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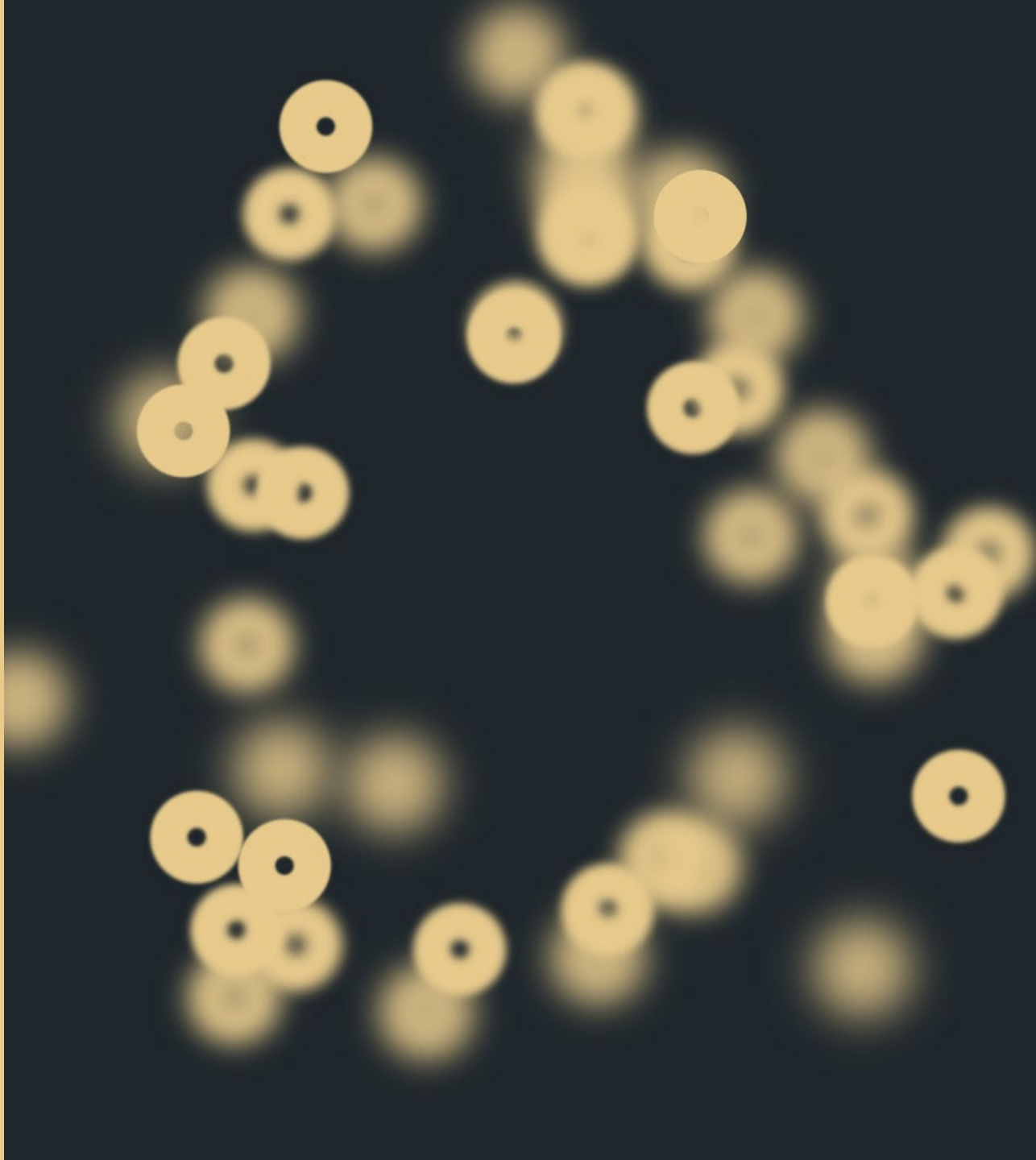
EHA-SWG Scientific Meeting on Recent Advances in the Pathogenesis and Treatment of Secondary Acute Myeloid Leukemias

Berlin, Germany
April 25-26, 2025



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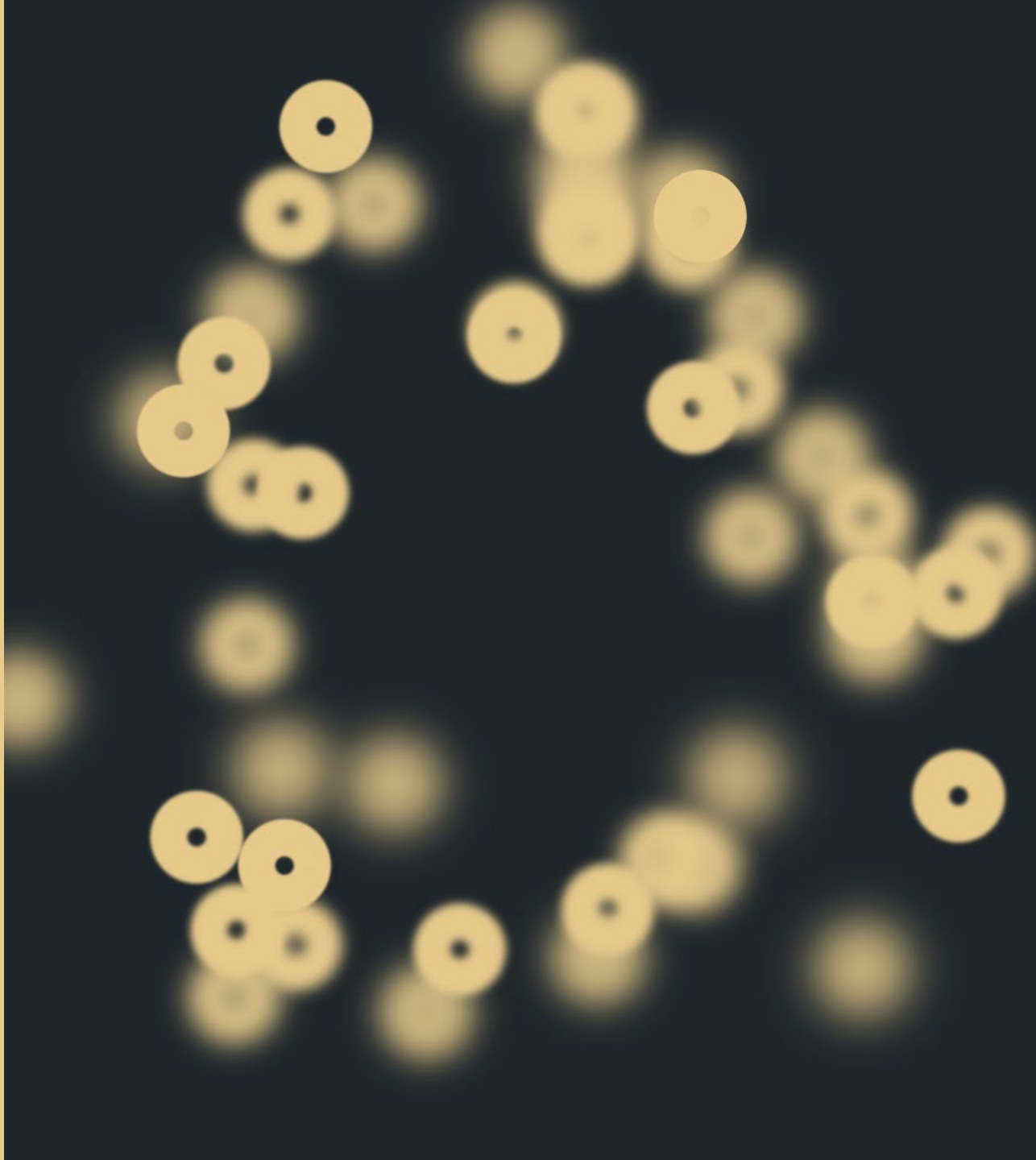
COMPARING OUTCOMES BETWEEN CPX-351 AND FLUDARABINE-BASED INDUCTION IN SECONDARY ACUTE MYELOID LEUKEMIA IN THE REAL-WORLD SETTING: THE PROGNOSTIC ROLE OF MEASURABLE RESIDUAL DISEASE

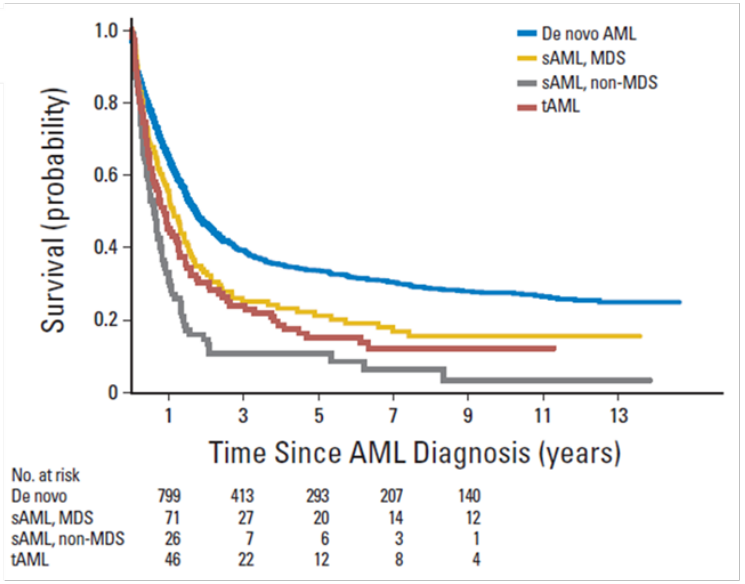
Carola Riva, MD



Background

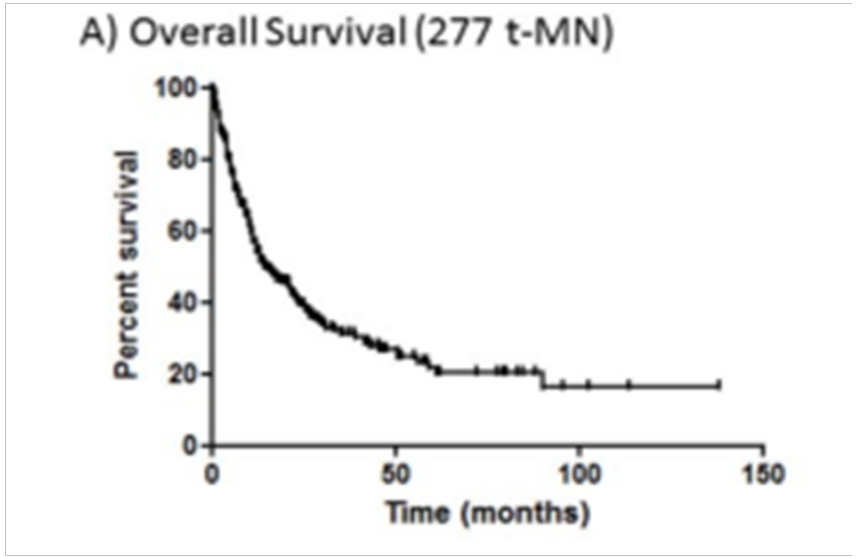
Secondary Acute Myeloid Leukemia (s-AML) arising from an antecedent hematologic disorder (MRC-AML) or developing after prior cytotoxic therapy (t-AML) is typically associated with inferior outcomes if compared to de novo AML, both in terms of decreased complete remission (CR) rates and overall survival (OS)

Danish Register. Overall survival



Granfeldt-Øsgtård, LS et al. J Clin Oncol. 2015;33:3641–3649.

Italian Register. Overall survival



Fianchi L, et al. Am J Hematol. 2015 May;90(5):E80-5.

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 ICC CLASSIFICATION

- **Acute promyelocytic leukemia (APL) with t(15;17)(q24.1;q21.2)/*PML::RARA* ≥10%**
- **APL with other *RARA* rearrangements* ≥10%**
- **AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* ≥10%**
- **AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11* ≥10%**
- **AML with t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A* ≥10%**
- **AML with other *KMT2A* rearrangements** ≥10%**
- **AML with t(6;9)(p22.3;q34.1)/*DEK::NUP214* ≥10%**
- **AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2; MECOM(EVI1)* ≥10%**
- **AML with other *MECOM* rearrangements*** ≥10%**
- **AML with other rare recurring translocations (see Supplemental Table 5) ≥10%**
- **AML with t(9;22)(q34.1;q11.2)/*BCR::ABL1*‡ ≥20%**
- **AML with mutated *NPM1* ≥10%**
- **AML with in-frame bZIP *CEBPA* mutations ≥10%**
- **AML and MDS/AML with mutated *TP53*† 10-19% (MDS/AML) and ≥20% (AML)**
- **AML and MDS/AML with myelodysplasia-related gene mutations 10-19% (MDS/AML) and ≥20% (AML)**
  - Defined by mutations in *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1*, or *ZRSR2*
- **AML with myelodysplasia-related cytogenetic abnormalities 10-19% (MDS/AML) and ≥20% (AML)**
  - Defined by detecting a complex karyotype (≥3 unrelated clonal chromosomal abnormalities in the absence of other class-defining recurring genetic abnormalities), del(5q)/t(5q)/add(5q), -7/del(7q), +8, del(12p)/t(12p)/add(12p), i(17q), -17/add(17p) or del(17p), del(20q), and/or idic(X)(q13) clonal abnormalities
- **AML not otherwise specified (NOS) 10-19% (MDS/AML) and ≥20% (AML)**
- **Myeloid Sarcoma**

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

Diagnostic qualifiers that should be used following a specific MDS, AML (or MDS/AML) diagnosis

Therapy-related
• prior chemotherapy, radiotherapy, immune interventions

Progressing from myelodysplastic syndrome
• MDS should be confirmed by standard diagnostics

Progressing from myelodysplastic/myeloproliferative neoplasm (specify)
• MDS/MPN should be confirmed by standard diagnostics

- **AML MDS-related** has been introduced (requires previous diagnosis of MDS or MDS-related cytogenetics)
- **t-AML** retained but as a **qualifier**

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

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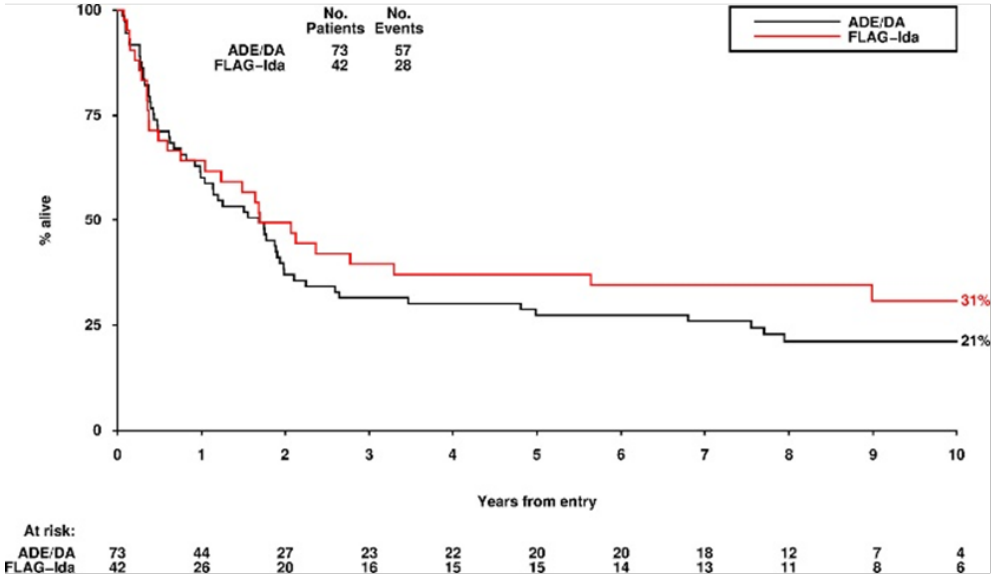
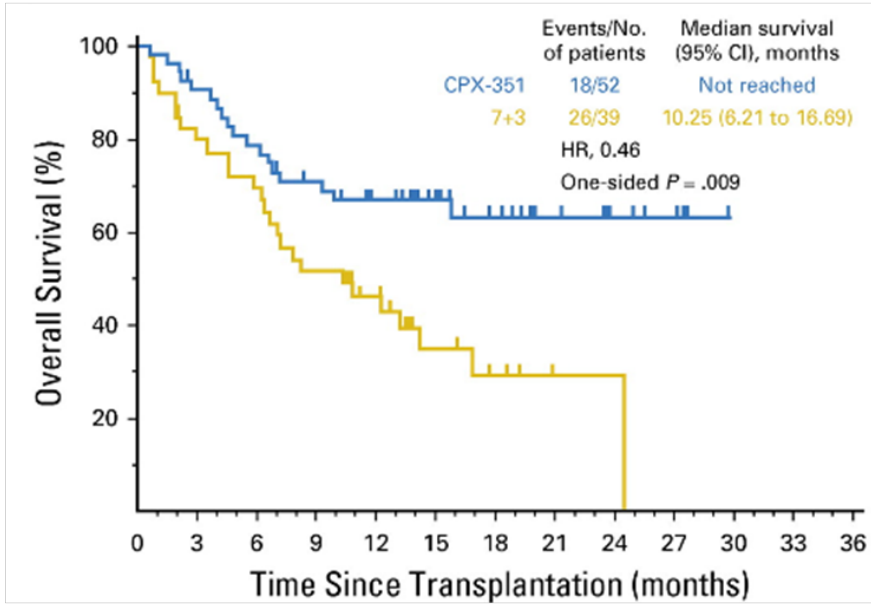
- Given the poor results achieved by the conventional 3+7 chemotherapy in s-AML, different induction strategies have been tested in order to increase the probability of achieving a CR and receiving HSCT consolidation
- Fludarabine combinations (**FLAG-Ida**) have historically shown **good antileukemic effect**, but are burdened by **significant toxicities**, thus limiting the feasibility in elderly s-AML
- More recently, **CPX-351** demonstrated **improved results compared to conventional 3+7 chemotherapy** in elderly s-AML, especially if followed by HSCT

3+7 vs FLAG-Ida in s-AML patients



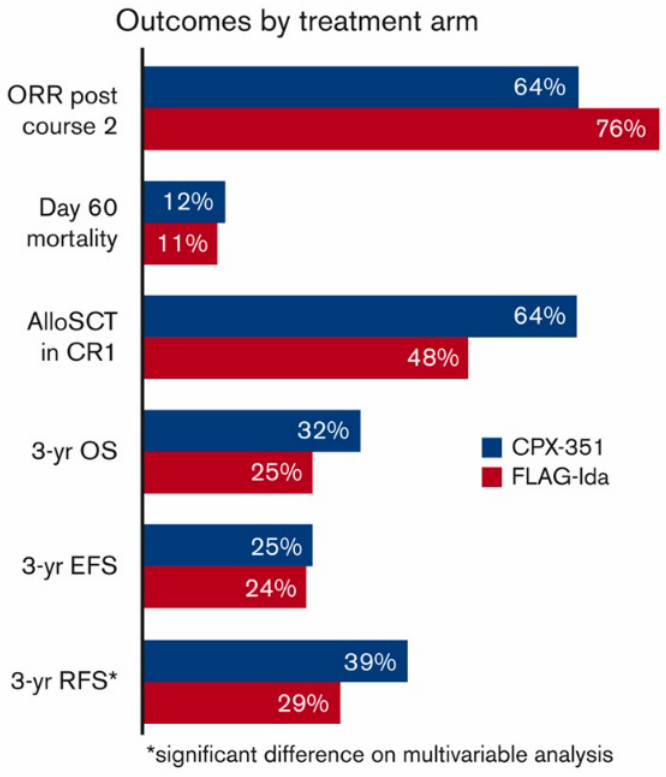
Burnett AK, et al. J Clin Oncol. 2013

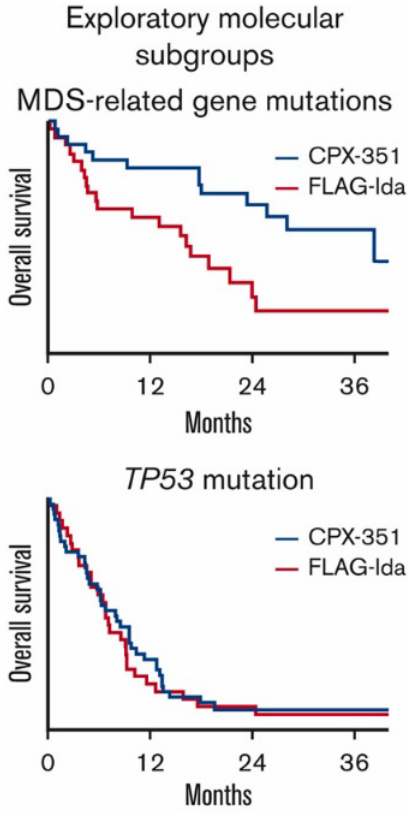
CPX-351 vs 3+7, s-AML patients receiving HSCT



Lancet JE, et al. Journal of Clinical Oncology 2018

CPX vs FLAG-Ida in younger patients: UK MRC-AML 19 trial





Othman J et al. Blood Advances 2023

- **189 HR AML patients** were randomized (median age 56y).
- Overall response rate (CR + CRi) after course two was 64% and 76% for CPX-351 and FLAG-Ida, with no difference between the arms
- There was **no difference in OS** in the whole cohort (13.3 months vs 11.4 months, p=0.17) or event-free survival (p=0.55) in multivariate analysis
- **Relapse-free survival** was **significantly longer with CPX-351**
  (median 22.1 vs 8.35 months, p<0.05)
- Notably, patients with **MDS-related gene mutations** had a significantly **better survival with CPX-351** (p<0.05)

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Aims of the study

MRD was evaluated only in a **minority of patients in the UK trial**, providing conflicting results, so that the **reasons of the better results achieved by CPX-351 are not completely elucidated yet**

- The **aim** of this study was **to compare** the probability of **achieving MRD negativity and its prognostic significance** in a cohort of **183 consecutive elderly patients** (median age 69, range 60-77) affected by **s-AML** treated with **CPX-351** (n=82) or receiving an age-adjusted **FLAG-Ida** regimen (n=101) in our Center

Methods

- **All patients** in both arms had **s-AML** as defined by the **2016 WHO** classification
- Patients treated **before January 2019** (n=101) received an **age-adjusted FLAG-Ida** (FLAI, 3 days of fludarabine, cytarabine and idarubicin)
- All 82 patients treated **after January 2019** received **CPX-351**

- CPX-351 was administered according to the EMA approval
- FLAI consisted in two identical induction cycles with fludarabine, cytarabine and idarubicin

- **MRD assessment** was performed in all patients achieving hematological CR with **multicolor flow cytometry (MFC)**
- **MFC-MRD negativity** was defined by the presence of **less than <0.1% leukemic cells**

Arber DA, et al. Blood 2016
Guolo F, et al. Haematologica 2017
Heuser M, et al. Blood 2021

Results: Patients' Characteristics

- In **CPX-351 arm**, 20 patients had **t-AML (24%)** and 62 had **MRC-AML (76%)**
- Thirty-two patients **(39%)** showed a **complex karyotype**
- **TP53** mutation was found in 22 patients (**27%**)
- Most patients (77/82, **94%**) had **MDS-defining cytogenetic and/or molecular abnormalities**
- ELN 2017 risk was **favorable** in 7 patients (**8%**), **intermediate** in 32 (**39%**) or **unfavorable** in 43 (**53%**) patients, respectively
- Ten patients (**12%**) received previous treatment with **HMA** for myelodysplastic syndrome

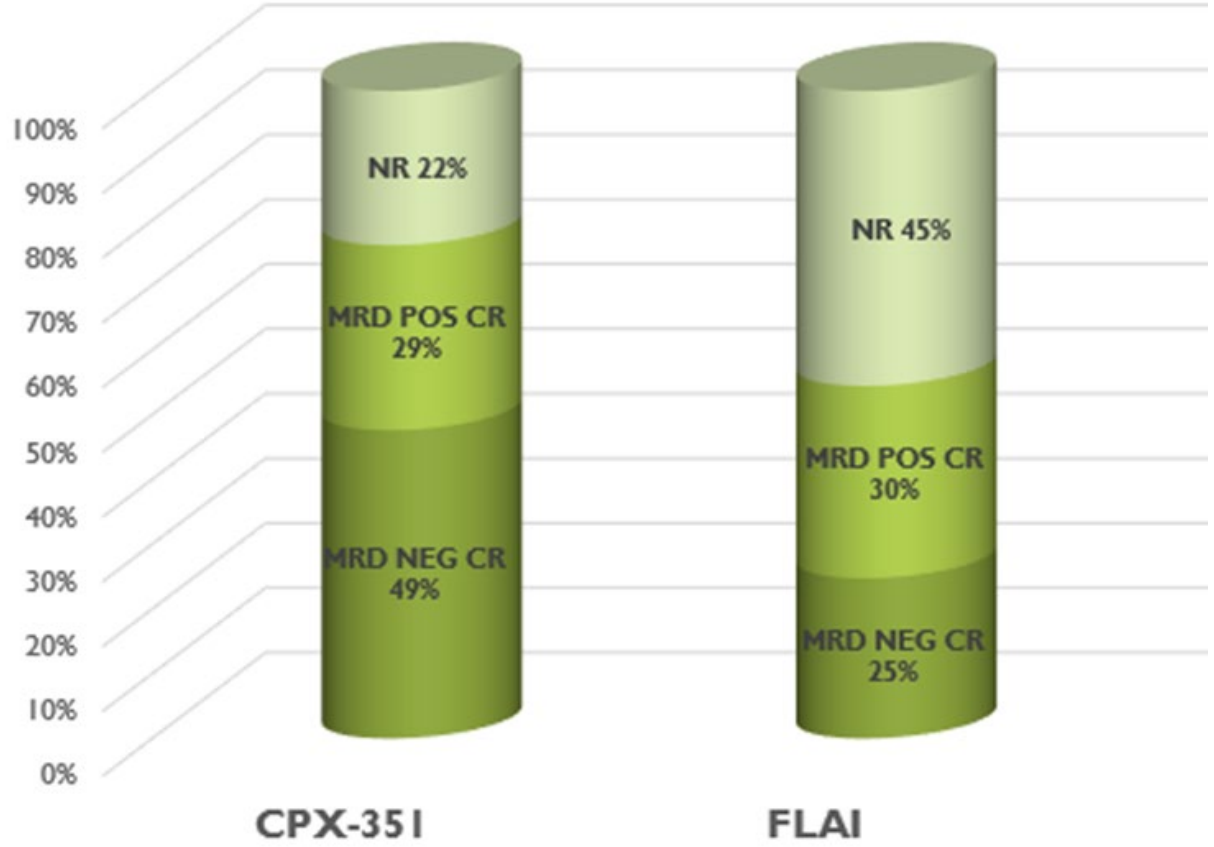
- In **FLAI arm**, 18 patients had **t-AML (18%)** and 83 had **MRC-AML (82%)**
- A **complex karyotype** was found in 40 patients (**40%**)
- ELN 2017 risk score was **favorable** in 11 (**10%**), **intermediate** in 49 (**49%**) and **unfavorable** in 41 (**41%**) patients
- Two patients had already received **HMA for MDS (2%)**

		OVERALL (n=183)	CPX-351 ARM (n=82)	FLAI ARM (n=101)	*p*
Median Age		69 (60-77)	68 (60-77)	69 (60-75)	n.s.
ELN 2017	Favorable	18 (10%)	7 (8%)	11 (10%)	n.s.
	Intermediate	81 (44%)	32 (39%)	49 (49%)	
	Unfavorable	84 (46%)	43 (53%)	41 (41%)	
Karyotype Risk Group	Low	5 (3%)	0 (0%)	5 (5%)	n.s.
	Intermediate	102 (55%)	47 (57%)	55 (55%)	
	High	76 (42%)	35 (43%)	41 (40%)	
WHO 2016	t-AML	38 (21%)	20 (24%)	18 (18%)	n.s.
	MRC-AML	145 (79%)	62 (76%)	83 (82%)	
Previous HMA	YES	12 (7%)	10 (12%)	2 (2%)	<0.05
	NO	171 (93%)	72 (88%)	99 (98%)	

Riva C, et al. Hematol Oncol. 2025

Results: Response Rate

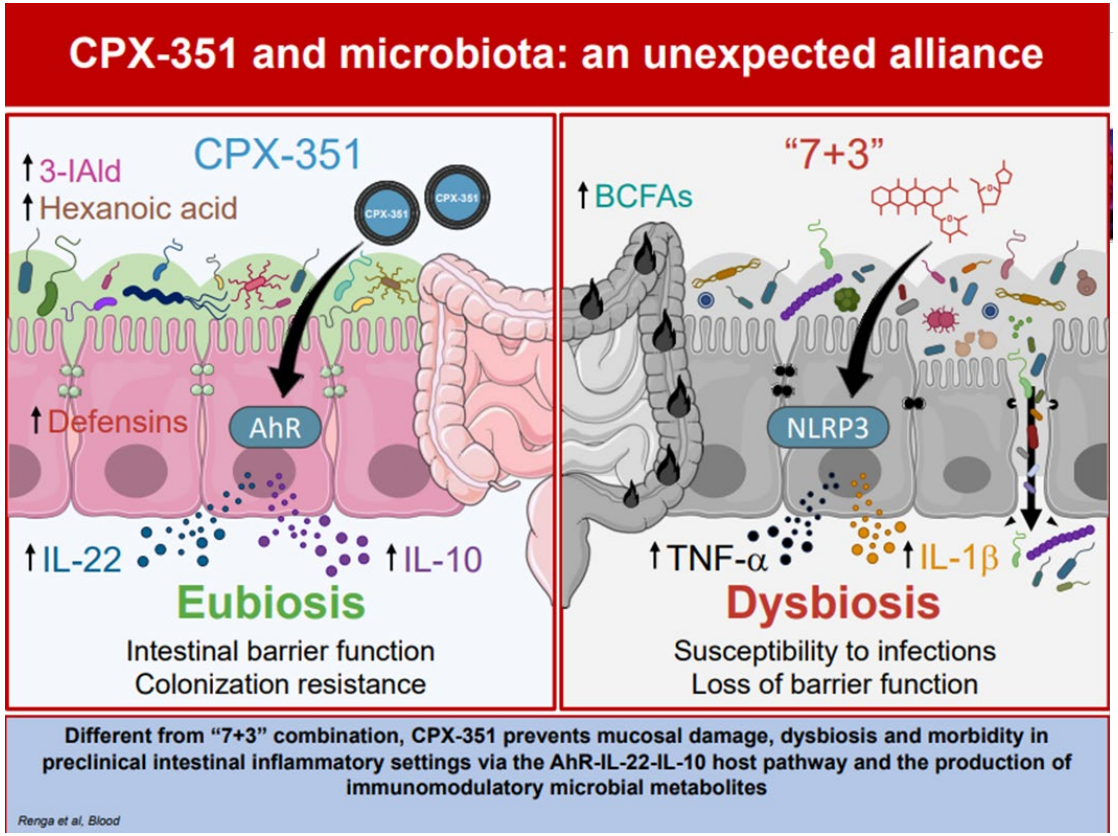
- After first cycle, **CR was achieved in 119 patients (65%)**
- **CR rate** was 64/82 in patients treated with **CPX-351 (78%)**, significantly **higher** when **compared** to patients receiving **FLAI** (55/101, **54.5%**, p<0.05)
- **MFC MRD negative CR rate** was 40/82 (**49%**) in patients receiving **CPX-351** vs 25/101 (**25%**) in patients who received **FLAI** (p<0.05)



Riva C, et al. Hematol Oncol. 2025

Results: Toxicity

- **Thirty-day mortality** was 3/82 (**3.6%**) in **CPX-351 arm**, compared to 8/101 (**8%**) in **FLAI** treated patients
- Severe **mucositis** was observed in 1 (**1%**) of **CPX-351** patients, significantly less likely if compared to 8 (**8%**) patients with severe mucositis in the **FLAI** arm ($p<0.05$)
- This observation is consistent with a recent evidence that the liposomal formulation of CPX-351 may have a **lower toxicity on gut mucosa** if compared to conventional chemotherapy



Renga G, et al, Blood 2024

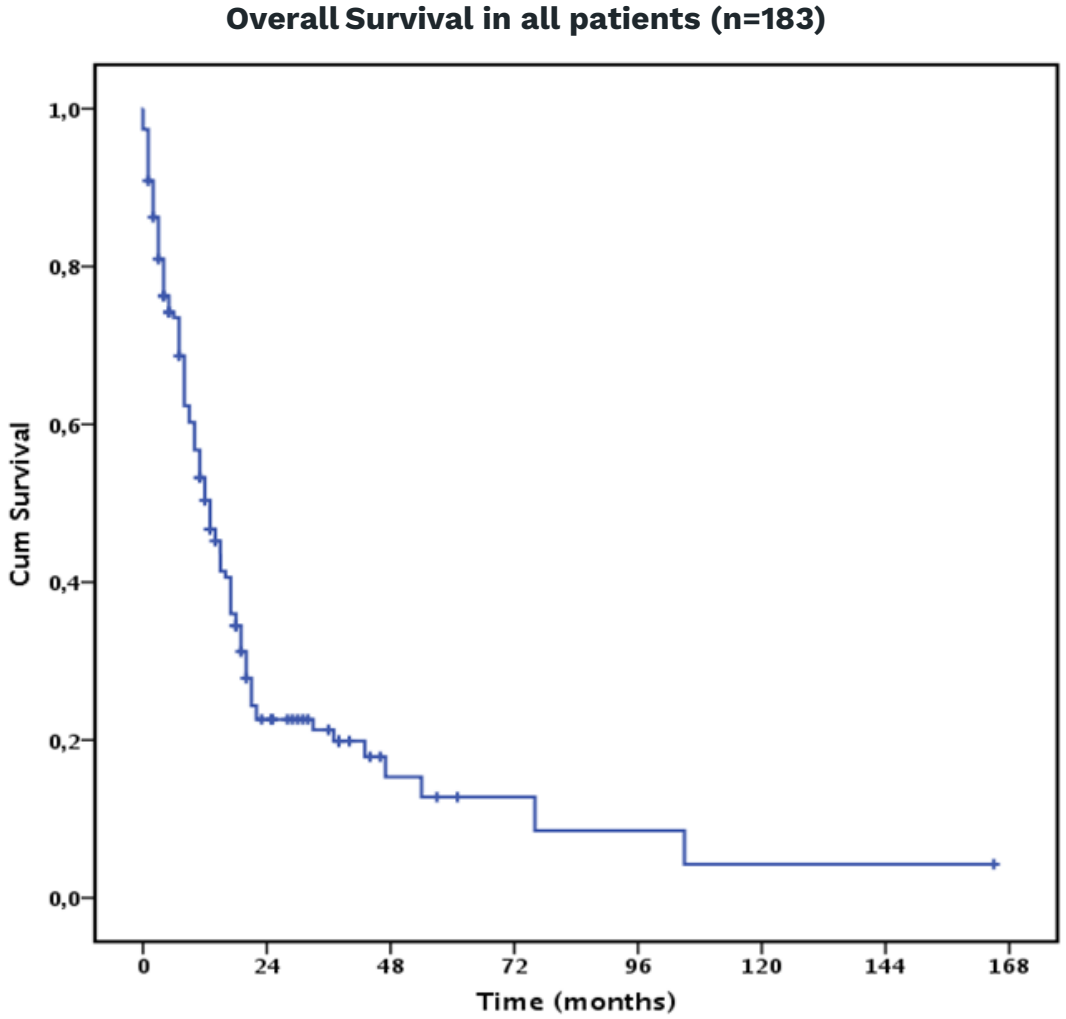
Results: Overall Survival

Median follow-up was

- **20.7 months** (CI 95% 16.49-26.37) in the **CPX-351** cohort
- **58 months** (CI 95% 34.97-72.98) in the **FLAI** cohort

Overall, **median OS** was **13.4 months** (CI 95% 8.04-16.97).

- **1 year OS** was **50.4%**
- **3 year OS** was **21.3%**



Riva C, et al. Hematol Oncol. 2025

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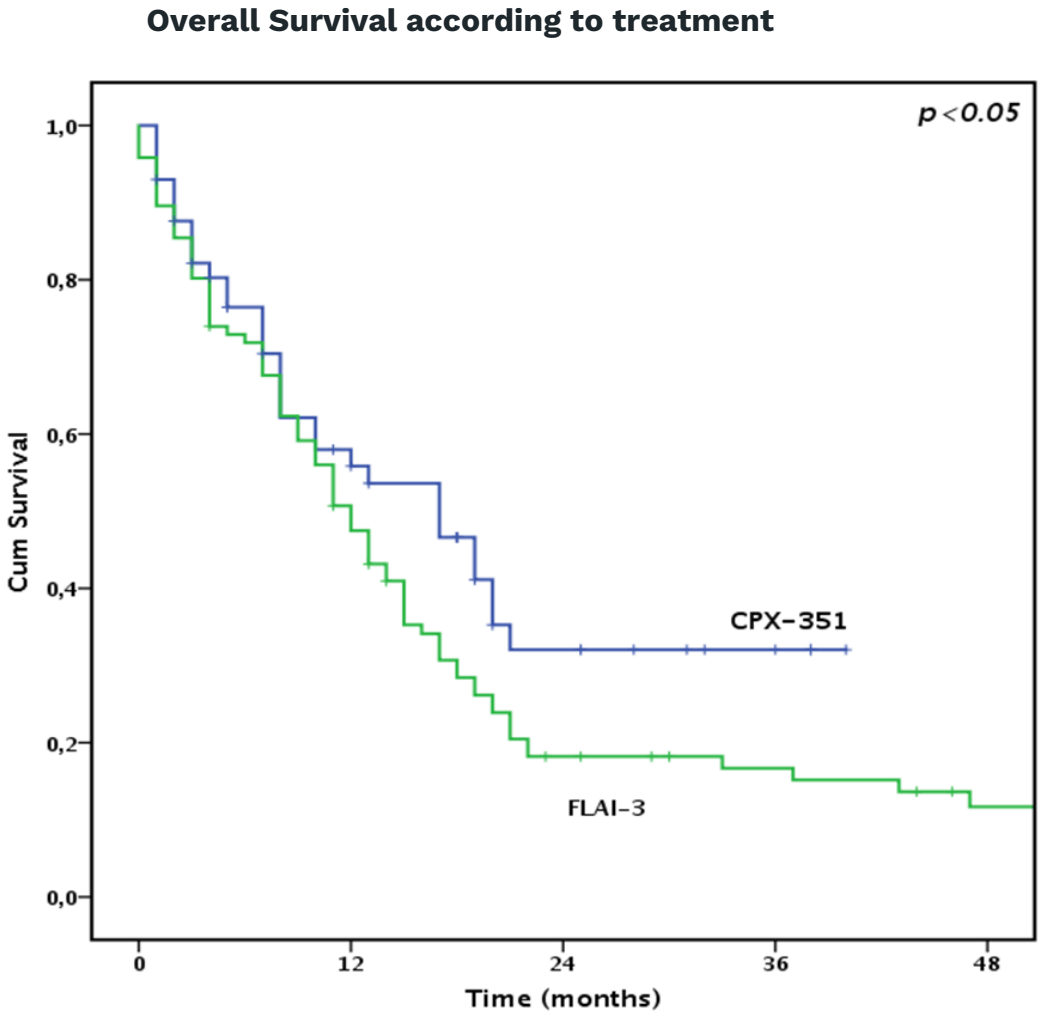
Results: Overall Survival according to treatment

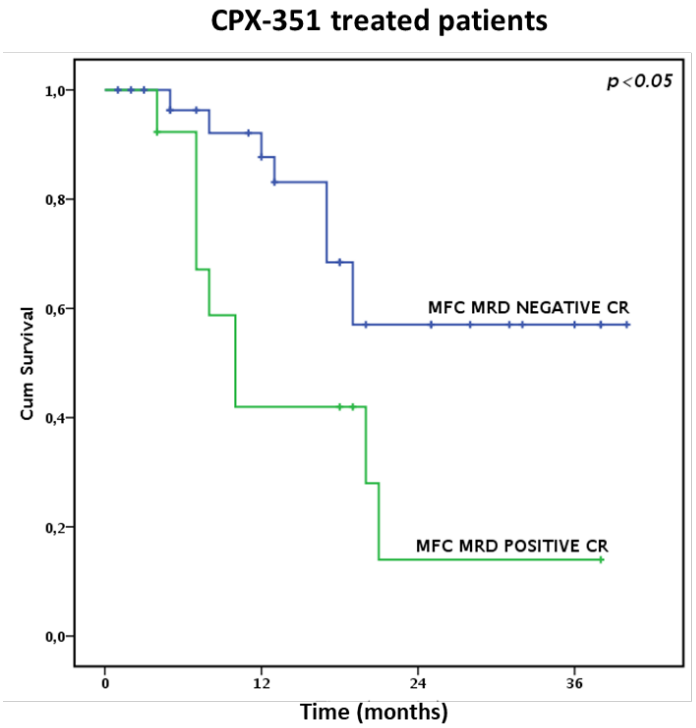
- Median **OS** was **significantly higher** in **CPX-351** cohort, **17.7 months** compared to **11.2 months in FLAI** cohort (p<0.05)
- One year OS was 55.8% in CPX arm vs 47.5% in FLAI arm
- **Three year OS** was **32.1% in CPX-351** arm compared to **16.7% in FLAI** arm

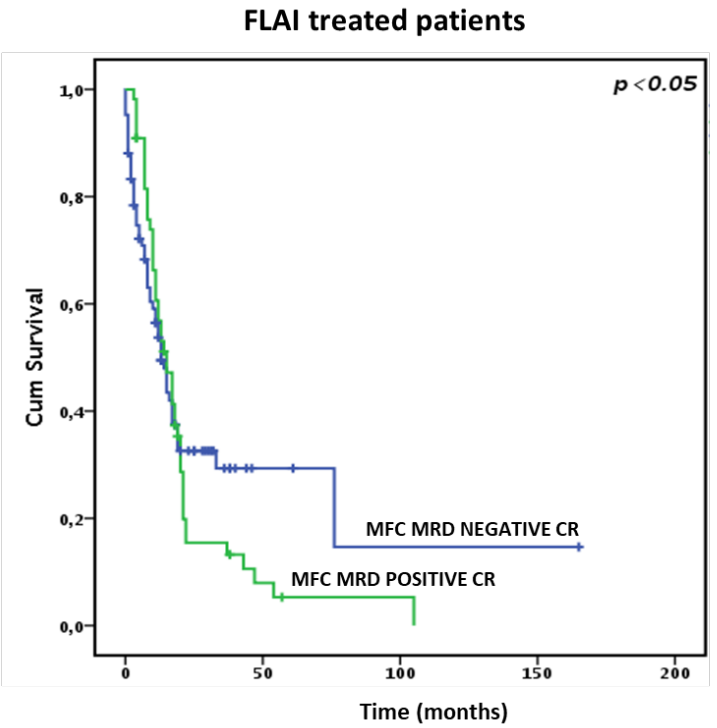


Riva C, et al. Hematol Oncol. 2025

Results: MRD

- **MRD** was the **strongest prognostic** factor for OS, **in both arms**
- **CPX-351** treated patients achieving **MRD negative CR** had a **2-year OS of 58%** (median not reached) compared to 13% (median 10.6 months) for patients with residual MFC-MRD ($p<0.05$)
- In the **FLAI** cohort the **2-year OS was 33%** (median 16 months) and 17% (median 16 months) in patients obtaining MFC-MRD negativity or not, respectively ($p<0.05$)

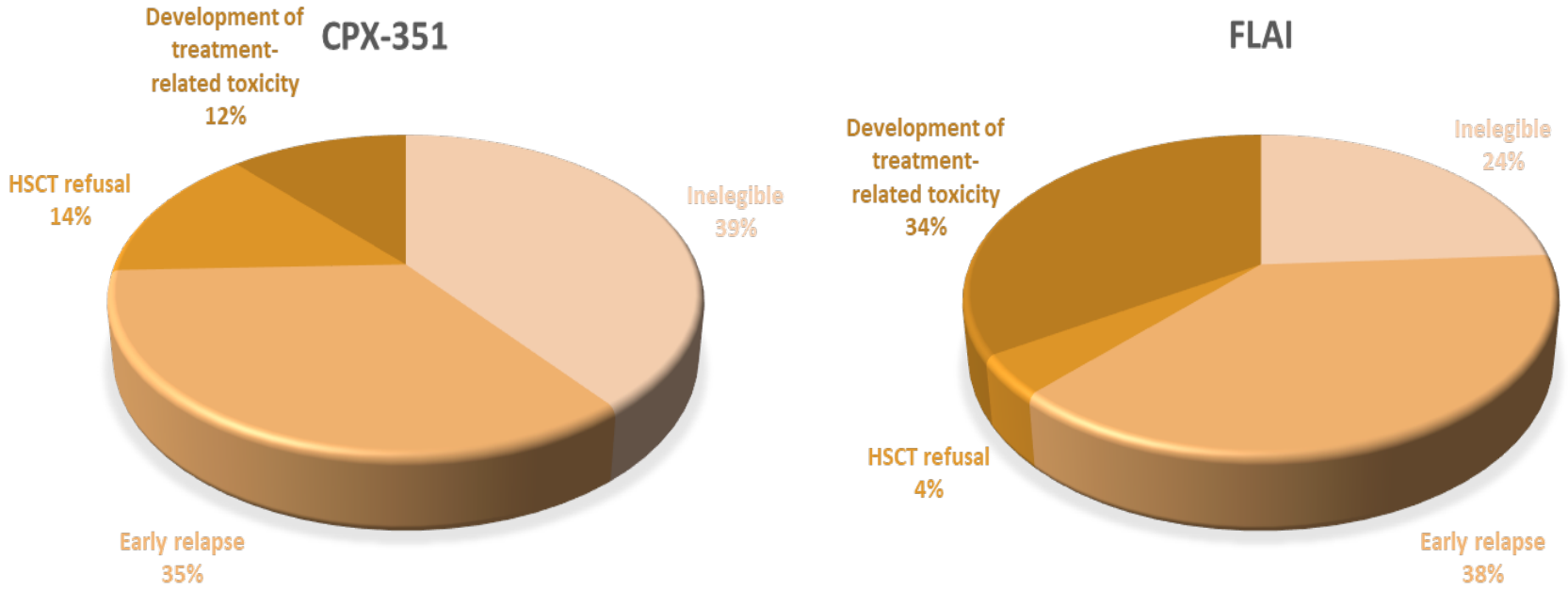




Riva C, et al. Hematol Oncol. 2025

Results: Rates of Allogenic Stem Cell Transplantation

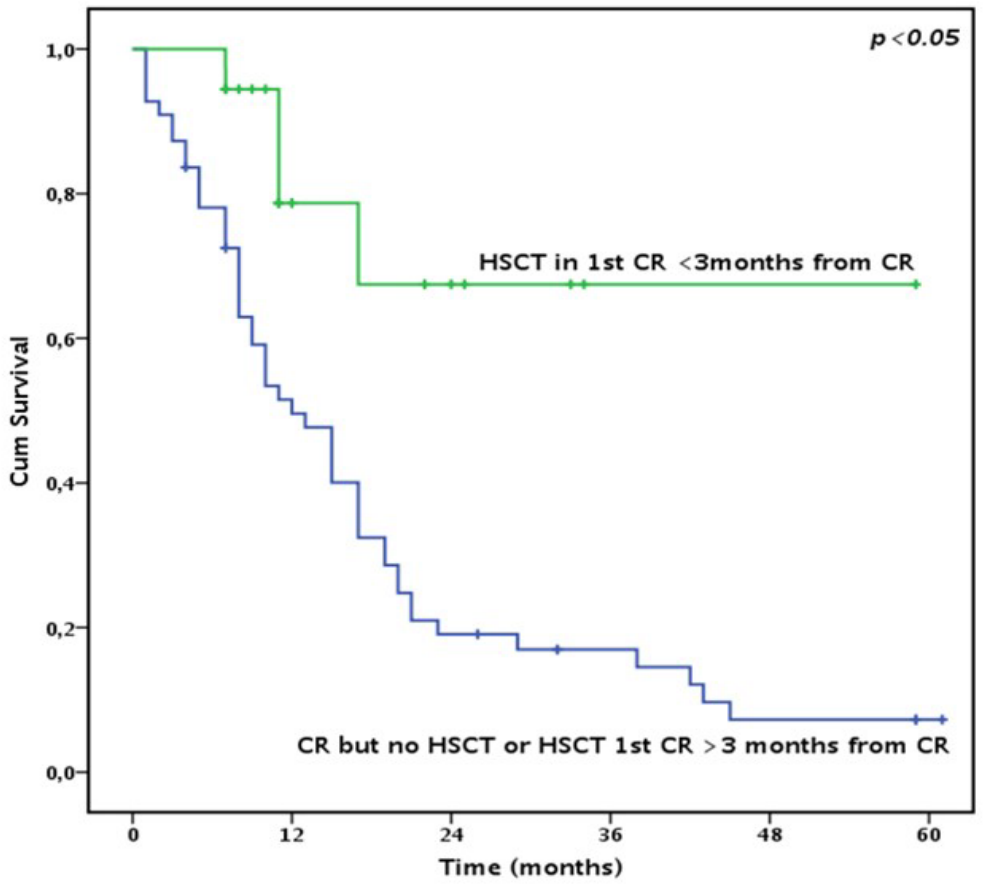
- Notably, **more CR patients**, 21/64 (32.8%), **treated with CPX 351 underwent HSCT**, compared to 5/55 (9%) CR patients treated with FLAI ($p<0.05$)
- In the **FLAI cohort**, more CR patients **did not proceed to HSCT** because of the **development of treatment-related toxicities**, (17/50, 34% and 5/43, 12% in the FLAI and CPX-351 cohort, respectively, $p<0.05$)
- In the CPX-351 cohort, more patients were considered ineligible to HSCT from the beginning of the treatment, likely due to higher comorbidity burden in the CPX-351 arm



Results: Relevance of Allogenic Stem Cell Transplantation

- A landmark analysis model was built to assess the impact of HSCT, including only patients achieving CR and alive at day 30
- In the landmark model, consolidation with HSCT was related to a longer survival (p<0.05)
- The **best results** were achieved among patients receiving **HSCT within 3 months after achieving a CR**, who had a **3 year OS of 68%** (median not reached)
- Receiving **HSCT within 3 months** after achieving a CR was the **strongest predictor of survival** among CR patients, both in univariate and multivariate analysis (p<0.05)

OS according to HSCT timing (landmark analysis)



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Conclusions

- With the limitations of a retrospective study, in our experience **s-AML** patients had a **better outcome with CPX-351**
- **MRD** was the **strongest prognostic** factor for OS, **regardless of treatment** received.
- CPX-351 compared to FLAI seemed to have a greater anti-leukemic activity, with **higher probability of MRD negativity**
- The improved **tolerance of CPX-351**, with lower risk of severe mucositis, enabled more patients to undergo HSCT
- The combination of the **deeper responses** achieved and the more frequent **HSCT consolidation** ultimately resulted in a better long-term OS
- Maintenance treatment and other post-remission strategies may be implemented in order to improve the outcome of patients who are not eligible to HSCT

Acknowledgements

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