Should intermediate-risk fit patients undergo alloHSCT in CR1?
- NO -

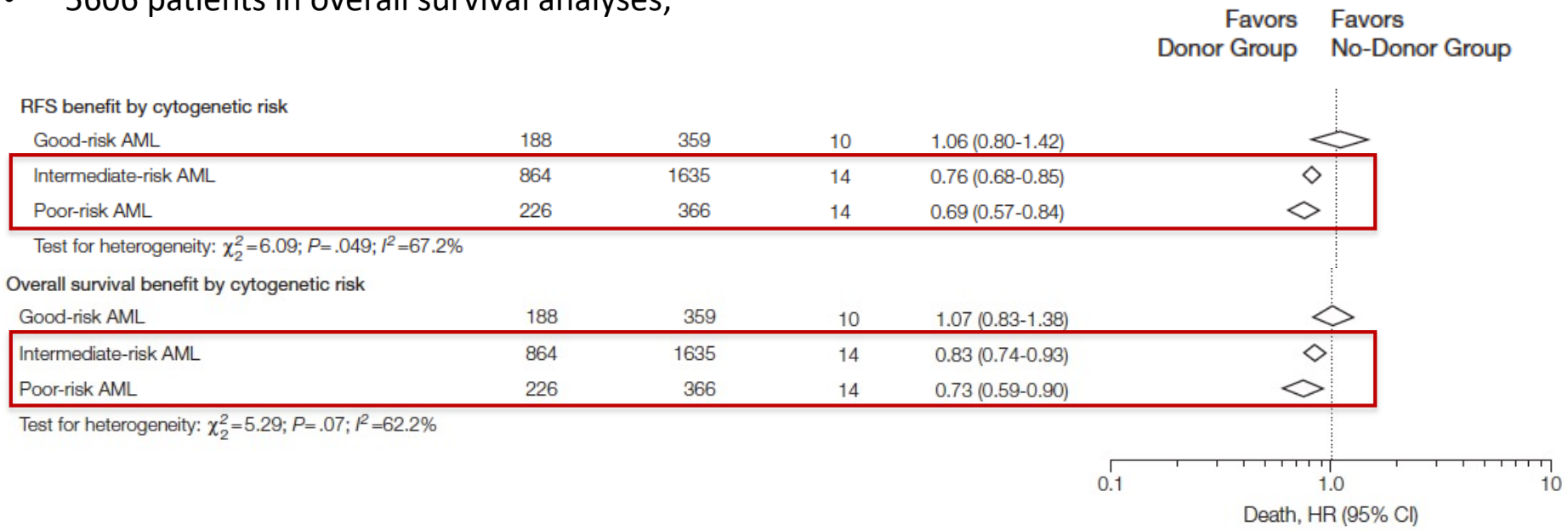
Prof. Francesco Buccisano

Tor Vergata University of Rome

Allogeneic Stem Cell Transplantation for AML in CR1

24 trials and 6007 patients analyzed

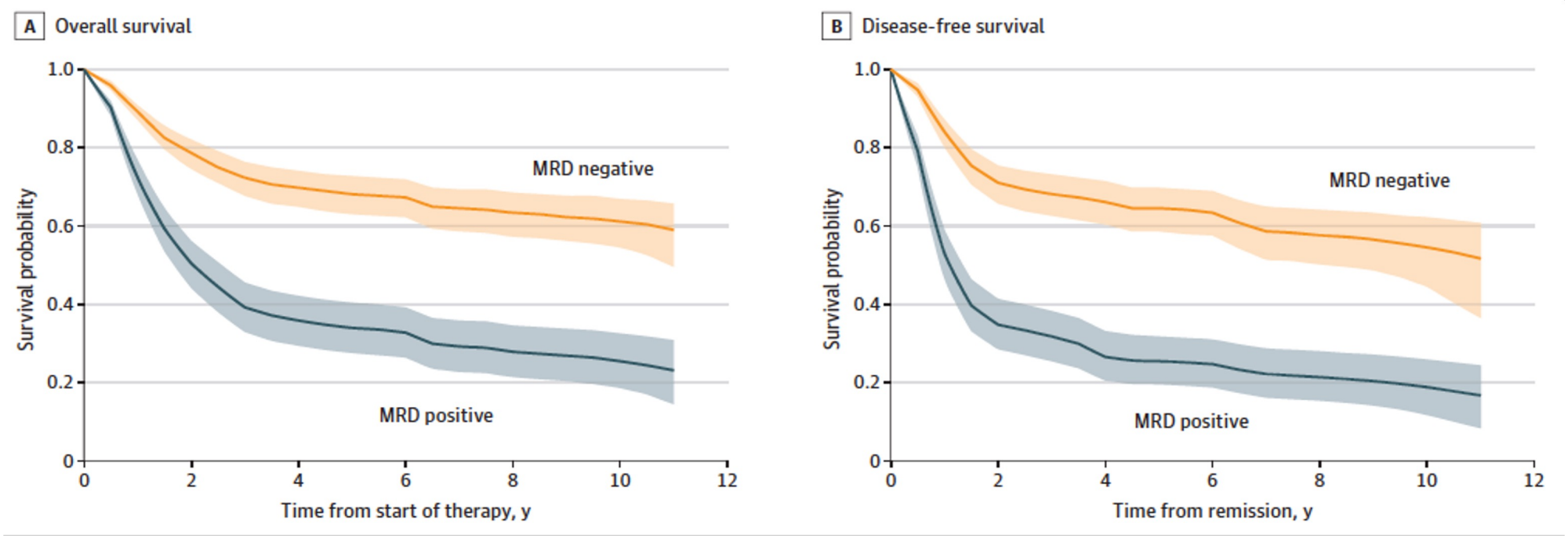
- 5951 patients in RFS analyses
- 5606 patients in overall survival analyses;



"the beneficial effect of ASCT takes place as soon as the risk of relapse exceeds 35-40%; when probabilities of relapse are below those percentages the risk of treatment-related mortality will attenuate the survival advantage of this procedure"

Koreth, JAMA 2009

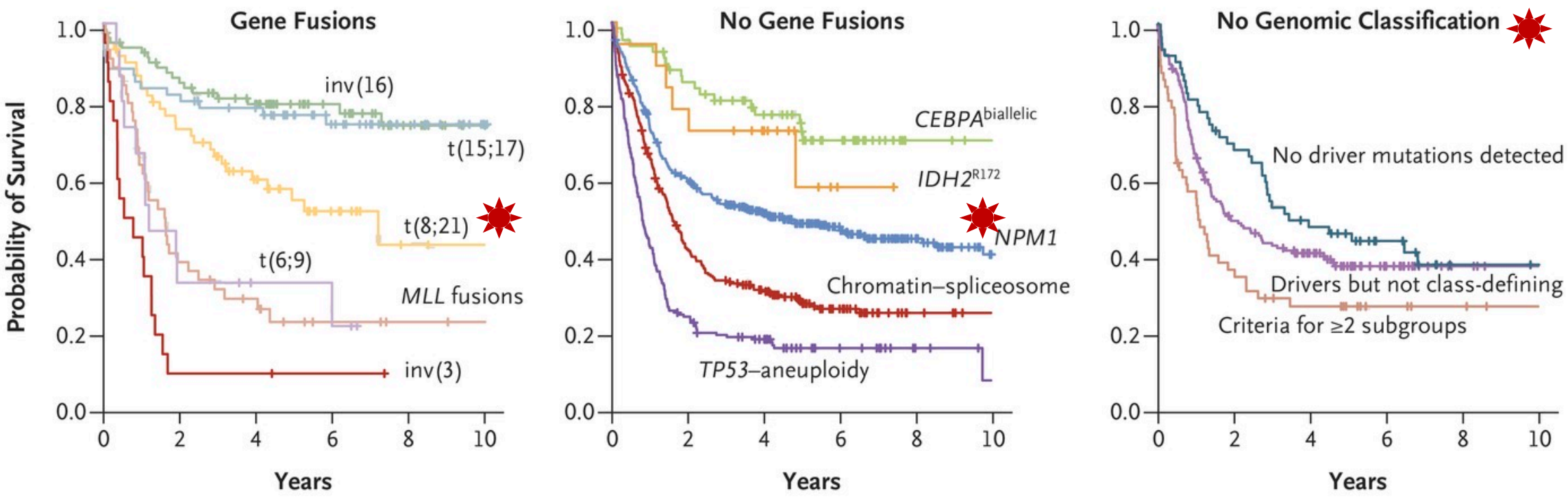
Association of MRD with survival outcomes in patients with AML



- Systematic review and meta-analysis of 81 publications reporting on 11’151 patients
- Estimated 5-year DFS was 64% for patients MRD^{NEG} and 25% for those MRD^{POS}
- Estimated OS was 68% for patients MRD^{NEG} and 34% for those MRD^{POS}
- The difference of 5-year restricted mean survival time of the MRD^{NEG} and MRD^{POS} groups was 15.4 months for OS and 19.6 months for DFS.

Short N, et al. JAMA Oncology. 2020

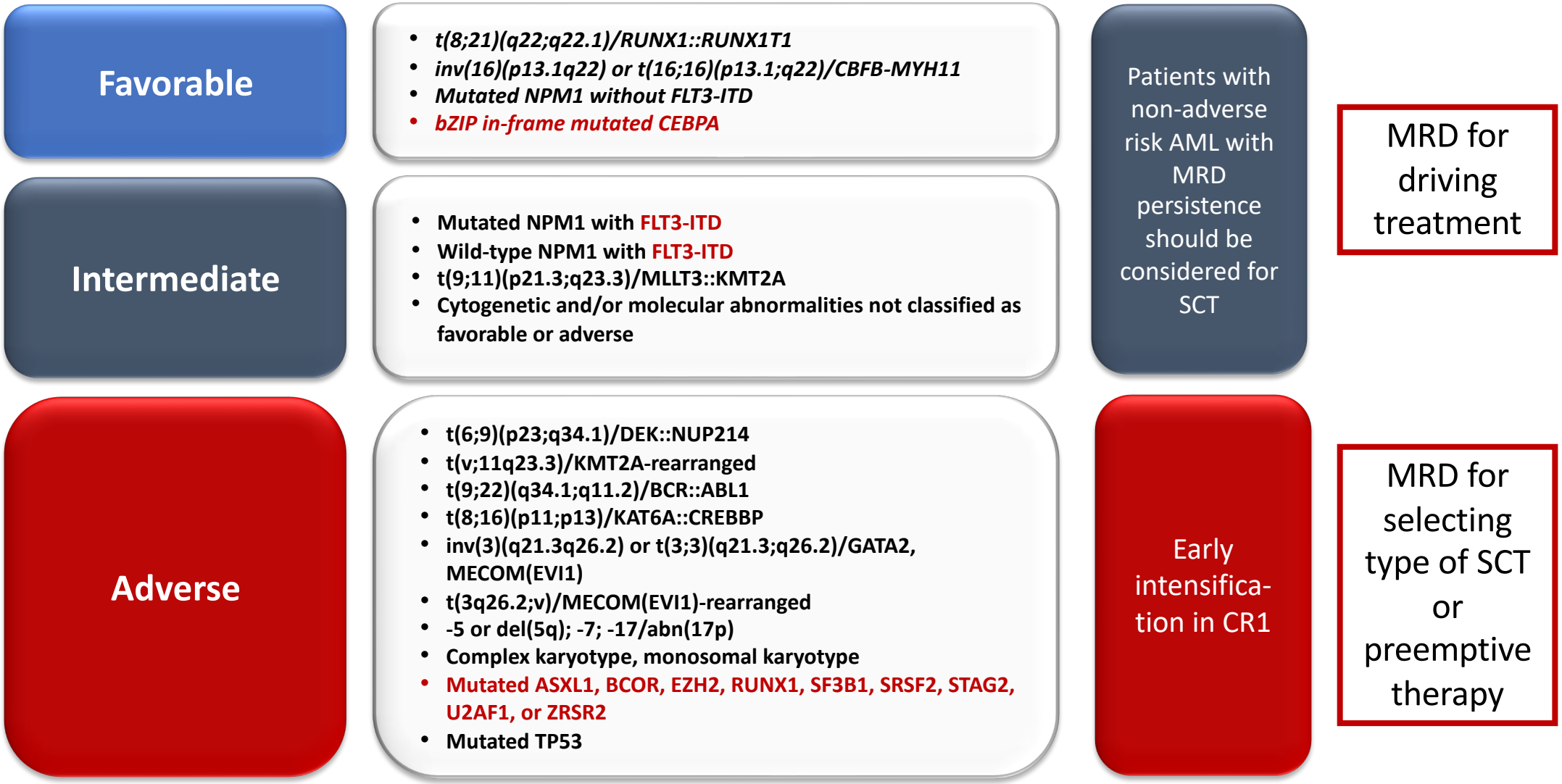
Is upfront molecular subclassification comprehensive?



Upfront genetic profiling may be inadequate for outcome prediction in some categories of patients: those with intermediate risk features and those lacking a prognostic molecular profiles

Papaemmanuil E et al. N Engl J Med ;374:2209-2221

ELN2022 clinical recommendations for AML treatment



Döhner H, et al. Blood. 2022

ELN general principles for clinical practice

Schuurhuis GJ, Blood 2018

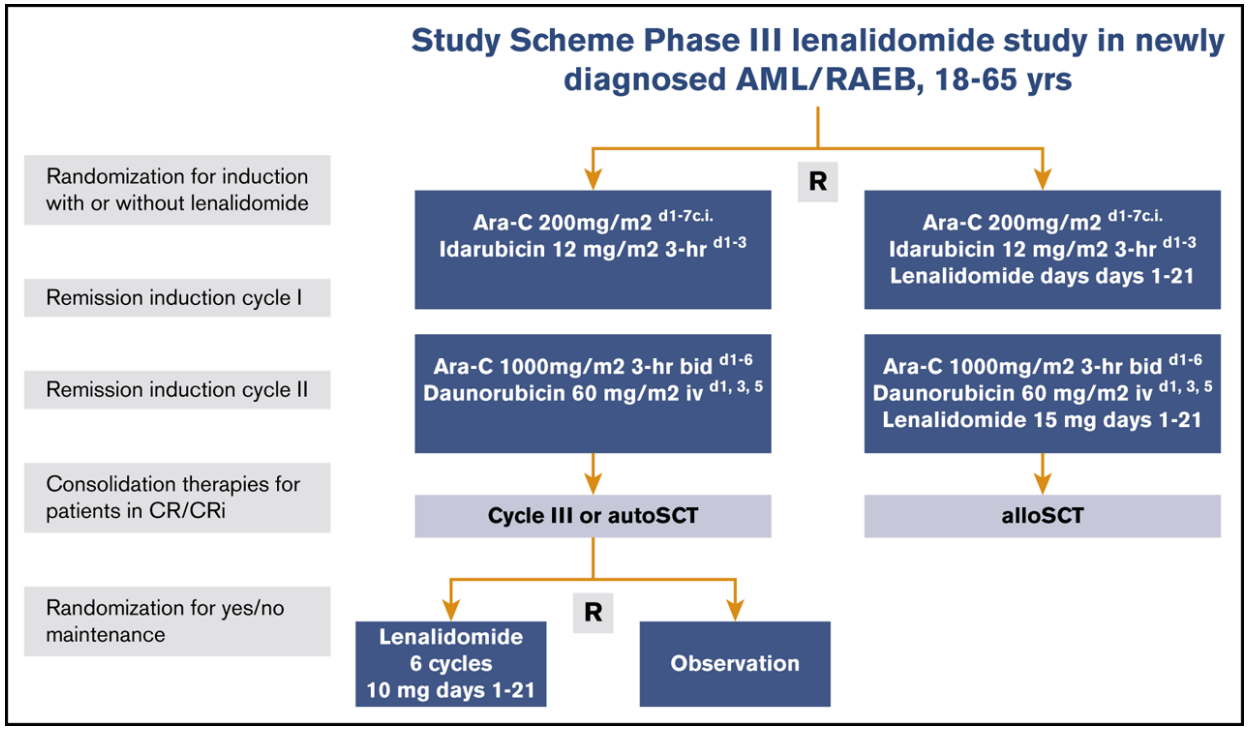
- Should be monitored using RT-qPCR
  - Acute promyelocytic leukemia
  - Core-binding factor AML
  - AML with NPM1 mutation
- AML subgroups NOT including APL, CBF AML, and AML with NPM1 mutation
  - Use MFC for MRD assessment

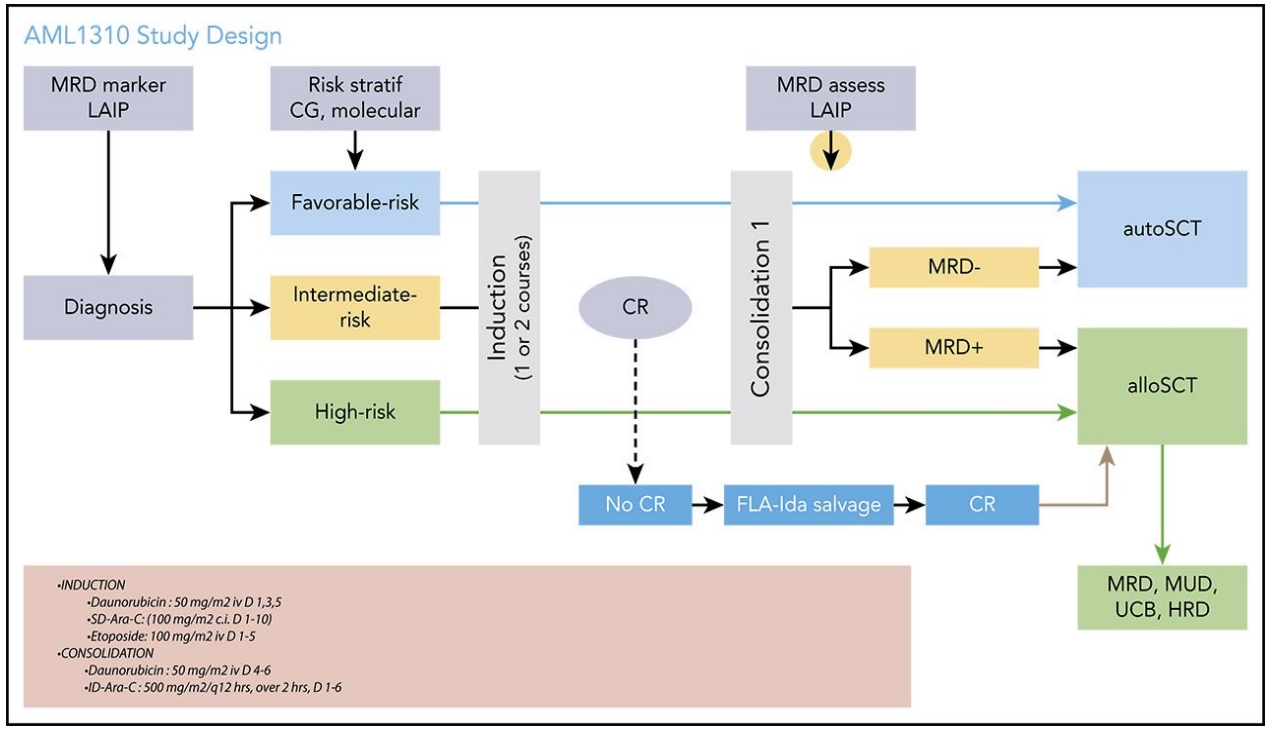
Update 2021

- For patients with mutant NPM1, CBF AML or APL we recommend molecular MRD assessment by qPCR or dPCR.
- AML patients outside these molecularly defined subgroups should be monitored for MRD using MFC.
- NGS-MRD monitoring is useful to refine prognosis in addition to MFC but, to date, there are insufficient data to recommend NGS-MRD as a stand-alone technique.

Prospective, MRD-driven trials

HOVON-SAKK-132, GIMEMA AML1310

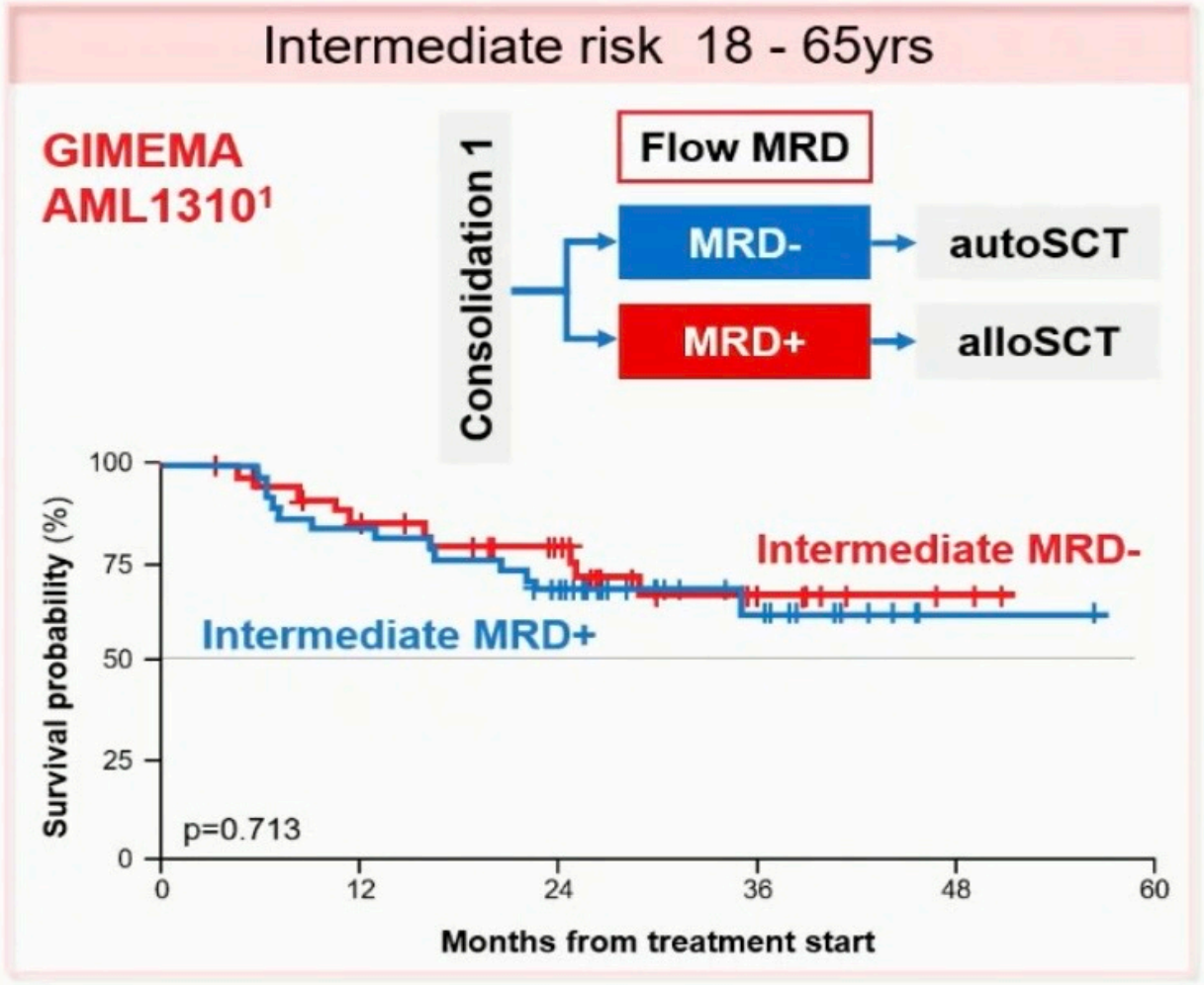


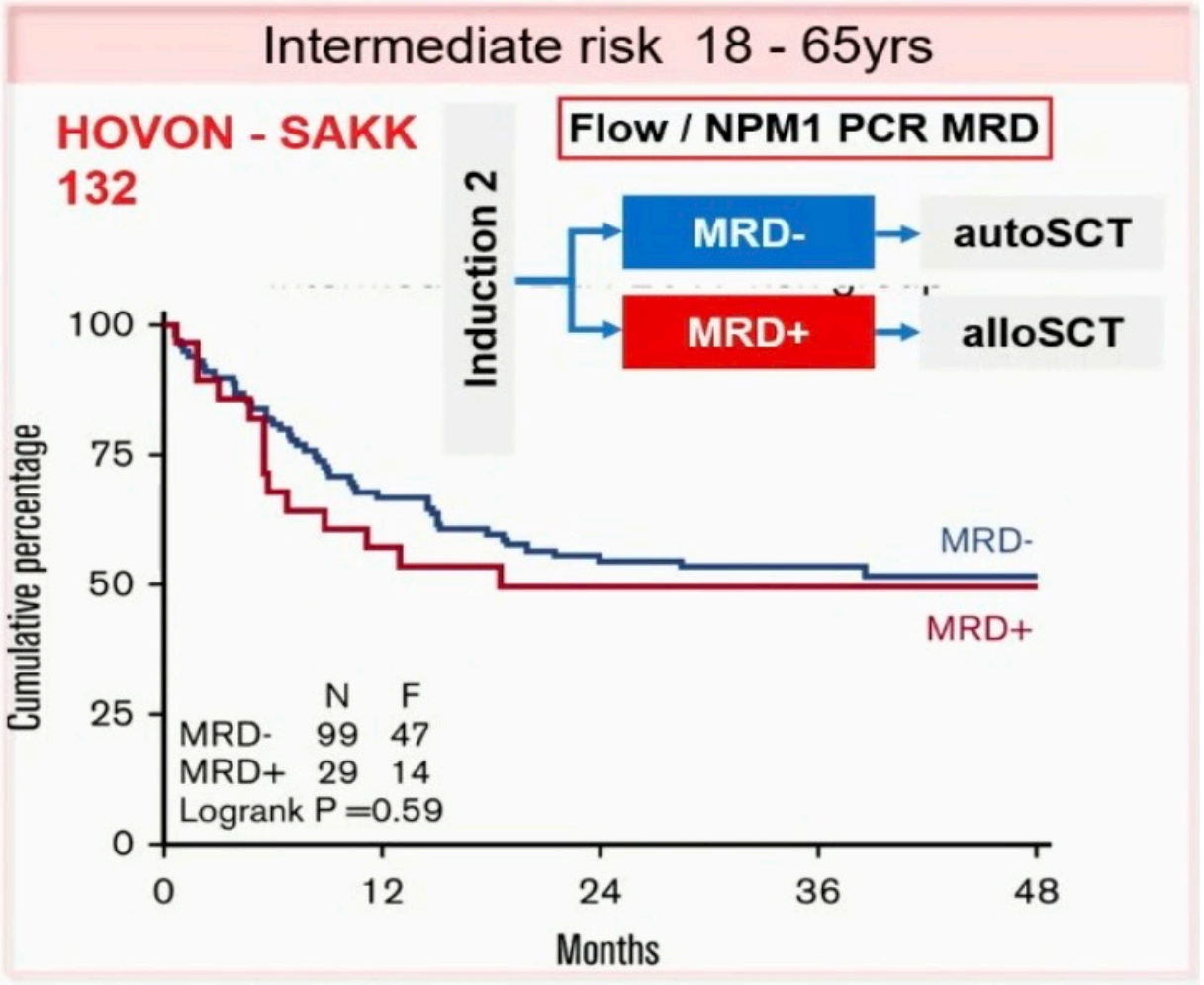


Lowenberg et al. Blood Adv 2021

Venditti A et al, Blood, 2019

Prospective MRD-driven clinical trials, outcome of IR patients



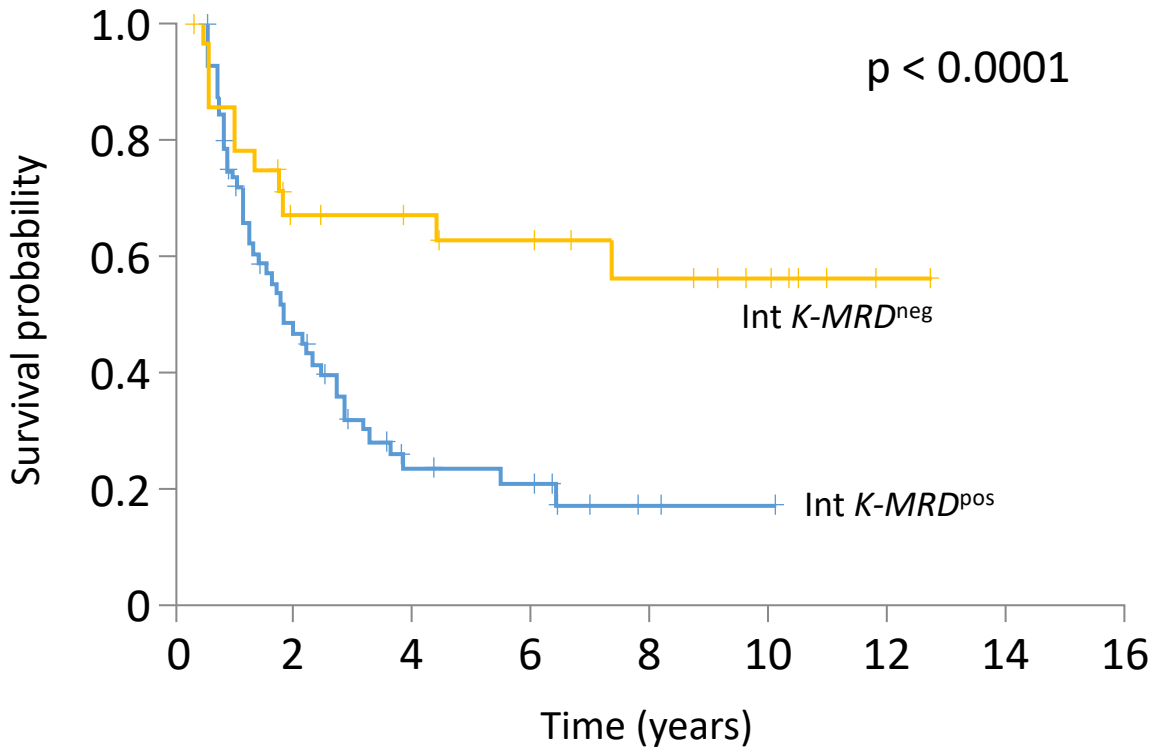


Venditti A et al, Blood, 2019

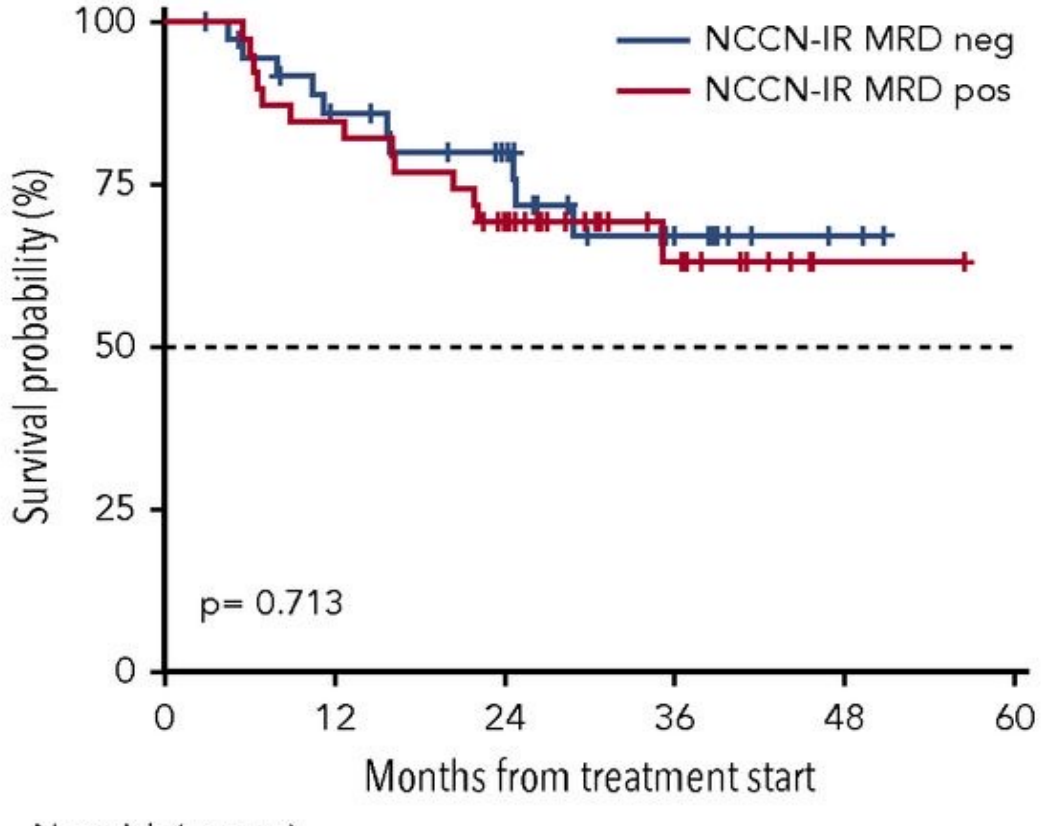
Lowenberg et al. Blood Adv 2021

MRD by MFC in Intermediate-risk patients

Retrospective *in house* observation
"donor vs. no donor"



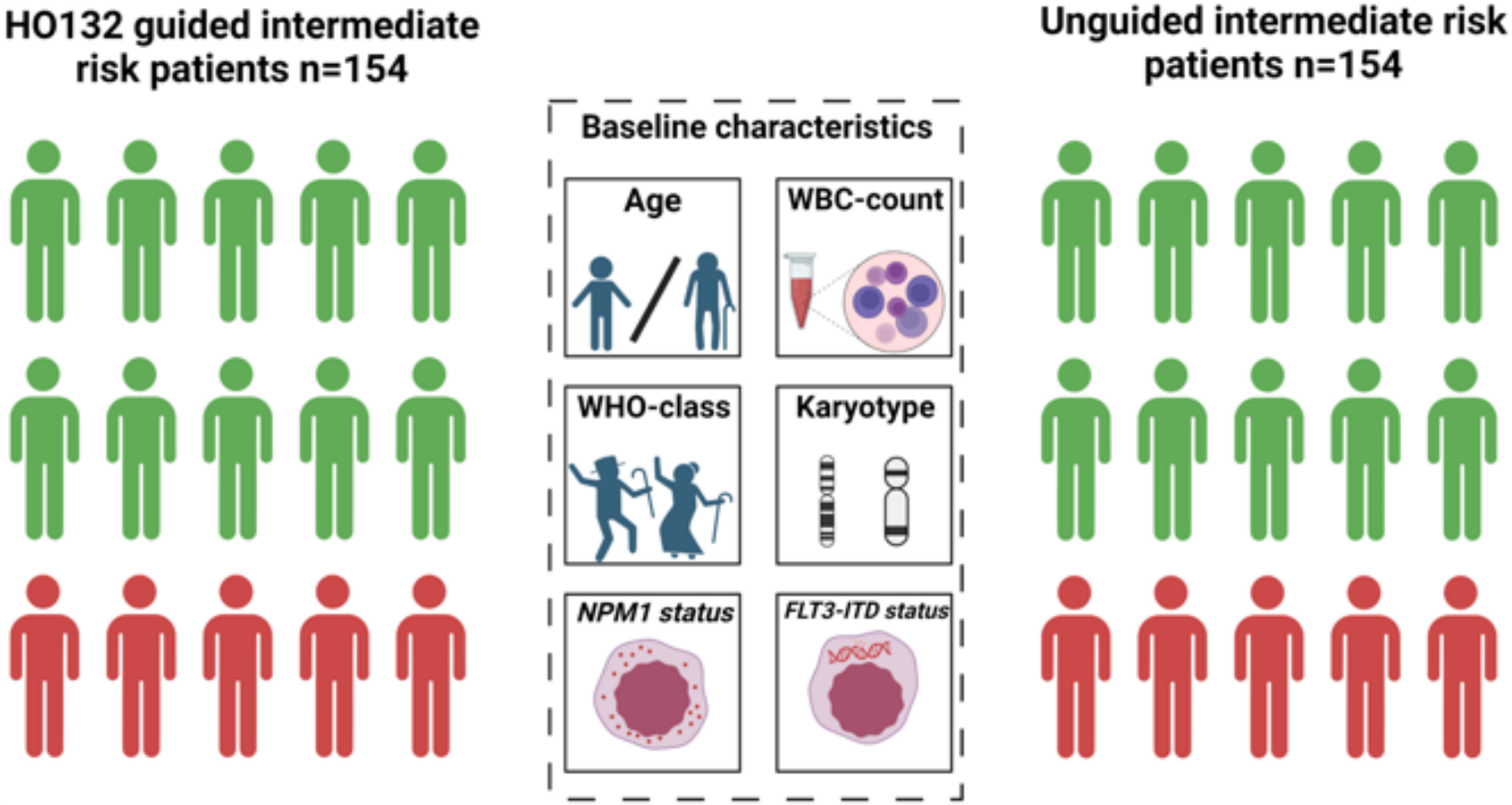
GIMEMA AML1310 protocol
"transplant vs. no transplant"



Modified from Buccisano F, et al. Blood. 2010.

Venditti et al. Blood 2019;134:935-945

Propensity Score Matching

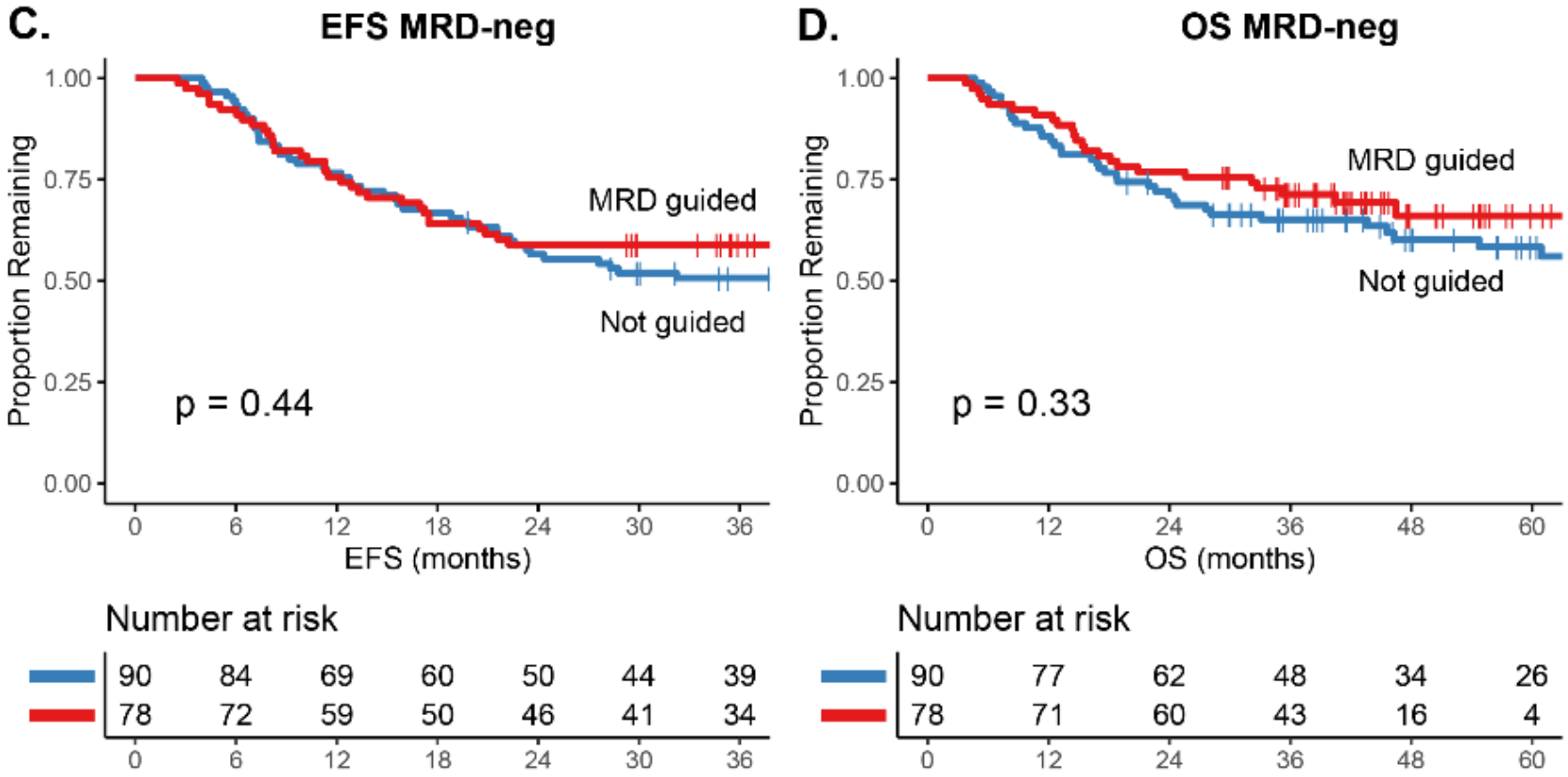


Courtesy of J. Tettero

110 matches

Created with BioRender.com

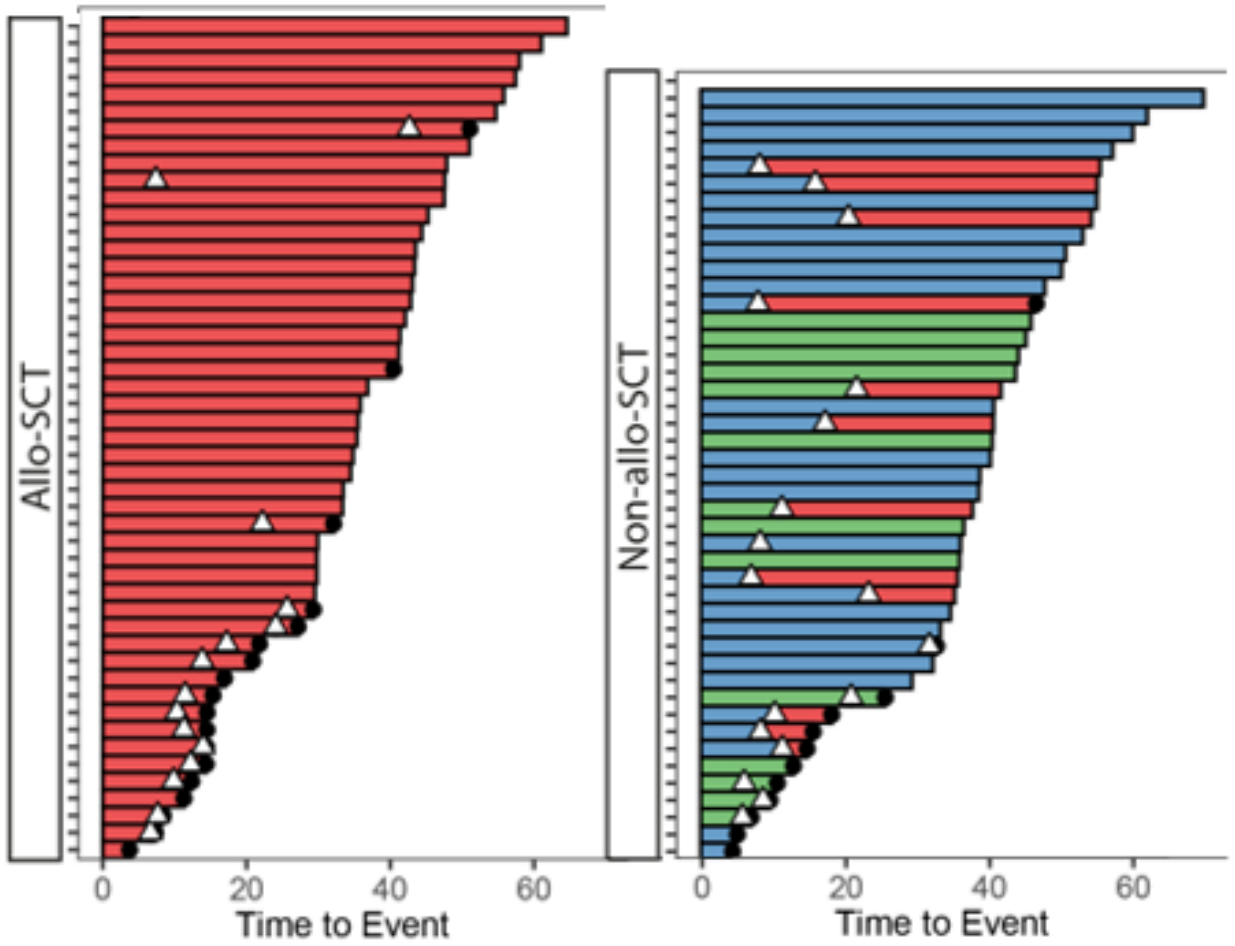
No survival difference between MRD-guided and non-guided cohorts after matching



MRD-negative patients

Tettero et al, 2023. *Haematologica*

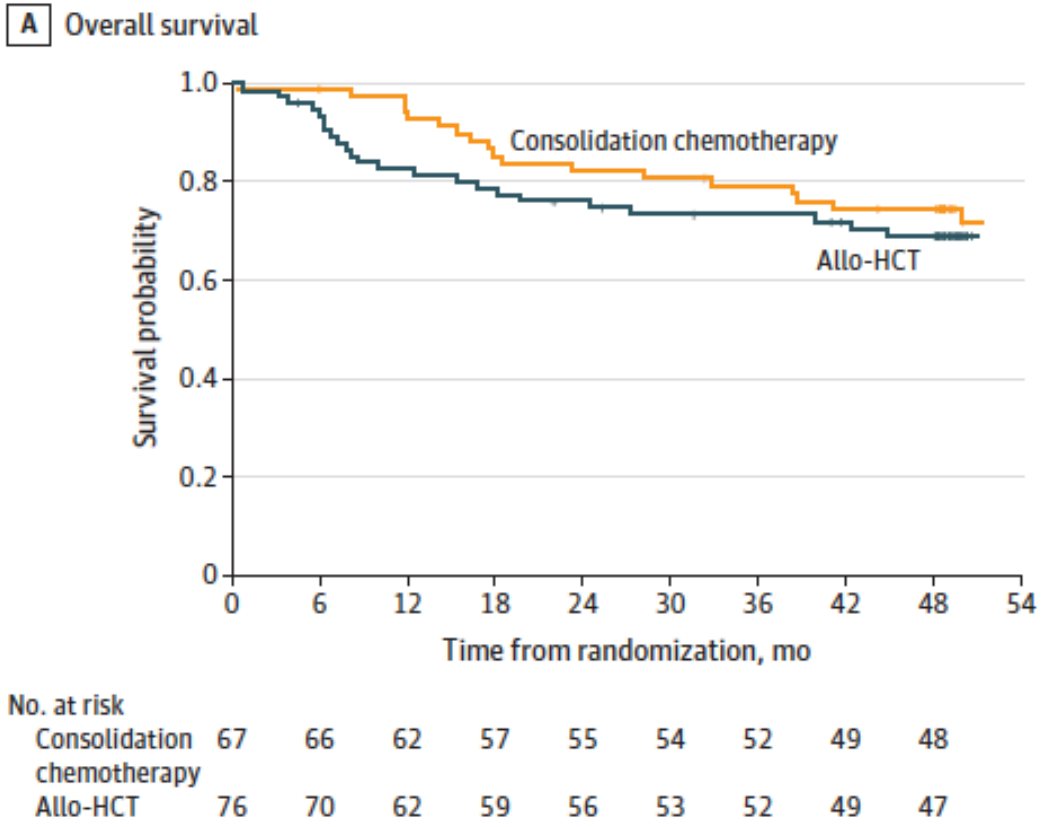
Time to event MRD-negative intermediate risk patients auto-SCT

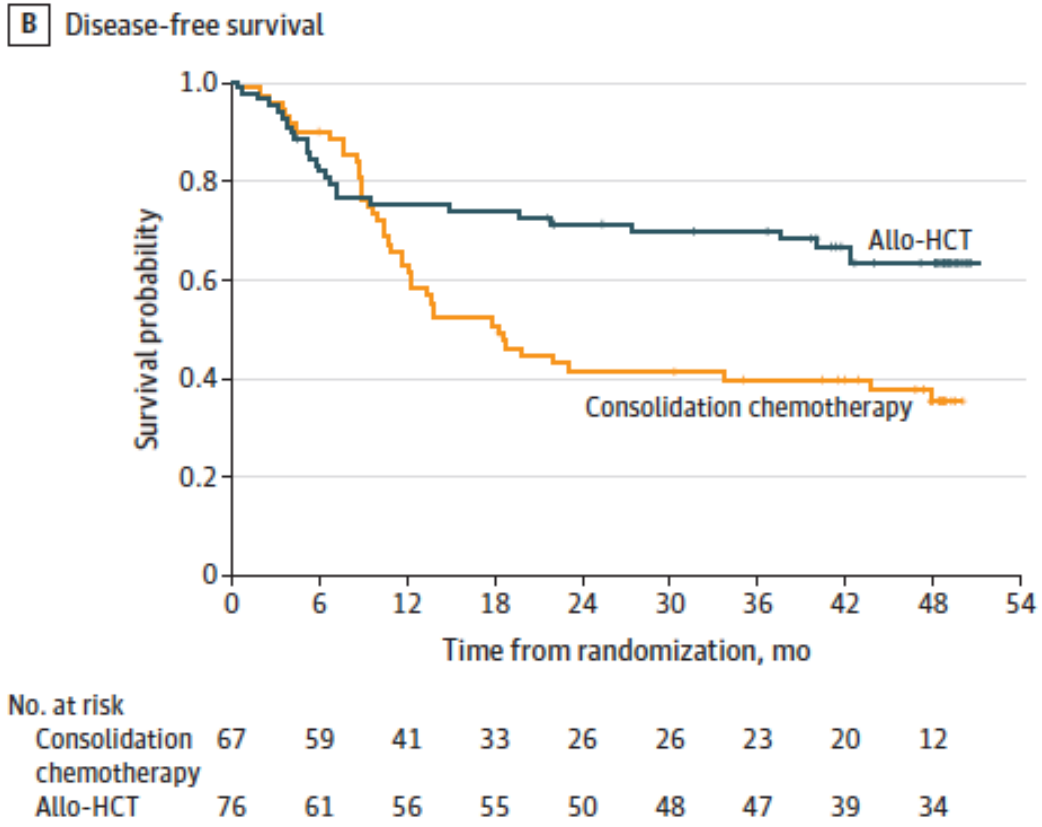


- 44 non-allo consolidation
- 12 salvaged (delayed) allo-SCT

Tettero et al, 2023. *Haematologica*

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





Bornhäuser M et al., JAMA 2023

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

POST-HOC ANALYSIS

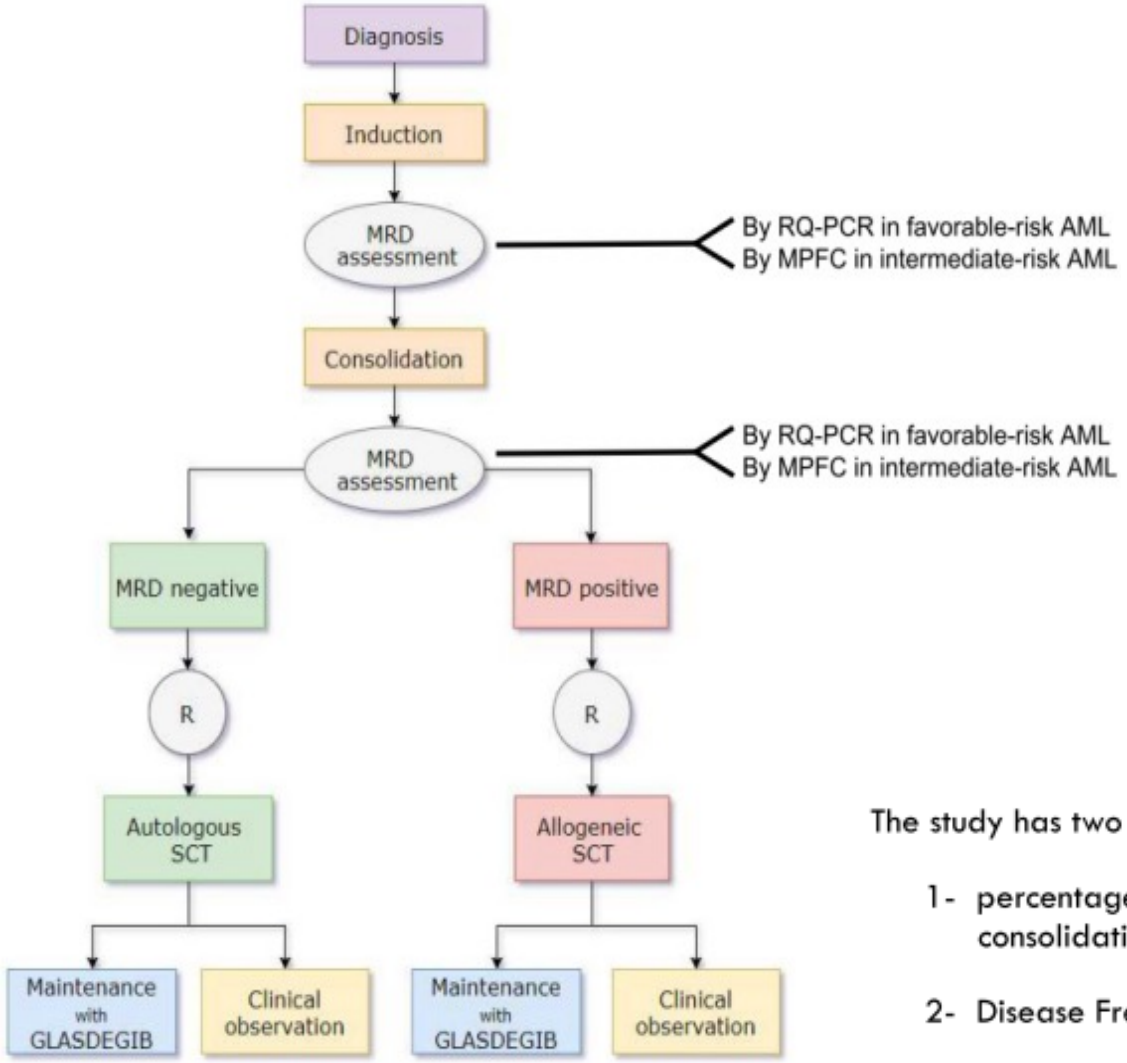
- Patients with intermediate-risk AML according to the 2017 ELN classifications revealed
  - **DFS after 2 years (70% after HCT and 39% after consolidation chemotherapy; P = .02)**
  - **No superiority with regard to OS (76% after allogeneic HCT vs 83% after consolidation chemotherapy)**
- **All 41 patients relapsing in the consolidation chemotherapy group proceeded to allo-HCT** directly (n=20) or after salvage therapy (n=21).

CONCLUSIONS

- Patients 60 years or younger with intermediate-risk AML, as defined by Medical Research Council cytogenetic criteria, despite an improved DFS, **do not benefit from allo-HCT during first CR with regard to OS**.
- **The early identification of a suitable donor allows timely rescuing** of those patients with relapse after conventional consolidation chemotherapy.
- Future studies that apply **longitudinal monitoring of residual disease** dynamics will help to personalize the ideal time point for allo-HCT in most patients.

Bornhäuser M et al., JAMA 2023

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

Maintenance post-transplant
Glasdegib 100 mg daily, orally for up to 1 year or until toxicity/relapse

The study has two co-primary endpoints:

1- percentage of MRD negativity after consolidation treatment in patients treated in induction and consolidation with chemotherapy plus GO;

2- Disease Free Survival (DFS) in patients randomized to glasdegib maintenance or clinical observation

Conclusions

- Upfront genetic profiling may be inadequate for treatment selection in some categories of patients
- Comprehensive determination of pre-treatment (karyotype, genetics) and post treatment (MRD) refines prognosis
- MFC and molecular biology are the techniques of choice in intermediate risk AML
  - High technical standard requirement
  - Complementary application (according to specific transcript or phenotypic array)
- New evidences coming from MRD-oriented prospective clinical trials

Should all intermediate-risk fit patients undergo alloHSCT in CR1?

- NO -

Provided a thorough estimate of remission quality and relapse risk is performed

TOR VERGATA UNIVERSITÀ DEGLI STUDI DI ROMA

Amsterdam UMC
Universitair Medische Centra

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

ESCCA
European Society
for Clinical Cell Analysis

ELN-DAVID

ISCCA
Italian Society for
Cytometric Cell Analysis

EHA | SWG
SPECIALIZED WORKING GROUPS