3rd Cuneo City ImmunoTherapy Conference (CCITC)

Immunotherapy in Hematological Malignancies 2023

CUNEO
May 18-20, 2023
Spazio incontri Fondazione CRC

The extra-value of uMRD in the allogeneic transplantation

Sara Galimberti – Hematology of Pisa

Organized by Prof. Massimo Massaia, SC Ematologia AO S.Croce e Carle, Cuneo, Italy
and Centro Interdipartimentale di Ricerca in Biologia Molecolare (CIRBM), Torino, Italy

DICHIARAZIONE

Relatore: SARA GALIMBERTI

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(JAZZ)**
- Partecipazione ad Advisory Board **(NOVARTIS, ASTRA ZENECA, JAZZ)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

MRD today

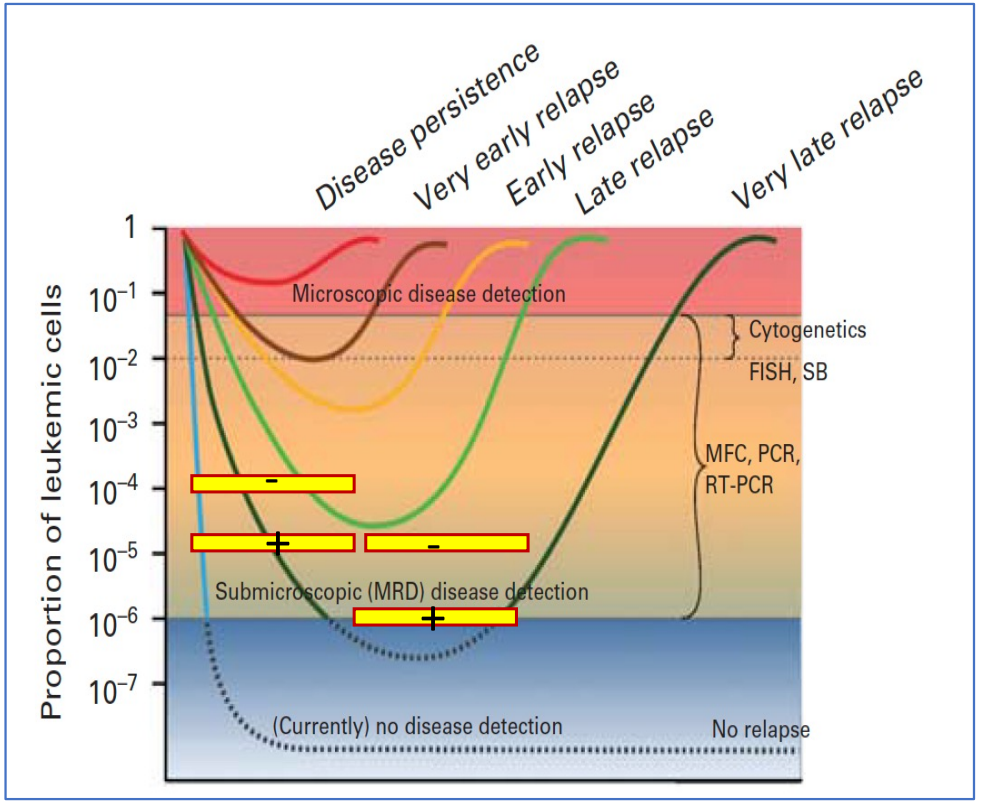
Undetectable

NOT negative!!!

«Measurable»

NOT «minimal»

residual disease



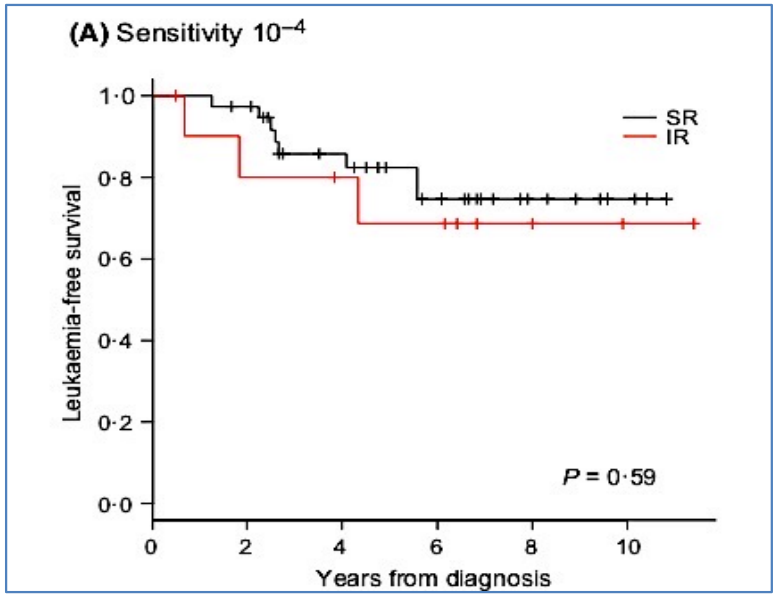
Buckley SA, BMT 2012

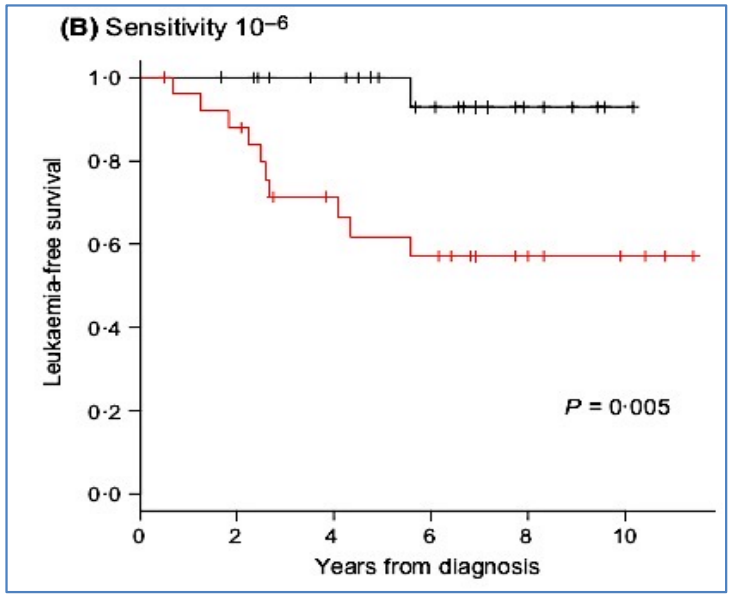
SUITABLE MARKERS

Disease	marker	
MDS/AML	Fusion genes, phenotype, mutations	Chimerism
ALL	Fusion genes, clonality, phenotype, mutations	
MM	Phenotype, clonality	
CLL/NHL	Phenotype, clonality	
sensitivity	$10^{-4}/10^{-6}$	10^{-2}

NGS & 10^{-6} in children ALL

higher sensitivity has a higher prognostic impact



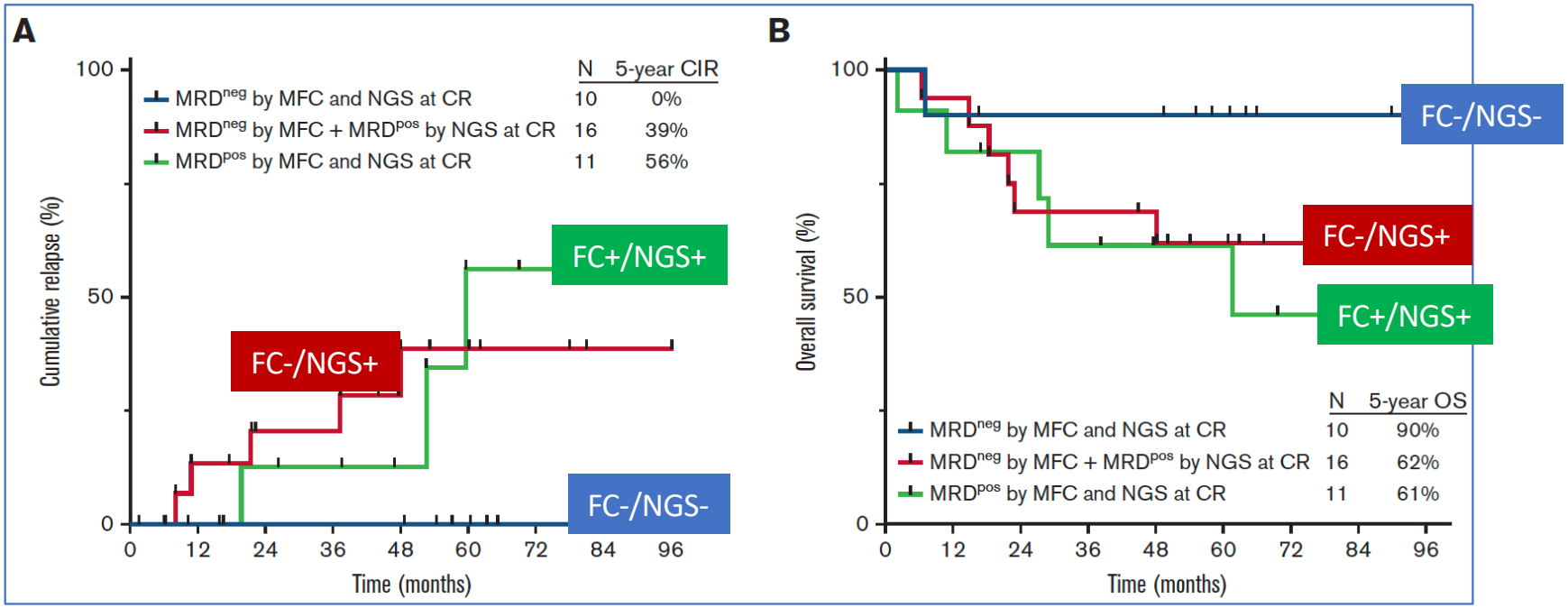


Sekiya Y, BJH 2016

NGS 10^{-6} vs FC 10^{-4} (AML)

NGS is a better prognostic factor than FC

74 AML pts
46% FC- NGS+



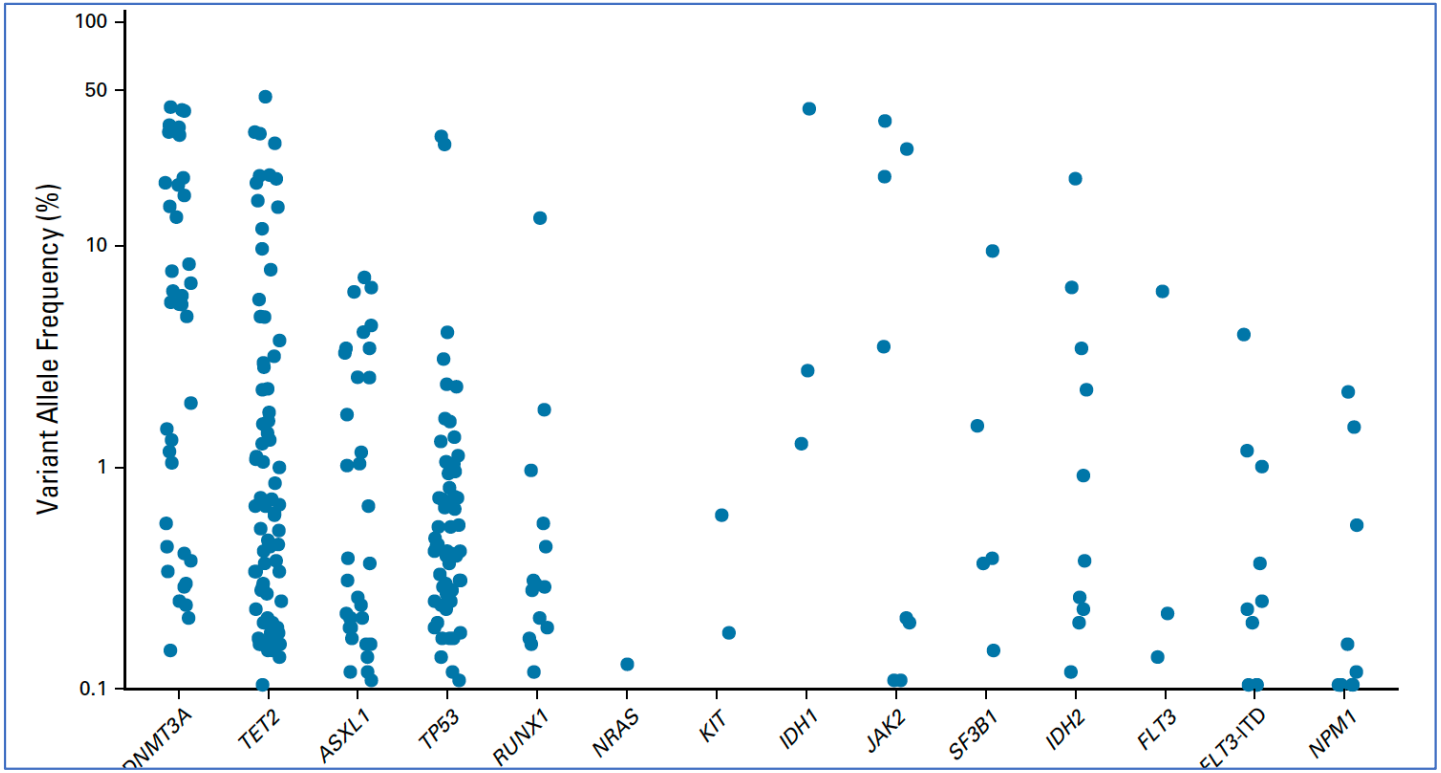
Short NJ, Blood Adv 2022

NGS: DNA amount

95% PROBABILITY OF **DETECTING 5 READS** OF THE TARGET SEQUENCE				
SENSITIVITY	DNA PER REPLICATE	# REPLICATES	READ DEPTH PER REPLICATE	# OF DIFFERENT SAMPLES FOR CLONOTYPE TRACKING PER RUN
$1x10^{-4}$	0.250 µg 0.500 µg	1 replicate of 0.250 µg 1 replicate of 0.500 µg	>310,000 >190,000	21 samples per run plus 3 controls
$1x10^{-5}$	1 µg	3 replicates of 1 µg each	>1,080,000	7 samples per run* plus 3 controls or
		4 replicates of 1 µg each	>820,000	5 samples per run plus 3 controls
$1x10^{-6}$	2.5 µg	9 replicates of 2.5 µg each	>4,000,000	1 sample over 2 runs**

AML: mutational MRD

1/3 of AML pts are mutated @alloSCT



Hourigan CS, JCO 2019

Mutational NGS in AML

National Comprehensive Cancer Network®

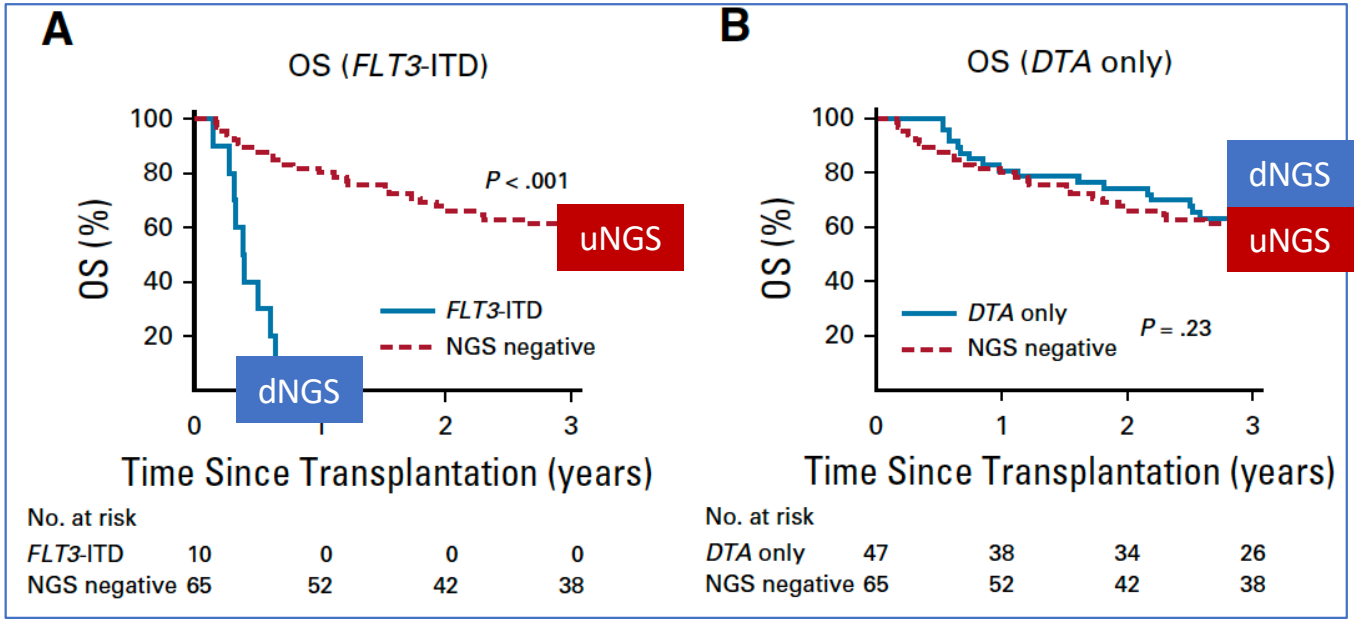
NCCN Guidelines Version 3.2023
Acute Myeloid Leukemia (Age ≥18 years)

MEASURABLE (MINIMAL) RESIDUAL DISEASE ASSESSMENT

- NGS–based assays is not routinely used, as the sensitivity of PCR-based assays and flow cytometry is superior to what is achieved by NGS;
- Mutations associated with CHIP and aging (DNMT3A, TET2, ASXL1) are not considered reliable markers for MRD.

AML: mutational MRD

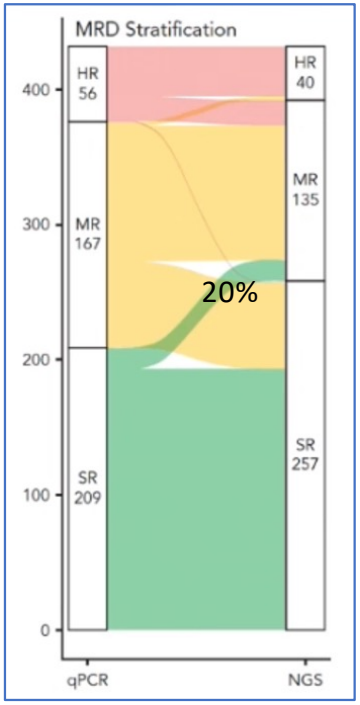
FLT3 mutations are worse
DTA = DNMT3A, TET2, ASXL1



Hourigan CS, JCO 2019

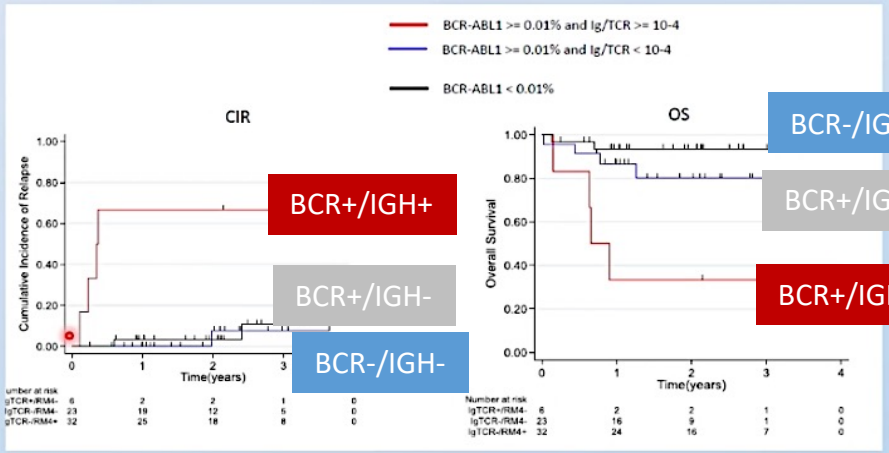
Clonality NGS vs ASO-PCR in childhood ALL

NGS allows a better risk stratification



Svaton, Blood 2023

Clonality NGS vs BCR::ABL1



Ig/TCR MRD revealed residual BCR-ABL1 clonal hematopoiesis in ~ 40% of adult Ph+ ALL

- BCR-ABL1 clonal hematopoiesis is not associated with a higher risk of relapse in the GRAAPH-2014 protocol
- Strong impact on interpretation of BCR-ABL1 follow-up results
- IG/TCR MRD maybe a better predictor of outcome
- Long-term follow-up will be necessary to inform optimal clinical management in those patients

Slide courtesy of Pr E.Clappier

Chimerism vs QT-PCR

Comparison chimerism and QT-PCR
No significant differences between methods

PCR+ before relapse = 55% in Ph'-, 33% in Ph'+, 67% in T-ALL

Not full chimerism before relapse = 55% in Ph'-, 50% in Ph'+, 50% in T-ALL

Wethmar K, BMT 2020

AGENDA

1. How assess MRD?
2. When?
3. Why?

@alloSCT

After alloSCT

AML: meta-analysis (<2017)

Pre-transplant MRD+ is associated with worse LFS, OS, RI

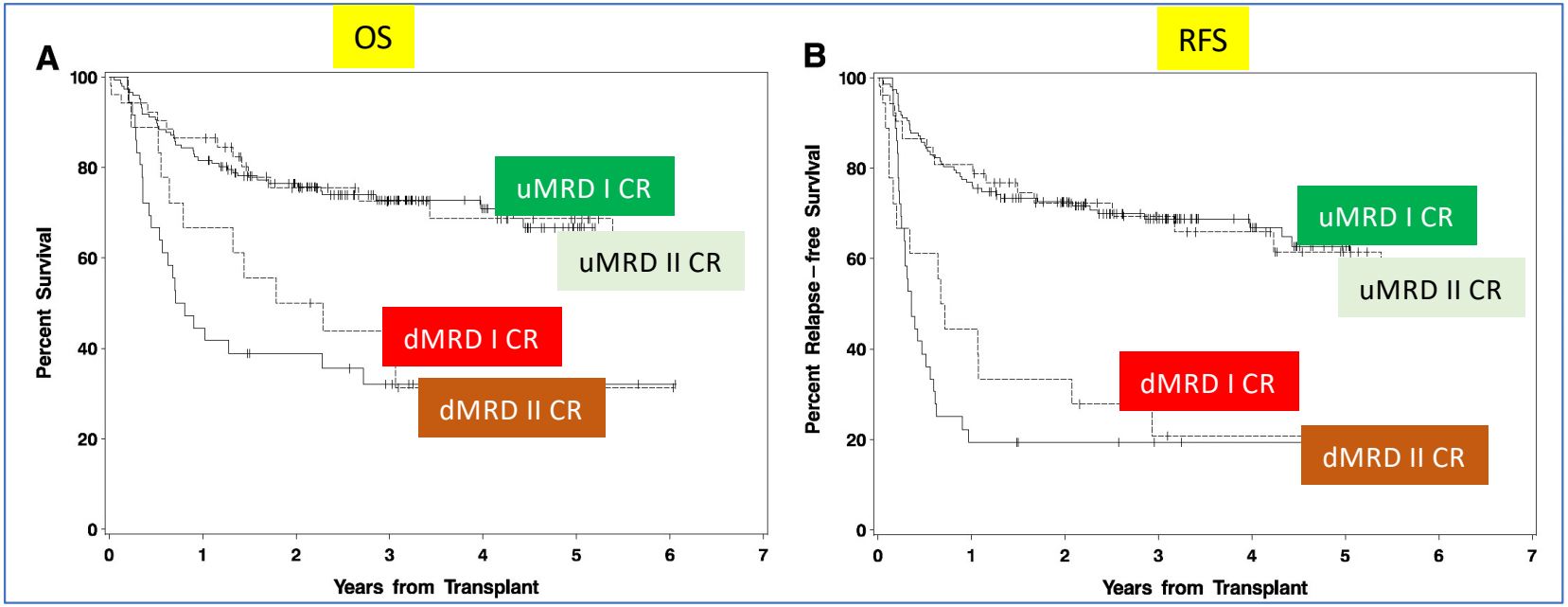
Independently from the method employed, age, conditioning regimen

Subset	All Studies OS	LFS	CIR	NRM
Method				
MFC	1.98 [1.26-3.10] ■	2.41 [1.36-4.29] ■	2.81 [1.94-4.08] □	1.11 [0.63-1.95] □
PCR	5.25 [3.08-8.95] □	5.80 [3.57-9.42] □	9.53 [4.48-20.29] □	1.51 [0.57-4.00] □
Combination	1.86 [1.25-2.77] □	1.79 [1.06-3.01] ■	3.73 [1.94-7.18] □	1.15 [0.57-2.33] □
Median age				
0-20	3.12 [1.29-7.57] ■	3.33 [0.95-11.6] ■	3.57 [0.67-18.91] ■	1.13 [0.52-2.4] □
21-40	2.60 [1.36-4.99] ■	3.02 [1.27-7.16] ■	5.13 [2.37-9.64] □	--
>40	2.25 [1.47-3.47] ■	2.69 [1.64-4.42] ■	3.33 [2.18-5.11] ■	1.23 [0.77-1.97] □
Conditioning				
>75% MA	2.64 [1.77-3.93] ■	2.86 [1.80-4.55] ■	4.21 [2.70-6.58] ■	1.39 [0.94-2.07] □
0% MA	2.05 [0.78-5.39] ■	2.09 [1.33-3.29] □	3.23 [1.88-5.53] □	0.58 [0.22-1.52] □

Buckley SA, Hematologica 2017

AML: MRD @alloSCT (FC)

MRD status (FC) impacts on OS and PFS, both in I CR and in II CR

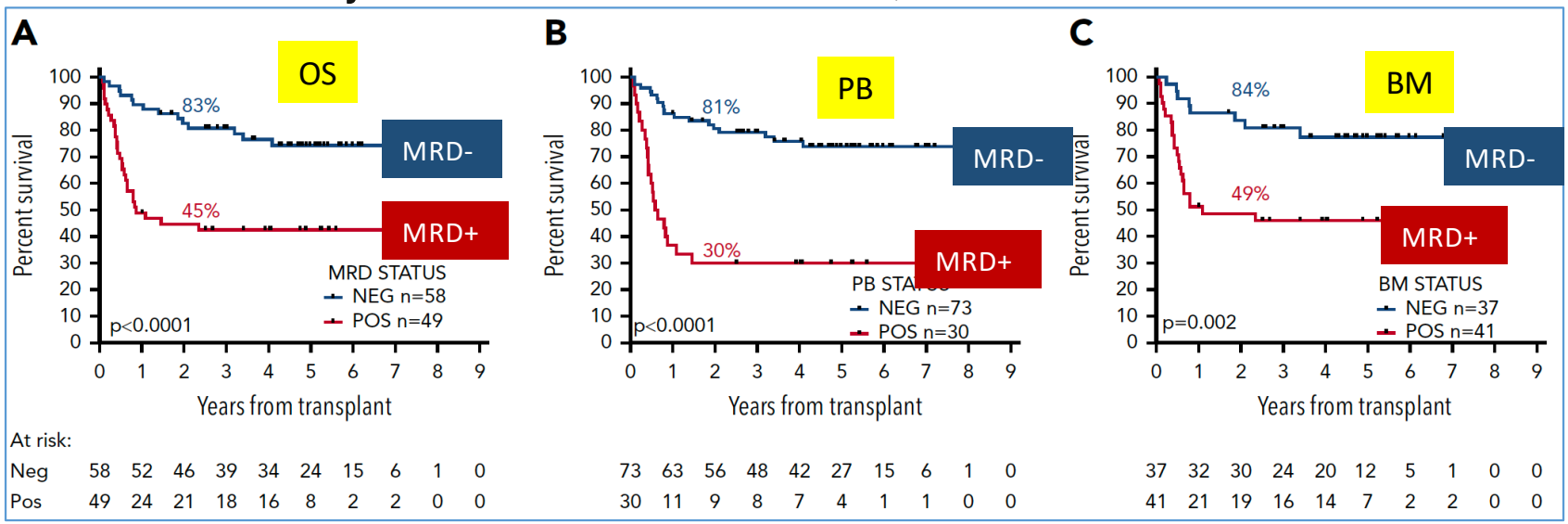


Walter RB, Blood 2013

AML: NPM1-mutated @alloSCT (PCR)

107 pts NPM1-mutated; QT-PCR, cut off 200 copies/10^{-5} ABL1 copies

OS is influenced by MRD status @alloSCT, both on BM and on PB



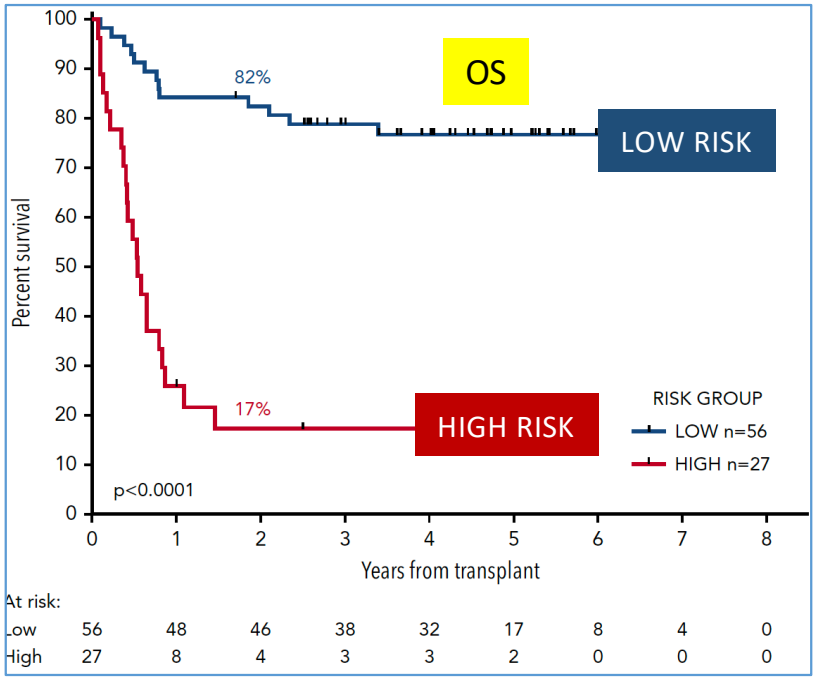
Dillon R, Blood 2020

NPM1-mutated ± FLT3-ITD @alloSCT (PCR)

LOW: NPM1 < $200/10^5$ ABL1 copies on PB or <$1000/10^5$ ABL1 on BM

HIGH RISK: NPM1+, NPM1 low/ FLT3-mutated

LOW RISK: NPM1-, NPM1 low/FLT3 wt



Dillon R, Blood 2020

ALL: MRD @alloSCT (EBMT series)

2780 pts who underwent alloSCT in CR between 2000 and 2017

76% TBI, 24% chemo

11 centers FC + 11 centers ASO-PCR, cut off 10^{-4}

35% MRD+

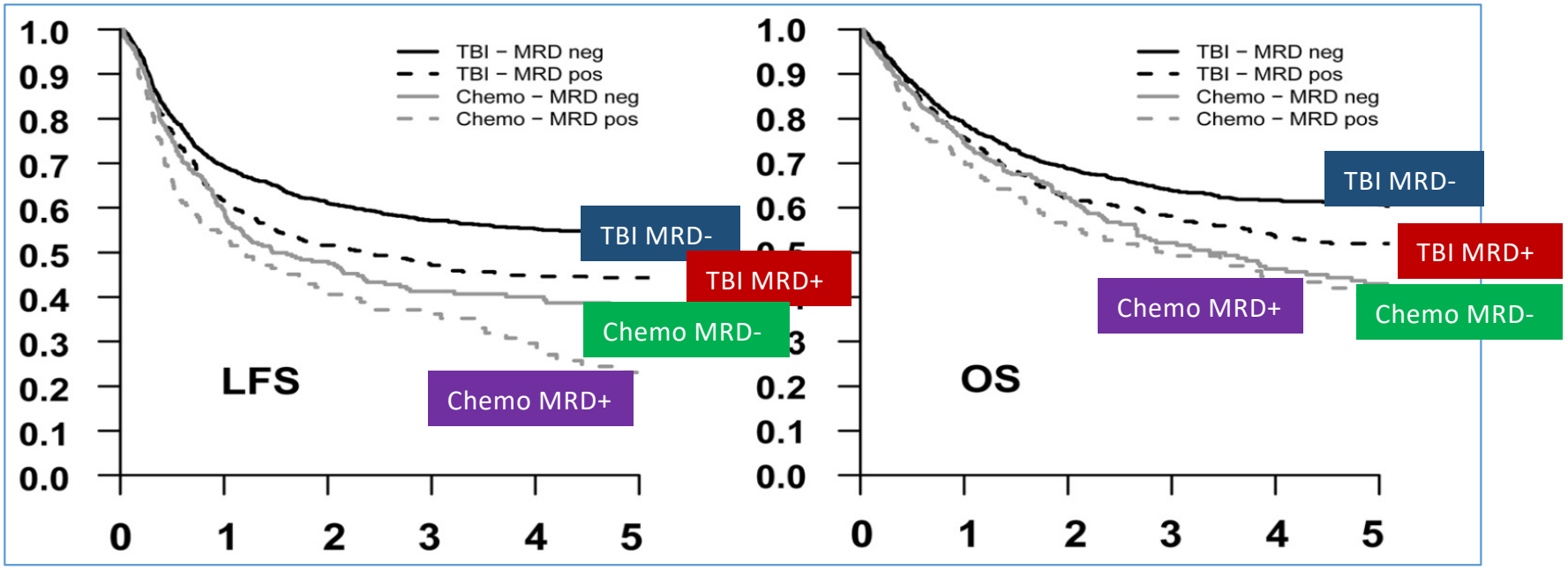
Ph' + = 66%

Ph' - = 44%

Pavlu J, J Hematol & Oncol 2019

ALL: MRD @alloSCT (EBMT series)

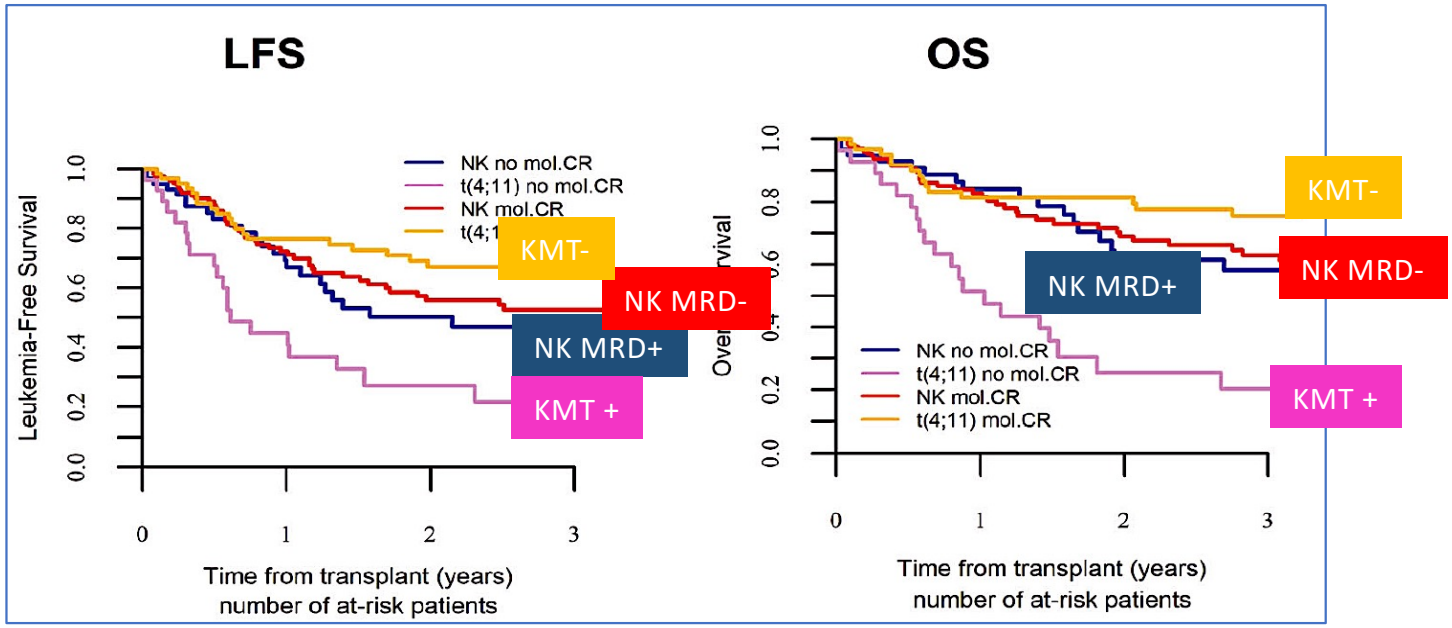
uMRD offers a significant advantage in OS and LFS, especially with TBI



Pavlu J, J Hematol & Oncol 2019

ALL: t(4;11) (KMT2A::AFF1) @alloSCT

Pts uMRD have a similar outcome to uMRD pts with normal karyotype; among patients with MRD+, outcome is worse than NK pts.



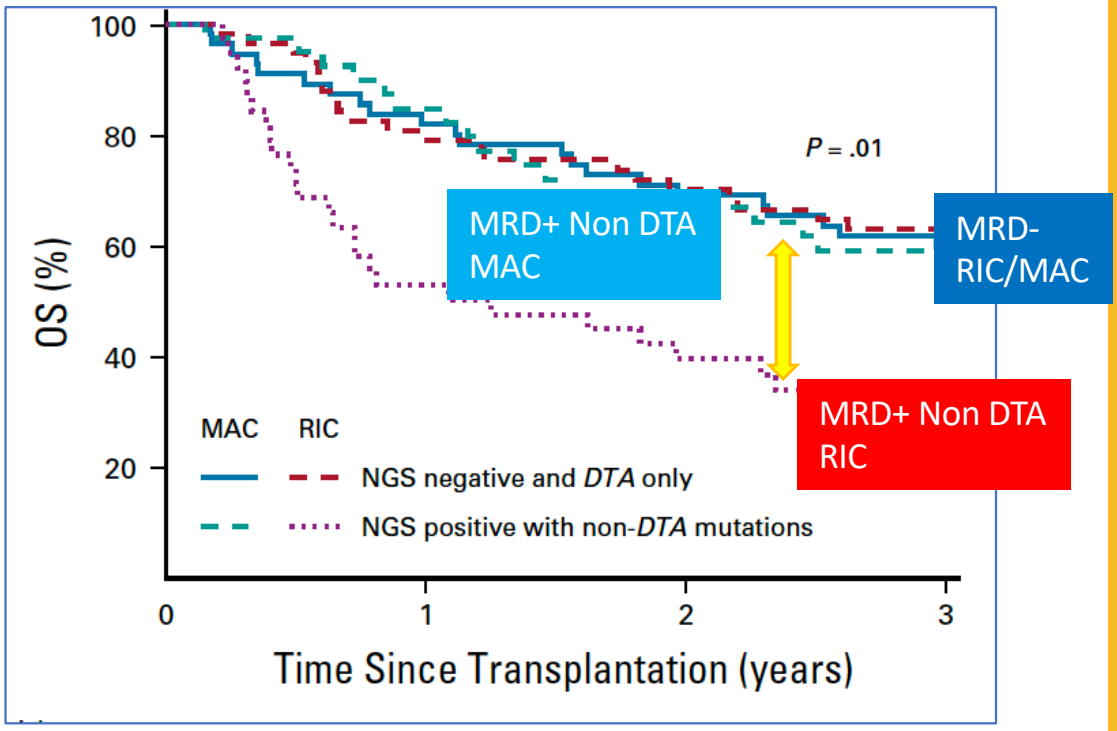
Esteve J, Leukemia 2021

AML: MAC for MRD+ non DTA

the mutational type is prognostically relevant

DTA = DNMT3A, TET2, ASXL1

In non DTA MRD+, MAC is better
In uMRD, MAC and RIC are equal

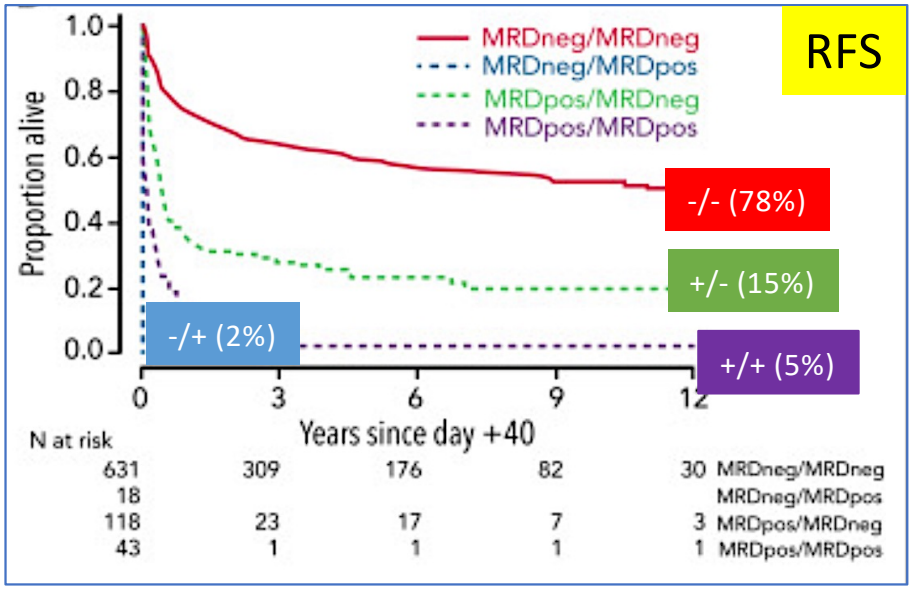


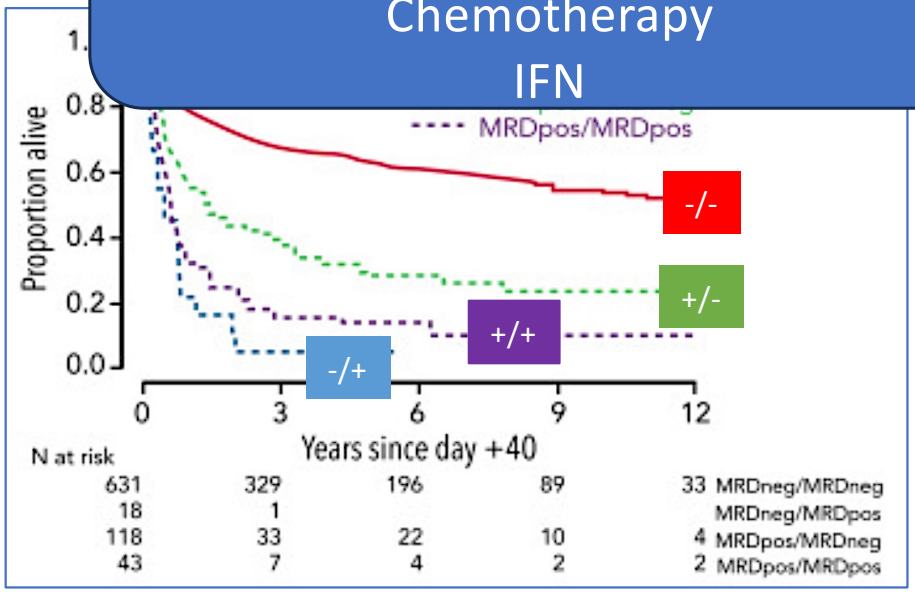
Hourigan CS, JCO 2019

AML after alloSCT: MRD kinetics (FC @+40)

810 pts: 515 MAC, 295 non-MAC, 590 HLA-
The MRD status @+ 40 days is prognostical

IS tapering
DLI
TKI
Chemotherapy
IFN



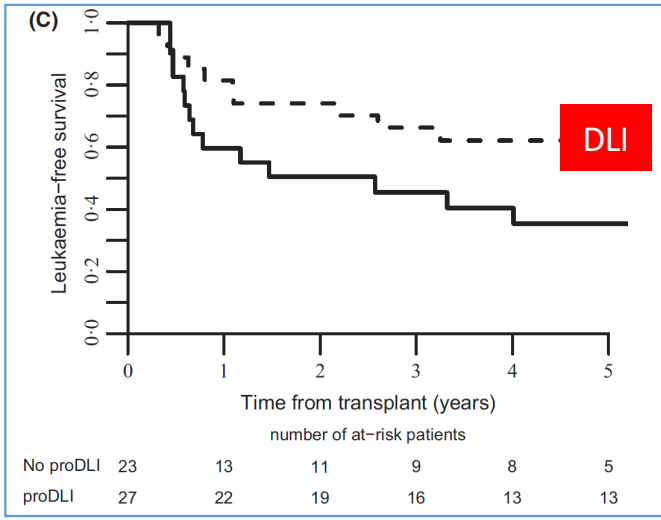


Paras G, Blood 2022

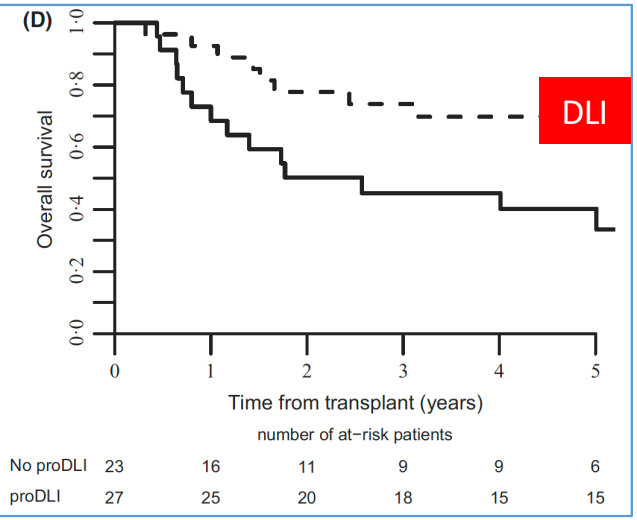
MRD & DLI - prophylactic

DLI increases LFS and OS in high-risk pts with AML or ALL
GVHD all grades 28%, grade 3-4 4.5%

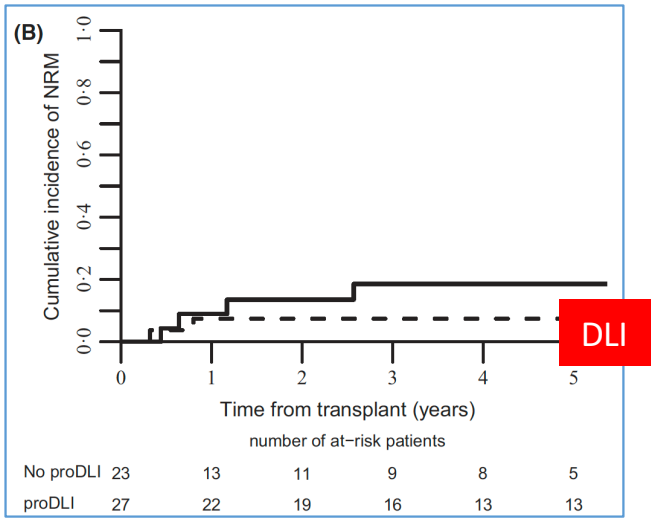
LFS



OS



NRM



Schmid C, BJH 2018

MRD & DLI – pre-emptive

318 pts transplanted for AML or ALL underwent to DLI
Pre-emptive for mixed chimerism, MRD+

MRD decreased in 71% of pts

Chimerism inceased in 70% of pts

6% of pts died for GVHD

Schmid C, BMT 2022

Our experience: gilteritinib at re-appearance of FLT3-ITD

F, 56 y, bone marrow donor, breast cancer
2020: tx-AML with complex karyotype
CPX-351 induction and consolidation
September 2020: alloSCT
January 2021: FLT3-ITD detected, WT1 increased, blasts 5% – DLIs +GILTERITINIB

January 2023

FLT3-ITD undetctable (GeneScan PCR)

Chimerism 99.5%

WT1 in the normal range

Our experience: ponatinib for Ph'+ ALL T315I-mutated

Female, 56 y	Treatment	Response	NGS
2014 –AP-CML	Dasatinib (reduced dose)	MR3	
2016	BC- ALL	PD	T315I
2016-2018	HyperCVAD+ ponatinib, blinatumumab, alloBMT	MR5 uMRD	T315I not detectable
2018	ponatinib 30 mg BCR::ABL1 reapperance - DLI	MR5 uMRD	T315I not detectable
2019	CNS relapse (T315I) – it MTX	MR4 uMRD	T315I not detectable
2020 - 2023	ponatinib 15 mg	MR5 uMRD	T315I not detectable

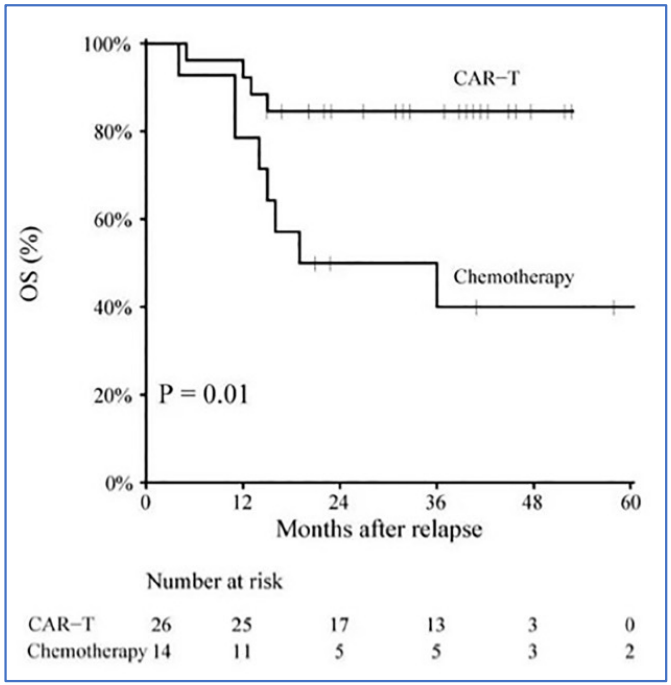
CAR-T & MRD

CR2: 100% CAR-T vs 93% chemo

relapse: 27% CAR-T vs 50% chemo

No different toxicities

MRD load: - 0.8 log vs chemo



Hu G, Frontiers in Immunology 2022

CONCLUSIONS

- Today, uMRD is a reality
- Different tools, the same purpose: the highest sensitivity
- The extra value of uMRD is clear, either before or after alloSCT, except for CHIP mutations
- On the basis of MRD status, we might choice conditioning regimen or adopt a pre-emptive immunotherapy

MRD & health resources (ALL)

MRD has got also an economical extra value…

Table 2. Hospital resource utilization

	% of patients with ≥1 hospital admission		Of the patients with ≥1 hospital admission, average number of hospital admissions		Of the patients with ≥1 hospital admission, average length of stay per admission	
	MRD+	MRD-	MRD+	MRD-	MRD+	MRD-
France	53.0	0.0	1.5	0.0	0.5	0.0
Germany	46.7	33.3	3.0	1.7	14.7	6.7
Italy	82.5	45.0	3.3	2.3	19.8	13.3
Spain	83.3	83.3	4.3	4.3	15.3	15.3
UK	40.0	10.0	3.5	1.5	7.5	2.5
Cross-country	64.7	39.3	3.2	2.1	13.2	8.9

Pigneaux, EHA 2020 #2262

AZIENDA OSPEDALIERO UNIVERSITARIA PISANA

Thank you for attention!!!

sara.galimberti@unipi.it