FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

CONVEGNO FISiM

Firenze, CSF Montedomini
"Il Fuligno"
24-25 ottobre 2025

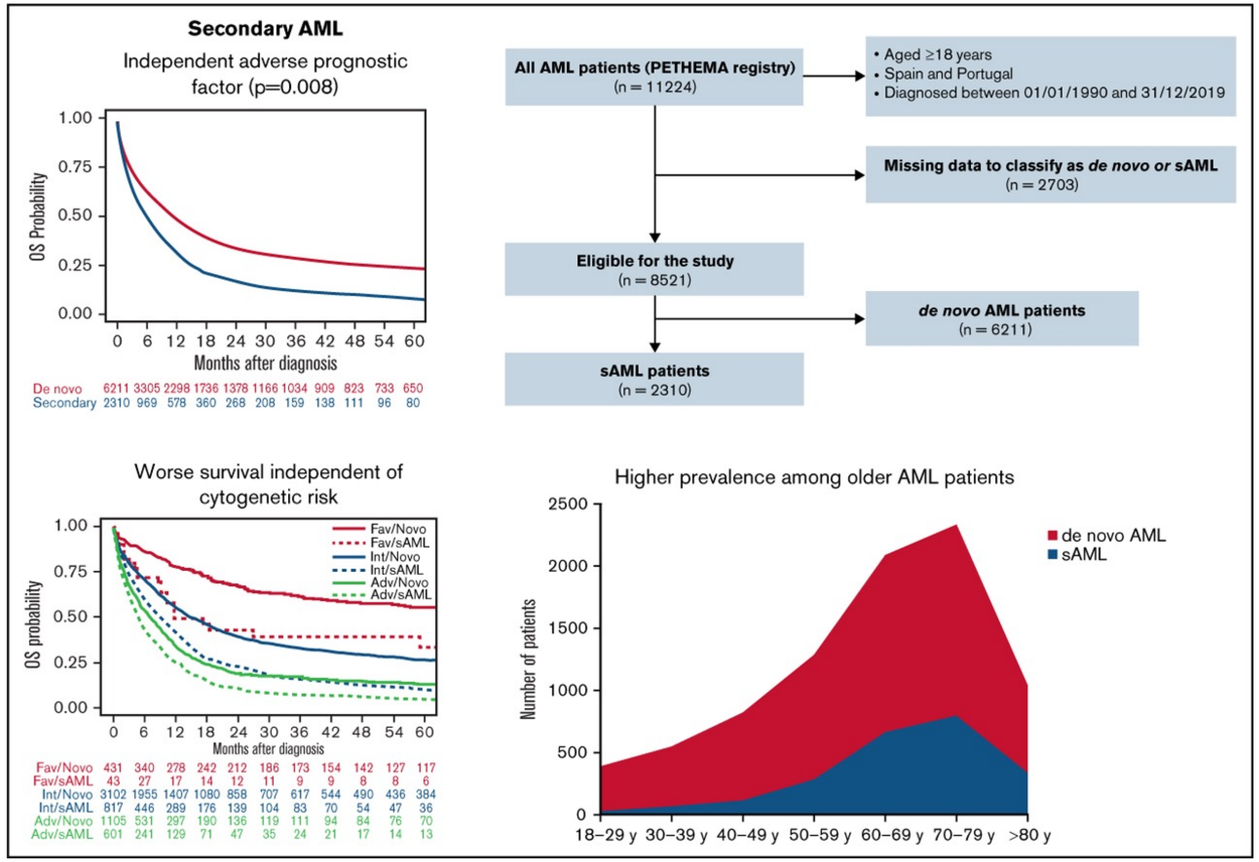
Attività di CPX-351 in LAM post MDS

Antonio Curti
IRCCS Azienda Ospedaliero-Universitaria di Bologna
Istituto di Ematologia «Seràgnoli»

Disclosures of Antonio Curti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	X					X	X
Jazz Pharma						X	X
Menarini-Stemline						X	X
Servier						X	X
Novartis							X
Pfizer	X					X	X

Secondary AML: current state-of-art



Martínez-Cuadrón D, Blood Adv (2022) 6 (4): 1278–1295

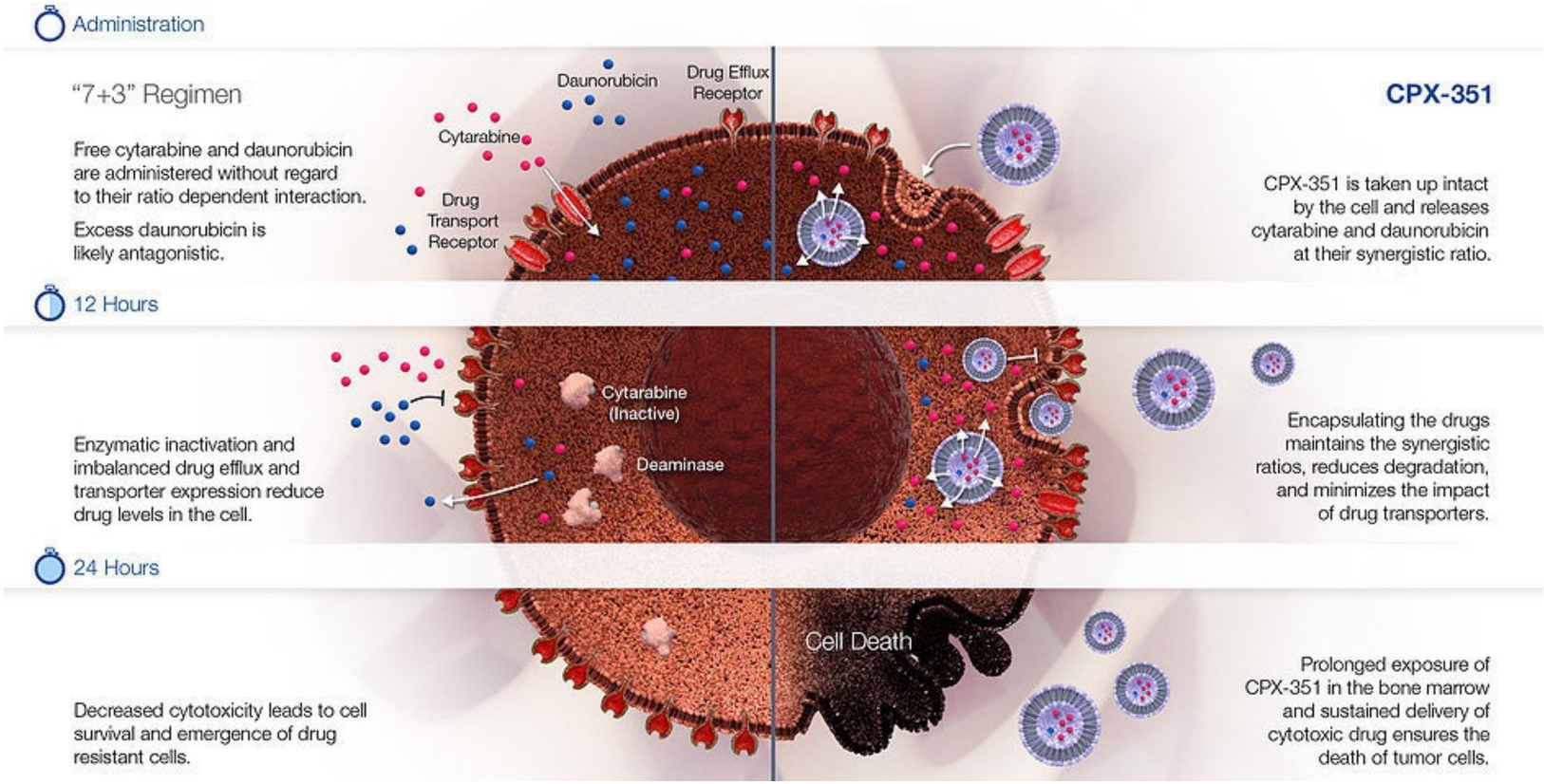
Secondary AML, especially those evolving from previous MDS, is closely associated with older age, comorbidities, worse performance status, and unfavorable genetic features.

Secondary AML itself should be considered an independent risk factor, especially for patients treated with IC approaches.

The best therapeutic results are obtained after IC followed by an allogeneic HSCT, but this strategy is only accomplished in a minority of patients.

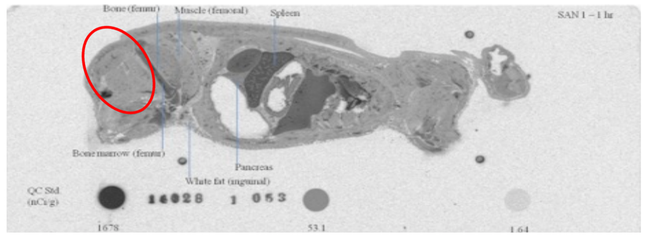
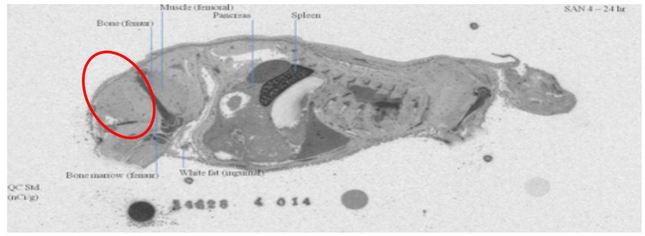
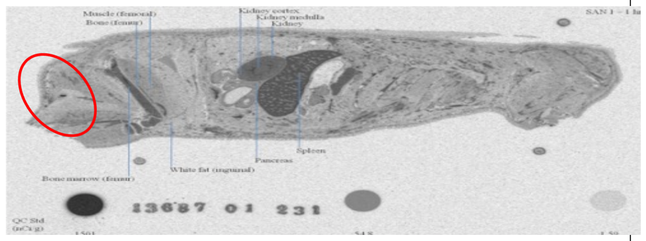
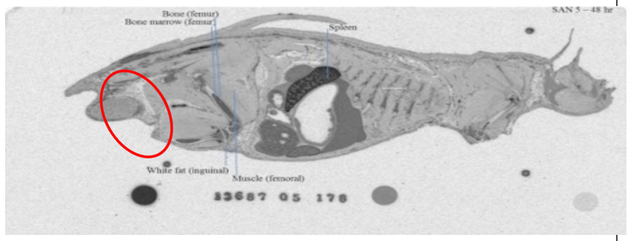
Unmet medical need

Schematic representation of CPX351(cytarabine:daunorubicin) liposome injection



The active agents, cytarabine and daunorubicin, are encapsulated in the aqueous space of both vesicles at a 5:1 molar ratio. The strength of CPX-351 is 5 units/mL, where 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin (base).

Coordinated pharmacokinetics, drug ratio maintained and preferentially driven to bone marrow

	Hours after administration	
	1	24
CPX-351 Cytarabine		
CPX-351 Daunorubicin		

- Markedly reduced drug exposure to healthy tissues reduces toxicity problems and increases exposure to tumour tissue
- Drug elimination occurs slowly and at the same rate for both drugs
- **CombiPlex gets the right ratio of drugs to the right site for the right amount of time**

Mayer, et al., Mol Cancer Ther, 5:1854-1863, 2006

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
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

Arber DA, Blood 2016

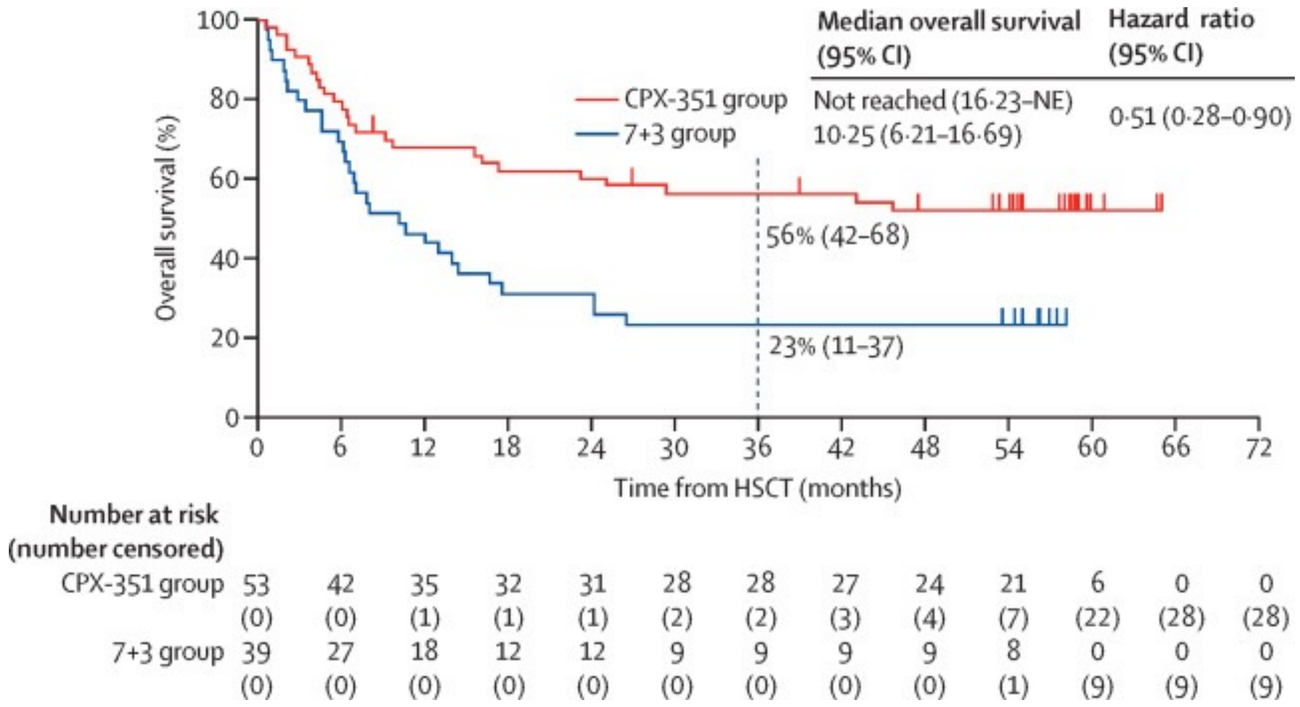
CPX-351(cytarabine:daunorubicin) liposome injection: approval history

In August 2017 the US FDA approved CPX-351 for the treatment of adults with newly diagnosed AML with myelodysplasia-related changes (AML-MRC) and therapy-related AML (t-AML)
On June 28, 2018, EMA adopted a positive opinion, recommending the granting of a marketing authorization for CPX-351

This is the first approved treatment specifically for patients with this subgroup of AML

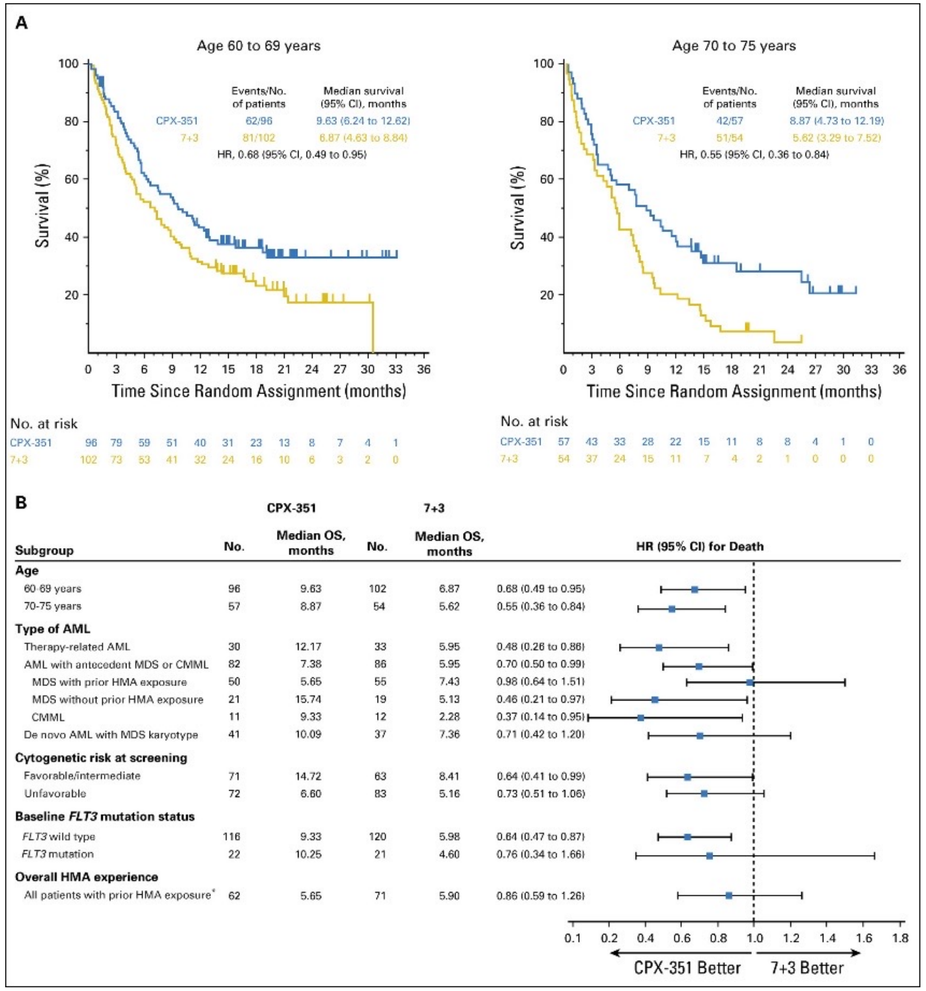
Study 301: 5-year results of a randomised, open-label, multicentre, phase 3 trial

- Phase 3, randomised, open-label, parallel-arm, multicentre study
- CPX-351 vs standard combination of cytarabine and daunorubicin (7+3)
- N=309 patients aged 60–75 years old
- Primary endpoint: OS
- Patient inclusion criteria:
  - Diagnosed with one of the following:
    - t-AML
    - AML with history of MDS
    - AML with history of CMML
    - *De novo* AML with myelodysplasia-related cytogenetic abnormalities
  - Previously untreated disease
  - Able to tolerate intensive therapy (ECOG PS 0–2)



Lancet JE, et al. *Lancet Haematol* 2021;8:e481–e491.

Overall survival by age subgroup and baseline patients' characteristics



CPX-351 is better for:

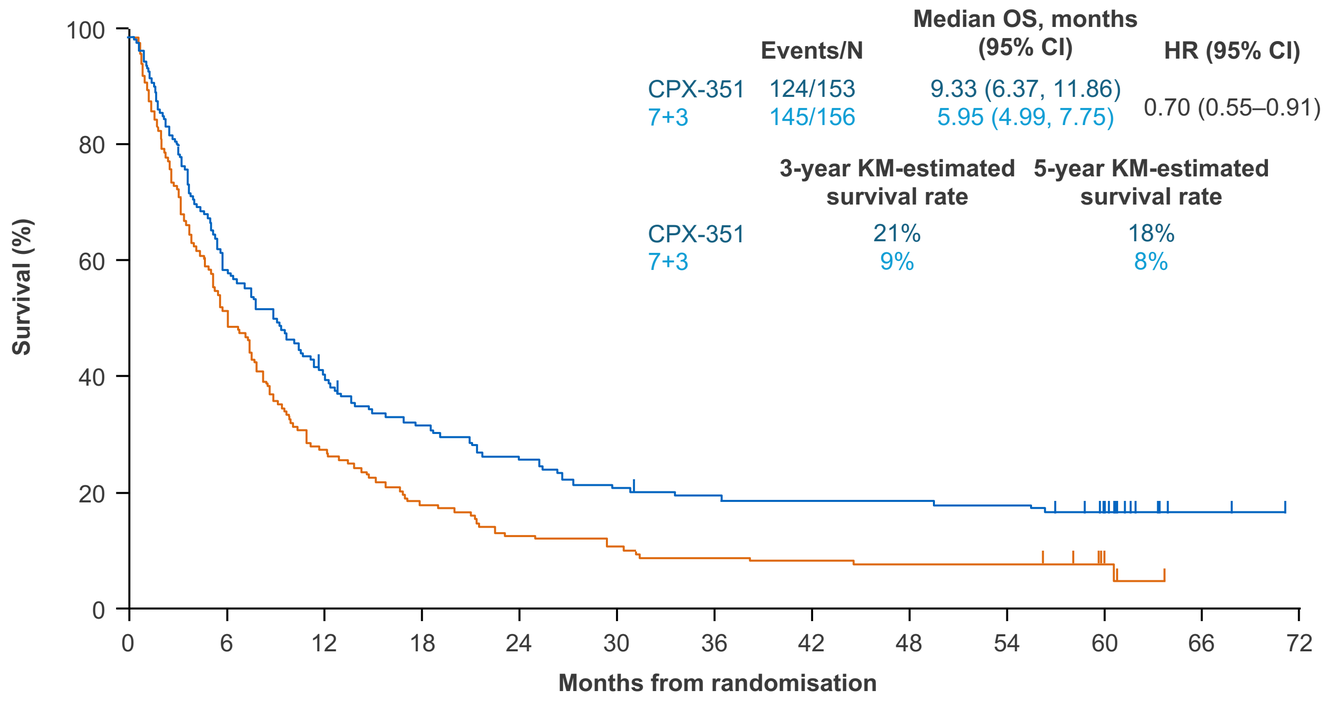
1) All age groups
2) sAML

Not clear advantages for:

1) Adverse cytogenetics
2) Patients, such as MDS patients, with previous treatment with HMAs

Lancet et al *Journal of Clinical Oncology* 2018 362684-2692.

Study 301 - 5-year analysis of OS in older adults with newly diagnosed secondary AML

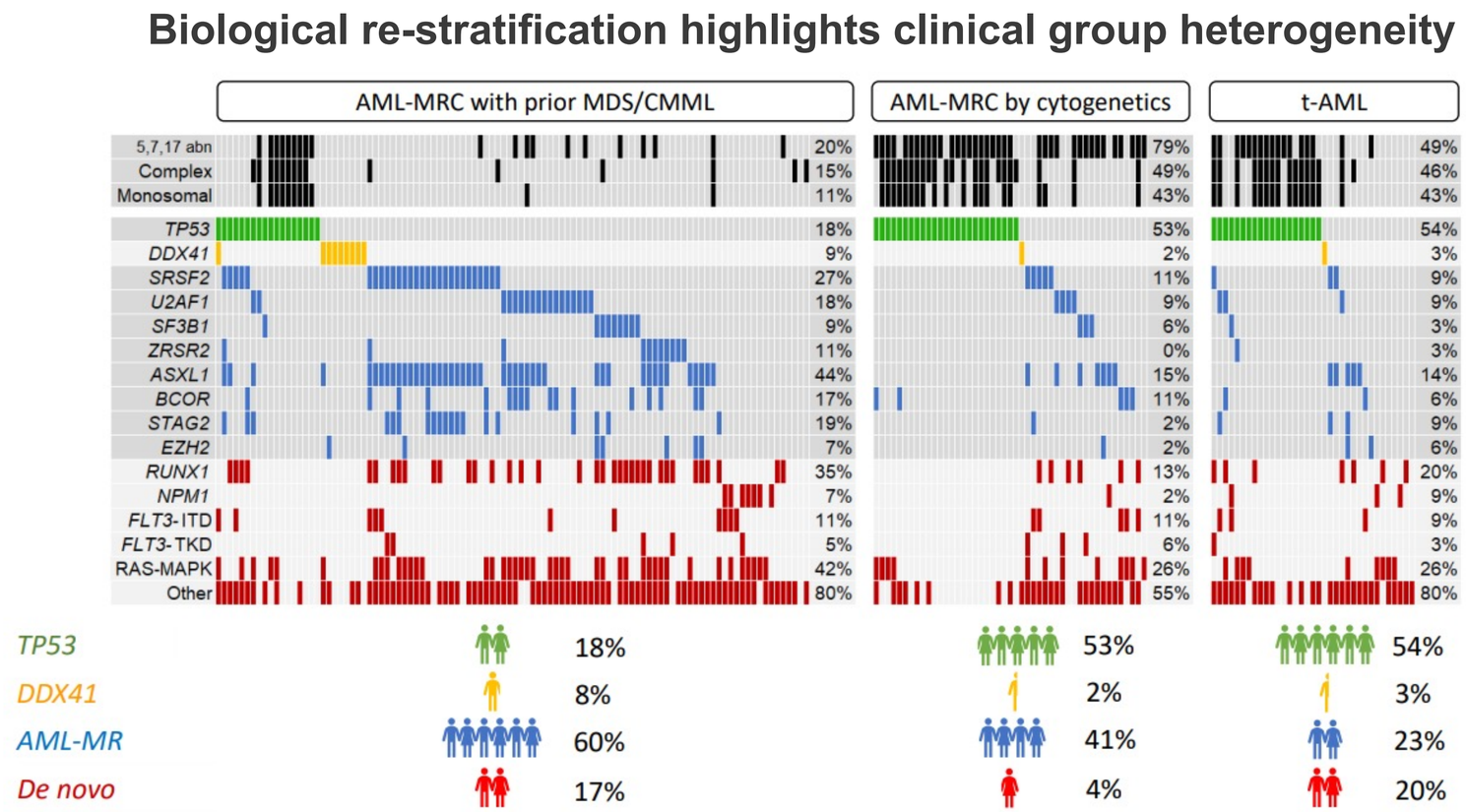


Adapted from Lancet JE, et al. *Lancet Haematol* 2021;8:e481–e491.

Study 301 *post hoc* analysis: background and genetic results

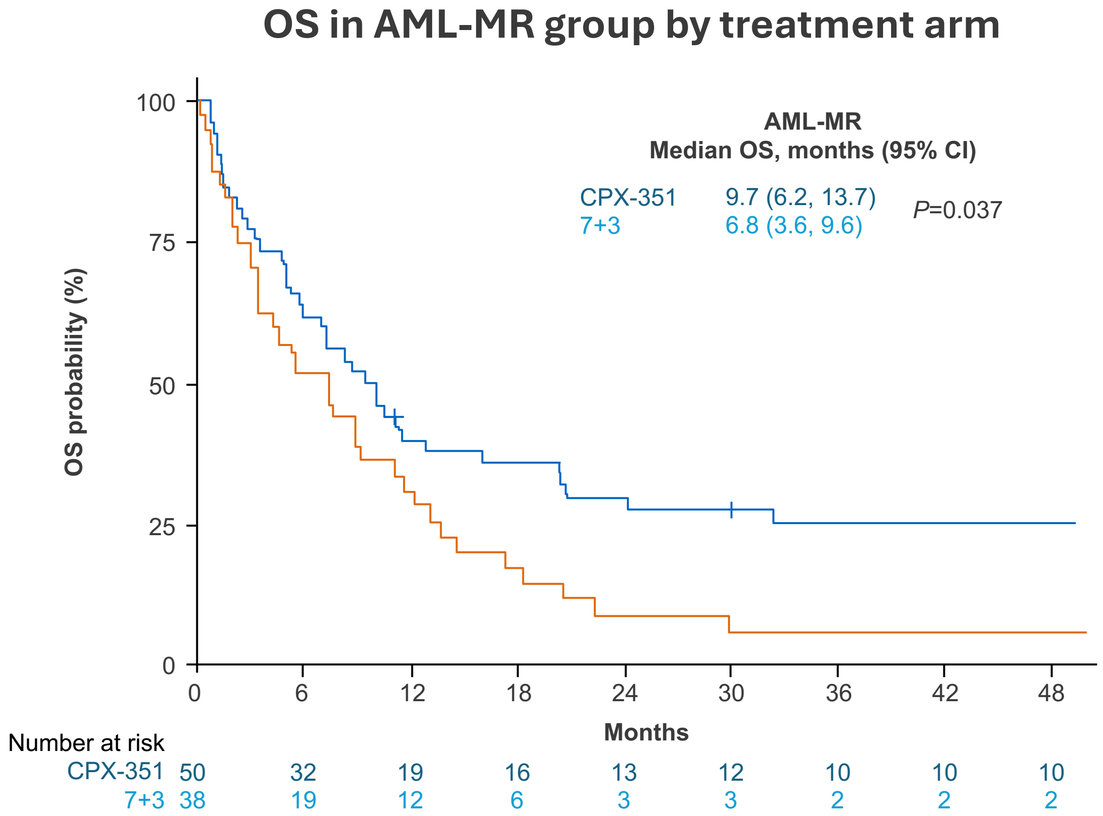
Mutational analysis of pre-treatment samples from 184 of 309 patients randomised in the phase 3 trial (CPX-351, n=93; 7+3, n=91)[1]

Groups were defined in hierarchical order based on the presence of a *TP53* mutation, a germline *DDX41* mutation without concurrent *TP53* mutation, at least one AML-MR defining mutation, or all remaining patients (*de novo*)[1]



1. Shimony S, et al. ASH 2024. Abstract 60.
2. Shimony S, et al. ASH 2024. Oral presentation 60.

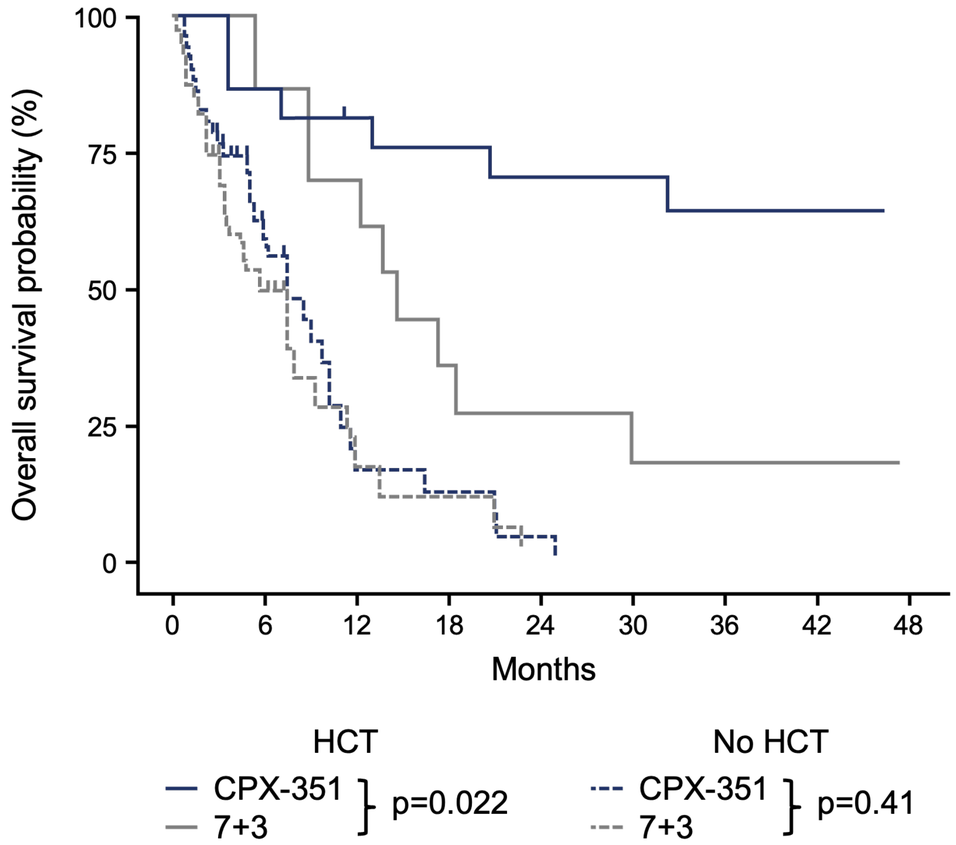
Study 301 *post hoc* analysis: OS in AML-MR group



- Median OS was significantly better with CPX-351 than with 7+3 in the AML-MR group only (9.7 months vs 6.8 months; *P*=0.037)
- This benefit was related to post-remission HCT (CPX-351 vs 7+3: *P*=0.022 for OS with HCT; *P*=0.41 for OS without HCT)
  - Transplantation rates were similar between arms in each group
- Patients with *TP53* mutations had similar outcomes, irrespective of treatment
  - *TP53* allelic state drives OS (*P*=0.0041 for single vs multi-hit)

Shimony S, et al. ASH 2024. Oral presentation 60.

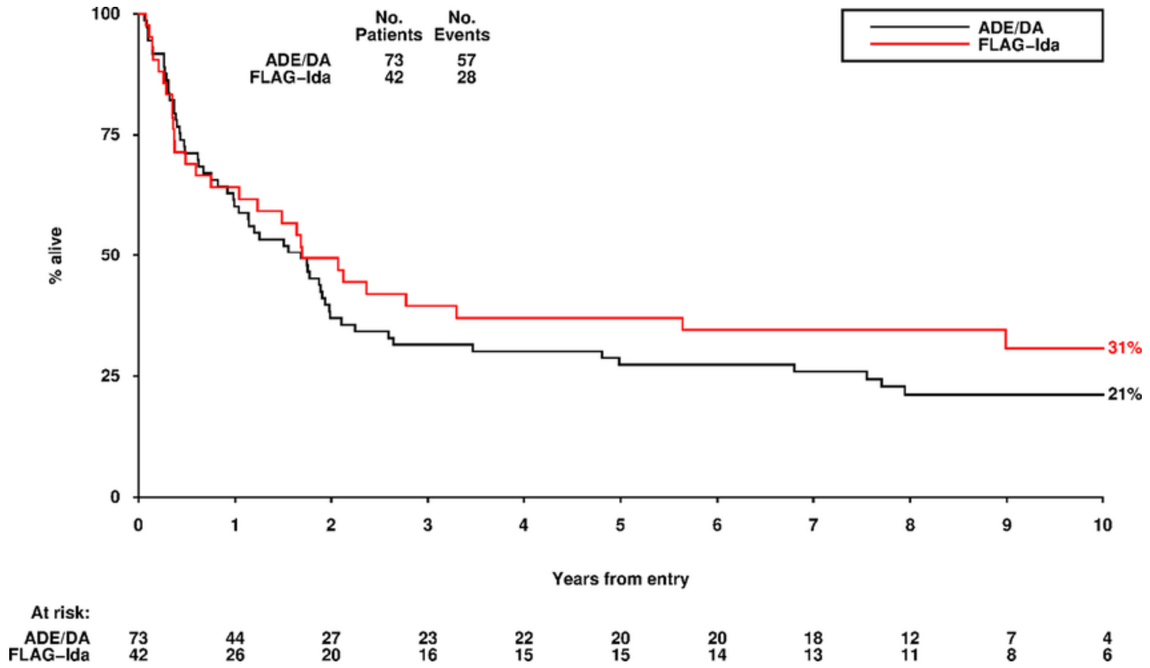
CPX-351 survival benefit in AML-MR is related to post-remission HCT



Results of a post hoc analysis of the pivotal phase 3 CPX-351-301 study indicated that the benefit of CPX-351 over 7+3 is driven by the presence of AML-MR defining mutations

Shimony S, et al. ASH 2024. Oral presentation 60.

Treatment intensification with FLAG-Ida may improve disease control in younger patients with secondary acute myeloid leukaemia: long-term follow up of the MRC AML15 trial

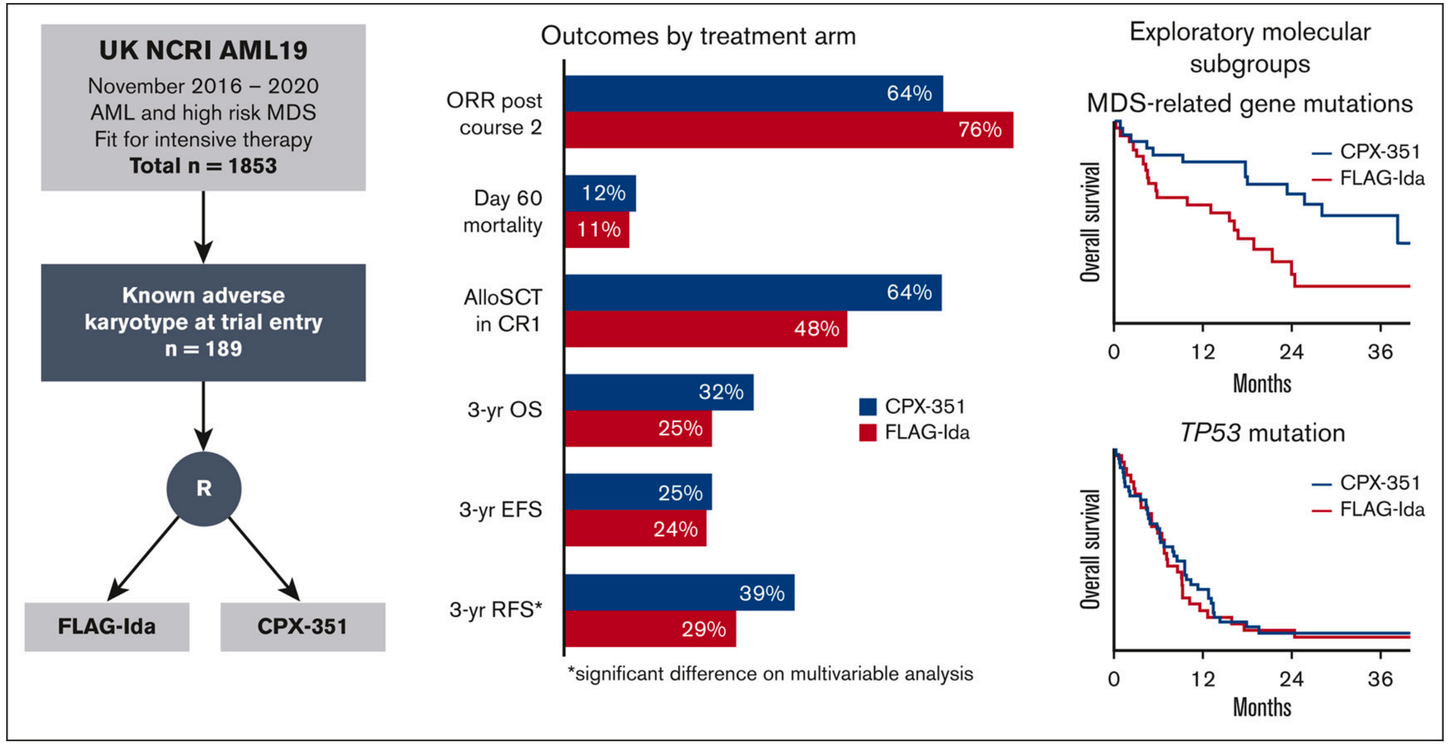


The MRC AML15 trial randomised younger patients(n = 115) between daunorubicin and ara-C (DA) and DA plus etoposide (ADE) and ADE and fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor (FLAG-Ida) induction.
Response to induction was not different [complete remission/complete remission with incomplete haematological response 81% vs. 79%),

5-year overall survival and relapse free survival was superior for FLAG-Ida (37% vs. 27%, P = 0·02 and 41% vs. 22%; P = 0·04, respectively).

Russell N et al, Br J Haematol. 2022 Mar;196(6):1344-1347

A randomized comparison of CPX-351 and FLAG-Ida in adverse karyotype AML and high-risk MDS: the UK NCRI AML19 trial



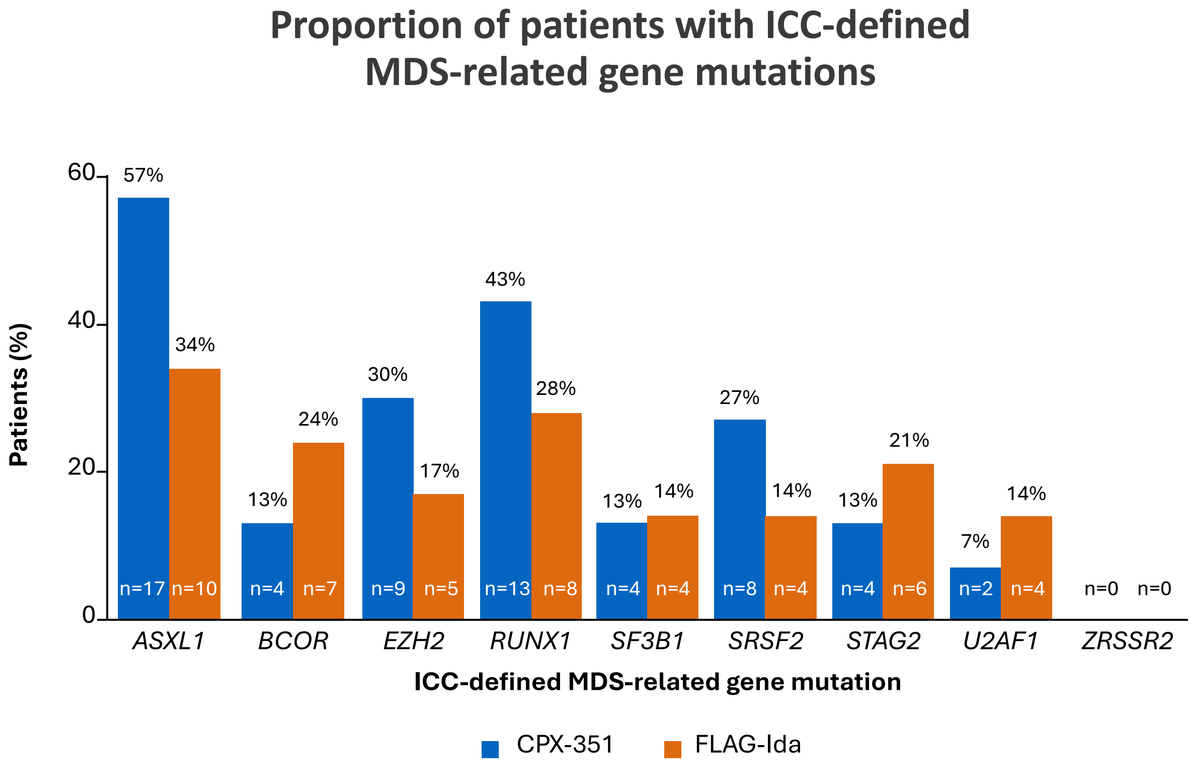
Key Points

- In high-risk AML and MDS, CPX-351 did not improve response or survival compared with FLAG-Ida but produced better relapse-free survival.
- In the exploratory subgroup of patients defined by the presence of mutations in MDS-related genes, CPX-351 improved OS.

Othman J et al, Blood Adv. 2023 Aug 22;7(16):4539-4549.

Subgroup analysis: patients with MDS-related gene mutations

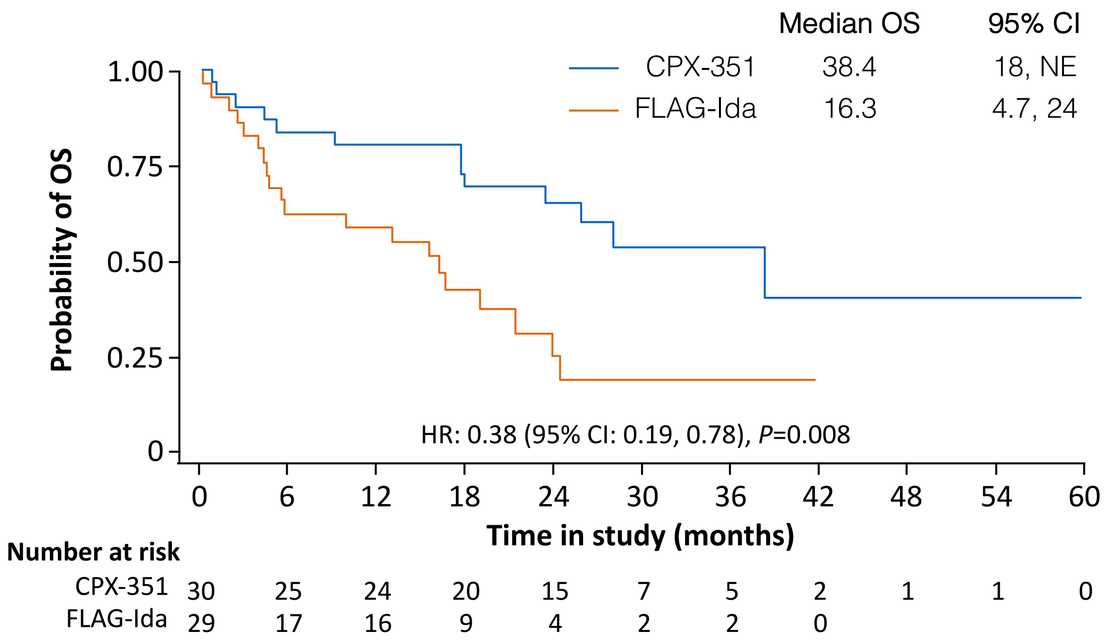
	CPX-351 (n=30)	FLAG-Ida (n=29)
Male, n (%)	19 (63)	17 (59)
Female, n (%)	11 (37)	12 (41)
Age, median (min, max) years	57.5 (40, 68)	58.0 (20, 67)
AML subtype, n (%)		
De novo	15 (50)	14 (48)
Secondary	4 (13)	7 (24)
High-risk MDS	11 (37)	8 (28)
WHO performance status, n (%)		
0 (normal activity)	16 (53)	20 (69)
1 (restricted activity)	12 (40)	8 (28)
2 (in bed <50% waking hours)	2 (7)	1 (3)
Cytogenetic risk group by Grimwade 2010 criteria, n (%)		
Normal	0	3 (10)
Intermediate	6 (20)	3 (10)
Adverse	23 (77)	22 (76)
Missing/not conducted	1 (3)	1 (3)



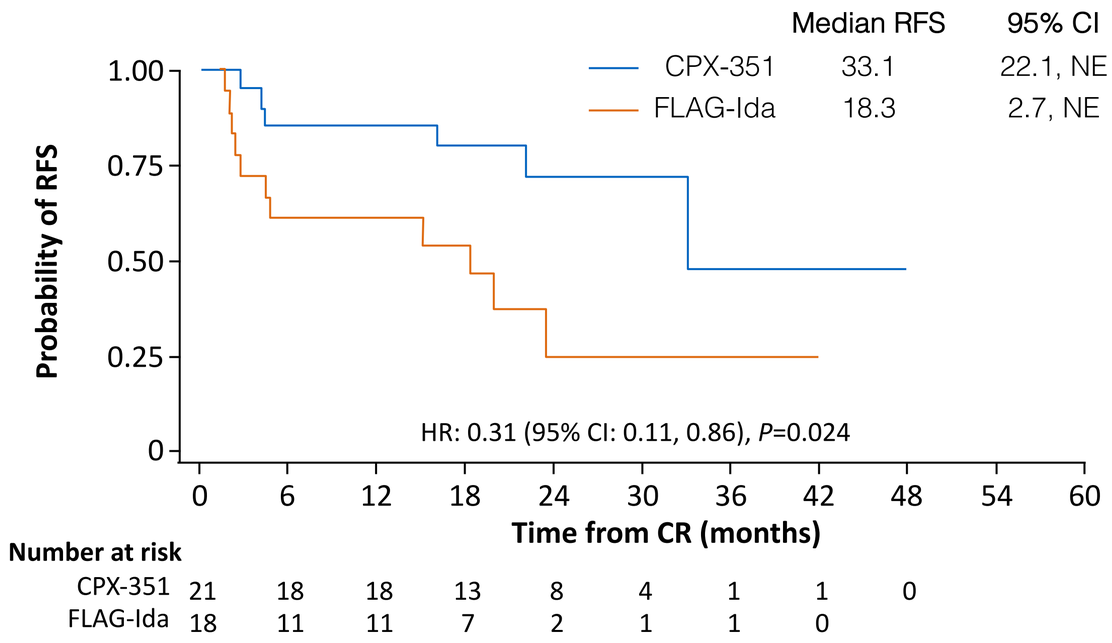
Mehta P, et al. ASH 2024. Oral presentation 55.

Survival outcomes: patients with MDS-related gene mutations

OS



RFS in patients who achieved CR



Median EFS was longer with CPX-351 vs FLAG-Ida (34.0 vs 5.9 months; HR: 0.53; 95% CI: 0.27, 1.03; *P*=0.062)

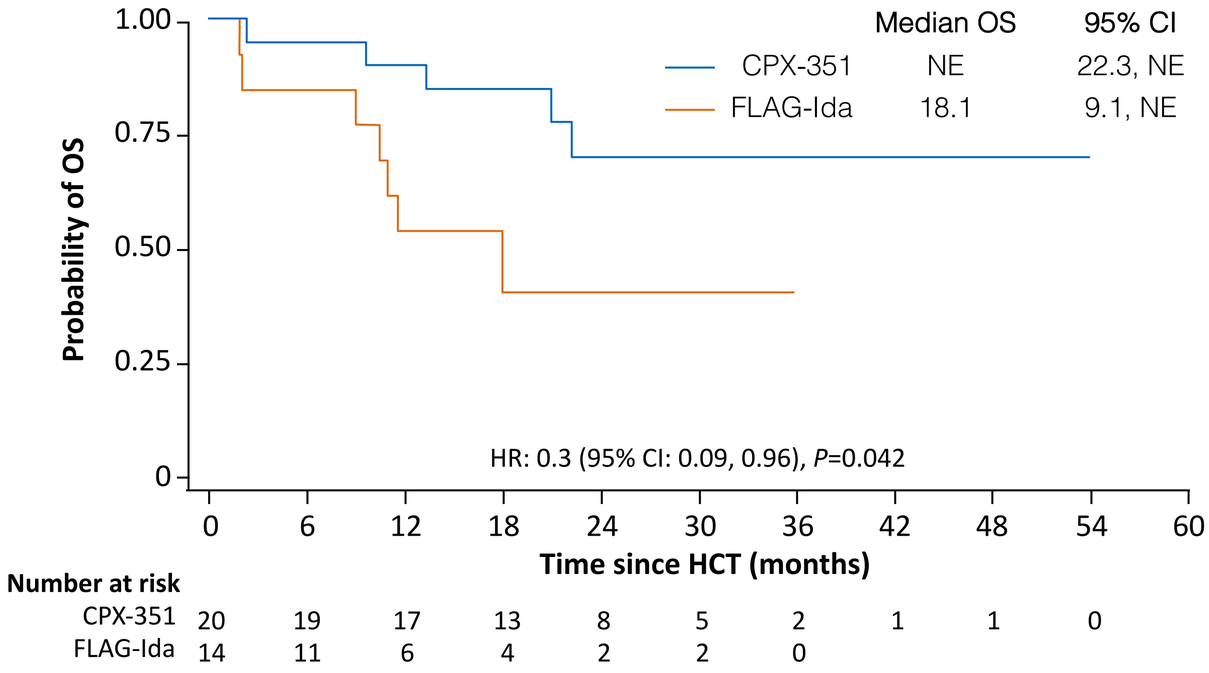
Mehta P, et al. ASH 2024. Oral presentation 55.

HCT rates and survival outcomes post-HCT in patients with MDS gene related mutations

HCT rates

Allogeneic Transplant	CPX-351 (n=30)	FLAG-Ida (n=29)	*P* value
Transplant at any time, n (%)	20 (67)	14 (48)	0.15
Transplant in first response, n (%)[a]	15 (75)	11 (48)	0.07

OS landmarked at HCT



Mehta P, et al. ASH 2024. Oral presentation 55.

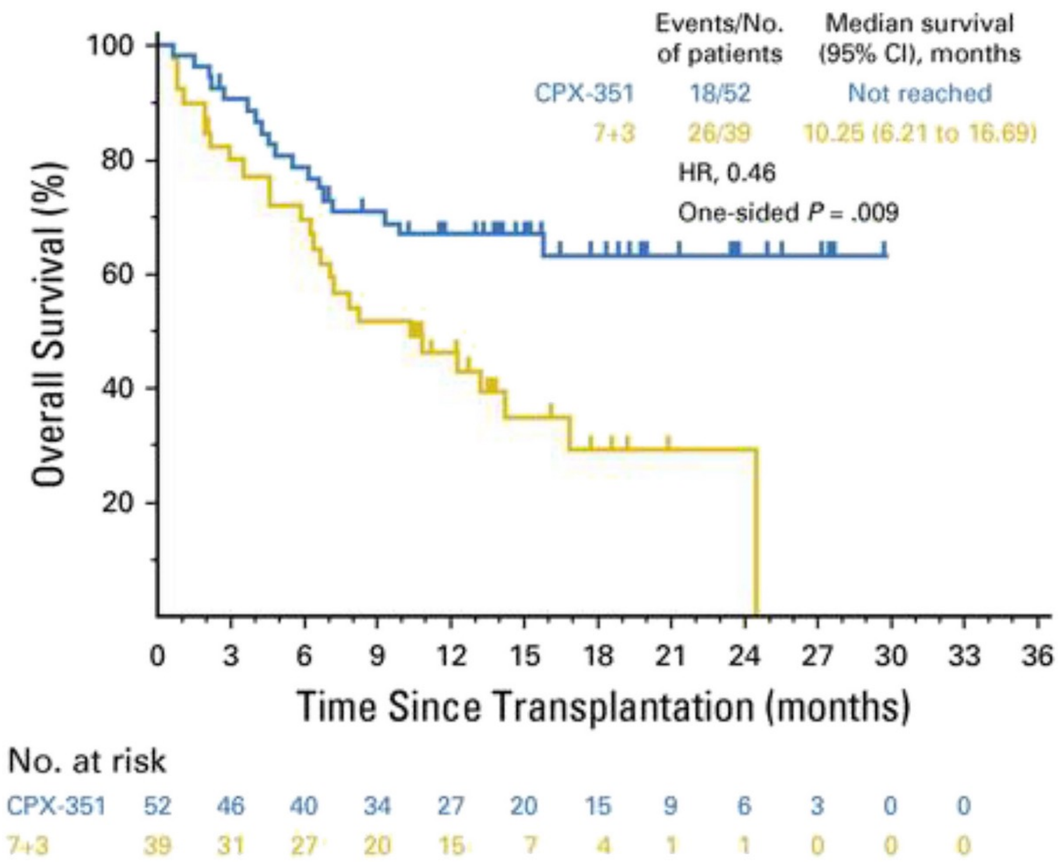
AML19 subgroup analysis

CPX-351 significantly improves median OS, RFS, and post-HCT OS vs FLAG-Ida in younger adults with high-risk AML/MDS and MDS-related mutations.
The CPX-351 arm showed less myelosuppression in Cycle 2 and fewer serious AEs vs FLAG-Ida, suggesting a better toxicity profile and potentially allowing more patients to reach HCT

Study 301 subgroup analysis

AML-MR mutations drive the benefit of CPX-351 over 7+3 in the pivotal phase 3 AML trial

Overall survival for patients who received allo-SCT



Major findings:
Patients treated with CPX-351 were more likely to receive HCT (32% versus 25%)

Patients receiving HCT demonstrated favorable long-term outcomes

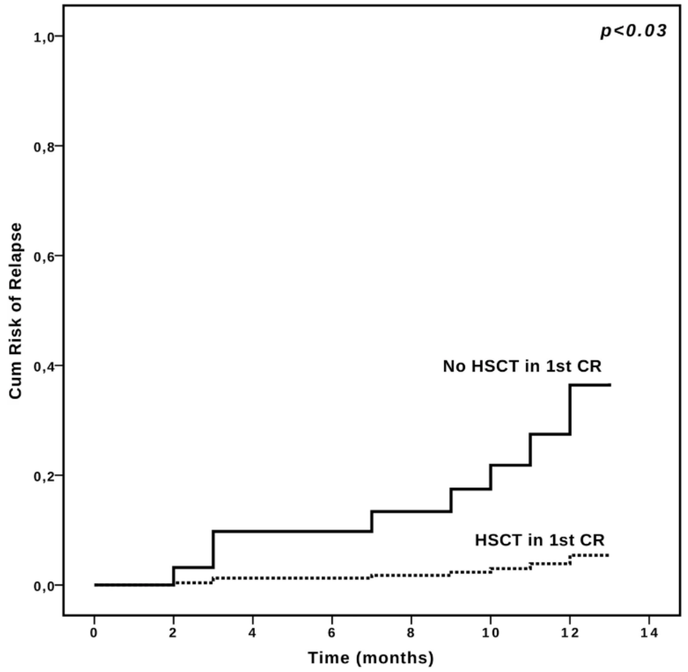
By 100 days post-transplant, mortality in transplant patients was 9.6% for patients receiving CPX-351 compared to 20.5% for 7 + 3

CPX-351 as a bridge-to-transplant strategy.

Lancet et al *Journal of Clinical Oncology* 2018 362684-2692.

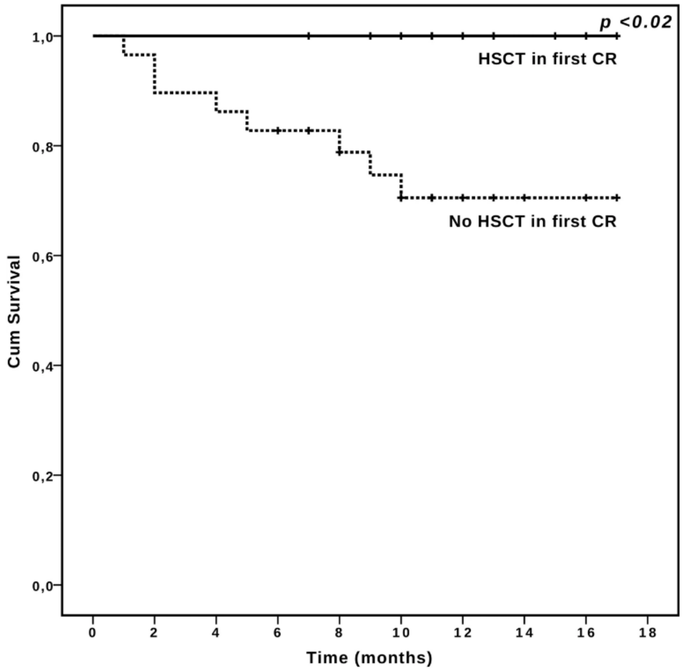
CPX-351 treatment in secondary acute myeloblastic leukemia is effective and improves the feasibility of allogeneic stem cell transplantation: results of the Italian compassionate use program

Relapse Risk in responding patients according to transplantation



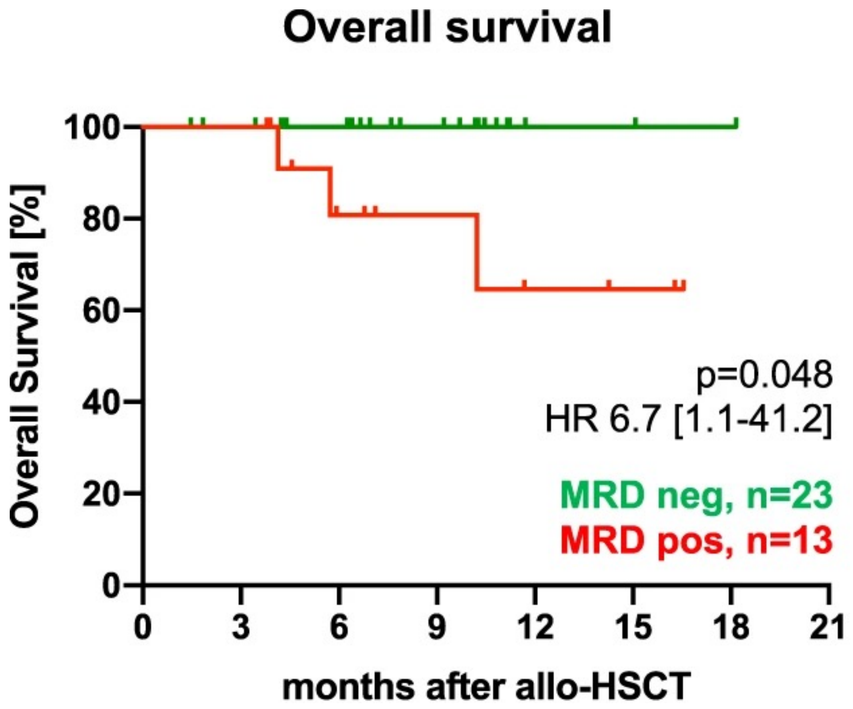
HSCT in CR1 was the only significant predictor of longer survival (12 months OS of 100 and 70.5%, for patients undergoing or not HSCT in CR1, respectively, p = 0.011).

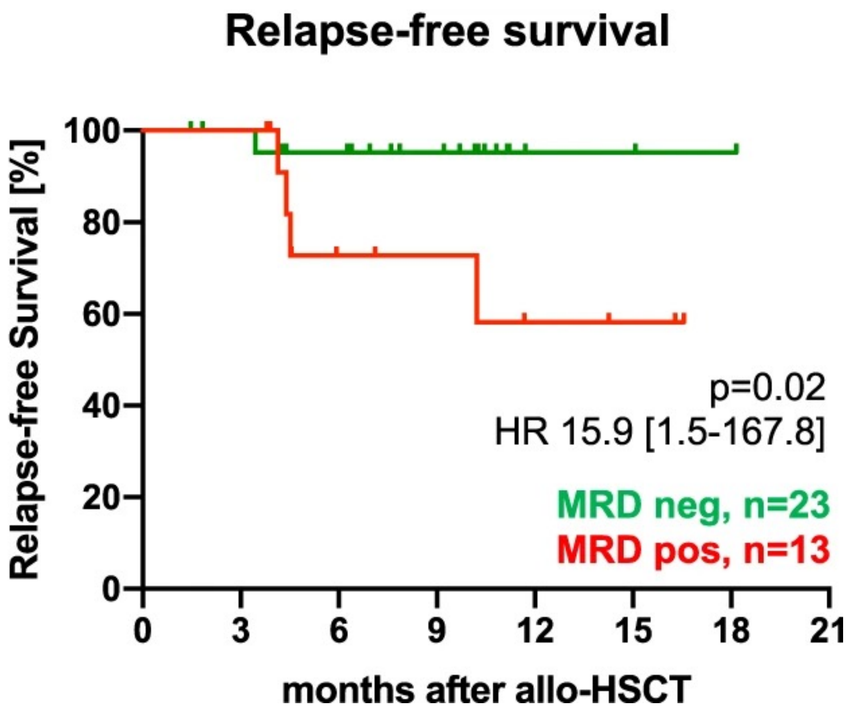
Overall Survival in responding patients according to transplantation



Guolo et al, Blood Cancer J. 2020 Oct 6;10(10):96.

Real-world experience of CPX-351 as first-line treatment for patients with acute myeloid leukemia: impact of MRD on post-transplant outcome





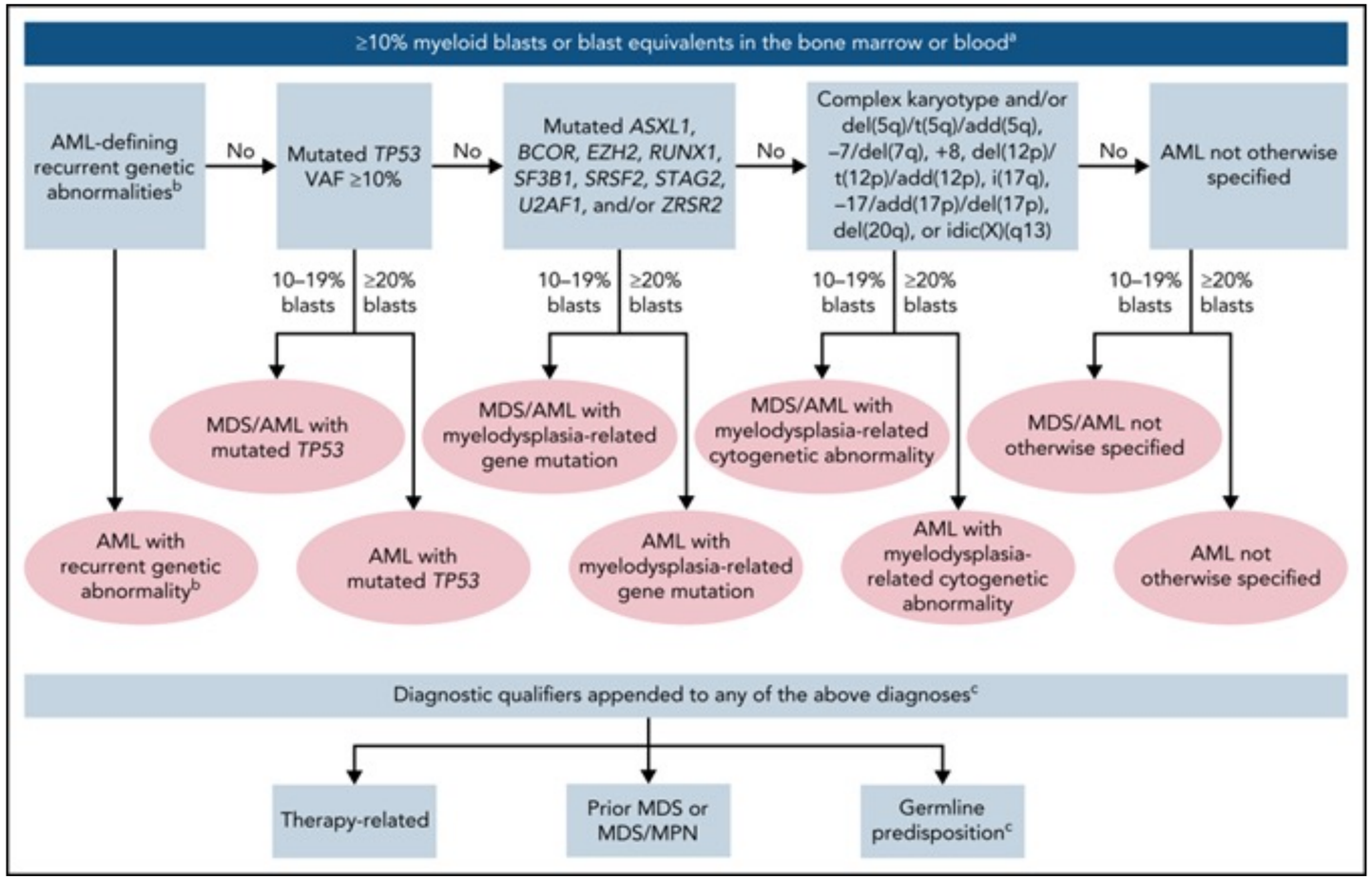
Among patients with CR/CRi (*n* = 85) after CPX-351-based induction data on MRD estimated by FC were available for 36 patients (42%) representing MRD negativity in 64% of the patients (*n* = 23).

Rautenberg C et al, Blood Cancer Journal,, volume 11, 164, October 2021

Who benefits from CPX-351?

- Not only over 60 years old patients
- Fit-to-chemotherapy (some interesting data about reduced-intensity regimen for patients at high risk of mortality)
- Candidate to allo-SCT (bridge-to-transplant)
- Better, but not excluded, if not previously exposed to HMAs and without adverse cytogenetics (optimal: untreated sAML)

Hierarchical classification of the International Consensus Classification of AML



Arber DA et al, Blood. 2022. ;140(11):1200-1228.