XIX Congresso della Società GITMO

RIUNIONE NAZIONALE GITMO

TORINO, CENTRO CONGRESSI LINGOTTO, 5 - 6 MAGGIO 2025

La leucemia acuta: il ruolo dal trapianto nei pazienti anziani e fragili – LAM/MDS

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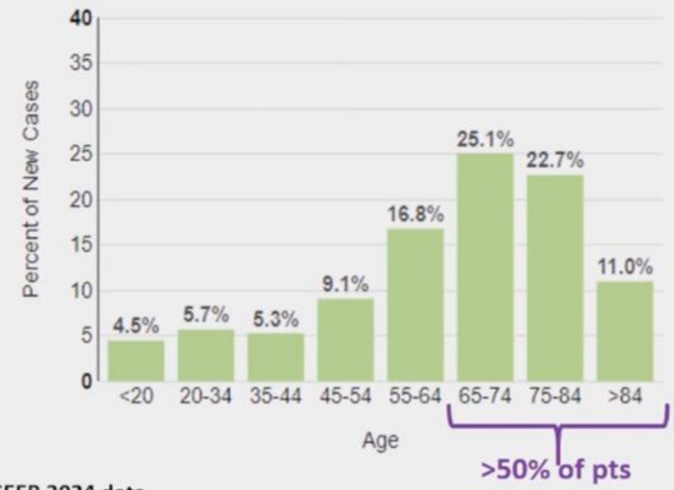
Disclosures of Alessandro Isidori

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie			x		x	x	
Astrazeneca			x		x		
Beigene			x		x		
Daiichi Sankyo					x	x	
Immunogen						x	
Jansenn			x		x		
Jazz					x		
Servier			x		x	x	
Syndax			x		x	x	

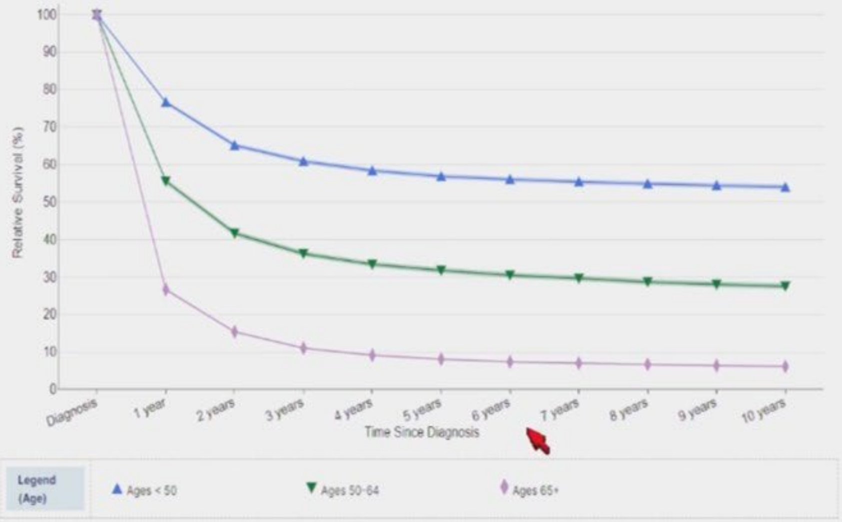
AML Epidemiology

Median age at diagnosis:
69 years

Incidence by Age Group

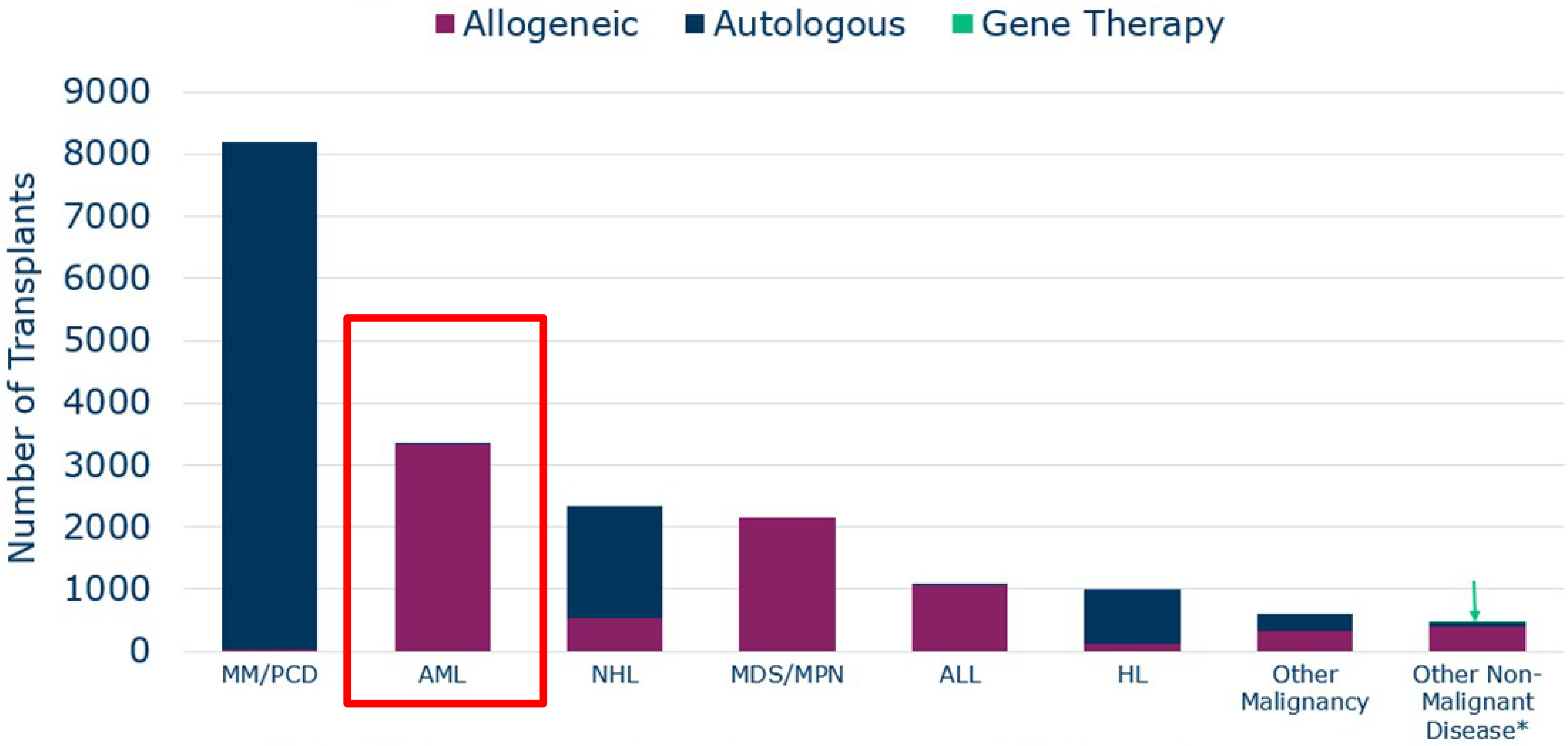


Survival by Age Group



SEER 2024 data
https://seer.cancer.gov/statfacts/html

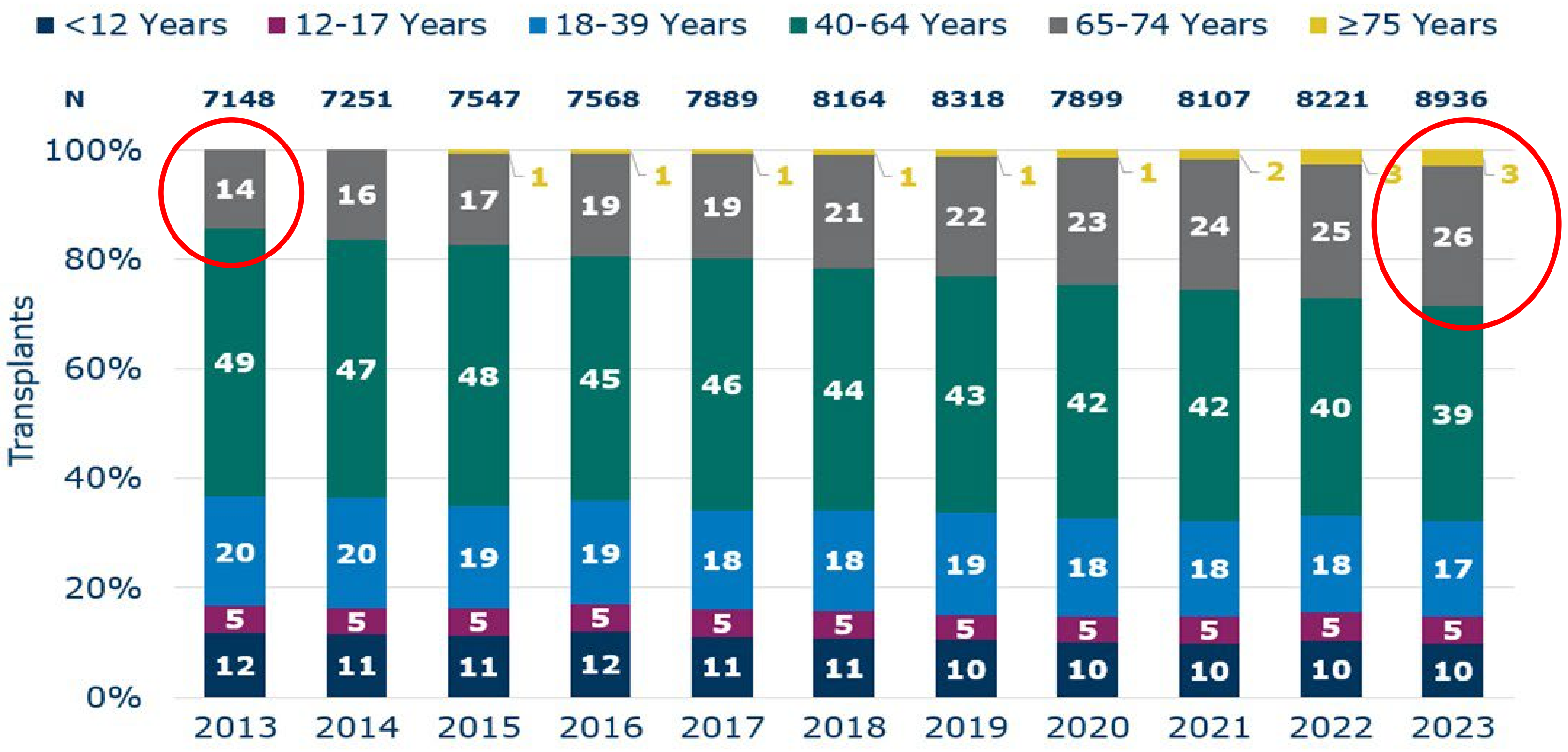
Number of HCTs by Indications in the US, 2023, Adult



*Includes 22 limited gene therapy events

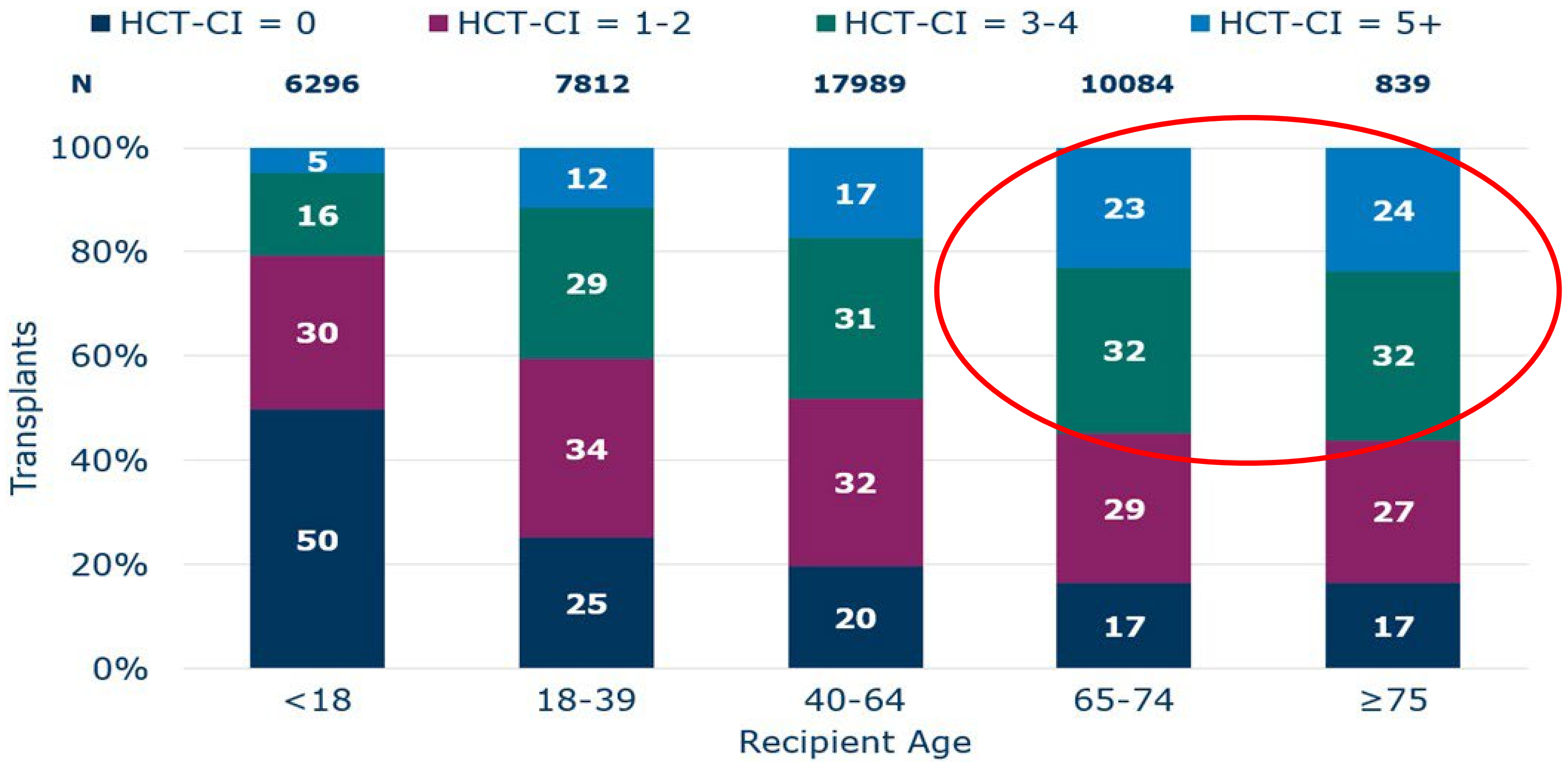
Abbreviations:
ALL, acute lymphoblastic leukemia;
AML, acute myeloid leukemia;
CLL, chronic lymphocytic leukemia;
HL, Hodgkin lymphoma;
MDS, myelodysplastic syndromes;
MM, multiple myeloma;
MPN, myeloproliferative neoplasms;
NHL, non-Hodgkin lymphoma;
PCD, plasma cell disorders.

Recipient Age of Allogeneic HCTs in the US



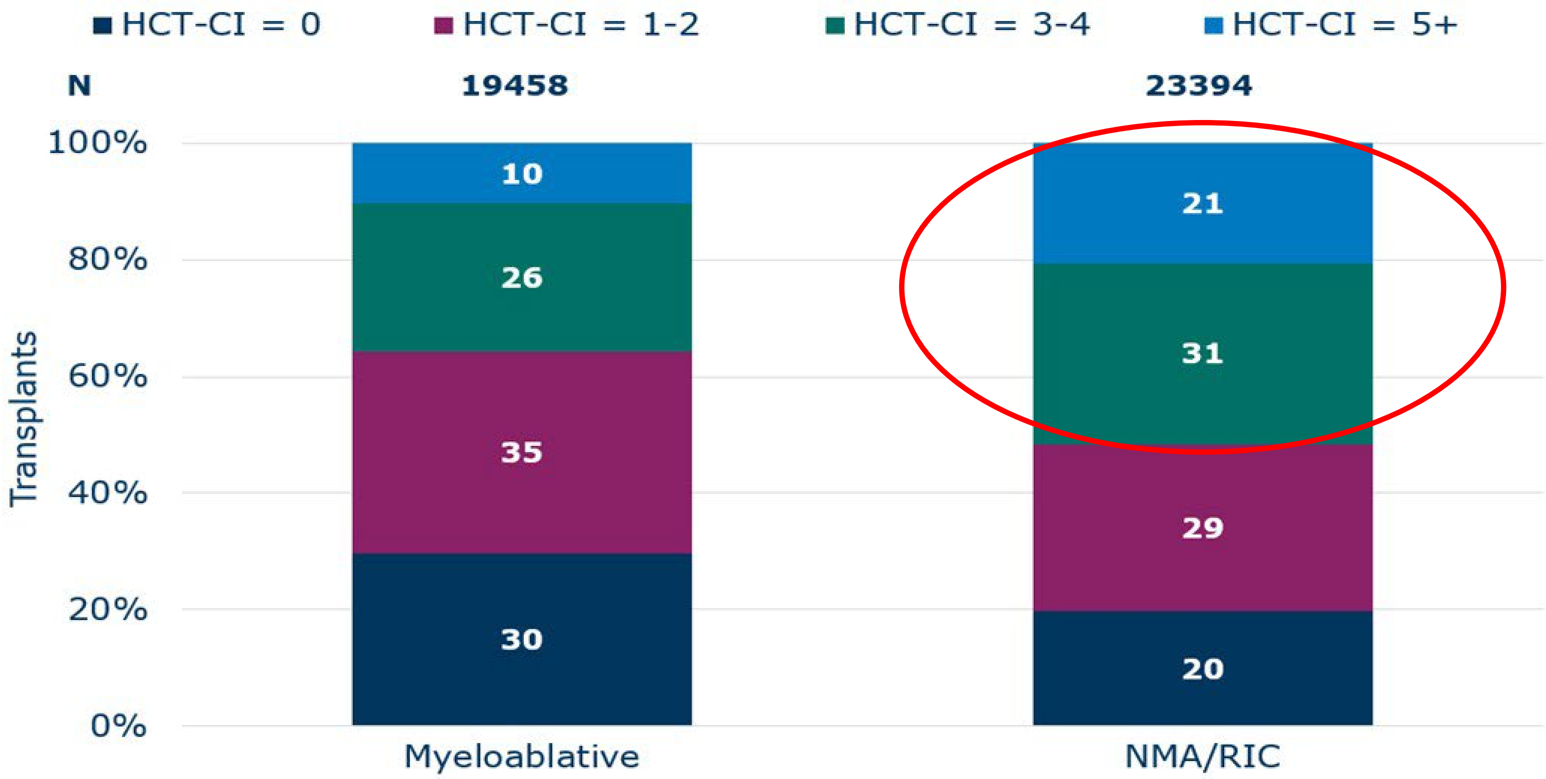
CIBMTR
A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

Comorbidity Index in Allogeneic HCTs in the US by Recipient Age, 2019-2023



Abbreviation: HCT-CI, Hematopoietic Cell Transplantation Comorbidity Index.

Comorbidity Index in Allogeneic HCTs in the US by Conditioning Intensity, 2019-2023



Abbreviations: HCT-CI, Hematopoietic Cell Transplantation Comorbidity Index; NMA/RIC, non-myeloablative regimen/reduced-intensity conditioning.

Il trapianto nei pazienti con LAM/MDS anziani e fragili: cosa dobbiamo considerare

- MORTALITA' DA TERAPIA 1L (non solo ICT)
- CLASSIFICAZIONE ELN
- RUOLO MRD (?)

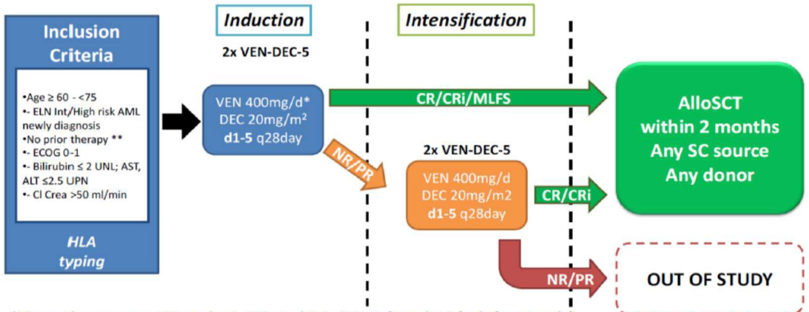
Opinione personale dello Speaker

MORTALITA' DA TERAPIA (EARLY DEATHS, d30, d60)

CHEMO-FREE REGIMEN: GITMO VEN/DEC (60-75y)

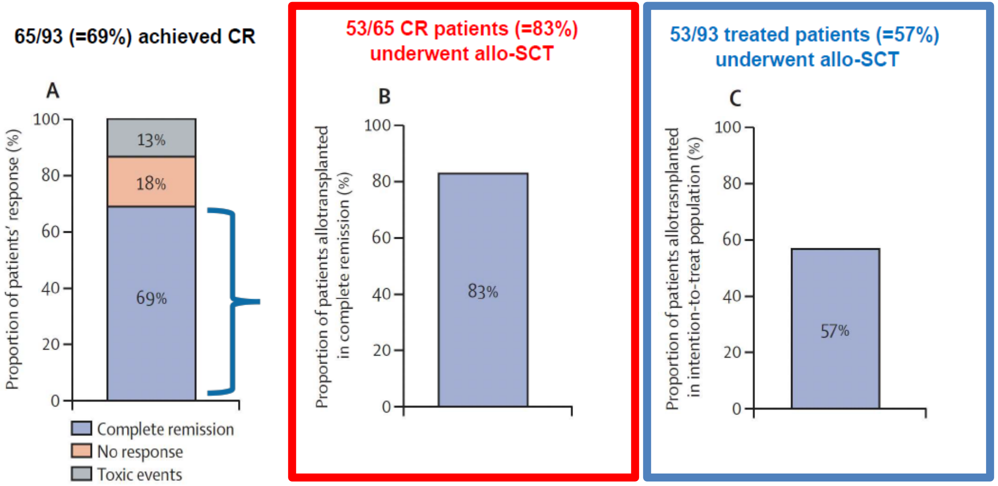
VEN-DEC GITMO study design

VEN-DEC GITMO trial is a no profit, prospective, phase II, multicentre, non-randomised, uncontrolled, single group assignment, open label study to evaluate the safety and efficacy of the "chemo-free" combination Venetoclax plus Decitabine (VEN-DEC) as "bridge" to allo-SCT in elderly (≥ 60 - < 75 years) AML patients.



*Venetoclax rump up: 100 mg day 1, 200 mg day 2, 400 mg from day 3 (only for 1st cycle)

** HU is allowed in case of WBC > 25.000



Early deaths (+100): 13%

Russo D et al, Lancet Hematol 2024

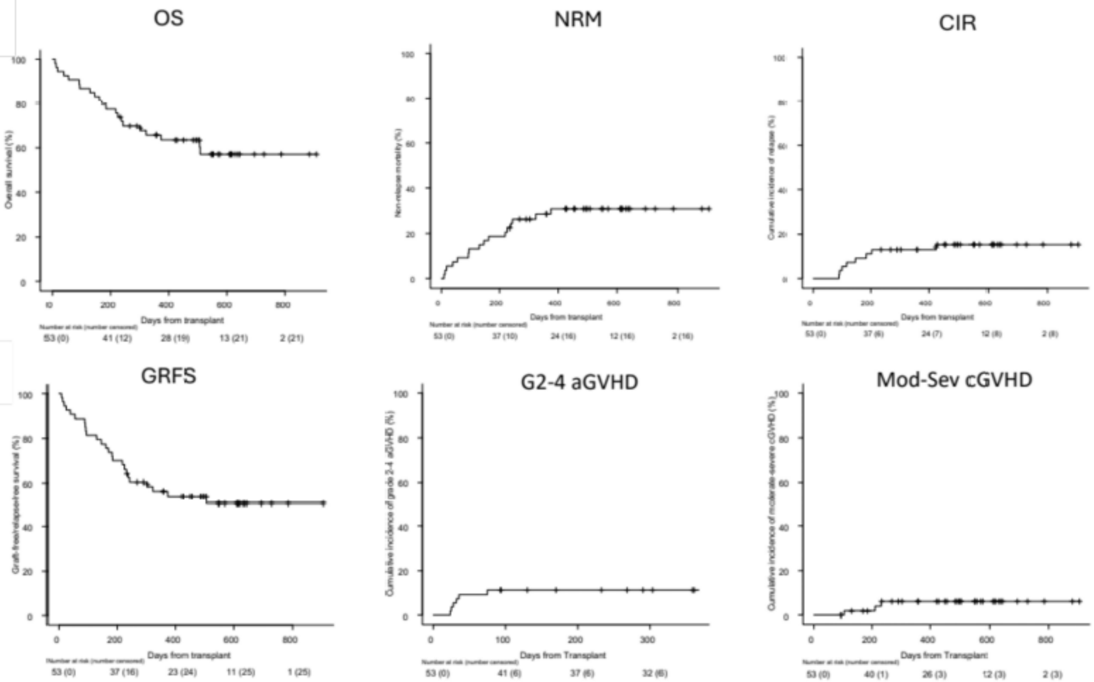
AlloSCT OUTCOME in VENDEC study

OS:
- 66% at 1 year
- 57% at 2 years

NRM:
- 13% at 100 days
- 29% at 1 year

aGVHD at 1 year: 25%
(grade 2-4 = 11%)

cGVHD at 2 years: 10%
(moderate-severe = 6%)

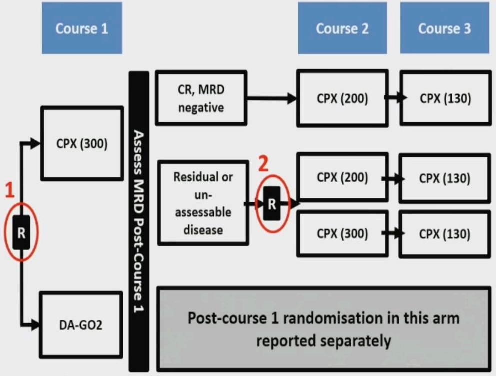


Russo D et al, Lancet Hematol 2024

MORTALITA' DA TERAPIA (EARLY DEATHS, d30, d60)

INTENSIVE CHEMOTHERAPY: NCRI AML 18 (60>y)

AML 18 version 2: CPX-351 vs DA-GO2



Abbreviations: DA – Daunorubicin/AraC; GO2 – Gemtuzumab Ozogamicin, 2 doses; MRD – measurable residual disease; CR – complete remission; R – randomisation

Key Eligibility Criteria

- Previously-untreated AML or high-risk MDS (defined by ≥10% marrow blasts)
- Aged ≥60yrs
- Not *known* to have adverse risk cytogenetics
- ECOG performance status 0-2
- Creatinine ≤1.5xULN

Following EMA approval of CPX-351 for secondary AML, these patients were *excluded* from trial entry:

- antecedent hematologic disorder
- prior chemotherapy
- known MDS-related cytogenetics

Clinical Response

	CPX-351 (n=295)	DA-GO2 (n=144)	P value	OR (95% CI)†
CR following course 1* : n(%)	129 (44%)	82 (57%)	0.020	0.62 (0.42-0.93)
CR+CRi following course 1*	140 (48%)	86 (60%)	0.016	0.61 (0.41-0.91)
CR following course 2	201 (68%)	113 (79%)	0.024	0.59 (0.37-0.94)
CRi following course 2	29 (10%)	9 (6%)	0.210	1.64 (0.75-3.55)
CR+CRi following course 2	230 (78%)	122 (85%)	0.095	0.64 (0.37-1.09)
Early deaths				
Day 30	20 (6.8%)	6 (4.2%)	0.276	1.67 (0.66-4.26)
Day 60	32 (10.9%)	6 (4.2%)	0.019	2.80 (1.14-6.86)

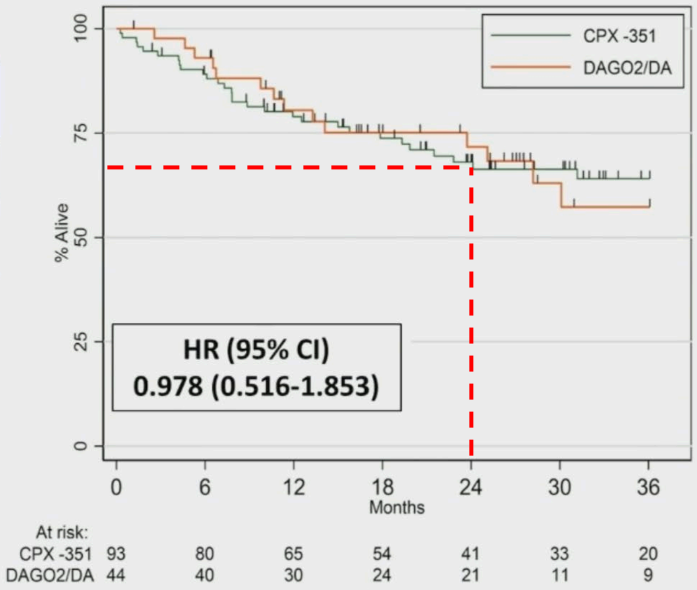
* Within 50 days of randomisation
† DA-GO2 as reference

Knapper et al, ASH 2024

Transplant in CR1 and Overall Survival

	CPX N= 295	DAGO2/DA N= 144
Allografts in CR1	93 (40%)	44 (36%)
Days to CR1 allograft. Median (range)	127 (84- 190)	137 (80 – 190)

Post-transplant survival (CPX v DA-GO2)



Knapper et al, ASH 2024

AML classification highlights the differential outcomes with standard intensive chemotherapy : AML is not one disease!

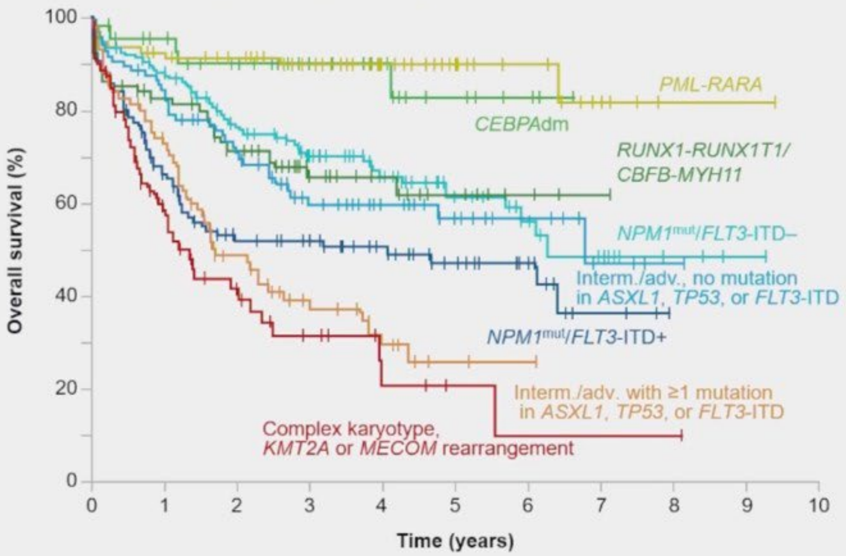
ELN 2022[1]

Favorable
- t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*
- Mut *NPM1* w/o *FLT3*-ITD
- bZIP in-frame mut *CEBPA*

Intermediate
- Mut *NPM1* with ***FLT3*-ITD**
- Wt *NPM1* with ***FLT3*-ITD**
- t(9;11)(p21.3;q23.3)/ *MLLT3::KMT2A*
- Cytogenetic and/or molecular

Adverse
- t(6;9)(p23.3;q34.1)/*DEK::NUP214*
- t(v;11q23.3)/*KMT2A*-rearr
- t(9;22)(q34.1;q11.2)/*BCR::ABL1*
- t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP*
- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2,MECOM(EVI1)*
- t(3q26.2;v)/*MECOM(EVI1)*-rearr
- −5 or del(5q); −7; −17/abn(17p)
- Complex/monosomal karyotype
- Mut *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1*, or *ZRSR2*
- Mut *TP53*

OS in patients aged <60 years with *de novo* AML (N=867)[2]

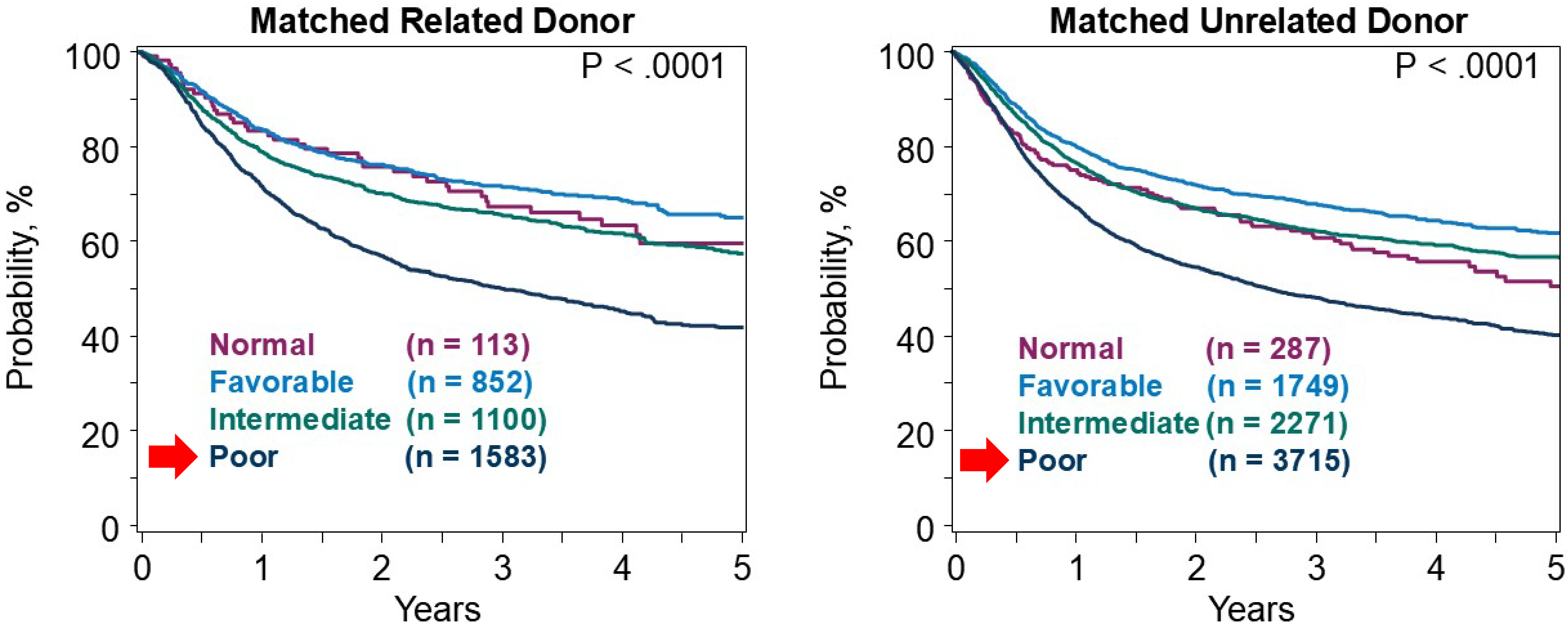


* **This population of patients had been treated with standard intensive chemotherapy.**

ELN, European LeukemiaNet

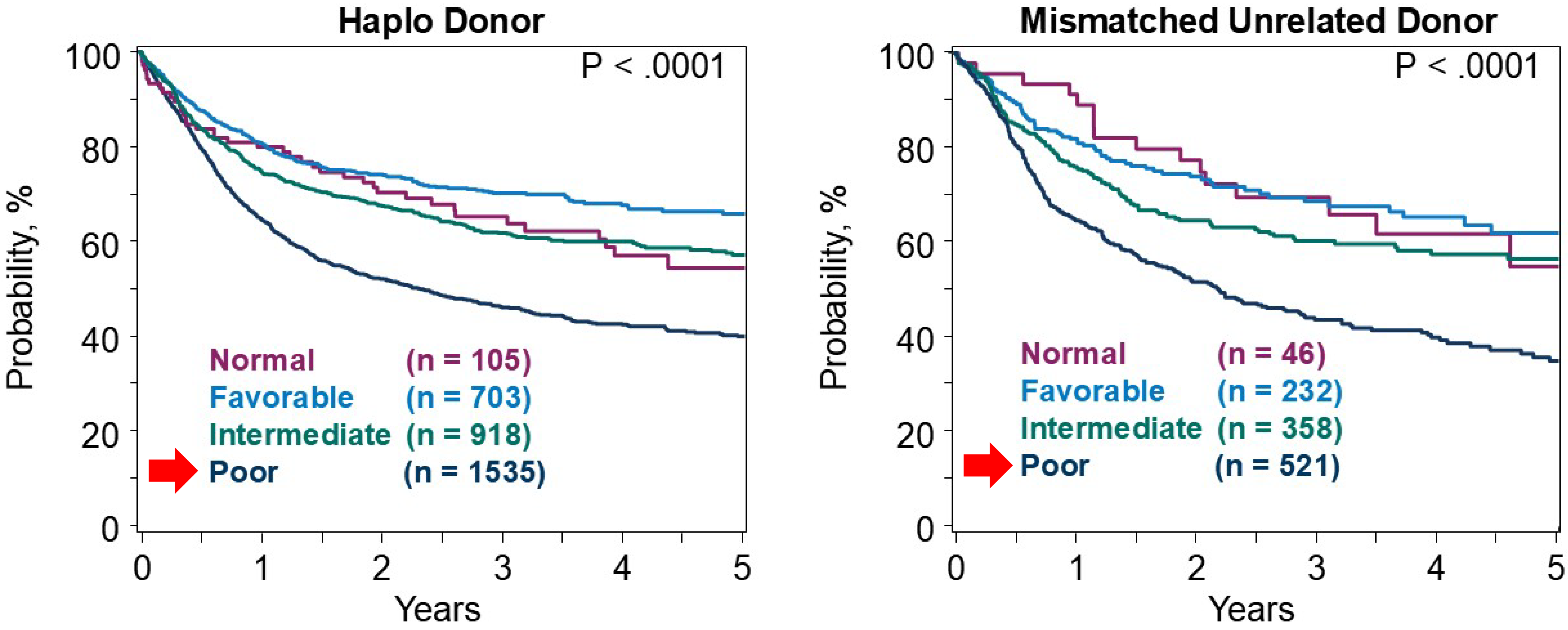
1. Döhner H, *et al. Blood* 2022; **144**:1345–1377; 2. Adapted from Haferlach C, *et al. Blood* 2016; **128**:286.

Survival after Allogeneic HCTs for Acute Myeloid Leukemia, Using Matched Donors in the US, 2017-2022, Adults, by ELN Cytogenic Risk Score



Abbreviations: ELN, European LeukemiaNet; HCT, hematopoietic cell transplantation.

Survival after Allogeneic HCTs for Acute Myeloid Leukemia, Using Mismatched Donors in the US, 2017-2022, Adults, by ELN Cytogenic Risk Score



Abbreviations: ELN, European LeukemiaNet; haplo, haploidentical; HCT, hematopoietic cell transplantation.

Updated AML classifications reflect the impact on genomics associated with DIFFERENT AML therapies

ELN 2022[1] (Intensive treated patients)

Favorable
- t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*
- Mut *NPM1* w/o *FLT3*-ITD
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Intermediate
- Mut *NPM1* with ***FLT3*-ITD**
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- t(9;11)(p21.3;q23.3)/ *MLLT3::KMT2A*
- Cytogenetic and/or molecular

Adverse
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- t(9;22)(q34.1;q11.2)/*BCR::ABL1*
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- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2,MECOM(EVI1)*
- t(3q26.2;v)/*MECOM(EVI1)*-rearr
- −5 or del(5q); −7; −17/abn(17p)
- Complex/monosomal karyotype
- Mut *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1*, or *ZRSR2*
- **Mut *TP53***

ELN 2024[2] (Less-intensive therapies)

Favorable
- **Mutated *NPM1*** (wild-type *FLT3-ITD, NRAS, KRAS, TP53*)
- Mutated *IDH2* (wild-type *FLT3-ITD, NRAS, KRAS, TP53*)
- Mutated *IDH1* (TP53* wild type*)*
- Mutated *DDX41*†
- Other cytogenetic and/or molecular abnormalities *(*wild-type *FLT3-ITD, NRAS, KRAS, TP53*)‡

Intermediate
- **Mutated FLT3-ITD and/or Mutated NRAS and/or KRAS** (TP53 wild-type)

Adverse
- **Mutated *TP53***

❖ This classification does not apply to pts that have received a prior HMA

* Favorable mutated *IDH1* risk applies specifically to patients treated with AZA + IVO and appears irrespective of signaling gene mutations

† Identification of a *DDX41* mutation (especially VAF ~ 50%) should prompt consideration of a germline mutation

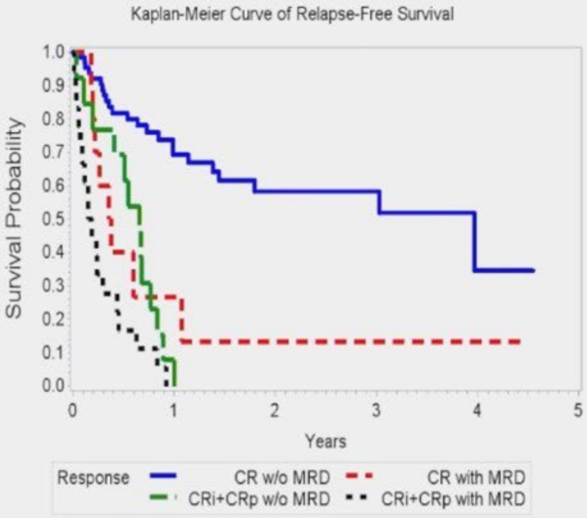
‡ For many genomic abnormalities, not enough data is currently available

ELN, European LeukemiaNet

[1]Döhner H, *et al. Blood* 2022; **144**:1345–1377, [2]Döhner H, *et al. Blood* 2024; **144**:2169-2173

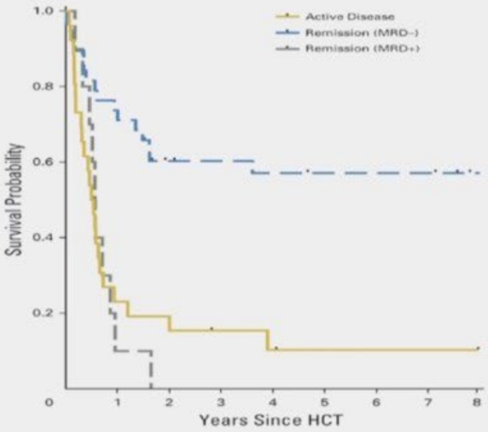
MRD associated with poor outcome after chemo or BMT

Chemotherapy



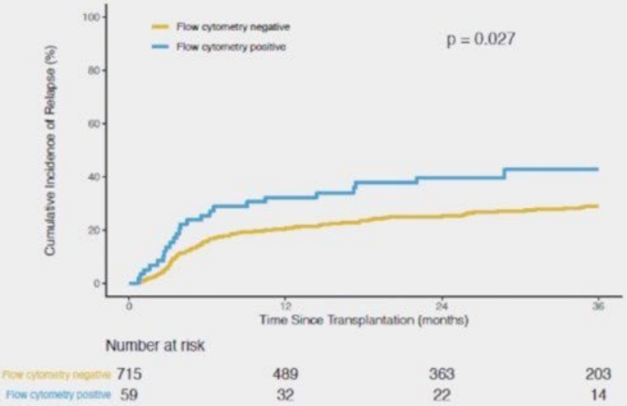
[1]Chen et al. JCO 33:1258, 2015

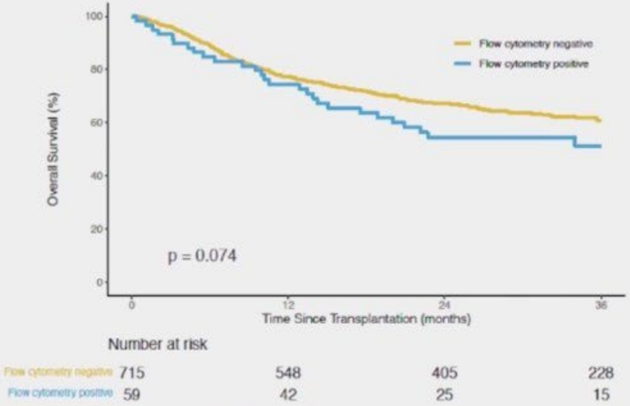
Transplant



Hourigan et al., JCO 2016

Flow vs NGS MRD in pts with NPM1/FLT3-ITD pre-alloHCT in AML CR1



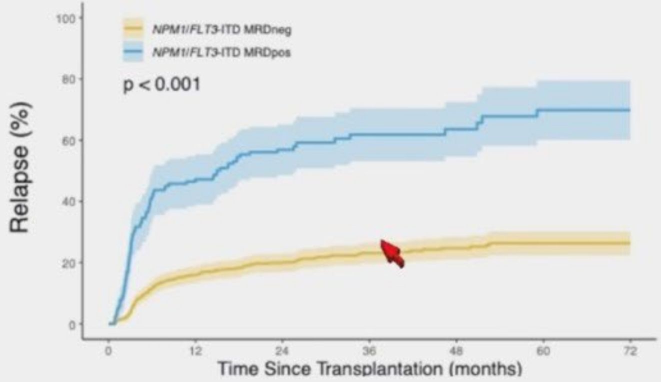


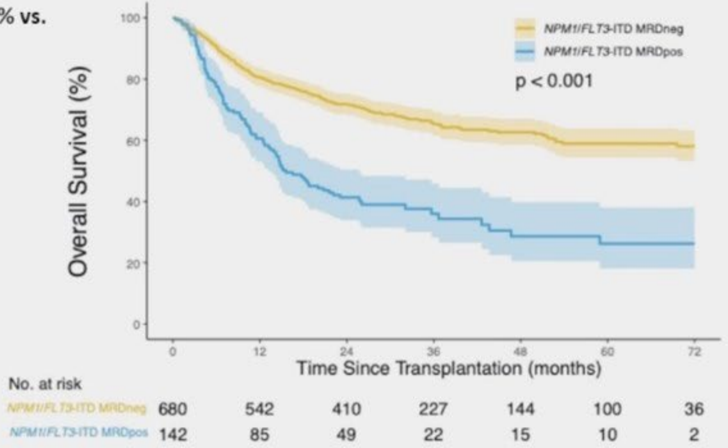
Flow (n=774)
7.6% pos

1yr CIR: **20% vs. 32%**
3yr OS: **61% vs. 51%**

***NGS** (n=822)*
21% pos

1yr CIR: **16% vs. 47%**
3yr OS: **66% vs. 36%**





@DrChrisHourigan #AMP24

JAMA. 2023;329(9)

Radich J, ASH 2024 Educational program

Il trapianto nei pazienti con LAM/MDS anziani e fragili: conclusioni

- Chemo-free does not mean mortality-free
- Eligibility for ICT does not preclude eligibility for SCT
- ELN 2022 and 2024 guide treatment
- Can MRD be a decision-making tool in this setting?

What defines an UNFIT "Transplant Ineligible" patient?

- Age $\geq$ 75*ish*
- ECOG PS $\geq$2
- Underlying organ dysfunction
  - Renal failure, liver disease, cardiomyopathy
- *Prior (especially treated) antecedent hematologic disorders?*
- *Unfavorable / high risk genetics?*
  - *Especially pts with TP53 mutations*
- *MRD positivity?*

Di Nardo C, Ash educational program, 2024