CPX-351:una semplice formulazione liposomiale di vecchi farmaci o un nuovo farmaco ?

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Disclosures of: Roberto M. Lemoli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie						v	
Janssen						v	
Jazz					v	v	
Daiichi Sankyo						v	
Servier					v		
Celgene	v						

WHO classification of acute myeloid leukemia and related neoplasms

AML with Recurrent Genetic Abnormalities		**~60-65%**
AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*	AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1*	
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	[a]AML with *BCR-ABL1* gene fusion	
APL with *PML-RARA*	AML with mutated *NPM1*	
AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*	AML with biallelic mutations of *CEBPA*	
AML with t(6;9)(p23;q34.1); *DEK-NUP214*	[a]AML with mutated *RUNX1*	
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*		
AML with Myelodysplasia-Related Changes*		**~30%**
Therapy-Related Myeloid Neoplasms		**~10%**
AML, Not Otherwise Specified (NOS)		
Myeloid Sarcoma		
Myeloid Proliferations Related to Down Syndrome		

[a]Provisional entity.

* Defined by MDS-cytogenetics in about 30% of cases

Arber et al., Blood 2016

AML-MRC

Cytogenetic abnormalities

Complex karyotype:

- ≥3 unrelated abnormalities, none of which are included in the AML with recurrent genetic abnormalities subgroup[2]

Unbalanced abnormalities[1]:

- -7/del(7q)
- i(17q)/t(17p)
- del(11q)
- idic(X)(q13)
- del(5q)/t(5q)
- -13/del(13q)
- del(12p)/t(12p)

Balanced abnormalities[1]:

- t(11;16)(q23:3;p13.3) *KMT2A/CREBBP*[3]
- t(3;21)(q26.2;q22.1) *RUNX1/MECOM*[3]
- t(2;11)(p21;q23:3)
- t(1;3)(p36.3;q21.1)
- t(5;12)(q32;p13.2) *ETV6/PDGFRB*[3]
- t(5;7)(q32;q11.2) *HIP1/PDGFRB*[3]
- t(5;17)(q32;p13.2) *RABEP1/PDGFRB*[3]
- t(5;10)(q32;q21.2) *CCDC6/PDGFRB*[3]
- t(3;5)(q25.3;q35.1) *NPM1/MLF1*[3]

IN THE ABSENCE of a WHO-defined recurrent genetic abnormality[1]:

t(8;21), inv(16), t(6;9), t(15;17), t(9;11), inv(3), t(1;22)

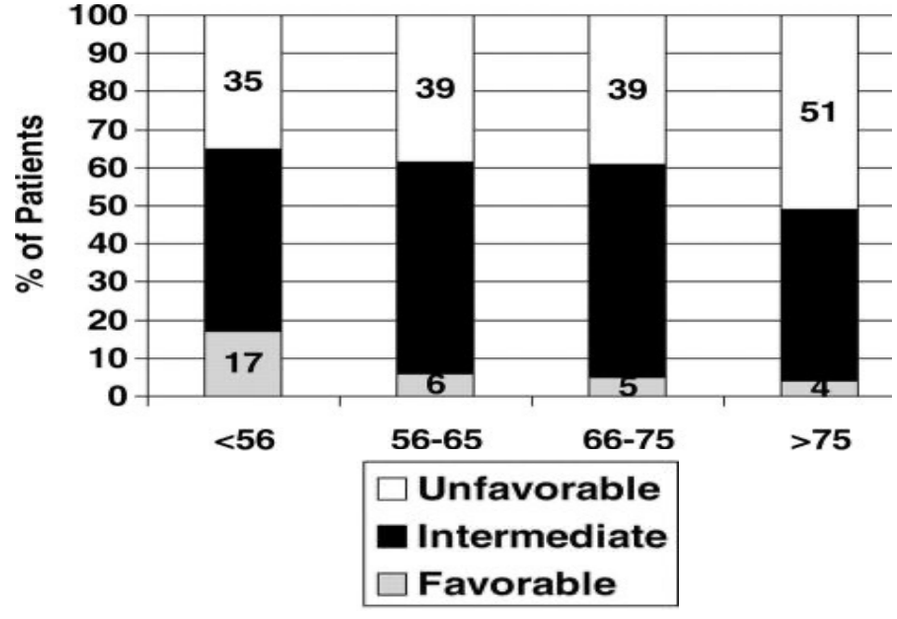
Previous history of MDS or MDS/MPN
Dysplasia in >50% of cells in 2 or more BM lineages,
in the absence of NPM1 or CEBPA mutations

. Arber DA, et al. *Blood* 2016;127:2391–405; 2. Arber DA, Erber HP. *Am J Clin Pathol* 020;154:731–41; 3. Atlas of Genetics and Cytogenetics in Oncology and Haematology. vailable at: http://AtlasGeneticsOncology.org (accessed May 2021)

Acute Myeloblastic Leukemia (AML) in elderly patients: unmet clinical need

Adverse cytogenetic features, (complex karyotype, monosomy, **del 5, del 7, abn3q etc**), often evolving from prior MDS

	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



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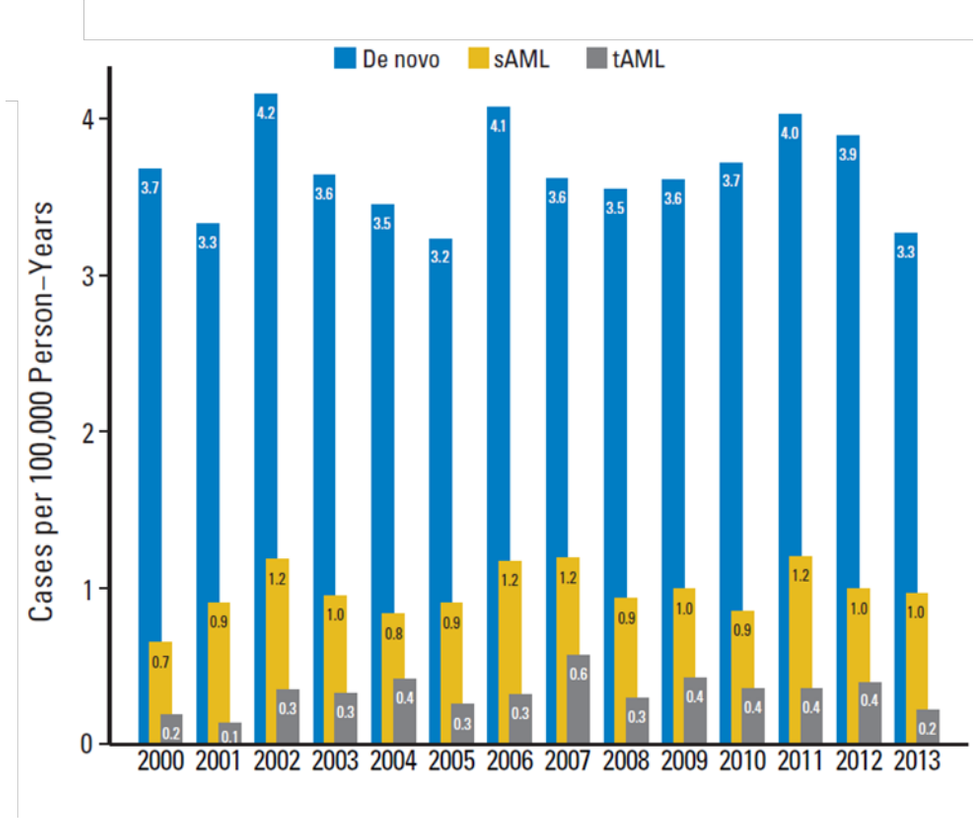
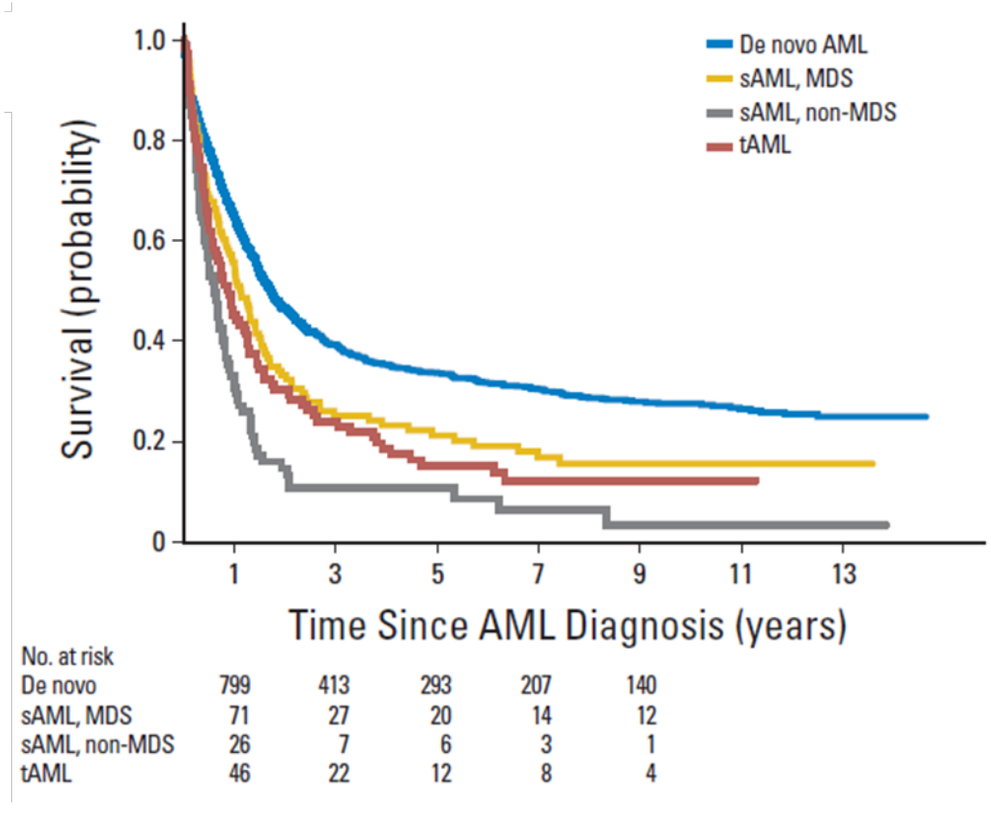
Appelbaum FR, et al. Blood. 2006 May 1;107(9):3481-5.

Secondary AML and therapy-related AML are associated with poor outcomes

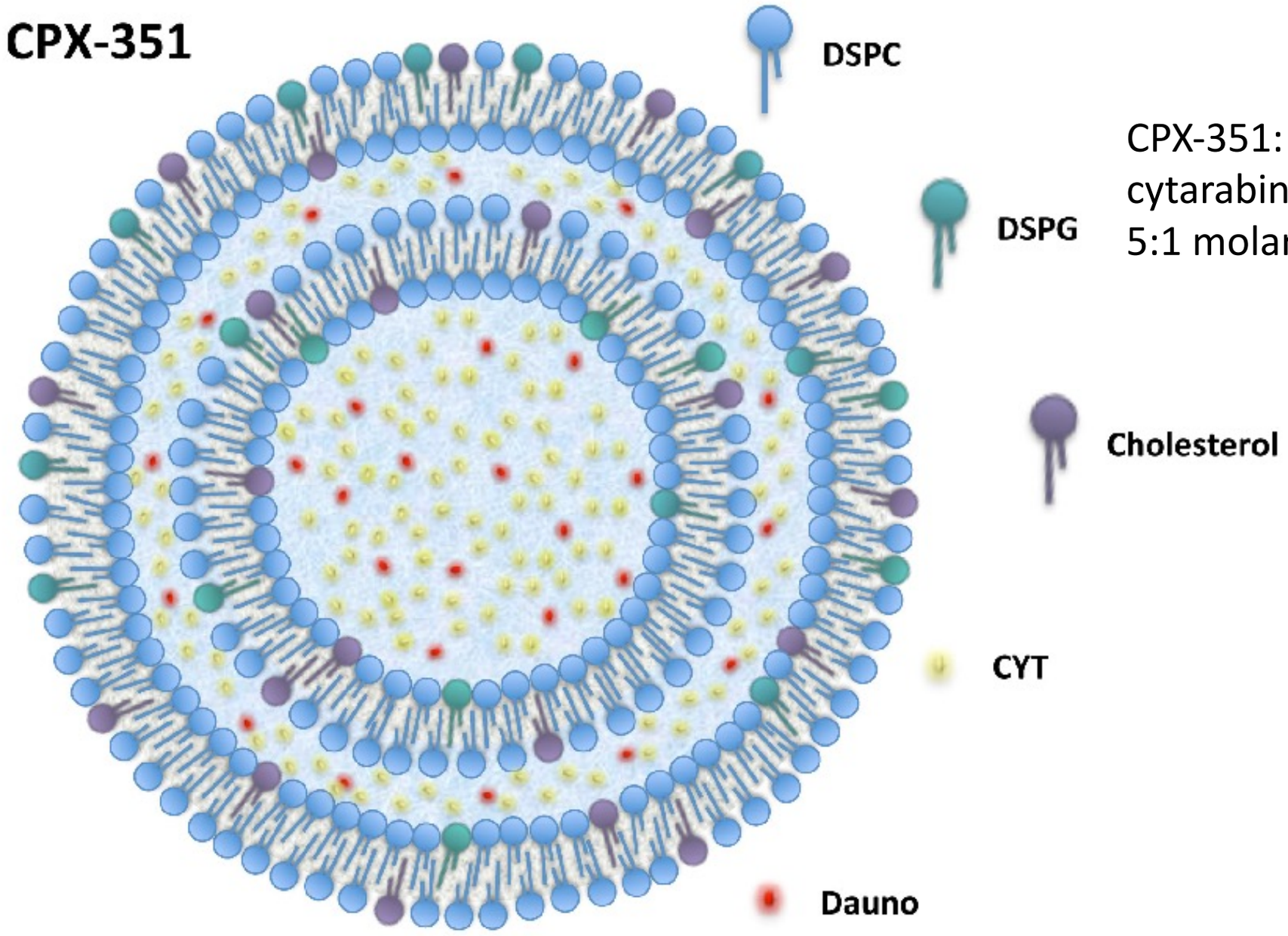
Incidence of AML in Denmark over time



Overall survival (n=1567)



Granfeldt-Østgård LS, et al. *J Clin Oncol* 2015;33:3641–49



CPX-351: liposomal formulation of cytarabine and daunorubicin with fixed 5:1 molar ratio

DSPC= phosphatidilcoline
DSPG= distearilphosphatidilglicerol

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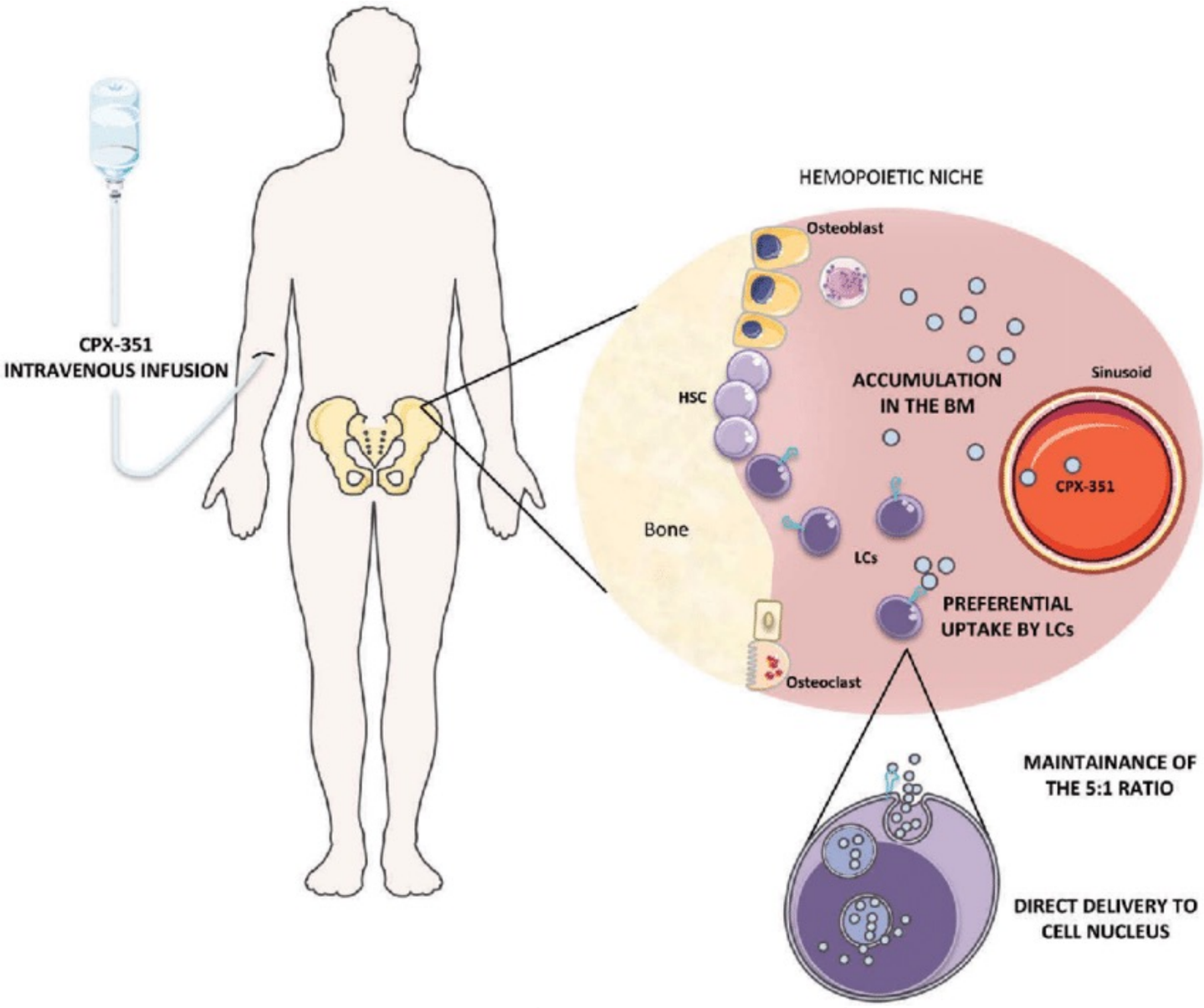

Liposomal formulation enhances bone marrow uptake while sparing, to some extent, normal tissues.

Vyxeos liposomal European SPC, October 2019 (accessed on Sept 16th 2020).
Lin et al. Leukemia Research 34 (2010) 1214–1223

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

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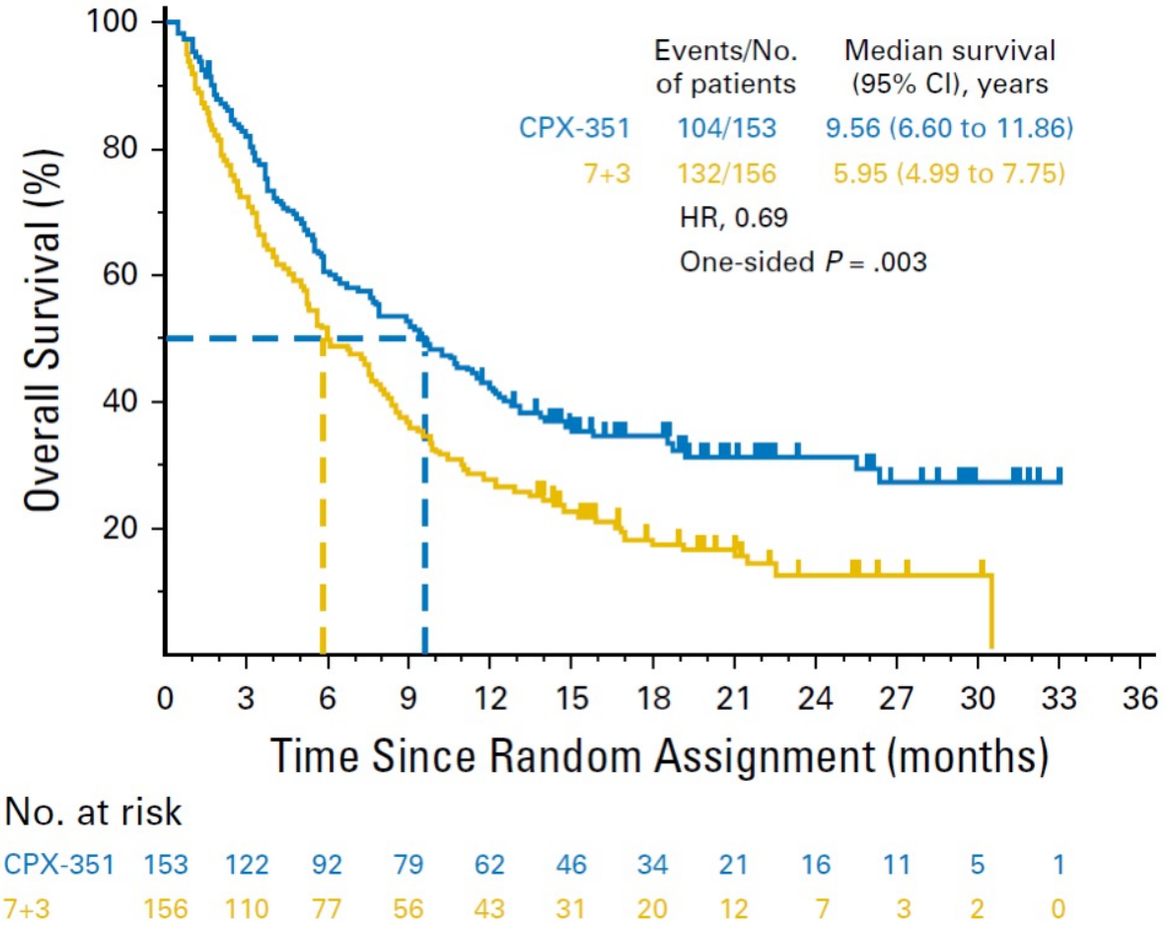

In a randomized Phase III study CPX-351 has shown better CR rate, OS and DFS compared to conventional "3+7" regimen in AML elderly patients (age 60-75 years) with secondary AML:

-t-AML (WHO 2017)

- Prior history of MDS

- MDS-related changes even in absence of a known MDS clinical history.

Lancet JL et al. J Clin Oncol. 2018 Sep 10; 36(26): 2684–2692.

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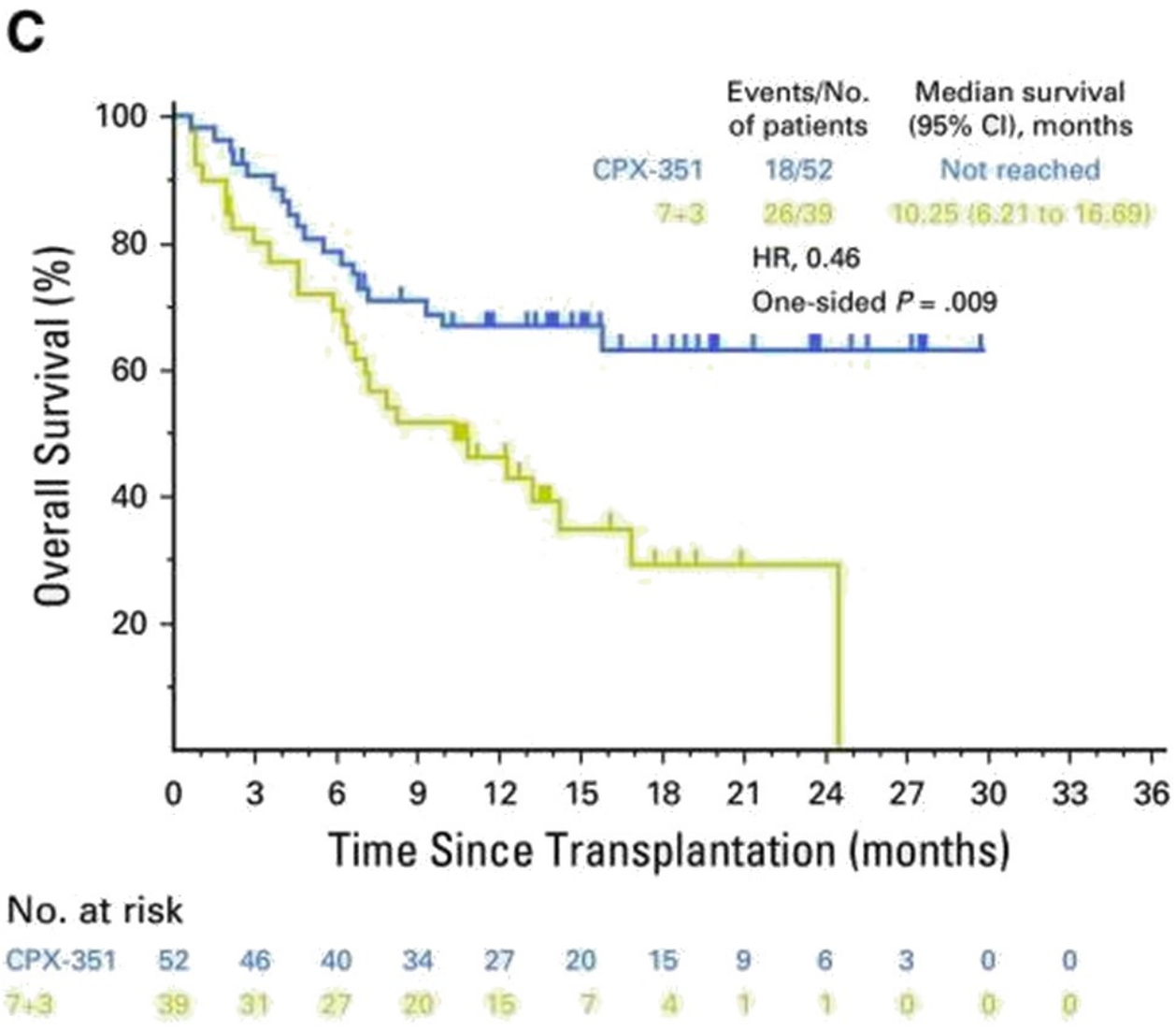

Better results were found, particularly, in patients undergoing allogeneic stem cell transplantation as consolidation strategy.

CPX-351-treated patients had a higher chance to proceed to transplantation and lower post-transplant morbidity and mortality

Lancet JL et al. J Clin Oncol. 2018 Sep 10; 36(26): 2684–2692.

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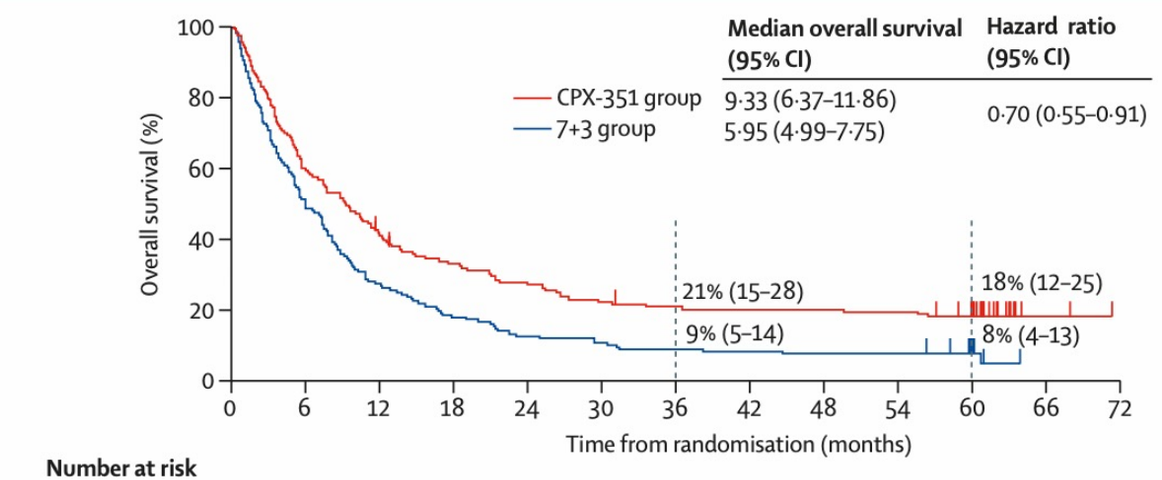
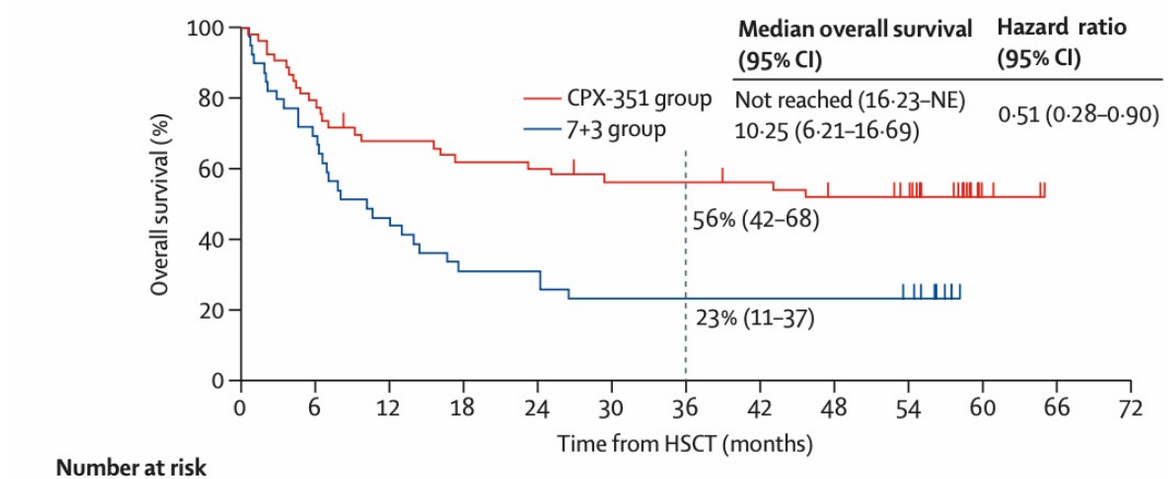
Phase III trial - 5 years follow-up data

Overall Survival



Overall Survival from HSCT



Lancet JE, et al. Lancet Hematology 2021

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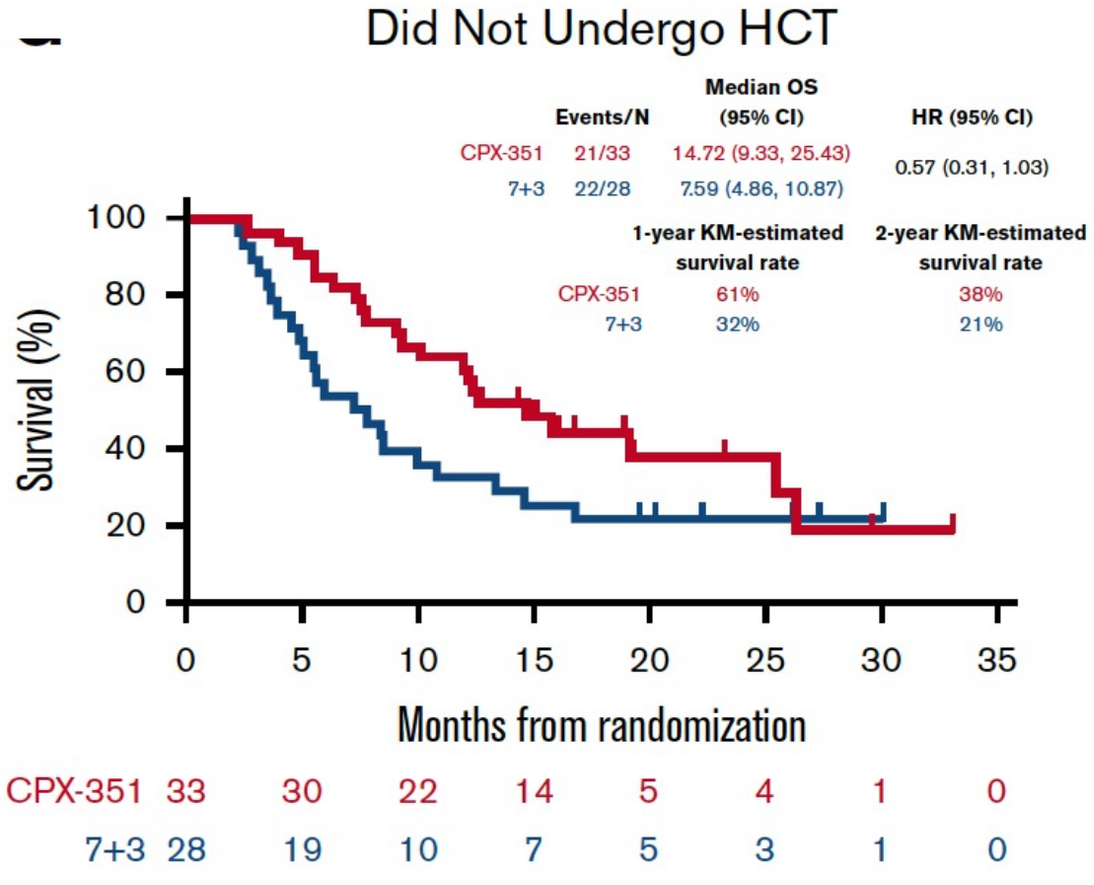
Phase III trial – *post hoc* analysis in CR-CRi patients

Older adults with newly diagnosed high-risk/secondary AML who achieved remission with CPX-351: phase 3 post hoc analyses



Lin TL et al. Blood Adv 2021

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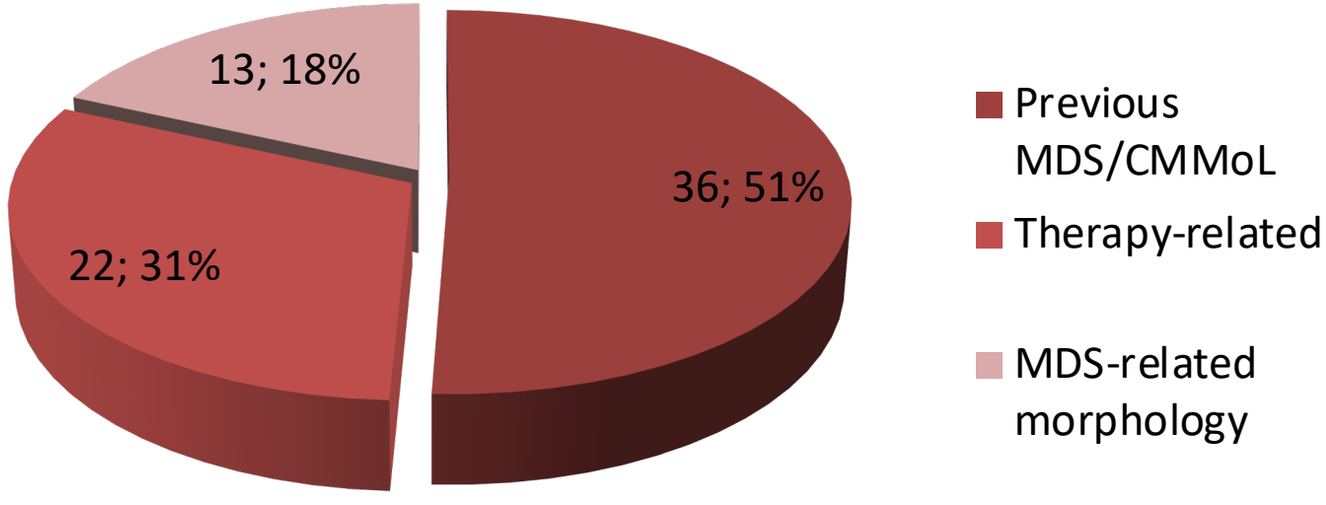
Patient characteristics

- Median age: 66 years (range 52-79)- Twenty patients (28.2%) >70 years
- **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 et al. Blood Cancer Journal 10(10):96, 2020

Clinical features



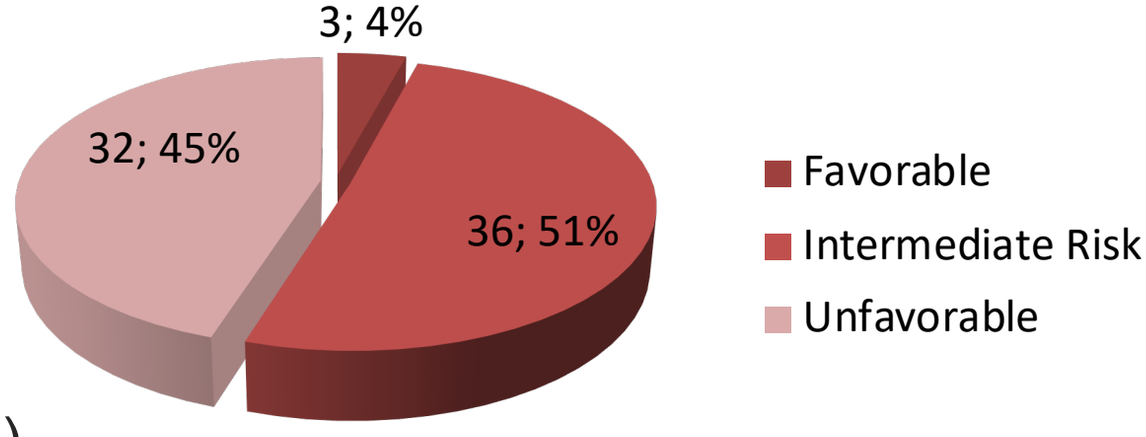
- Previous MDS diagnosis in 31 patients (43.7%)
- Previous CMMoL diagnosis in 5 patients (7%)
- MDS-related changes in 13 patients (18%)
- t-AML in 22 patients (31%)

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

Risk Assessment

- **Cytogenetics:**
  - **abnormal in 40/71 patients (56.3%),**
  - **complex karyotype in 18/71(25.3%)**
  - del(5q) or del(7q) in 15/71 (21.1%)

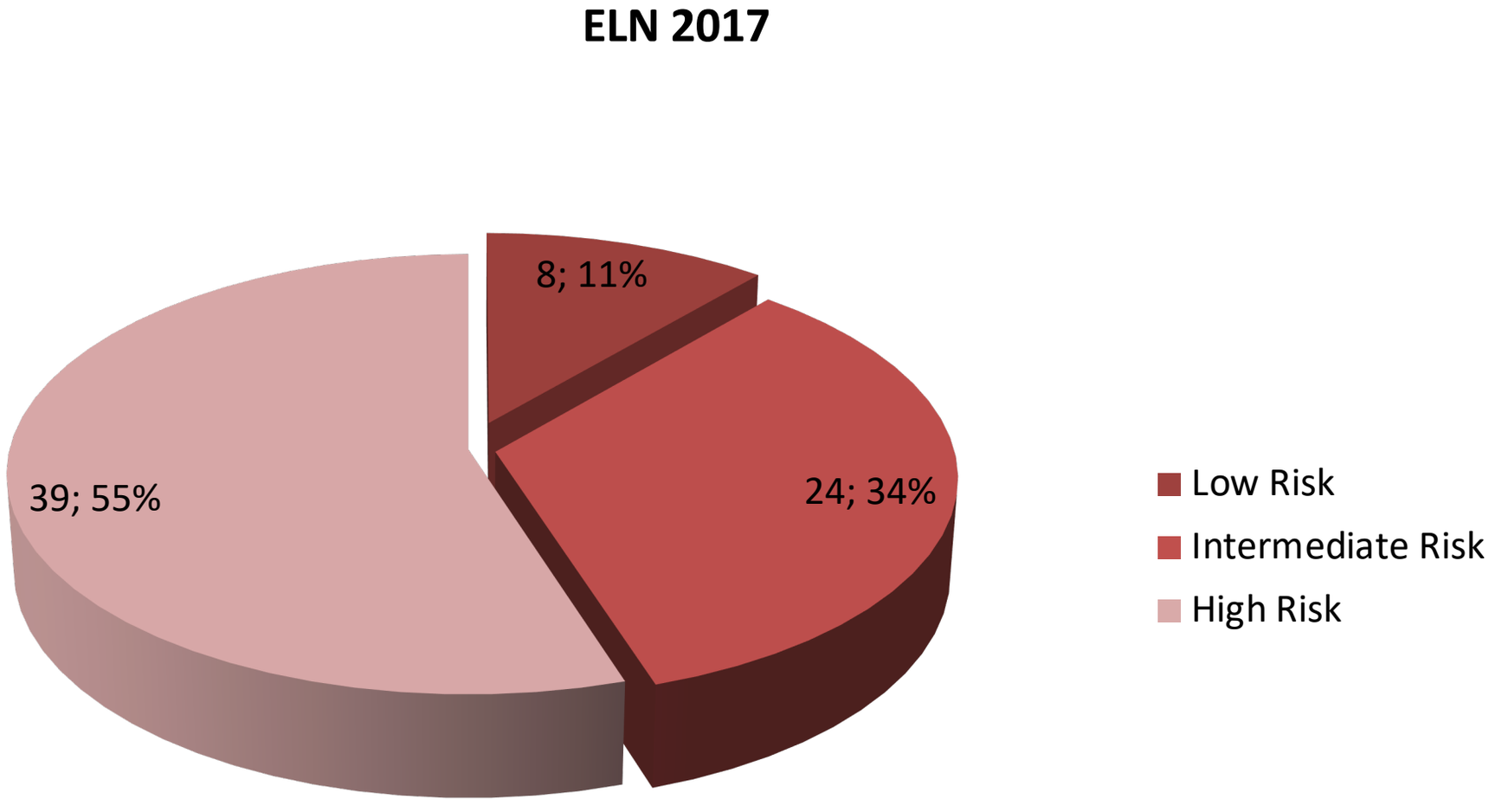
Cytogenetic risk assessment according to MRC classification



- **Molecular features:**
  - *NPM1* mutation was found in 5/68 (7.3%)
  - *FLT3-ITD* in 5/69 (7.2%). All patients had low allelic burden and no patient had concomitant FLT3-ITD and NPM1 mutation.
  - ***TP53* status was assessed in 37 patients and mutations were found in 13 (35.1%)**

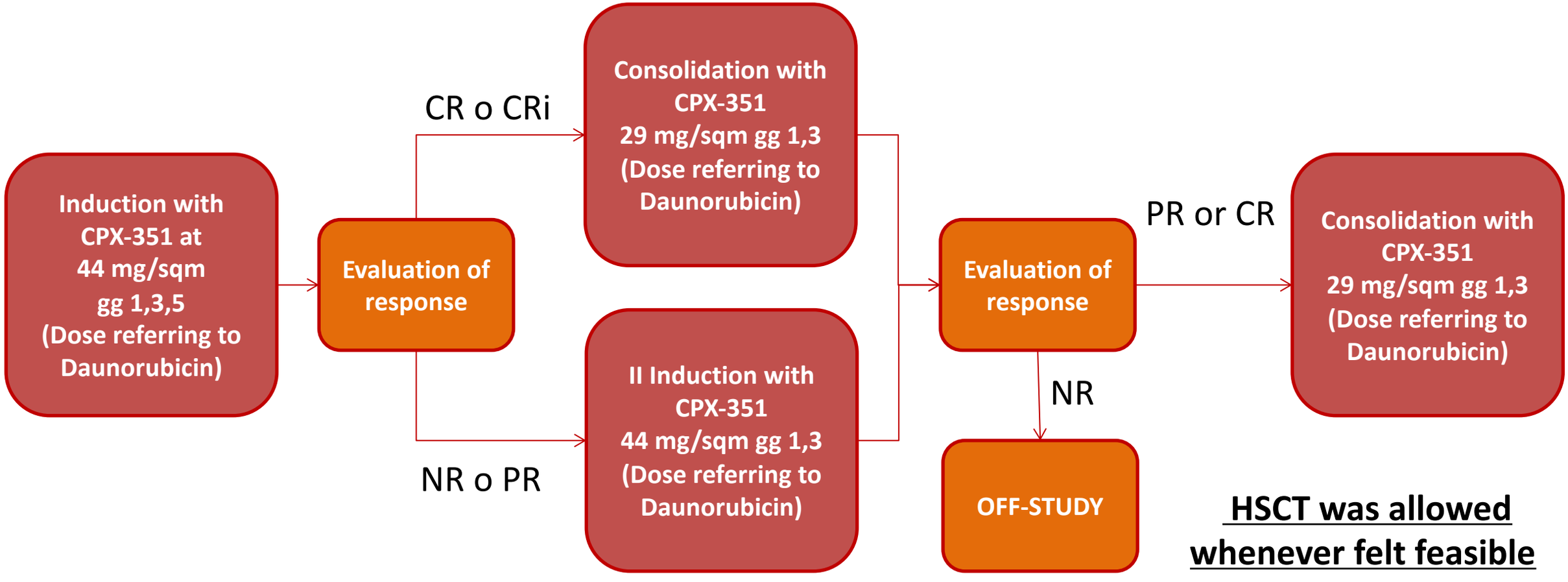
Guolo et al. Blood Cancer Journal 10(10):96, 2020

European Leukemia Net 2017 Risk Assessment:



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

Treatment outline



HSCT was allowed whenever felt feasible

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

Response assessment after induction

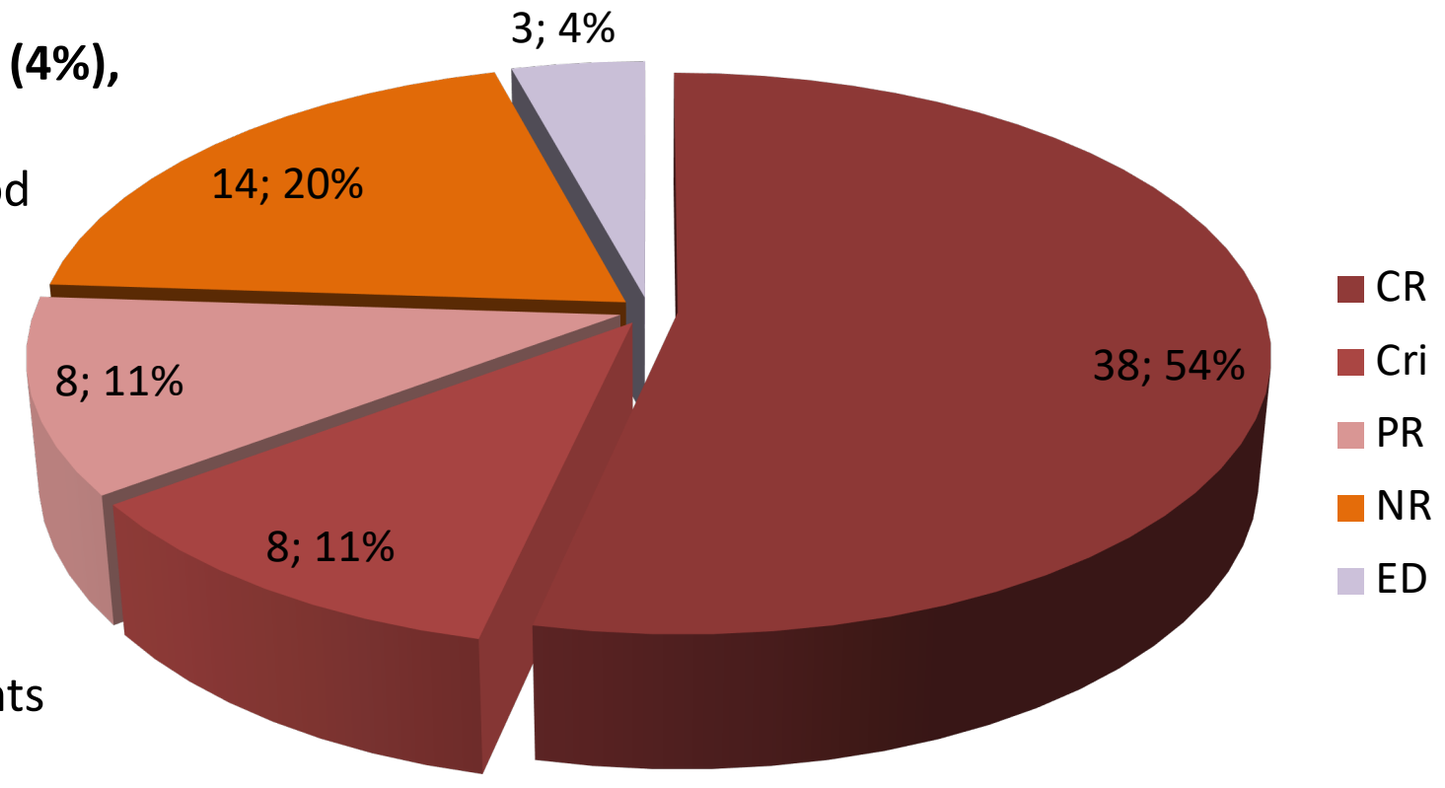
- **3 patients died before response assessment (4%),**

- 38 patients achieved CR with complete blood count recovery (53.5%)

- 8 patients achieved CRi, all with incomplete PLT recovery (11.3%)

- 8 patients achieved PR (11.3%)

- Induction failure was observed in 14 patients



Median time to response assessment was 36 days (range 15-89)

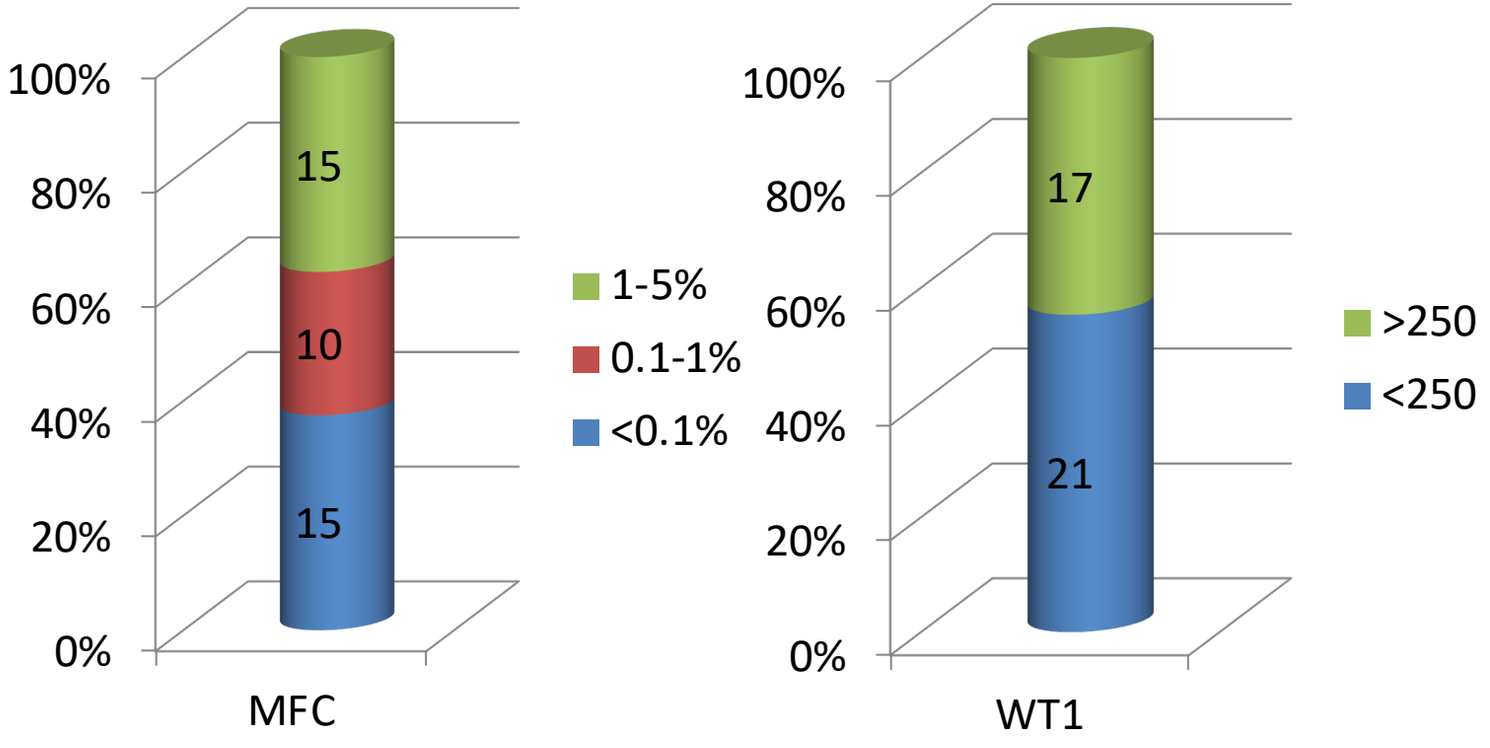
In the whole cohort CR+CRi rate was 46/71 (64.8%)

CR probability after cycle 1 was not affected by any of the analyzed variables

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

MRD assessment after induction

- MFC and *WT1* MRD assessment on BM samples was avaible in 40/71 and 38/71 patients, respectively



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

<u>- MFC MRD negative CR (<0.1%)</u>
in 15/40 patients (37.5%)

<u>- *WT1* MRD negative CR (<250x10^{-4} *Abl*)</u>
in 21/38 patients (53.8%)

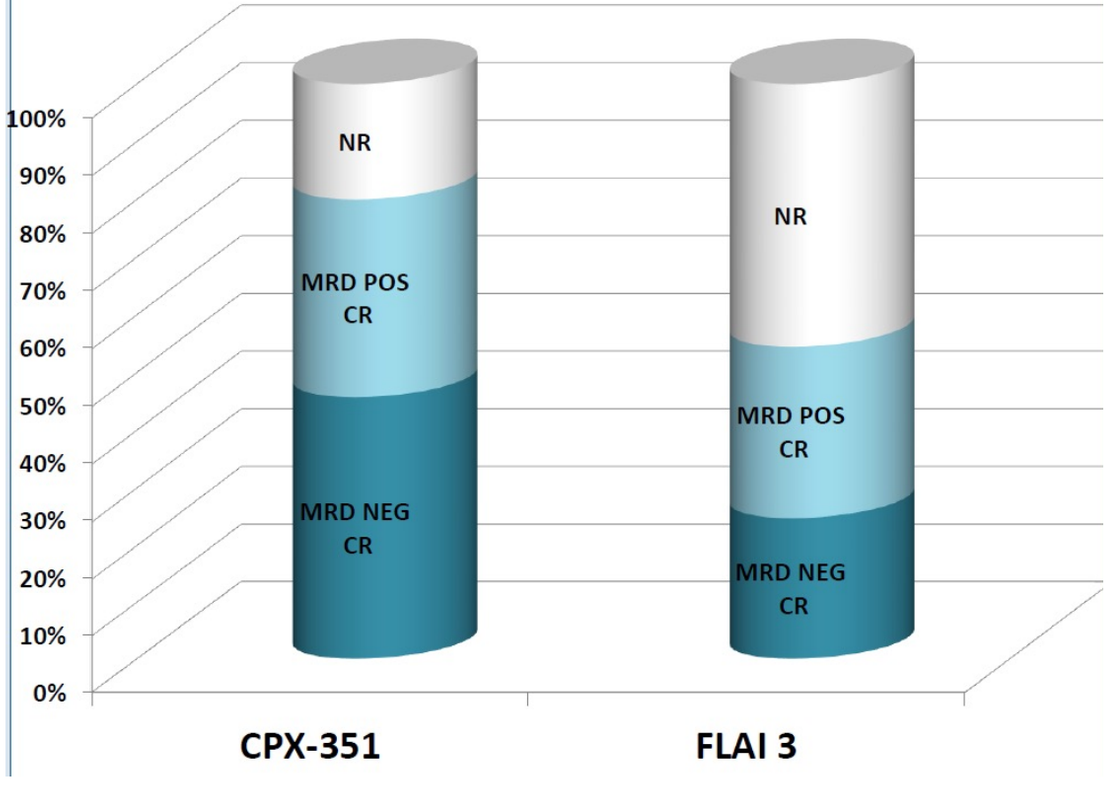
6 patients had MFC MRD POS CR
(all between 0.1% e 1%) with *WT1* NEG

Minetto P, et al. BJ Haematol 2019
Guolo F, et al. Haematologica 2017

Focus on MRD: historical comparison

50 patients treated with CPX-351 in our center, compared to MRC-AML or t-AML patients from an historical cohort who received an age-adapted fludarabine-idarubicine-high dose cytarabine induction (FLAI)

***Figure 1**: CR Rate and MFC MRD status after induction therapy for CPX-351 and FLAI 3. p<0.05*



MRD was evaluated with MFC after induction in all patients

- CR rate was overall higher among CPX-treated patients (80% vs 61%)
- Among CR patients, MRD negative CR was more frequent in patients treated with CPX-351 (57% vs 45% of CR patients)
- MRD negative CR was significantly correlated with a longer OS

Guolo F, et al. *presented at EHA 2021*

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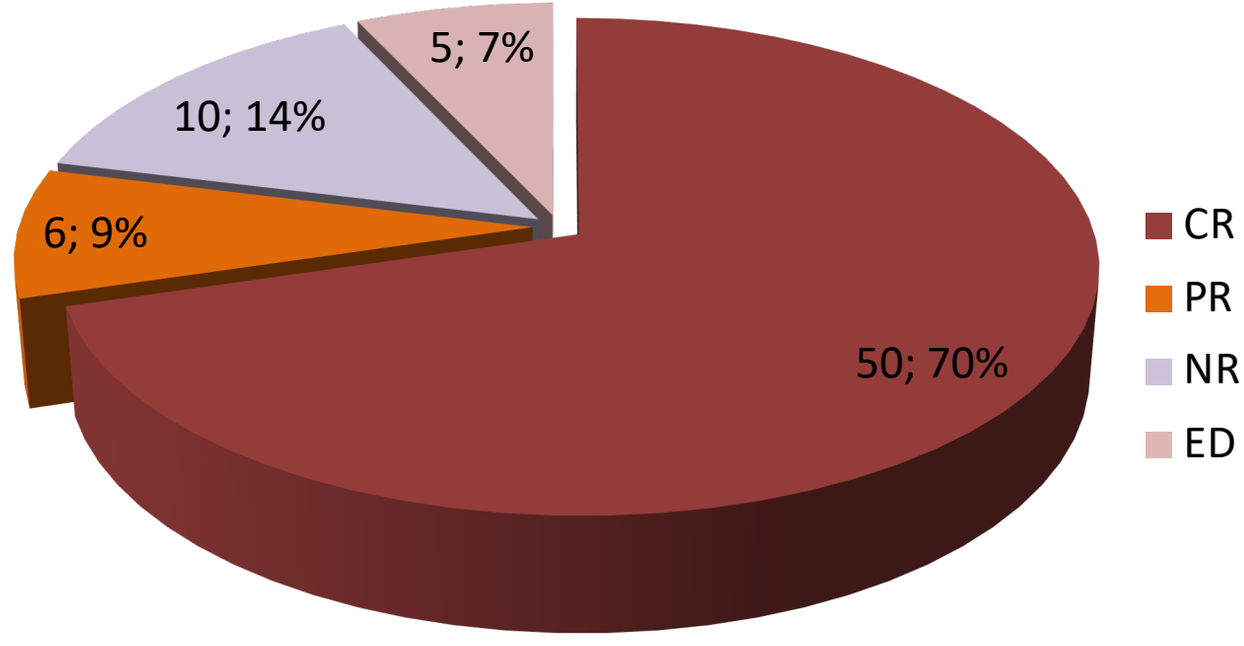
End of Treatment Response assessment

- **Treatment-related mortality was 5/71 (7%)**
- **CR was achieved in 50 pts (70.4%)**
- PR was achieved in 6 pts (8.5%)
- Treatment failure was observed in 10 patients (14.1%)



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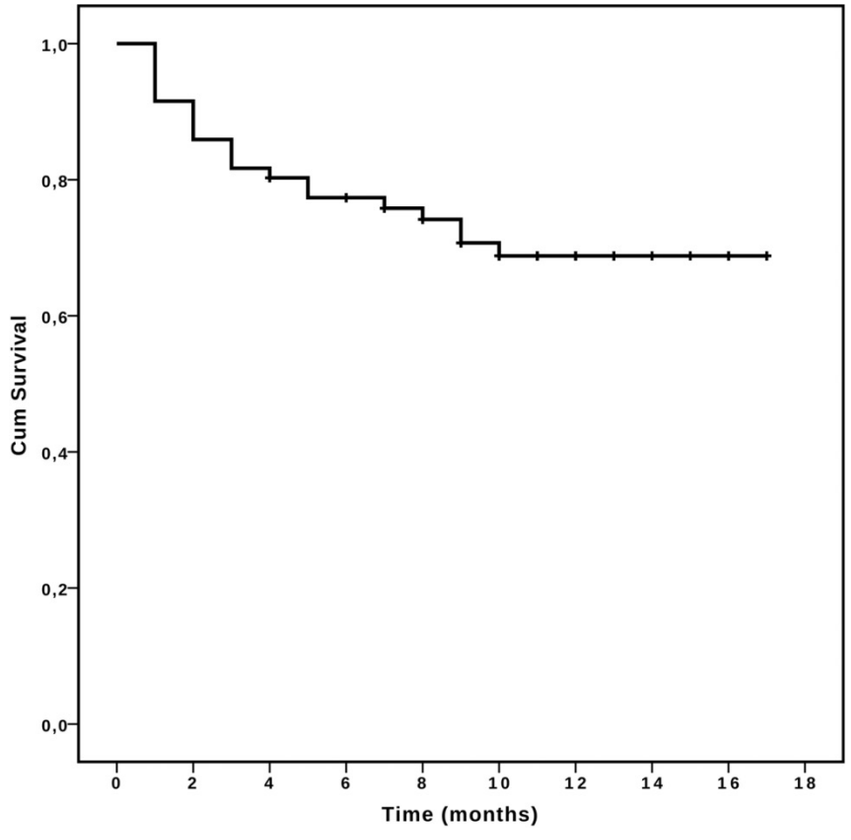
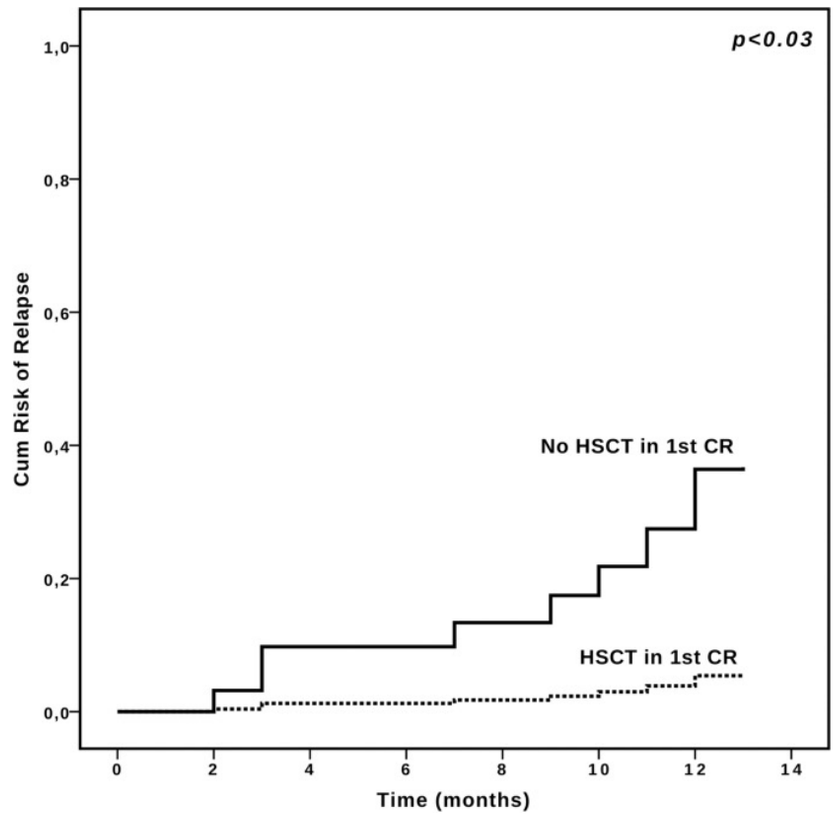
Cumulative Incidence of Relapse and Overall Survival analysis

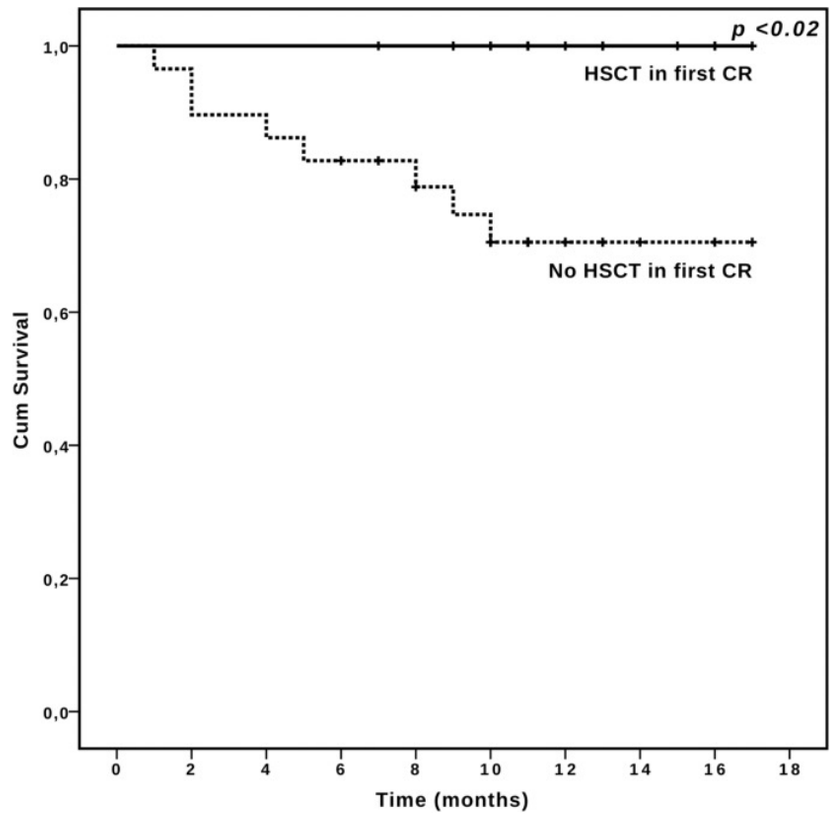
Overall Survival in all patients



CI of relapse according to transplantation



OS according to transplantation



- **Median follow up 11.0 months**
- CI of relapse was 23.6% at 12 months
- **OS was 68.6% at 12 months**

20 patients proceeded with allogeneic stem cell transplantation

Transplantation was the main predictor of long OS and low risk of relapse

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

After an extended follow-up of 24 months:

- 4 more patients received transplantation
- Median OS: 13 months.

Median OS not reached for transplanted patients

2-year OS for transplanted patients: 57.6%

Unpublished data

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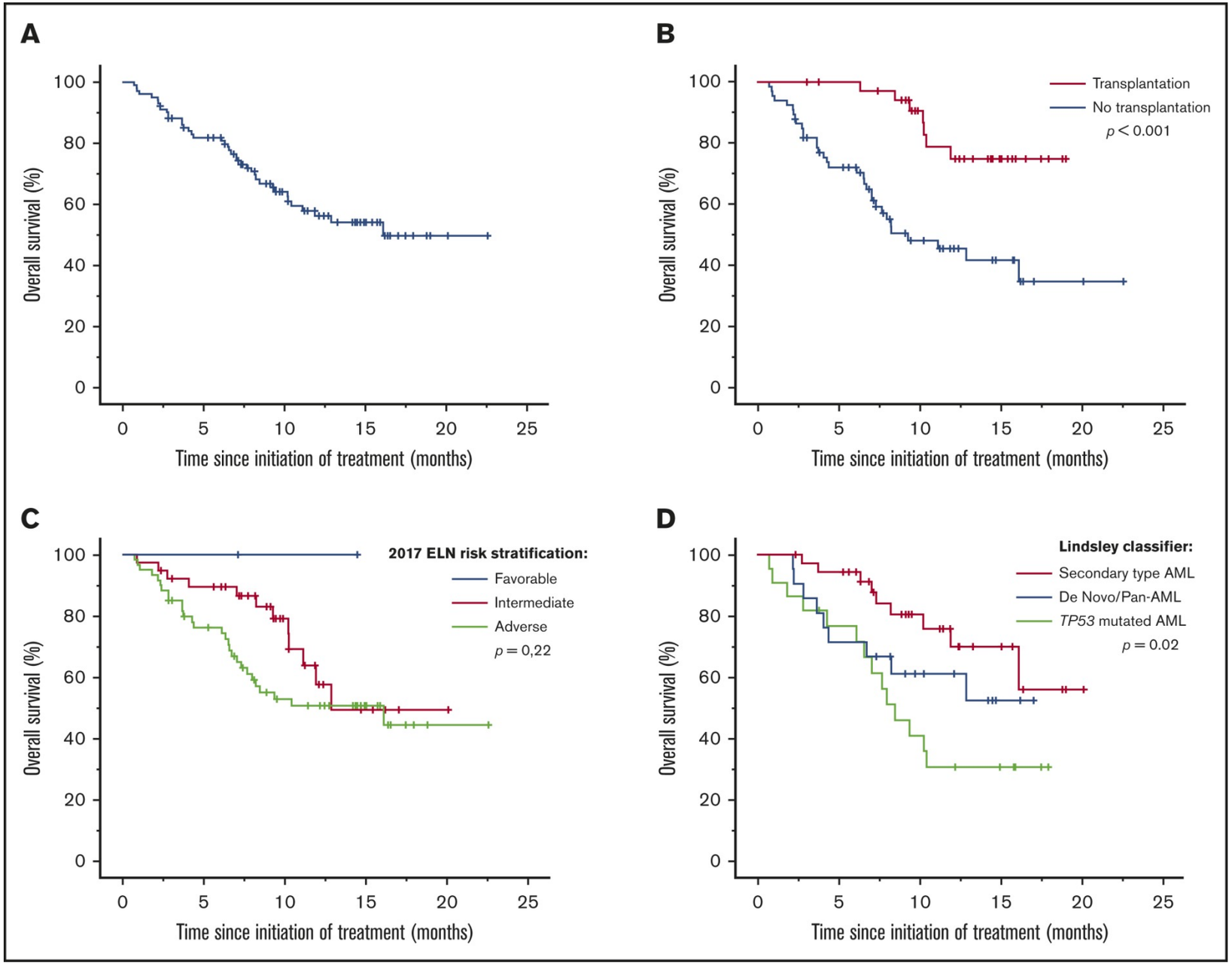

- CR + CRi rate was 59%.
- Median follow up 8.6 months
- Median OS 16.1 months

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 to allogeneic stem cell transplantation

Survival was significantly better among patients receiving transplantation.

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

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Real life data: German Experience

188 patients from 25 Centers.

Median age 65 years (range 26-80).

24% of patients <60 yrs

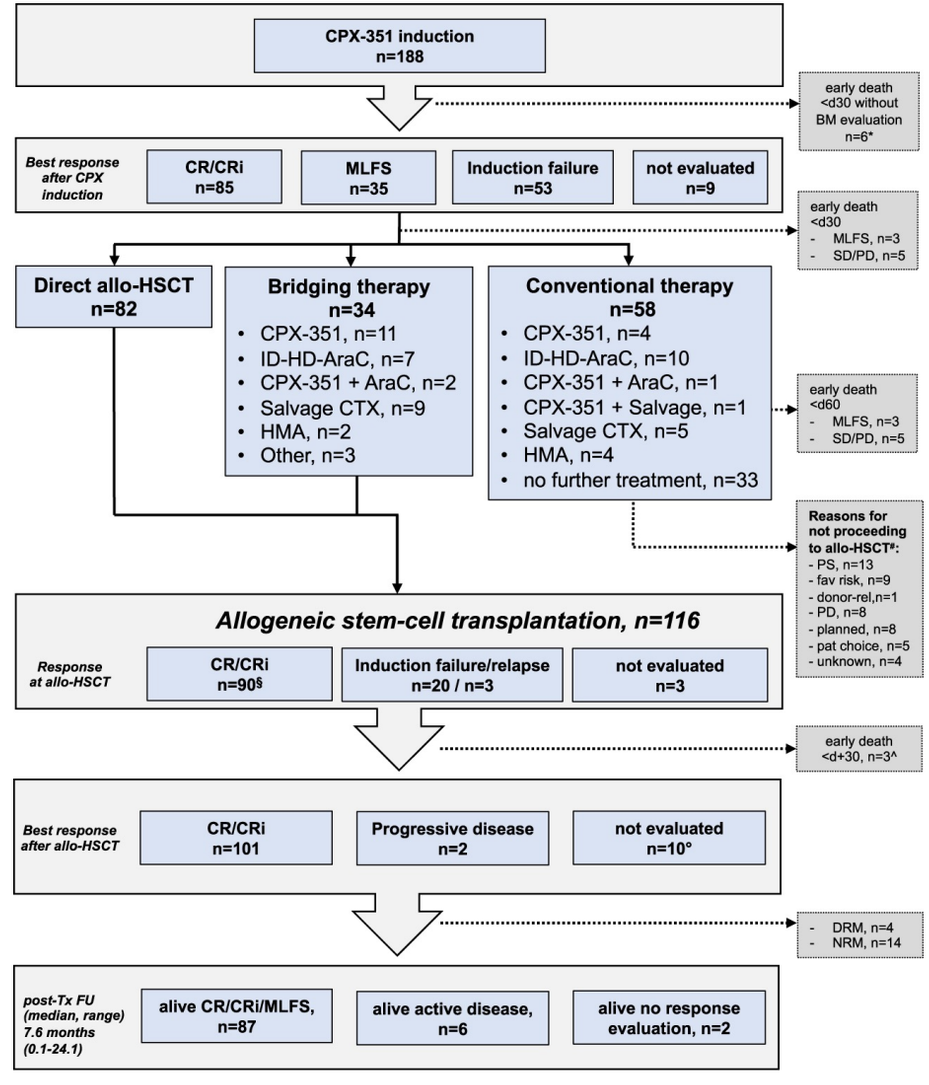
80% of patients had a good performance status (Karnofsky score >80% at diagnosis)

10% had previously received HMA for MDS

29% were t-AML

60% were considered HR according to ELN 2017

The most frequent mutations were: ASXL1 (16%), RUNX1 (13%), NPM1 (10%), TP53 (7%)



*n=1 received allo-HSCT 18 days after 1st day of CPX-351 induction
#n=2 no information whether patient proceeded to allo-HSCT or not
§n=4 after receiving salvage-CTX and n=1 had no response evaluation after CPX-351 induction
^n=2 had active disease prior allo-HSCT
°n=6 had post-transplant follow-up <30 days and no BM evaluation

Rautenberg C., et al. *Blood Cancer J.* 11, 164 (2021).

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CR + CRi rate was 47% after cycle 1.

In multivariate analysis, CR rate was only influenced by the presence of a complex karyotype (CR rate 33%)

In particular, CR rate was not influenced by TP53 (CR rate 54% among mutated patients)

MRD was measured by flow cytometry in 36/85 CR-CRi patients (42%).

A flow negative CR was demonstrated in 64% of the analyzed patients (23/36).

Therapy was generally well tolerated.

Median time to ANC recovery: 33 days (range: 6–99 days)

Median time to PLT recovery and 30 days (range: 7–77 days)

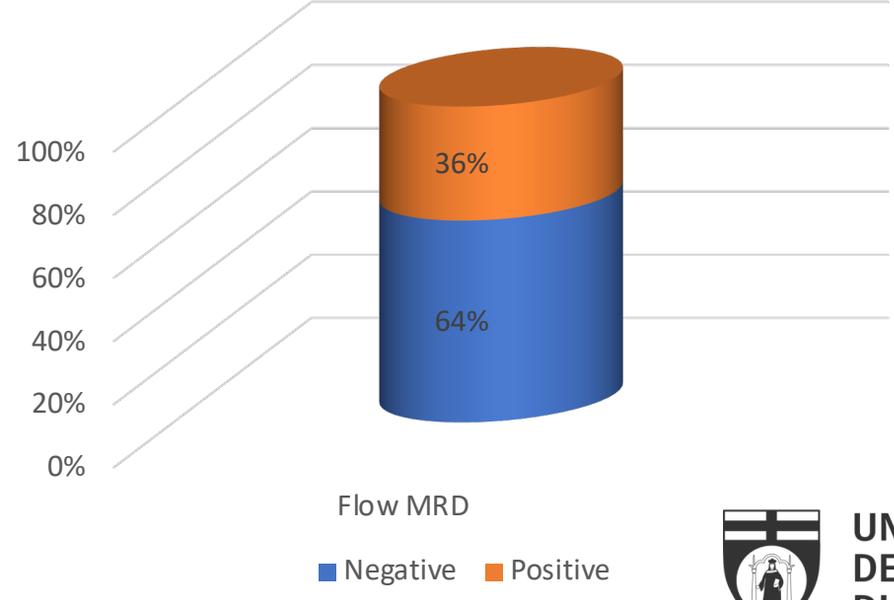
Adverse events (AE) ≥ grade III were reported in 130 patients (69%), mainly related to infectious complications.

Gastrointestinal side effects were infrequent (4%).

30-day early death rate was 8% in the entire cohort, significantly higher in patients ≥ 65 years (11% vs. 3%, p = 0.047).

Variable	Overall survival			Response rate		
	P		HR	*P*		HR
Prior treatment with HMA						
Yes	0.02		2.4 [1.1–5.3]		n.s.	
No						
ELN risk stratification						
Adverse	<0.0001		4.2 [1.9–8.9]		–	
Favorable/intermediate						
Karyotype						
Complex		–		0.0001		4.3 [1.9–9.2]
Not complex						
NPM1						
wt		n.s.	–			
mut						
TP53						
mut		n.s.	–			
wt						
Age at diagnosis (median)						
≥65		n.s.	–			
<65						
Gender						
Female		–	n.s.			
Male						

ELN European Leukemia Net, *HMA* hypomethylating agents, *HR* hazard ratio, *mut* mutated, *n.s.* not significant, *P p* value, *wt* wild type.



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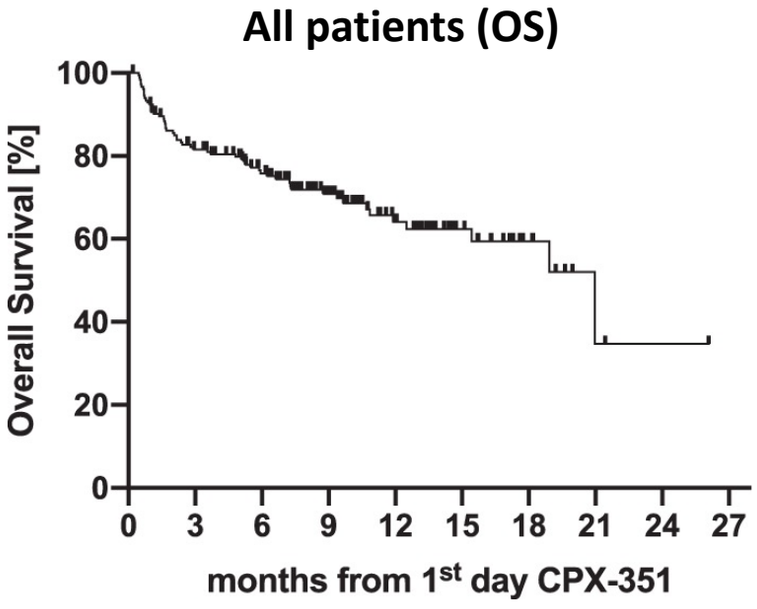

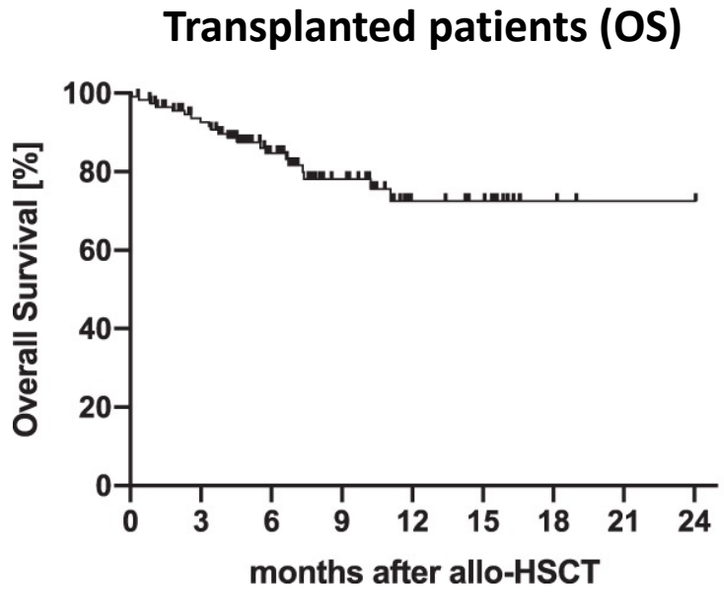

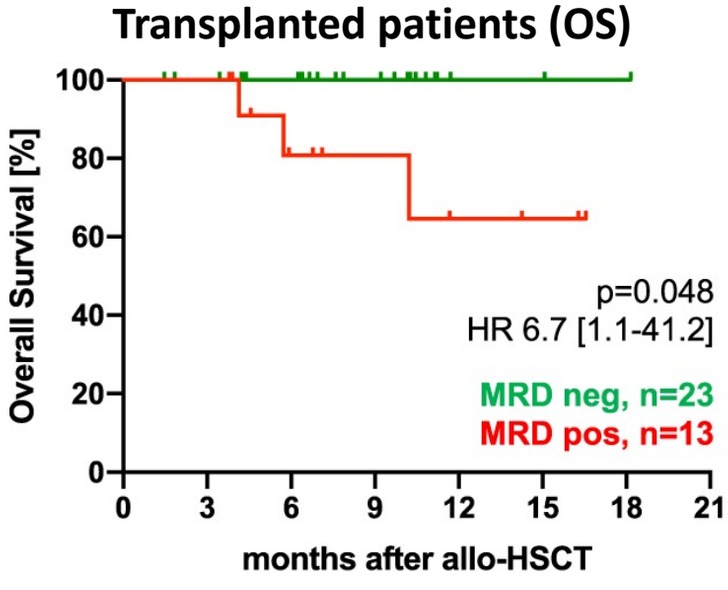

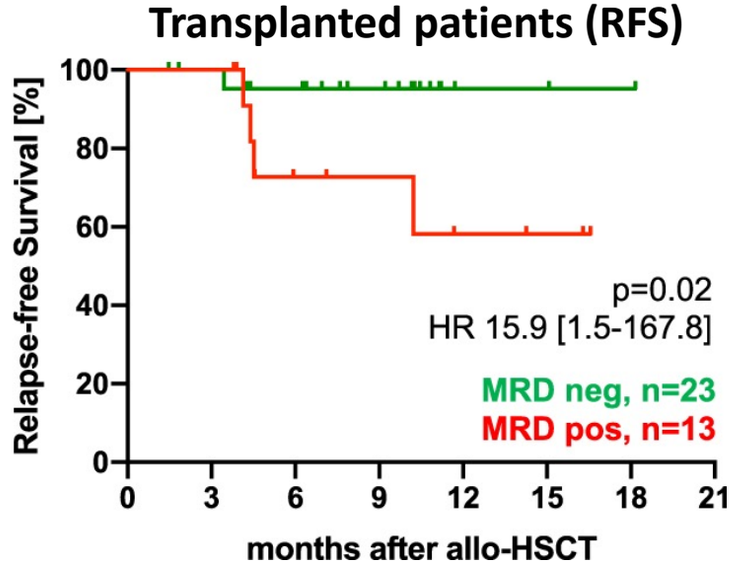

- Median follow up 7.6 months (0.1-24.1)
- 2-year OS was 73%.
- Among 111 patients in CR after the end of treatment, 90 proceeded to HSCT (81%)
- HSCT was a significant predictor of longer OS and RFS
- Patients transplanted in a flow-MRD negative status had the best outcome.

Rautenberg C., et al. *Blood Cancer J.* 11, 164 (2021).

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Conclusions: tolerability

- CPX-351 therapy is,overall, rather well tolerated (mortality rate 7%-8%), despite the long time required for WBC and PLT recovery after induction.

- Extra-hematological toxicity is relatively low. The low incidence of severe mucositis may explain the reduced probability of life-threatening infections.

Conclusions: efficacy

- CR rate is good in a high risk cohort (the majority of patients enrolled in studies were considered as intermediate/high risk according to ELN 2017)

- CR probability is not consistently affected by any of the analyzed variables

- **CR duration in HR patients is usually short-> bridge to HSCT in transplant eligible-patients**

- The role of MRD assessment in this setting may be important for the outcome

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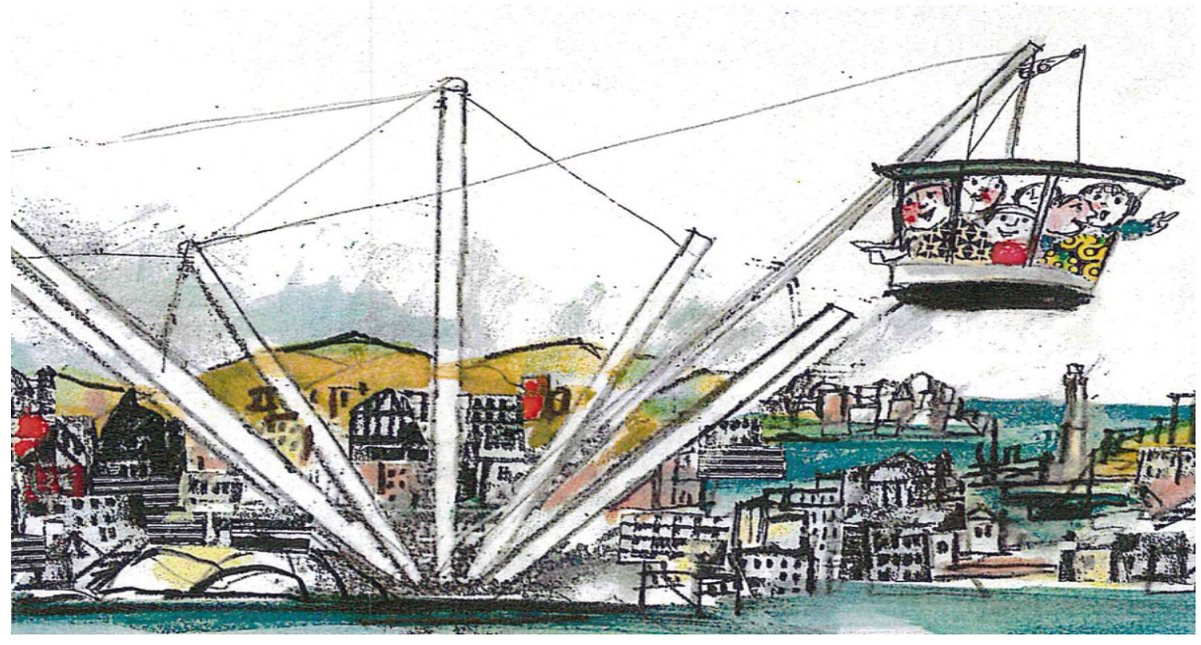

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