What is the best induction treatment for ELDERLY HIGH RISK AML? CPX-351

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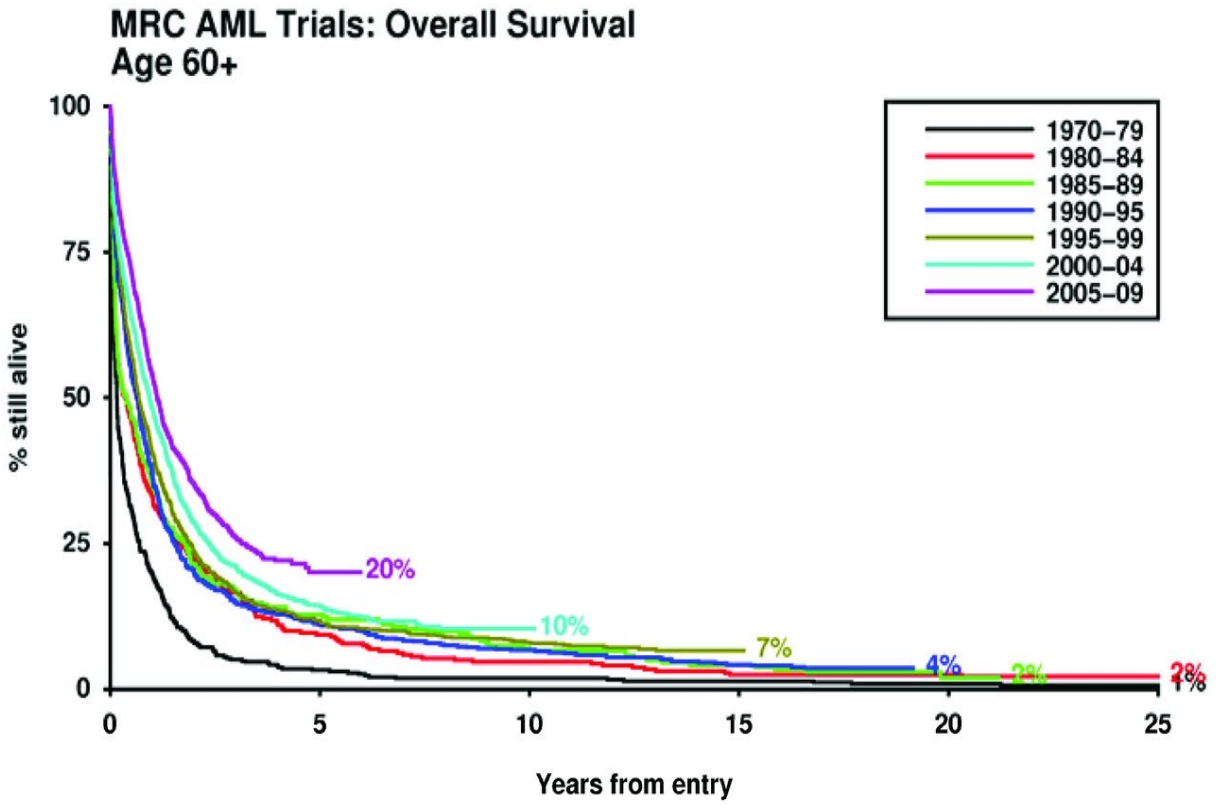
Disclosures of Paola Minetto

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NA							

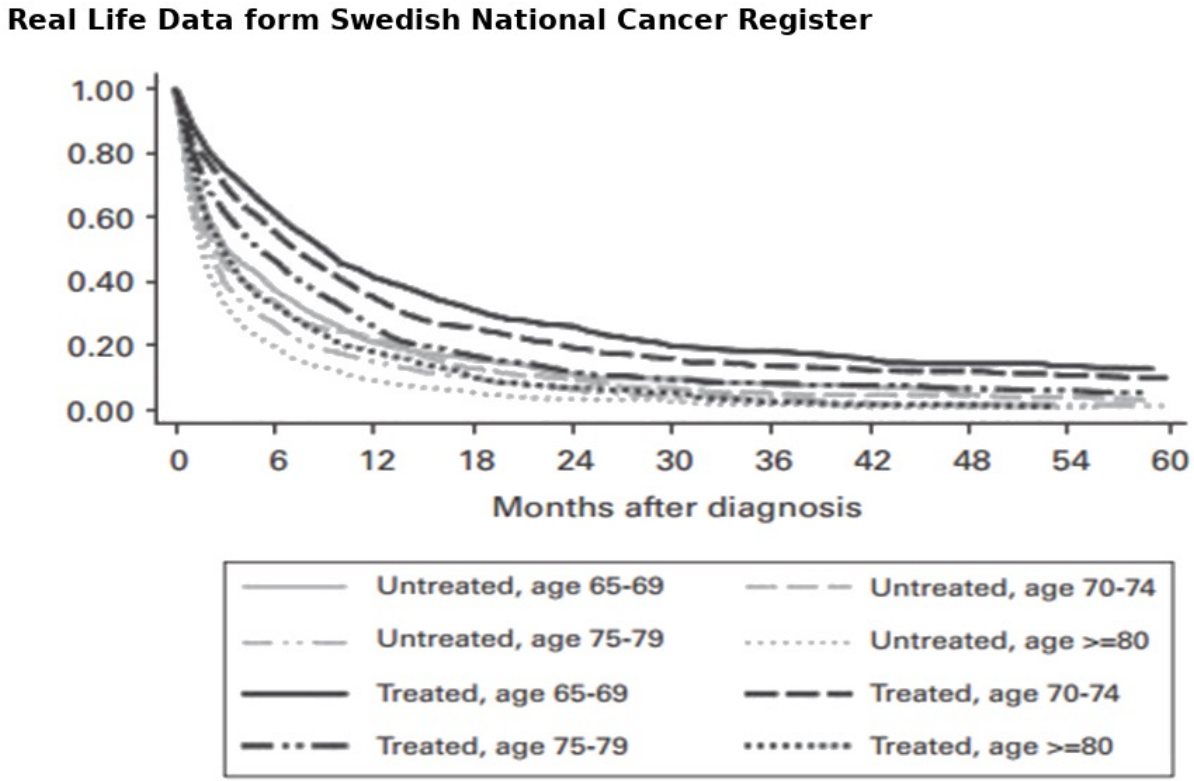
AML in the elderly: still room for improvements

Elderly AML patients show poor prognosis with little improvement over the years.

However, active treatment allows to achieve better results



Alan K. Burnett Hematology 2012;2012:1-6



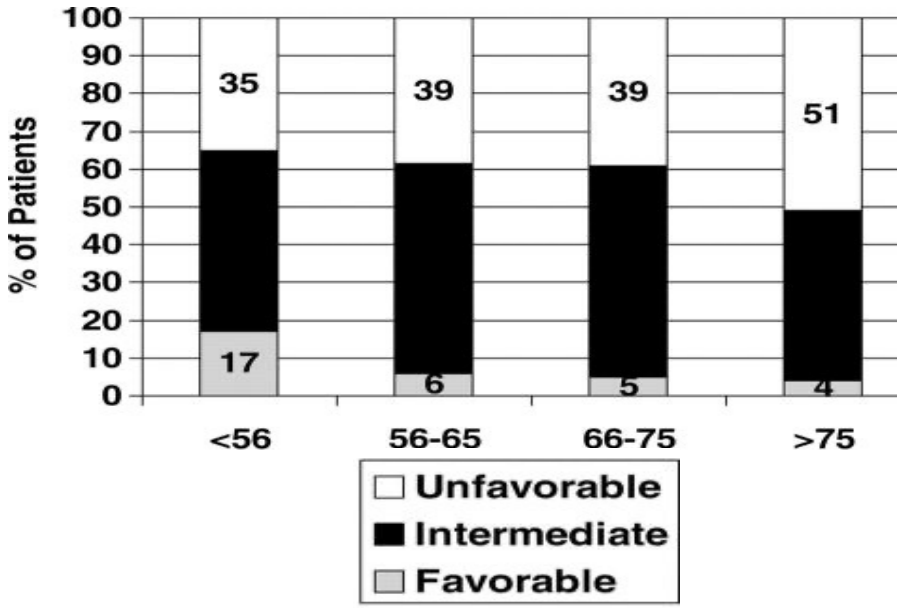
Ustun et al. Bone Marrow Transplantation 2013

Acute Myeloblastic Leukemia (AML) in elderly patients

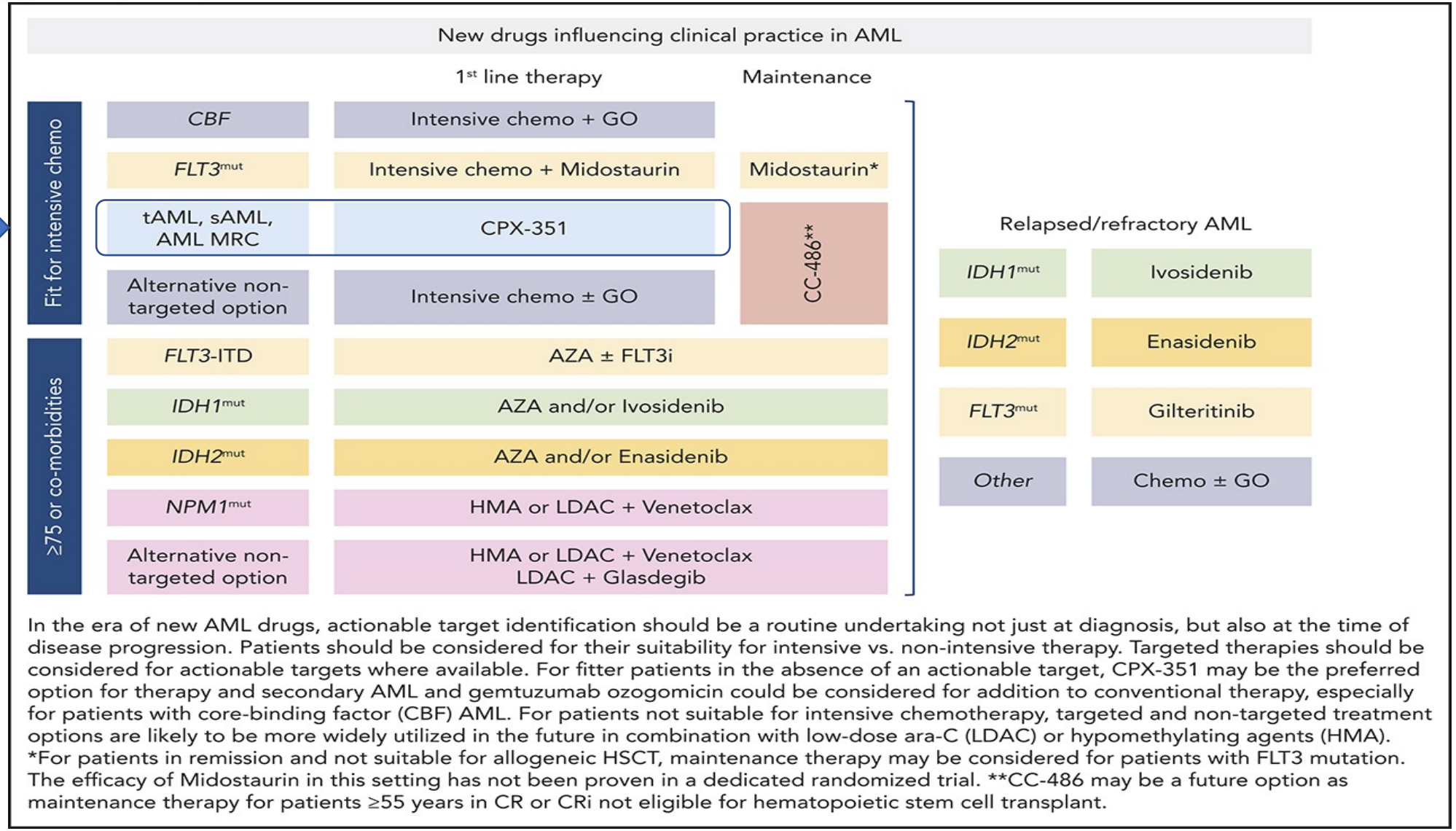
Adverse cytogenetic features are common (complex karyotype, monosomy, del 5, del 7, abn3q etc),

leukemia often evolves from prior MDS, even in absence of clinical records

	Younger than 56 y	56-65 y	66-75 y	Older than 75 y	P*
No. patients	323	183	199	54	
Cytogenetic risk group, no. (%)					< .001†
Favorable	51 (16)	10 (5)	10 (5)	2 (4)	
Intermediate	149 (46)	101 (55)	110 (55)	24 (44)	
Unfavorable	108 (33)	70 (38)	78 (39)	27 (50)	
Unknown	15 (5)	2 (1)	1 (1)	1 (2)	
Specific abnormalities, no. (%)					
−5 or 5q−	21 (7)	27 (15)	28 (14)	14 (26)	< .001
−7 or 7q−	28 (9)	35 (19)	36 (18)	12 (22)	< .001
17p	6 (2)	16 (9)	14 (7)	6 (11)	.001
t(8;21)	22 (7)	7 (4)	4 (2)	0 (0)	.019
inv(16)	31 (10)	4 (2)	7 (4)	4 (7)	.002



Appelbaum FR, et al. Blood. 2006 May 1;107(9):3481-5.



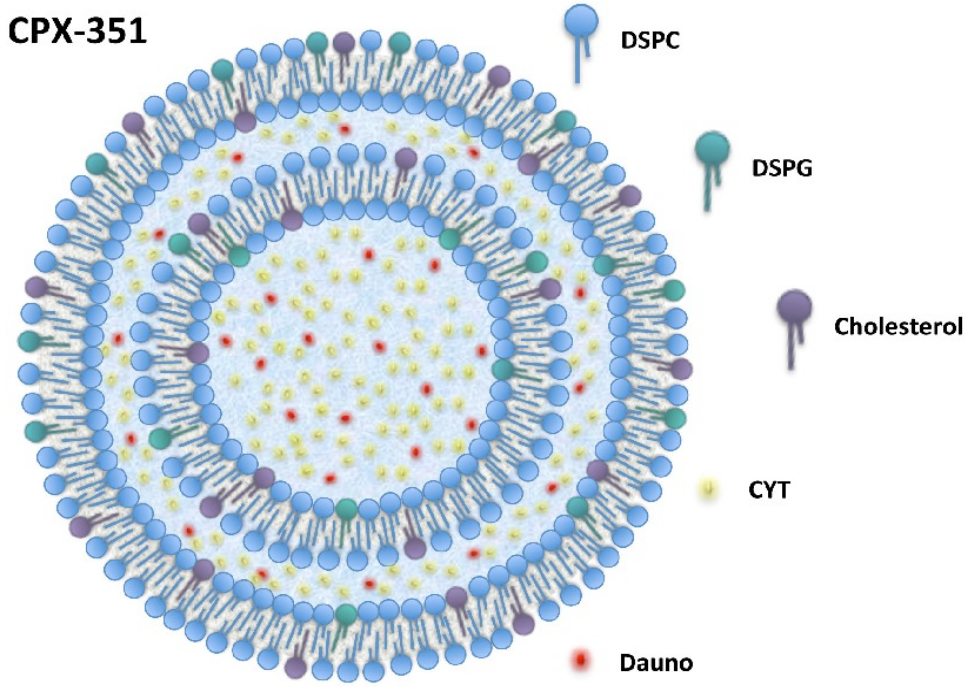
In the era of new AML drugs, actionable target identification should be a routine undertaking not just at diagnosis, but also at the time of disease progression. Patients should be considered for their suitability for intensive vs. non-intensive therapy. Targeted therapies should be considered for actionable targets where available. For fitter patients in the absence of an actionable target, CPX-351 may be the preferred option for therapy and secondary AML and gemtuzumab ozogomicin could be considered for addition to conventional therapy, especially for patients with core-binding factor (CBF) AML. For patients not suitable for intensive chemotherapy, targeted and non-targeted treatment options are likely to be more widely utilized in the future in combination with low-dose ara-C (LDAC) or hypomethylating agents (HMA).
*For patients in remission and not suitable for allogeneic HSCT, maintenance therapy may be considered for patients with FLT3 mutation. The efficacy of Midostaurin in this setting has not been proven in a dedicated randomized trial. **CC-486 may be a future option as maintenance therapy for patients ≥55 years in CR or CRi not eligible for hematopoietic stem cell transplant.

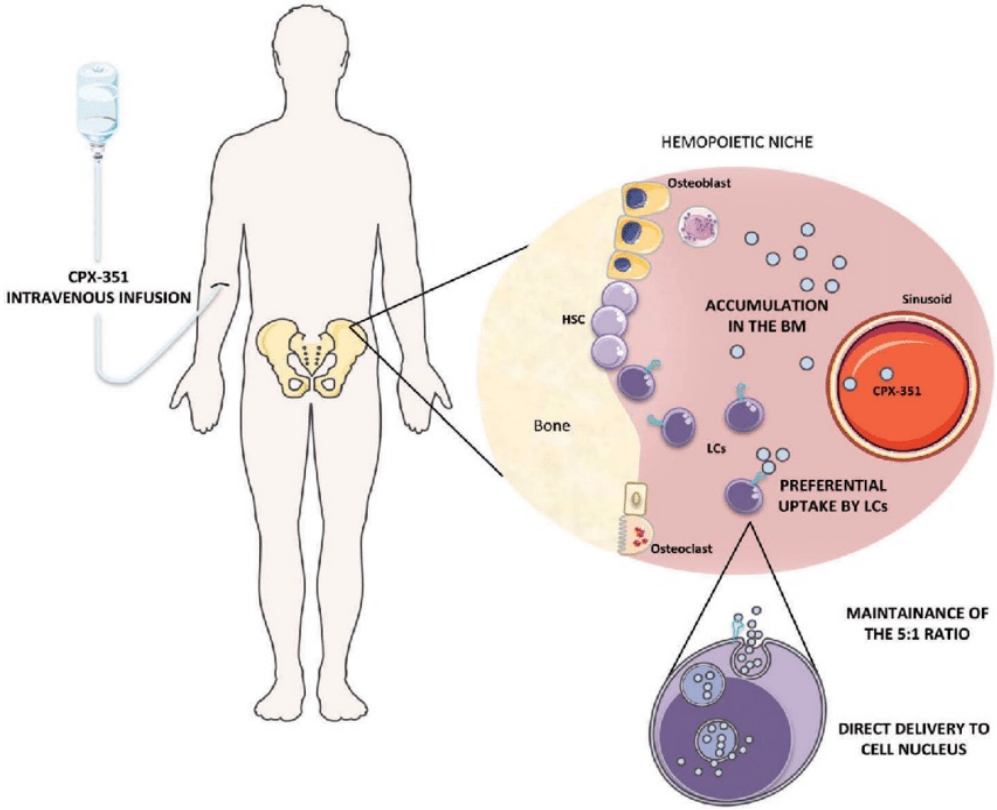
Di Nardo CD, Wei AH. Blood. 2020; 135 : 85–96.

CPX-351

- Dual drug **liposomal encapsulation** of cytarabine and daunorubicin which enables to deliver a **synergistic ARA-C/DAUNO 5:1 molar drug** ratio into leukemic cells

- Bilamellar liposome also **enhances drug accumulation in BM** and a preferential uptake by leukemia cells

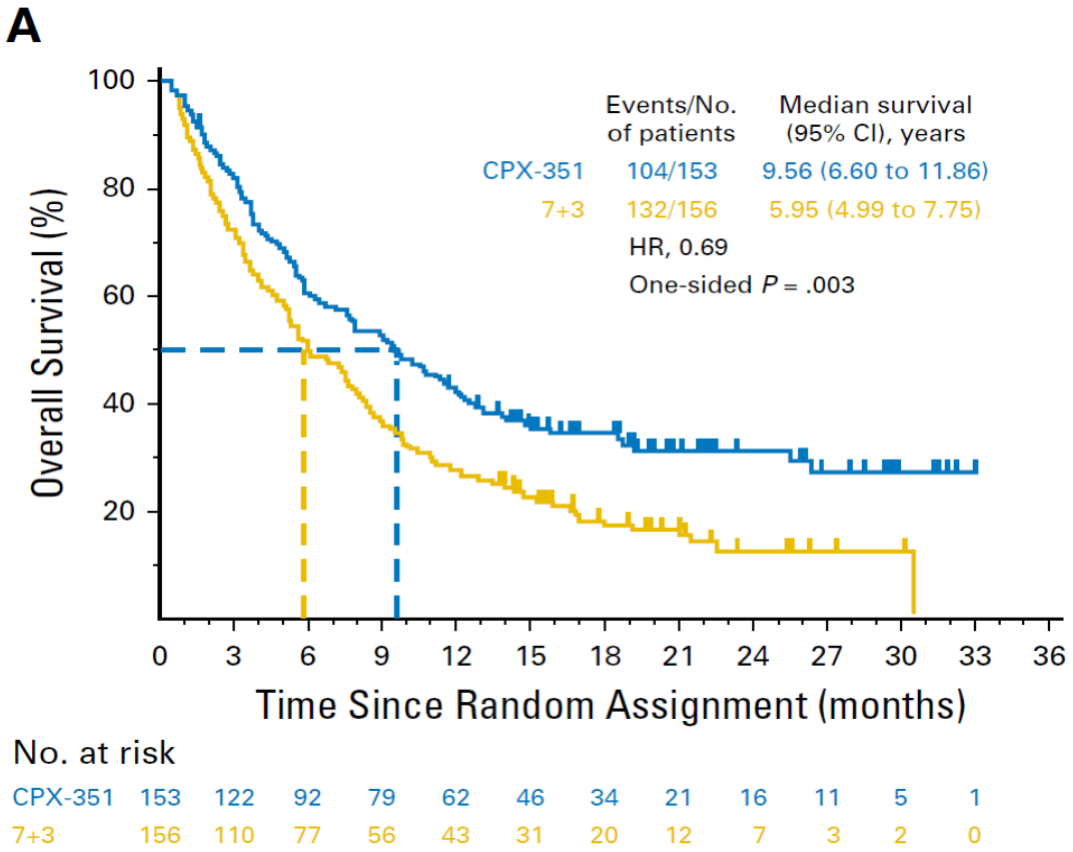




DSPC= phosphatidylcholine
DSPG= distearoyl phosphatidylglycerol

CPX-351

CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia



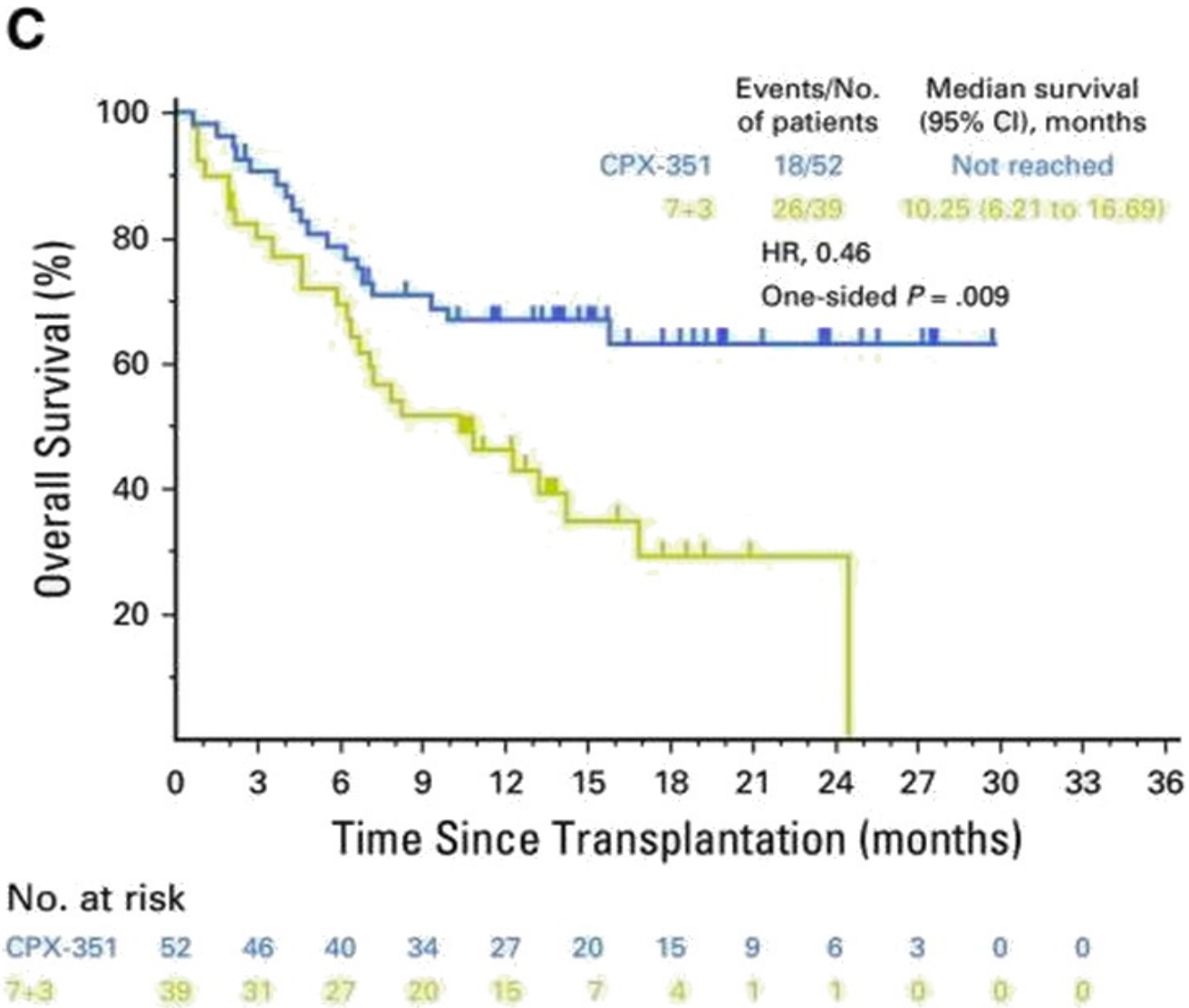
Increased CR rate, Overall and Disease Free Survival among:

-Therapy related Myeloid Neoplasm
- AML with MDS-related changes

The increase in OS at 2 years in the whole study population is 15-20% when compared to standard “3+7”

Lancet JL et al. J Clin Oncol. 2018; 36: 2684–2692.

CPX-351



The improvement in survival is even more evident among patient achieving CR and undergoing to allogeneic stem cell transplantation.

This observation may indicate deeper responses as well as lower toxicity from transplantation in CPX-treated patients

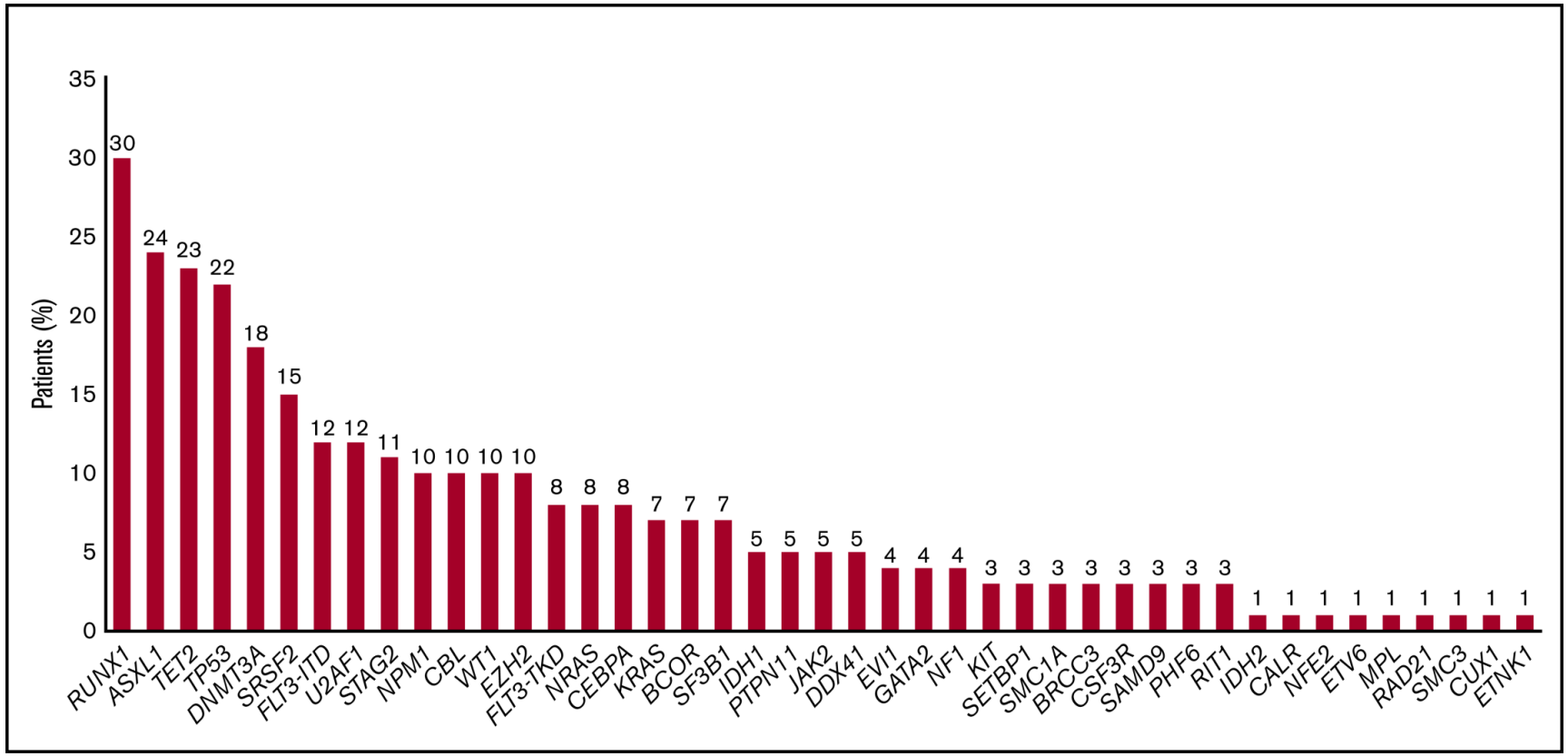
Lancet JL et al. J Clin Oncol. 2018; 36: 2684–2692.

Real life data from French register

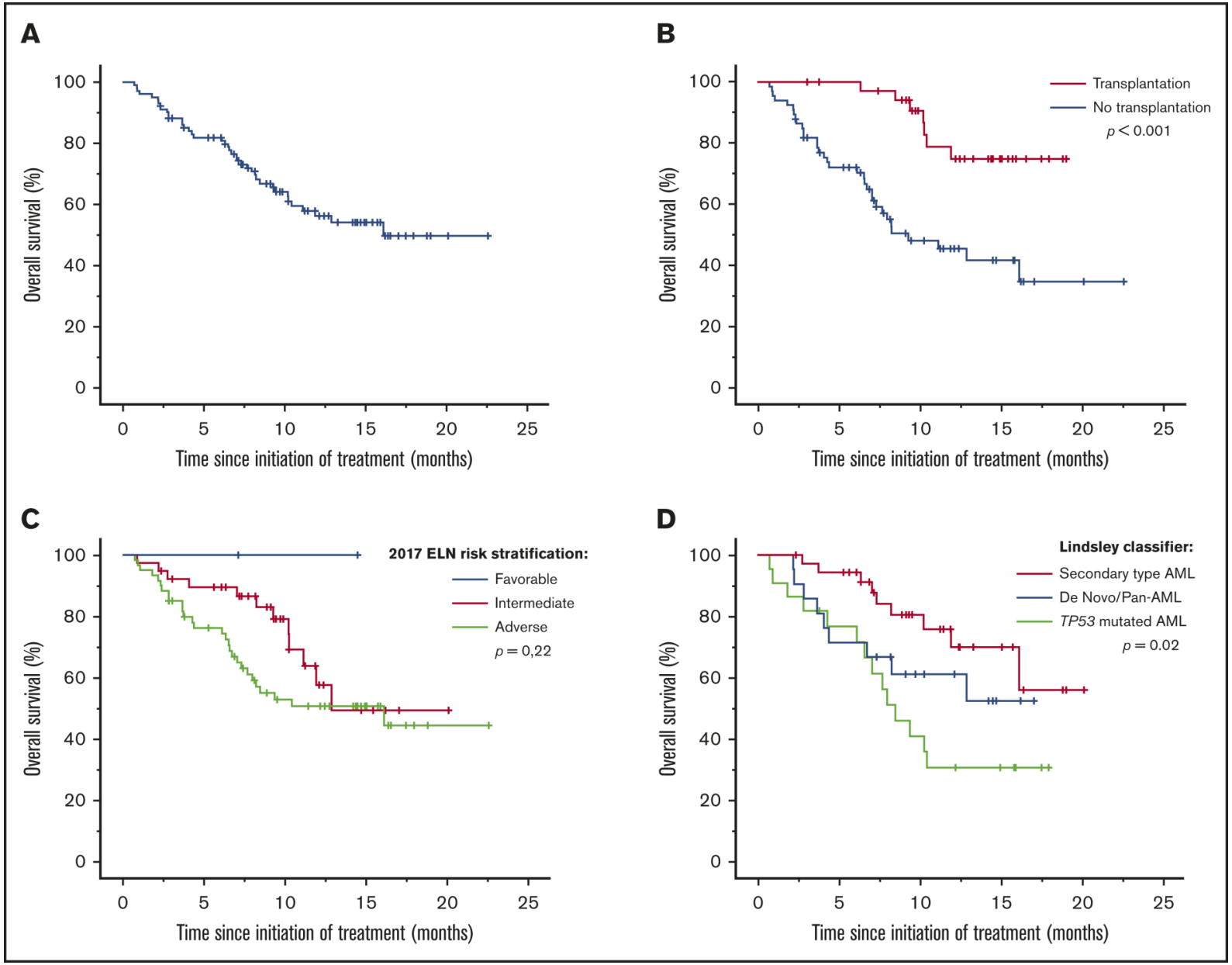
103 patients from 12 French centers.

Median age 67 years.

61% of patients were considered at high risk according to ELN 2017 classification



Chiche E, et al. *Blood Adv* (2021) 5 (1): 176–184.



- CR + CRi rate was 59%.
- Median follow up 8.6 months
- Median OS 16.1 months

Among the 61 patients who achieved CR/CRi, 28 (46%) were evaluable for MRD at the time of the first consolidation cycle and among them 16 (57%) had reached complete molecular response defined as MRD <10−3

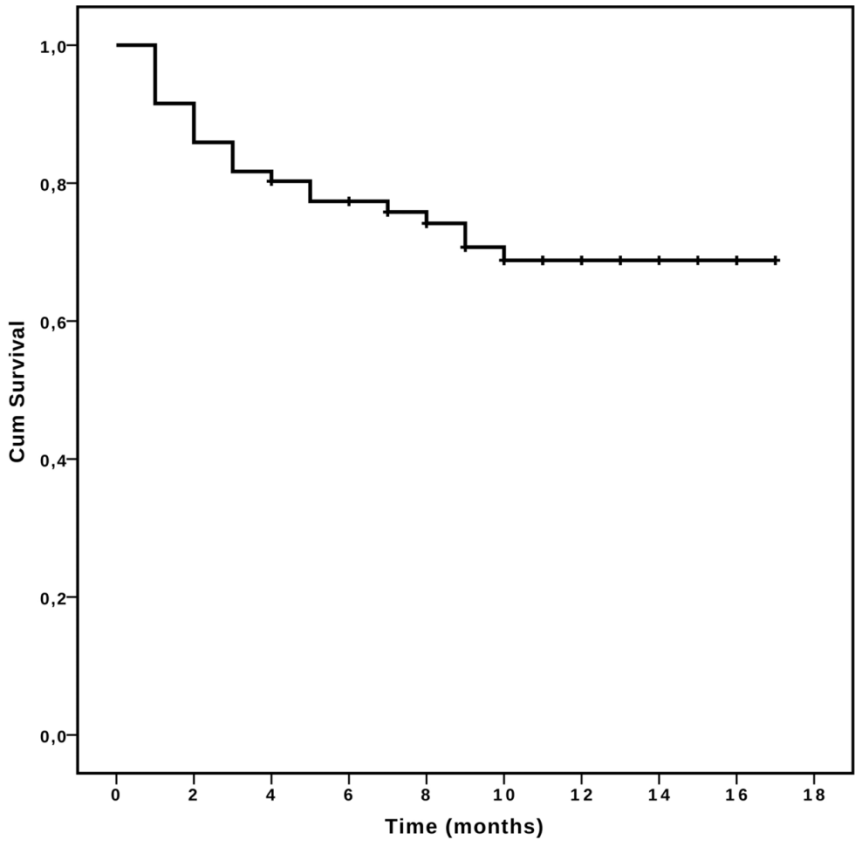
36 patients proceeded with allogeneic stem cell transplantation

Survival was significantly better among patients receiving transplantation.

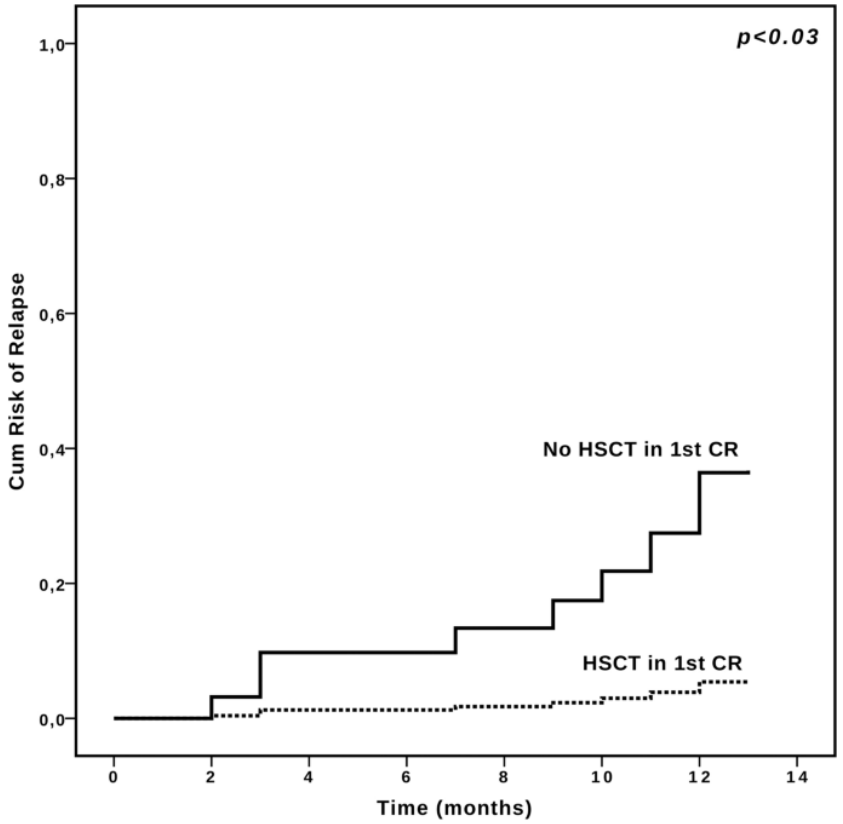
Chiche E, et al. *Blood Adv* (2021) 5 (1): 176–184.

Italian Compassionate Use Program of CPX-351

Overall Survival in all patients



CI of relapse according to transplantation



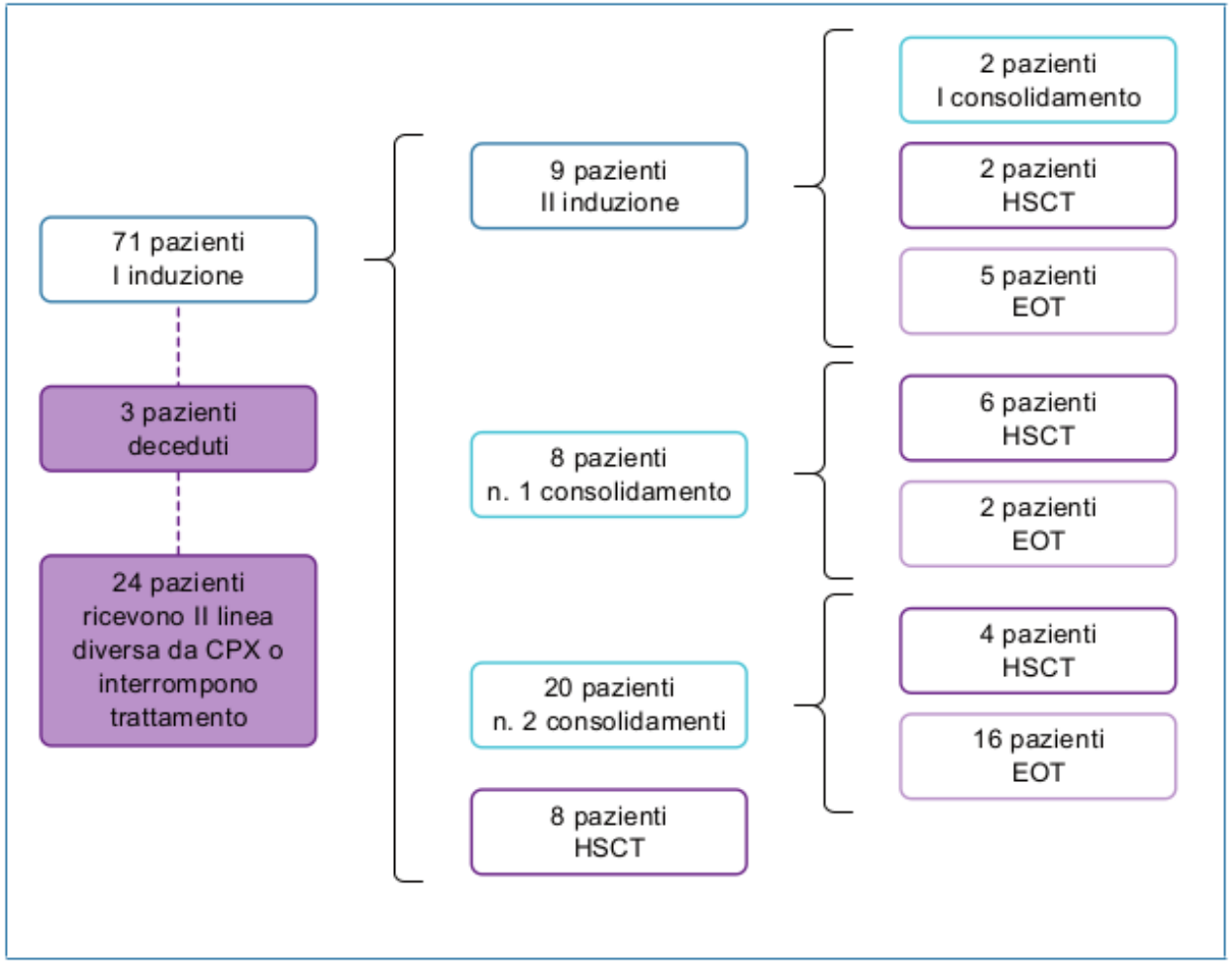
- 71 patients treated in 31 different Italian Centers
- Age: 52-79 years (median 65)
- Twenty patients (28.2%) >70 years
- ELN Risk stratification:
  - 55% High
  - 35% Intermediate
  - 10% Low
- Median Follow-UP: 12 months
- CR rate about 70%
- **OS was 68.6% at 12 months**

Real life data confirm the good tolerability despite the prolonged hematological recovery after CPX-351 induction.

Guolo F, et al. *Blood Cancer Journal (2020) 10:96.*

Compassionate Use Program: patients and treatment

Treatment outline in Italian CUP



Median age: 65 years (range 52-79)

Previous HMA therapy in 17 patients (23.9%)

3 DAC e 14 5-AZA, median of 4 cycles (range 1-78)

Relevant comorbidities in 62/71 patients (88.0%; mostly CV)

Twenty five patients (35%) had prior cancer diagnosis and 23 had received chemo and/or radiotherapy. Four patients did undergo ASCT

Guolo f, Minetto P et al, Blood Cancer Journal 2020

Treatment-related toxicities

Despite the difficult patient population, overall, CPX-351 treatment was well tollerated

- 30-day mortality: 4.2% (3/71 patients). 60-days mortality: 7% (5/71 patients)

- Adverse events grade greater than 1(CTCAE) in 57 patients (80.3%):

  Most frequent AEs were infections:

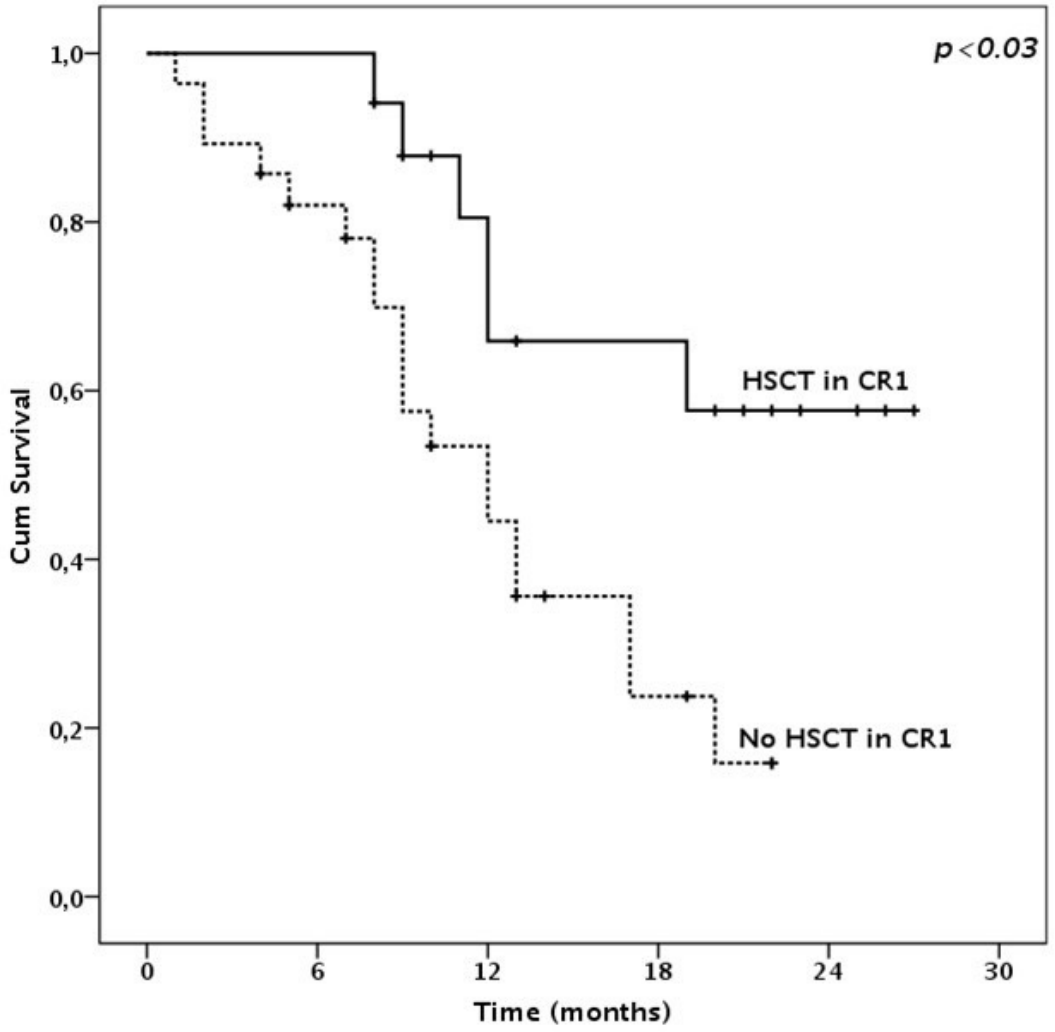
  - FUO in 20/71 (28%)
  - sepsis in 20/71 (28%)
  - pneumonia in 8/71(11.3%)

- Median time to **ANC >0.5 × 10^9/L and platelet >25 × 10^9/L** recovery was **38 (range 12–60)** and **28 (range 12–60)** days, respectively.

- **Relatively low incidence of severe (grade>2) mucositis: 5/71 (7%)**

- A peculiar AE was a diffuse skin rash with a late onset (12-15 days after CPX-351 administration), observed in 18/71 patients (25.4%).

Guolo F, et al. *Blood Cancer Journal (2020) 10:96*



Extended follow up of Italian CPX-351 CUP confirm the good activity CPX-351.
Two-year OS for transplanted patients is high despite the difficult patient population

Median follow up: 22 months.
Median overall survival (OS) was 18 months (11.2 - 22.8 95% IC). Two-years OS was 28.6%.

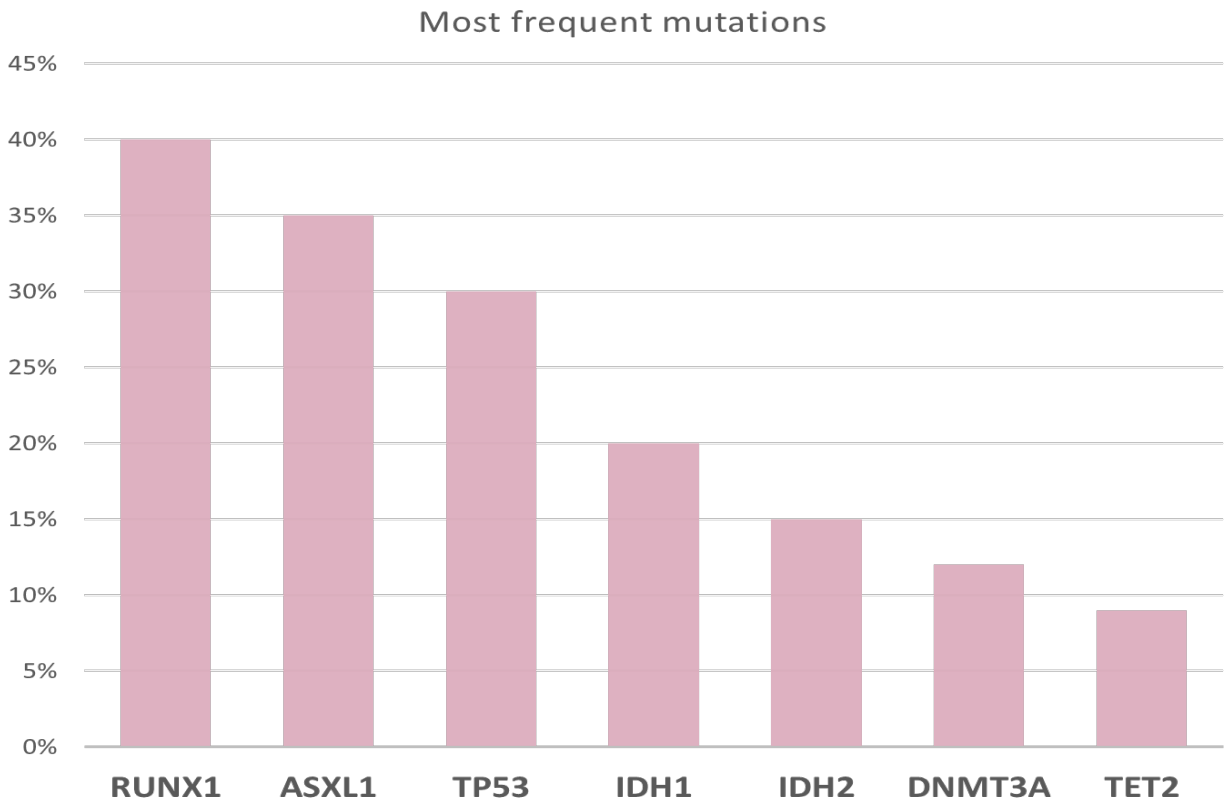
HSCT performed in first CR after CPX-351 was the only significant predictor of longer survival.

Median OS was not reached for patients transplanted in first CR Vs 12 months for patients who did not undergo HSCT.
Two-year OS for patients who received HSCT was 57.6% vs 15.8% for patients who did not undergo HSCT.

Minetto P, Guolo F et al. Presented at ASH 2021

Impact of HR features on CR and survival: Genoa experience

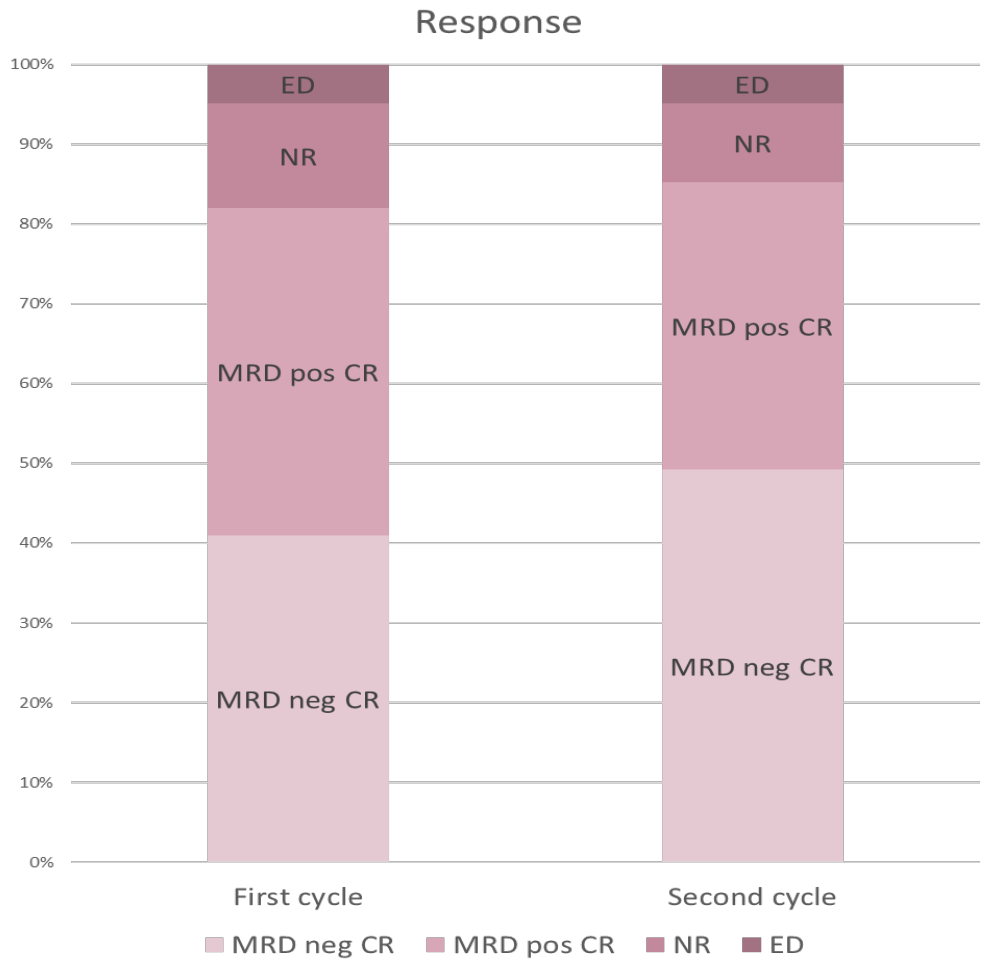
- 61 patients treated, median age 68 years (50-77)
- ELN risk score was high in 31 patients, intermediate in 27 patients and low in 3 patients.
- **Median mutational burden in NGS analysis was 4** (range 2-8).
- Most frequent mutations were: RUNX1 (40%), ASXL1 (35%), IDH1(20%), IDH 2 (15%), TP53 (30%), DNMT3A (12%), TET2 (9%).



Riva C, Minetto P, et al. Presented at 28° EHA Congress (Frankfurt, D)

CR and MRD negative CR probability seems not to be affected by HR features

- After first induction cycle, 50 patients (81%) achieved CR, with a MFC MRD negative in 25/50 responding patients (50%).
- **Both CR rate and MRD negativity probability were not affected by ELN risk group, TP53, RUNX1 or ASXL1 mutations, mutational burden or other analyzed variables.**
- CR rate after cycle 2 was 52/61 (85%), with MFC MRD negative in 30 (58%).



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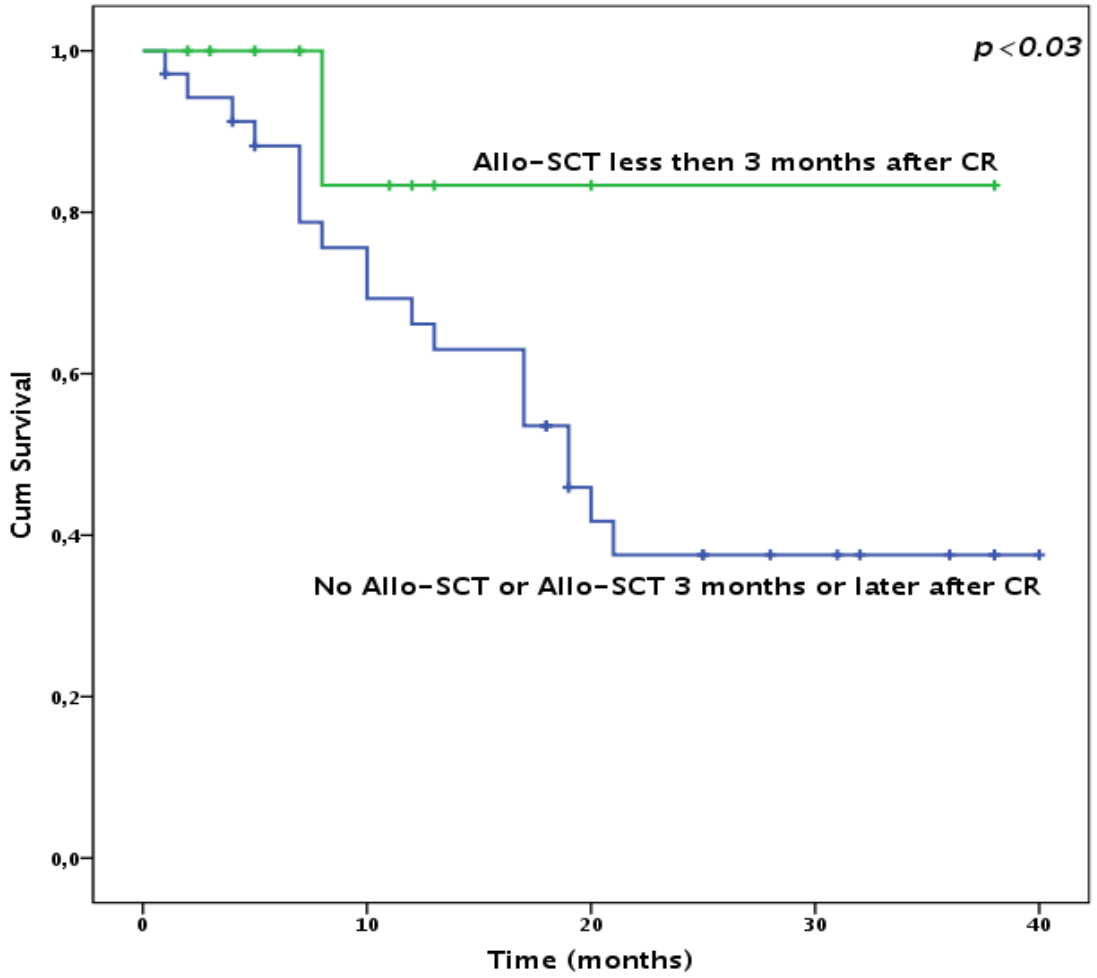
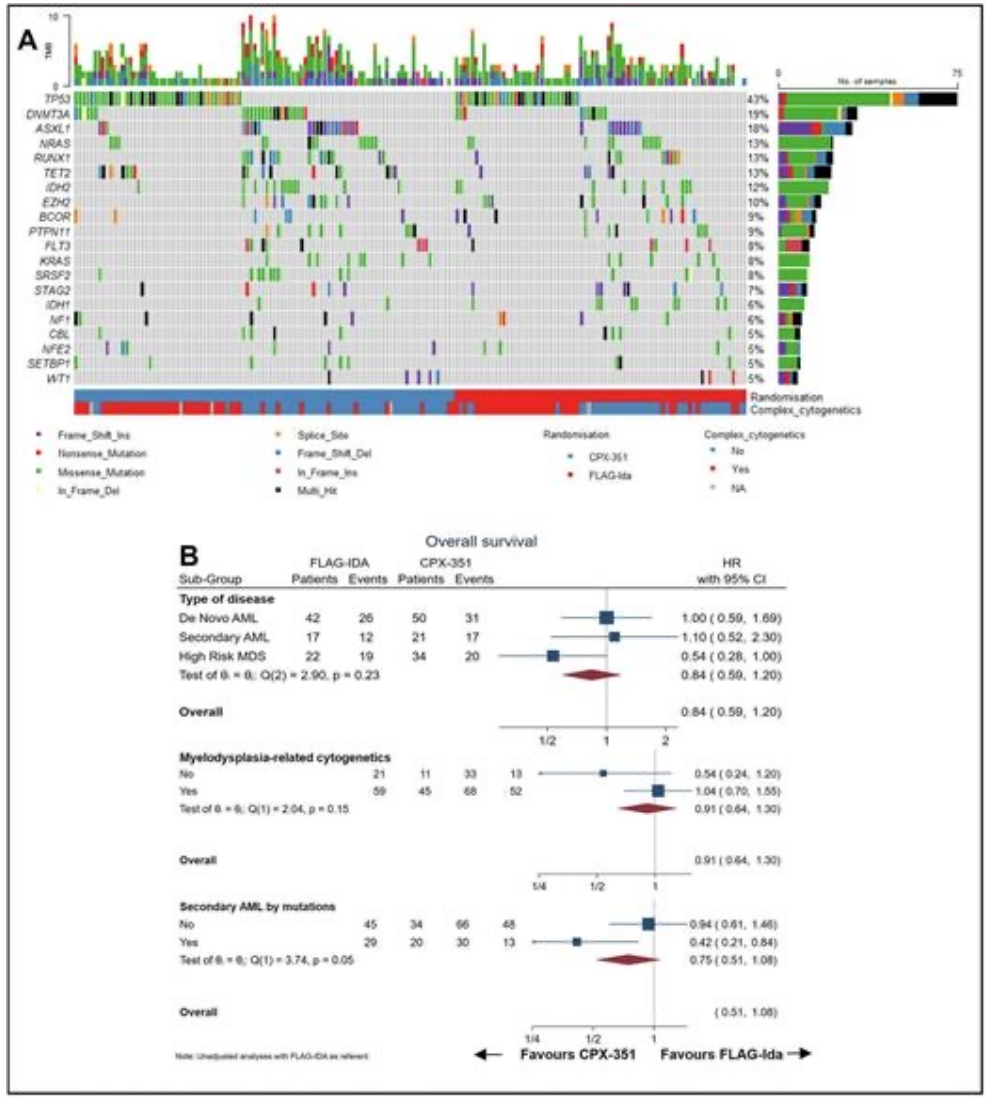
Survival: role of transplantation



In landmark analysis, patients achieving CR and proceeding to allogeneic stem cell transplantation consolidation (HSCT) within 3 months from CR (N=12) had a significantly better outcome if compared to CR patients who did not receive HSCT or proceeded to transplant later (2-year OS: 83.5% and 32.4, respectively, p<0.03).

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



A. Oncoplot showing variants in the top 20 most mutated genes
B. Overall survival subgroup analyses based on clinical categorisation; the presence or absence of myelodysplasia-related cytogenetic abnormalities; and the presence of absence of secondary AML mutations (*ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1*, or *ZRSR2*, without *TP53* mutation)

CPX-351 vs FLAG-Ida in younger adults with newly-diagnosed adverse cytogenetic AML or high-risk myelodysplastic syndromes (MDS).

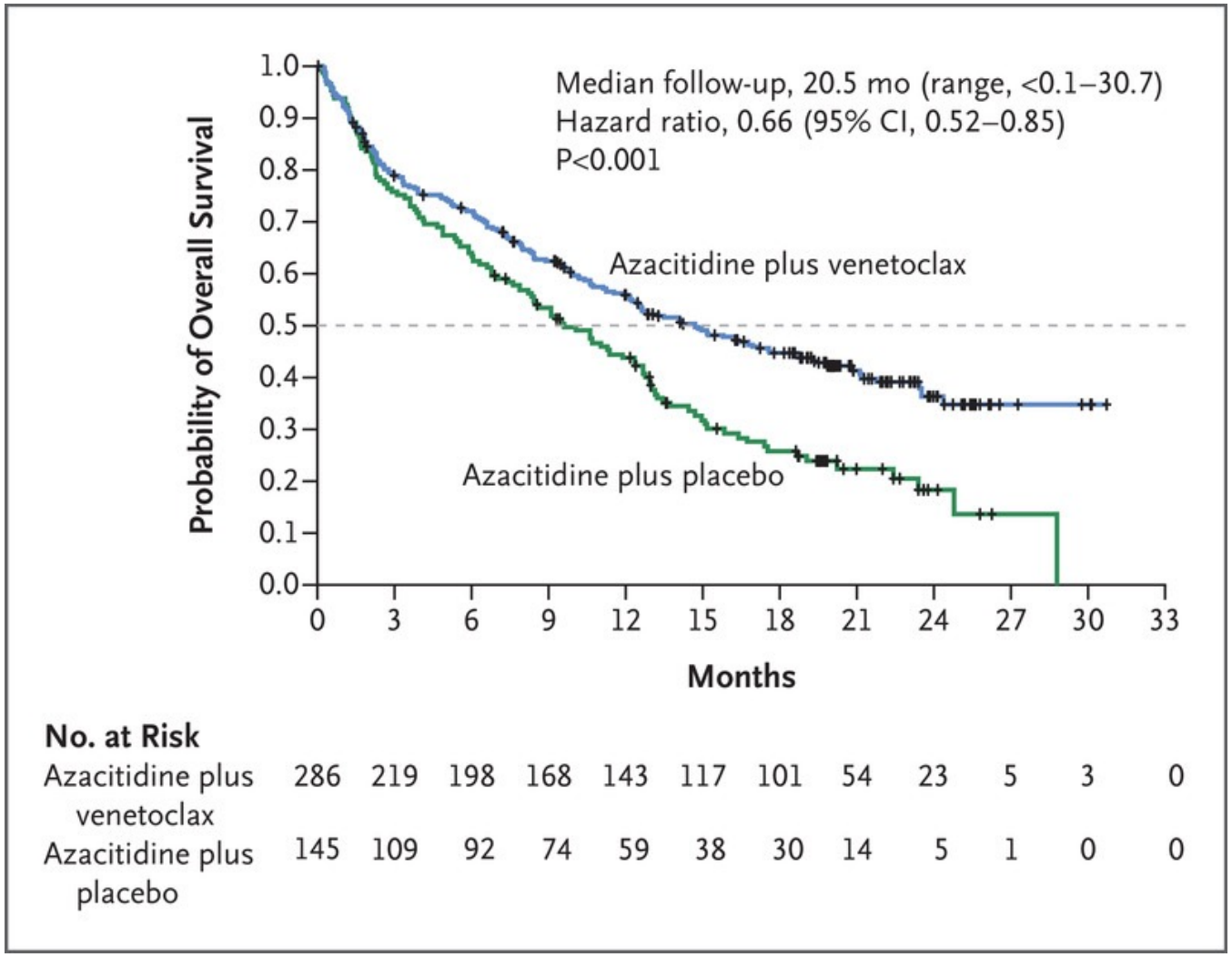
189 patients were randomized (median age 56y).
The overall response rate (CR + CRi) after course two was 64% and 76% for CPX-351 and FLAG-Ida (OR:0.54, 95%CI 0.28-1.04, p=0.06).

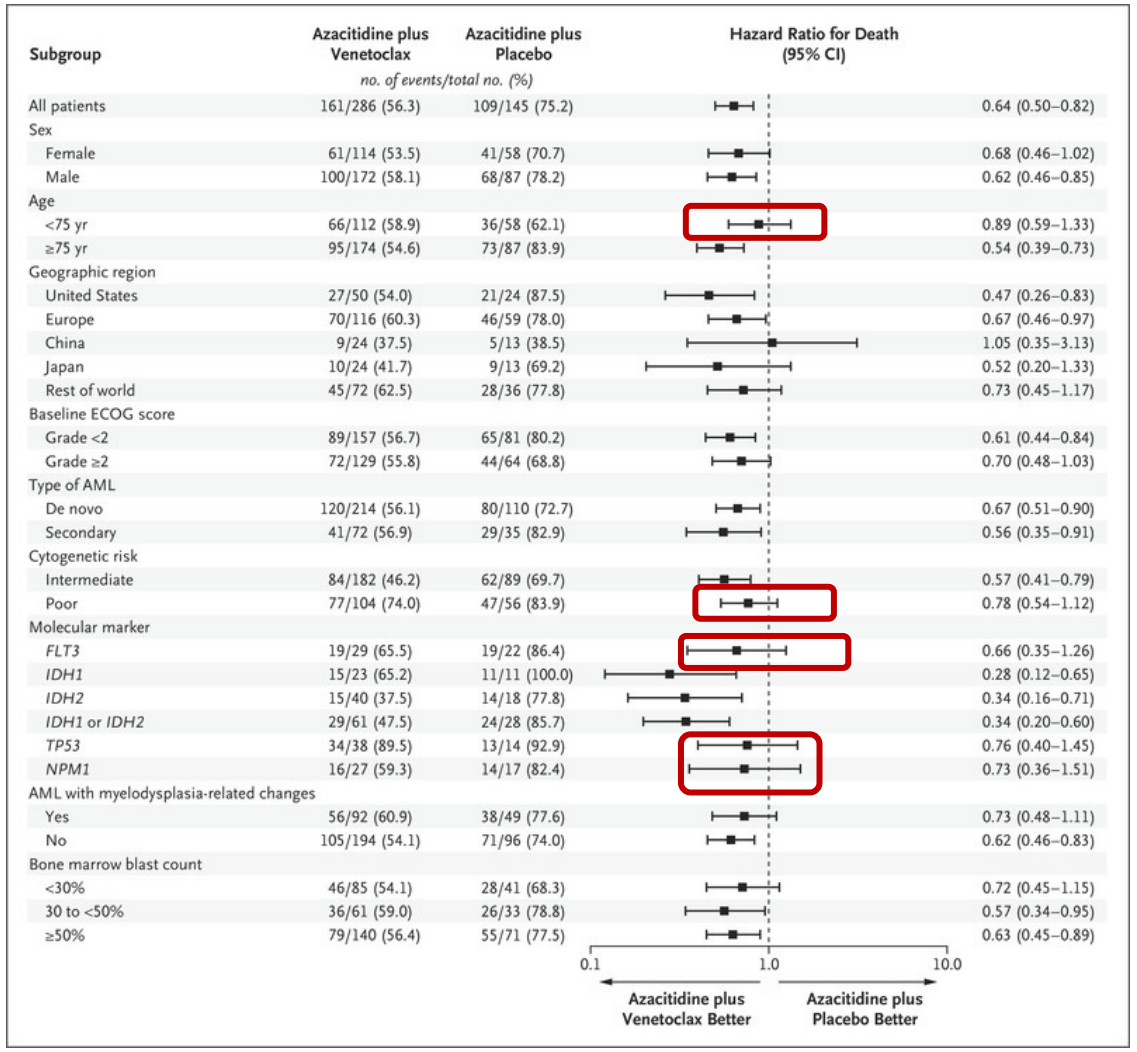
There was no difference in OS (13.3 months vs 11.4 months, HR:0.78, 95%CI 0.55-1.12, p=0.17) or event-free survival (HR:0.90, 95%CI 0.64-1.27, p=0.55) in multivariable analyses.

However, relapse-free survival was significantly longer with CPX-351 (median 22.1 vs 8.35 months, HR:0.58, 95% CI 0.36-0.95, p=0.03).

OS in younger patients with adverse risk AML/MDS was not significantly different between CPX-351 and FLAG-Ida.

Othman J, et al. Presented at ASH 2022
Othman J et al. Blood Advances 2023 (ahead of print)





Di Nardo et al. New Engl Journ Med 2020

Conclusions and open questions

- CPX is able to induce high quality CR in most patients
- The low probability of severe mucositis with CPX may explain the low probability of life-threatening infections.
- Many patients across all the clinical experiencies were able to proceed to allogeneic stem cell transplantation, which is the only curative option for HR-AML
- CPX-351 represents a good treatment option for elderly patients affected by HR-AML, especially if previously treated with hypomethilating agents or with s-AML/t-AML
- Maintenance therapy may improve the prognosis of patients achieving CR but not able to consolidate with HSCT
- The activity of CPX-351 seems to be consistent across different AML subgroups and to be less affected by HR features

Thank you for your attention