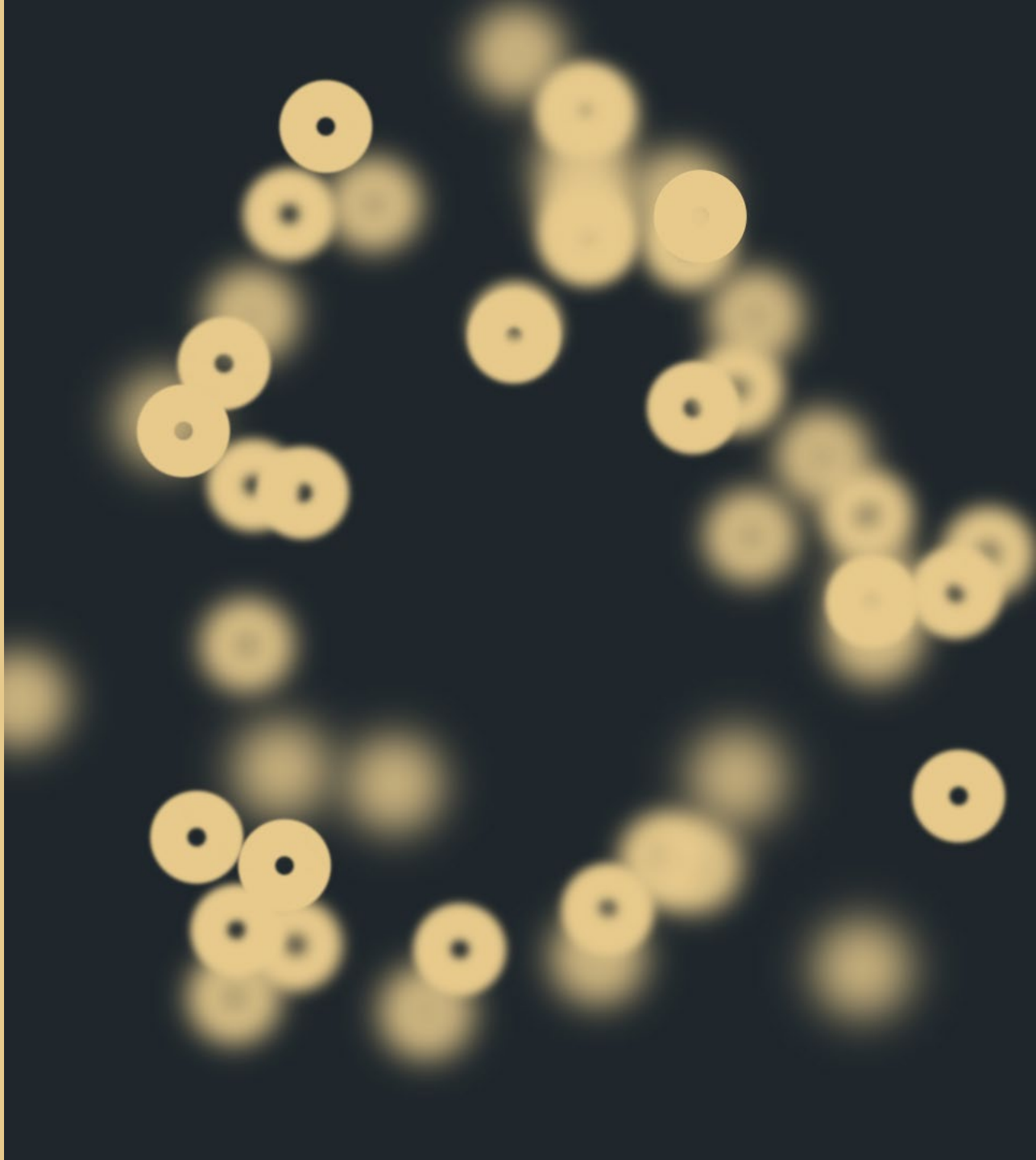
eha

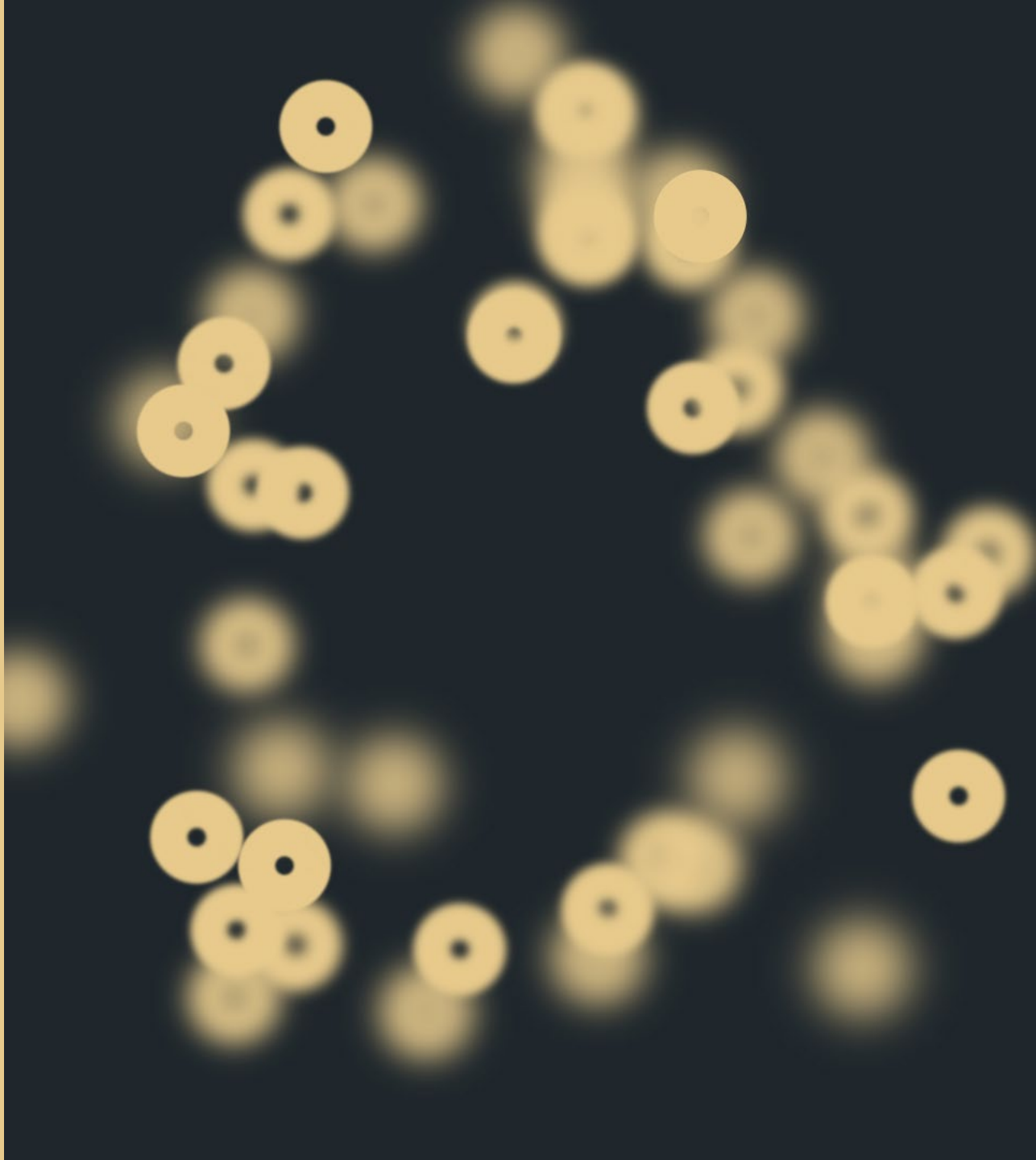
EHA-SWG Scientific Meeting on Recent Advances in the Pathogenesis and Treatment of Secondary Acute Myeloid Leukemias

Berlin, Germany
April 25-26, 2025



EFFICACY OF CPX-351 IN SECONDARY ACUTE MYELOID LEUKEMIA DEFINED ACCORDING TO WHO 2022 CLASSIFICATION

Fabio Guolo, MD, PhD



Background

2016 WHO CLASSIFICATION

Acute myeloid leukemia (AML) and related neoplasms

- AML with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
  - APL with *PML-RARA*
  - AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
  - AML with t(6;9)(p23;q34.1);*DEK-NUP214*
  - AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
  - AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
  - *Provisional entity: AML with BCR-ABL1*
  - AML with mutated *NPM1*
  - AML with biallelic mutations of *CEBPA*
  - *Provisional entity: AML with mutated RUNX1*
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, NOS

2022 WHO CLASSIFICATION

AML with defining genetic abnormalities

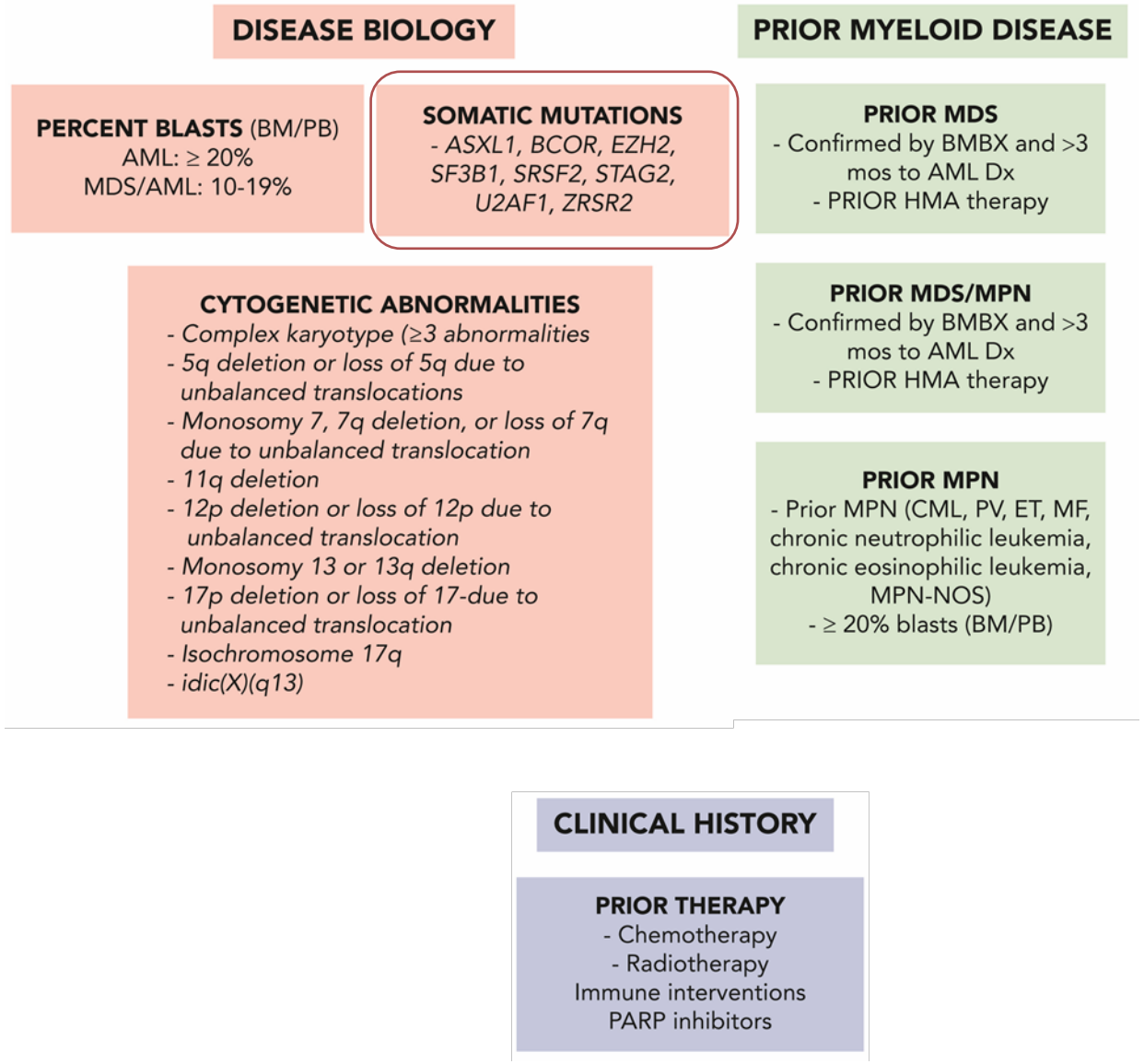
- Acute promyelocytic leukemia with *PML::RARA* fusion
- AML with *RUNX1::RUNX1T1* fusion
- AML with *CBFB::MYH11* fusion
- AML with *DEK::NUP214* fusion
- AML with *RBM15::MRTFA* fusion
- AML with *BCR::ABL1* fusion
- AML with *KMT2A* rearrangement
- AML with *MECOM* rearrangement
- AML with *NUP98* rearrangement
- AML with *NPM1* mutation
- AML with *CEBPA* mutation
- AML, myelodysplasia-related
- AML with other defined genetic alterations
  - AML with *RUNX1T3::GLIS2* fusion
  - AML with *KAT6A::CREBBP* fusion
  - AML with *FUS::ERG* fusion
  - AML with *MNX1::ETV6* fusion
  - AML with *NPM1::MLF1* fusion

AML defined by differentiation

- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute basophilic leukemia
- Acute myelomonocytic leukemia
- Acute monocytic leukemia
- Acute erythroid leukemia*
- Acute megakaryoblastic leukemia

Advances in **understanding of Acute Myeloid Leukemia** (AML) **ontogeny** are leading to a **switch from a clinical to a molecular definition** of **secondary AML** (s-AML).

Arber AD et al. Blood 2016
Khoury JD et al. Leukemia 2022



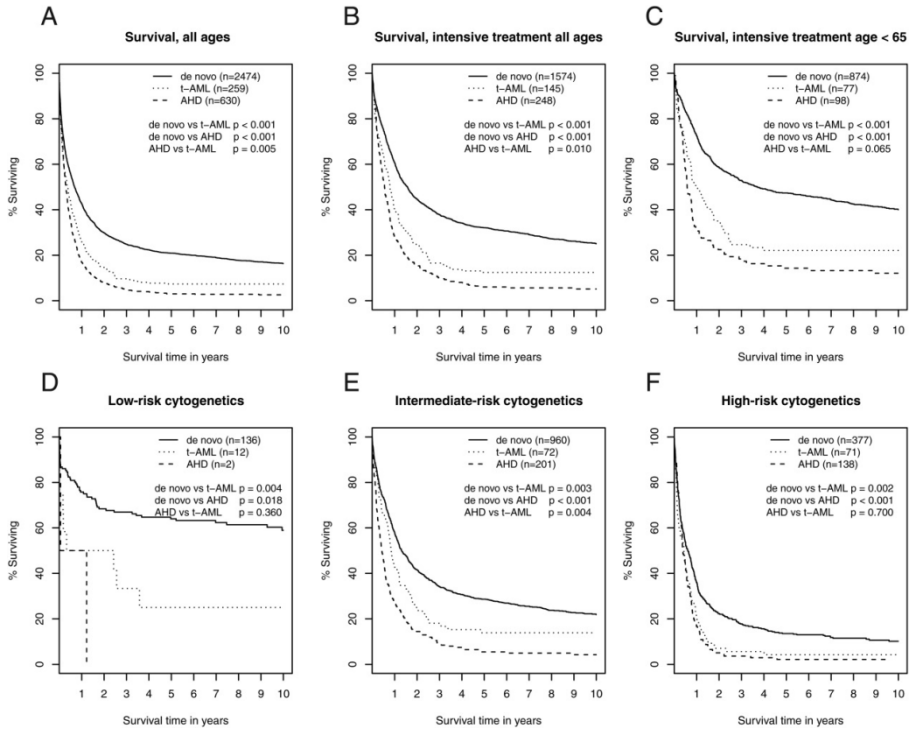
Adapted from Green SD et al. Blood 2025

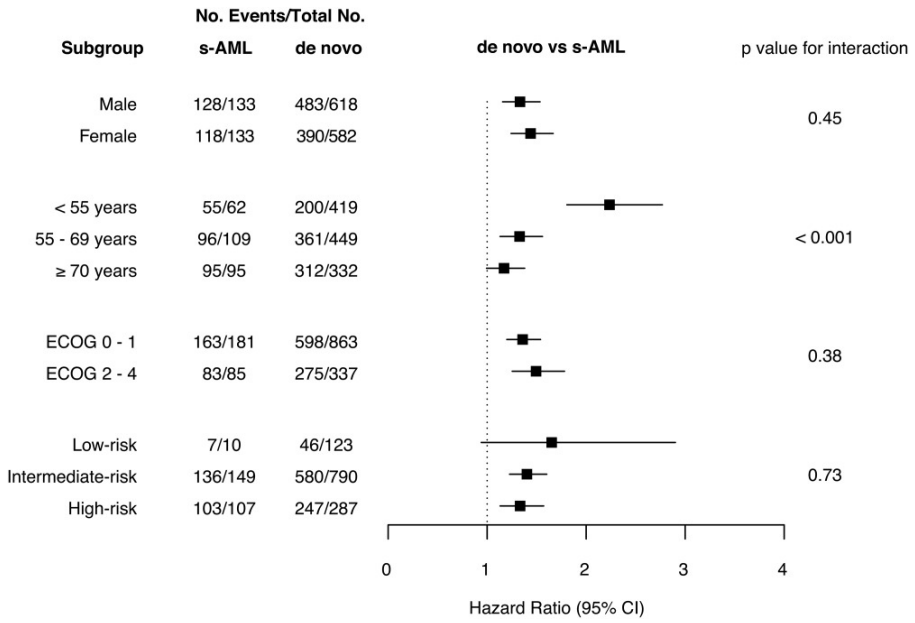
This is reflected in the modern WHO 2022 classification where s-AML is **hierarchically defined** by:

1. the presence of **myelodysplasia** (MDS) **related gene mutations**
2. **MDS** related **cytogenetic aberrations** if no MDS-gene mutations are found
3. **clinically**, if **an antecedent history of MDS** is present

Therapy-related AML is retained as a diagnostic qualifier

Khoury JD et al. Leukemia 2022

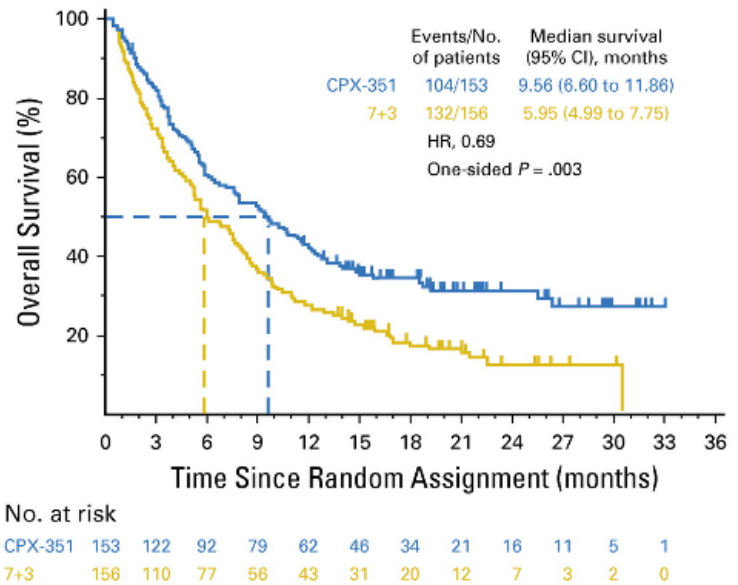




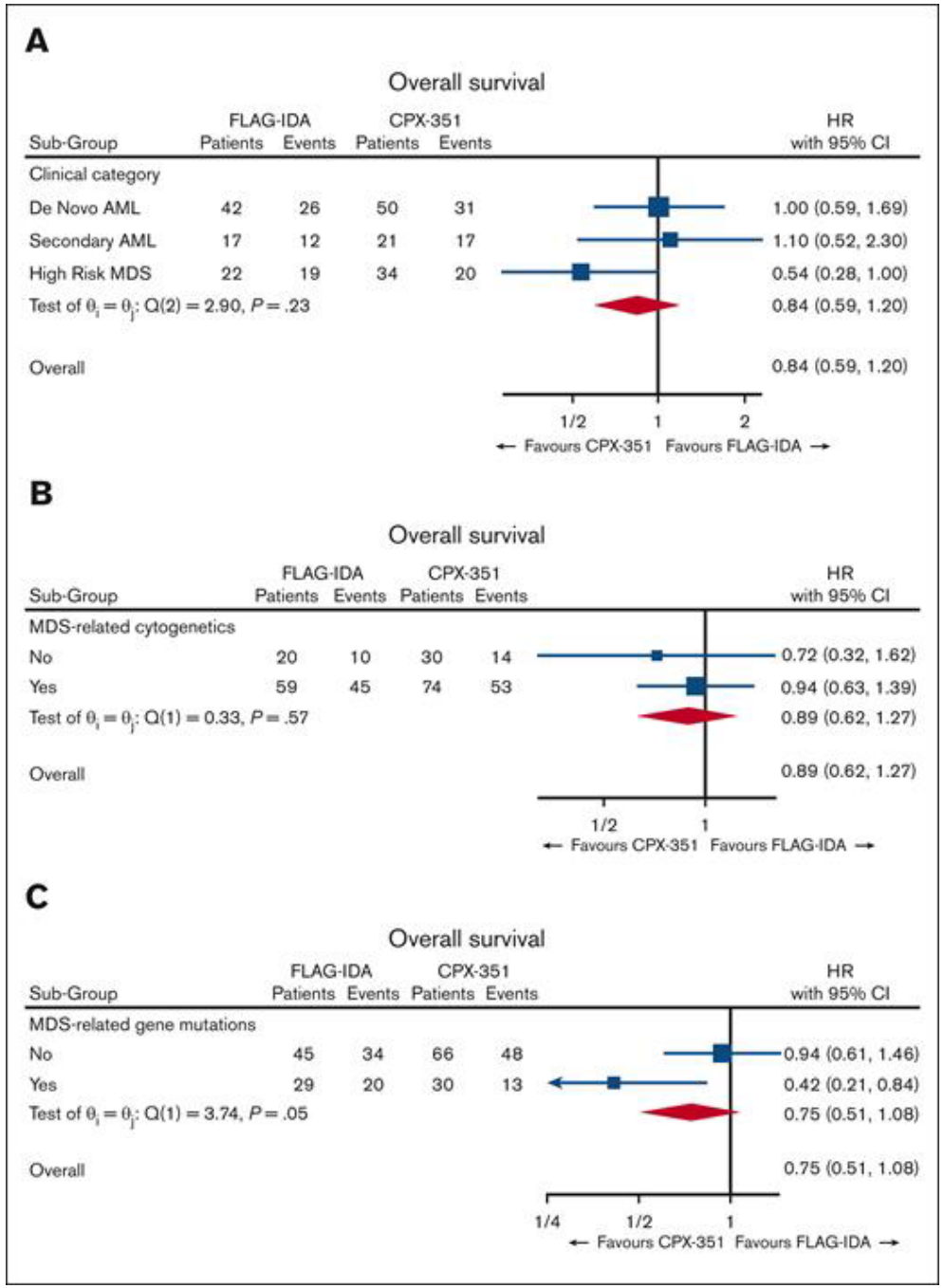
Hulegardh E, Am Journ Hematol 2014

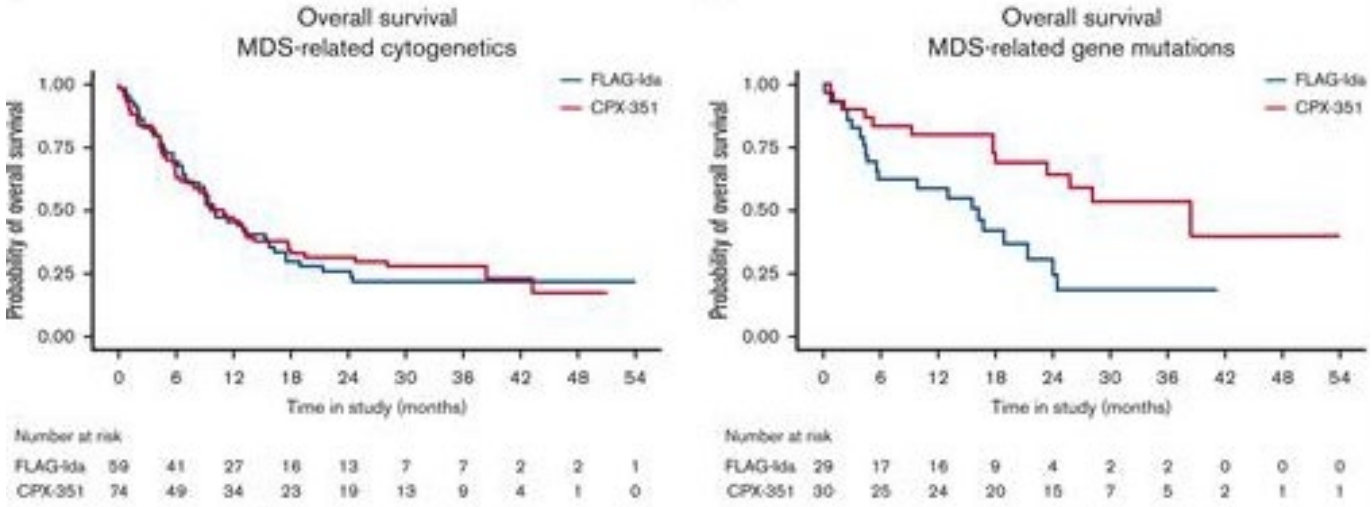
- Historically, **secondary AML** has been characterized by a **worse prognosis** compared to the **de-novo counterpart** in the **same cytogenetic group** when treated with **conventional chemotherapy**.

- **CPX-351** proved to be **more effective than conventional 3+7** in a Phase III randomized trial in **elderly s-AML patients**
- The definition of s-AML in the Phase III trial was **based** on the **2016 edition of WHO classification**, including **AML with Myelodisplasia-related changes** (cytogenetic, anamnesthic or morphological criteria) and **therapy-related AML**



Arber AD et al. Blood 2016
Lancet J, et al. Journ Clin Oncol 2018





- In the **UK NCRI AML 19 clinical trial**, High risk AML patients were **randomized** to receive either **CPX-351 or FLAG-Ida**
- In the **whole cohort**, there **was no difference** in terms of survival **between the two arms**
- However, in **HR patients who had MDS-related genes aberrations** *(ASXL1, BCRO, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2)*, **CPX-351** proved to be **superior to FLAG-IDA**

Othman J et al. Blood Advances 2023

Study Rationale and Aims

CPX-351, compared to conventional 3+7, proved to be **more effective** as **frontline treatment for s-AML** patients as **defined by the WHO 2016** classification, which **did not consider MDS related gene mutations**.

In the British trial, MDS-related aberrations were analysed, but the trial enrolled HR AML, regardless of having *de novo* or secondary disease.

The implication of the WHO 2022 classification on **treatment choice** remains **unclear**, since **conflicting data** about the **efficacy of CPX-351** in **s-AML** defined **according the new classification** are available.

<u>The aims of this study were:</u>

- **to evaluate** the **outcome** of a cohort of **elderly s-AML** patients **receiving** commercially available **CPX-351 treatment, stratifying the cohort** according to the **WHO 2016 and WHO 2022 subgroups of secondary AML.**
- **to evaluate** the **outcome of s-AML patients** harbouring **secondary-type mutations,** with the aim **of confirming the efficacy** of the drug in **the molecularly-defined s-AML** subgroup.

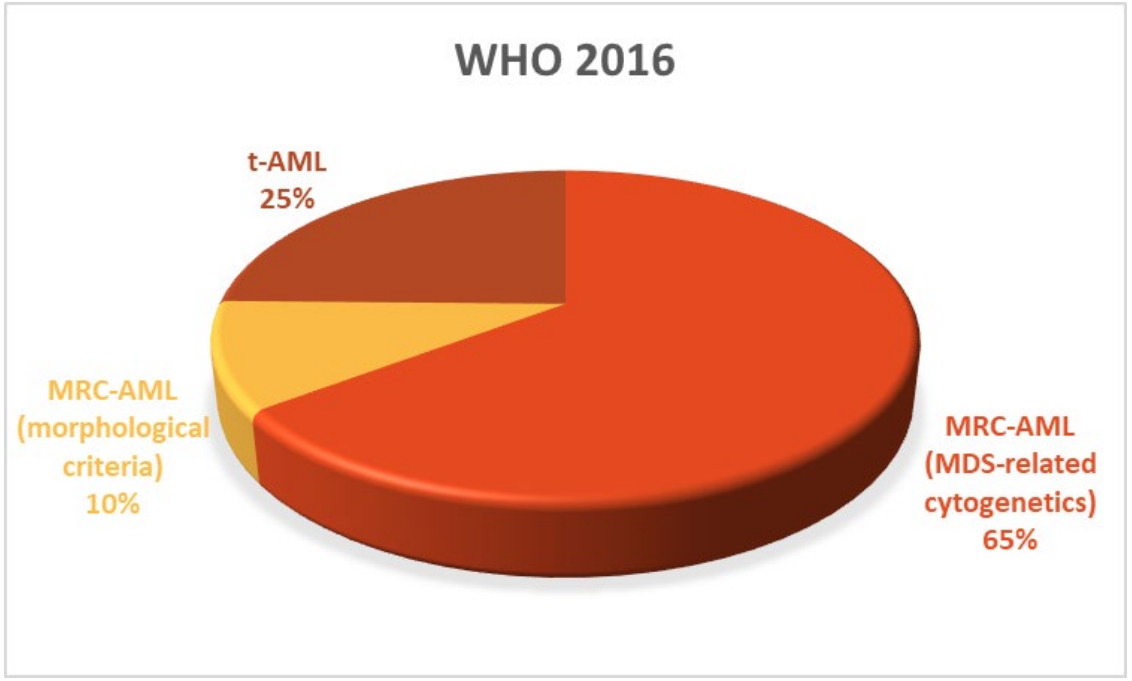
Patients and methods

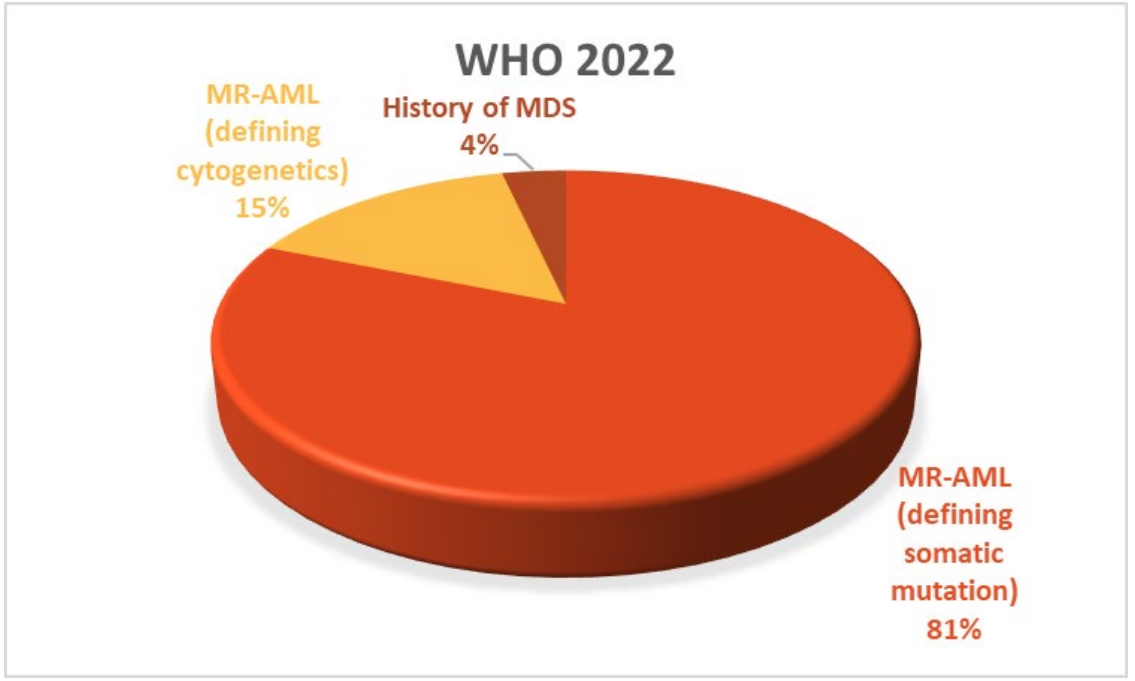
- **A total of 85 patients** (median age 69, range 37-77) **affected by s-AML defined by former WHO 2016 classification** and **treated with CPX-351** in our Centre were included.
- **NGS** was performed using the **Myeloid Solution panel by SOPHiA Genetics**, encompassing 34 critical gene mutations. Samples were processed on an Illumina MiSeq platform, and analysis was performed with SOPHiA DDM® Software.
- **Patients** where divided in s-AML subgroups according to **WHO 2016 and 2022**, taking into account **cytogenetic and genetic data**.
- Minimal residual disease was evaluated in all patients with **MFC**, with a **threshold for positivity of 0.1%** and a minimum of 100000 acquired events.

Arber AD et al. Blood 2016
Khoury JD et al. Leukemia 2022

Results: s-AML subgroups

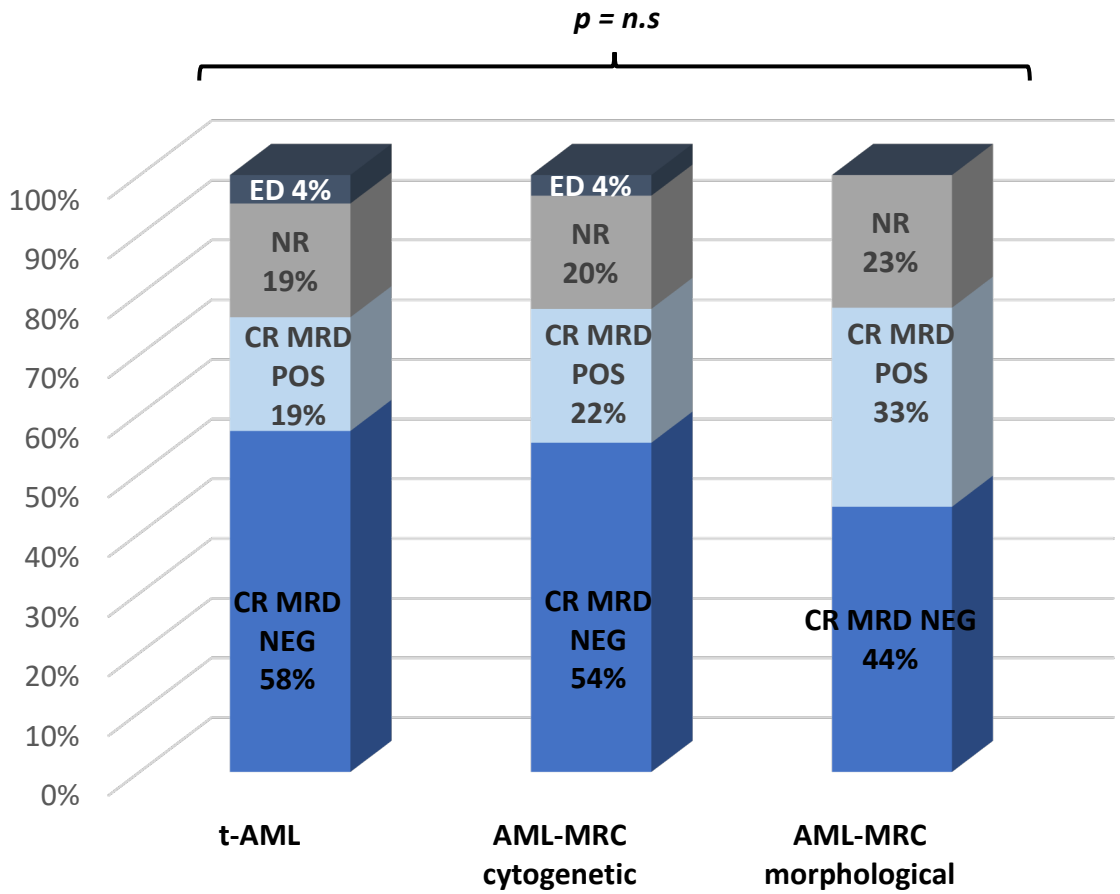
- Following **WHO 2016 classification, 21 patients (25%) had t-AML, 55 (65%) had s-AML with MDS-related cytogenetics and 9 (10%) had s-AML defined by morphological criteria alone**.
- According to **WHO 2022**, **68 patients (81%) had s-AML with** MDS-related **genetic aberration, 12 patients (15%) had s-AML** with MDS-related **cytogenetic aberrations** whereas **3 patients** had a previous **history of MDS only (4%).**
- Two patients **were no longer be considered** affected by **s-AML** in the **new classification (2%).**
- **ELN 2022 risk** score was favourable, **intermediate or unfavourable** in 3 (3%), **28 (33%) and 54 (64%) patients, respectively**.



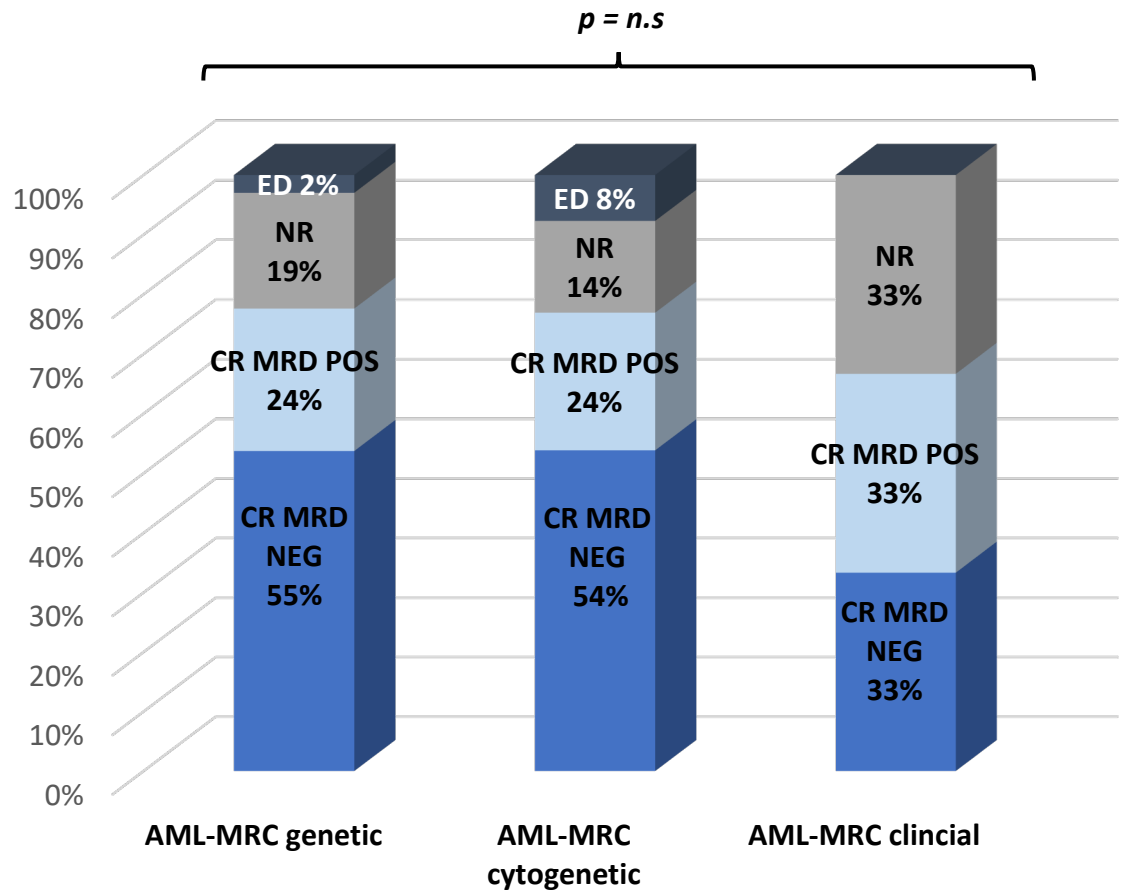


Results: Response

- **After induction, 66 patients (78%) achieved complete remission (CR),** whereas early death rate was 3/85 (3.8%). Among 66 CR patients, **MRD was negative in 48 (72%**). **Both CR rate and MRD** negativity were **not affected by s-AML subcategory**, either **according to WHO 2016 or 2022**, nor by **ELN risk score**.



WHO 2016 s-AML subgroups

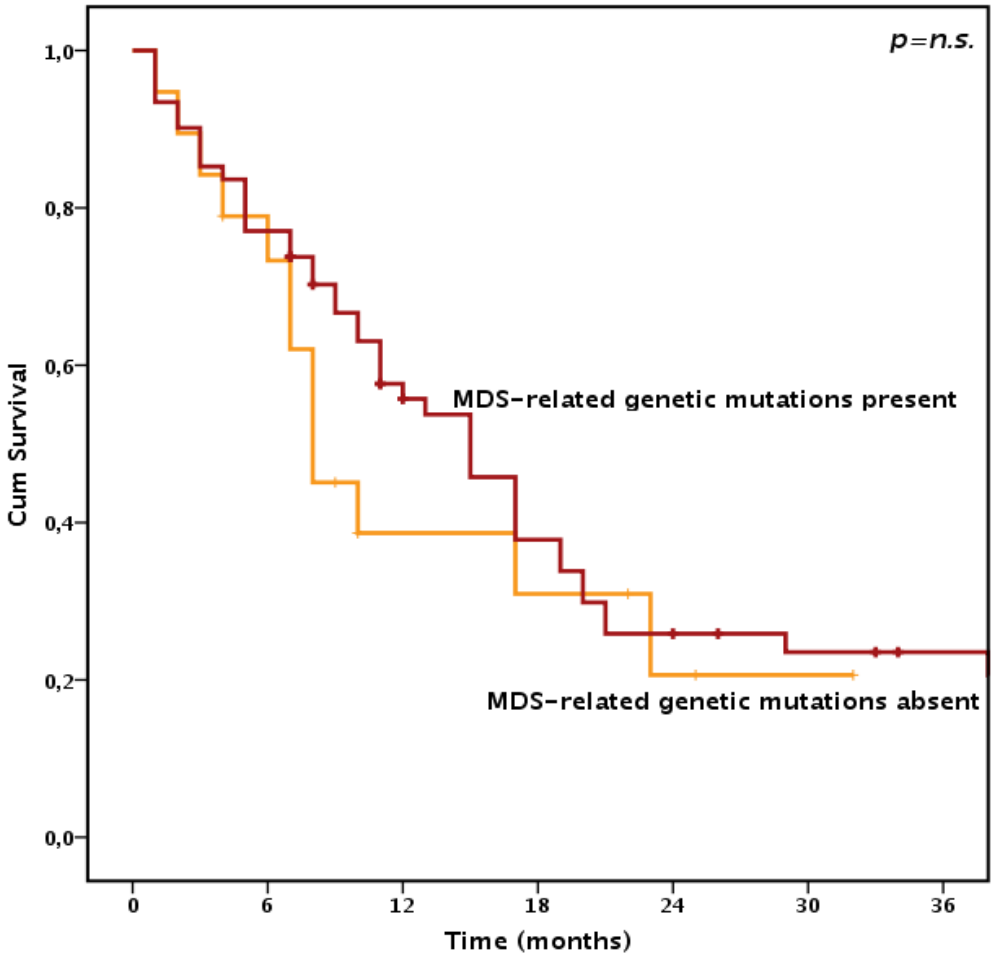


WHO 2022 s-AML subgroups

Results: Survival

- After a **median follow-up of 42.1 months** (CI 95% 31-62 months), **median OS was 19 months** (CI 95% 15.89-20.69) **and 2-year OS was 40.2%.**
- Survival was **not different between s-AML subcategories**, **either in WHO 2016 or 2022 was adopted**.
- **Survival was not affected** by the presence of **MDS-related gene mutations.** Median OS was 21 and 18 months in patients **with or without** s-AML defined by **the presence of MDS-related genes mutations (p=n.s).**

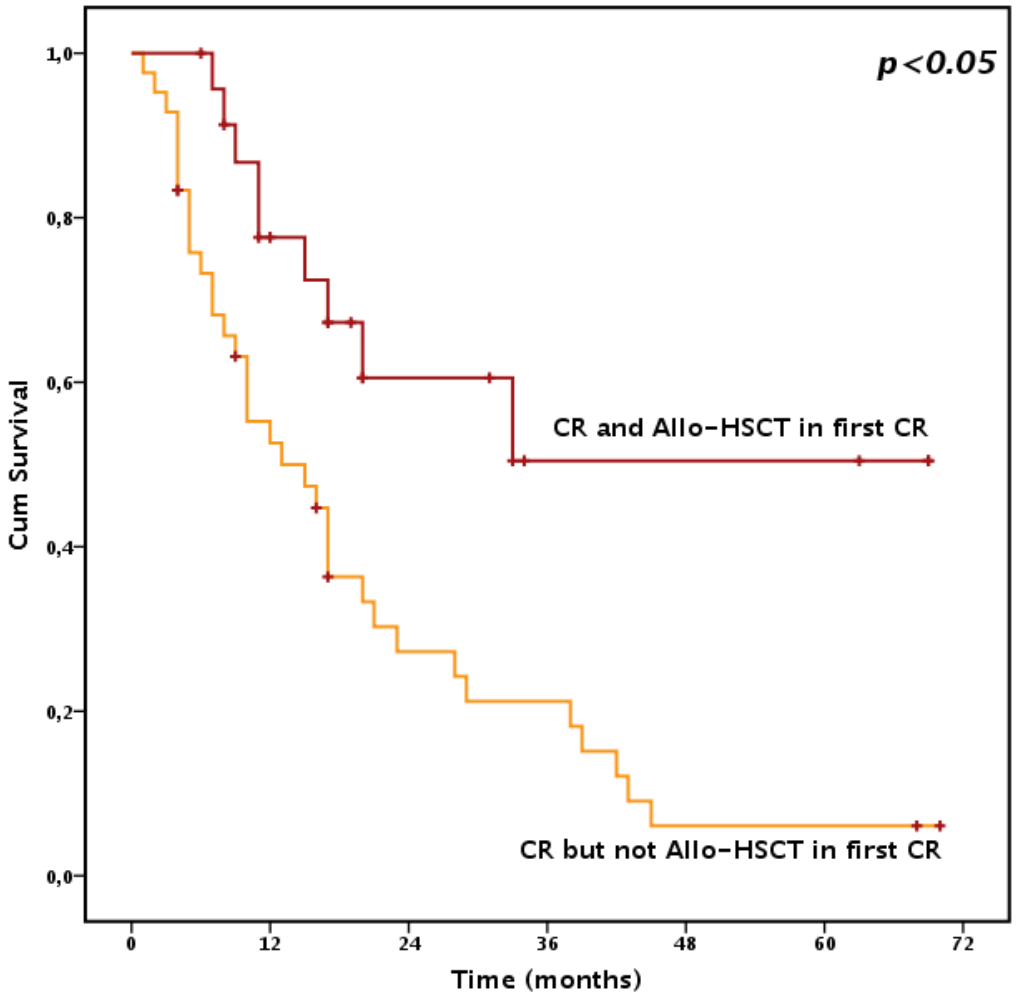
OS according to MDS-related gene mutations



Results: allo-HSCT

- A total of **23 patients** underwent **allogeneic hematopoietic stem cell transplantation** (allo-HSCT) in first CR, **14 of them (61%) with MRD negative status**.
- In order to assess the impact of allo-HSCT, a landmark analysis was performed including only patients alive and in CR ad day 60.
- Median OS was **not reached in CR patients proceeding to HSCT patients, compared to 20 months** among patients **achieving CR but not receiving HSCT**.
- Receiving **HSCT was the only independent factor** related to a **longer overall survival**, both in univariate and multivariate analysis (p<0.05). Survival among **HSCT was not influenced** by the **presence of MDS-related gene mutations** (p=n.s.).

OS according to HSCT (landmark analysis)



Conclusions

- **CPX-351 has high activity in s-AML**, regardless of the s-AML subtype.
- Patients with **MDS-related gene mutations** had a **superimposable outcome** to the other patients, with overall high CR rate, allowing a significant proportion of patients to receive allo-HSCT with negative MRD.
- **Allogeneic HSCT** remains the **most effective consolidation strategy** in order to achieve long term survival.
- Combined with the British data, those results suggest that **CPX-351 is a reasonable option** also for patients with **genetically defined s-AML**.
- **Further study** on s-AML patients defined with WHO 2022 **are needed** in order to confirm those results.

Acknowledgements

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria

IRCCS Ospedale Policlinico San Martino, Genoa, Italy
Head: Prof. R.M. Lemoli

UNIVERSITÀ DEGLI STUDI DI GENOVA

Acute Leukemia Team

Dr. Paola Minetto
Dr. Fabio Guolo
Dr. Carola Riva

Dr. Elena Maio
Dr. Giada Zecchetti
Dr. Ylenia Azzanelli
Dr. Stefano Nicoletta

Molecular Biology Laboratory

Dr. Enrico Carminati
Dr. Clara Nurra
Dr. Francesco Puglisi
Dr. Giuseppina Fugazza

Flow Cytometry Service

Dr. Elisabetta Tedone
Dr. Sara Rosellini
Dr. Nicoletta Colombo
Dr. Alessia Parodi

eha