XX Congresso della Società GITMO

RIUNIONE NAZIONALE GITMO

ROMA, ERGIFE PALACE HOTEL, 7-8 MAGGIO 2026

Negativizzare l'MRD pre-trapianto allogenico nella AML a rischio intermedio

Sì: first, relapse prevention

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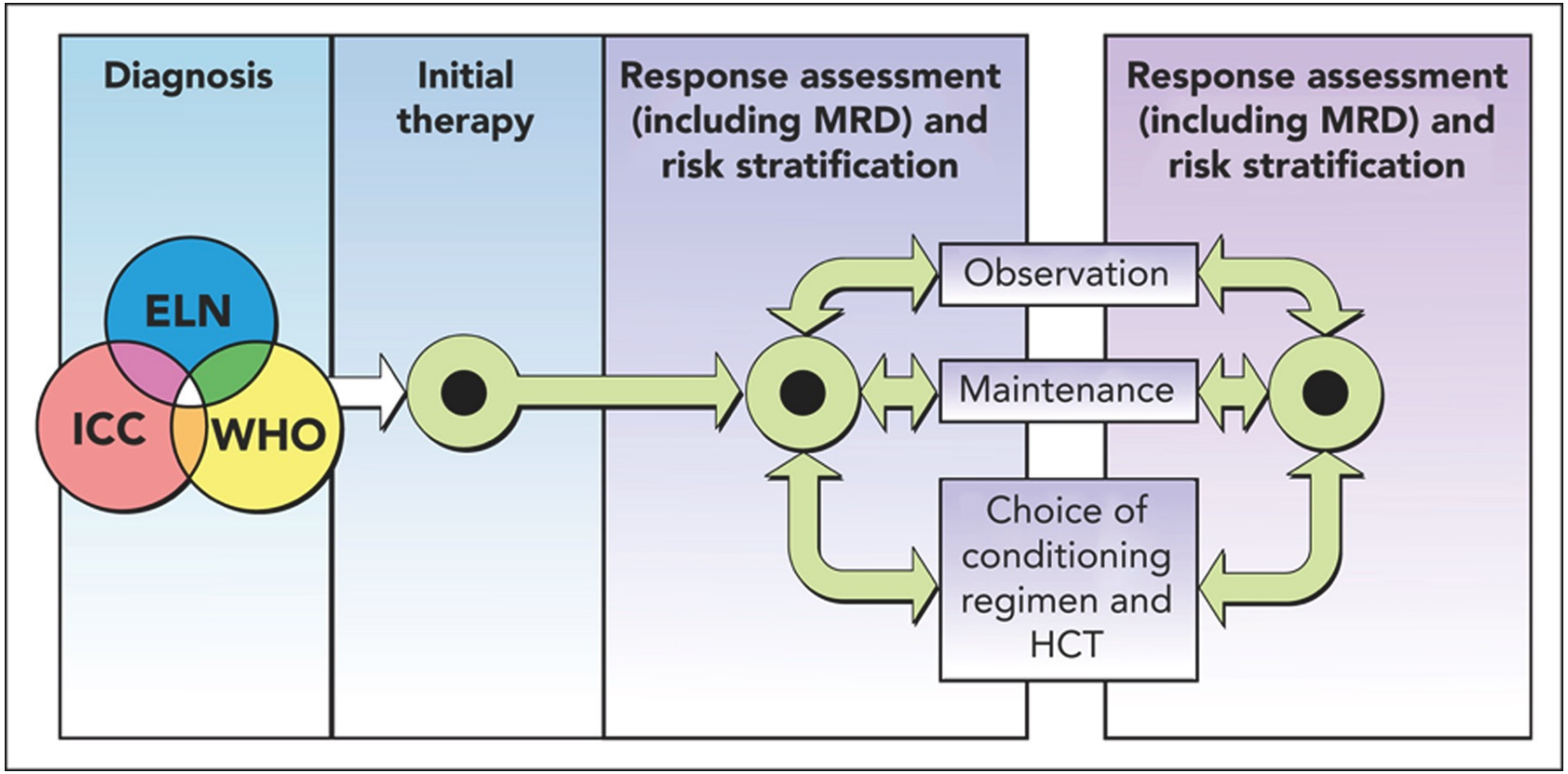
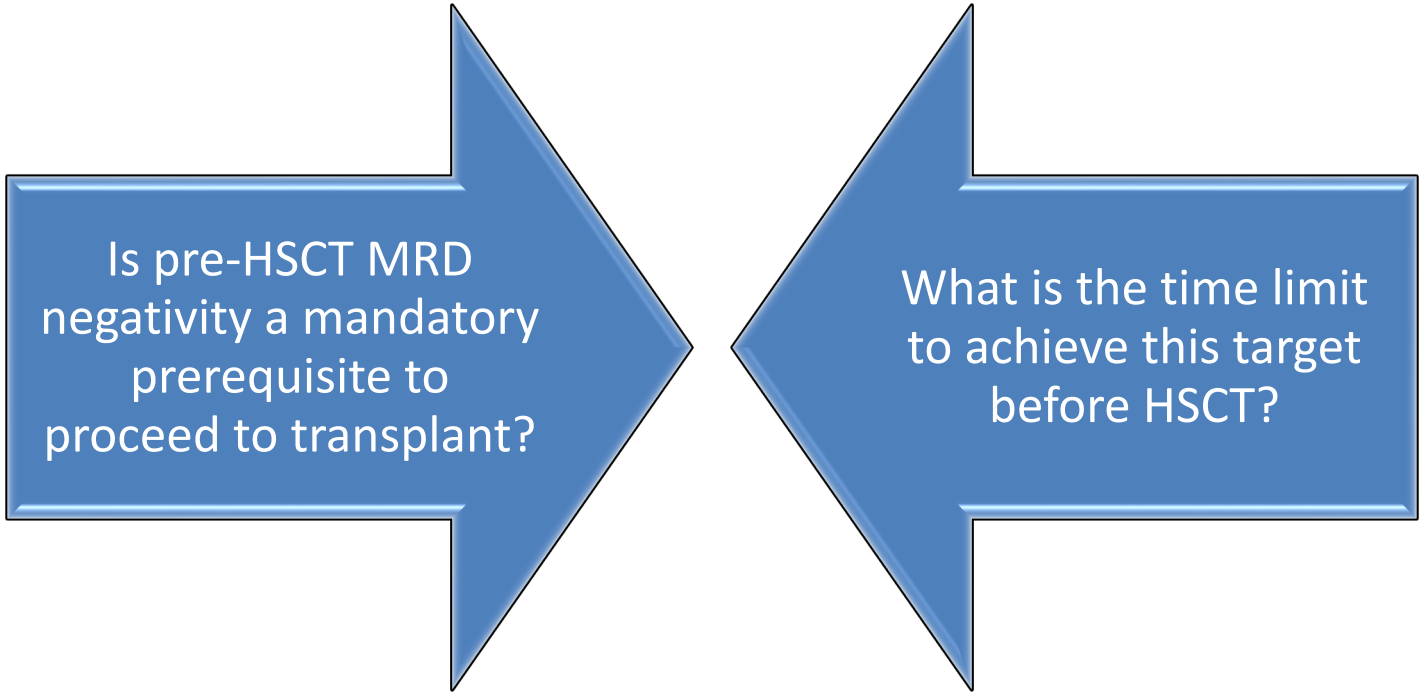
Disclosures of Francesco Buccisano

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
JAZZ PHAMACEUTICALS					X	X	
NOVARTIS						X	
ASTELLAS					X		
SERVIER					X		



Firas El Chaer et al., Blood 2023

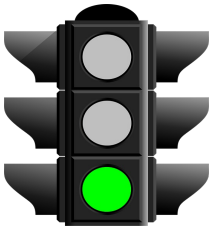

Is pre-HSCT MRD negativity a mandatory prerequisite to proceed to transplant?
What is the time limit to achieve this target before HSCT?

Recommended MRD assay per ELN Int-risk

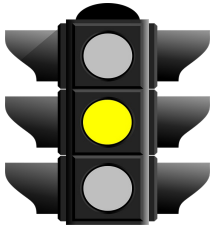
Subgroup	Assay	After 2 cycles or pre-HCT	Follow-up
FLT3-ITD and NPM1^{mut}	qPCR for NPM1 **or** FLT3-ITD UHS-NGS (if available)	NPM1-qPCR: PB	mutNPM1-qPCR: PB or BM
		and FLT3-ITD UHS-NGS BM>PB	FLT3-ITD UHS-NGS: PB or BM
FLT3-ITD and NPM1^{wt}	FLT3-ITD UHS-NGS if available **or** MFC	FLT3-ITD UHS-NGS: BM>PB	FLT3-ITD UHS-NGS: PB or BM
		MFC: BM	MFC: BM (every 3 months for 12 months)
Other (with LAIP/DfN)	MFC	BM	BM (every 3 months for 12 months)
KMT2A::MLLT3, other fusion genes[4]	qPCR if available or MFC	qPCR and MFC: BM	qPCR: PB or BM
			MFC: BM (every 3 months for 12 months)

Cloos J on behalf of ELN-DAVID, Blood 2025

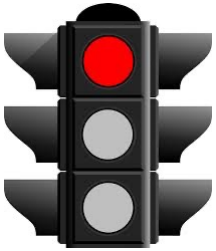
Clinical consequences of MRD assessment



Patients with an optimal MRD response should continue their planned treatment according to their ELN risk at diagnosis



Patients in the warning category should continue their planned treatment, including alloHCT, if indicated. These patients should be closely monitored for MRD relapse



MRD responses in the categories “high risk of treatment failure” and “MRD relapse” both warrant strong consideration of urgent intervention

ELN-DAVID

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MRD after 2 cycles of intensive chemotherapy or before alloHCT	Tissue	MRD value	MRD burden	Qualitative MRD response
qPCR monitoring by NPM1^{mut} using cDNA as mutNPM1/ABL1 copies (%)	PB	<0.001% or undetectable	Negative	Optimal
		≥0.001% to <0.01% and detectable	Low-level positive	Warning
		≥0.01% and detectable	Positive	Warning
Targeted FLT3-ITD UHS-NGS (FLT3-ITD$^+$/mutNPM1 or FLT3-ITD$^+$/NPM1 wild type	BM > PB	<LOD	Negative	Optimal
		≥LOD	Positive	High risk of treatment failure
MFC-MRD as LAIP$^+$ or DfN$^+$ blasts/CD45-expressing cells (%)	BM	<0.01% or <LOD	Negative	Optimal
		≥0.01% to <0.1% and >LOD	Low-level positive	Warning
		≥0.1%	Positive	High risk of treatment failure

Cloos J on behalf of ELN-DAVID, Blood 2025

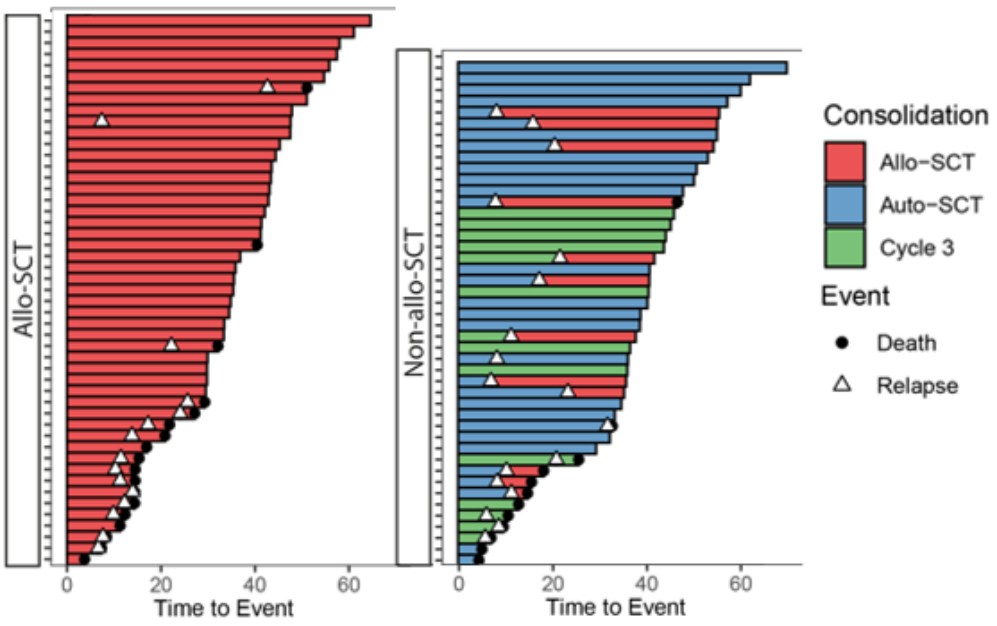
Clinical consequences of MRD assessment

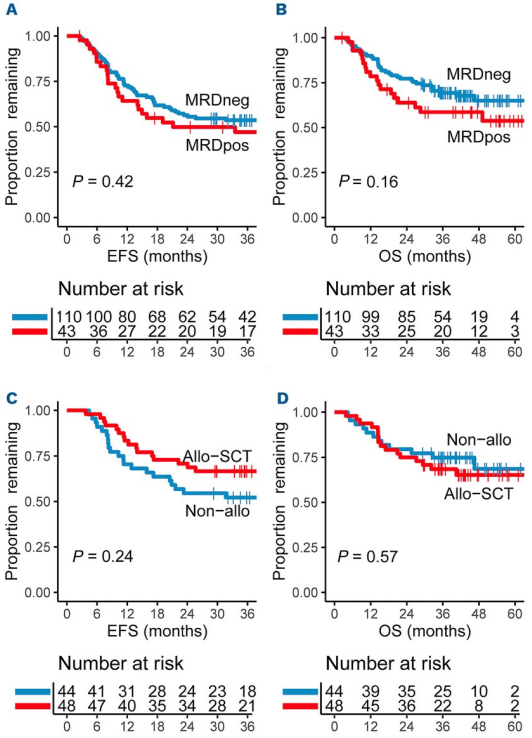
- ✓ For ELN intermediate-risk patients with optimal MRD response, the value of HSCT may be discussed.
- ✓ Individualized decision making for HSCT should be made carefully after comprehensive discussion with the patient considering multiple factors including age, comorbidities, donor type, as well as MRD status.
- ✓ Prospective nonrandomized data suggest that MRD negative ELN intermediate-risk patients have an overall survival with chemotherapy consolidation comparable with MRD-positive patients who undergo HSCT.

ELN-DAVID

Cloos J on behalf of ELN-DAVID, Blood 2025

MRD-negative intermediate risk patients in the HOVON132 trial

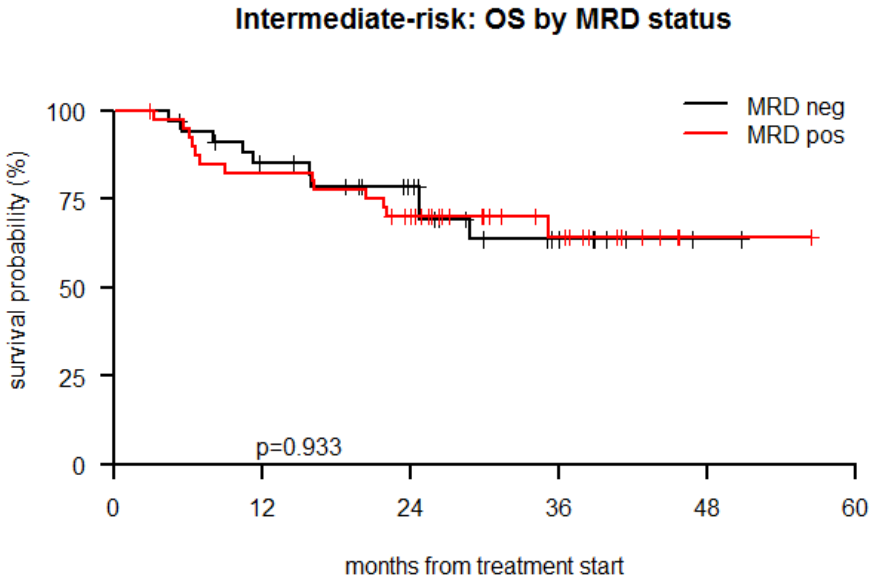


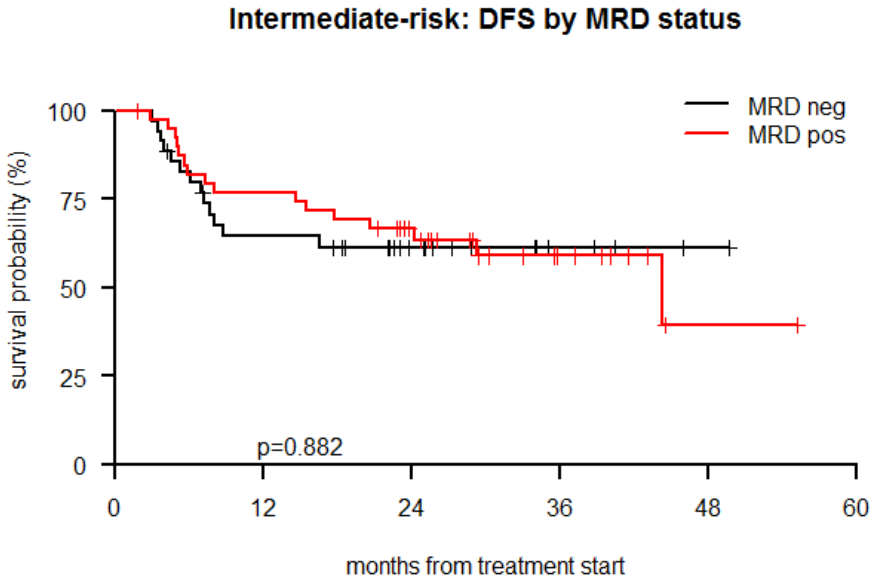


12/44 salvaged (delayed) HSCT

Tettero et al,. Haematologica 2023

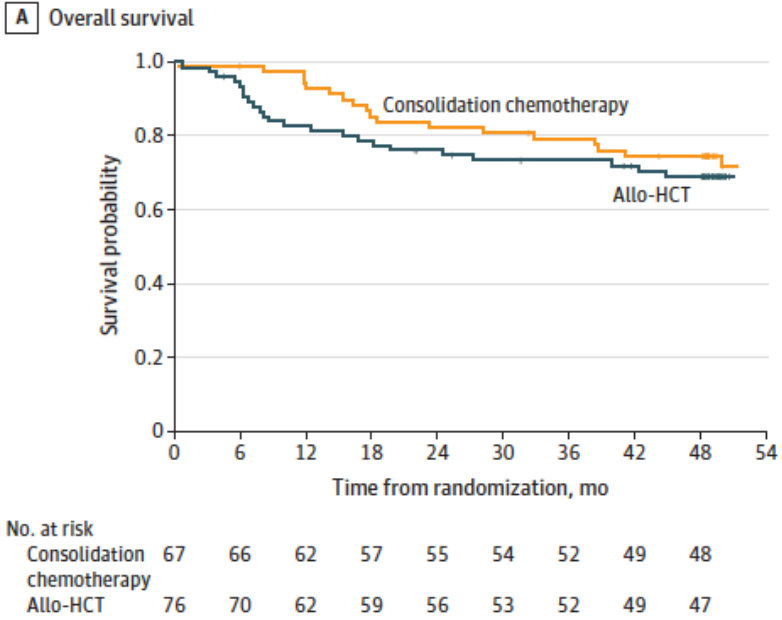
Prospective MRD-driven clinical trial AML1310, outcome of IR patients

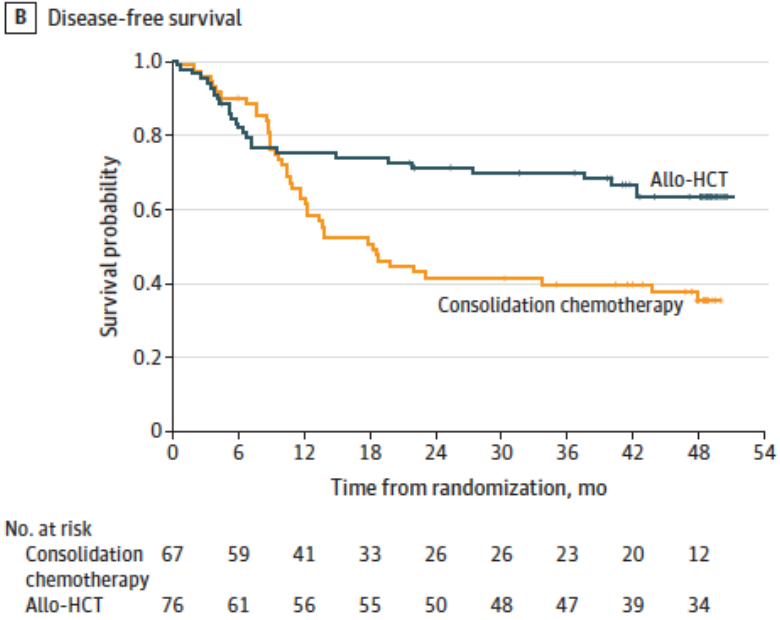




Venditti A et al, Blood, 2019

ASCT vs Standard Consolidation Chemotherapy in Patients With Intermediate-Risk AML: A Randomized Clinical Trial





Bornhäuser M et al., JAMA 2023

Randomized trial of chemo vs alloHCT in MRD negative ELN intermediate risk patients: RESOLVE trial

Arm A: AML Patients*

- Newly diagnosed de novo AML or MDS/AML
- Age 18 – 70 years
- ELN intermediate risk
- CR/CRi/CRh after 1-2 cycles of standard induction chemotherapy
- MFC-MRD negative in BM
- AlloHCT donor available
- Exclusion: *FLT3*-ITD high AR >0.5 or VAF>33%

N = 360

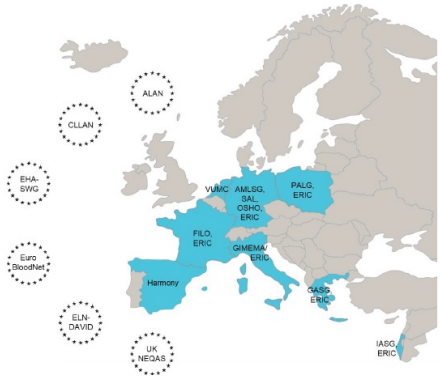
1 : 1

Group 1: alloHCT

Group 2: Chemotherapy, MRD-guided alloHCT

Primary endpoint
Non-inferiority of overall survival

*only key inclusion criteria are shown, refer to the protocol for the full list of in- and exclusion criteria



Courtesy of M. Heuser

Resolve MRD guided treatment
Funded by the European Union

MRD after 2 cycles of intensive chemotherapy or before alloHCT	Tissue	MRD value	MRD burden	Qualitative MRD response
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Cloos J on behalf of ELN-DAVID, Blood 2025

Caveat of MRD convention attempts

- ✓ Additional therapy can compromise transplantation success
  - ✓ Immediate complications of the additional chemotherapy
  - ✓ Increased transplant toxicity
  - ✓ Drive clonal evolution (eg TP53+)
- ✓ Thus far, excessive delaying of HSCT to attain MRD negativity is not recommended.
  - ✓ Pre-HCT MRD persistent vs MRD relapse might be a different scenario
- ✓ MRD is a tool to shape the transplantation modality (intensity, immunosuppression, etc)
- ✓ Rethink the whole induction strategy is potentially a better strategy

Craddock C, ASH Educational Program, 2022

MRD and transplant

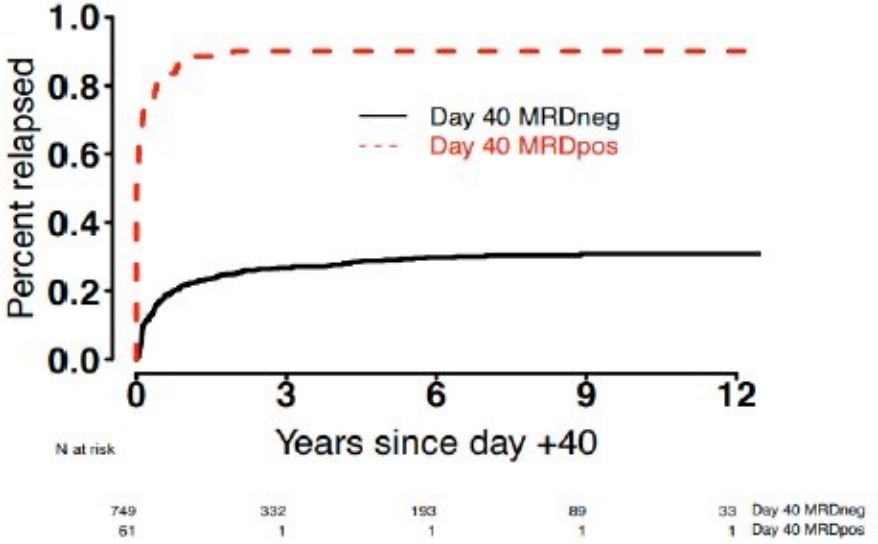
- ✓ Pretransplant MRD positivity should not be viewed as a contraindication to stem cell transplantation.
- ✓ HSCT may improve the outcome of patients who test MRD-positive compared with continued chemotherapy or observation.
- ✓ In patients with detectable MRD before HSCT, myeloablative conditioning should be considered.
- ✓ Detectable MRD does not represent a contraindication for HCT.
- ✓ HCT should not be delayed because of MRD positivity.
- ✓ Pre-transplantation MRD evaluation should be performed in all patients considered for HCT within 4 weeks of the start of conditioning.

Cloos J et al., Blood 2025

Sanz J et al., Lancet Oncology 2025

Rate of MRD-negative conversion after ASCT

- ✓ MFC-MRD assessment day 20-40 after HSCT
- ✓ 7.5% were MRD positive
- ✓ Of 161 MRD+ before HSCT, 118 became MRD-after HSCT (73%)



73% MRD conversion by alloHCT

Paras G et al, Blood 2022

Caveat of MRD convention attempts

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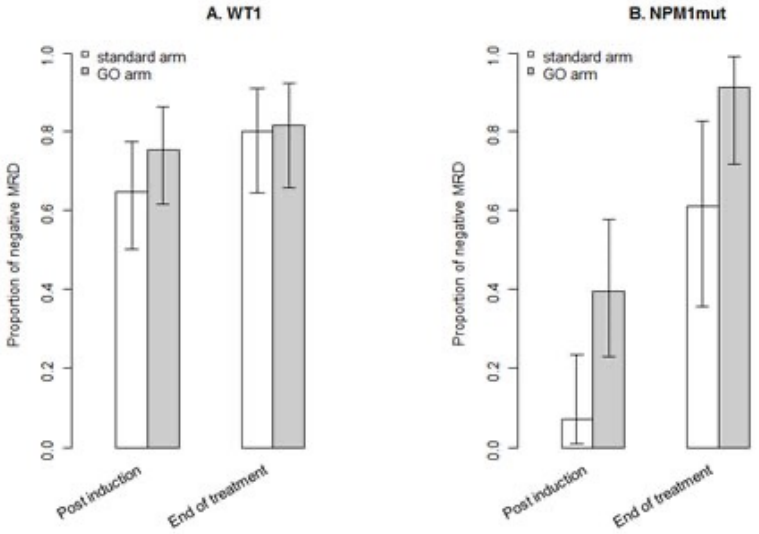
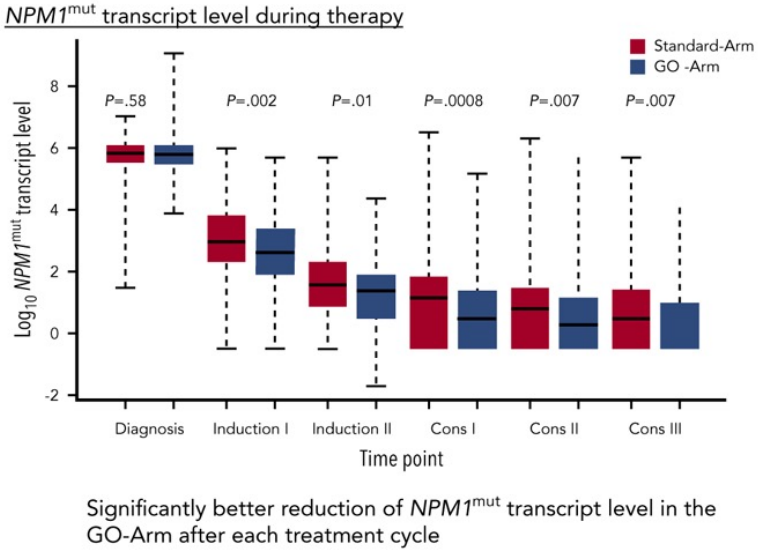
Craddock C, ASH Educational Program, 2022

Effect of GO treatment on MRD



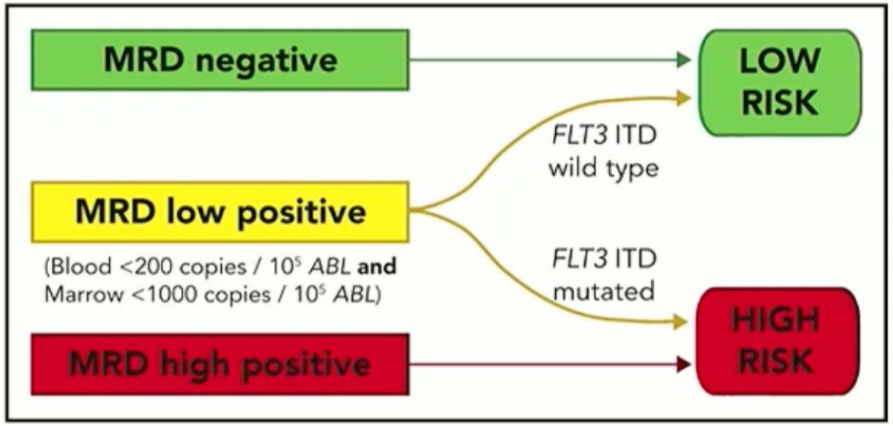


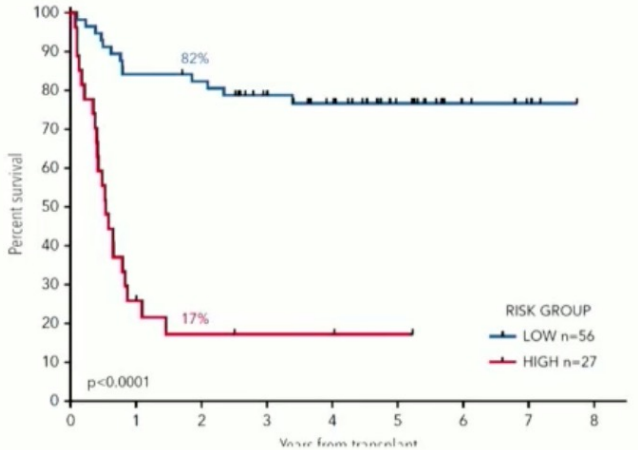
Significantly better reduction of *NPM1*^{mut} transcript level in the GO-Arm after each treatment cycle

Lambert J et al., Oncotarget 2014

Kapp-Schwoerer S et al., Blood 2024

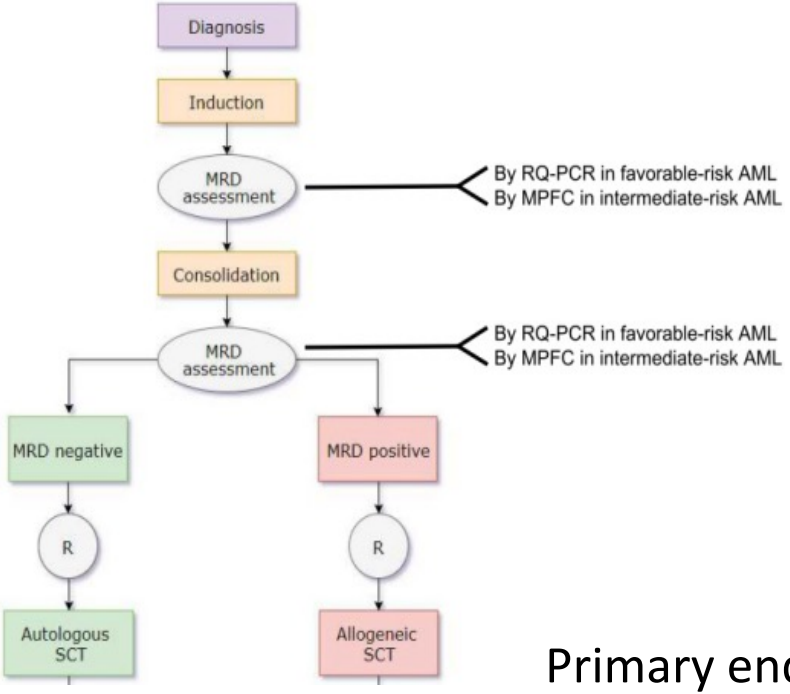
OS from transplant according to the risk group: NCRI AML17





Dillon R et al., Blood 2024

GIMEMA AML1819 study (Low-Int. Risk pts, <60aa)



Diagnosis

De novo ELN2017 favorable/intermediate-risk AML
Age 18-60 years

Induction

GO 3 mg/m^2 day 1, 4, 7 (flat dose capped at 5 mg)
Daunorubicin 60 mg/m^2 day 1-3
Cytosine Arabinoside 200 mg/m^2 day 1-7

Consolidation

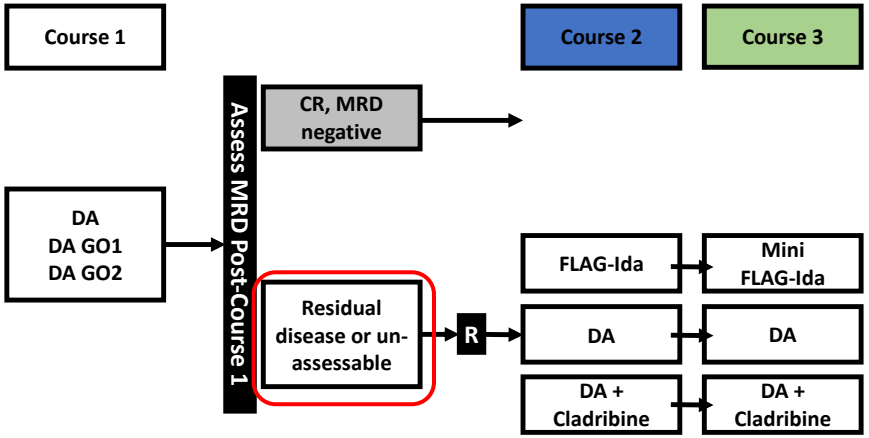
GO 3 gm/m^2 day 1 (flat dose capped at 5 mg)
Daunorubicin 50 mg7m^2 day 4-6
Cytosine Arabinoside 500 mg/m^2, twice a day, day 1-6

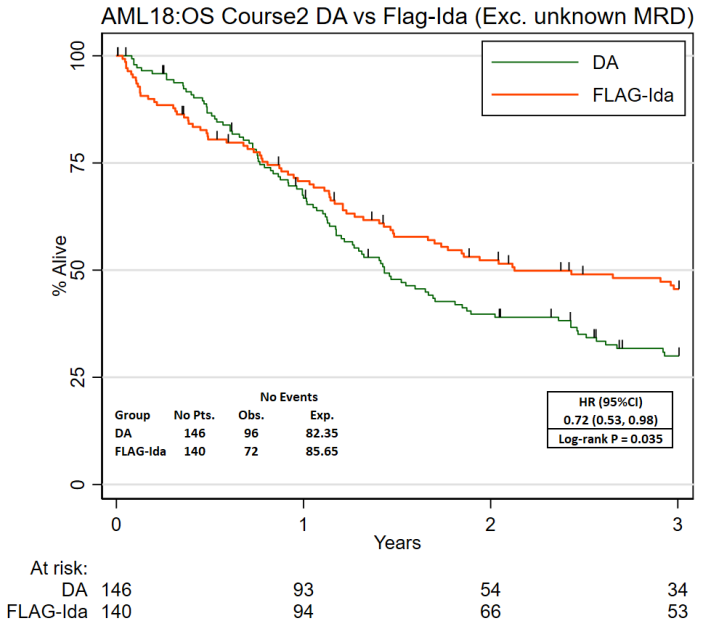
Primary endpoint:

- ✓ percentage of MRD negativity after cycle 2

Chemo intensification for Flow MRD persistence post induction

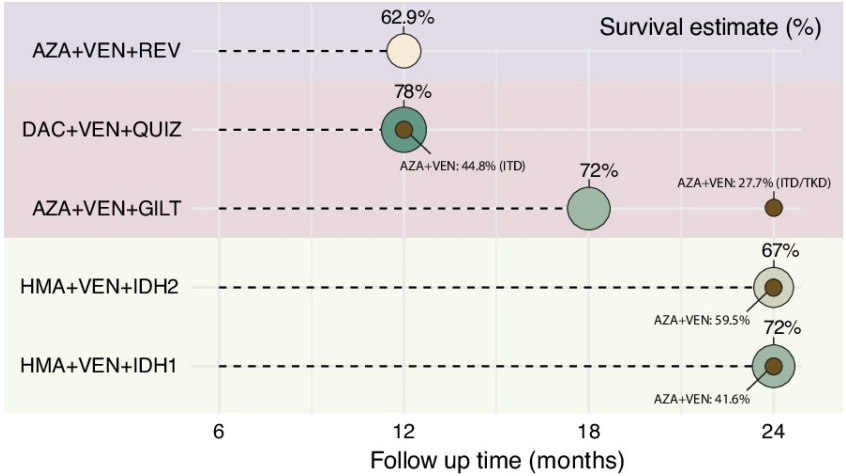
AML18: Fit Adults ≥ 60 years with AML or high risk MDS

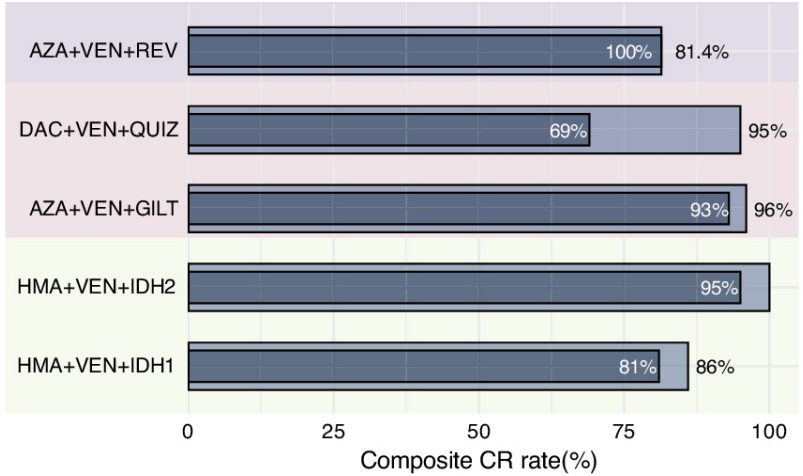




Russell et al JCO 2025

Optimizing lower intensity triplet therapy in AML





Yen W-Y et al, Blood Cancer Journal (2026)

Conclusions

- ✓ A high quality of CR (MRD negative) is a key determinant of outcome in AML patients, even for those addressed to HSCT
- ✓ Time to MRD negative CR is a window of opportunity that should not exceed a limited timeframe (2 cycles of intensive CHT according to ELN)
- ✓ The goal of MRD negativity implies from the beginning a treatment planning that may increase the chance of a deeper disease eradication
- ✓ Points of discussion:
  - Less-intensive induction strategies
  - Conditioning intensity
  - Maintenance after transplant