FCR:YESTERDAY, TODAY AND TOMORROW

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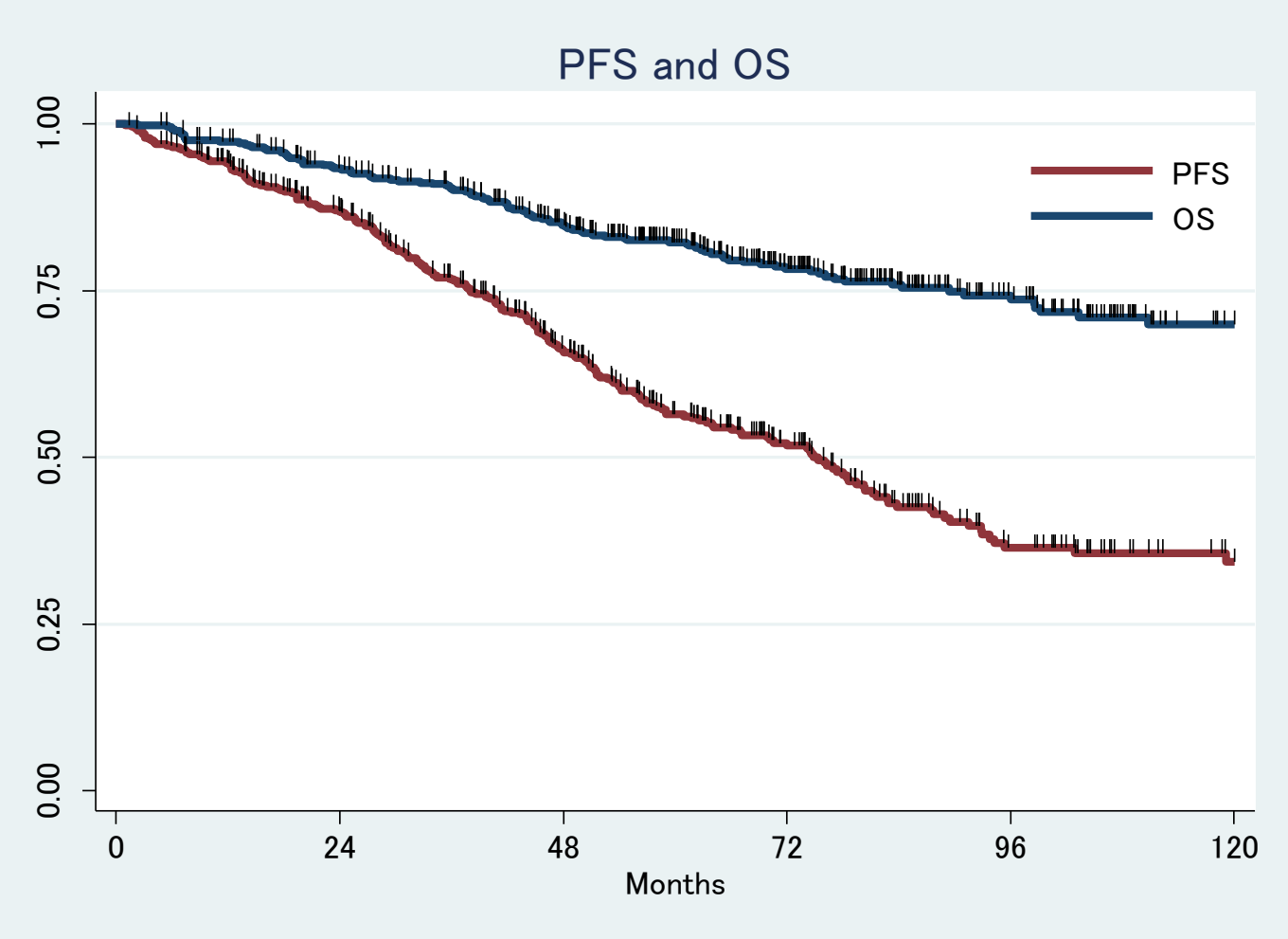
Response to FC + Rituximab (NCI-WG: 300 Patients)*

Response	# Pts.	(%)	
CR	217	(72%)	95%
Nodular PR	31	(10%)	
PR	37	(12%)	
No Response	13	(4%)	
Early Death	2	(1%)	

*Previously untreated CLL Patients

Tam CS, et al, *Blood.* 112(4):975-980, 2008 Aug 15

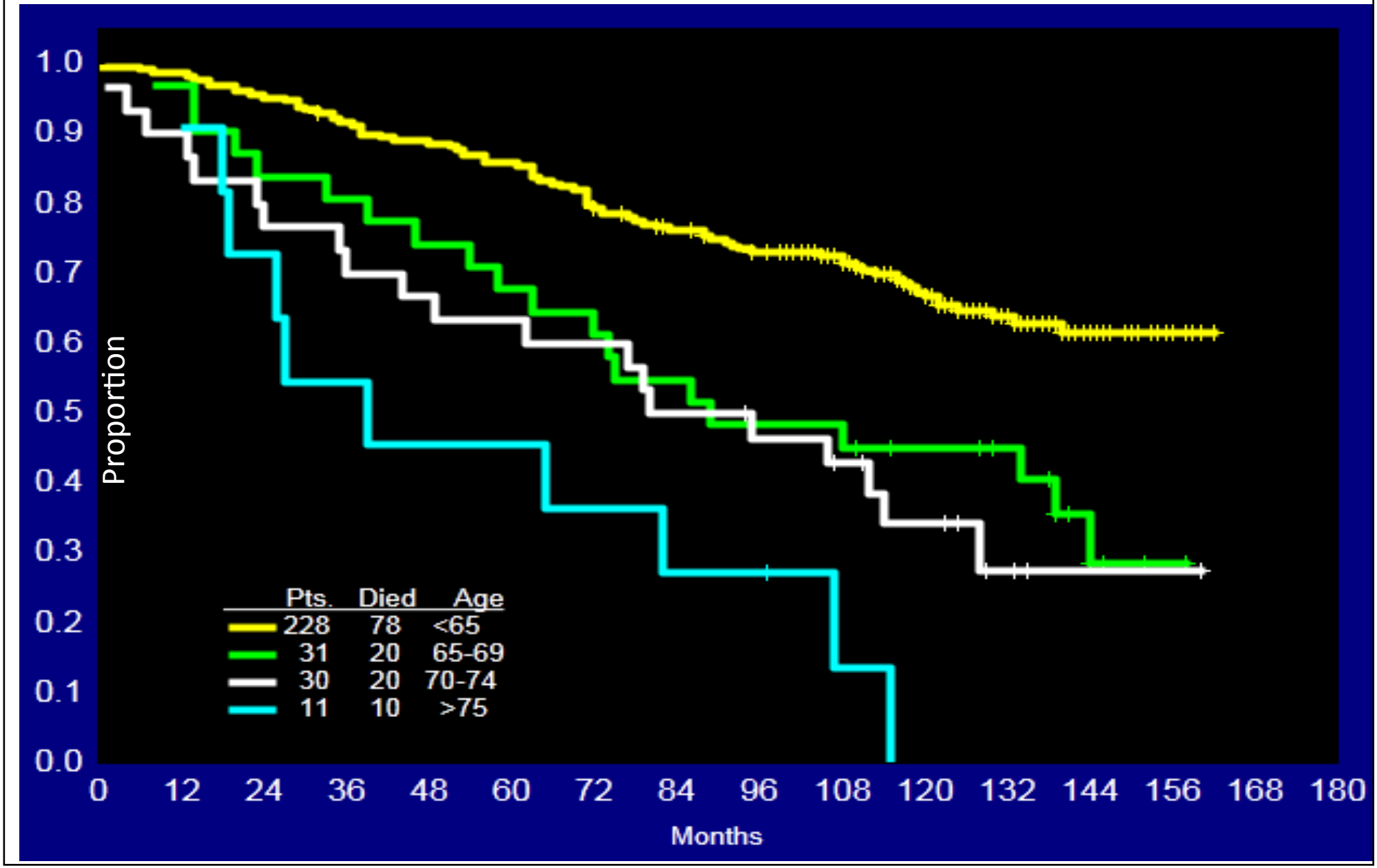
PFS and OS of all FCR patients



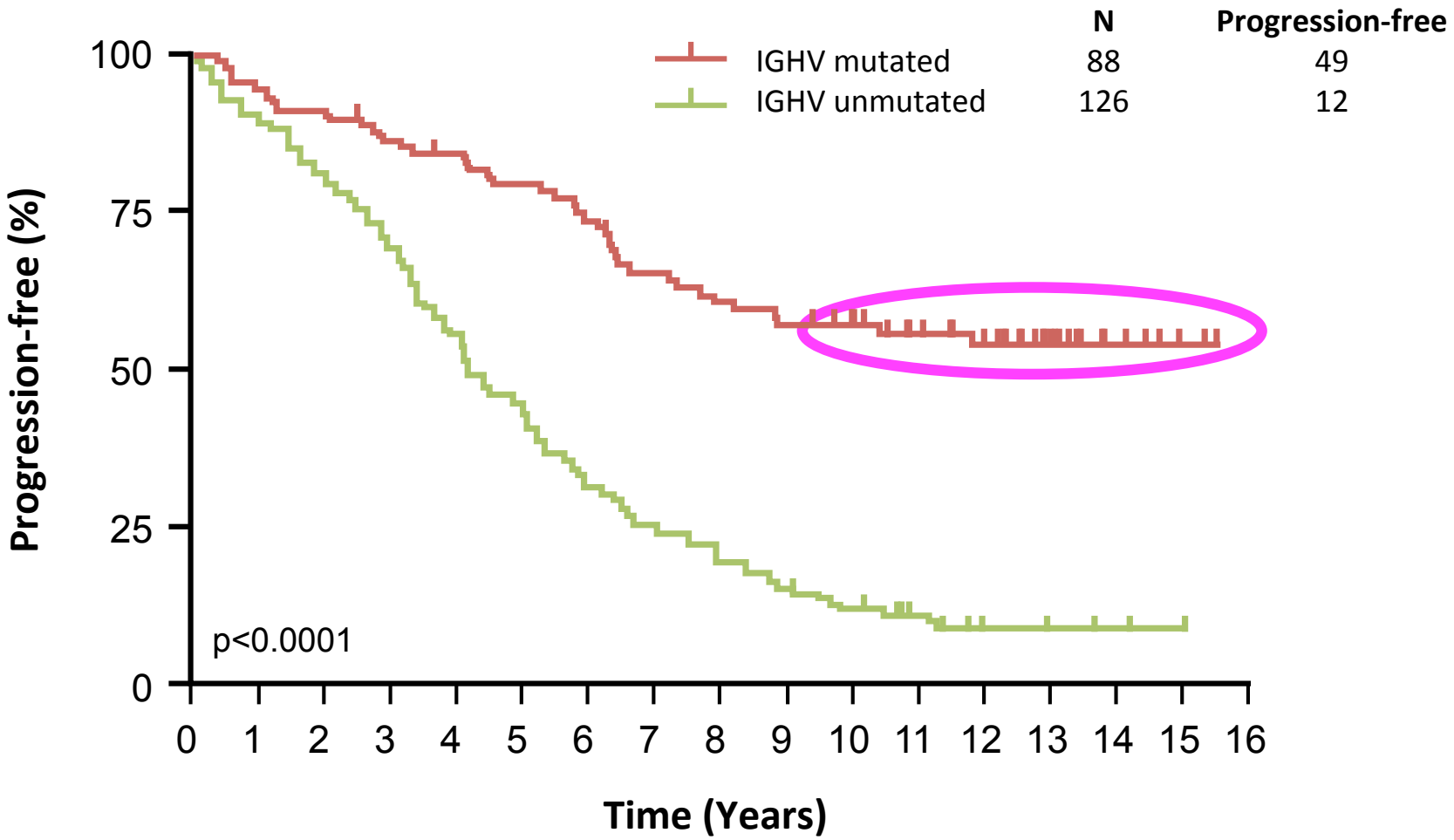
	PFS	OS
Median	75.4 mo	NR
5-yr	56.5%	82.3%
10-yr	34.3%	70.0%

FCR300
Median PFS: 6.4 years
Median OS: 12.7 years

Survival by Age -- FCR 300



FCR300: PFS by IGHV Mutation Status



Thompson PA, *et al. Blood* 2016; **127**:303–309.

Newer Prognostic Factors in CLL

Parameter	Bad
B_2Microglobulin	increased
FISH	11q-, 17p-
VH Mutation Status	unmutated
CD38	positive
ZAP70	positive

Keating, M., Personal Communication

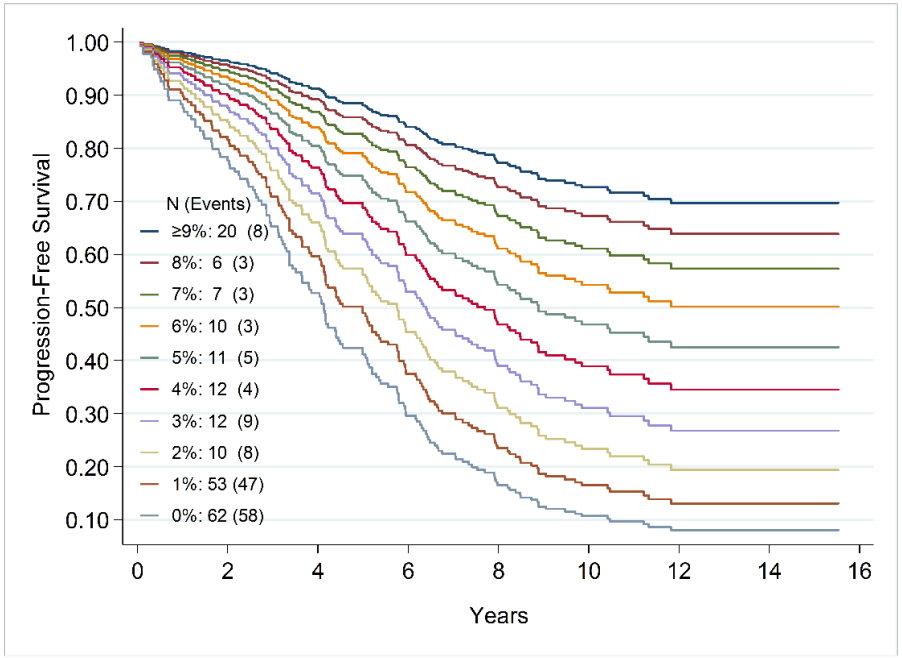
The absolute percent deviation of IGHV mutation rather than a 98% cut-off predicts survival of CLL patients treated with frontline FCR

Jain P et al BJH 2017 (in press)

FCR- Original clinical trial (n=203)

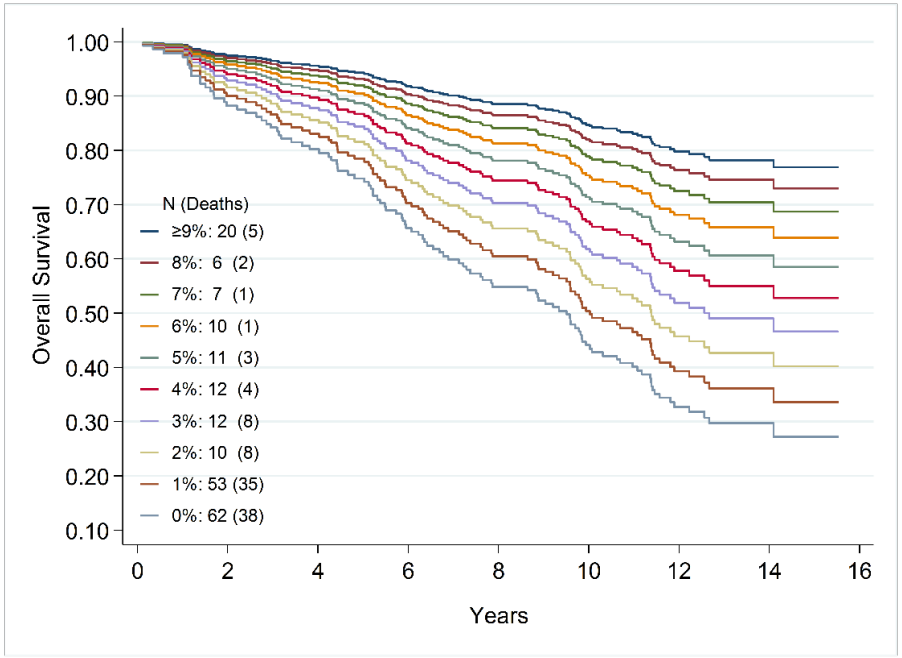
Median Follow up - 10.7 (0.1-15.5)

PFS



(HR: 95%; CI: 0.81 (0.76-0.87); P <0.001)

OS

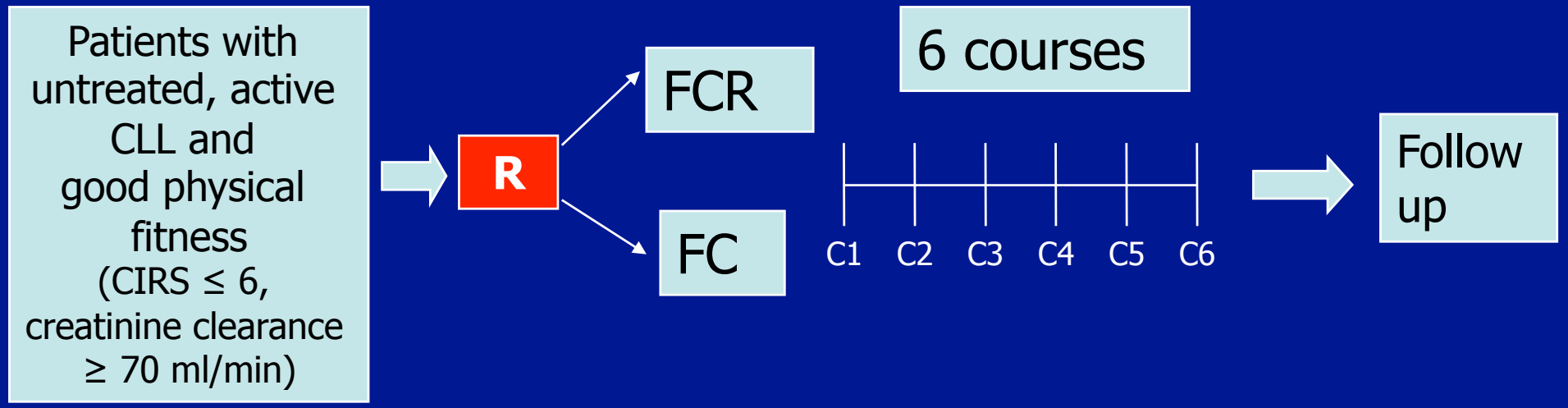


(HR: 95%; CI: 0.84 (0.78-0.91); P < 0.001)

A sustained increase in the percentage deviation of IGHV mutations is significantly associated with a lower risk of PFS and OS

Jain P et al BJH 2017 (in press)

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

Hallek M et al. *Blood.* 2008;112. Abst 325

Can we improve on FCR? 2004--2017

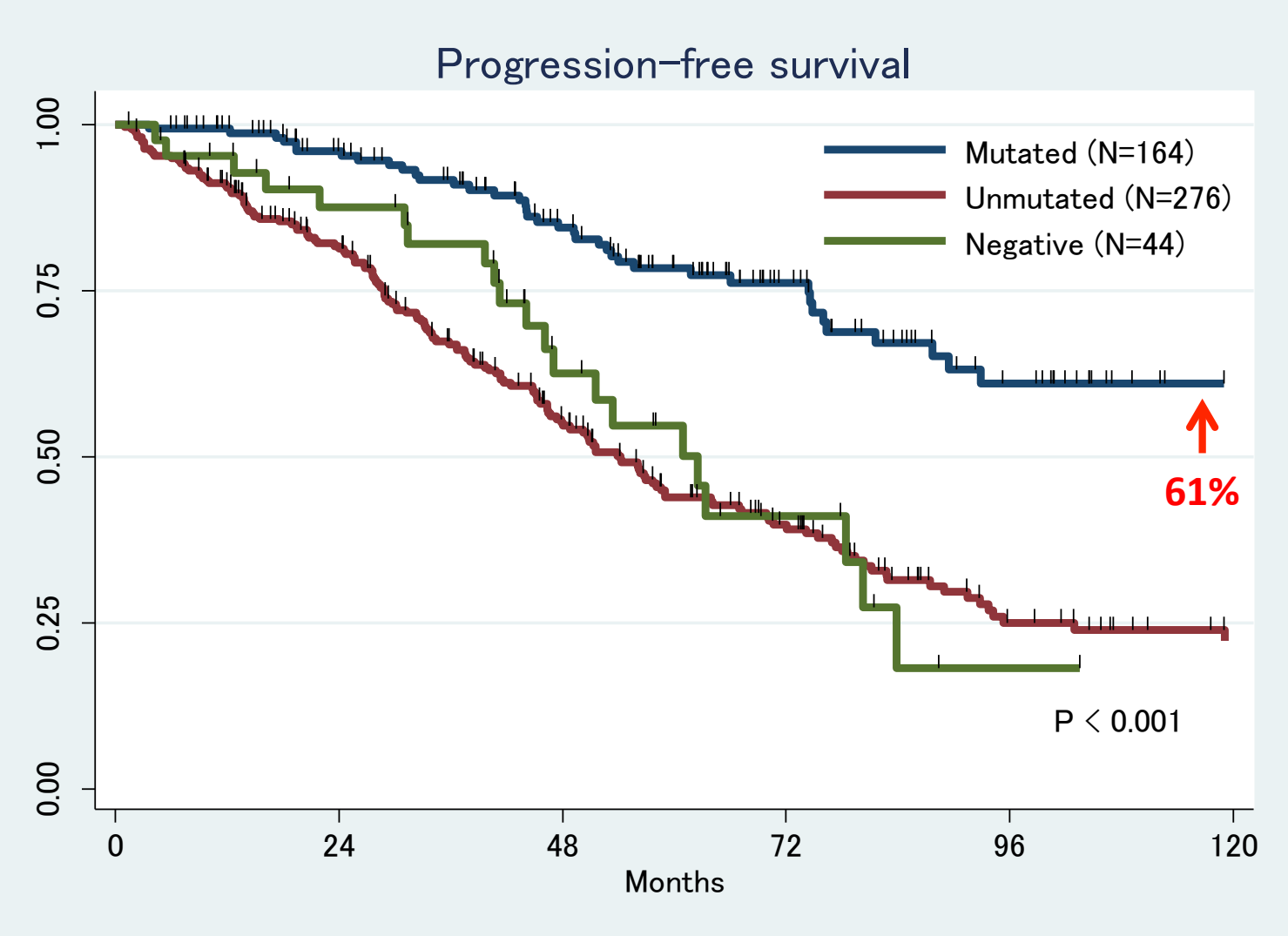
- 5 prospective trials
  - FCR3: 3 doses rituximab
  - FCM-R: Mitoxantrone
  - CFAR: Campath
  - FCR + GM-CSF
  - FCR (MRD)

FCR-BASED

- FCR: MRD assessment
- FISH and Mutation status in great majority

FCR-BASED	N (%)
Total No. of patients	492
Male	332 (67)
Median age (range)	59 (28-84)
Mutated IGHV	164 (33)
del(11q)	100 (20)
del(17p)	39 (8)

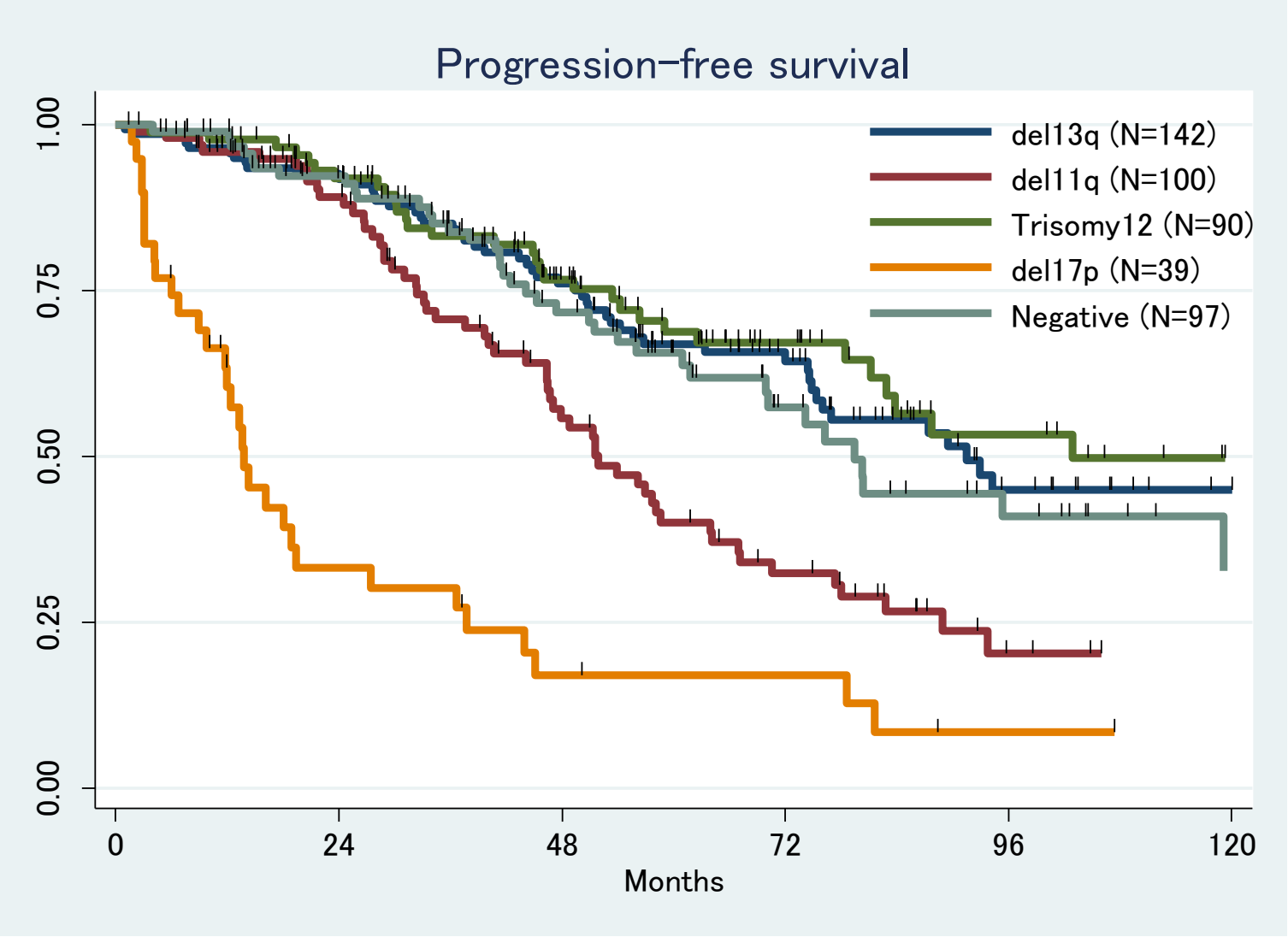
PFS in all patients based on IGHV



Plateau in mutated patients reproduced in this cohort

Negative group do worse similar to unmutated

PFS based on FISH hierarchy



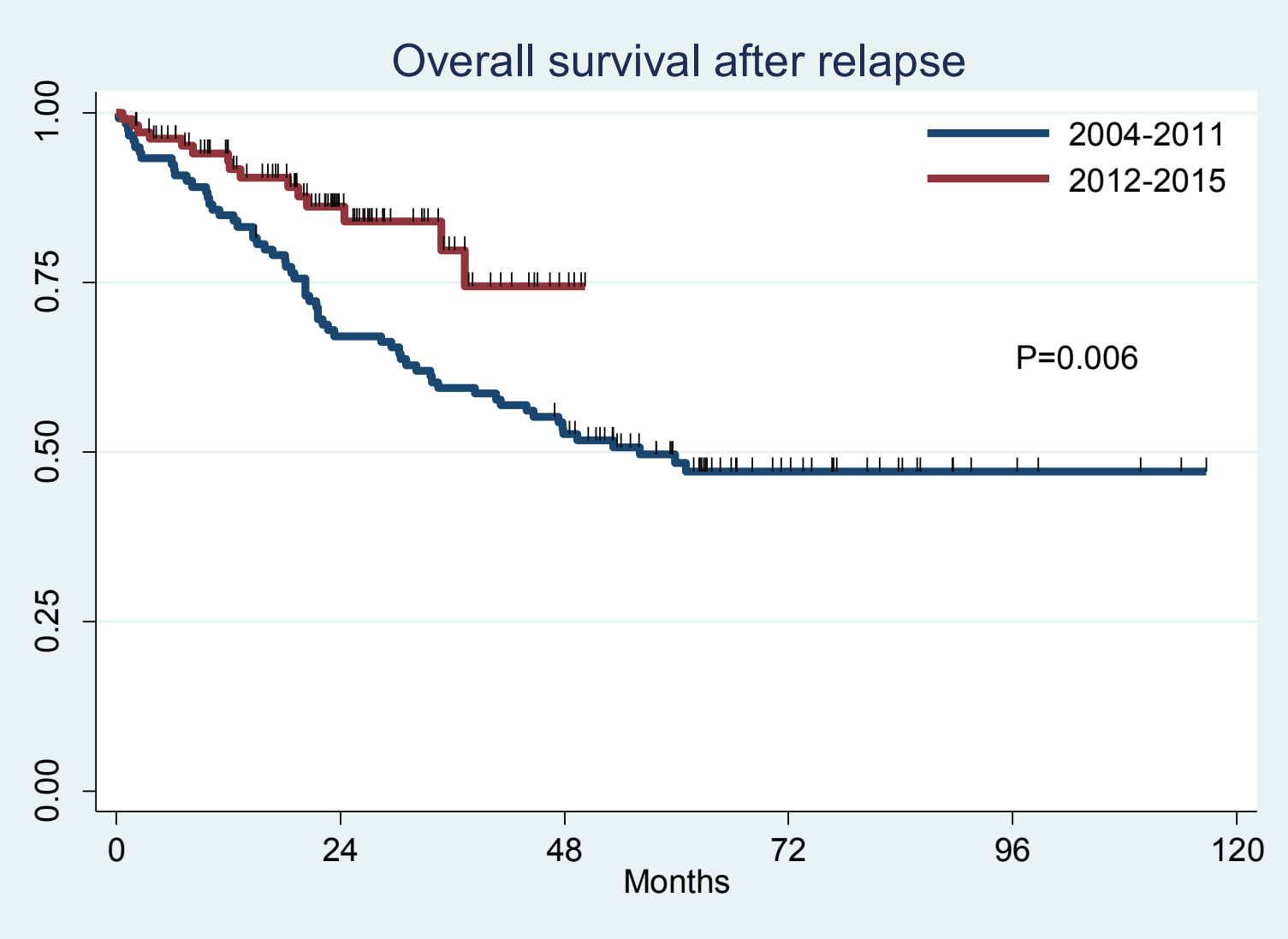
Consistent with previous studies

FISH and IGHV interelationship

	Mutated	Unmutated	Negative
del(13q)	78 (56)	55 (39)	7 (5)
del(11q)	5 (5)	80 (82)	13 (13)
Trisomy12	29 (32)	48 (53)	13 (14)
del(17p)	7 (18)	29 (74)	3 (8)
Negative	37 (39)	50 (53)	8 (8)

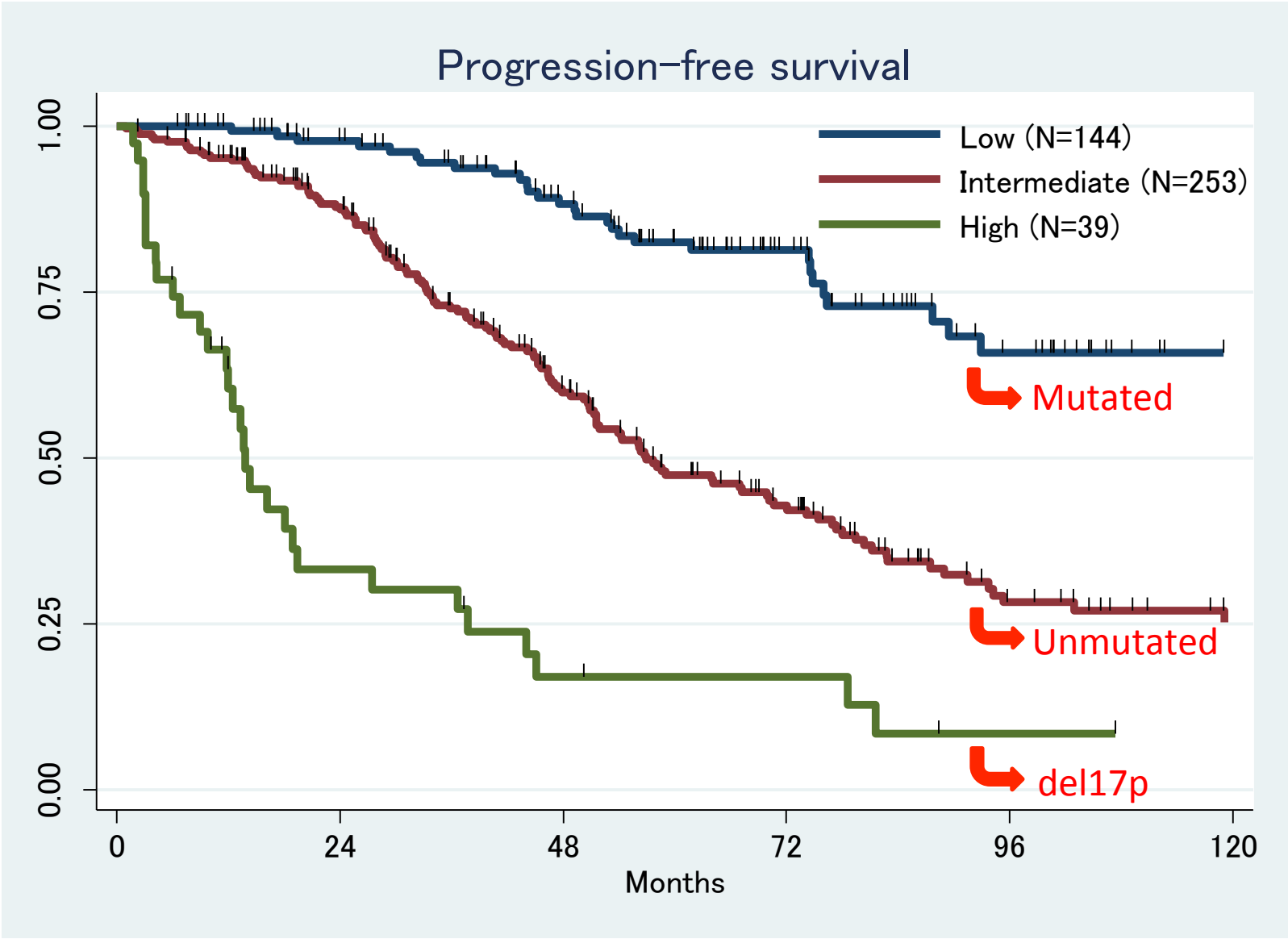
P<0.001

Survival after relapse



Salvage treatments are getting better !!

Rossi risk group (Blood 2015)

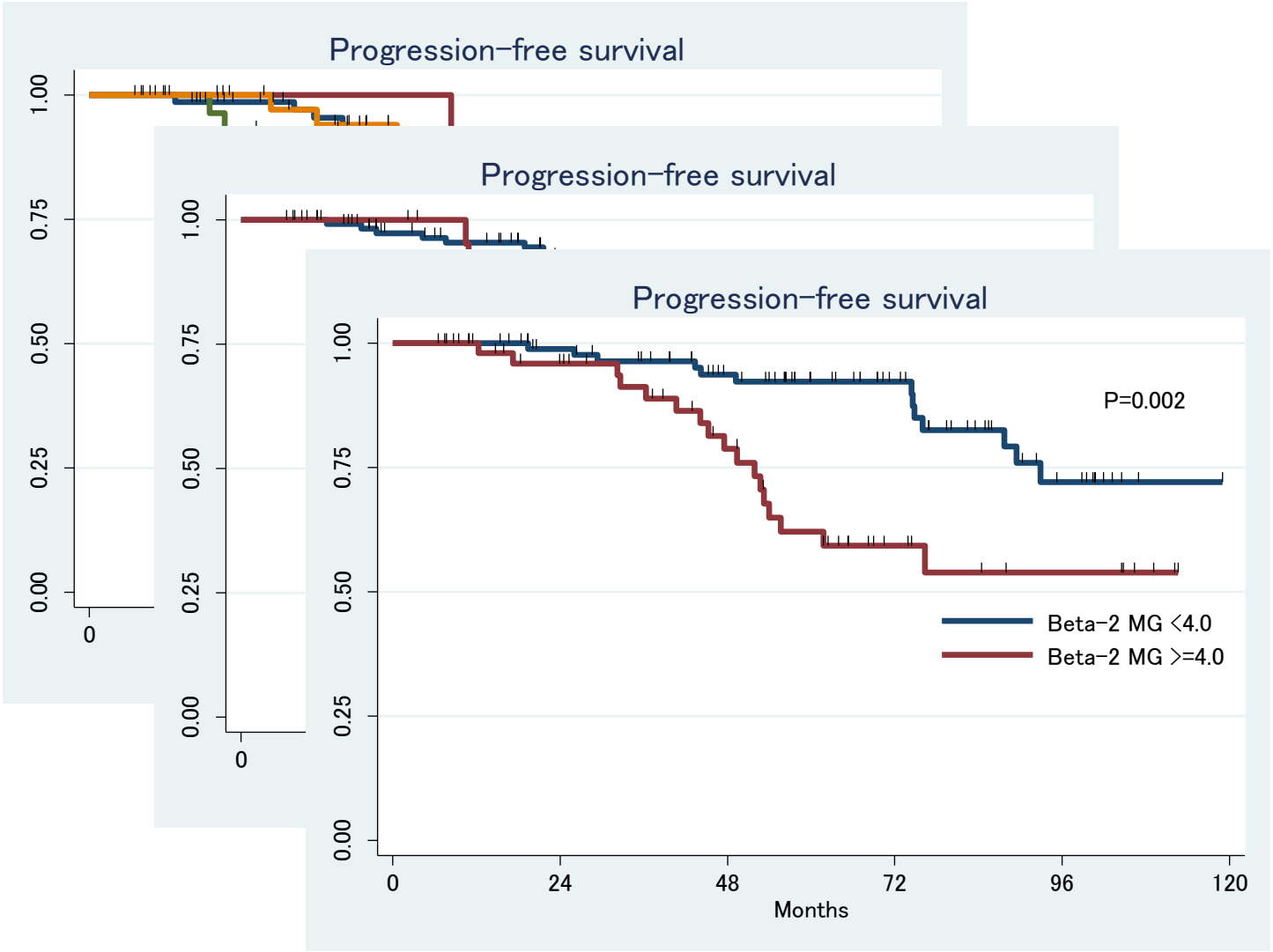


LOW
Mutated, non del11q or del17p

INTERMEDIATE
Unmutated or del11q

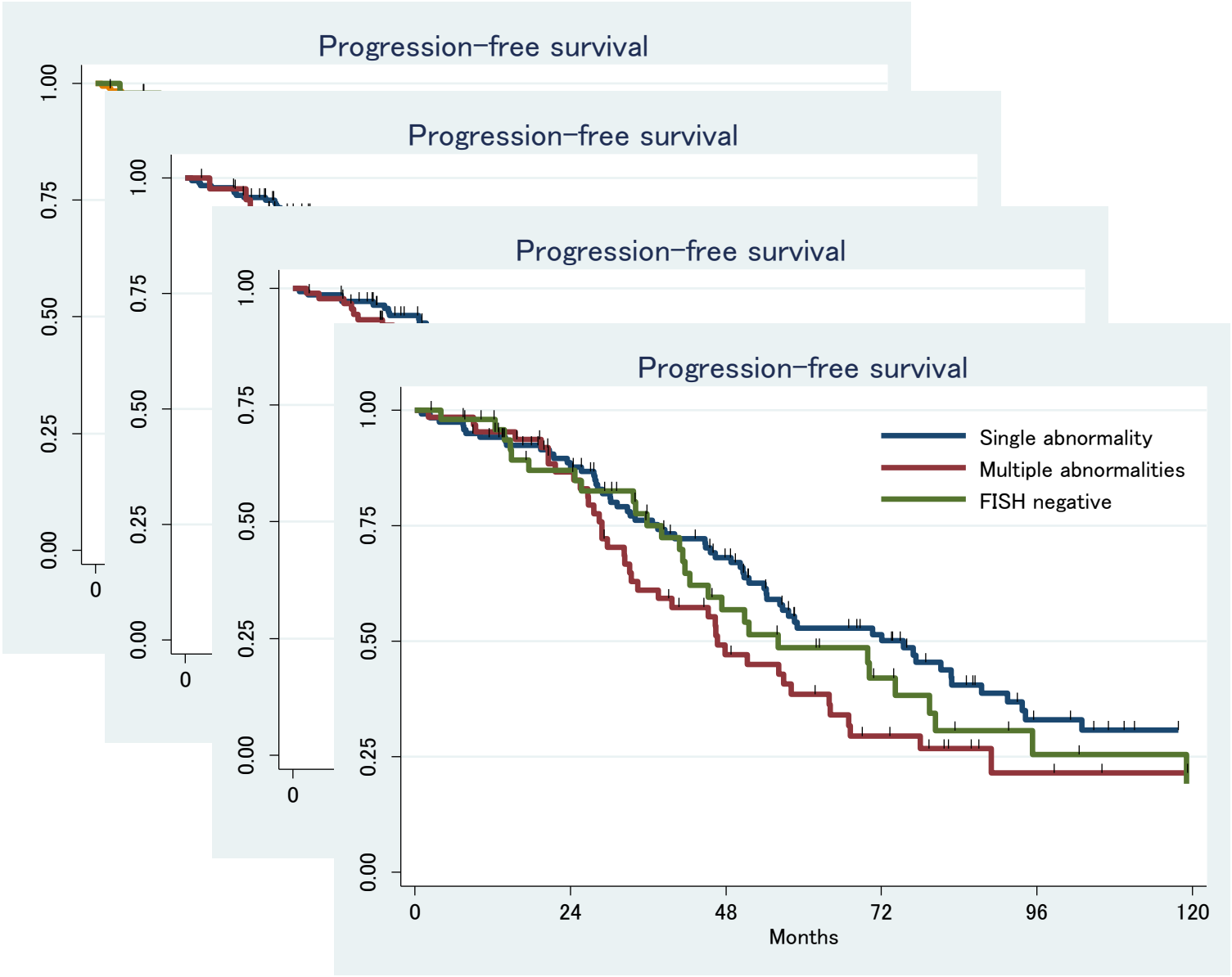
HIGH
del17p

Mutated IGHV (N=157)



Age >65 is not associated with shorter PFS

Unmutated IGHV (N=247)

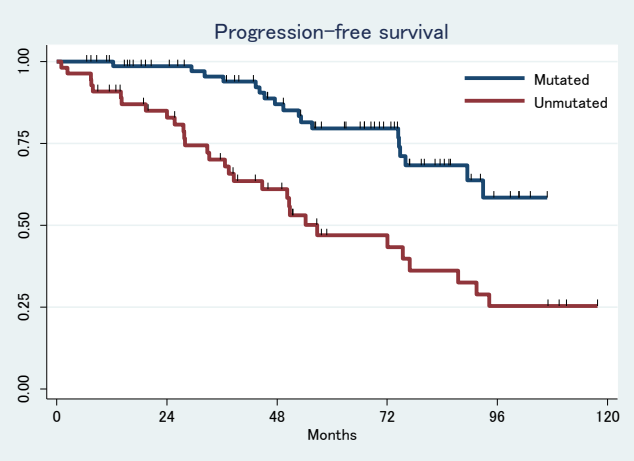


Trisomy12 is associated with longer PFS

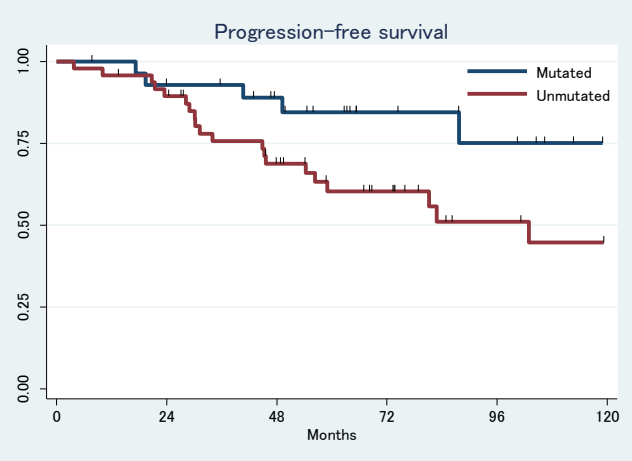
No plateau..

Mutation status by FISH

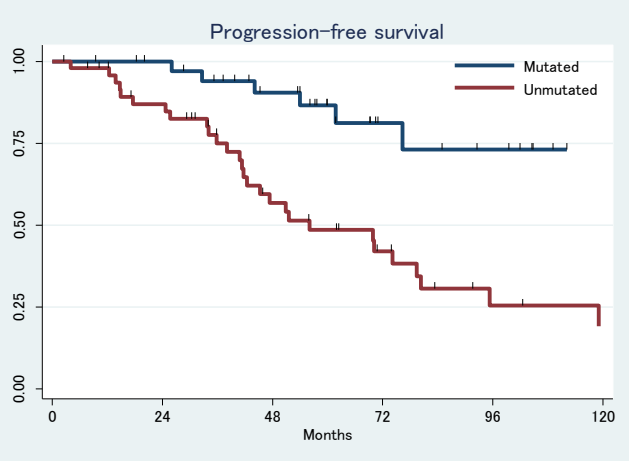
del13q



Trisomy12



Negative

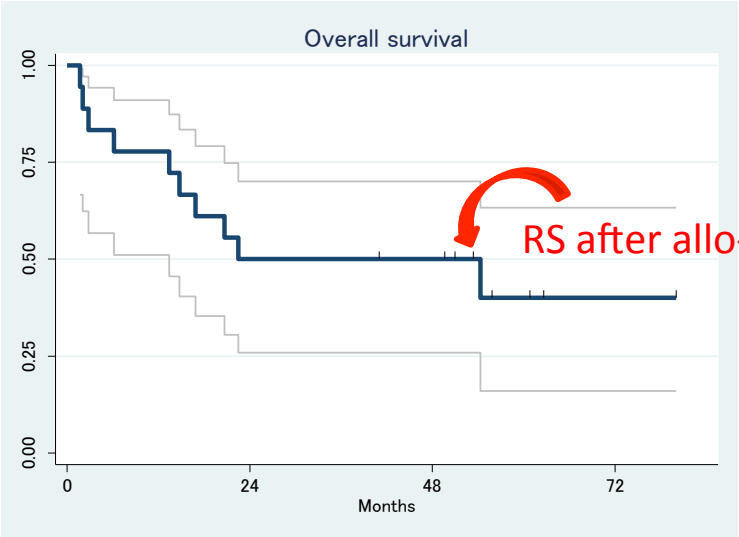


Mutated Trisomy 12 and Negative patients may do better than del13q in long term

del 17P (N=39)

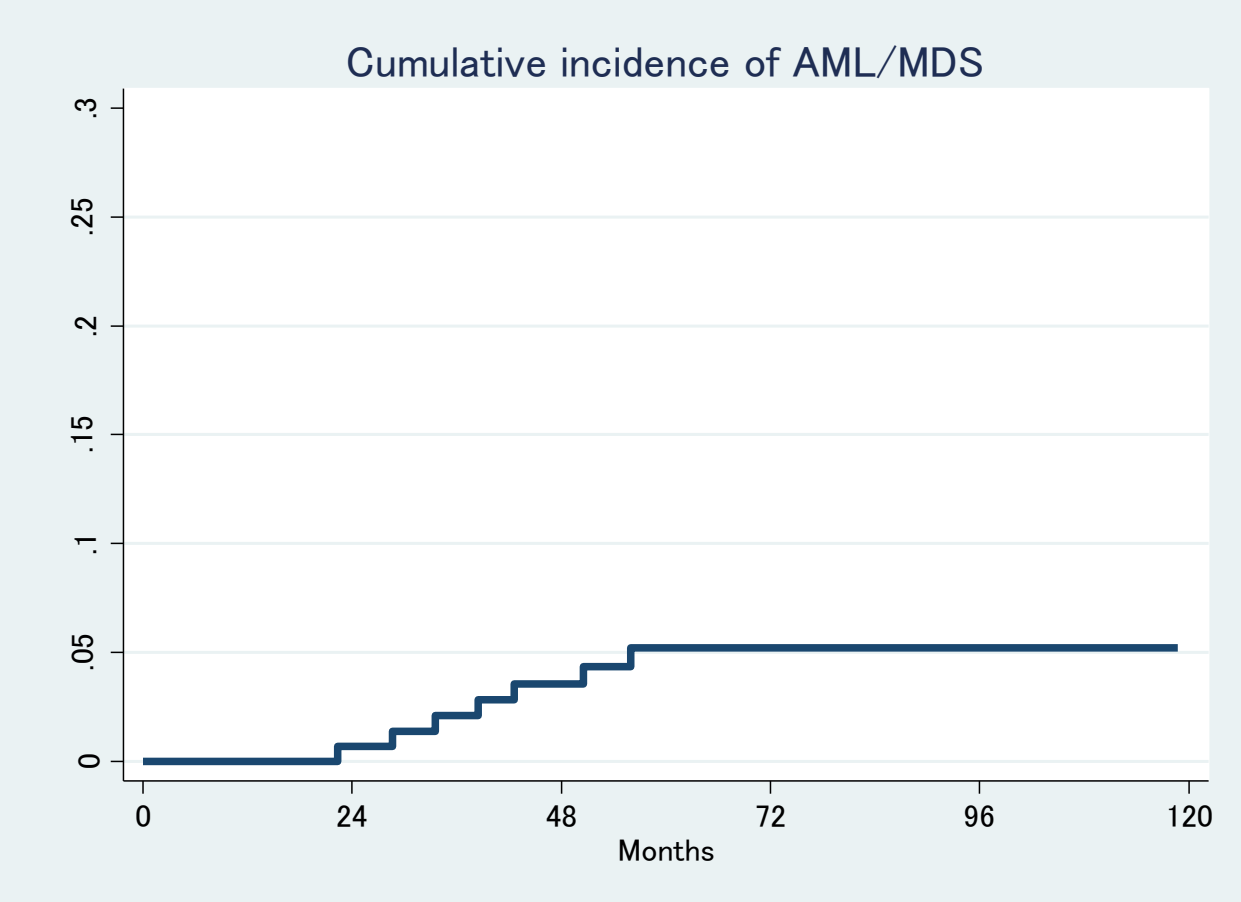
- Response to FCR based regimen
  - ORR: 72% (95%CI: 55-85%)
  - CRR: 51% (95%CI: 35-68%)
  - Median PFS: 13.8 mo (95%CI: 9.8-19.4 mo)
- 12 pts eventually experienced RS
- 18 pts underwent all-SCT
- 4 pts have > 36 mo PFS
  - 3 ongoing
  - 1 died from colon cancer

Survival after Allo-SCT



Median OS: 25.5 mo (13.4-NR)

AML/MDS post FCR in Mutated



Years	CI (95% CI)
3-yr	2.1% (0.6-5.5%)
5-yr	5.2% (2.3-9.9%)
10-yr	5.2% (2.3-9.9%)

Risk factors by CRR

AML

	SHR	95%CI
Age >60	3.95	1.44-10.8

RS

	SHR	95%CI
Beta2MG >4.0	3.72	1.56-8.89
del 17P	19.6	5.1-75.0
Unmutated	3.31	0.97-11.3
No result	7.13	1.73-29.5

Multivariate

	SHR	95%CI
del 17P	8.98	2.39-33.7
No result	8.71	1.80-42.0

CLL10 Study: FCR VS BR in FrontLine

DEUTSCHE STUDIENGRUPPE

Response to therapy (Best response)

Response	FCR n=274	BR n=273	p value
CR (CR + CRi)	**47.4%**	**38.1%**	**0.031**
CR	40.1%	36.3%	
CRi	7.3%	1.8%	
PR	50.4%	59.7%	
ORR	**97.8%**	**97.8%**	**1.0**

Eichhorst et al. ASH 2013, Abstract 526.

Can We Replace Cytotoxic Chemotherapy as Frontline Treatment?

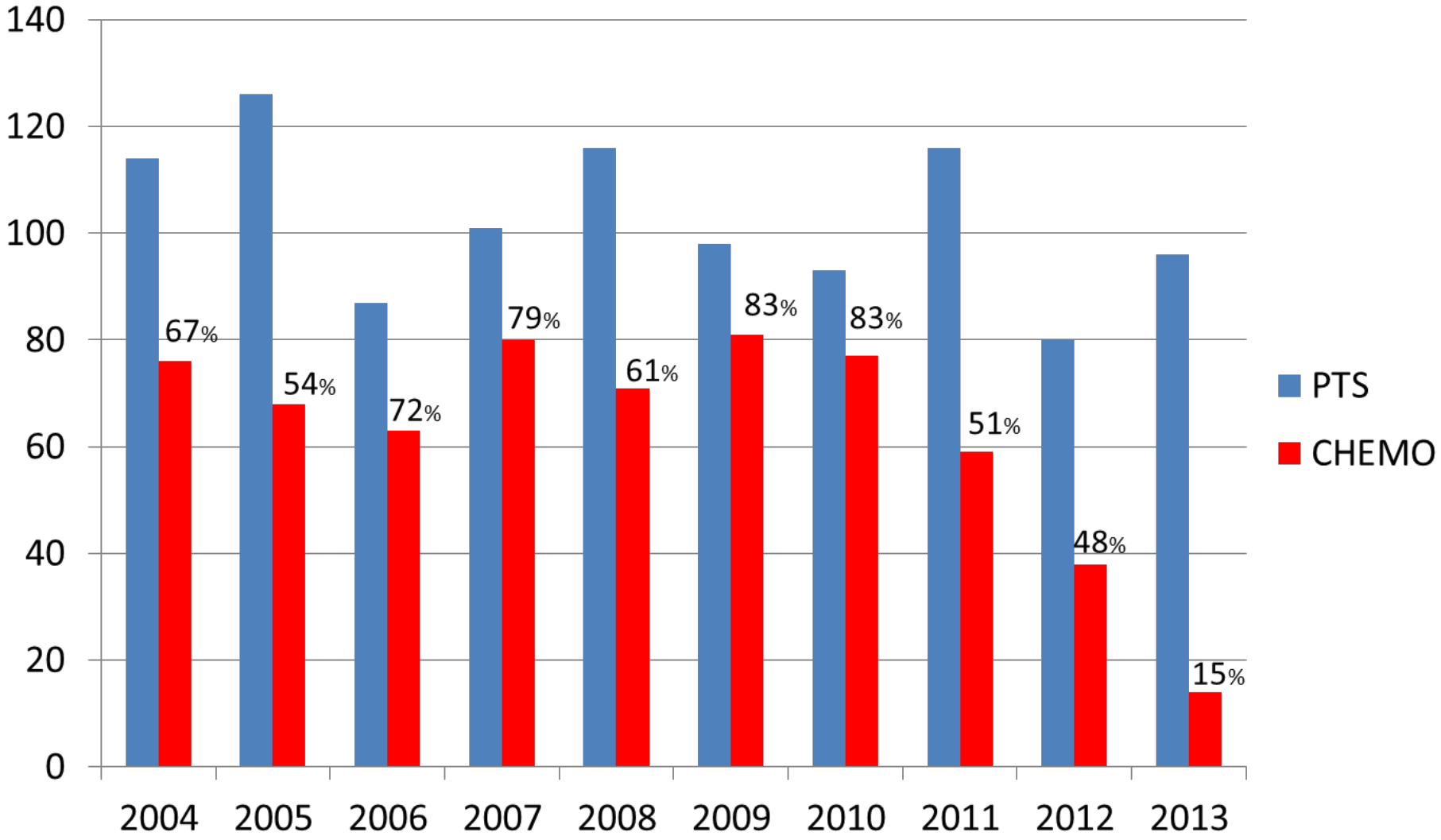
45% of deaths of CLL patients are associated with second malignancies including 73% of deaths in first remission!

Risk of 2nd malignancies for fcr-based vs non-genotoxic regimens as initial therapy for CLL in patients >65 years

Malignancy	FCR-based (n=120)	Non-genotoxic* (n=170)
Solid tumors	13 (11%)	18 (11%)
Richter's transformation	8 (7%)	2 (1%) p=.02
AL/MDS	10 (8%)	7 (4%)

Antibody regimens(n=53), Lenalidomide regimens (n=68), BCR antagonist regimens (n=49)

Proportion Of Frontline CLL Patients Receiving Chemo Immunotherapy By Year



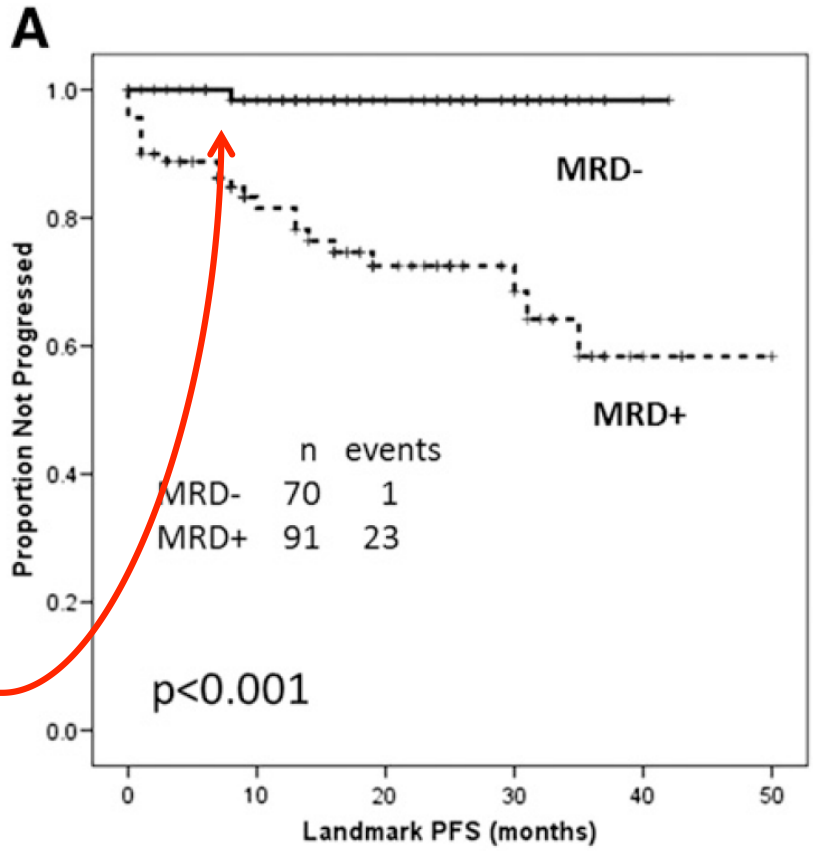
Can we define Cure in CLL?

- PROPOSE 10 YEAR PFS AS A USEFUL END POINT

- Deaths in remission due to Non-hematologic cancers may be incurable by this definition.
- Deaths in remission due to Richter's , Leukemic transformations may be prevented by non-genotoxic or immunotoxic therapy.
- Deaths in remission may be reduced by non-marrow-toxic therapy.
- Deaths in remission due to old age ,comorbidities are probably inevitable at this time

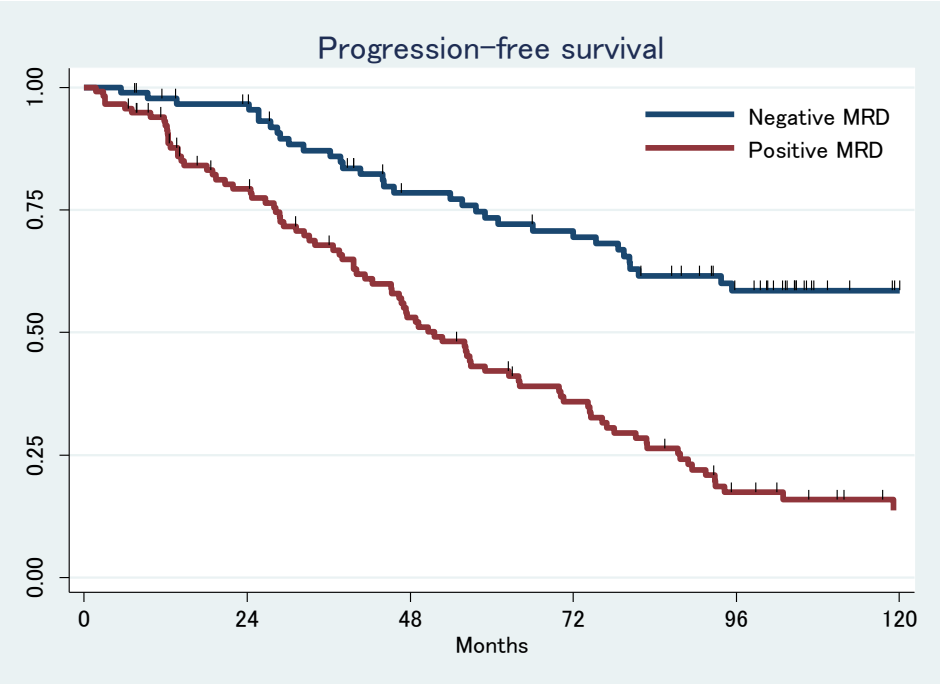
MRD…

- 2008-0431
  - Strati P, et al
    - (Blood, 123 (24): 3272-32)
  - MVA for MRD
    - Mutated
    - Trisomy 12
  - Only 1/70 who achieved negative MRD experienced relapse
  - Median f/u: 28 months



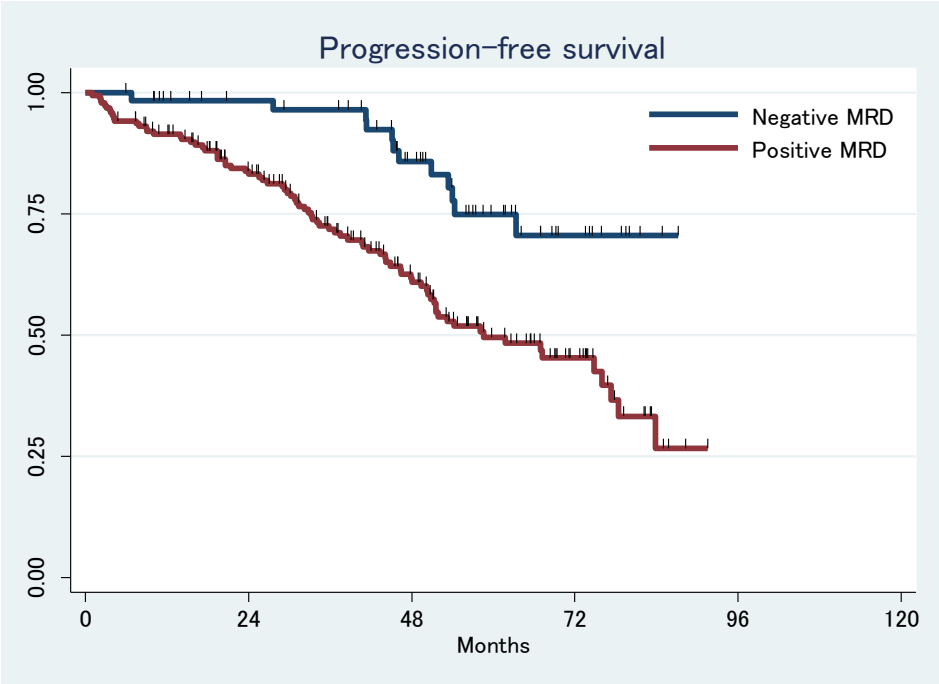
MRD at 3 months

4 studies



HR: 3.13 (95%CI: 2.09-4.67)

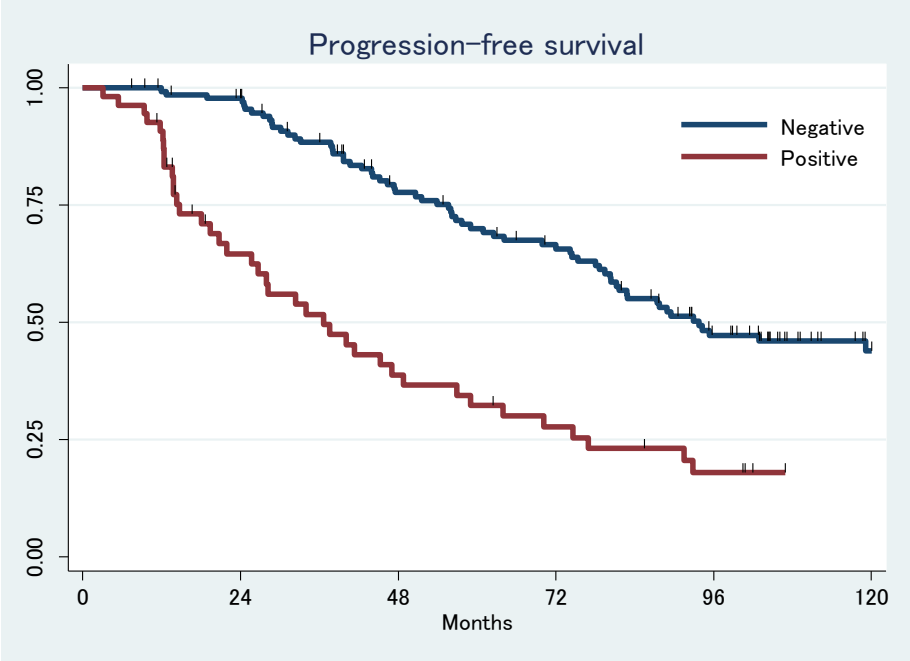
2008-0431



HR: 2.92 (95%CI: 1.59-5.35)

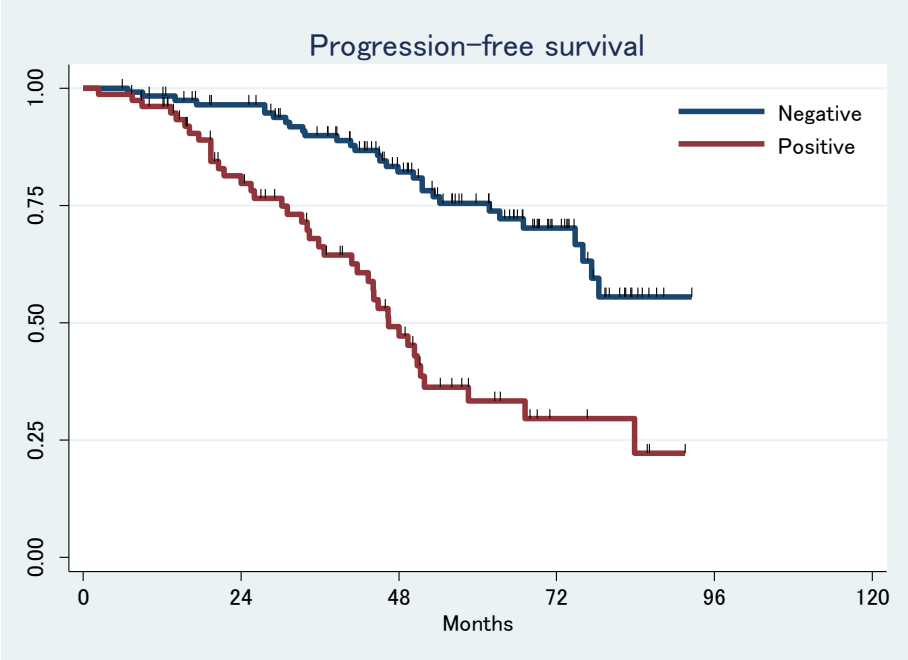
MRD at 6 months

4 studies - FCR-BASED



HR: 2.87 (95%CI: 1.92-4.29)

2008-MRD



HR: 3.30 (95%CI: 2.05-5.33)

First-line iFCG protocol

- First-line protocol for CIT-eligible patients with mutated IGHV EXCLUDING del(17p)
- Primary objective
  - Achievement of CR/CRi and marrow MRD negativity after 3 courses

	C1D1	C1D2	C1D3	C1D4	C1D8	C1D15	C2-3 D1	C2-3 D2	C2-3 D3
Obinutuzumab	100mg	900mg	-	-	1000mg	1000mg	1000mg	-	-
Fludarabine	-	25mg	25mg	25mg	-	-	25mg	25mg	25mg
Cyclophosphamide	-	250mg	250mg	250mg	-	-	250mg	250mg	250mg
Ibrutinib	420 mg once daily continuous								

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Response at 3 months iFCG Trial

	N=20	BM MRD
ORR	20/20	16/20 neg
CR/CRi	7	7/7 neg
PR	13	9/13 neg

80% (16/20) BM MRD neg at 3 mos

Most PR patients due to Cat scan noe (s) >1.5 cm

Comparison: FCR 3 cycles, 26% marrow MRD neg

Ibrutinib-Venetoclax Treatment Plan

	C1=3 D1-28	C4D1 ---> C27D28
Ibrutinib	420mg once daily	420mg once daily until progression
Venetoclax	-	- - 20mg daily x1 week then; 50mg daily x1 week then; 100mg daily x1 week then; 200mg daily x1 week then; 400mg daily continuous

Ibr+Venetoclax -- Clinical Response, Untreated Cohort

	3 MTHS (IBR N=35		VEN + IBR N=18	
	ORR (%)	BM MRD Neg (%)	ORR (%)	BM MRD Neg (%)
	35/35 (100	0(0)	18/18 (100)	8/18 (44)
CR	1/35 (3)	0(0)	12/18 (67)	5/12 (42)
PR	34/35 (97)	0(0)	6/18 (33)	3/6 (50)

Thank you very much!!