

# MRD guided treatment in AML



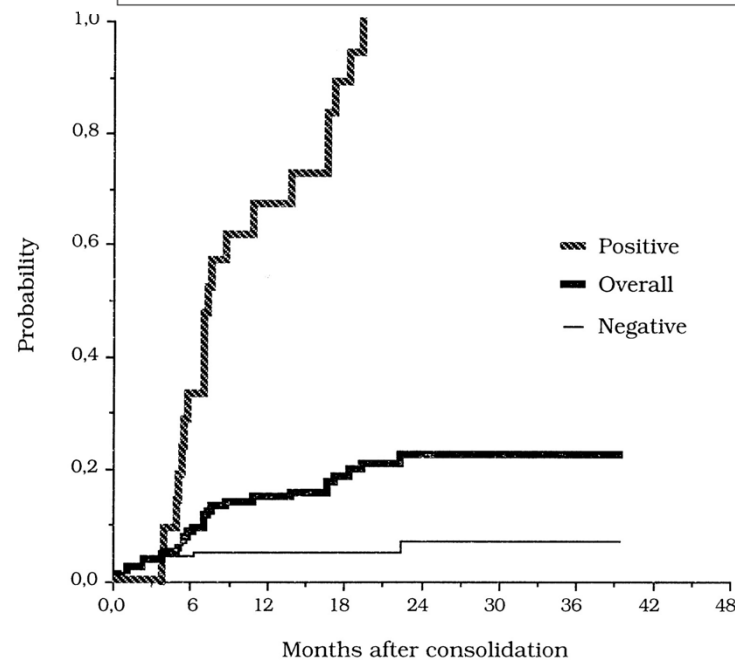
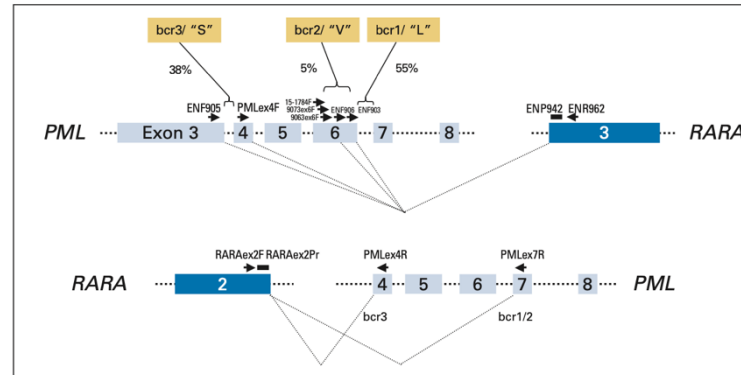
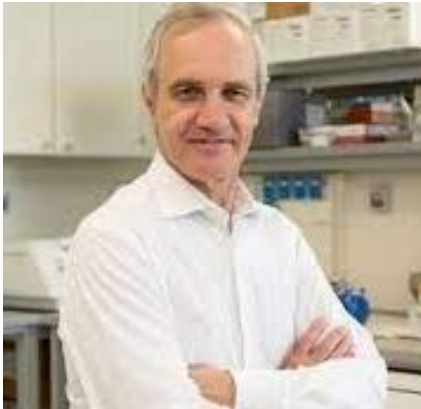
Richard Dillon, Guy's Hospital / King's College London  
FILO2024, Angers, September 2024

1) Can and should we use MRD monitoring for relapse surveillance/ pre-emptive treatment?

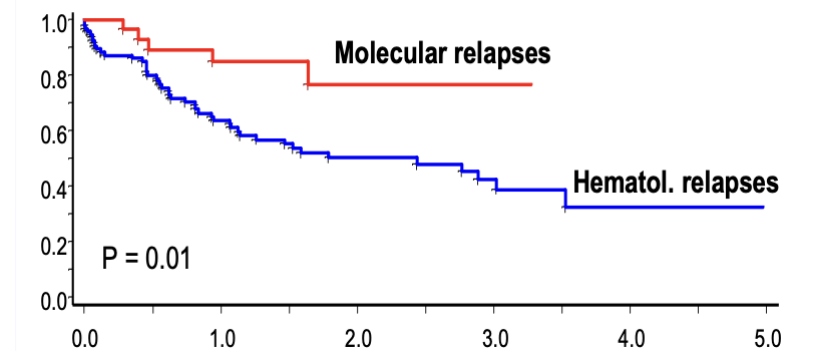
2) Can we use MRD to select patients for transplant ?

“The future of all oncology needs to be measurement of miniscule disease burden, to guide serial pre-emptive therapy, to prevent relapse”

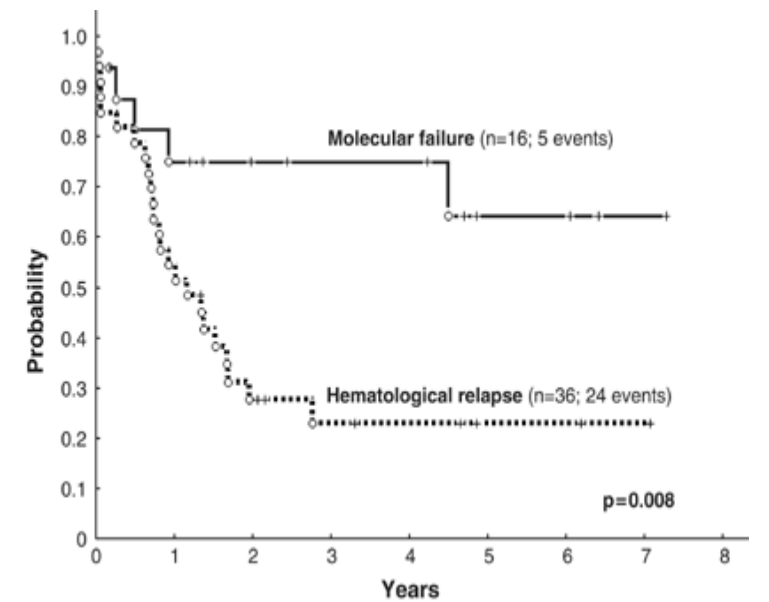
# APL: a model for MRD guided therapy



Diviero, D. et al, Blood, 1998

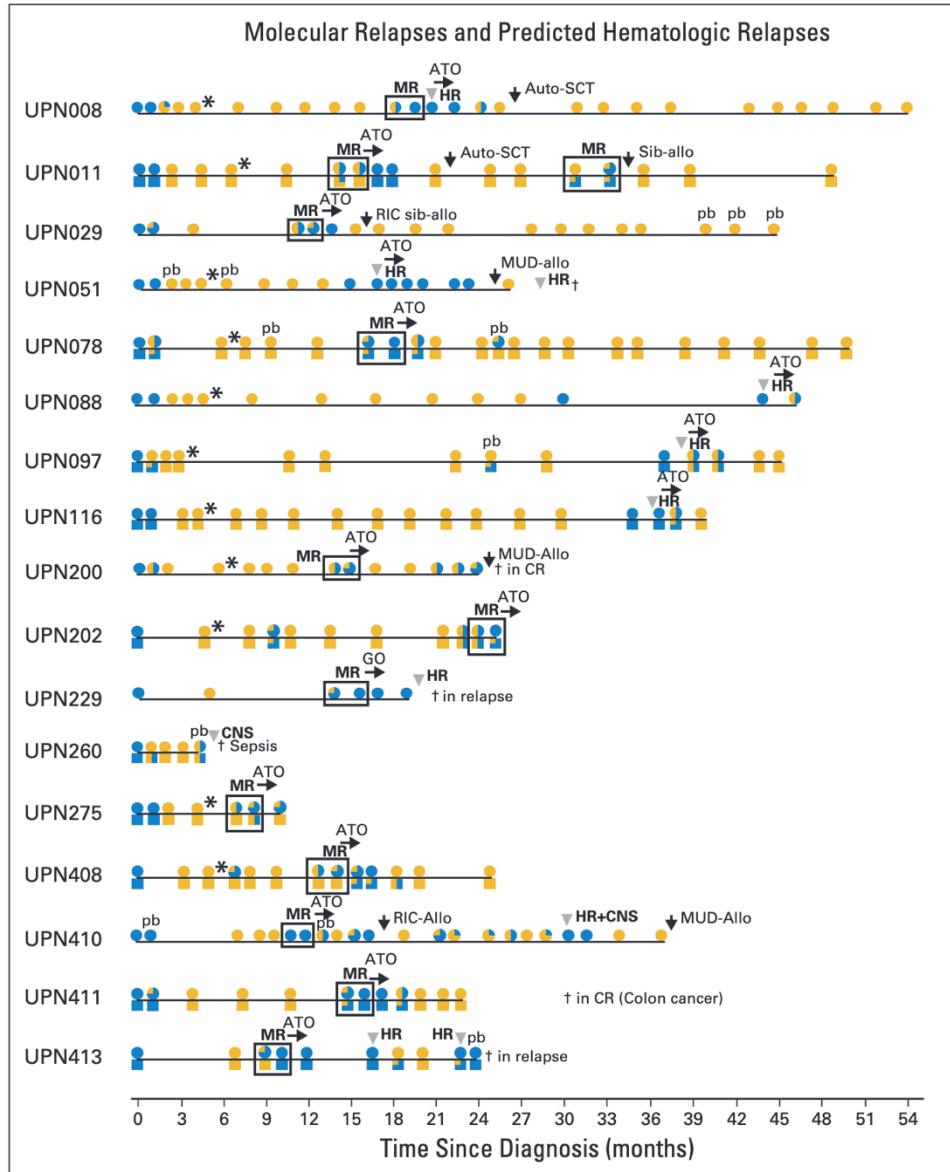


Lo Coco F. et al, Semin Haematol, 2002



Esteve, J. et al, Leukaemia, 2007

# APL: a model for MRD guided therapy

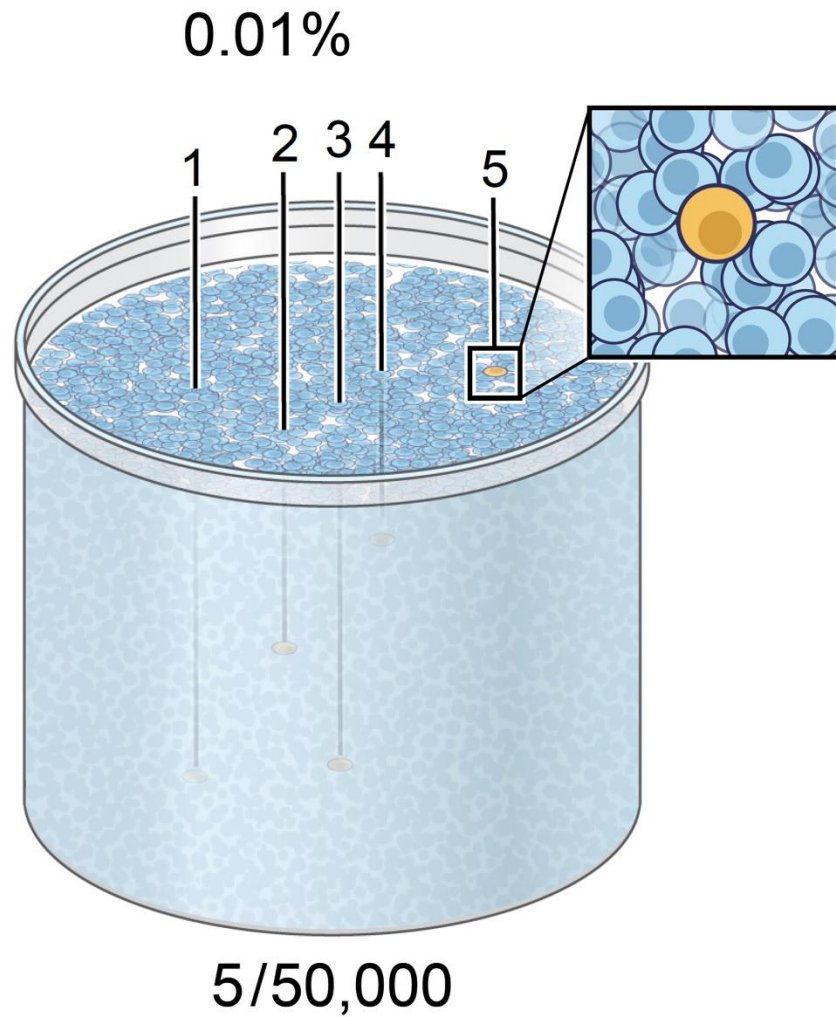


1) Almost eliminated frank relapse

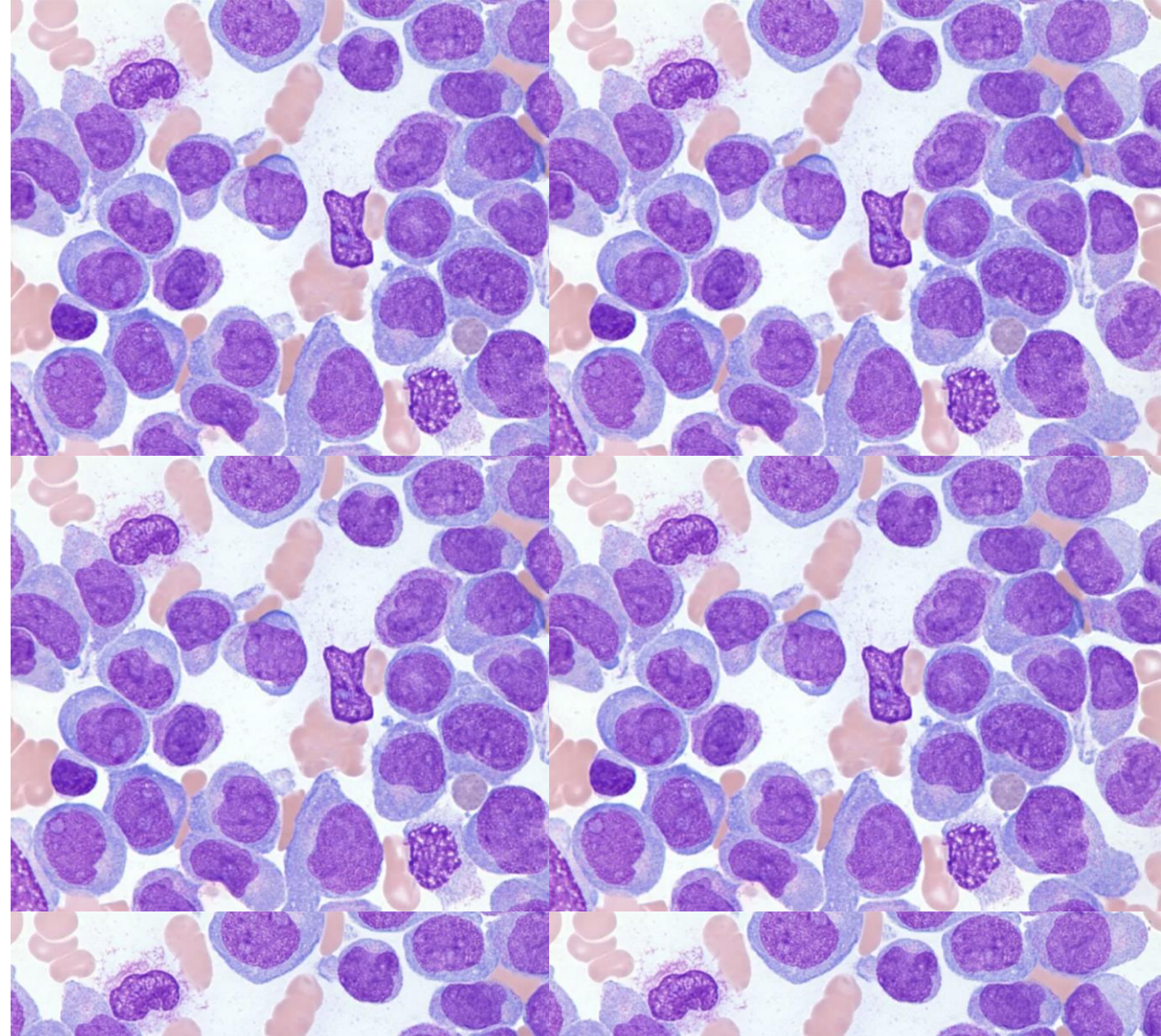
2) Made frontline ATO trials possible



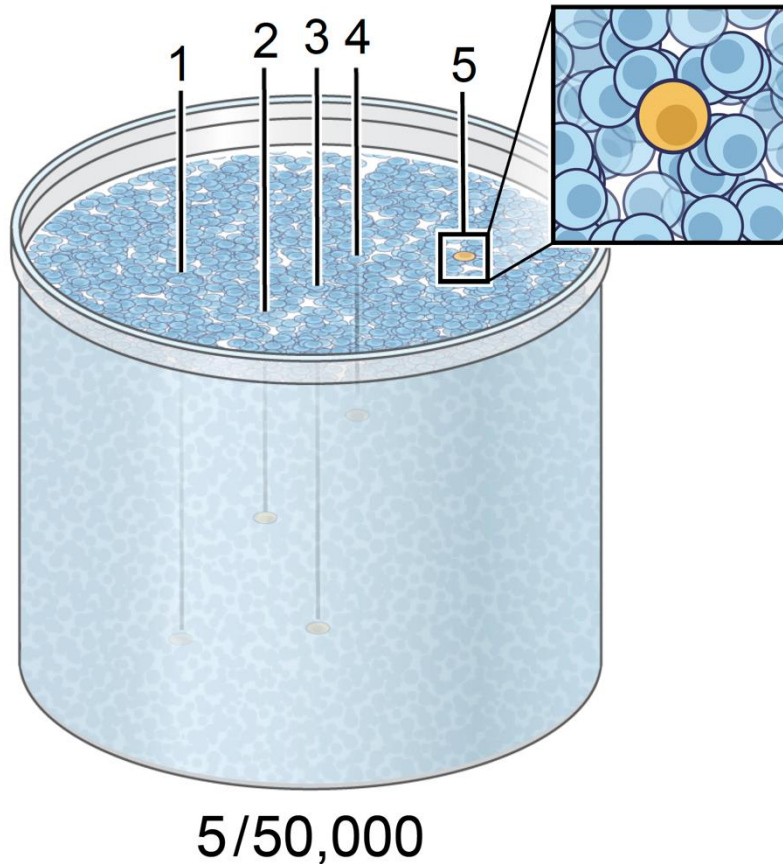
# MRD relapse



# Morphological relapse

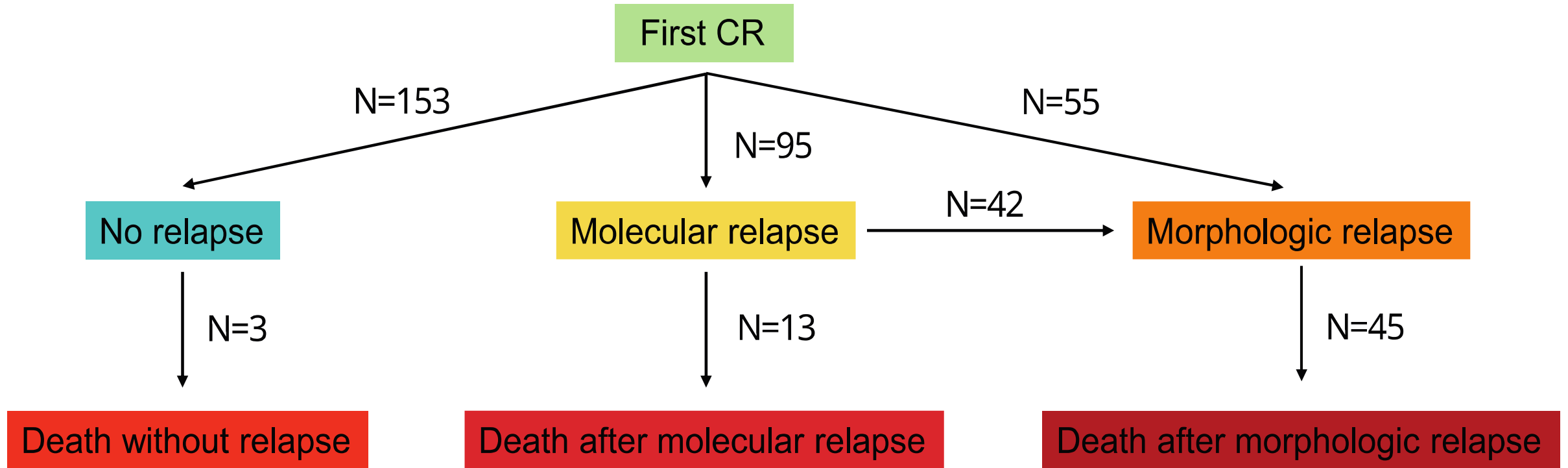


# Theoretical advantages of treatment at MRD relapse



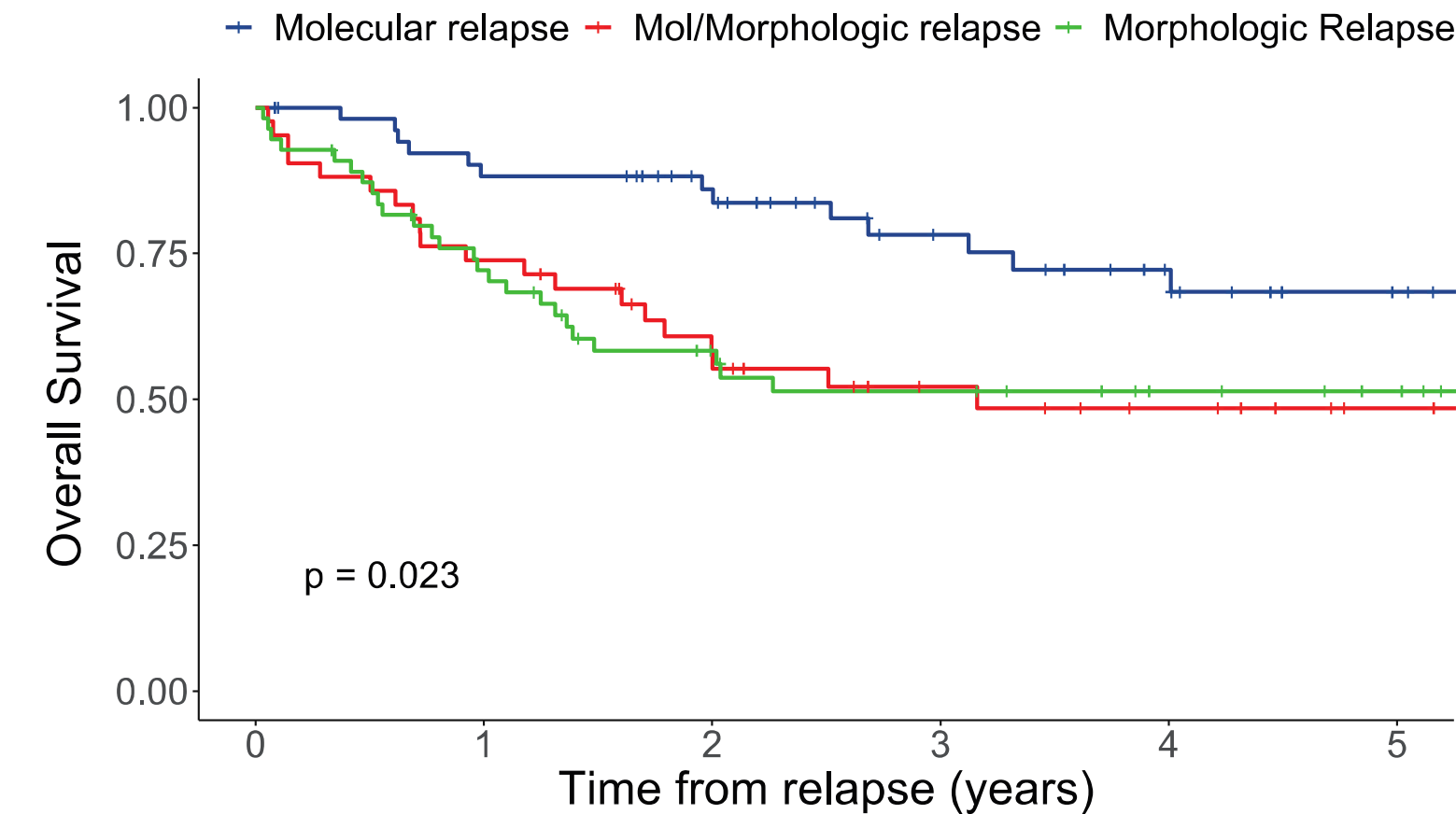
- ▶ More time to act
- ▶ No cytopenias
- ▶ Patient clinically well
- ▶ Can treat as outpatient
- ▶ May need less salvage treatment
- ▶ Salvage treatment may be less toxic
- ▶ Salvage treatments may be more effective
  - targeted therapies - less chance for clonal evolution
  - immunotherapies - better effector to target ratio

# Feasibility of MRD relapse treatment: FILO Group Experience



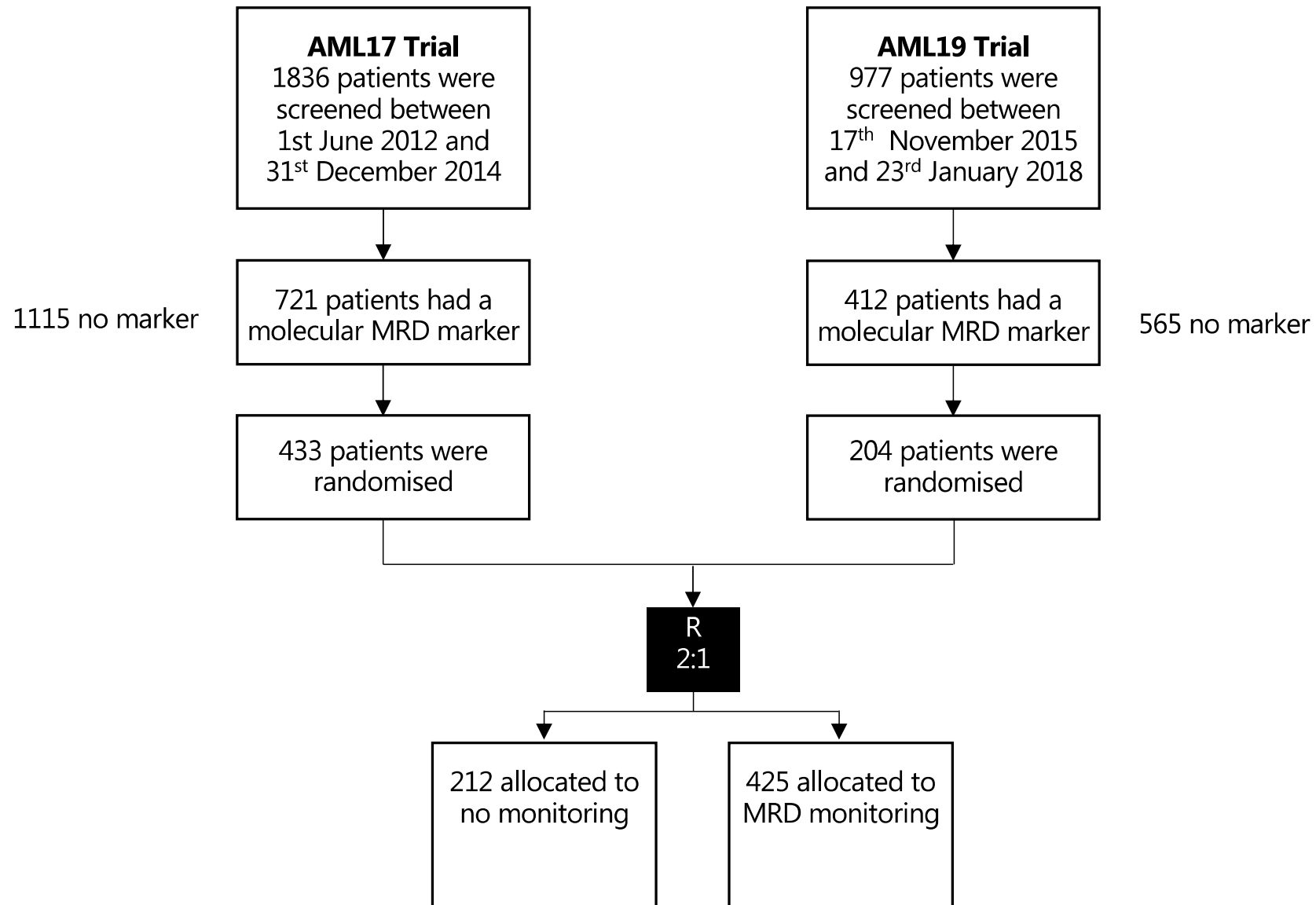


# Feasibility of MRD relapse treatment: FILO Group Experience

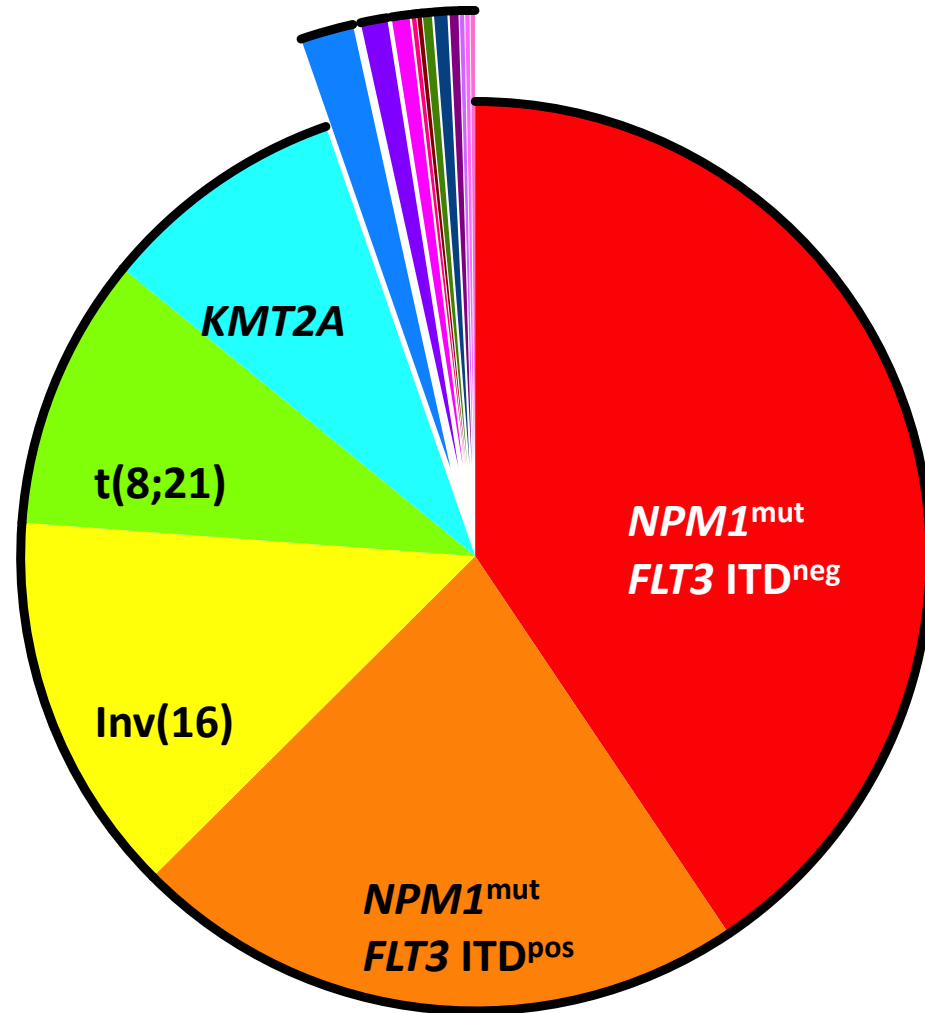


Molecular relapse	53	45	38	26	19	11
Mol/Morphologic relapse	42	31	21	14	10	5
Morphologic Relapse	55	38	26	22	17	14

# UK NCRI Monitor vs No-monitor study



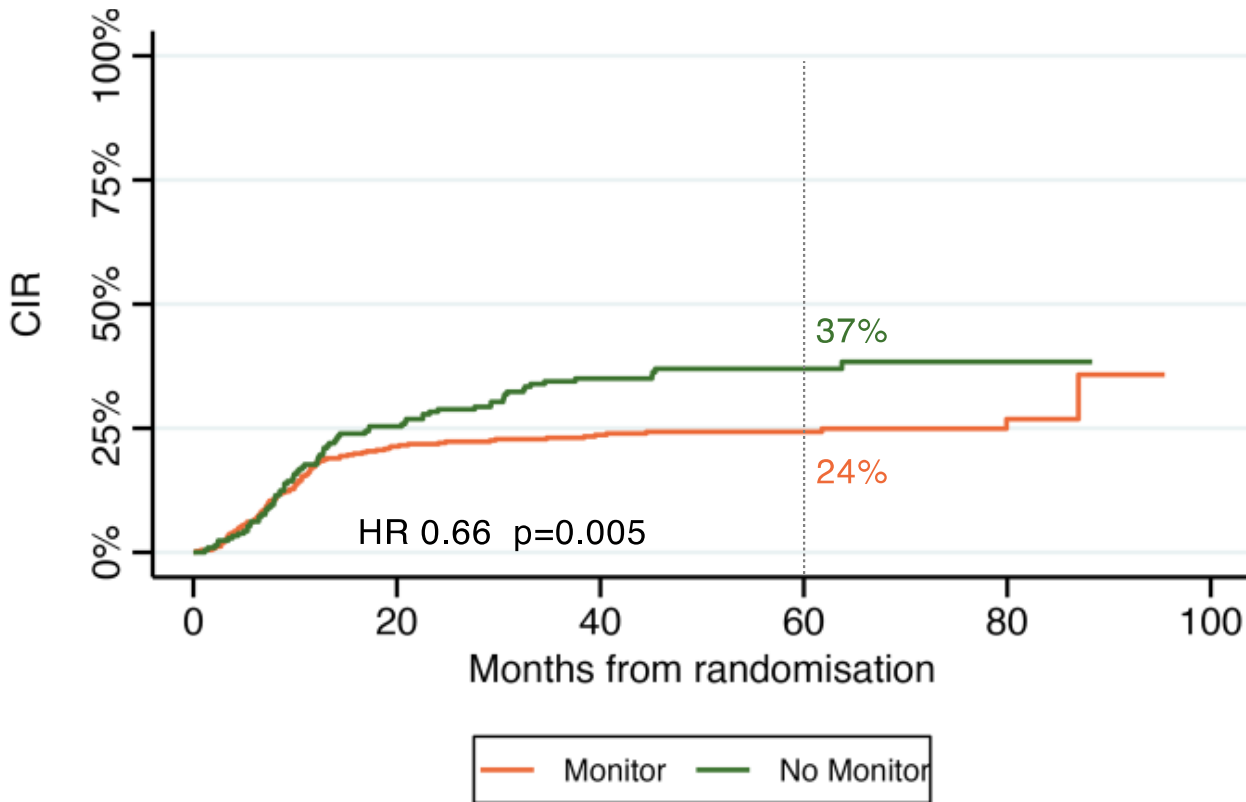
# UK NCRI Monitor vs No-monitor study



- NPM1* without *FLT3* ITD
- NPM1* with *FLT3* ITD
- CBFB::MYH11*
- RUNX1::RUNX1T1*
- KMT2A::R*
- DEK::NUP214*
- NUP98::R*
- KAT6A::CREBBP*
- BCR::FGFR1*
- ETV6::PDGFRA*
- RUNX1::MECOM*
- BCR::ABL*
- PICALM::MLLT10*
- RUNX1::CBFA2T3*
- RUNX1::PRDM16*
- NPM1::MLF1*

# UK NCRI Monitor vs No-monitor study

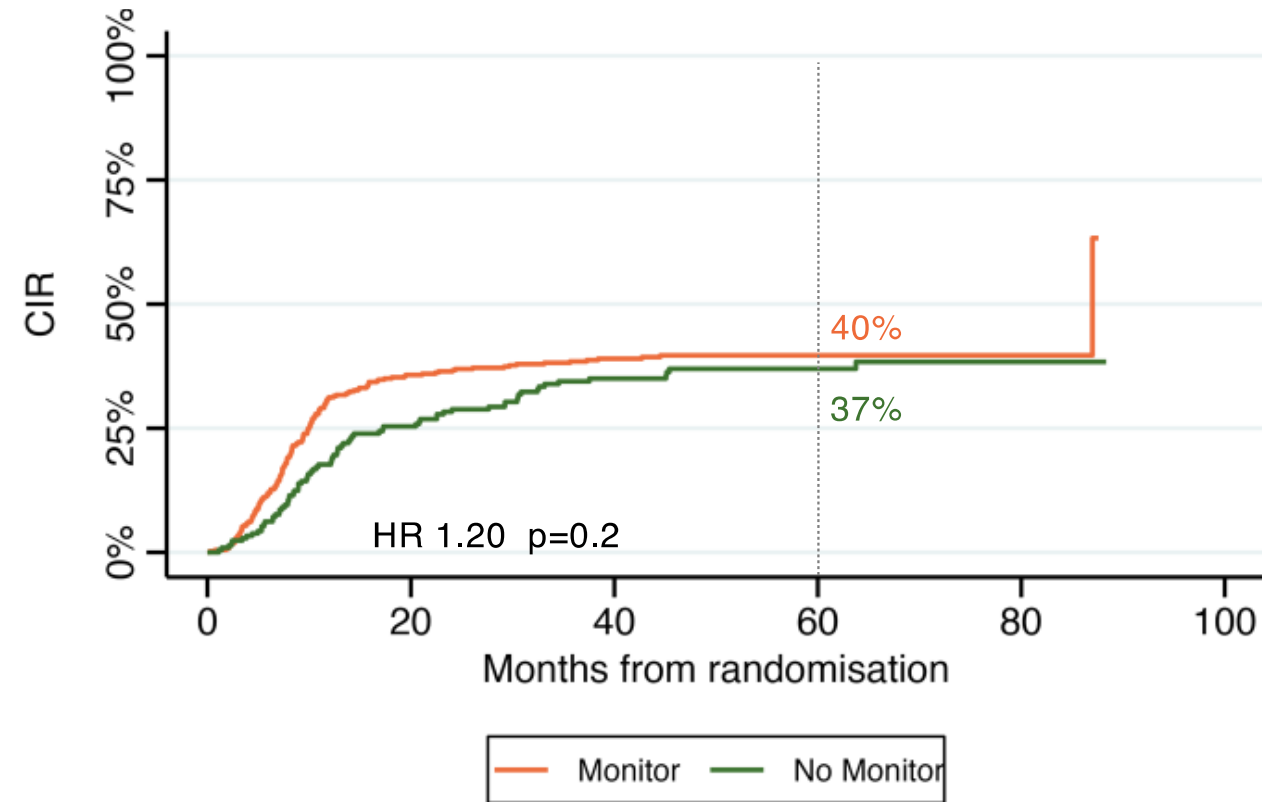
## Morphological relapses



Number at risk (number censored)

425 (0)	283 (6)	212 (51)	109 (96)	27 (77)	1 (25)
212 (0)	132 (5)	92 (20)	46 (41)	11 (31)	0 (11)

## MRD & morphological relapses

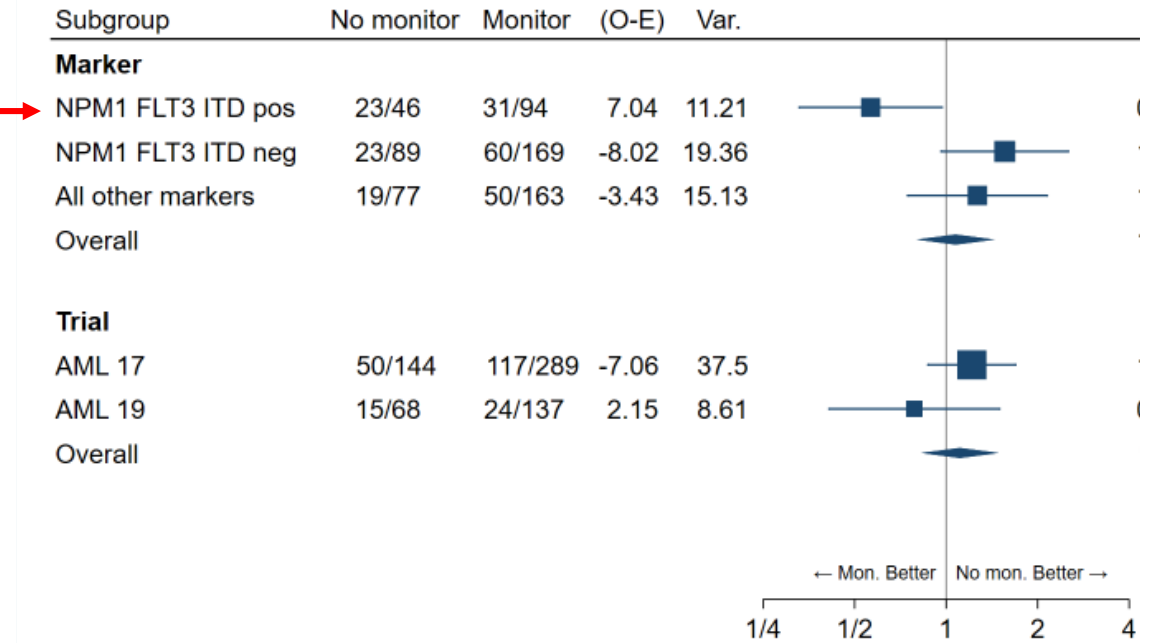
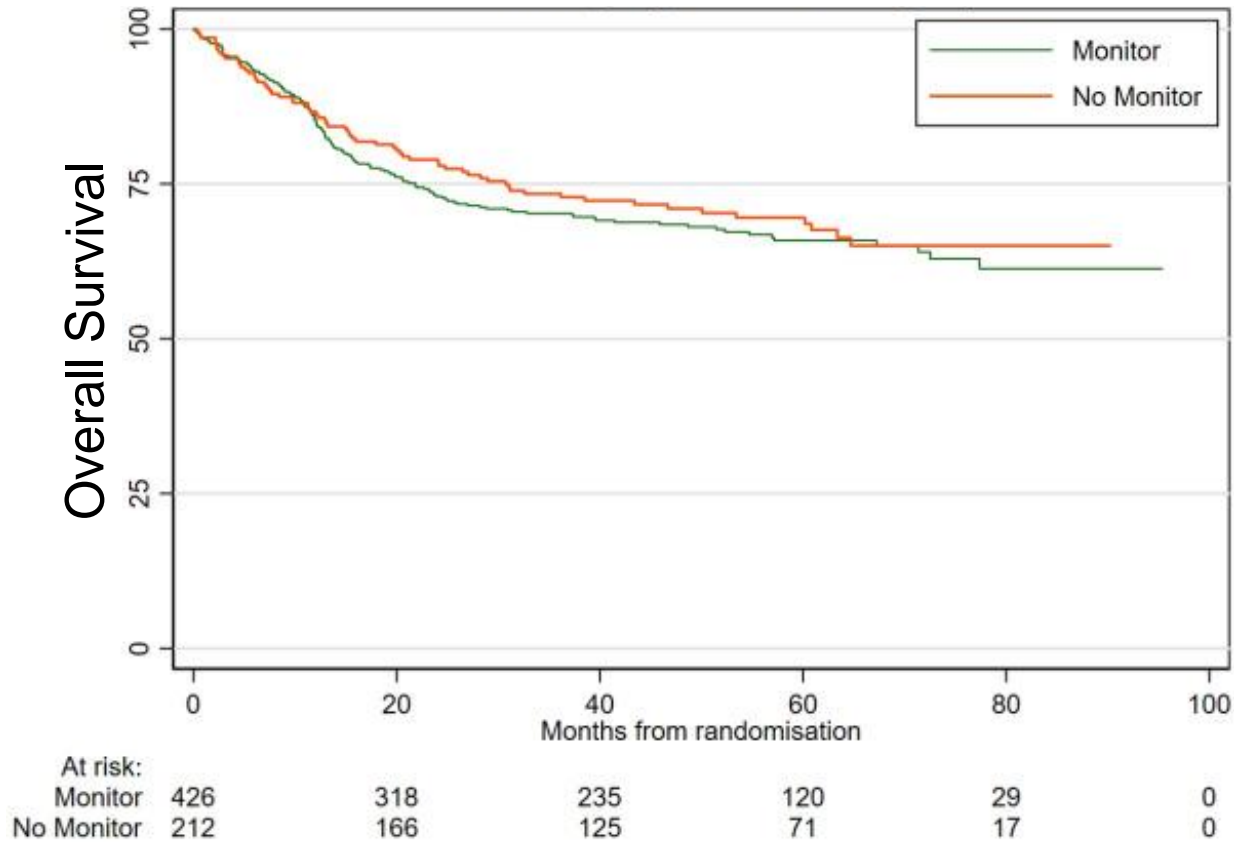


Number at risk (number censored)

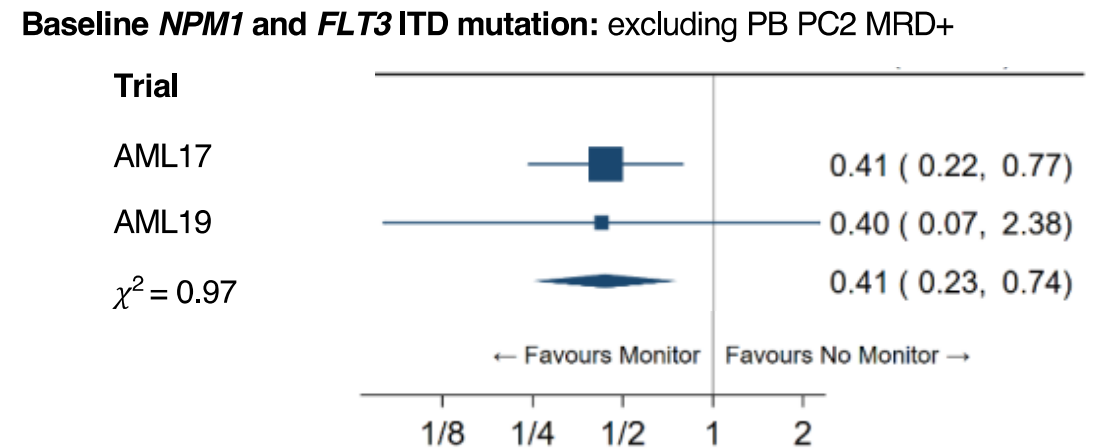
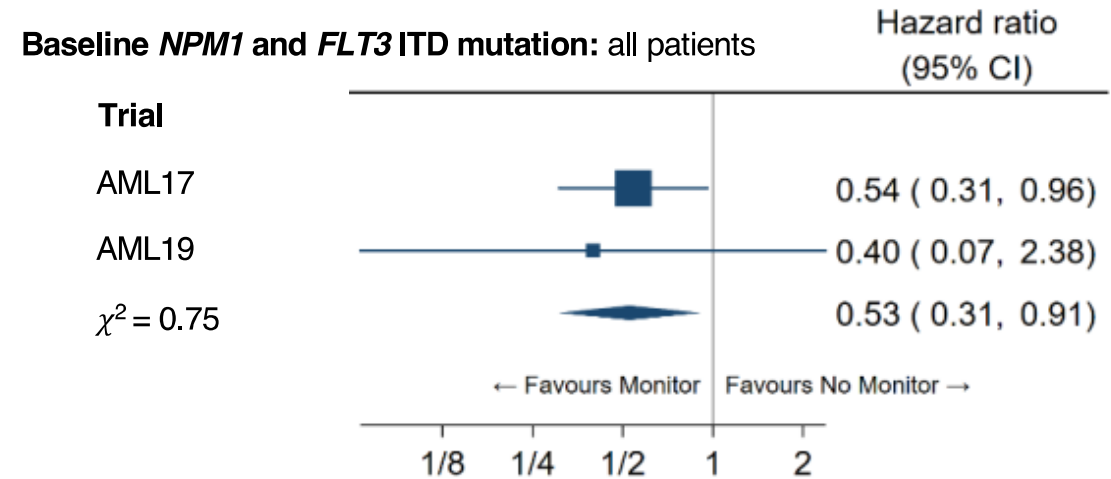
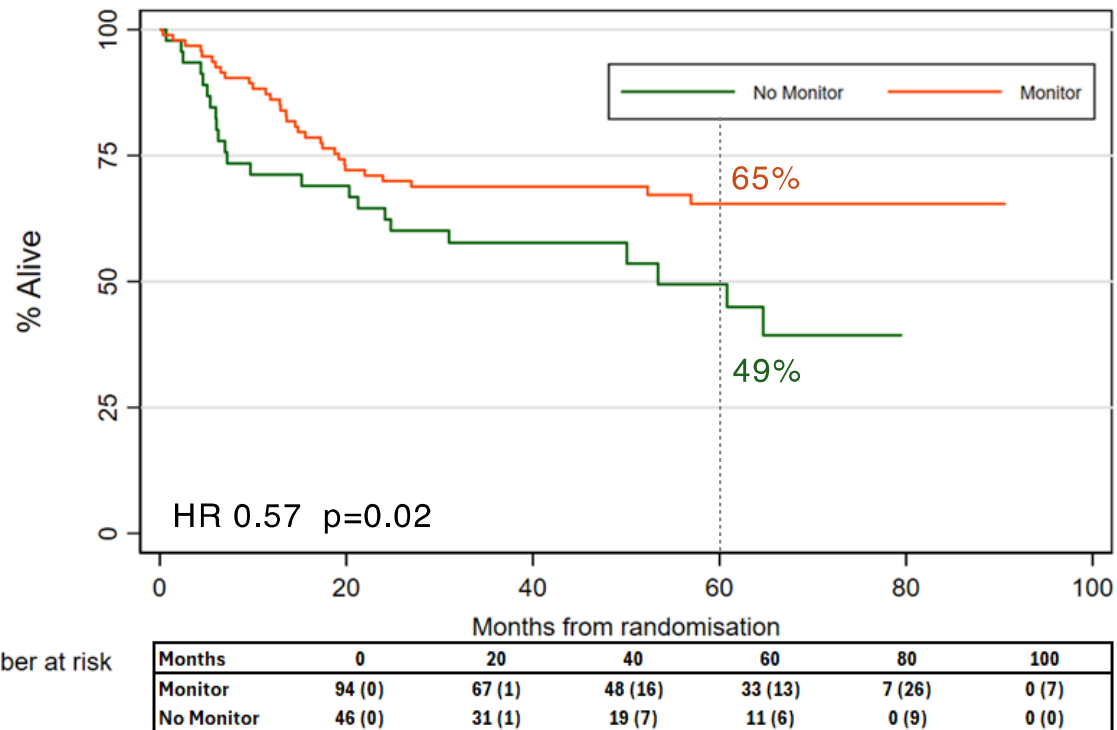
425 (0)	238 (3)	173 (46)	89 (80)	20 (67)	0 (19)
212 (0)	132 (5)	92 (20)	46 (41)	11 (31)	0 (11)



# UK NCRI Monitor vs No-monitor study

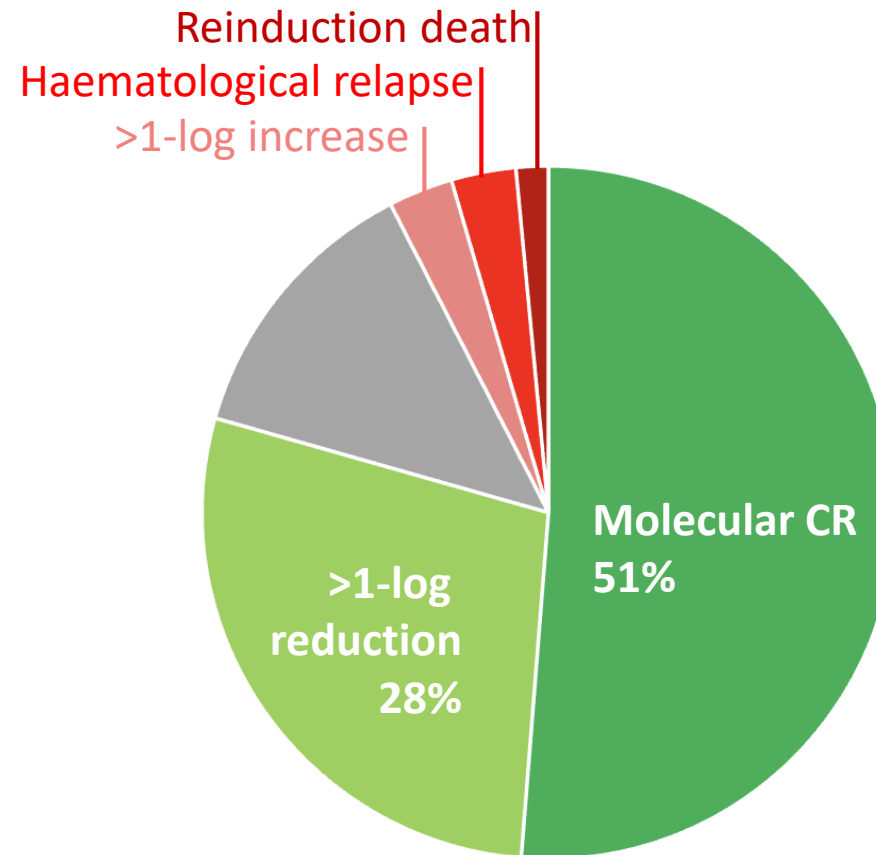


# UK NCRI Monitor vs No-monitor study



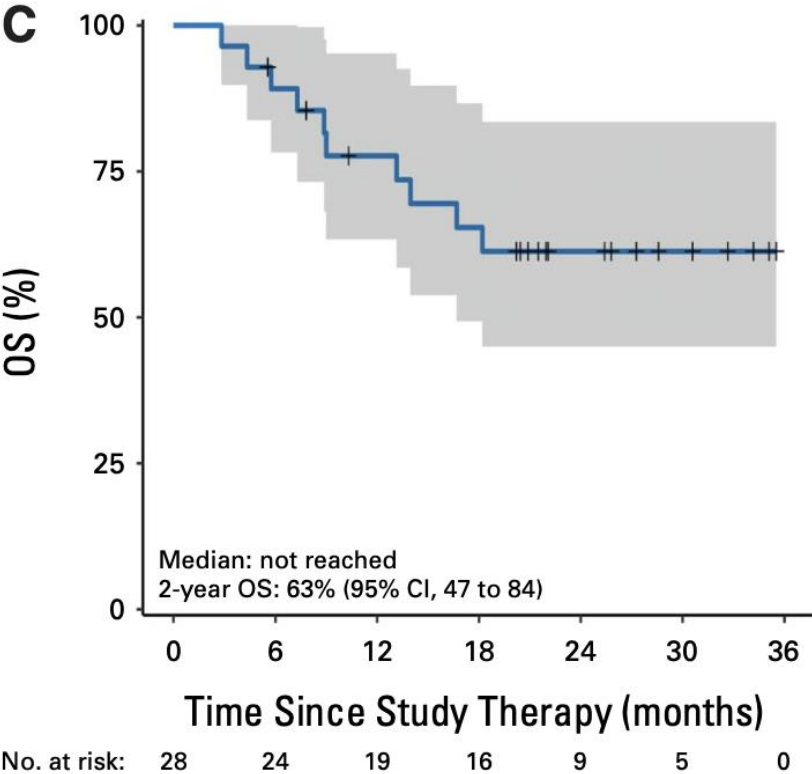
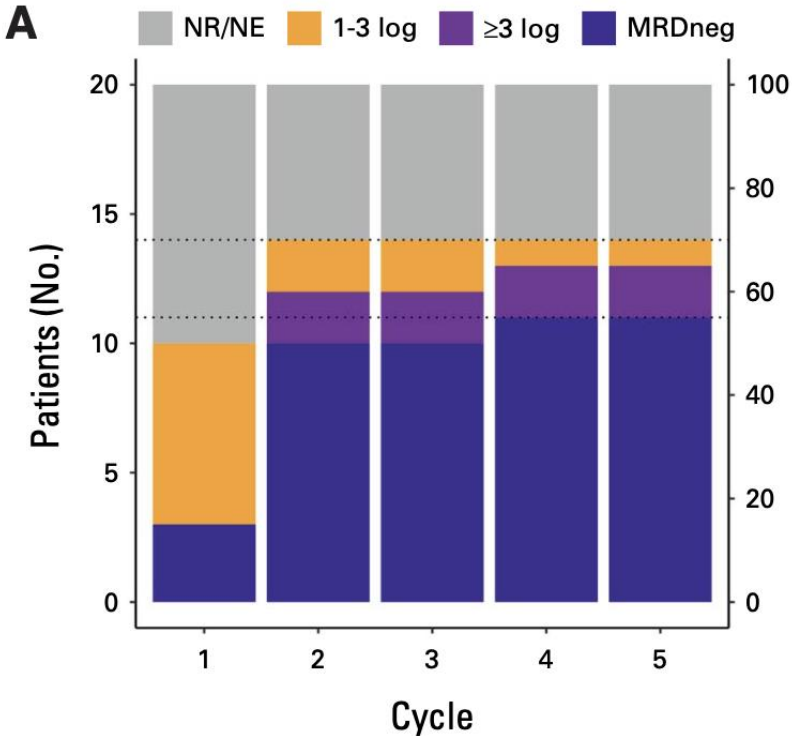
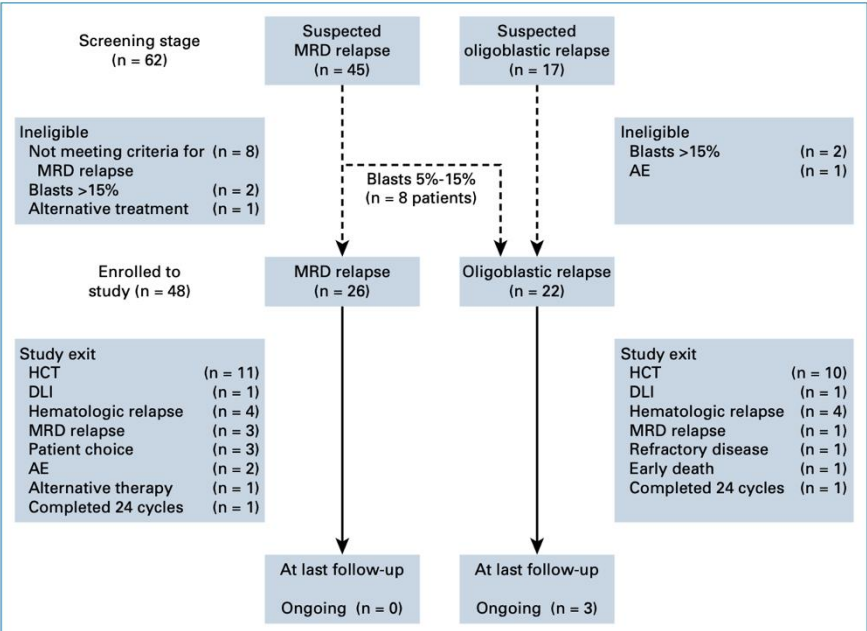
# UK NCRI Monitor vs No-monitor study

## Treatment of MRD relapse with Salvage Chemotherapy



# Targeted Therapy for MRD Relapse

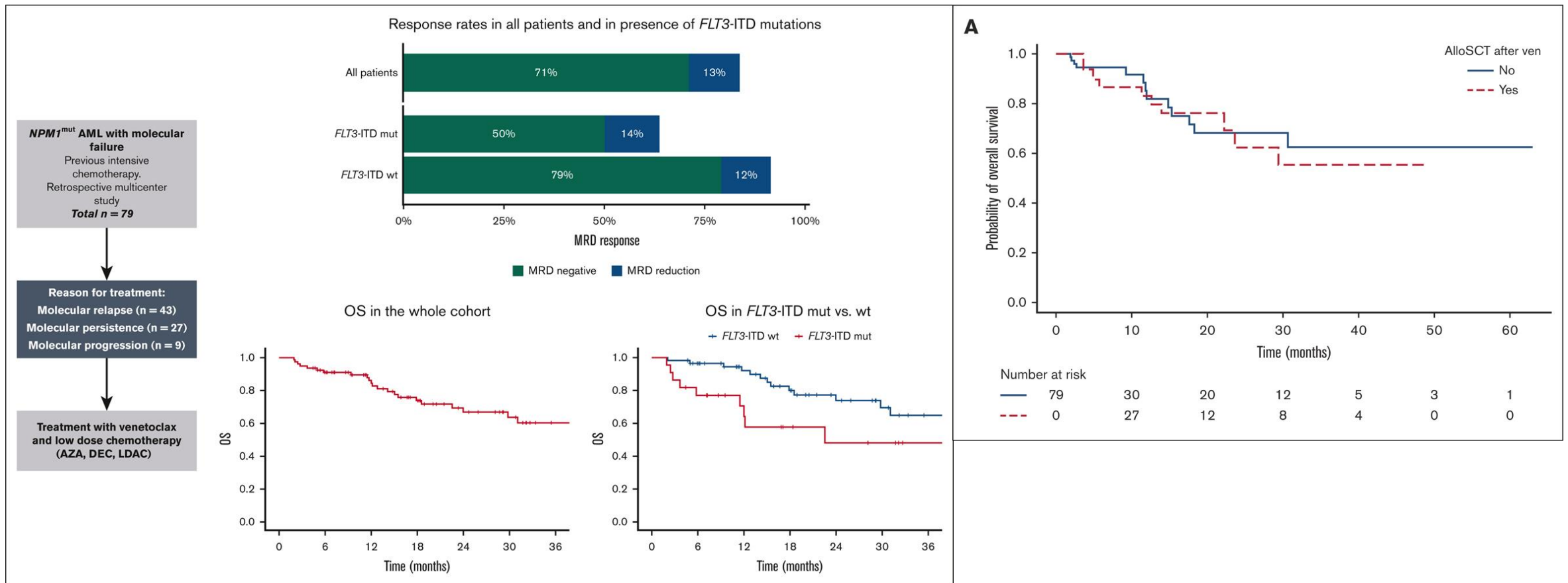
## VALDAC Study: Venetoclax and Low Dose Cytarabine for MRD or Oligoblastic Relapse





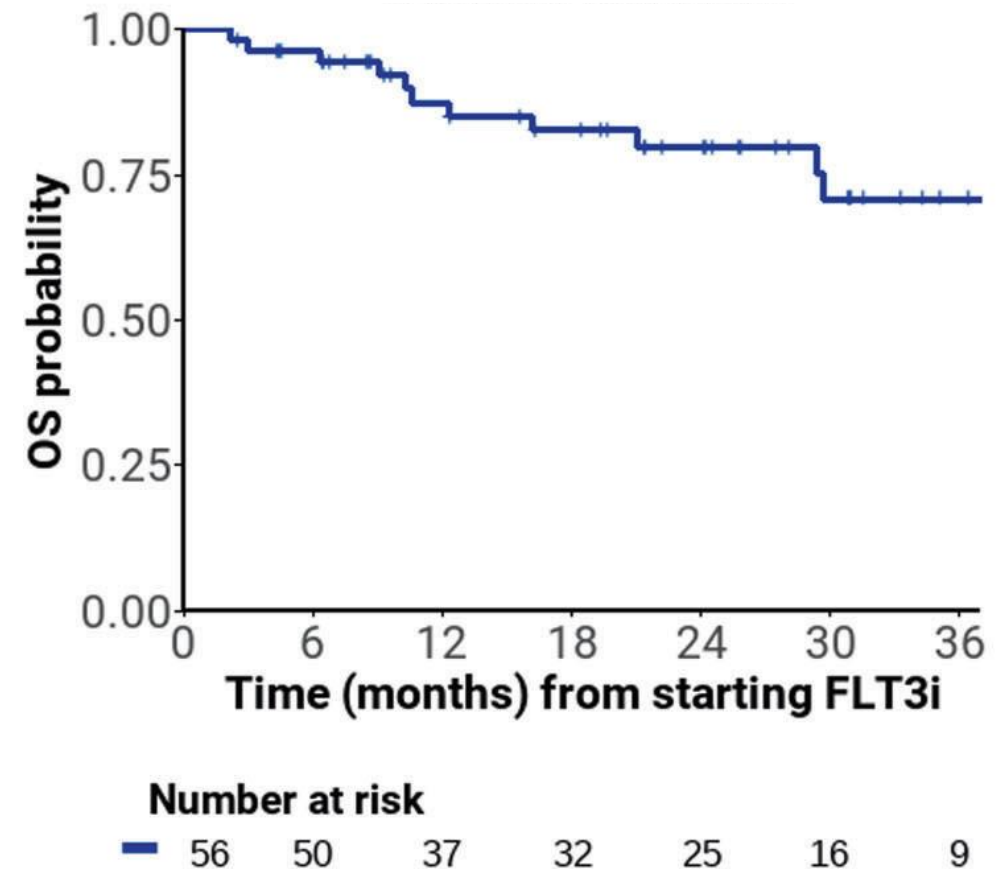
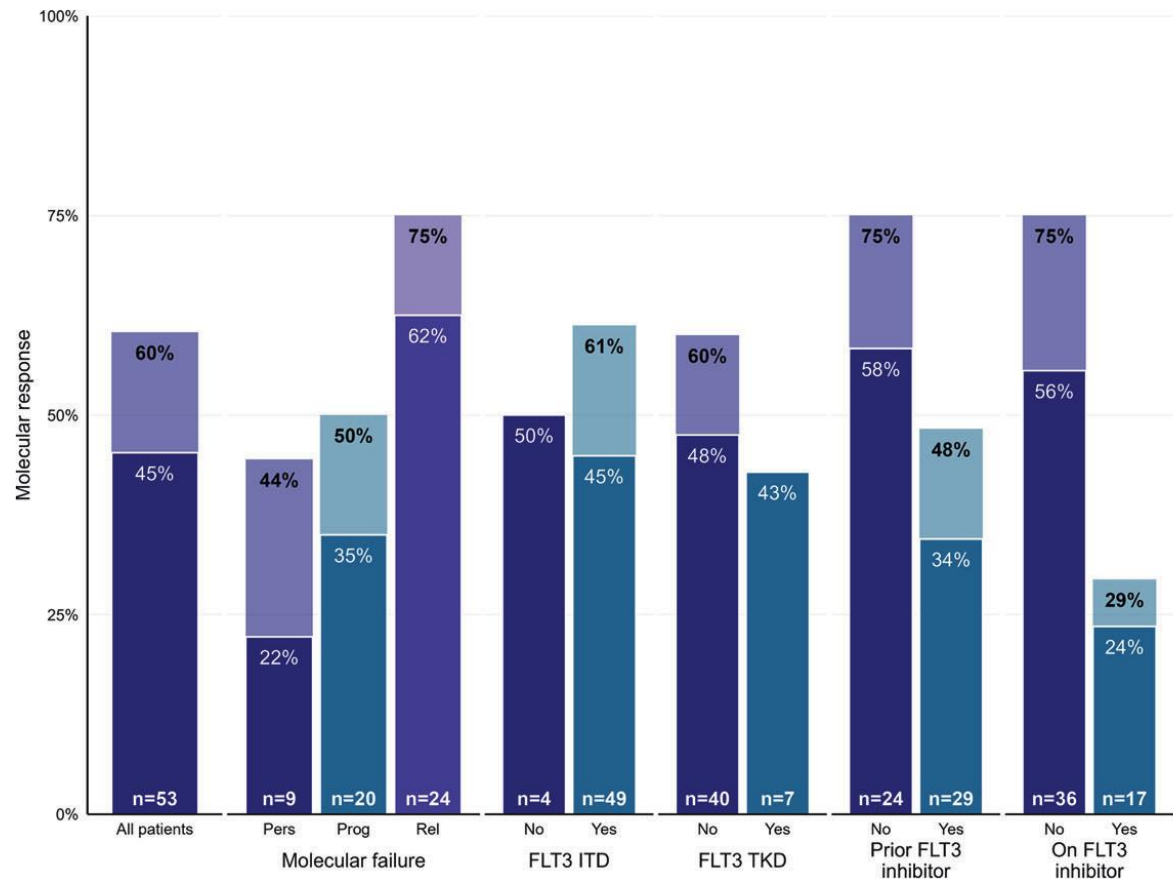
# Targeted Therapy for MRD Relapse in *NPM1*<sup>mut</sup> AML

## European Multicentre Real World Data Using Venetoclax for *NPM1*<sup>mut</sup> MRD failure



# Targeted Therapy for MRD Relapse in *FLT3*<sup>mut</sup> AML

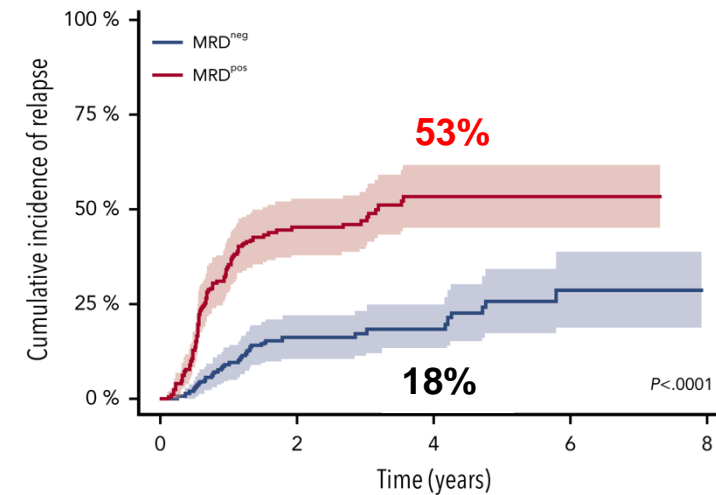
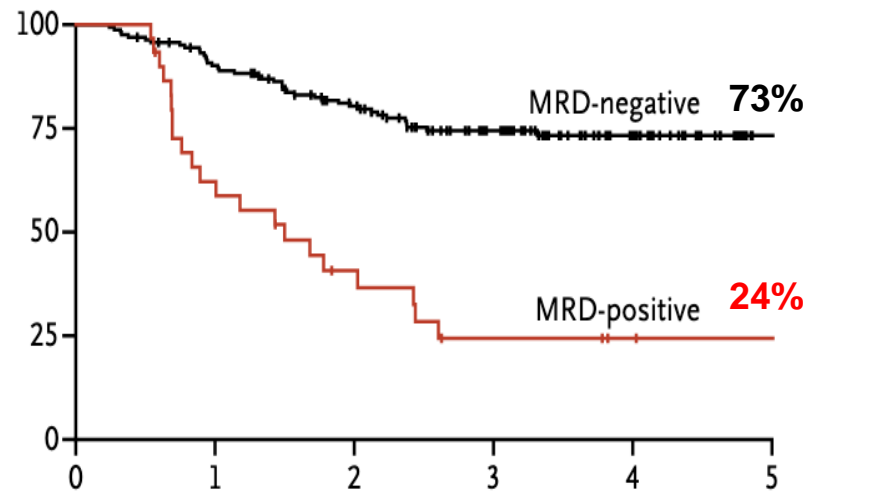
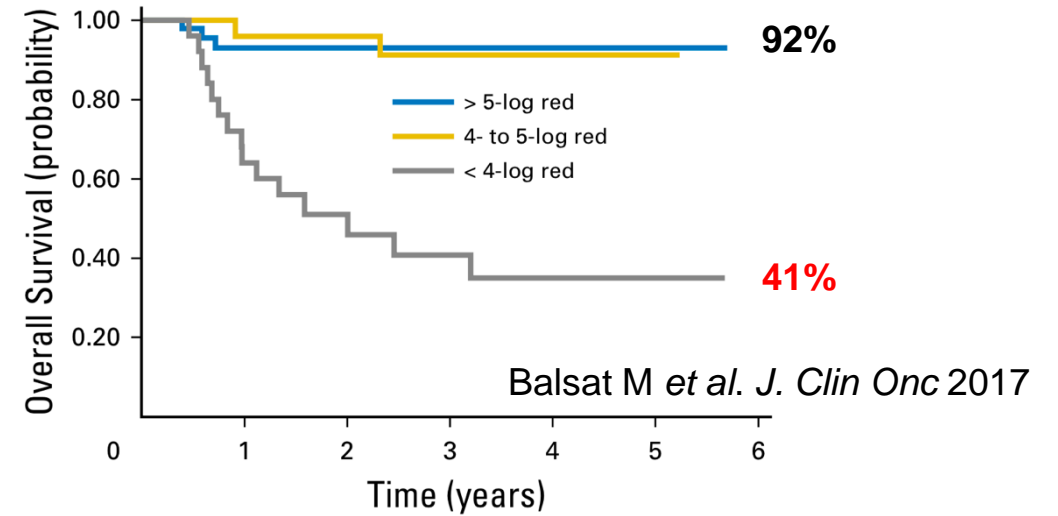
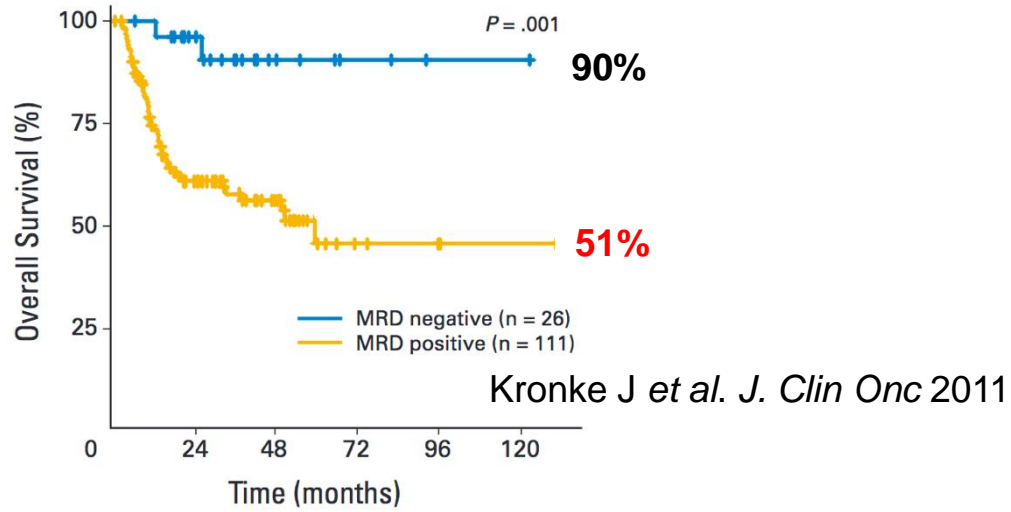
## FLT3 Inhibitors at MRD Relapse in Patients with Baseline *FLT3* Mutation



1) Can and should we use MRD monitoring for relapse surveillance/ pre-emptive treatment?

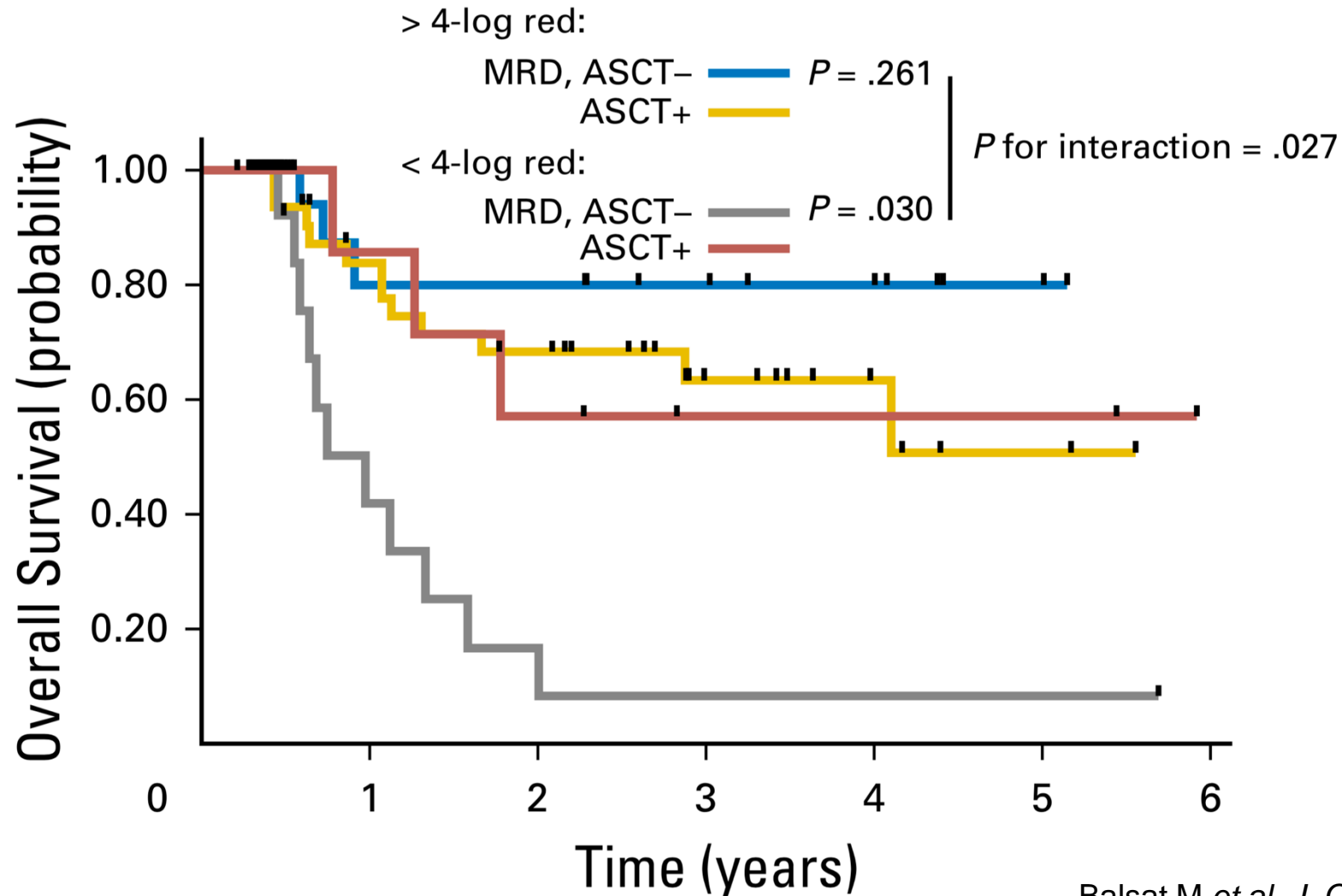
2) Can we use MRD to select patients for transplant ?

# Post-Induction *NPM1* MRD Predicts Relapse and Death

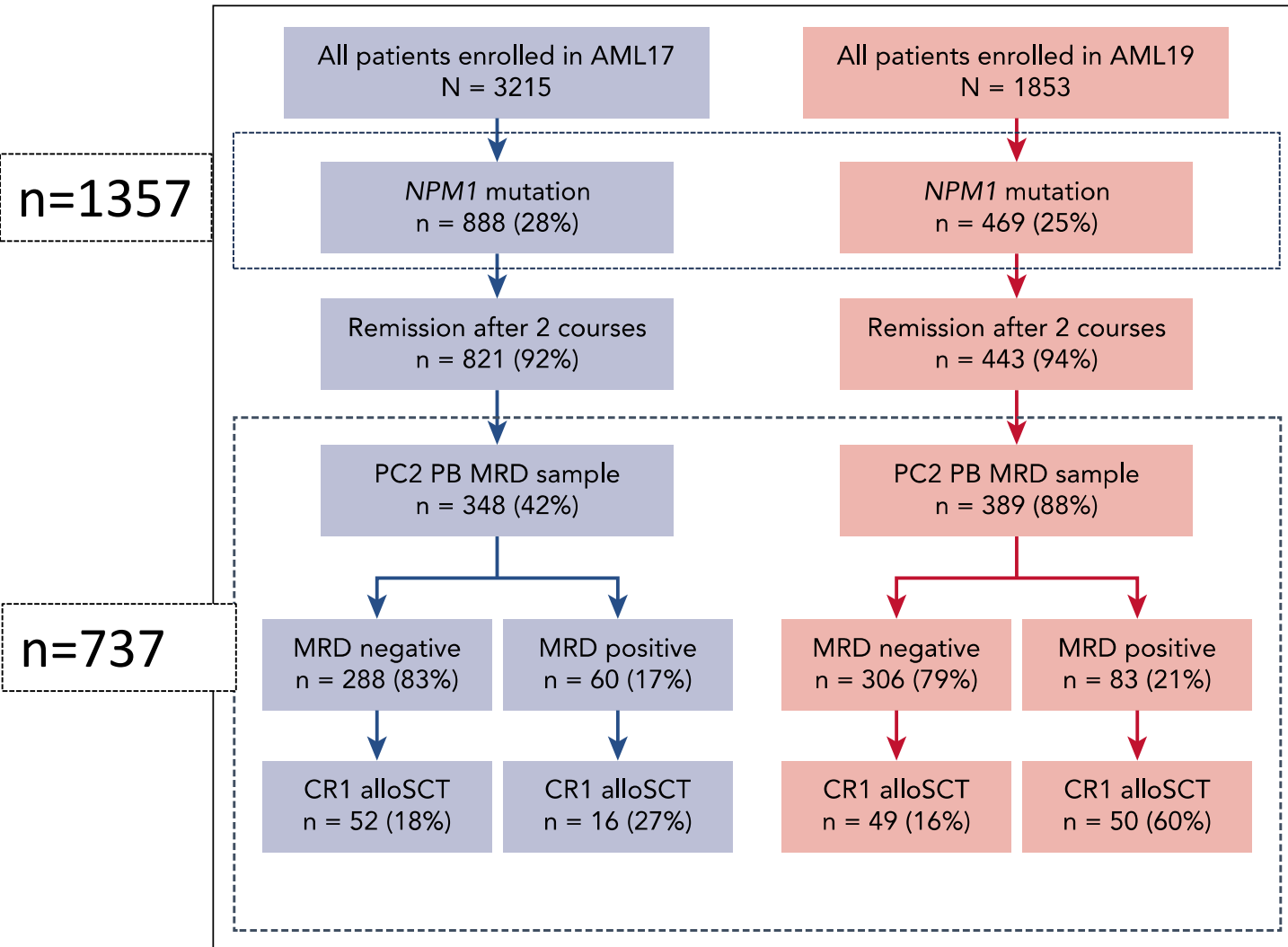




# *NPM1* MRD Informs Patient Selection for CR1 SCT



# Untangling Molecular Risk Factors in *NPM1*mut AML

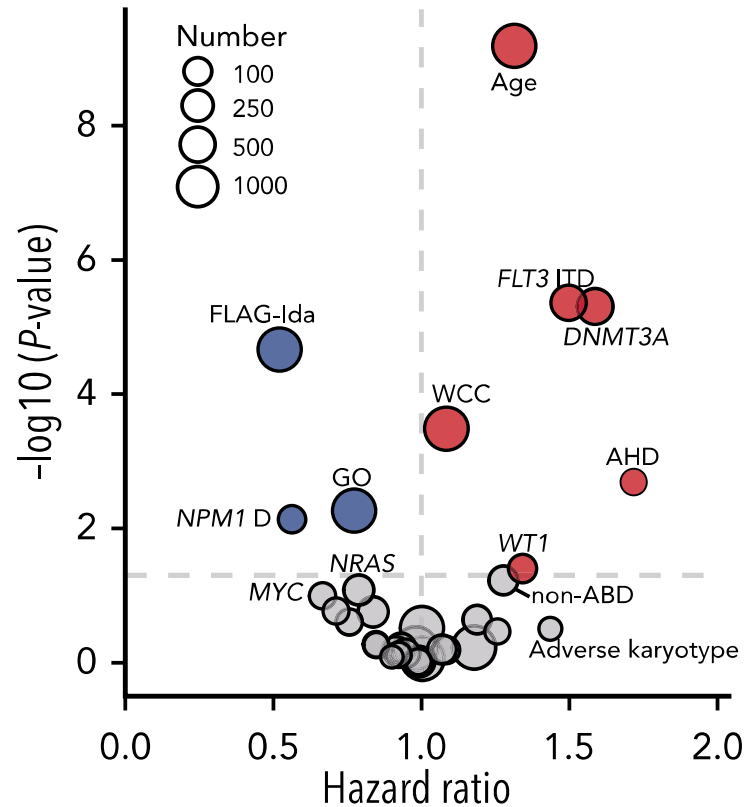


1) Does becoming MRD negative “cancel” baseline genetic risk ?

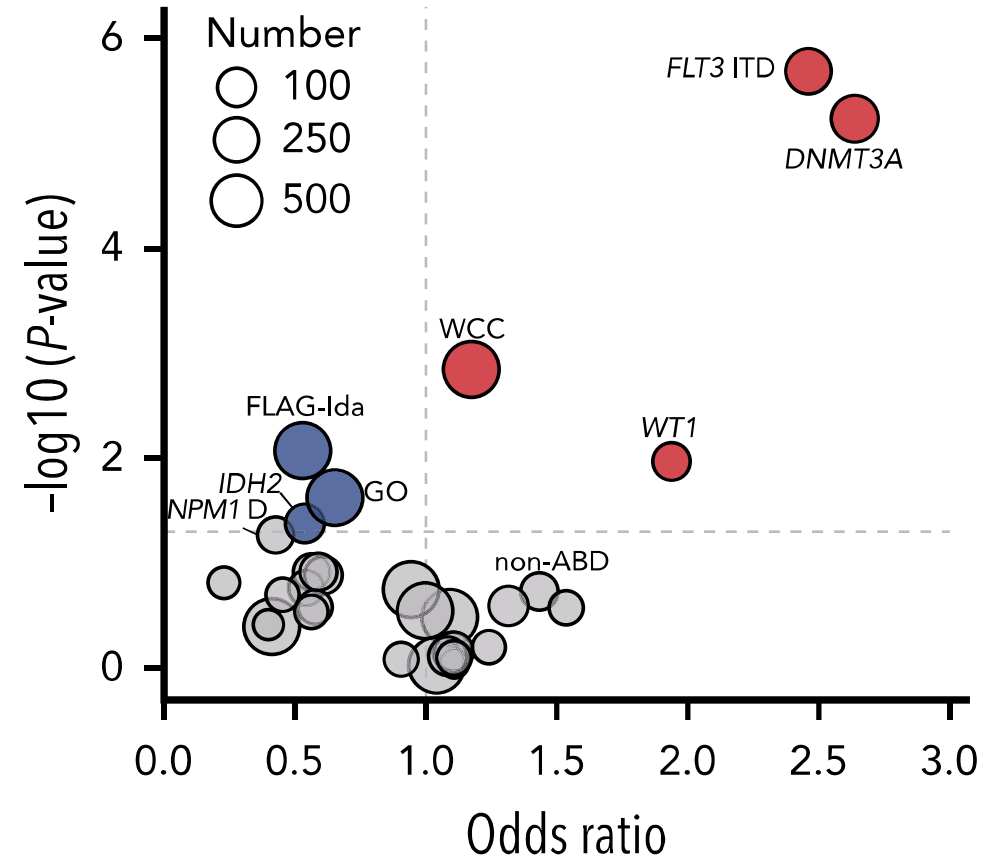
2) Should any MRD negative patients receive a transplant in 1<sup>st</sup> CR ?

# Untangling Molecular Risk Factors in *NPM1*mut AML

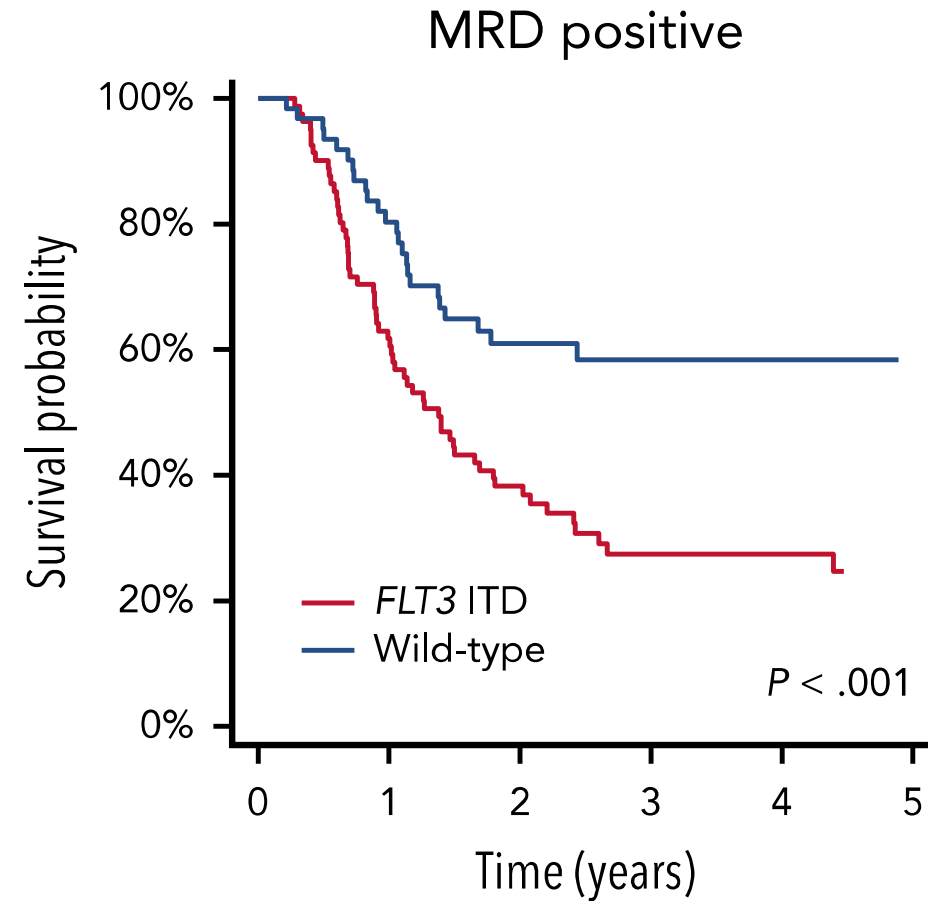
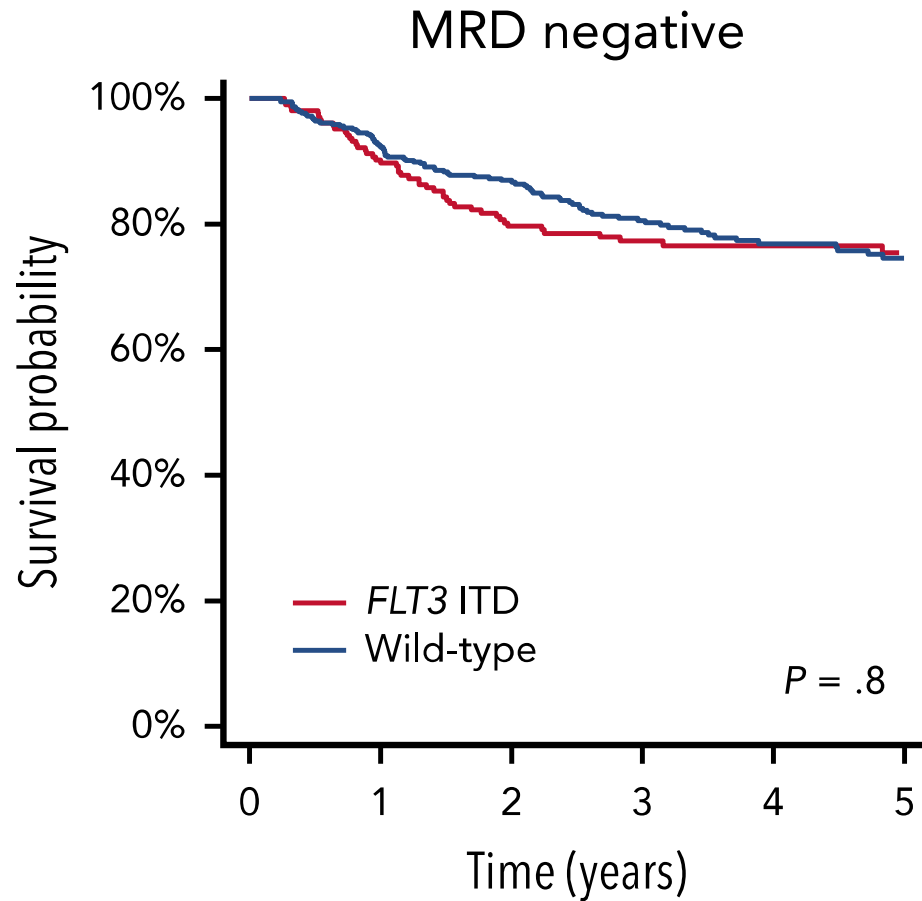
Hazard ratio for Overall Survival



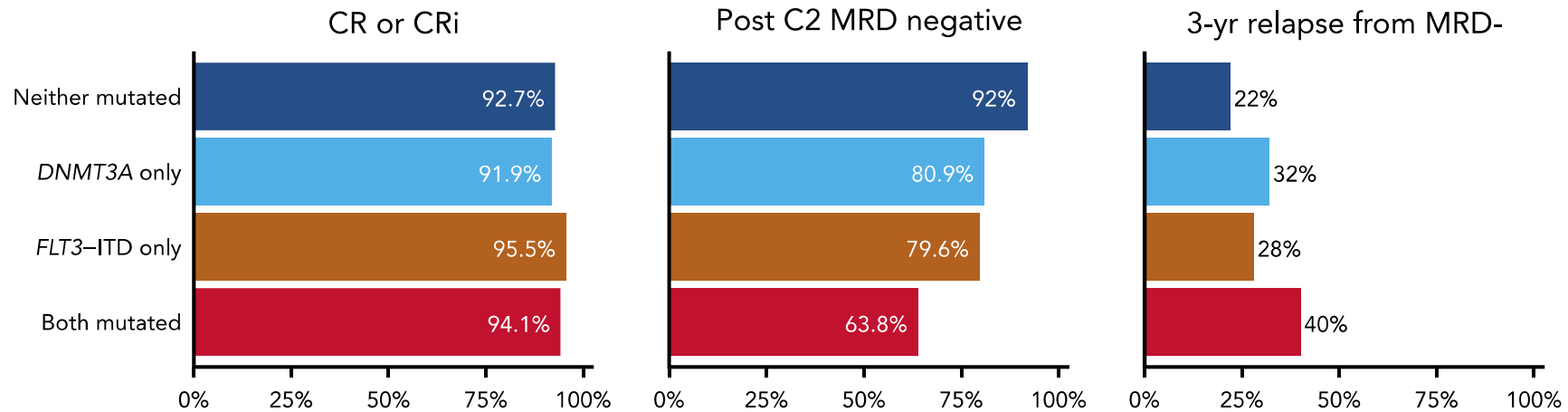
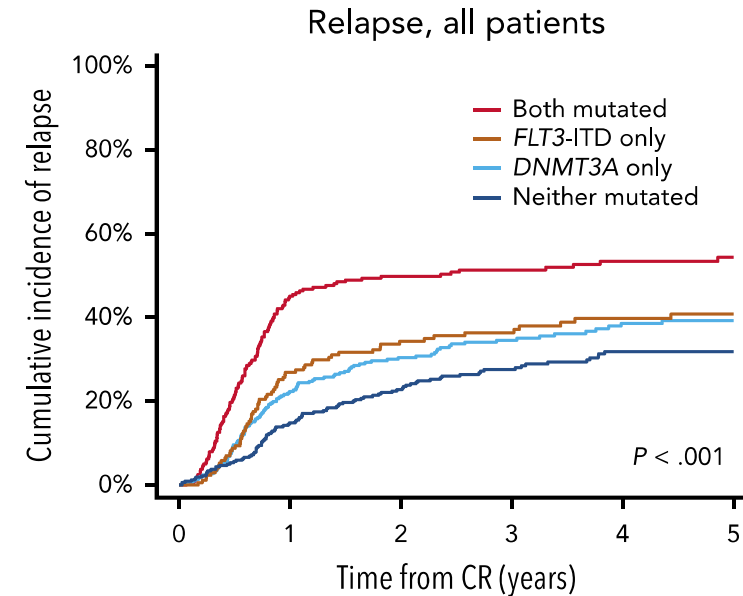
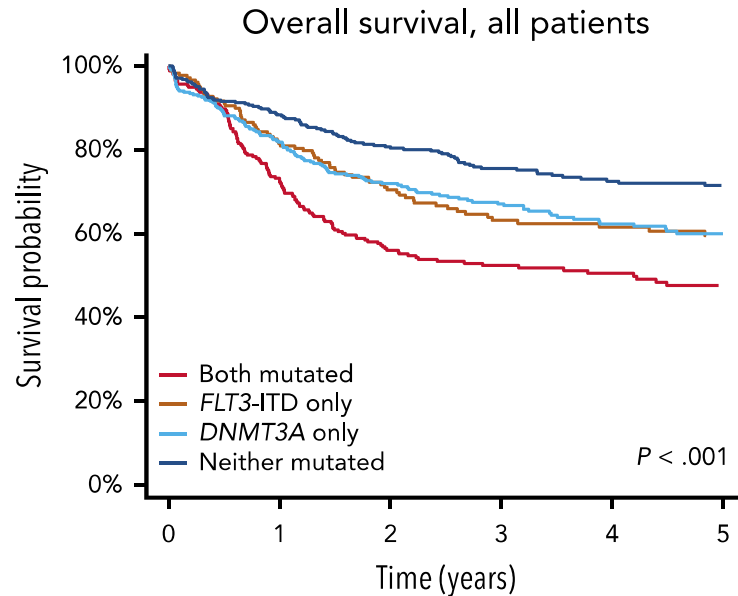
Odds Ratio for MRD negativity



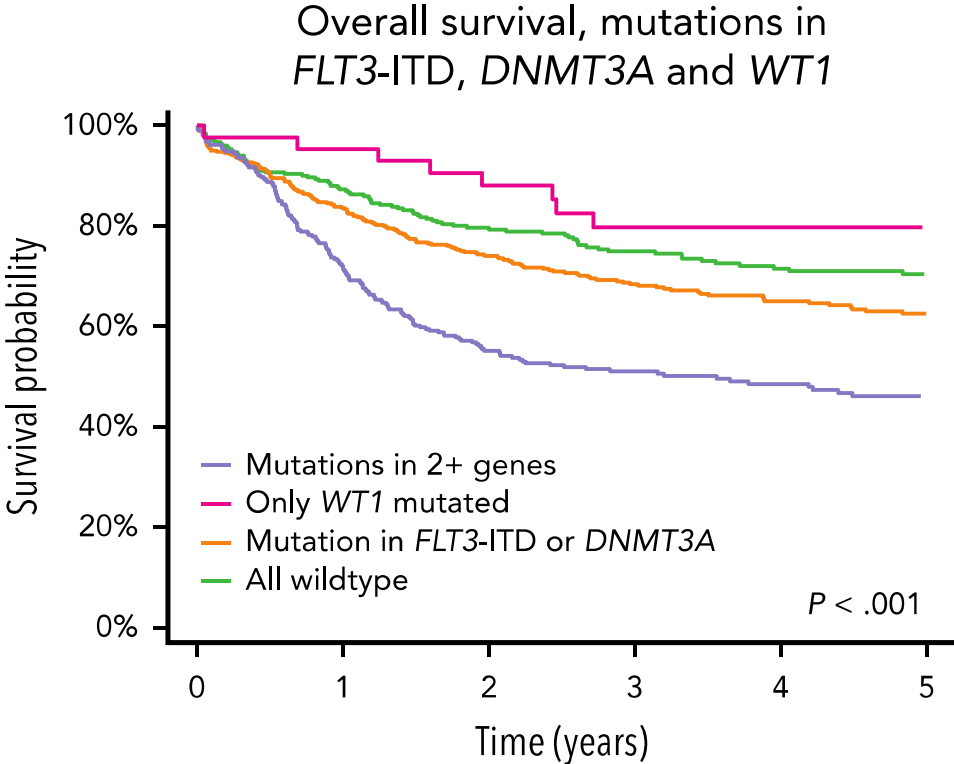
# MRD negativity “cancels” effect of *FLT3* ITD on survival



# Interaction of *FLT3* and *DNMT3A* mutations and MRD

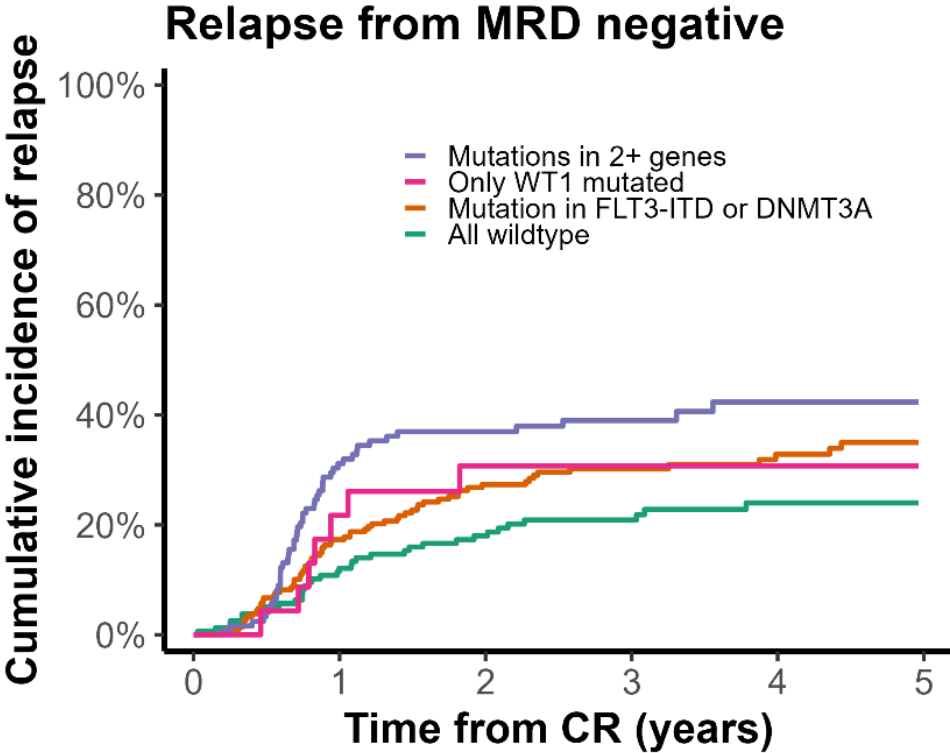


# Interaction of WT1, *FLT3* & *DNMT3A* mutations and MRD



Number at risk

301	256	217	173	138	109
441	366	296	232	171	136
313	224	159	116	85	61
43	41	35	24	18	12

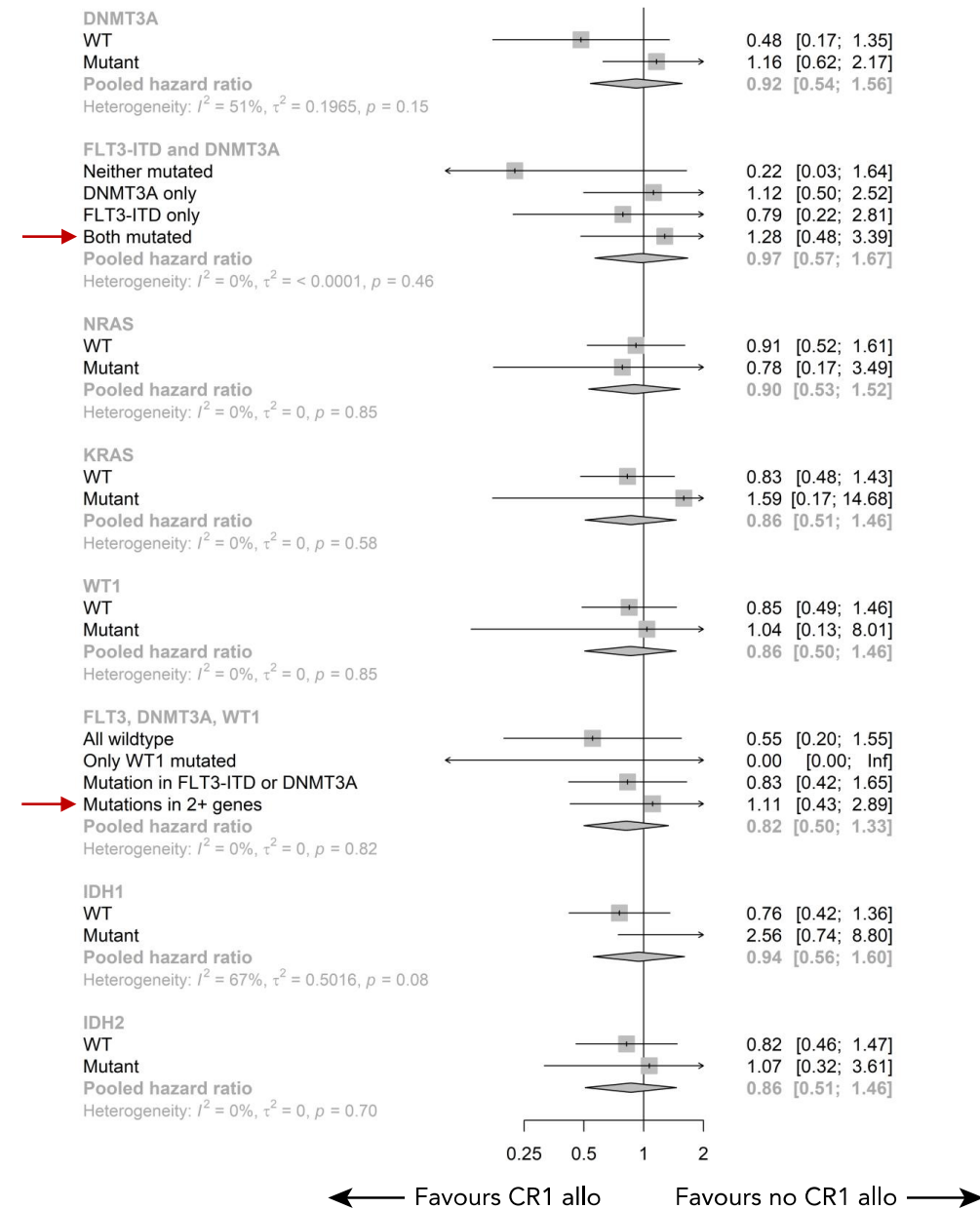
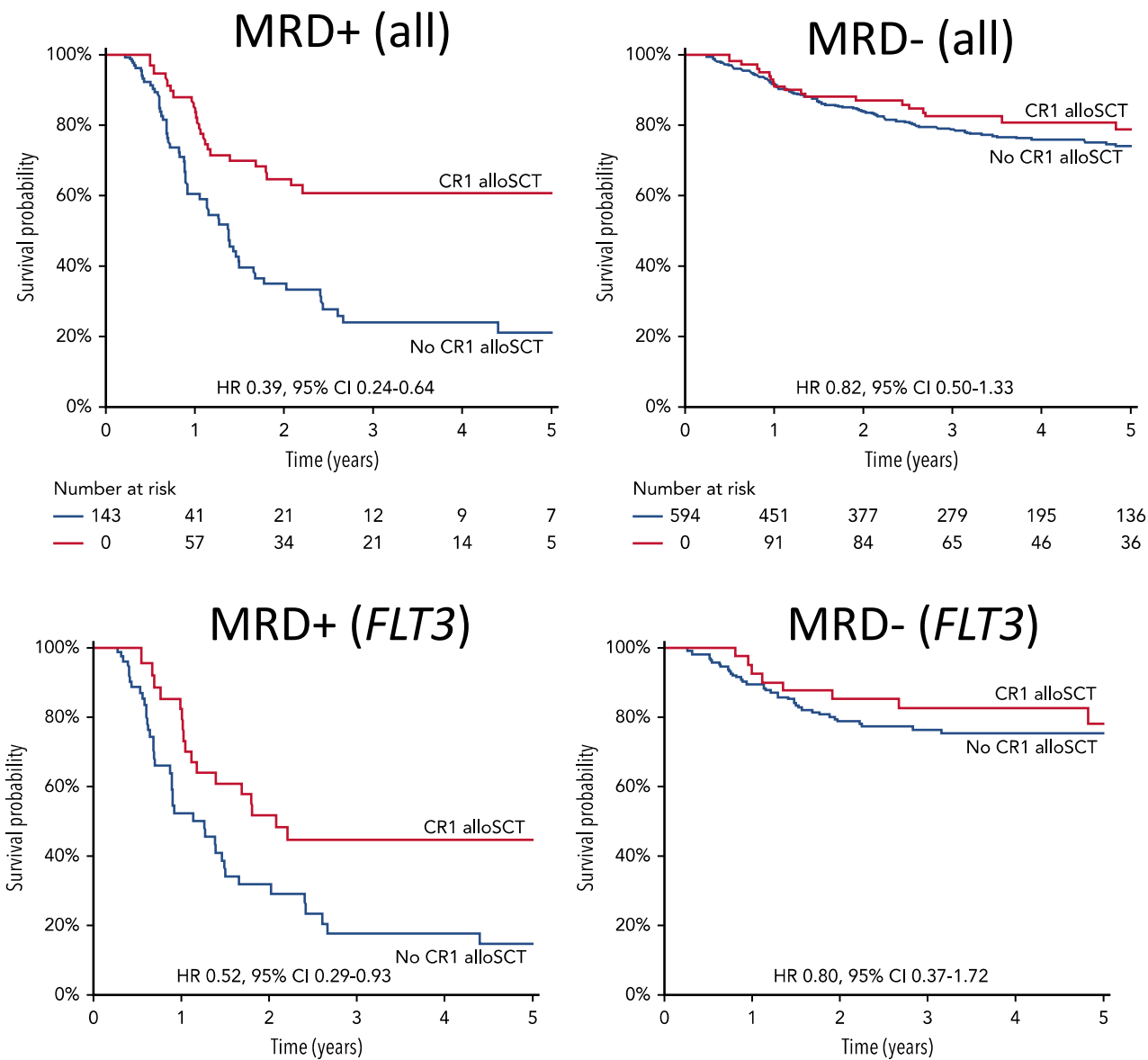


Number at risk

162	135	112	82	60	47
208	159	120	88	60	44
123	79	62	39	26	17
23	17	13	10	8	5



# MRD identifies patients benefitting from CR1 allograft



# Clinical implications of MRD in Core Binding Factor AML

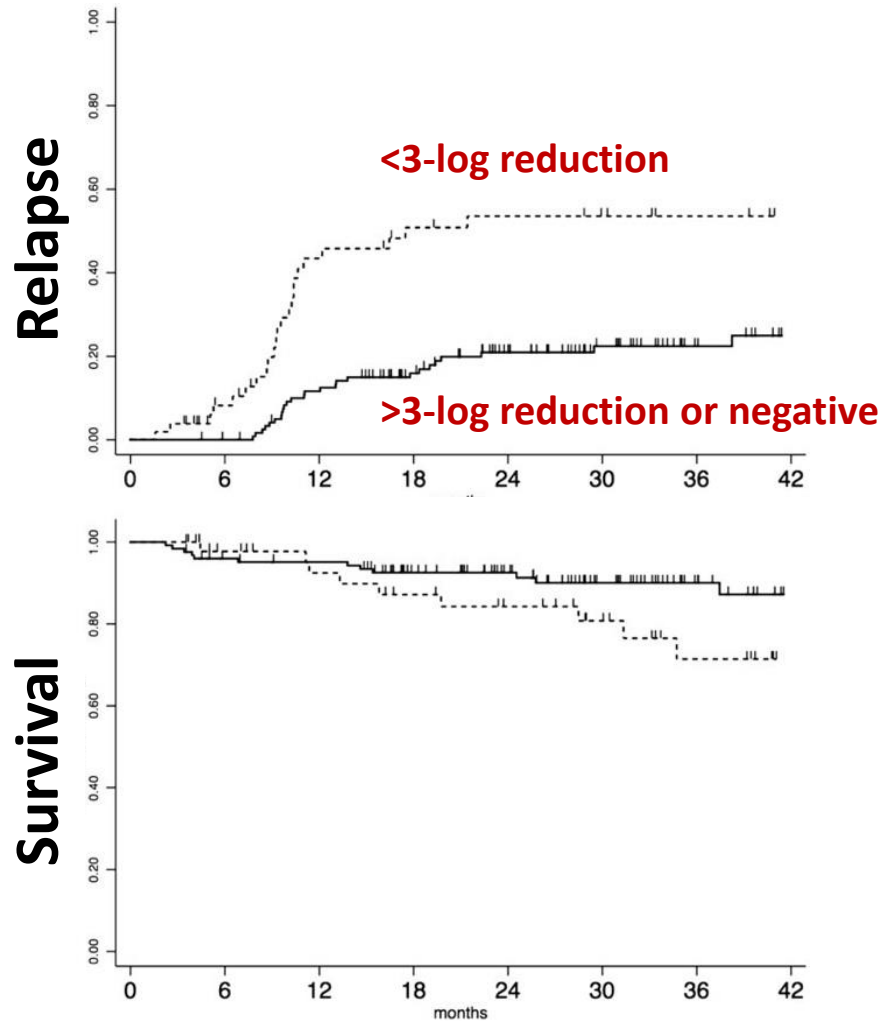
KIT mutant

MRD  
positive

FLT3 ITD



BM qPCR MRD after cycle 2



Multivariate analysis for specific hazard of relapse

	All patients		
	SHR	95% CI	P value
Log(WBC)*	1.96	0.99-3.85	.051
RTK gene mutation	1.62	0.89-2.94	.11
MRD2 reduction $\geq 3$ logs	0.31	0.17-0.57	<.001

Multivariate analysis for OS from CR

	All patients		
	HR	95% CI	P value
Log(WBC)*	1.06	0.39-2.89	.91
RTK gene mutation	1.73	0.70-4.30	.24
MRD2 reduction $\geq 3$ logs	0.51	0.20-1.31	.16

# Clinical implications of MRD in Core Binding Factor AML

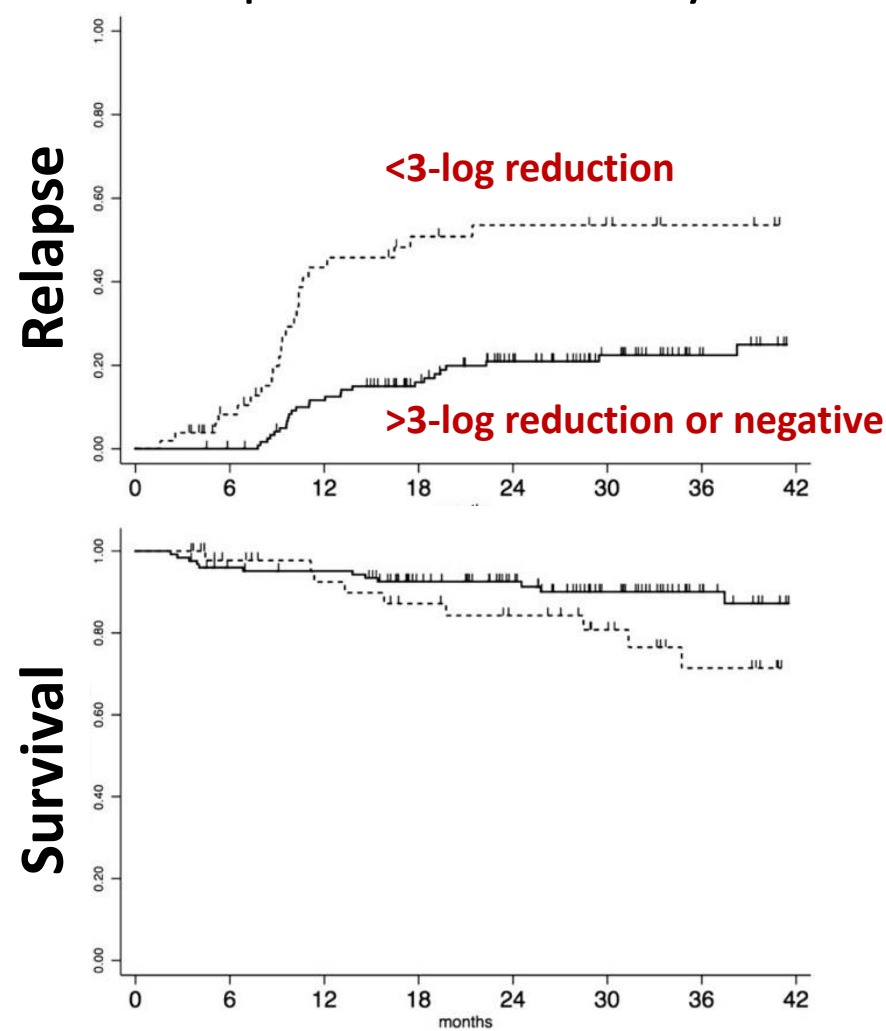
KIT mutant

MRD positive

FLT3 ITD

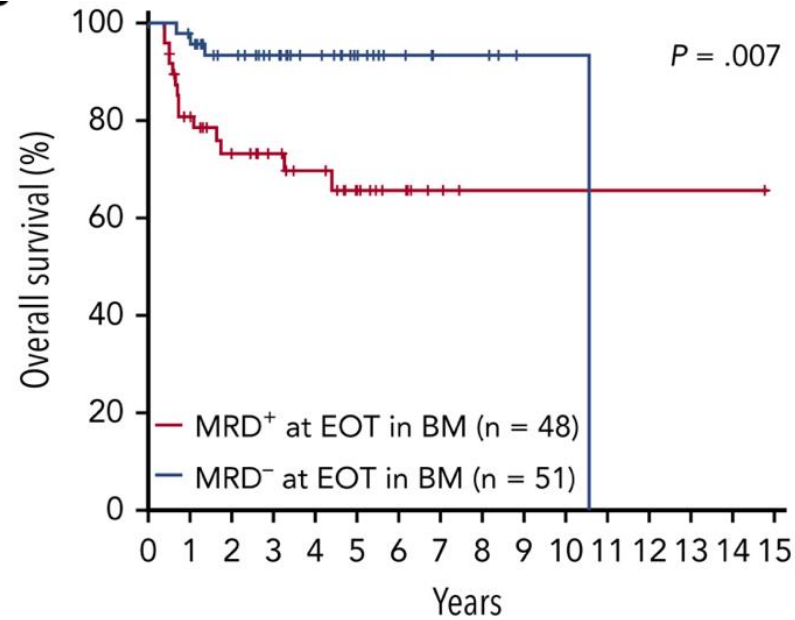
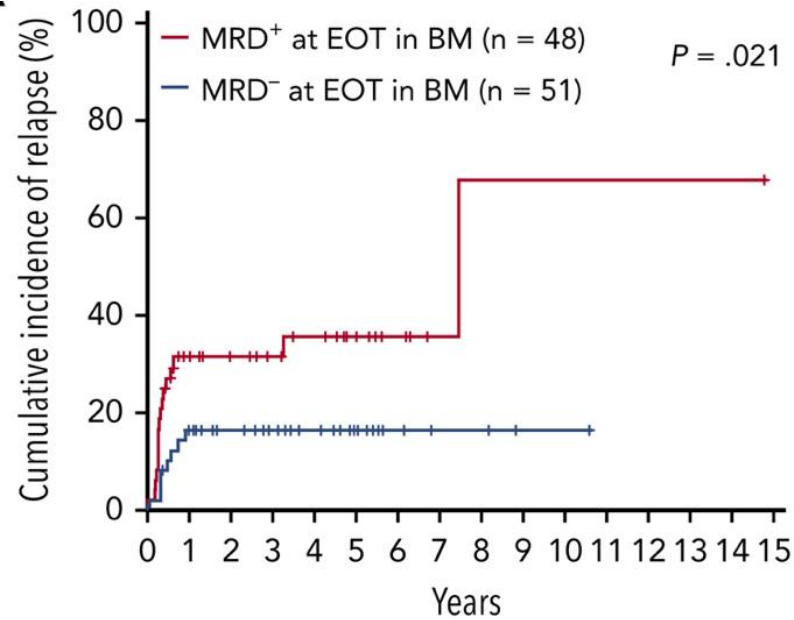


BM qPCR MRD after cycle 2

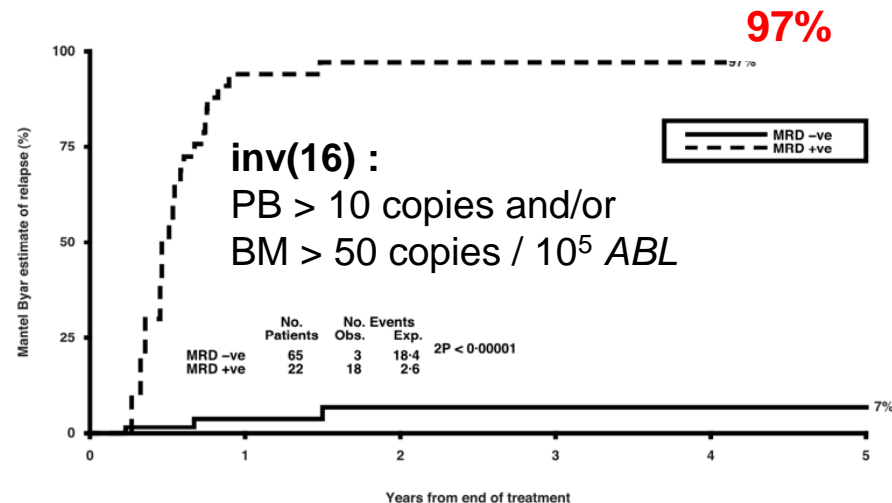
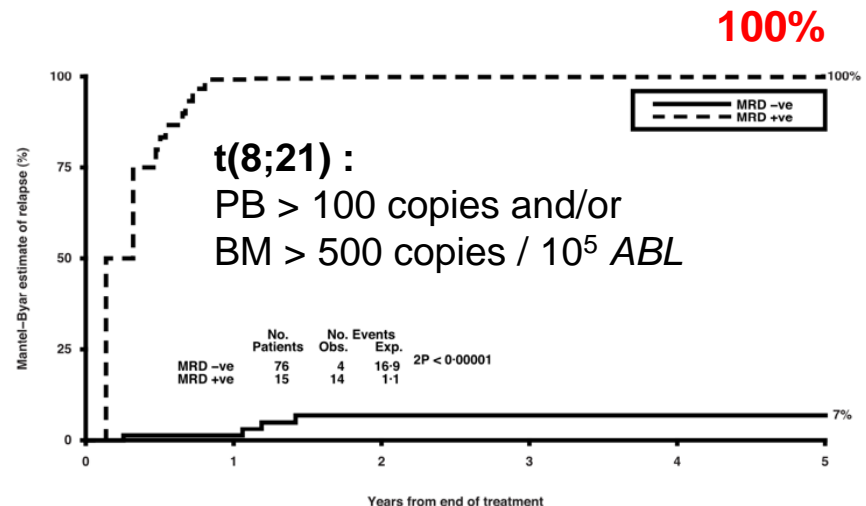


Patient subsets	All patients		
	Patients (n)	CIR (95% CI)	OS from CR (95% CI)
RTK unmutated with 3-log MRD2 reduction	84	18% (11-29)	89% (79-94)
RTK mutated with 3-log MRD2 reduction	38	33% (19-52)	92% (76-97)
RTK unmutated without 3-log MRD2 reduction	28	45% (28-67)	83% (55-94)
RTK mutated without 3-log MRD2 reduction	23	61% (40-83)	56% (18-83)

# Clinical implications of MRD in Core Binding Factor AML



AMLSG t(8;21)

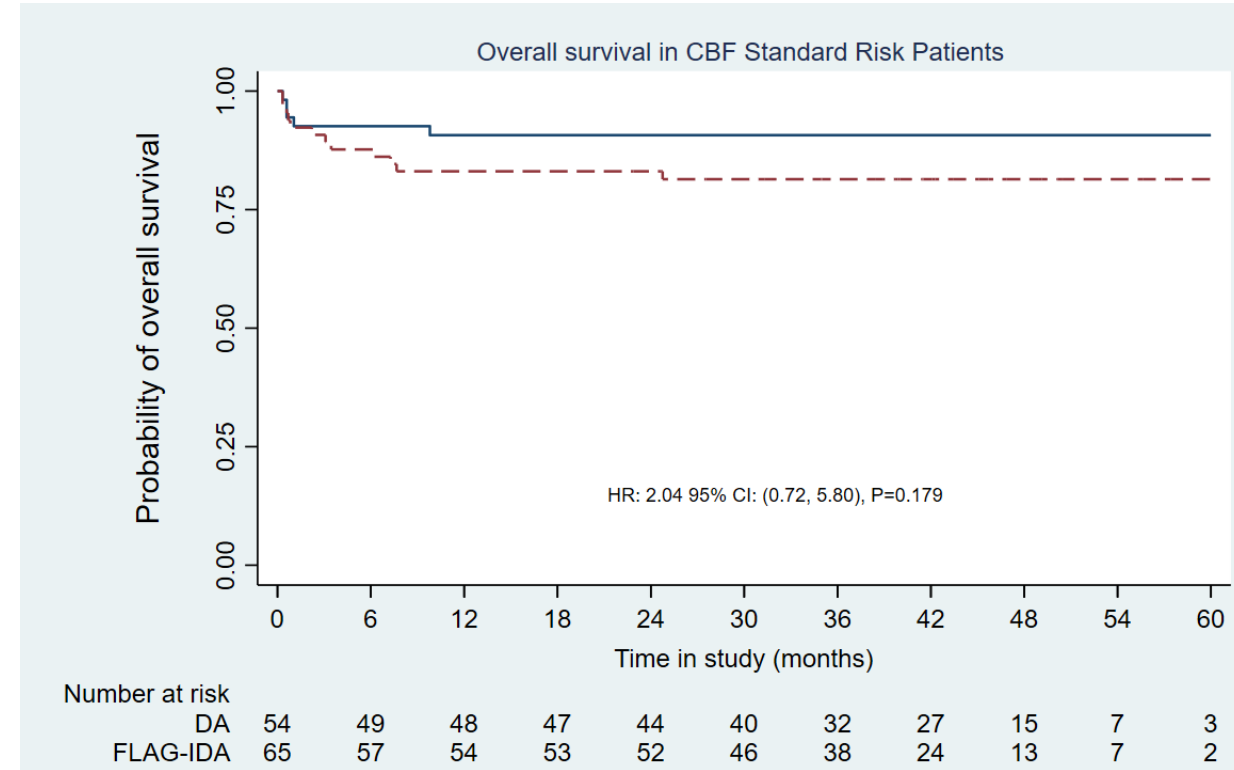


NCRI AML15

Rücker et al, Blood 2019  
Yin et al, Blood 2012

# UK NCRI Approach to Core Binding Factor AML

- ✗ Intensification based on post induction MRD
- ✓ Intensification based on end-of-treatment MRD **repeatedly** above thresholds
- ✓ Pre-emptive salvage for MRD relapse

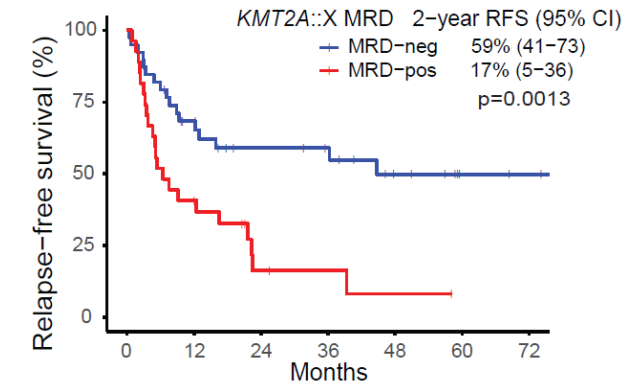
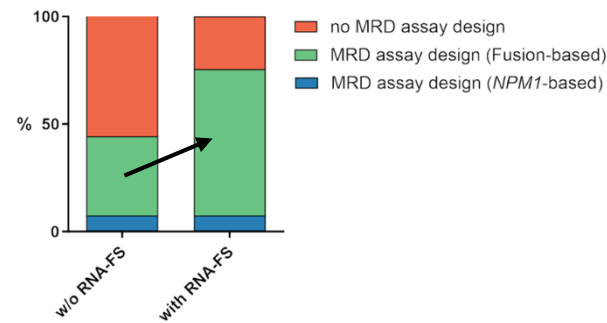
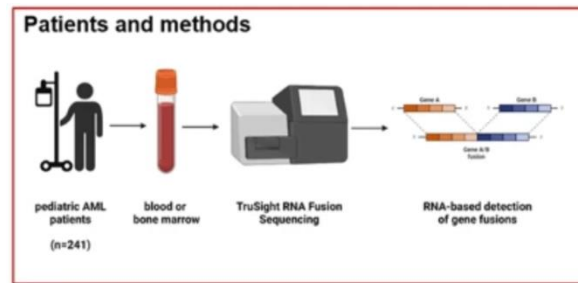


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— DA-GO

# Future directions

- Modern diagnostics - more patients will have trackable marker  
e.g. *KMT2A* fusions and other rare fusion genes



Hoffmeister, L.M. et al, Leukemia 2024

Loo, S. et al, Blood 2024

- More prospective studies of targeted therapies for MRD relapse  
- e.g. ALLG INTERCEPT study
- *FLT3* ITD MRD by NGS



Many thanks for your attention. We gratefully acknowledge all trial participants and their families.

