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AIL President: P. Toro
Coordinators: A.M. Carella, S. Amadori

MRD Driven Strategy in Adult ALL

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UNDER THE AUSPICES OF:
fondazione GIMEMA onlus
GITMO
SIE - Società Italiana di Ematologia

COI disclosures: Renato Bassan

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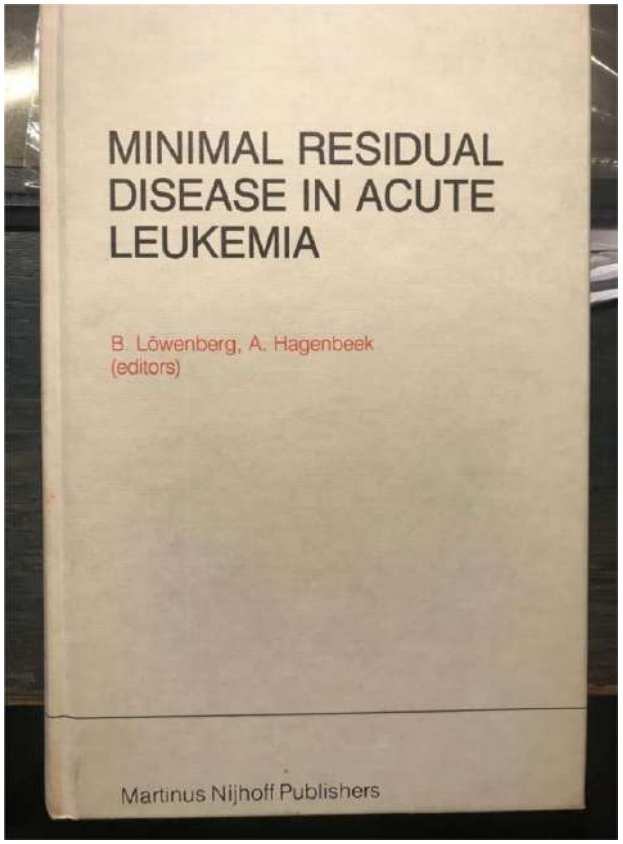
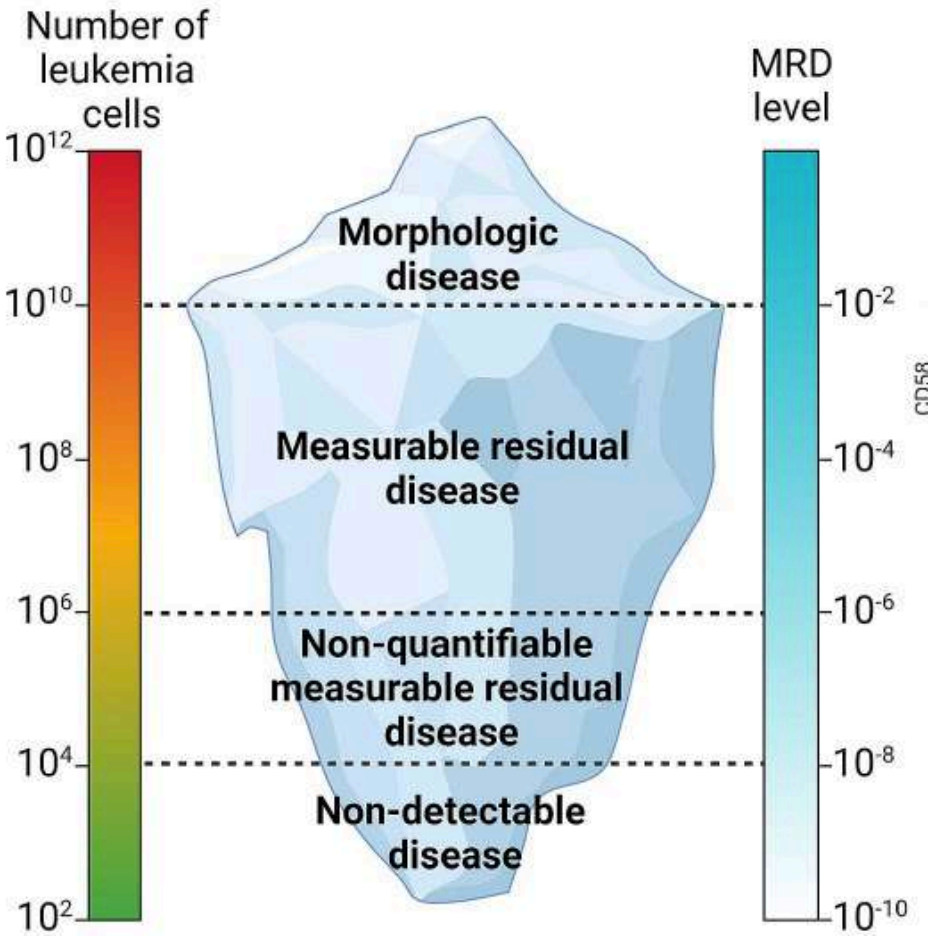
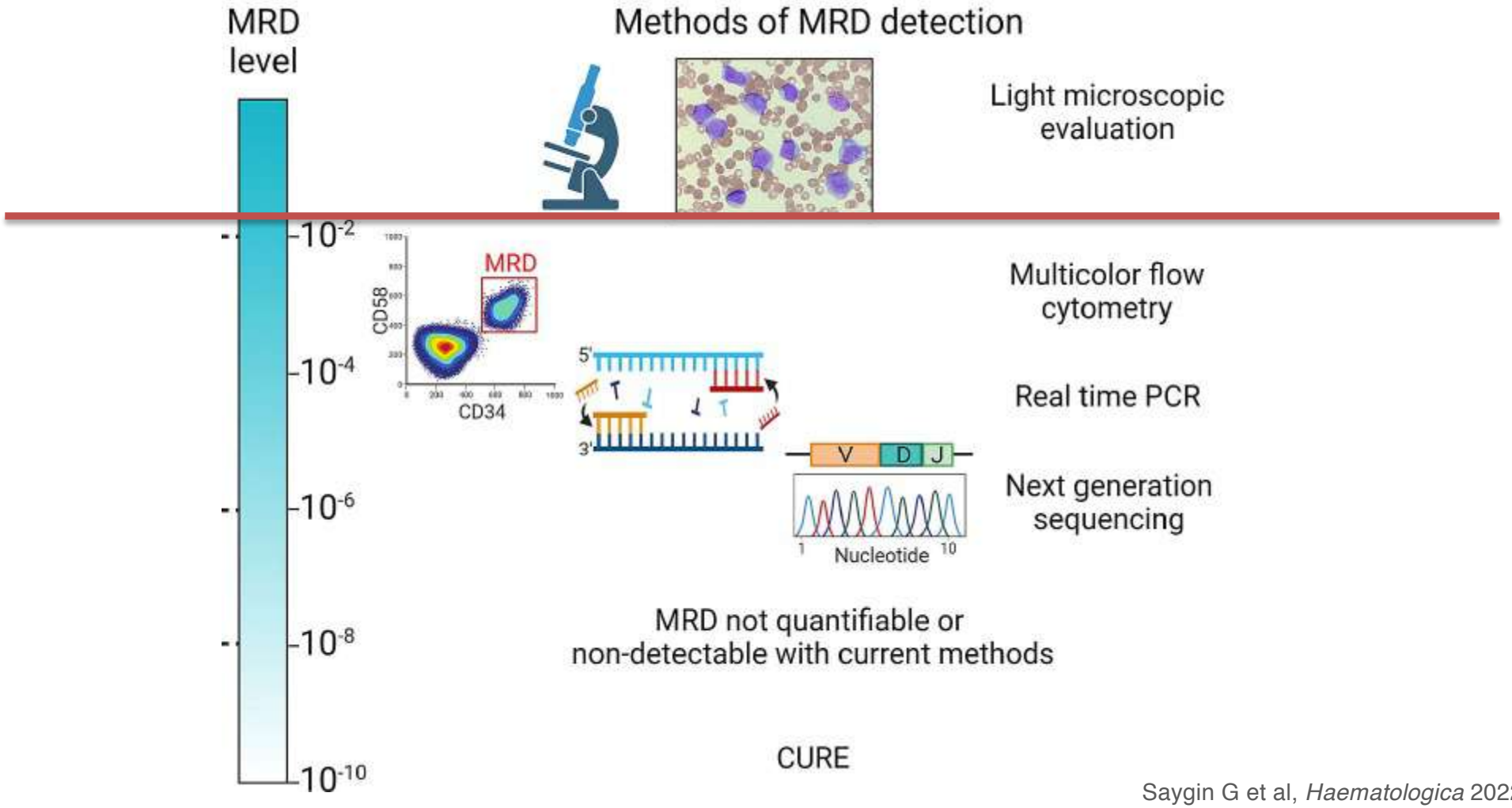
Minimal or measurable ?





Saygin G et al, *Haematologica* 2022

How to measure the minimal



Saygin G et al, *Haematologica* 2022

Pitfalls in MRD analysis

- **Patients without MRD study**
  - *No or poor BM cell sampling*
  - *Technical failure/no IG/TCR molecular probe (less concerns with gene rearrangements and MFC)*

STUDY (N)	CR (%)	Key MRD timepoint(s)	MRD evaluable
NILG 09/00 (N 304)[1]	258 (85)	wk 16-22	77.5 %
NILG 10/07 (N 163)[1]	142 (87)	wk 10-22	77 %
GMALL 07/03 (N 2061)[2]	1857 (90)	wk 16	53 % (2003-2009) 69 % (2010-2016)

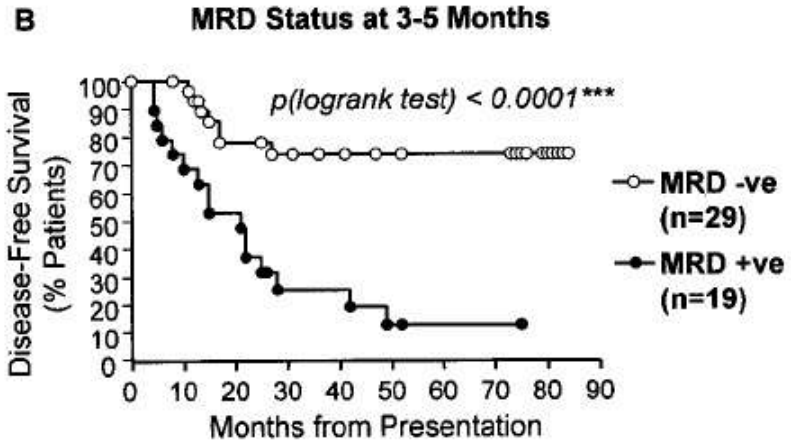
- **Maximum sensitivity 10^{-5}** (likely to improve)
  - *25% MRD negative patients will relapse*

  SUGGESTING, *«true» MRD negativity lower than commonly reported*

[1]Bassan R et al, *Clin Lymph Myeloma Leuk* 2017; [2]Goekbuget N et al, *Blood* 2017 [abstr]

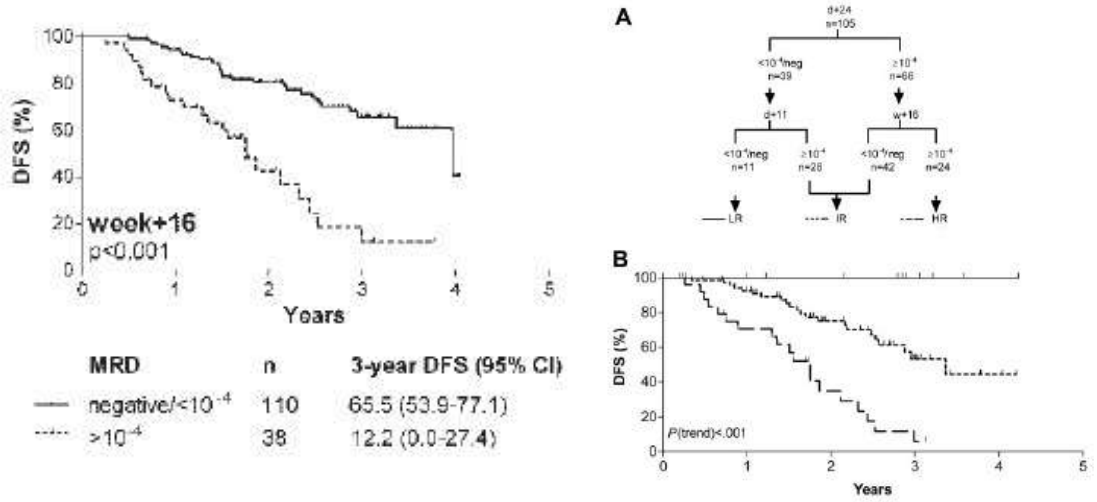
Descriptive studies - I

UKALL XII
B-ALL patients
(cumulative chemo/SCT)



Mortuza FY et al, *J Clin Oncol* 2002

GMALL 05-06
Standard risk B/T-ALL patients
(*chemo – 1-year maintenance)*

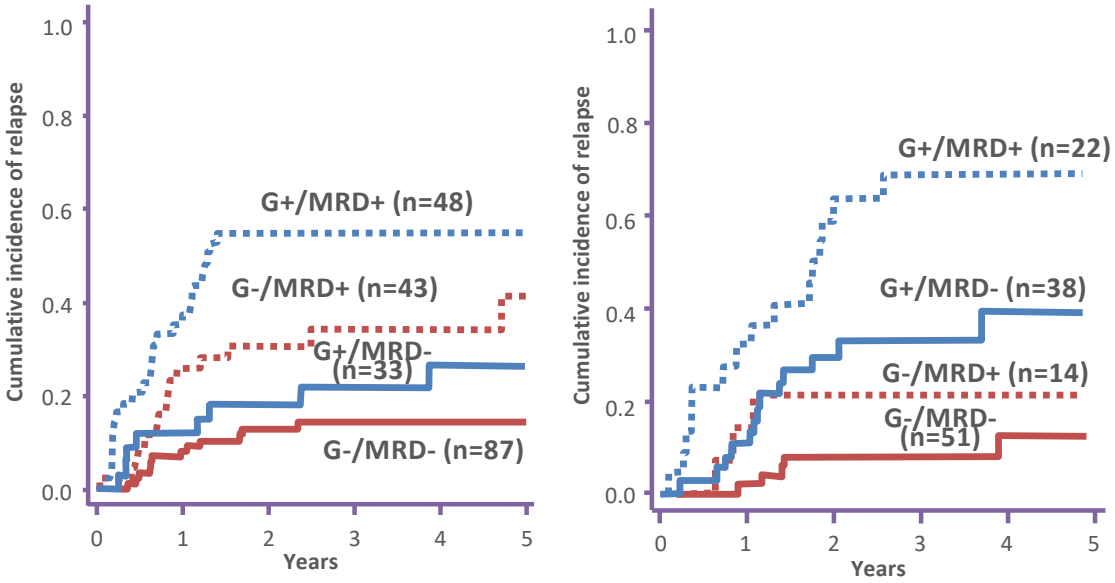


High relapse rate with 'limited' chemo

Bruggemann M et al, *Blood* 2006

Descriptive studies - II

GRAALL 2003-2005

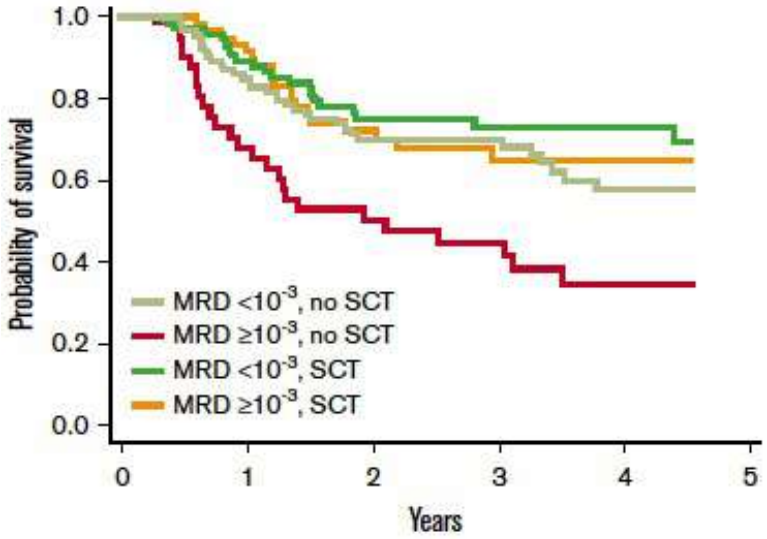


Four gene prognostic classifier (adverse, G+) and MRD

B-ALL: *MLL* rearrangement and/or *IKZF1* deletion

T-ALL: Unmutated *NOTCH/FBXW7* and/or *RAS/PTEN* abnormalities

Beldjord K et al, *Blood* 2014

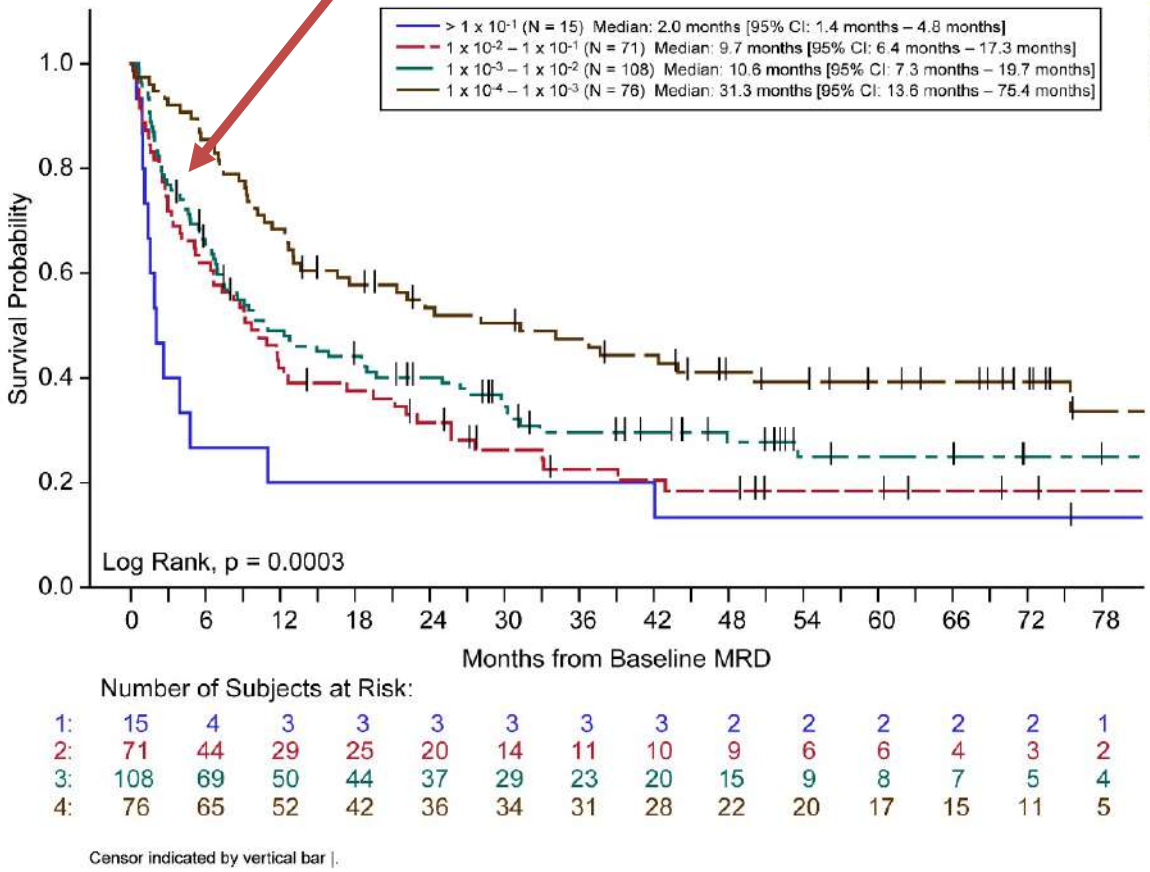


Allogeneic SCT vs. MRD in HR ALL

Dhédin N et al, *Blood* 2015

Quantitative risk

Risk of very early relapse in allo-SCT eligible patients



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HEMATOLOGY
2019, VOL. 24, NO. 1, 337–348
https://doi.org/10.1080/16078454.2019.1567654

Taylor & Francis
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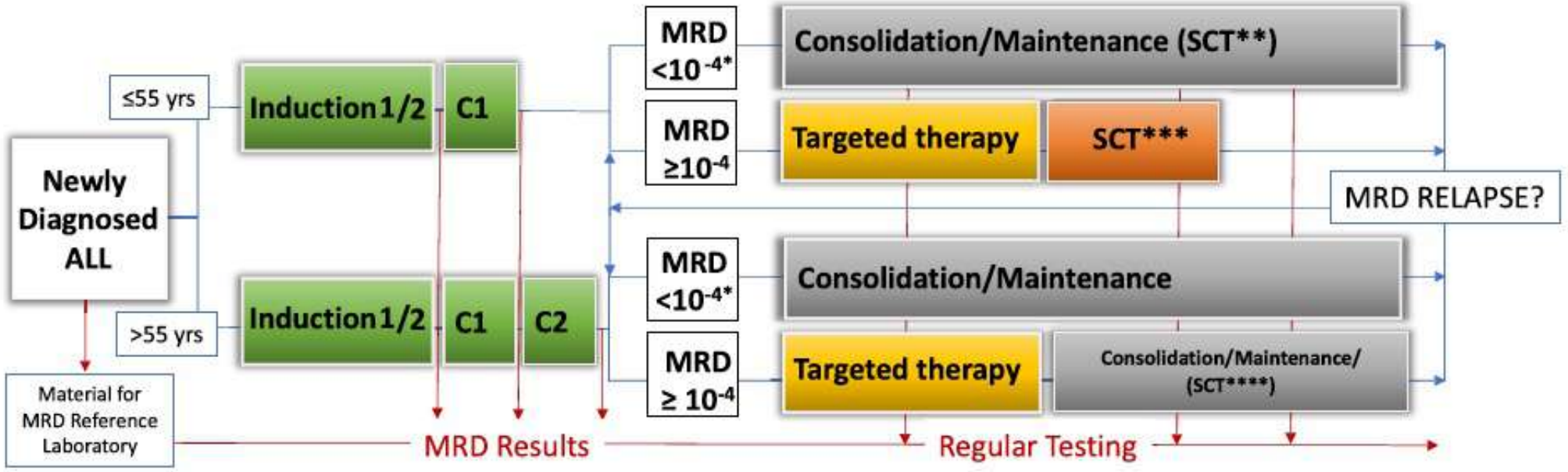
Minimal residual disease level predicts outcome in adults with Ph-negative B-precursor acute lymphoblastic leukemia

Nicola Gökbuget[a], Hervé Dombret[b], Sebastian Giebel[c], Monika Bruggemann[d], Michael Doubek[e], Robin Foà[f], Dieter Hoelzer[a], Christopher Kim[g], Giovanni Martinelli[h], Elena Parovichnikova[i], Alessandro Rambaldi[j], Josep-Maria Ribera[k], Marieke Schoonen[l], Julia M. Stieglmaier[m], Gerhard Zugmaier[m] and Renato Bassan[n]

In the clinics: to take decisions



* In case of low-positive MRD more frequent controls
** SCT independent of MRD in defined high-risk patients; compatible donor; age adapted conditioning
*** compatible donor; age adapted conditioning
**** SCT in selected points depending on donor availability and general condition

Figure 1. Flow of MRD surveillance and treatment decisions (GMALL strategy).

Goekbuget N, *ASH* Educational 2021

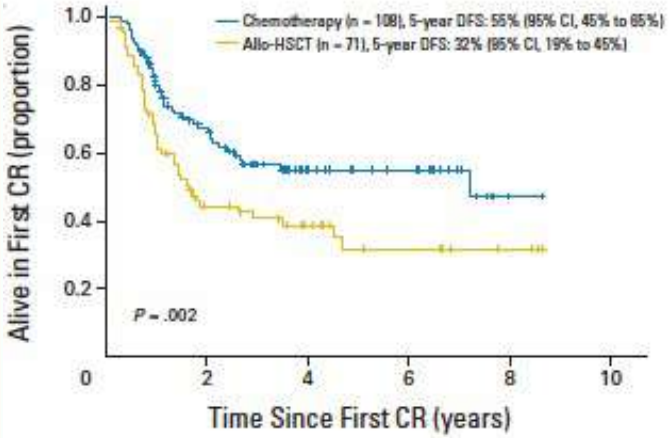
Interventional studies - I

PETHEMA ALL-AR-03 and HR-11

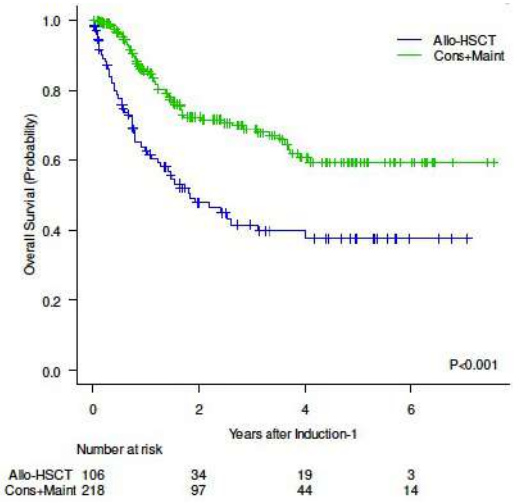
HR patients

RISK ORIENTED:

d14 BM blasts and MRD



MRD

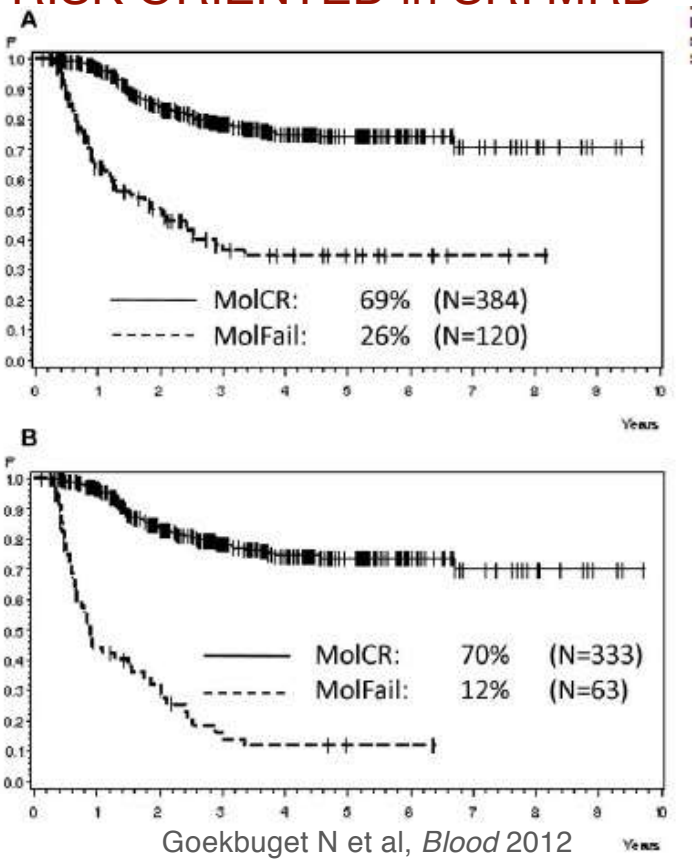


Ribera JM et al, *J Clin Oncol* 2014 and *Blood* 2020

GMALL 06-07

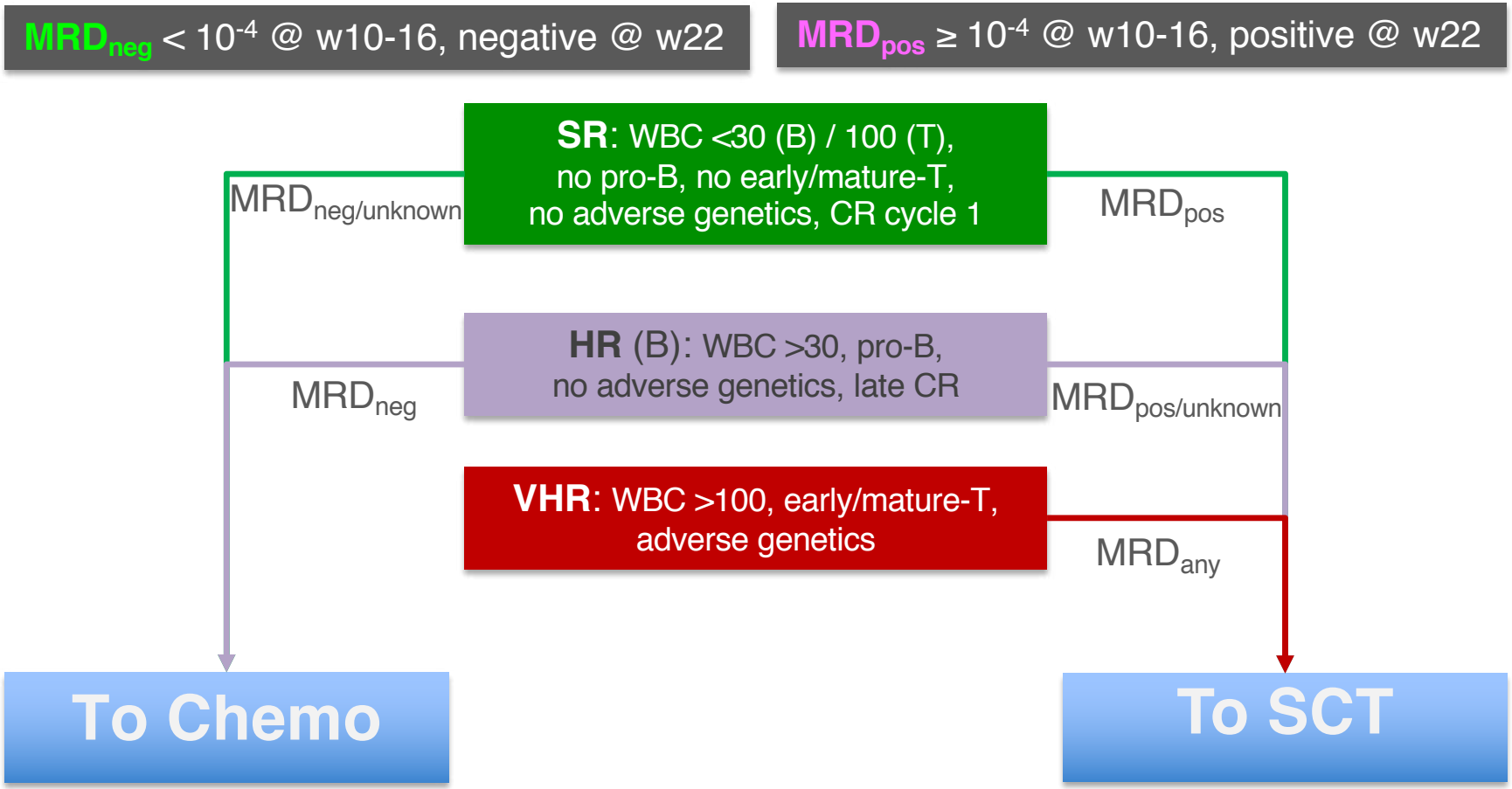
SR B/T-ALL patients (HR to allo-SCT)

RISK ORIENTED in SR: MRD



Goekbuget N et al, *Blood* 2012

NILG and GIMEMA strategy



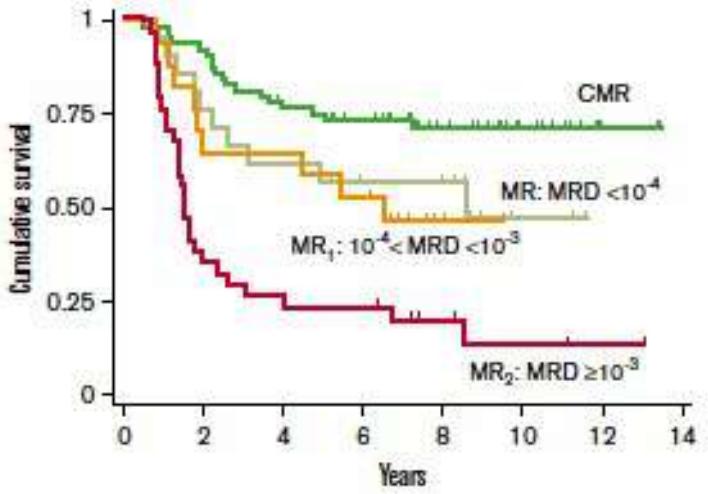
Interventional studies - II

NILG 09/00 and 10/07; GIMEMA LAL 1913

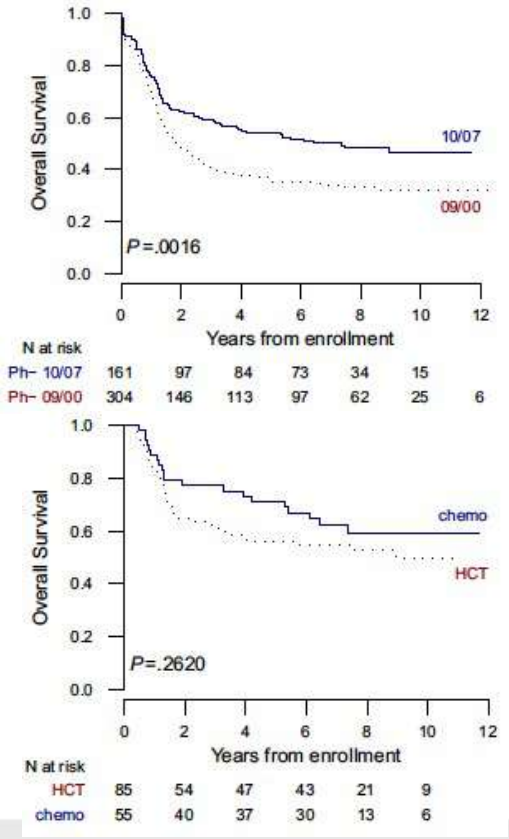
Age 18-65, SR and HR patients (VHR to allo-SCT)

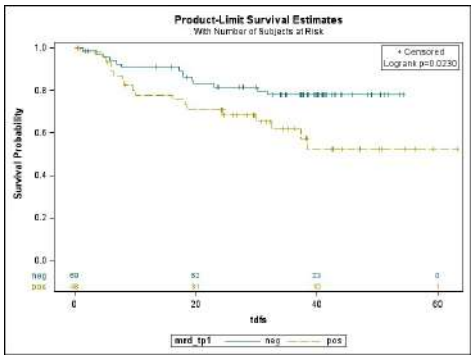
RISK ORIENTED: MRD

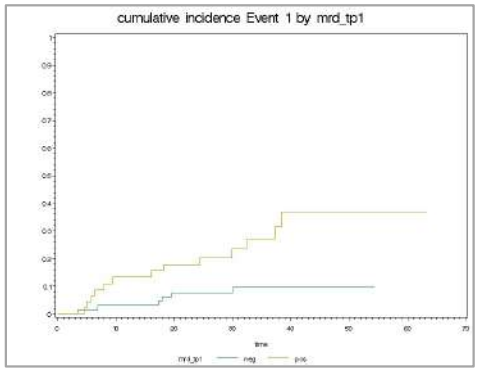
58.6% with end of induction MRD <10^{-4}



Bassan R et al, *Blood* 2009; *Blood Cancer J* 2014 and 2019







Bassan R et al, *EHA* 2022

Improving risk stratification - II

Prognostic Index$_{UKALL}$
T(MRD*)×-0.218
+ **CYTO-GR**×-0.440
+ **CYTO-HR**×1.066
+ **log(WCC*)**×0.138

**continuous risk variables*

Relapse 42% → **MAC**

EFS 31% → **RIC**

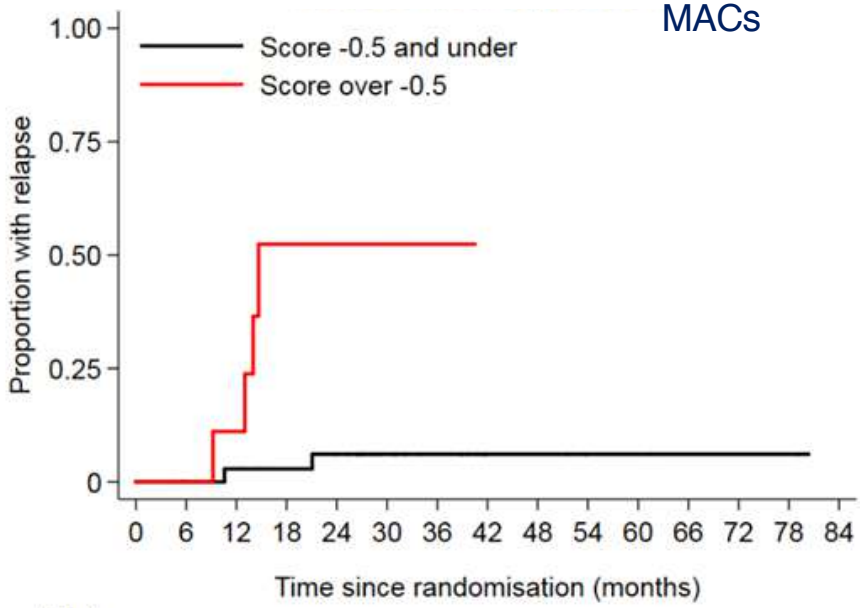
EFS 90% → **chemo**

Selected examples of how PI$_{UKALL}$ can be used to identify patients on the same treatment pathway who have differential outcomes			
	Hazard ratio (95% CI)	3 years rates (95% CI)	p value
Risk of relapse after myeloablative alloSCT (n=53)			
PI2 score ≤ -1.5	1	5% (1-19)	0.006
PI2 score > -1.5	11.1 (2-62)	42% (18-78)	
Event free survival (EFS) after RIC alloSCT (n=105)			
PI2 score ≤ -2.0	1	62% (45-75)	0.004
PI2 score > -2.0	2.3 (1.3-4.1)	31% (17-46)	
EFS of standard risk patients after maintenance chemotherapy (n=51)			
PI1 score ≤ -2.25	1	90% (66-98)	0.041
PI1 score > -2.25	5.1 (1.1-24.3)	71% (45-86)	

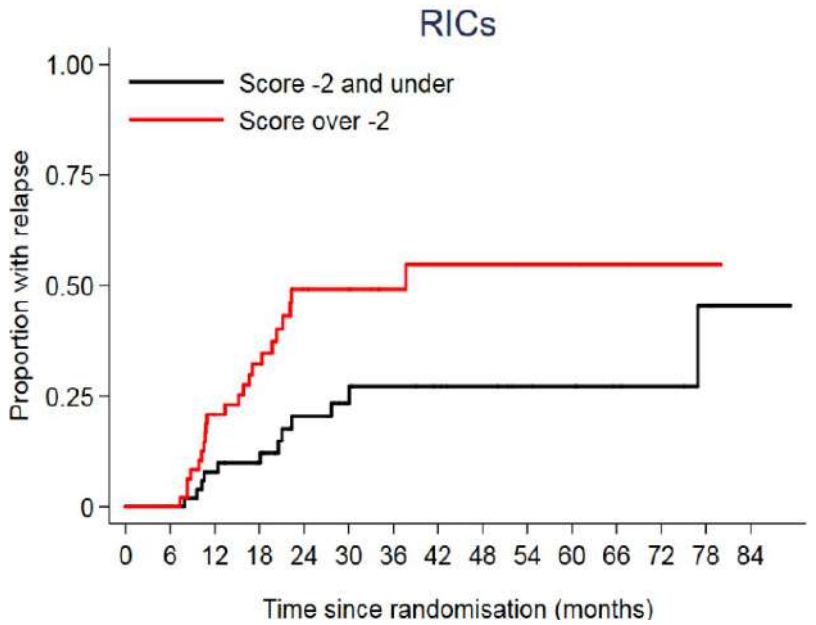
Moorman A, et al. HemaSphere 2019;3:748–9 (abstr #S1621).

PI_{UKALL} vs. SCT

MACs



RICs

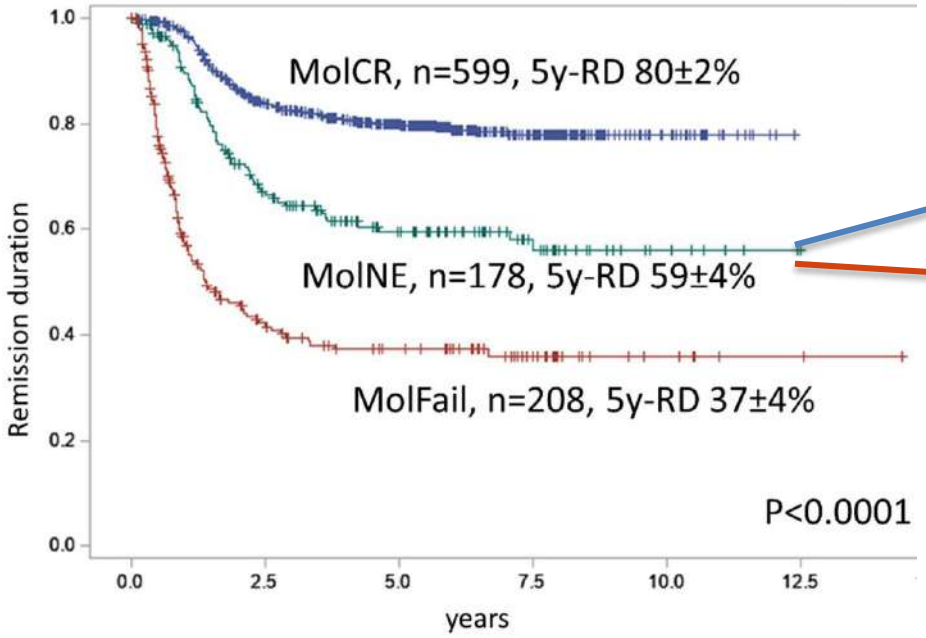


PI2 score	P-value	Relapse rate (3-year)	EFS (3-year)
≤-0.5		6% (2–22)	65% (46–79)
>-0.5	0.011	52% (23–88)	38% (10–66)

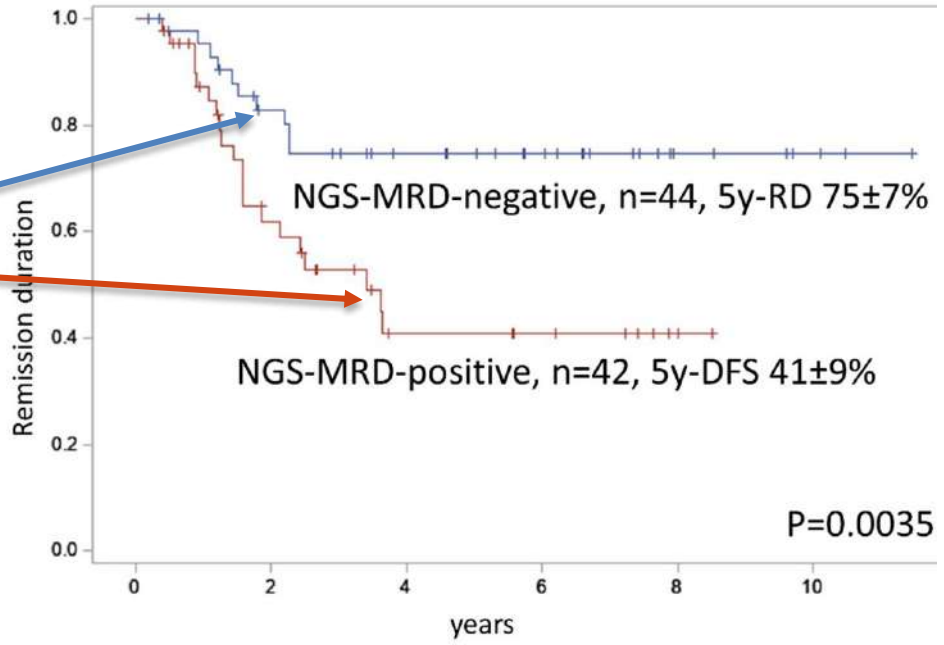
PI2 score	p value	Relapse rate (3 yr)	EFS (3 yr)
≤-2		27% (16-45)	62% (45-75)
>-2	0.011	49% (35-65)	31% (17-46)

Improving MRD analysis: NGS

RQ-PCR



NGS



Uncertain prognostic effects of molecular MRD Not Evaluable (**MolNE**) by RQ-PCR with probe sensitivity at least 10^{-4}

- **MolCR**: negative
- **MolFail**: $\geq 10^{-4}$

Kotrova M et al, *Blood Adv* 2022

Summing up

- **MRD** as key prognostic factor and determinant of allo-SCT choice

- **MRD** interacts with other (WBC / GENETICS)
  toward integrated risk models
- **MRD** analysis can be improved (NGS, ddPCR)

- **MRD is a therapeutic target and supports progress in ALL therapy**
  – New MRD-oriented therapies

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