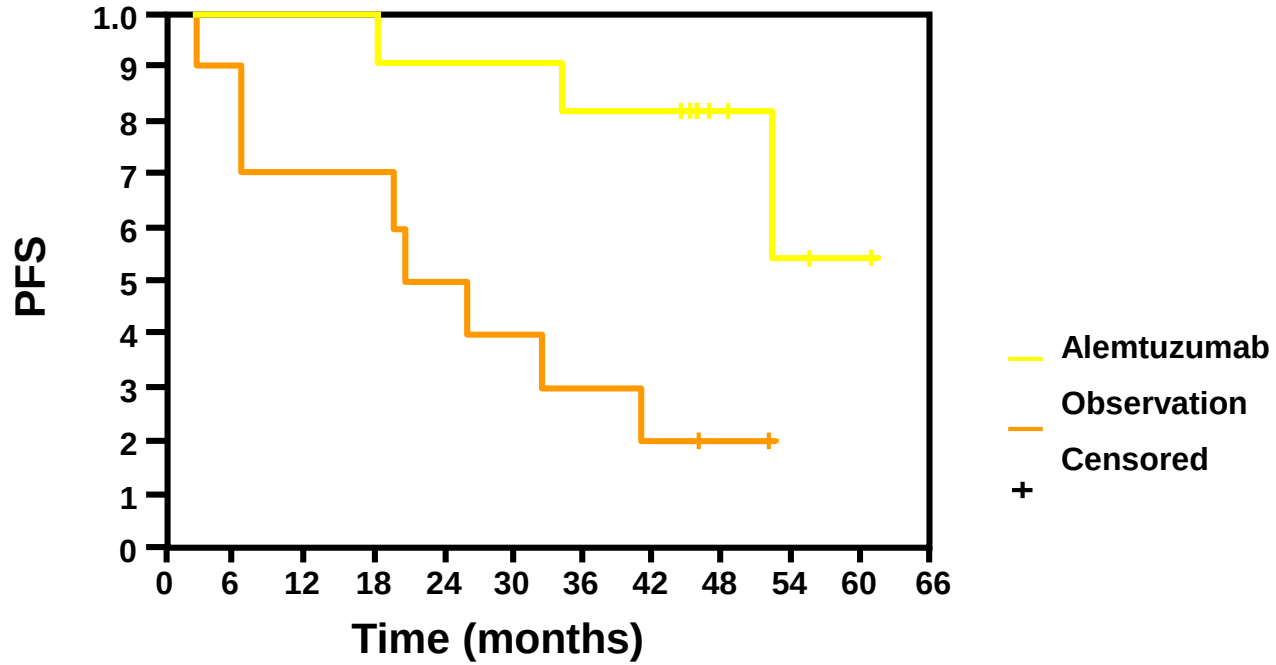


- After a median of 4 weeks, treatment was interrupted in 7 patients treated with alemtuzumab because of grade 3/4 infections

Schweighofer *et al.*, 2008, *BJHaem*, 144, 95–98.

Alemtuzumab consolidation

German CLL4B study (n=21)



Median follow-up since randomization to CLL4B = 48 months

Events (progressive disease) →Alemtuzumab = 3; Observation = 8

Progression-free survival (*P* = 0.0035)

- Alemtuzumab = not reached
- Observation = 20.6 months

Schweighofer *et al.*, 2008, *BJHaem*, 144, 95–98.

Alemtuzumab consolidation

Group and Lead Author	Induction	Interval from Induction to Campath	Dose, Route and Duration	Improvement in response after consolidation	N	Deaths
CALGB (Rai '02)	4 X Flu	2 months	30 IV tiw, 6 wks	23%	36	1
CALGB (Rai '03)	4 x Flu	2 months	30 SQ tiw, 6 wks	10%	18	0
Hainsworth '05	FR	4 weeks or 8 weeks	30 IV tiw, 4 wks	17%	37	0
GMCLLSG (Wendtner '03)	6 x F or 6 x FC	10 weeks	30 IV tiw, 12 wks	18% PFS longer	21	0
Montillo '04	F or FC	16 weeks	10 SQ tiw, 6 wks	44%	34	0
MDACC (O'Brien '03)	N/A	5 months	10 SQ tiw, 4 wks 30 SQ tiw, 4 wks	39% 65%	24 34	0 0
Delmer, '06	3 x FC	2 months	10 SQ tiw, 8 wks	27%	33	0
CALGB (Lin, 07)	6 x FR	3 months	30 SQ, 6 wks	??	51	6

Total = 288 7

Alemtuzumab consolidation

Results of interim analysis of NCRI CLL207 (April 2009)

MRD Result after Treatment	N (%)
MRD positive → MRD Negative	18 (75.0%)
MRD Positive remaining positive	4 (16.7%)
Missing	2 (8.3%)

MRD Result	Number of Weeks of Treatment						
	3	4	6	7	8	12	Total
Negative	1	.	7	5	2	3	18
Positive	.	.	1	1	1	1	4
Missing	.	1	1	.	.	.	2
Total	1	1	9	6	3	4	24

*** Hillmen *et al.*, Abstract 0361 EHA 2009**

Alemtuzumab combination therapy

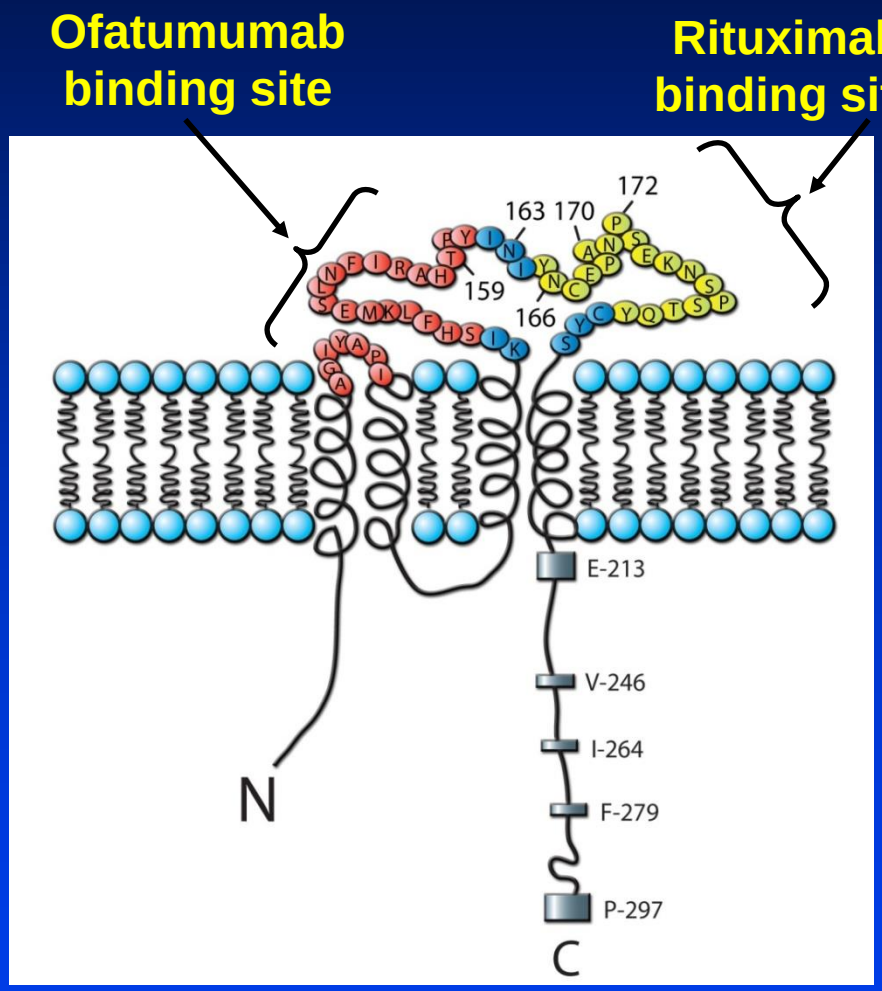
- French FCR vs FCAlemtuzumab
  iwCLL 2009 and ASH 2009

  100 patients randomised

  Trial stopped by SMC
  7 deaths in Alemtuzumab arm
  Mix of infectious and EBV driven LPD

  Apparent inferiority of ORR in FCA arm

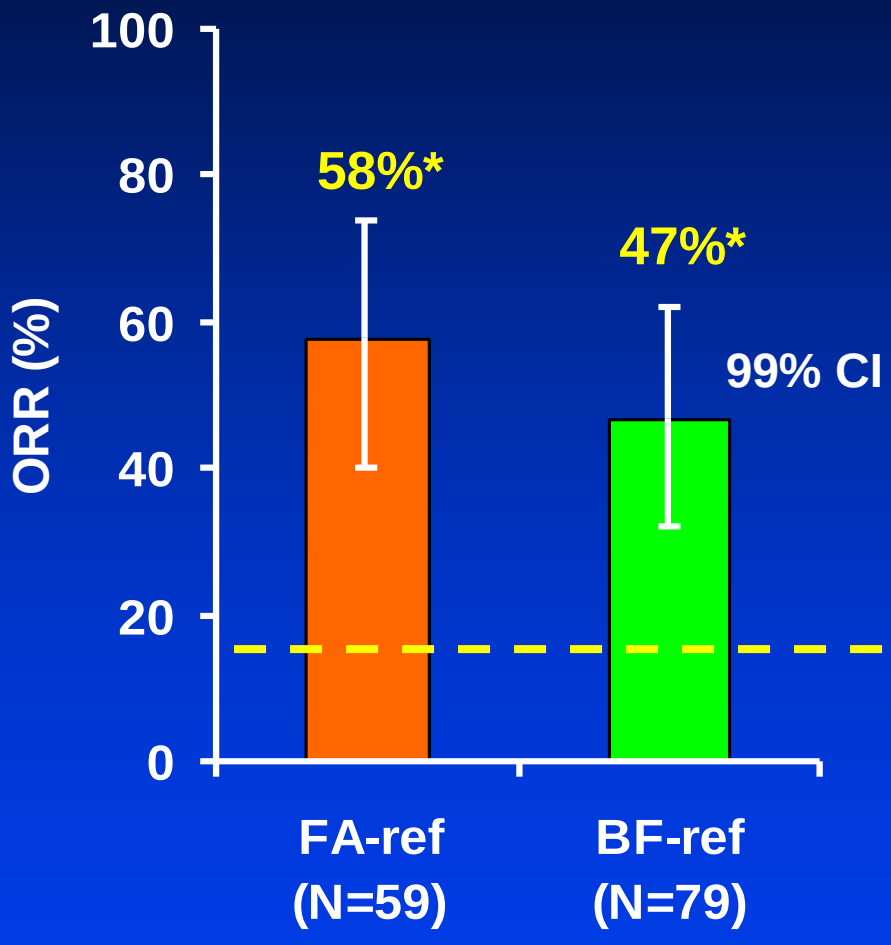
Ofatumumab



- Human CD20 monoclonal antibody (mAb)
- Binds to small loop of CD20
- Potent lysis of B cells
- More effective *in vitro* CDC compared with rituximab
- Effective CDC of cells with low CD20 expression, including in CLL cells
- Promising activity in pilot CLL study: ORR 50% in high-dose group (n=27)[3]

1. Teeling et al. *J Immunol* 2006; 177: 362; 2. Teeling et al. *Blood* 2004; 104: 1793; 3. Coiffier et al. *Blood* 2008; 111: 1094

Ofatumumab in refractory CLL



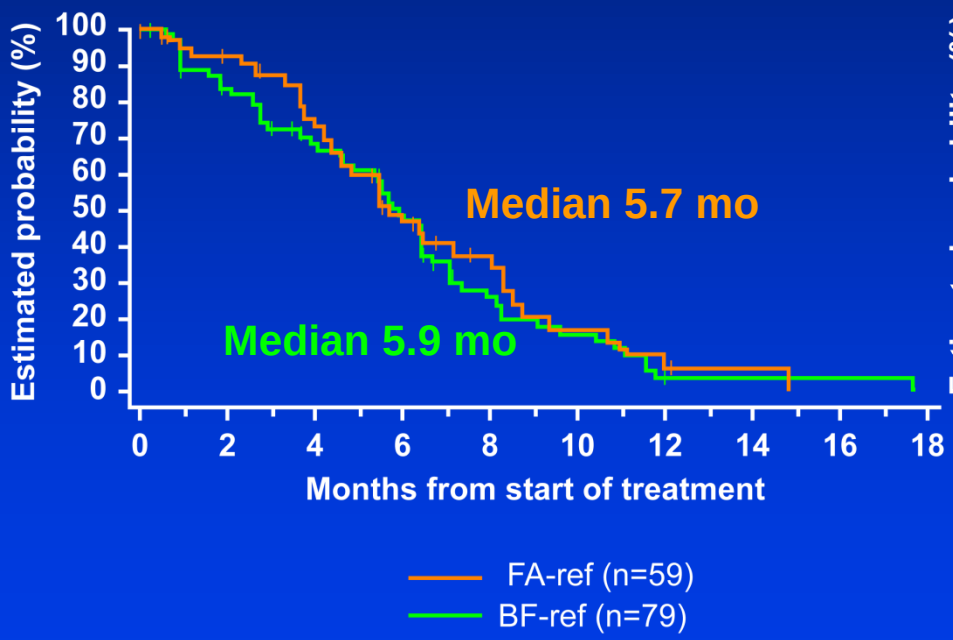
*p<0.0001 versus H_0

All PRs except one CR in BF-ref group.

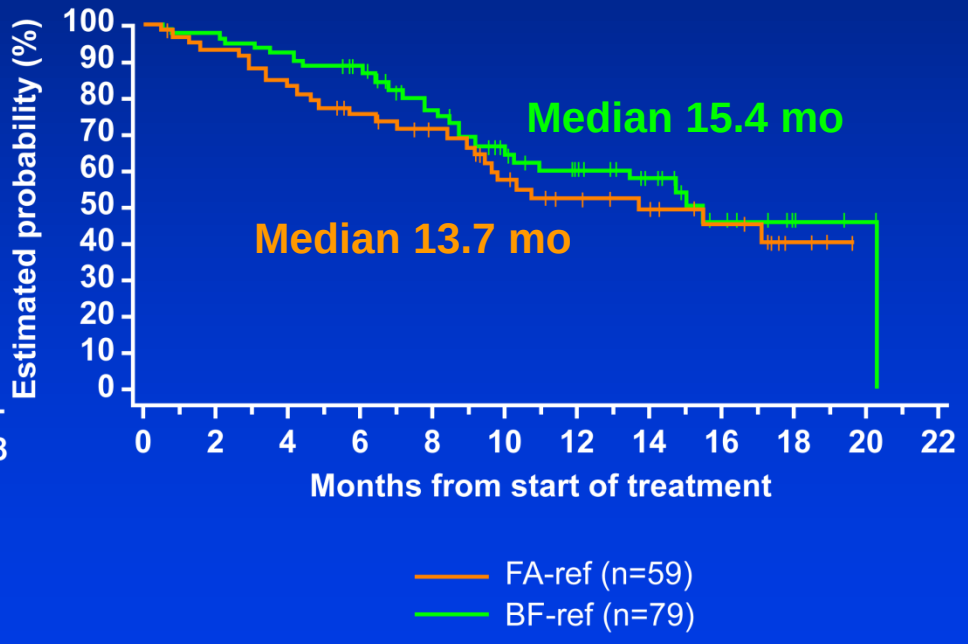
*The null hypothesis of ORR=15% was tested against the corresponding two-sided alternative hypothesis ORR≠15% using an exact test.

Ofatumumab in refractory CLL

Progression-free survival*



Overall survival**



*Time from start of treatment to progression (assessed by IRC) or death.
**Time from start of treatment to death.

Ofatumumab in 1st Line CLL 407 Trial

- 1st Line CLL patients in need of therapy
- Progressive A, B, C
- FC + either 500mg or 1000mg Ofatumumab
- 61 Patients treated (2 from the UK)

For presentation at ASH 2009

- ORR approx 75% in both arms
- CR rate appears higher with 1000mg

50% vs 32%

(original MD Anderson FCR: ORR 95%, CR 72%
German CLL8 FCR: ORR 92%, CR 44%)

Ofatumumab in 1st Line CLL COMPLEMENT1 study

- Phase III open randomised trial
- CBL vs CBL + Ofatumumab
- 4 UK patients recruited

GA101 in CLL

- Humanised, glycoengineered,
- type II monoclonal antibody
  (High direct cell apoptosis, lower CDC)
- High FCγRIIIa affinity
  (High ADCC)
- Marked B cell depletion in Cynomolgus monkeys
- HuCD20tg mice – effective B cell depletion (including the splenic marginal zone)
- Effective tumour kill in mouse xenograft models

GA101

- ASH 2008
- 24 patients with CD20+ LPD treated since September 2007
- Dose escalating phase I schedule
- Pharmacokinetics variable (inter and intra-patient)
- Toxicity acceptable (No DLTs, infusional s/e)

- Of 12 patients evaluable at day 85:
  - 7 / 12 = OR (responses in all dose cohorts)
  - 3 / 12 = CR

Other antibodies

- Anti-CD23 (lumiliximab)
  - Monotherapy data not very encouraging (2007)
  - Combination with FCR in relapse (MDACC CR 52%)
  - FCR vs FCR-L in relapse recruiting internationally
- Anti-CD22 (epratuzumab)
  - Monotherapy has some efficacy in CLL
  - Combination with R-chemo in NHL 1st line
  - 90Y-tagging (Not aware of trials actively recruiting)

Antibody therapy is a unifying feature of current and future CLL trials

UK Phase II / III Trials

ARCTIC
FC-R vs FCM-miniR

ADMIRE
FC-R vs FCM-R

CLL7
CBL vs CBL-Ofatumumab

CLL207 / CLL8
Alemtuzumab maintenance

CLL210
Cam / Dex / Rev

GCLLSG11
CBL-GA101 etc

CLL9
?

The Future

- Combinations of agents targeted at specific genetic subtypes of CLL
- Treatment and maintenance therapies to keep disease below detectable MRD
- (Don’t forget transplant strategies!)

Acknowledgements

- Addenbrooke's Haematology Trials Team
- Cambridge Cancer Centre
- LRF
- Our patients who sign up for the clinical trials

haematology.trials@addenbrookes.nhs.uk