MRD in AML current status and future perspectives

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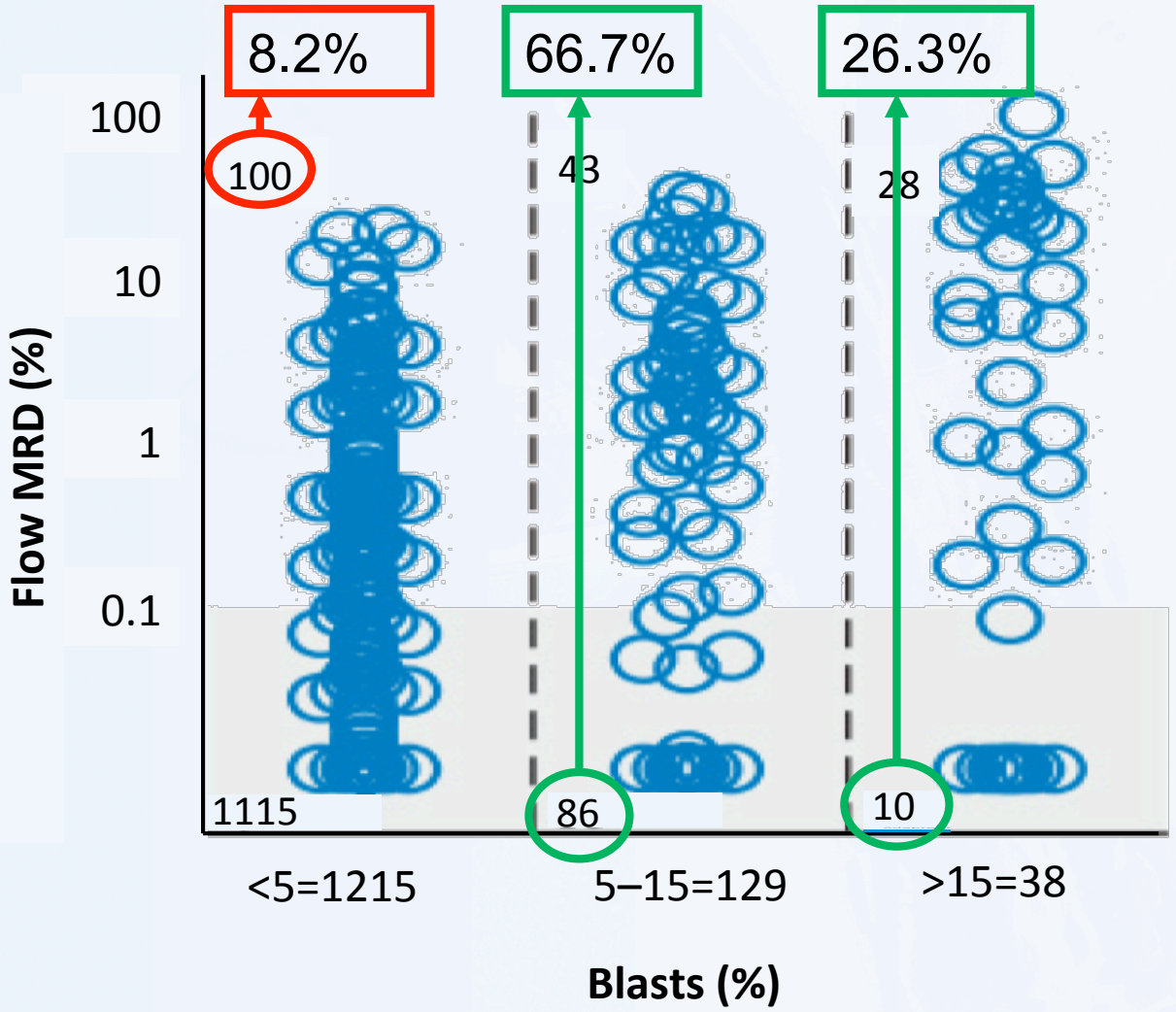
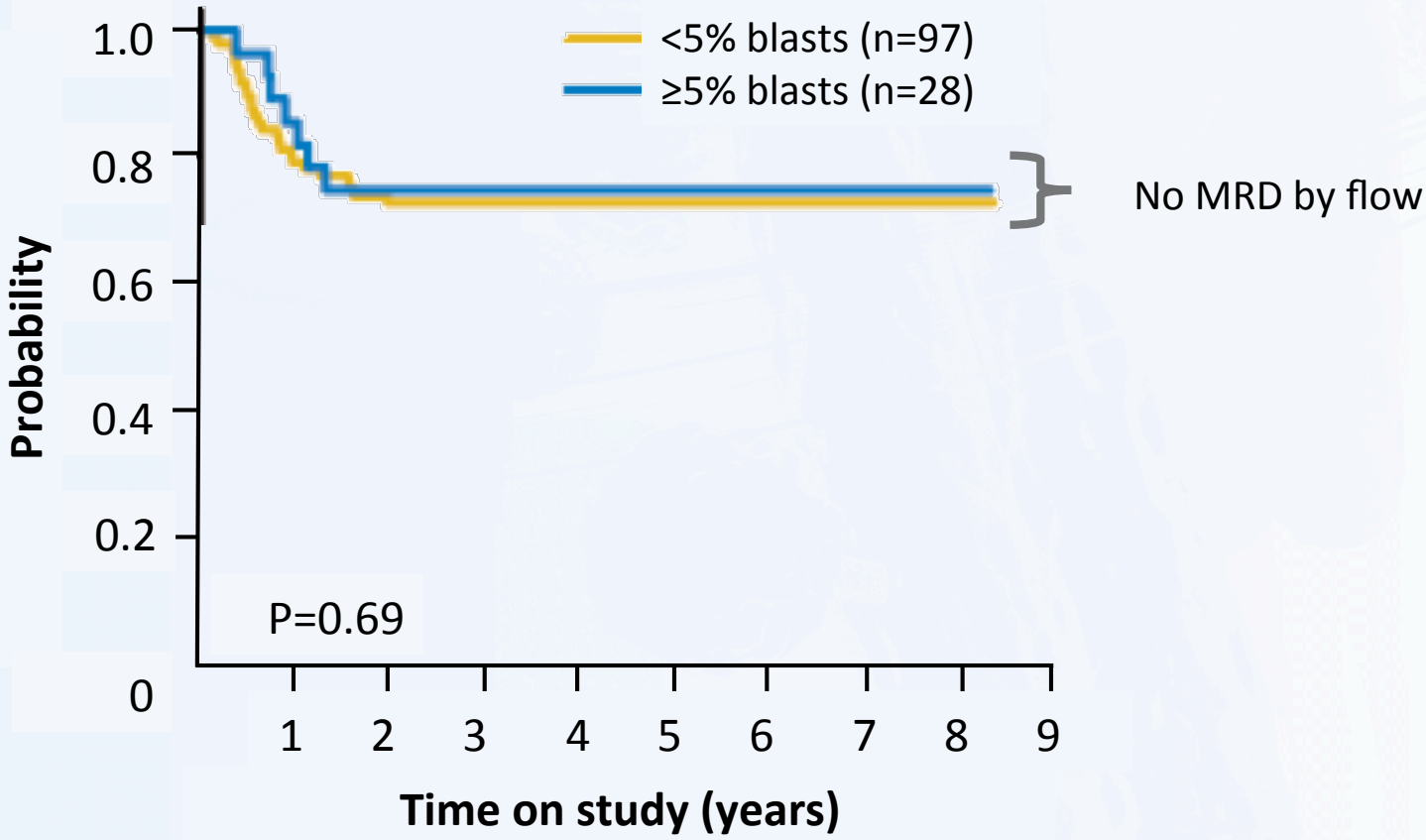
Why ‘MRD’ in AML?



Adapted from Inaba H *et al*. *J Clin Oncol* 2012;30:3625–3632

Why ‘MRD’ in AML?

Event-free survival



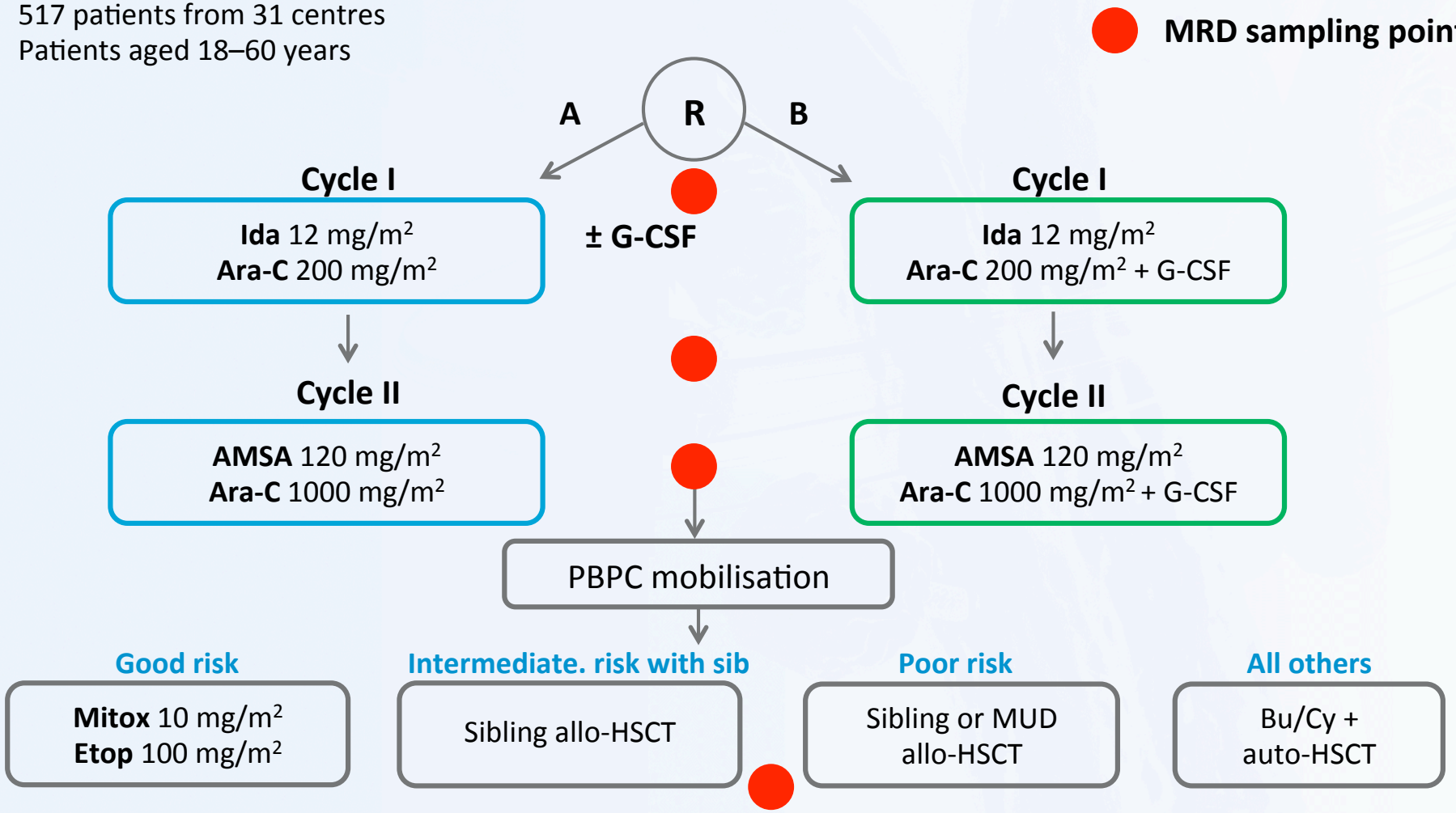
Adapted from Inaba H *et al. J Clin Oncol* 2012;30:3625–3632

Advantages of determination of MRD

- Identification of BM blasts below the threshold of morphology
- Amending morphologic misjudgments due to limited sensitivity and operator inter-variability
  - Apparent situation of CR
  - Apparent situation of disease persistence
- MRD is a very robust proof of AML chemo-resistance
  - Informs about the quality of response
- MRD captures differences in biology of AML and inter-patient variability in drug availability and metabolism
  - Both affecting response to treatment

HOVON/SAKK 42a: Study design

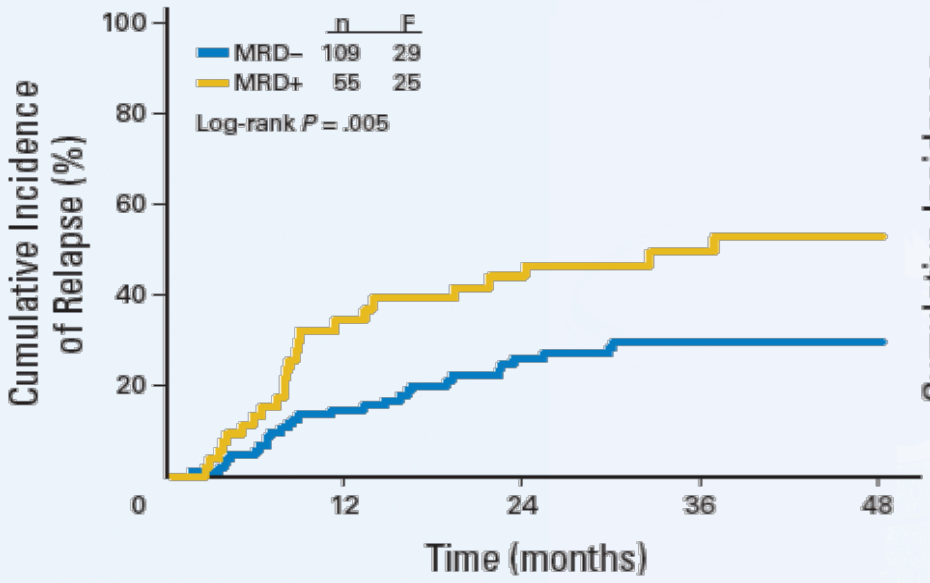
- 517 patients from 31 centres
- Patients aged 18–60 years



Courtesy of Gert Ossenkoppele, presented at ISAL 2017

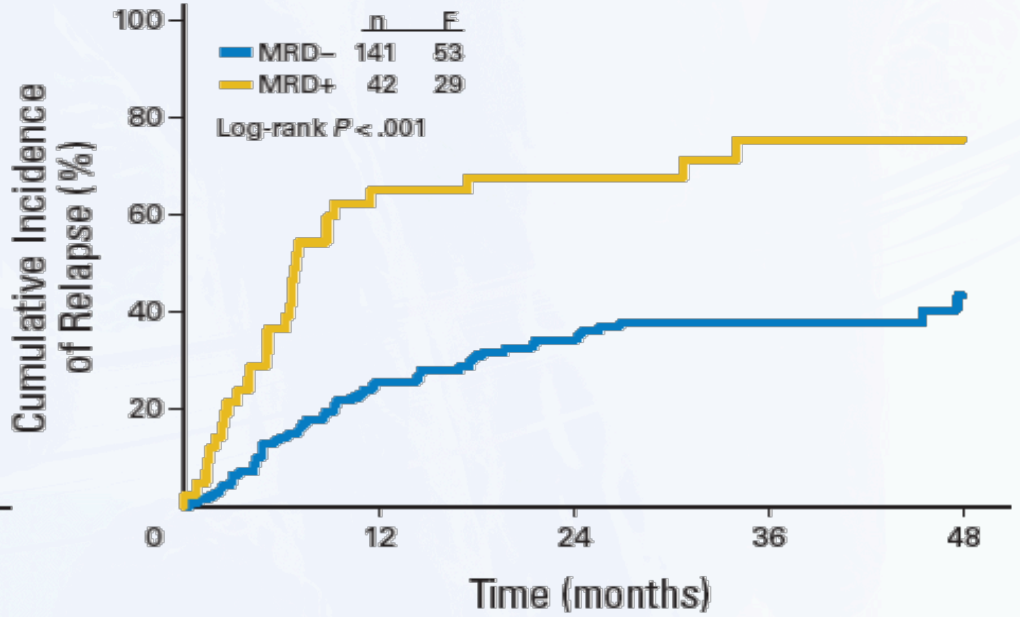
HOVON/SAKK 42a: Cumulative incidence of relapse [1]

Induction 1



No. at risk					
MRD-	109	81	62	45	11
MRD+	55	28	22	15	8

Induction 2



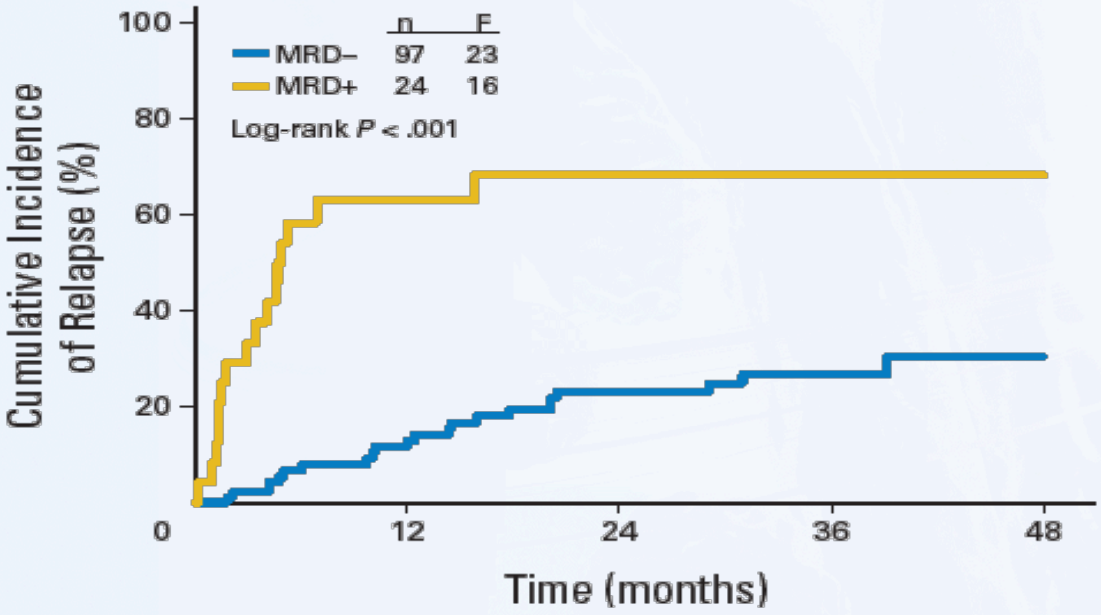
No. at risk					
MRD-	141	96	78	57	18
MRD+	42	13	12	6	2

MRD negativity ≤0.1%

Adapted from Terwijn M *et al. J Clin Oncol* 2013;31:3889–3897

HOVON/SAKK 42a: Cumulative incidence of relapse [2]

Consolidation

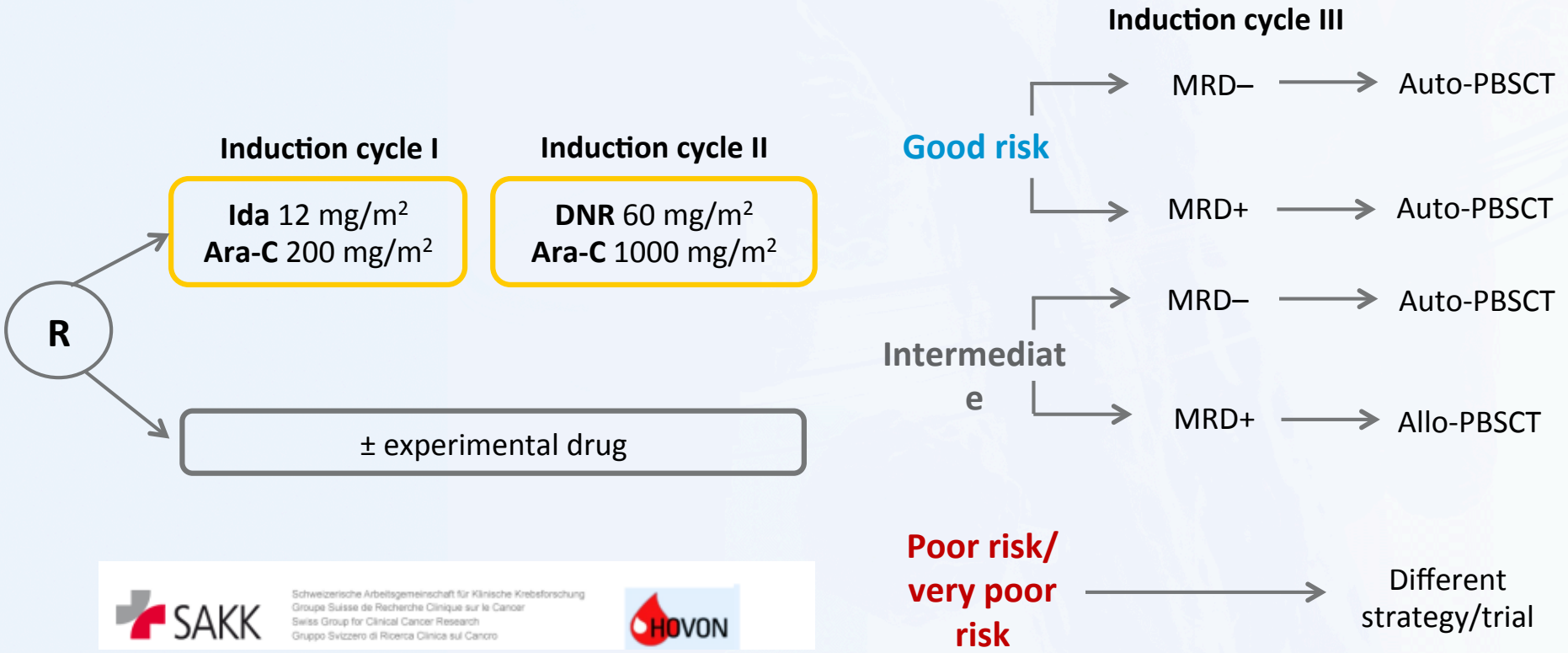


No. at risk					
MRD-	97	69	53	24	5
MRD+	24	8	5	3	1

MRD negativity ≤0.1%

Adapted from Terwijn M *et al. J Clin Oncol* 2013;31:3889–3897

MRD-directed therapy in HOVON/SAKK trials



Courtesy of Gert Ossenkoppele, presented at ISAL 2017

MRD assessment in standard-risk AML

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Assessment of Minimal Residual Disease in Standard-Risk AML

A. Ivey, R.K. Hills, M.A. Simpson, J.V. Jovanovic, A. Gilkes, A. Grech, Y. Patel, N. Bhudia, H. Farah, J. Mason, K. Wall, S. Akiki, M. Griffiths, E. Solomon, F. McCaughan, D.C. Linch, R.E. Gale, P. Vyas, S.D. Freeman, N. Russell, A.K. Burnett, and D. Grimwade, for the UK National Cancer Research Institute AML Working Group

Molecular remission

Absence of detectable *NPM1*-mutated transcripts on RT-qPCR in a sample affording a sensitivity of ≥1 in 10,000

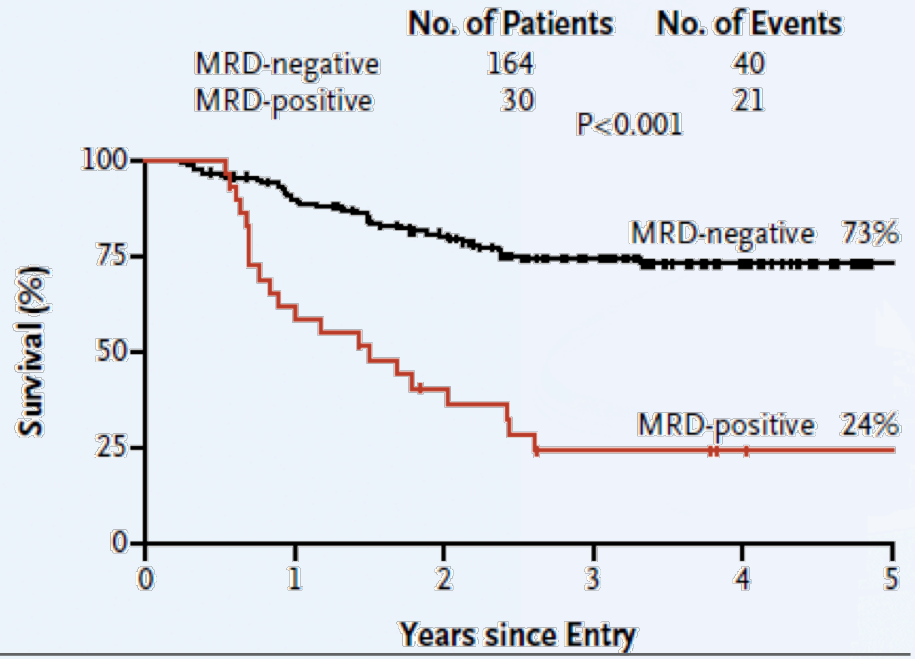
Molecular relapse

Detection of increasing levels of *NPM1*-mutated transcripts in two successive samples in the absence of hematologic relapse

Ivey A *et al. N Engl J Med* 2016;374:422–433

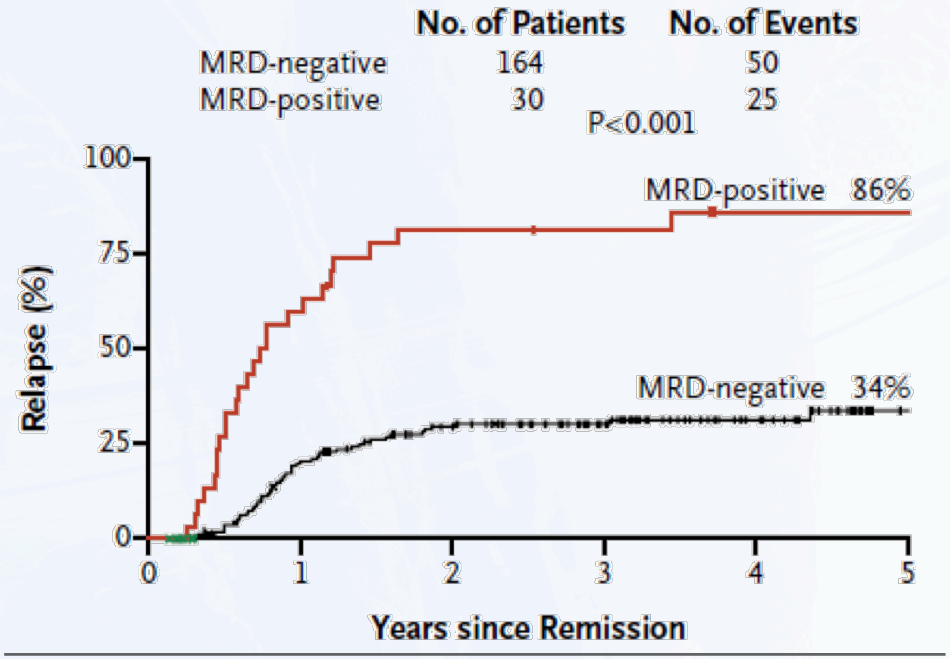
MRD in peripheral blood after the second cycle of chemotherapy and clinical outcomes

Rates of overall survival (all pts)



No. at risk						
MRD–	164	144	116	77	39	8
MRD+	30	18	10	5	3	2

Cumulative incidence of relapse (all pts)

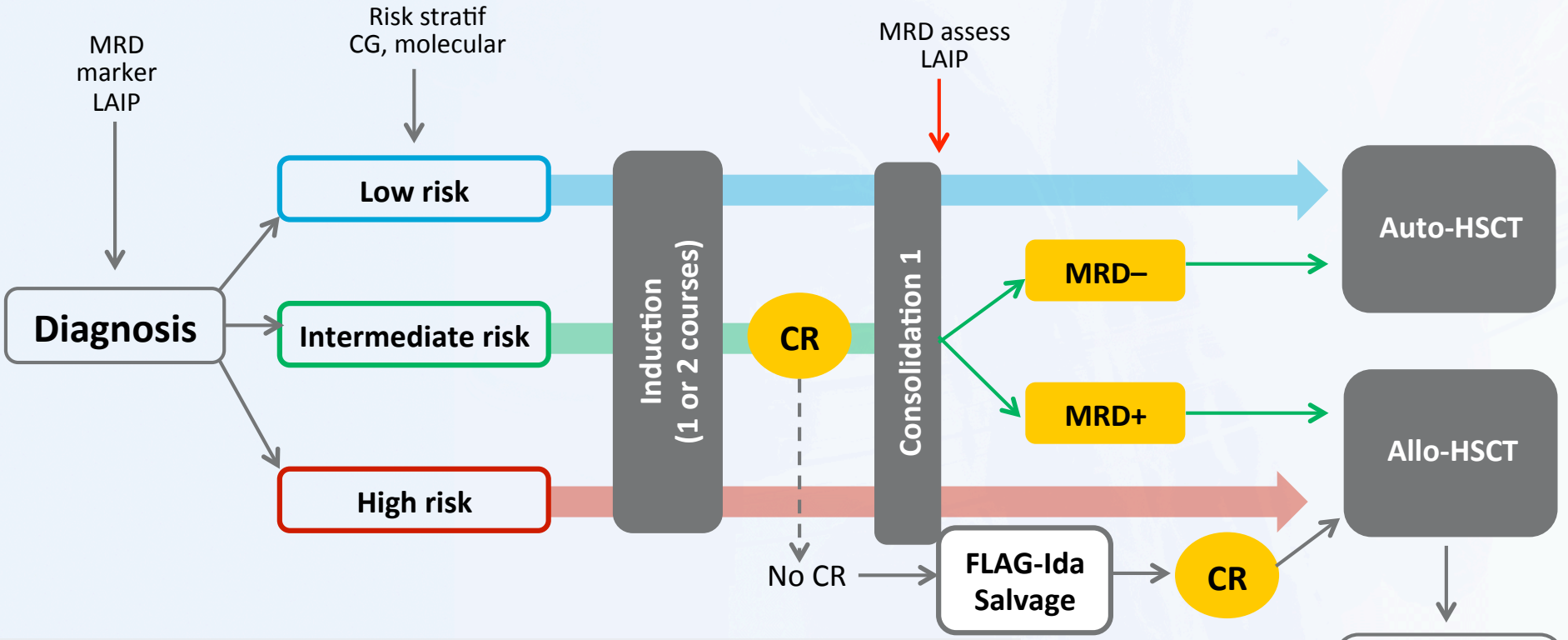


No. at risk						
MRD–	164	120	93	64	33	6
MRD+	30	12	5	4	1	1

The presence of MRD, as determined by quantitation of *NPM1*-mutated transcripts, provided powerful prognostic information independent of other risk factors

Adapted from Ivey A *et al. N Engl J Med* 2016;374:422–433

AML1310 (MRD– vs MRD+): Study design



INDUCTION

- Daunorubicin : 50 mg/m² IV D 1,3,5
- SD-Ara-C: 100 mg/m² c.i. D 1–10
- Etoposide: 100 mg/m² IV D 1–5

CONSOLIDATION

- Daunorubicin : 50 mg/m² IV D 4–6; ID-Ara-C : 500 mg/m²/q12 hours, over 2 hours, D 1–6

Adapted from Buccisano F. Oral presentation at EBMT 2013. https://clinicaltrials.gov/ct2/show/NCT01452646 Accessed May 2017
Venditti A *et al. Blood* 2012;120:1422–1431
Courtesy of the GIMEMA study group. Unpublished data

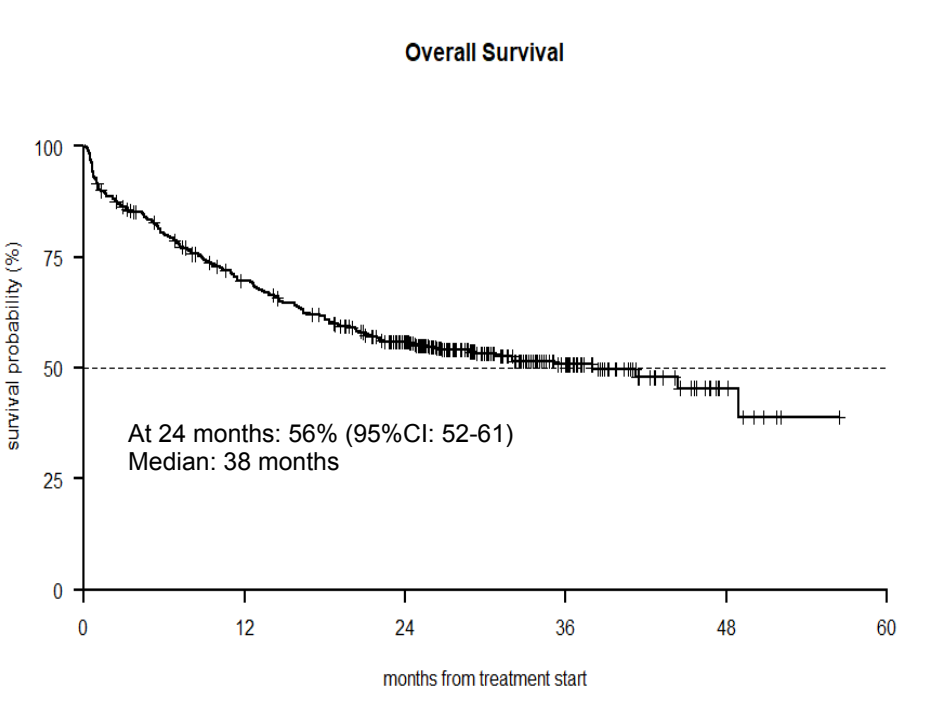
AML1310: characteristics (n=500)

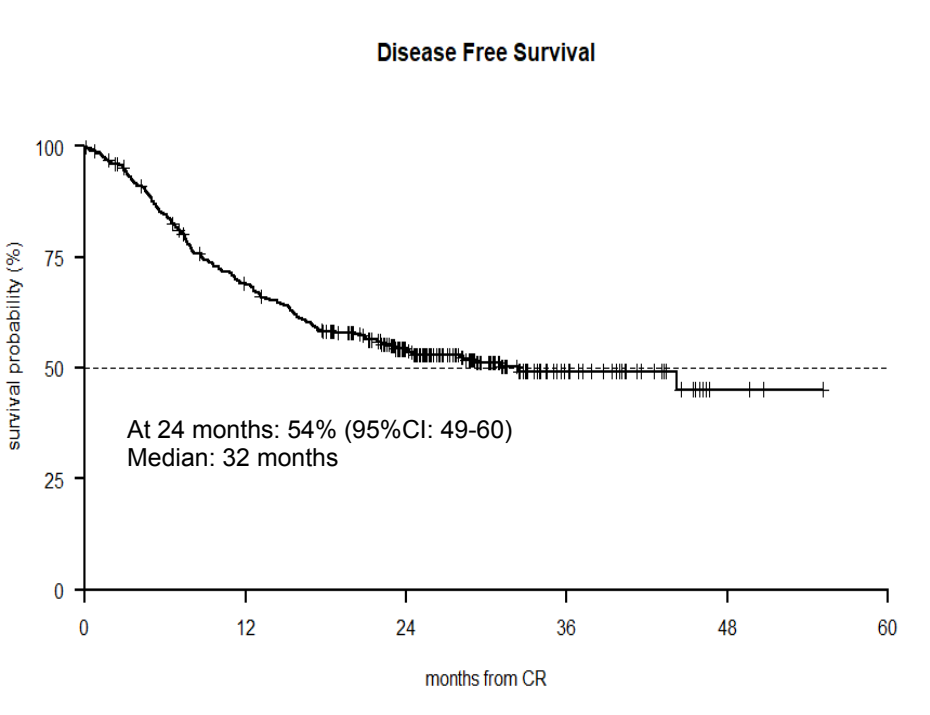
fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche.

Age, yrs		
median	49	
range	18-61	
Gender		
M/F	260/240	
WBCcx10^9/L		
median	13.9	
range	0.16-352	
ELN category		
Favorable	138 (28%)	AutoSCT
Intermediate	174 (35%)	Wait for MRD after Cons
Adverse	188 (38%)	AlloSCT
LAIP not detected		
Favorable	4	AutoSCT
Intermediate	43	
Adverse	0	
Total	47 (9%)	

AML1310: results
median follow-up: 27.8 months

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche.





AML1310: results
OS and DFS by ELN category

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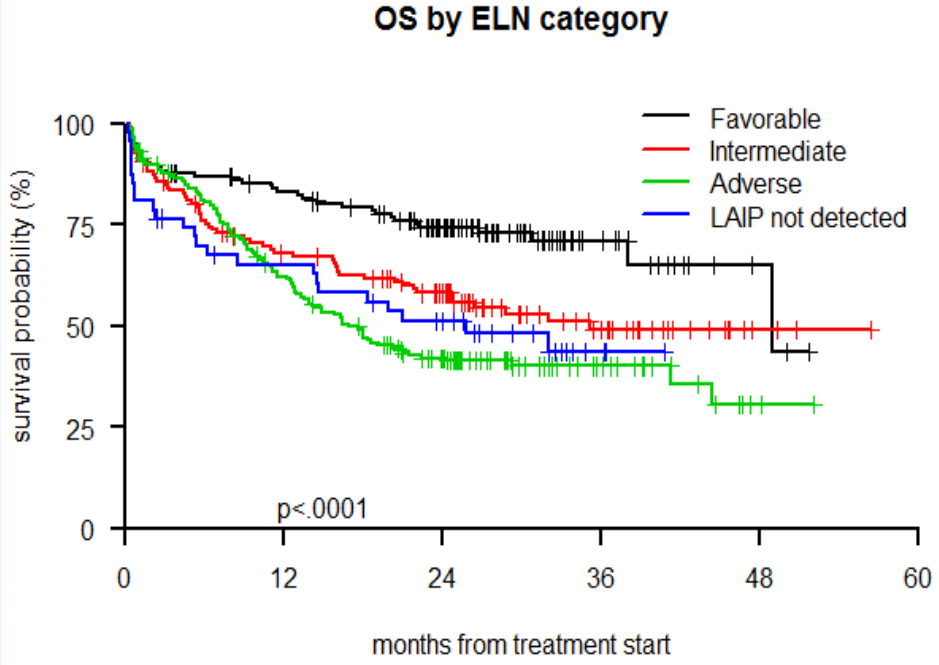
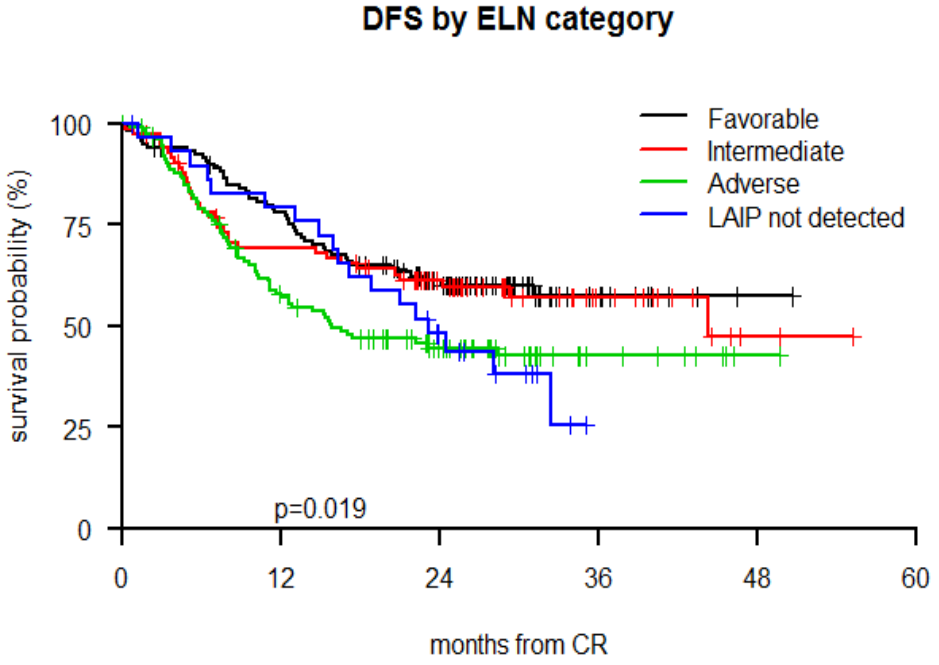
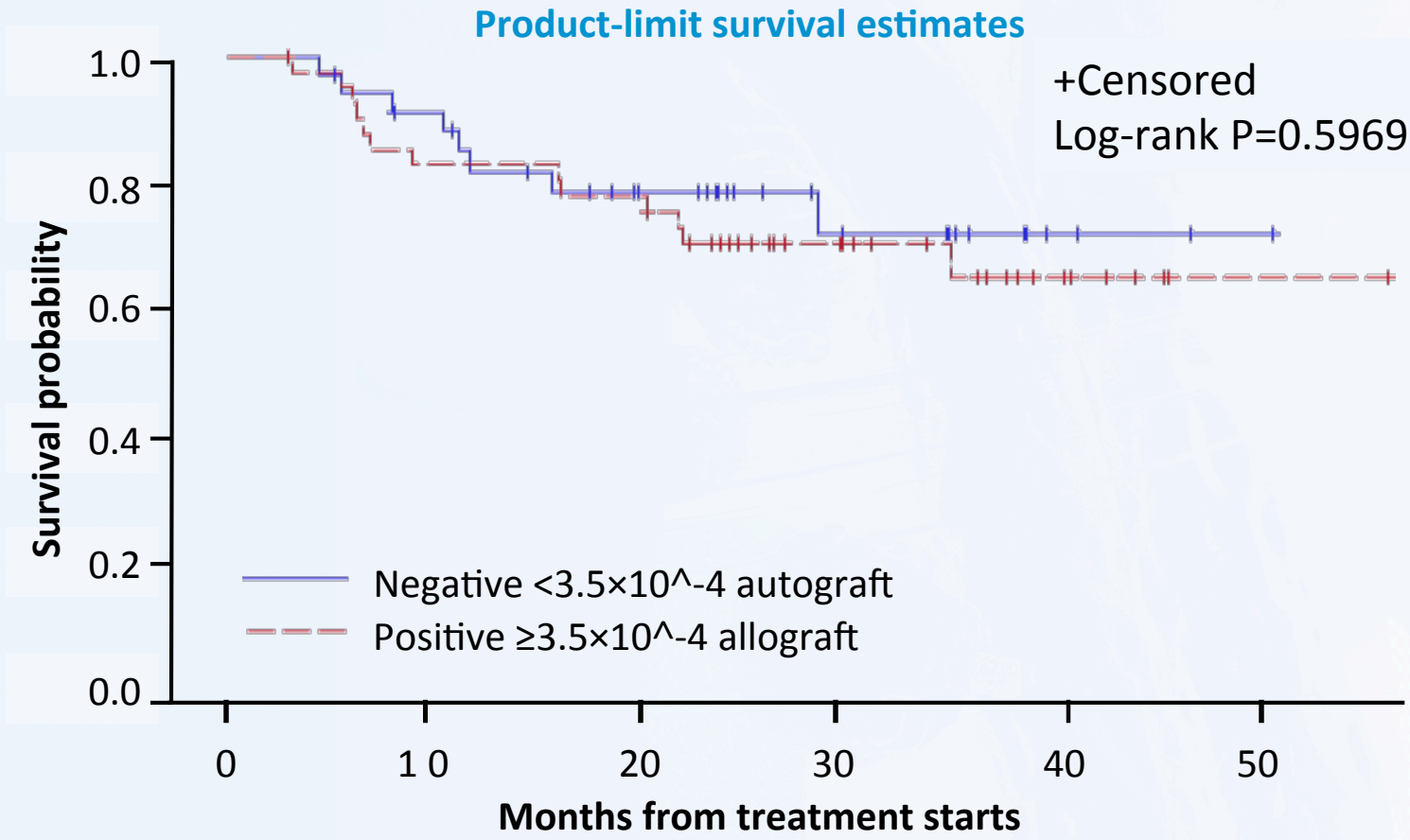


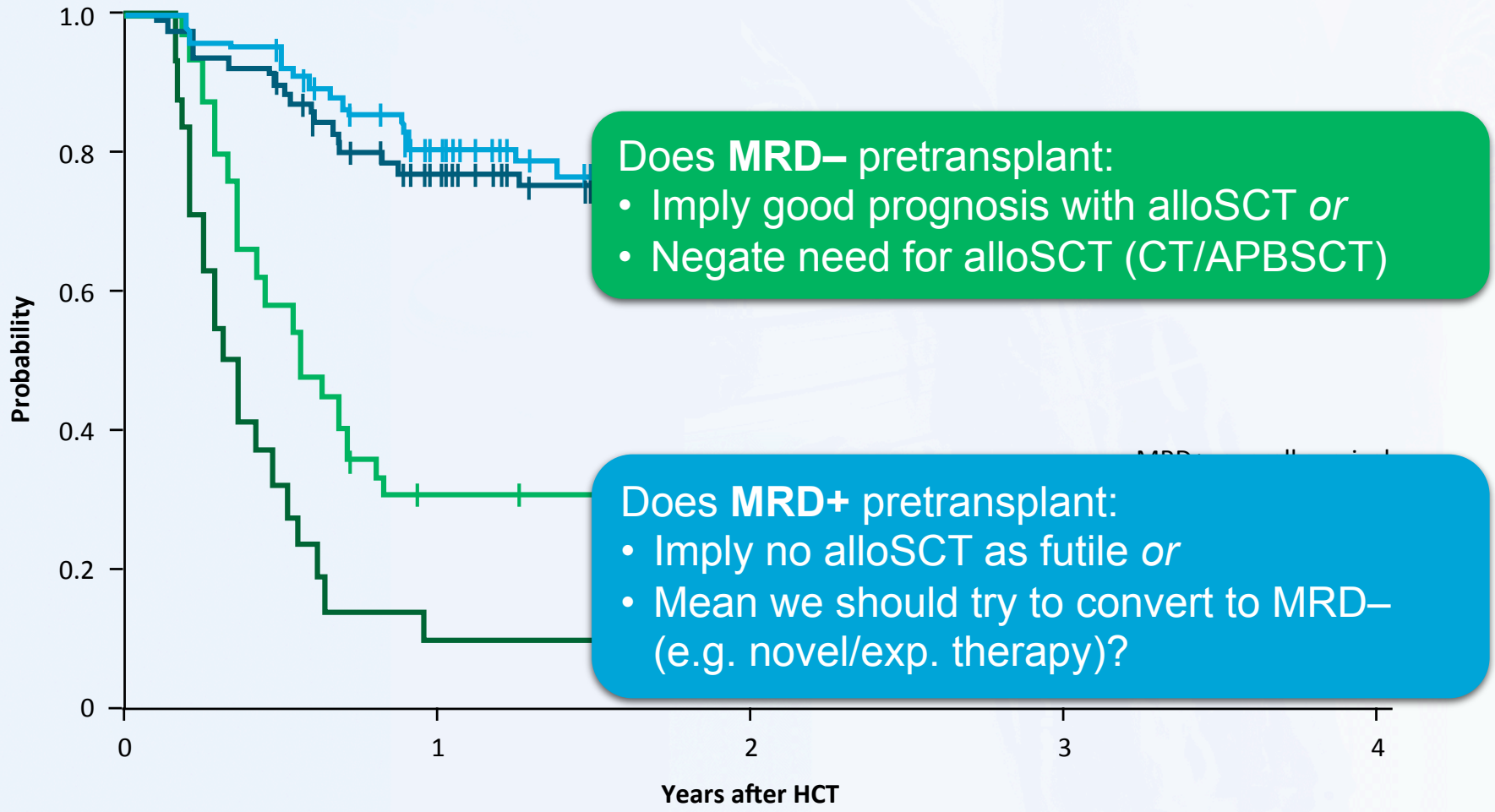


AML1310 (MRD– vs MRD+): OS



Challenge: Clinical implications of pre-transplant MRD

OS and DFS with MRD– vs MRD+ multi-parameter flow cytometry



Does **MRD–** pretransplant:
- Imply good prognosis with alloSCT *or*
- Negate need for alloSCT (CT/APBSCT)

Does **MRD+** pretransplant:
- Imply no alloSCT as futile *or*
- Mean we should try to convert to MRD– (e.g. novel/exp. therapy)?

Walter RB *et al. J Clin Oncol* 2011;29:1190–97

Conclusions

1. MRD status associated with outcome
2. MRD-driven interventions seem to make sense
3. MRD-orientated prospective clinical trials are warranted (to confirm MRD is also a predictor of outcome)

Questions

- How can we identify MRD– patients who will relapse?
  - Failure to predict relapse in 25–40% of MRD– patients
  - Role of LSC
- PCR vs Flow
  - PCR for LR-AML?
  - Flow for IR-AML?
- BM vs PB?
- Threshold and timing (variable according to protocols)
- Therapeutic implications (still to be extensively explored)
- Role of MRD pre-transplant
- Surrogate endpoint for development of new agents?

ELN MRD recommendation expert panel

Flow MRD

- Gerrit Jan Schuurhuis
- Paresh Vyas
- Brent Wood
- Wolfgang Kern
- Luca Maurillo
- Claude Preud'homme
- Francesco Buccisano
- Jeffrey Jorgensen
- Jacqueline Cloos
- Marie-Christine Bene
- Sylvie Freeman

Molecular MRD

- Christian Thiede
- Bert van de Reijden
- Michael Heuser
- Konstanze Döhner
- Torsten Haferlach

Clinical MRD

- Gert Ossenkoppele
- Robert Hills
- Gail Roboz
- Roland Walter
- Adriano Venditti