FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

CONVEGNO FISiM

Firenze, CSF Montedomini
"Il Fuligno"
24-25 ottobre 2024

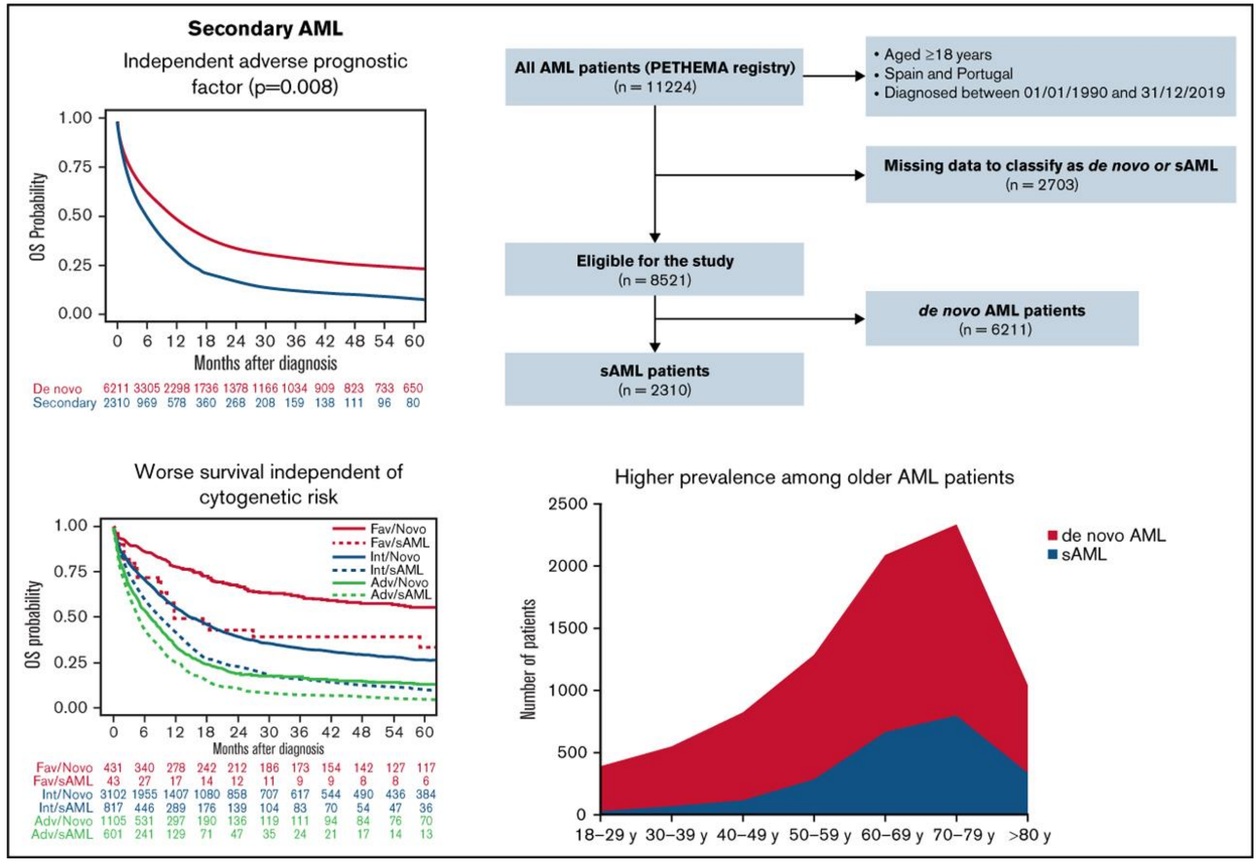
Trattamento delle LAM post MDS

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.

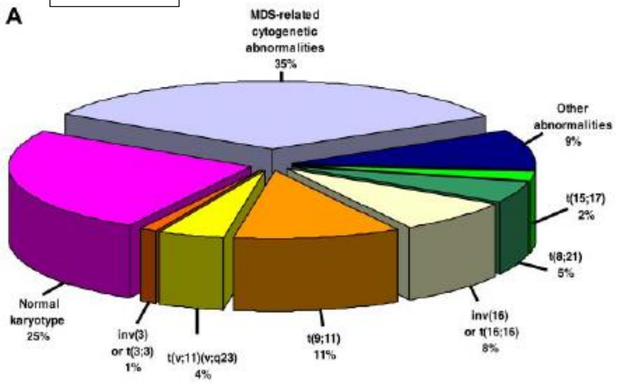
Secondary AML itself should be considered an independent risk factor, especially for patients treated with IC approaches.

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

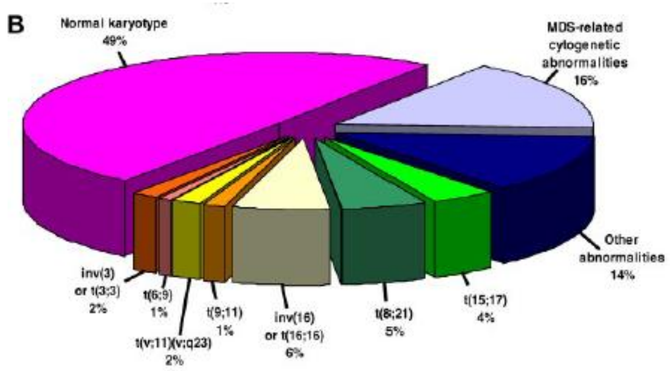
Unmet medical need

Secondary AML vs De Novo AML: cytogenetics

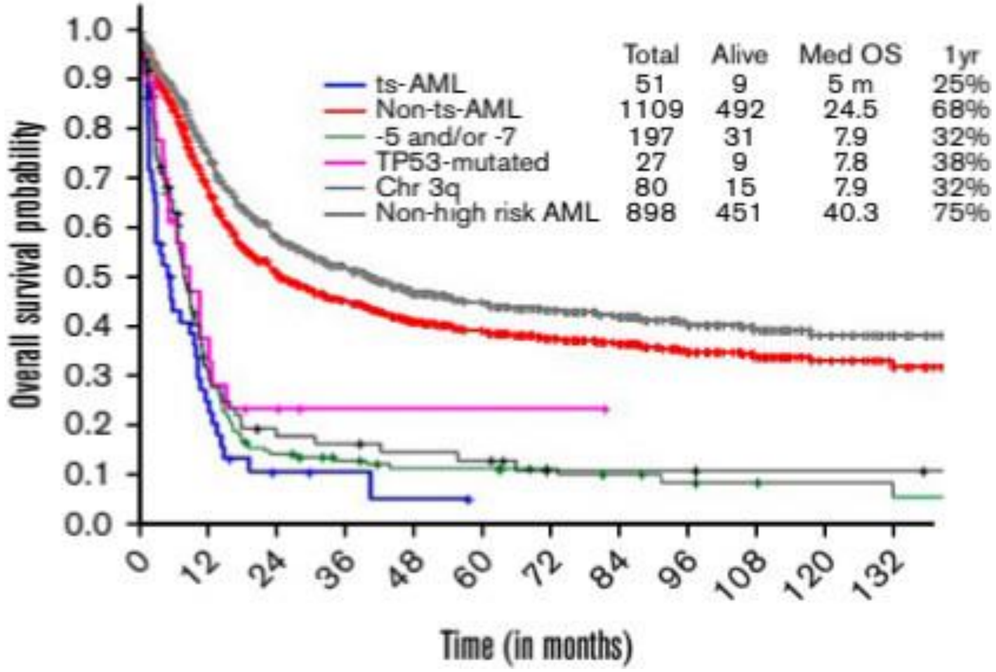
sAML



DE NOVO-AML

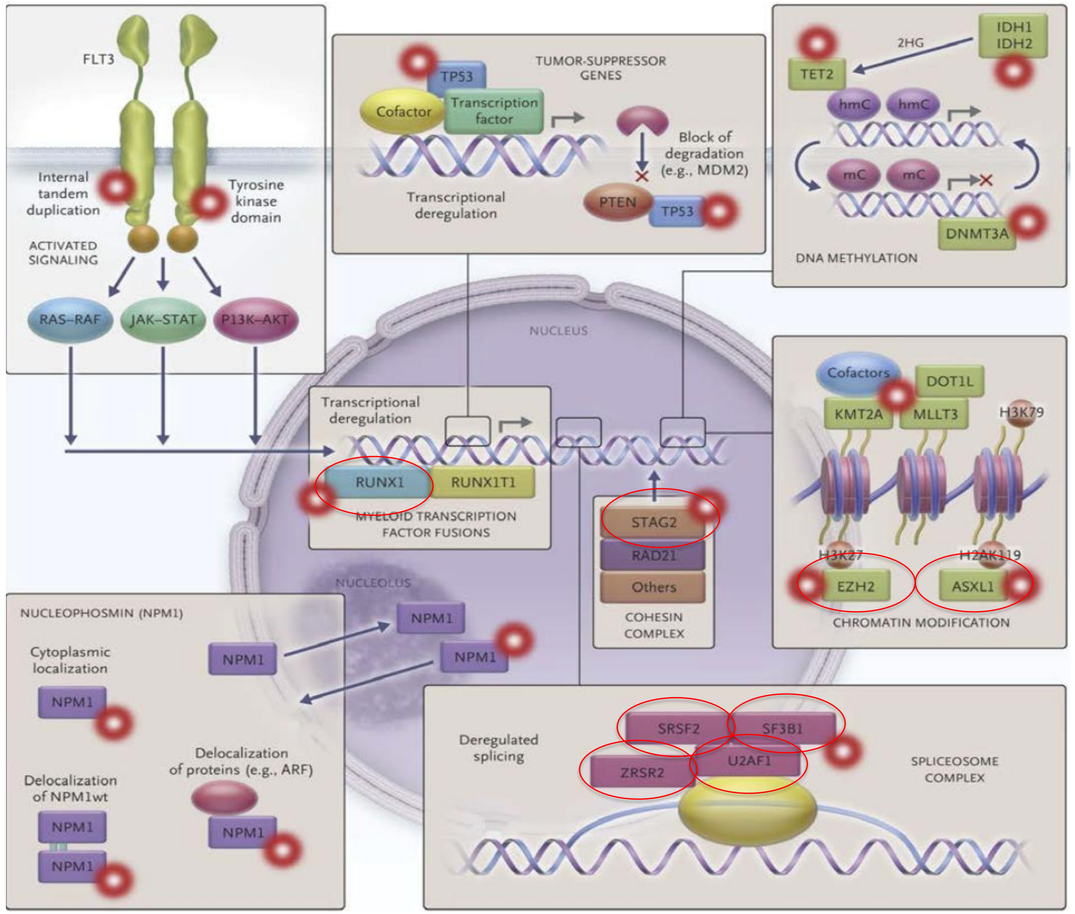


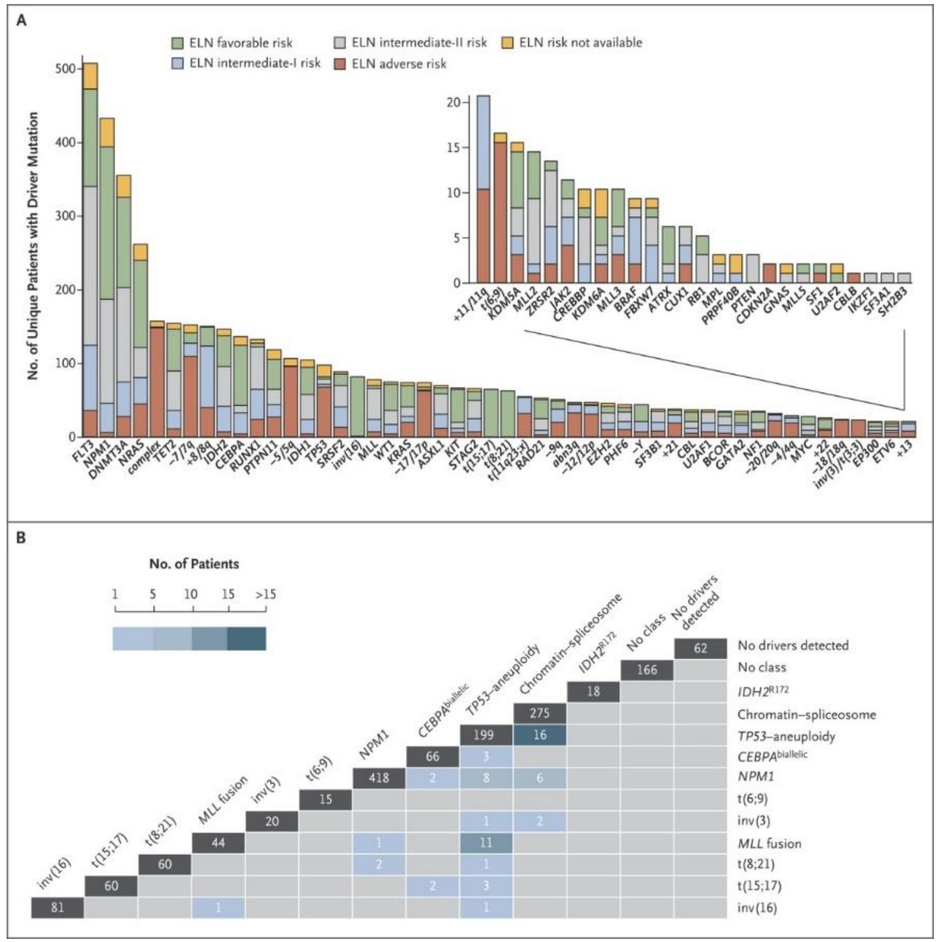
Kaiser S., Blood 2011



Br J Haematol, 2019; Volume: 188, Issue: 1, Pages: 116-128

Landscape of Driver Mutations in Acute Myeloid Leukemia





Dohner et al N Engl J Med 2015

Papaemmanuil E et al. N Engl J Med 2016;374:2209-2221

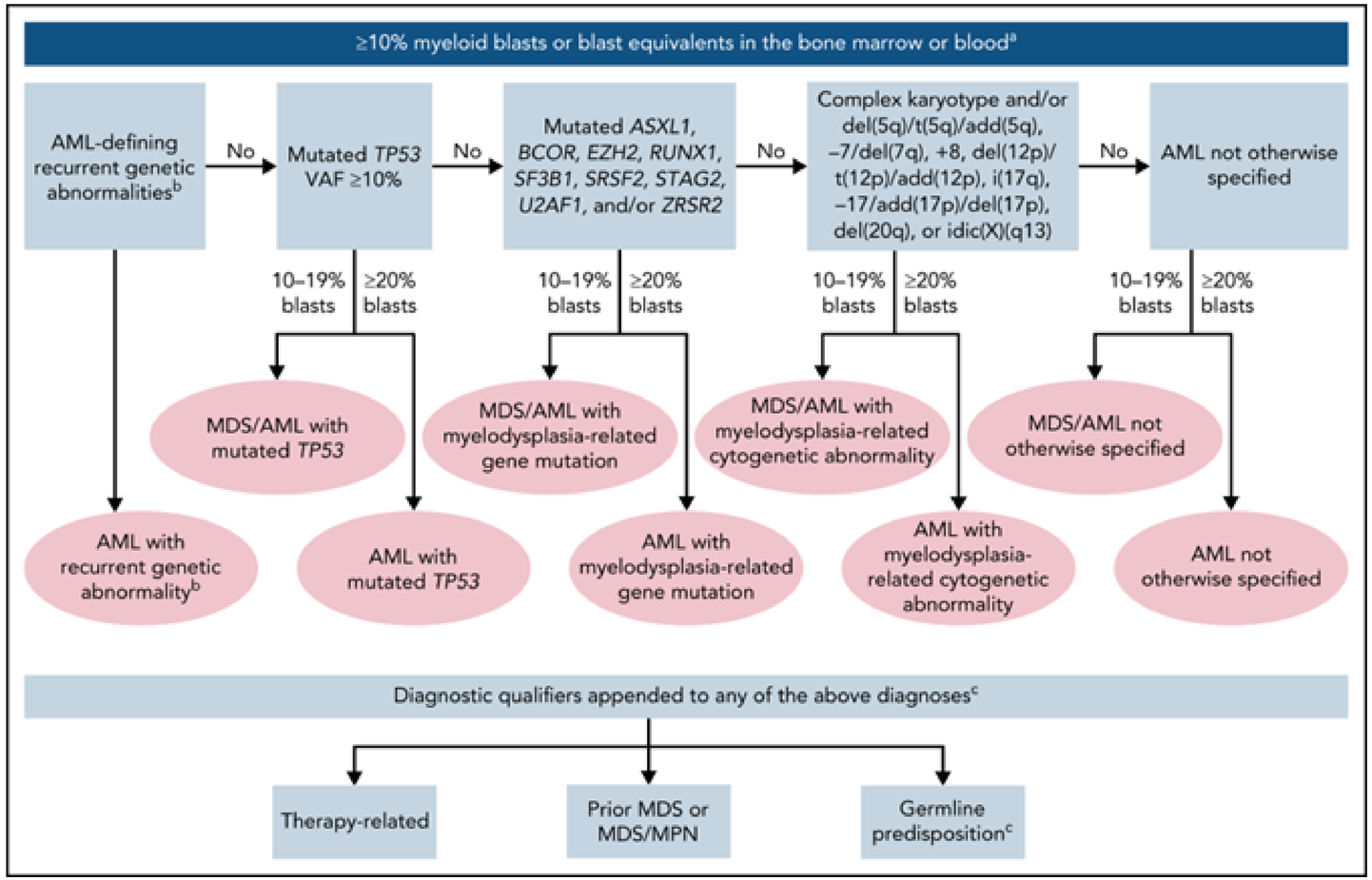
The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: acute myeloid leukemia

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with PML::RARA fusion
Acute myeloid leukaemia with RUNX1::RUNX1T1 fusion
Acute myeloid leukaemia with CBFB::MYH11 fusion
Acute myeloid leukaemia with DEK::NUP214 fusion
Acute myeloid leukaemia with RBM15::MRTFA fusion
Acute myeloid leukaemia with BCR::ABL1 fusion
Acute myeloid leukaemia with KMT2A rearrangement
Acute myeloid leukaemia with MECOM rearrangement
Acute myeloid leukaemia with NPM1 mutation
Acute myeloid leukaemia with CEBPA mutation
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations

The most recent iterations of the 2022 AML classification systems, emphasize genetic factors over morphological and clinical features in defining AML subtypes

Khoury JD et al, Leukemia. 2022 Jul;36(7):1703-1719

Hierarchical classification of the International Consensus Classification of AML



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

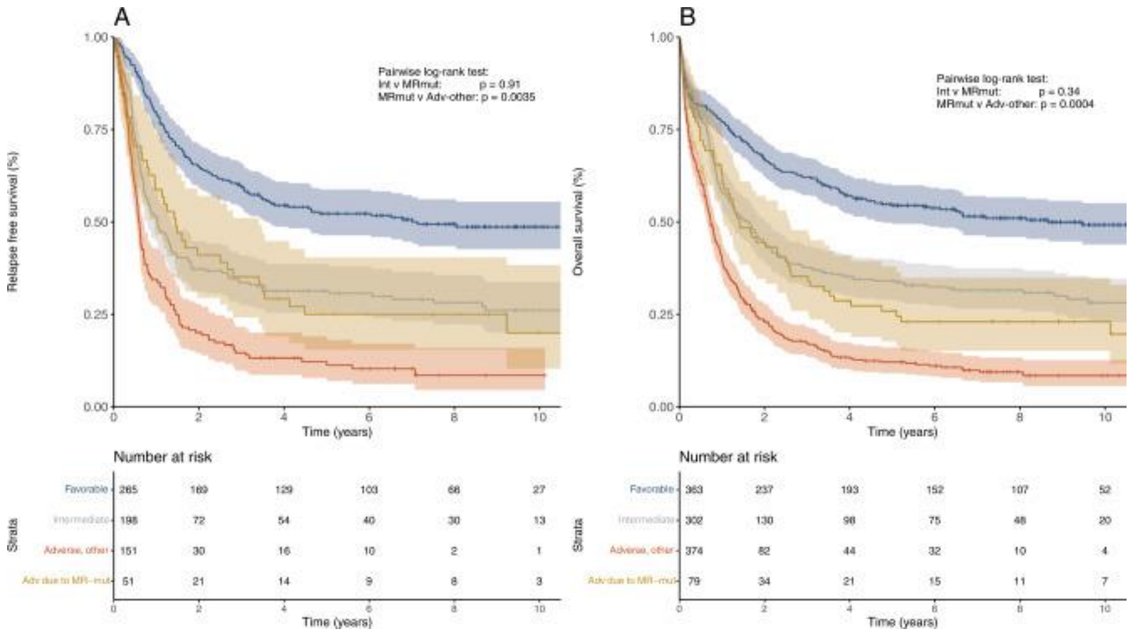
2022 European Leukemia Net risk classification by genetics at initial diagnosis

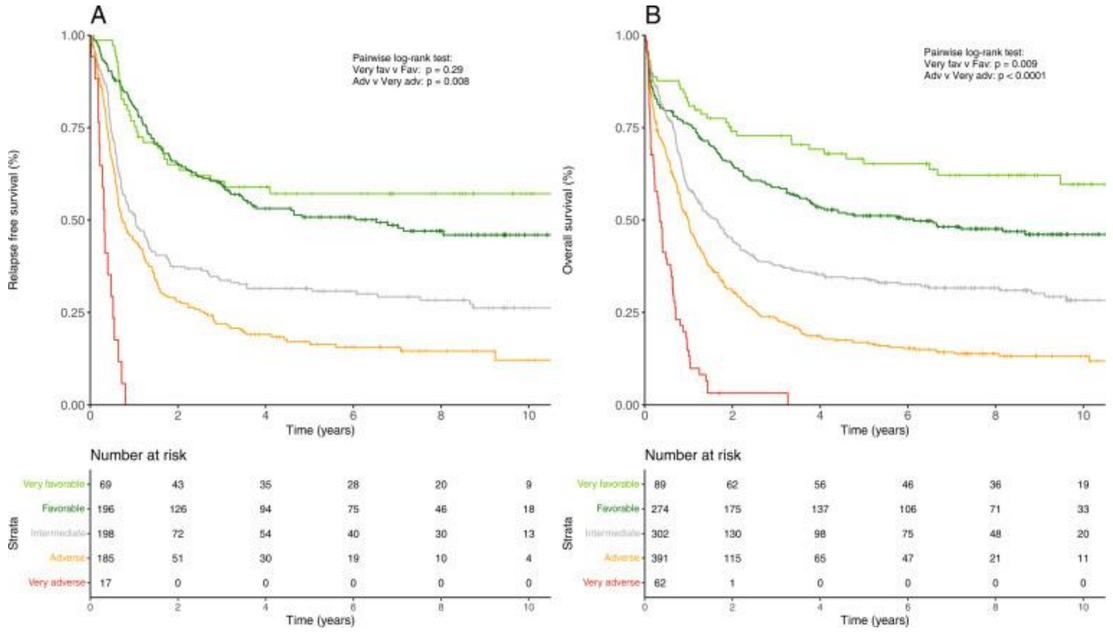
Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/or *ZRSR2*‡‡ • Mutated *TP53*[a]

Beyond the previously considered *ASXL1* and/or *RUNX1* genes, adverse risk category now includes pathologic variants mostly related to myelodysplasia-related alterations in at least one of the *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1,* or *ZRSR2* genes

Döhner H et al, *Blood* (2022) 140 (12): 1345–1377

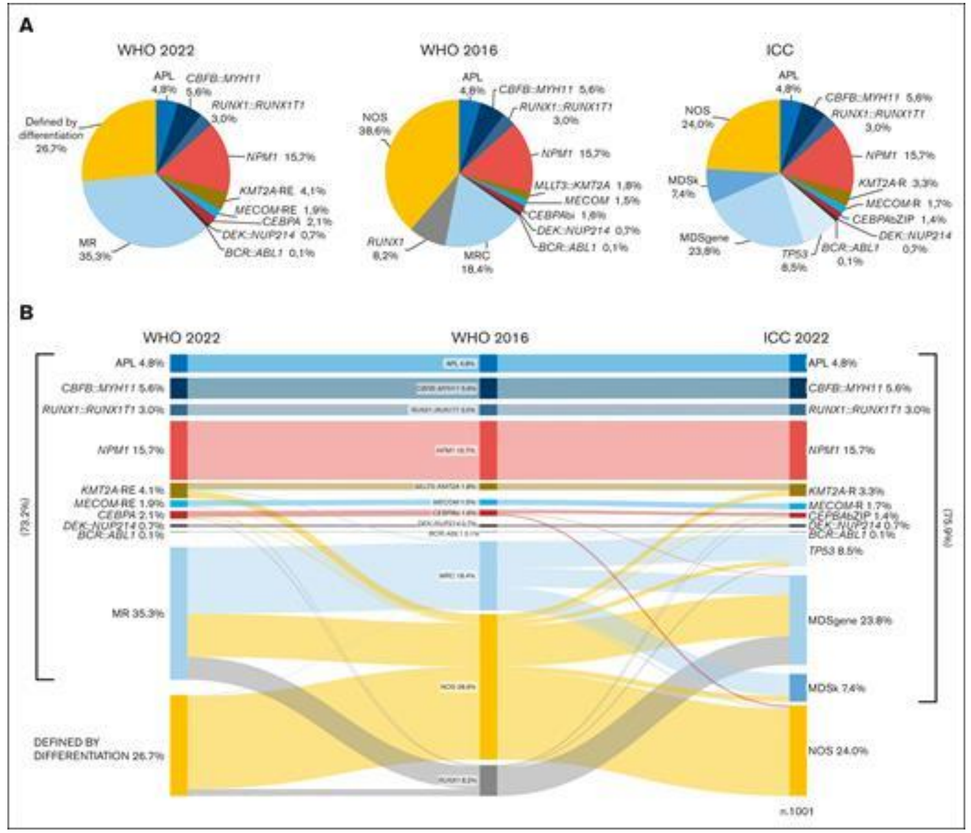
Validation and refinement of the 2022 European LeukemiaNet genetic risk stratification of acute myeloid leukemia

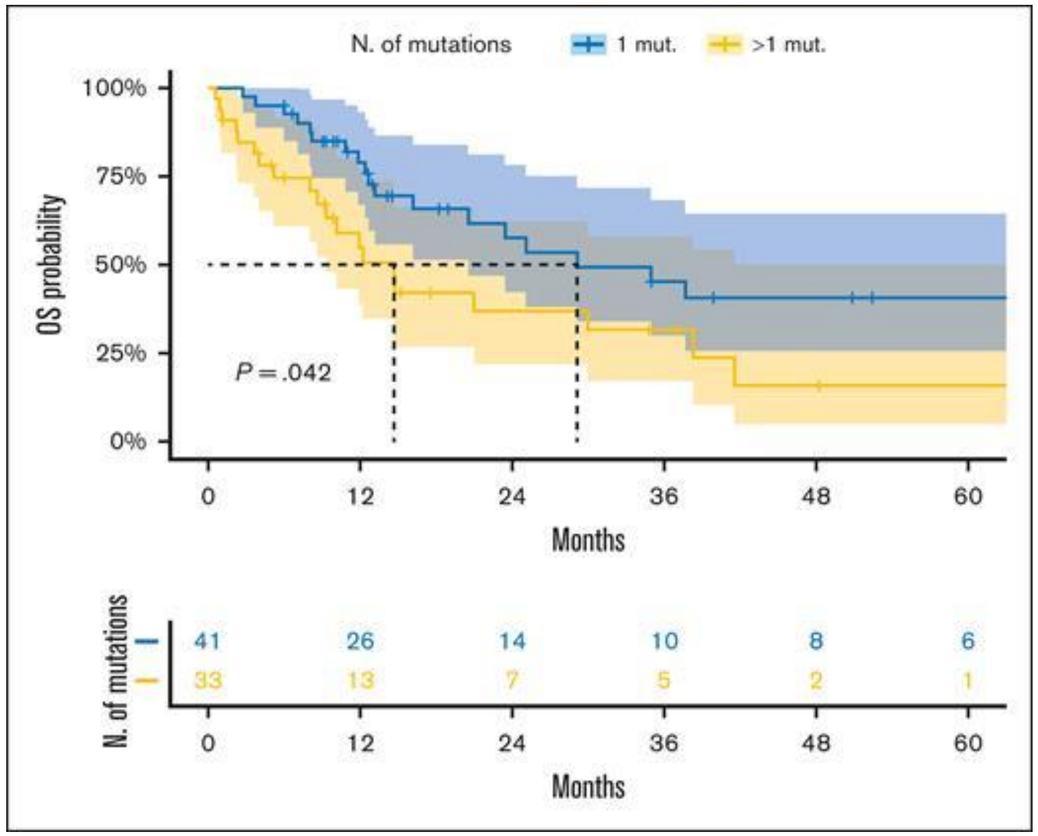




Rausch C et al, Leukemia, 11 Apr 2023, 37(6):1234-1244

Applicability of 2022 classifications of acute myeloid leukemia in the real-world setting





Attardi E et al, Blood Adv (2023) 7 (17): 5122–5131

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

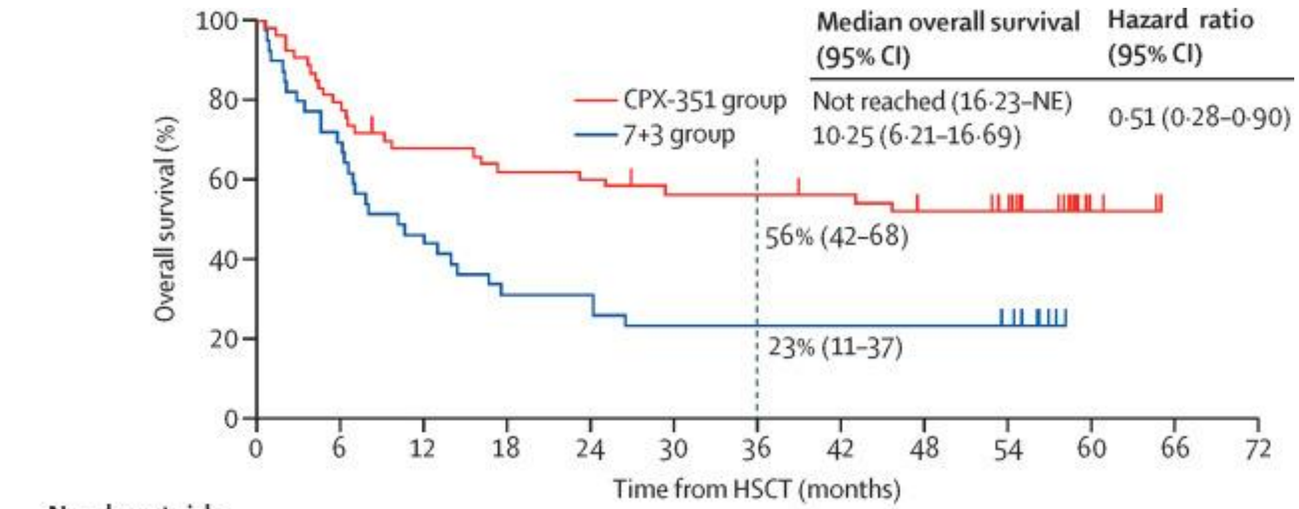
CPX-351(cytarabine:daunorubicin) liposome injection: approval history

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

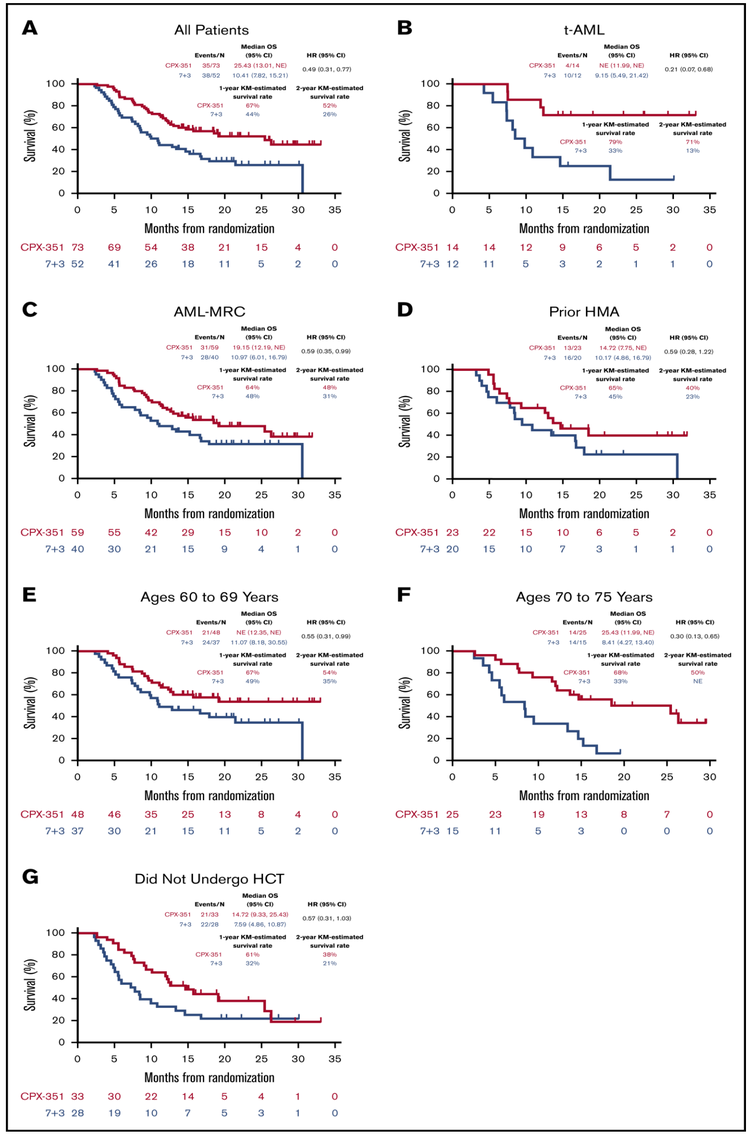
This is the first approved treatment specifically for patients with this subgroup of AML

CPX-351 versus 7+3 cytarabine and daunorubicin chemotherapy in older adults with newly diagnosed high-risk or secondary acute myeloid leukaemia: 5-year results of a randomised, open-label, multicentre, phase 3 trial



Number at risk (number censored)													
CPX-351 group	53 (0)	42 (0)	35 (1)	32 (1)	31 (1)	28 (2)	28 (2)	27 (3)	24 (4)	21 (7)	6 (22)	0 (28)	0 (28)
7+3 group	39 (0)	27 (0)	18 (0)	12 (0)	12 (0)	9 (0)	9 (0)	9 (0)	9 (0)	8 (1)	0 (9)	0 (9)	0 (9)

Lancet et al, Lancet Hematol. July, 2021



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

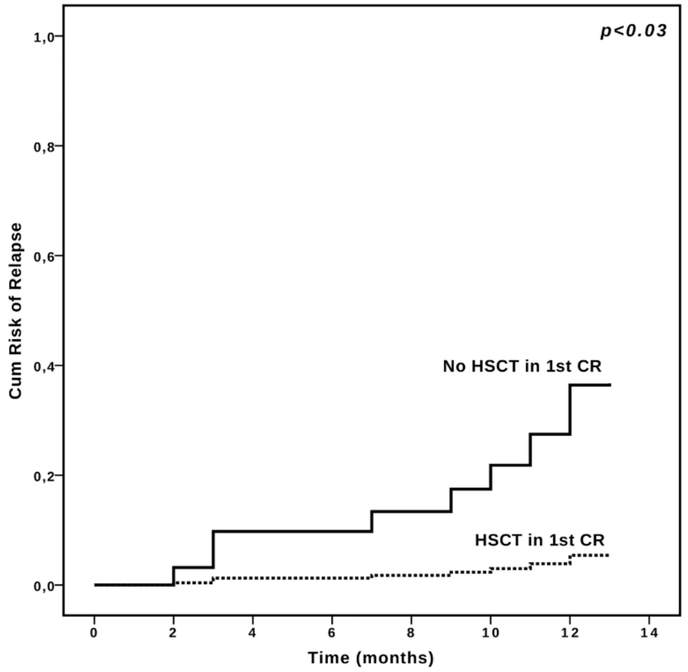
Key Points

- CPX-351 demonstrated longer median OS vs 7+3 among older adults with newly diagnosed high-risk/secondary AML who achieved remission.
- The OS benefit was observed across the evaluated patient subgroups and irrespective of subsequent hematopoietic cell transplantation.

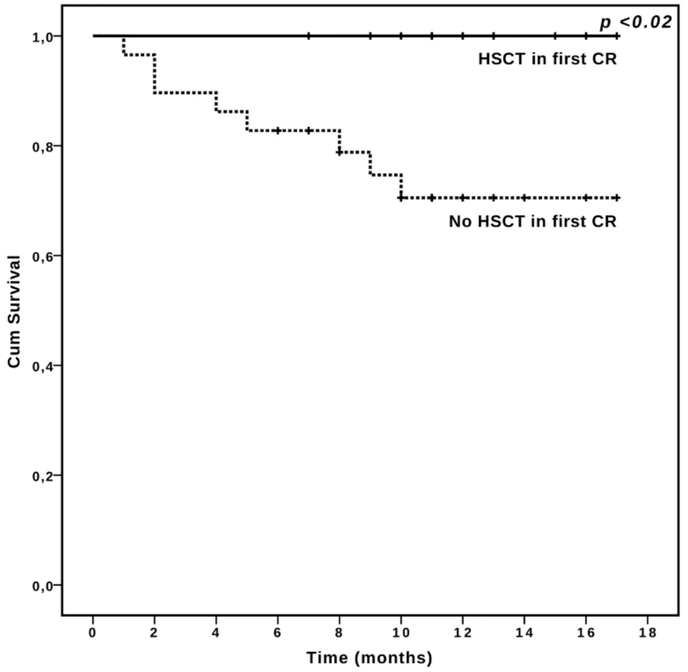
Lin TL et al, Blood Adv. 2021 Mar 23;5(6):1719-1728.

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



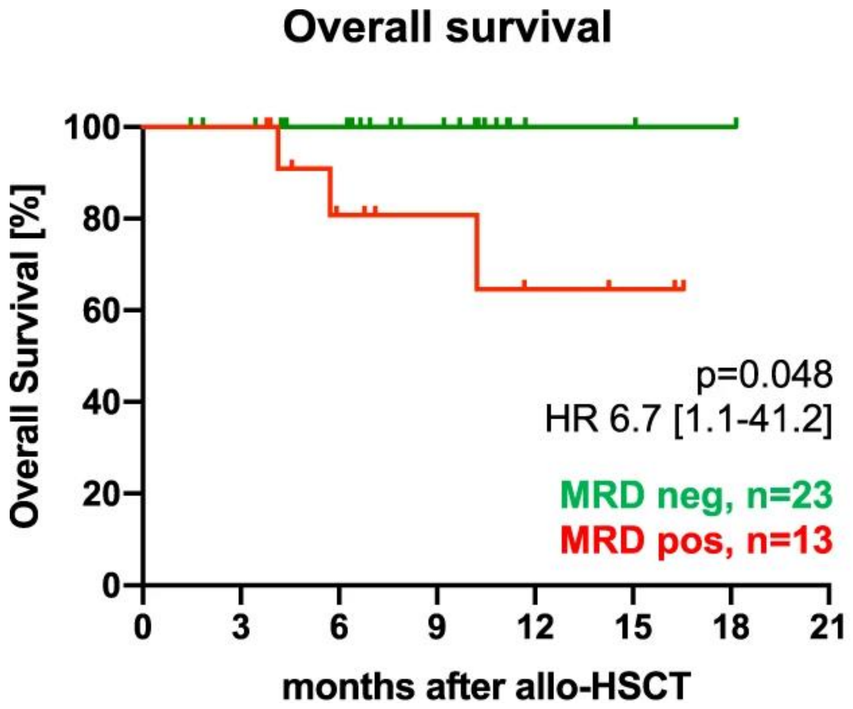
Overall Survival in responding patients according to transplantation

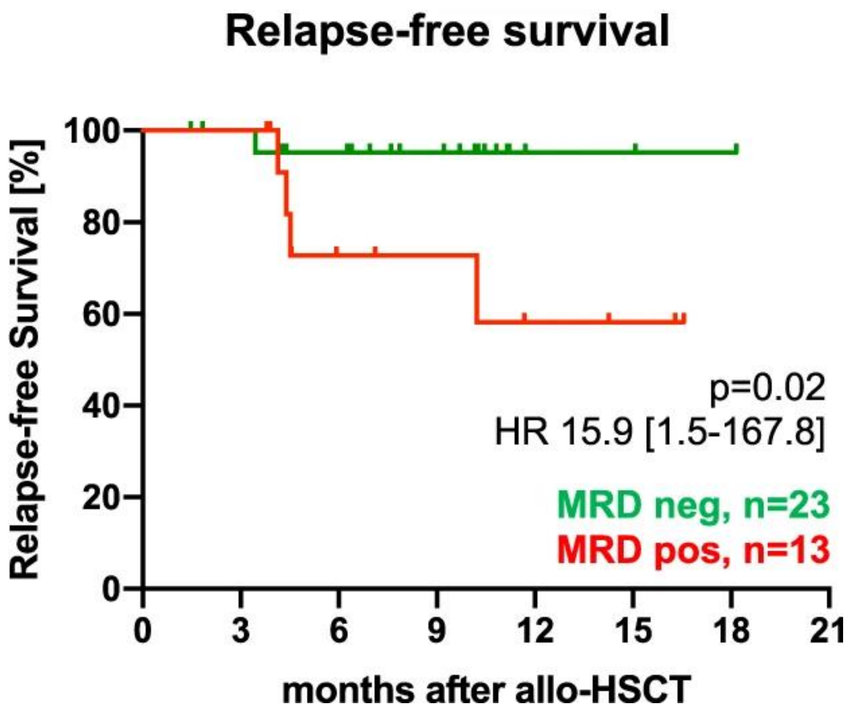


HSCT in CR1 was the only significant predictor of longer survival (12 months OS of 100 and 70.5%, for patients undergoing or not HSCT in CR1, respectively, p = 0.011).

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

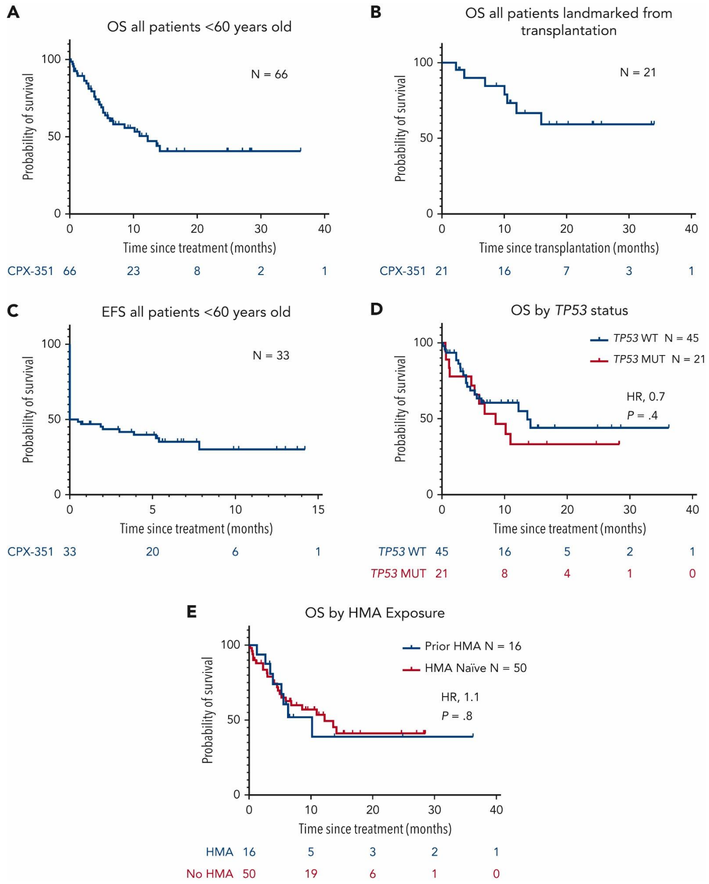




Among patients with CR/CRi (*n* = 85) after CPX-351-based induction data on MRD estimated by FC were available for 36 patients (42%) representing MRD negativity in 64% of the patients (*n* = 23).

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

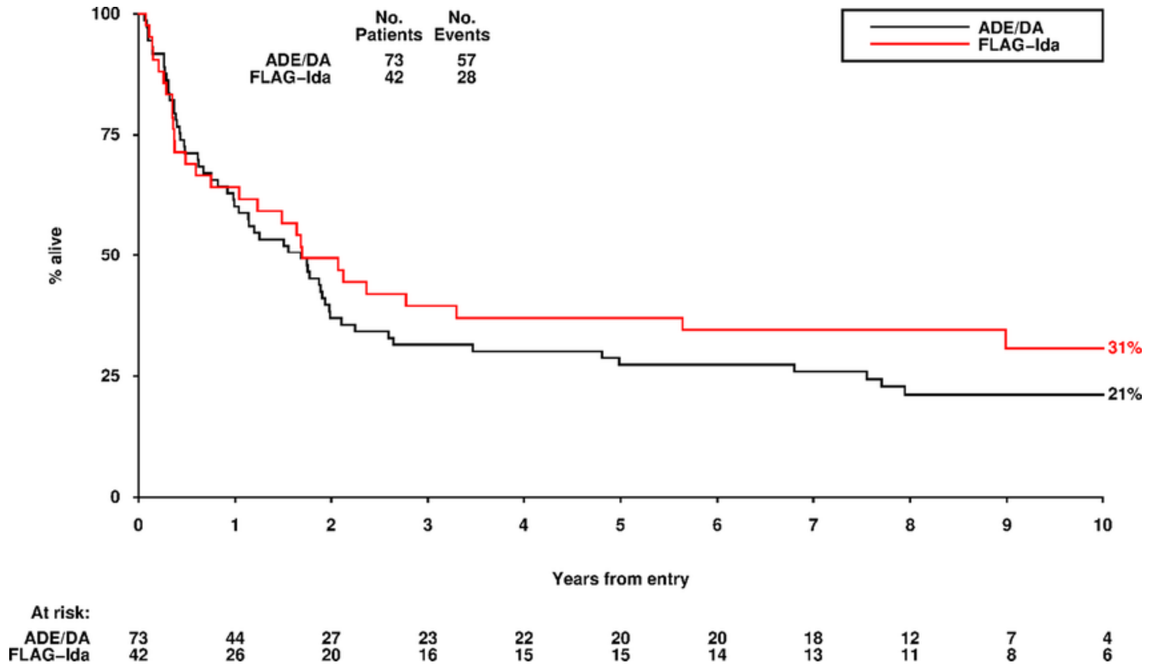
Safety and efficacy of CPX-351 in younger patients (<60 years old) with secondary acute myeloid leukemia



- A total of 66 patients with confirmed s-AML or t-AML treated with CPX-351 were included in this study.
- Median age was 54.9 years (range, 23-59).
- The majority (N = 52, 79%) of patients had AML-MRC, and 14 (21%) had t-AML.
- Of the 66 patients, 16 had received previous hypomethylating therapy (HMA) for antecedent MDS. Cytogenetics were complex in 30 (46%), monosomal in 17 (26%), normal in 10 (15%), −7 in 7 (11%), +8 in 4 (6%), −17p in 3 (5%), and −5q in 2 (3%) patients.
- The most common mutations were TP53 (29%), RUNX1 (21%), DNMT3A (17%), NRAS (17%), ASXL1 (11%), and NPM1 (11%)

Przespolewski P , Blood, 2023

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

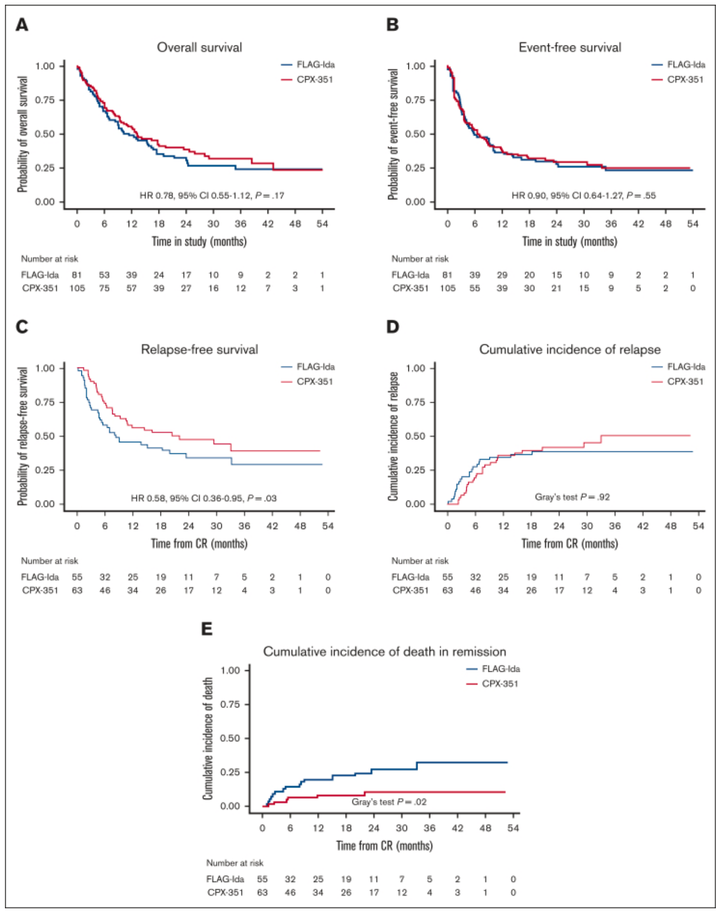


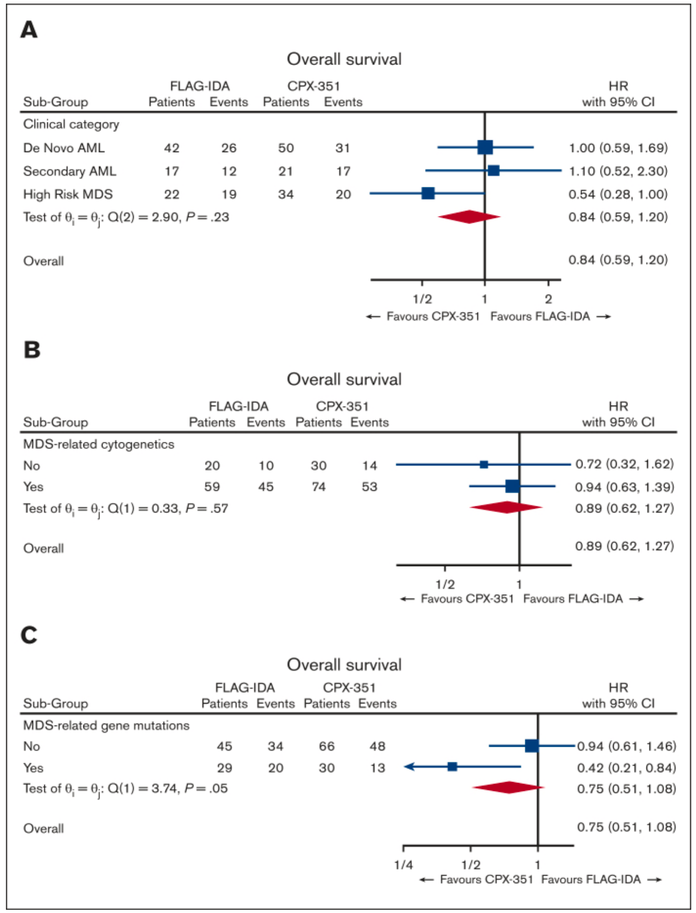
The MRC AML15 trial randomised younger patients(n = 115) between daunorubicin and ara-C (DA) and DA plus etoposide (ADE) and ADE and fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor (FLAG-Ida) induction.
Response to induction was not different [complete remission/complete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

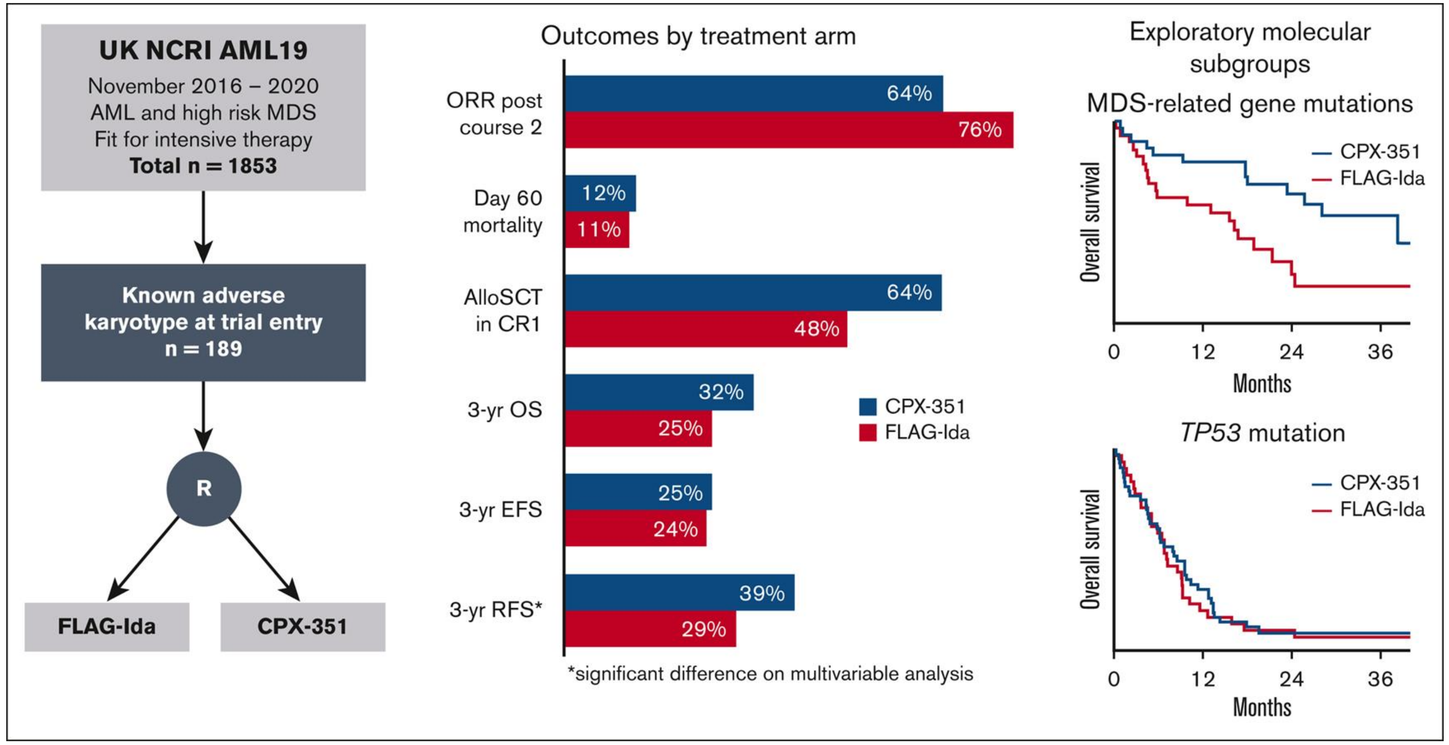
A randomized comparison of CPX-351 and FLAG-Ida in adverse karyotype AML and high-risk MDS: the UK NCRI AML19 trial





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

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.

CREST-UK: Real-world effectiveness, safety and outpatient delivery of CPX-351 for first-line treatment of newly diagnosed therapy-related AML and AML with myelodysplasia-related changes in the UK

Risk category		*n*	CR *n* (%)	CR/CRi *n* (%)
Grimwade classification	Intermediate	72	37 (51.4)	50 (69.4)
	Adverse	57	15 (26.3)	20 (35.1)
ELN 2017 risk category	Favourable	12	12 (100.0)	12 (100.0)
	Intermediate	37	15 (40.5)	23 (62.2)
	Adverse	65	17 (26.2)	25 (38.5)
NPM1	Wild-type	88	35 (39.8)	48 (54.5)
	Mutated	14	11 (78.6)	12 (85.7)
FLT3	Wild-type	95	41 (43.2)	54 (56.8)
	Mutated	11	5 (45.5)	6 (54.5)
TP53	Wild-type	50	29 (58.0)	38 (76.0)
	Mutated	17	4 (23.5)	4 (23.5)
Any secondary gene mutation	Mutated	31	12 (38.7)	19 (61.3)

Despite their adverse prognosis, 61% of evaluable best response patients with a known secondary gene mutation achieved CR/CRi.

Mehta P et al, Br J Haematol. 2024 Oct;205(4):1326-1336.

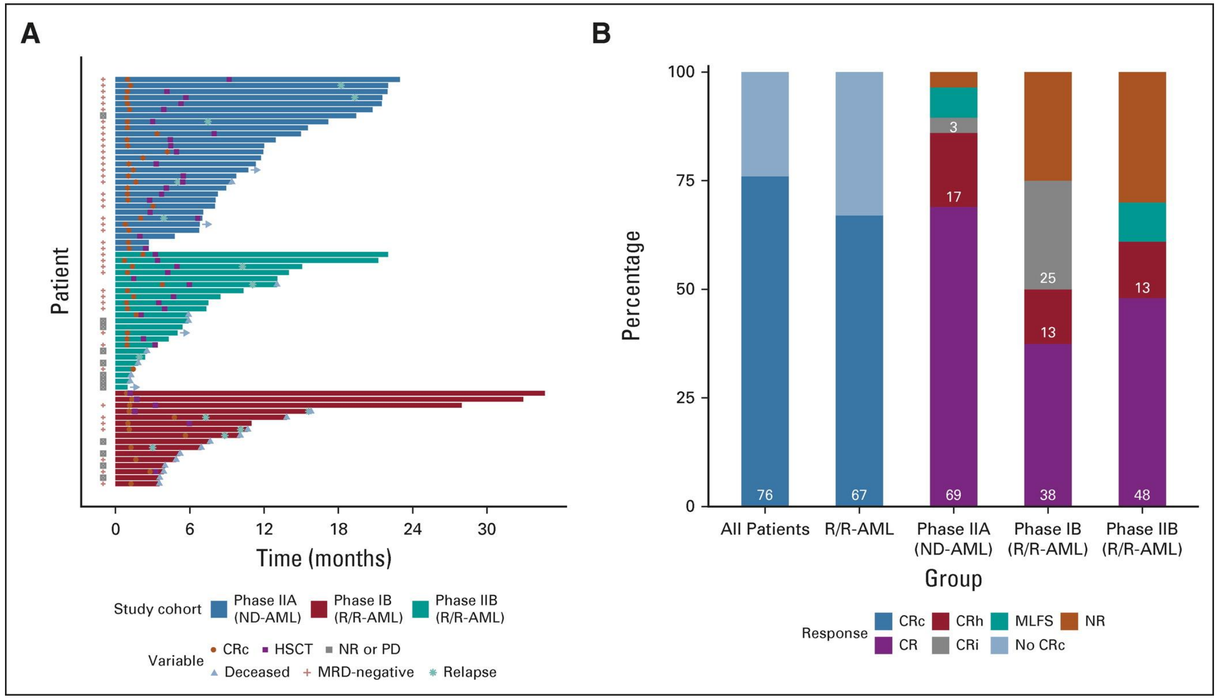
Real-life experience with CPX-351 and impact on the outcome of high-risk AML patients: a multicentric French cohort

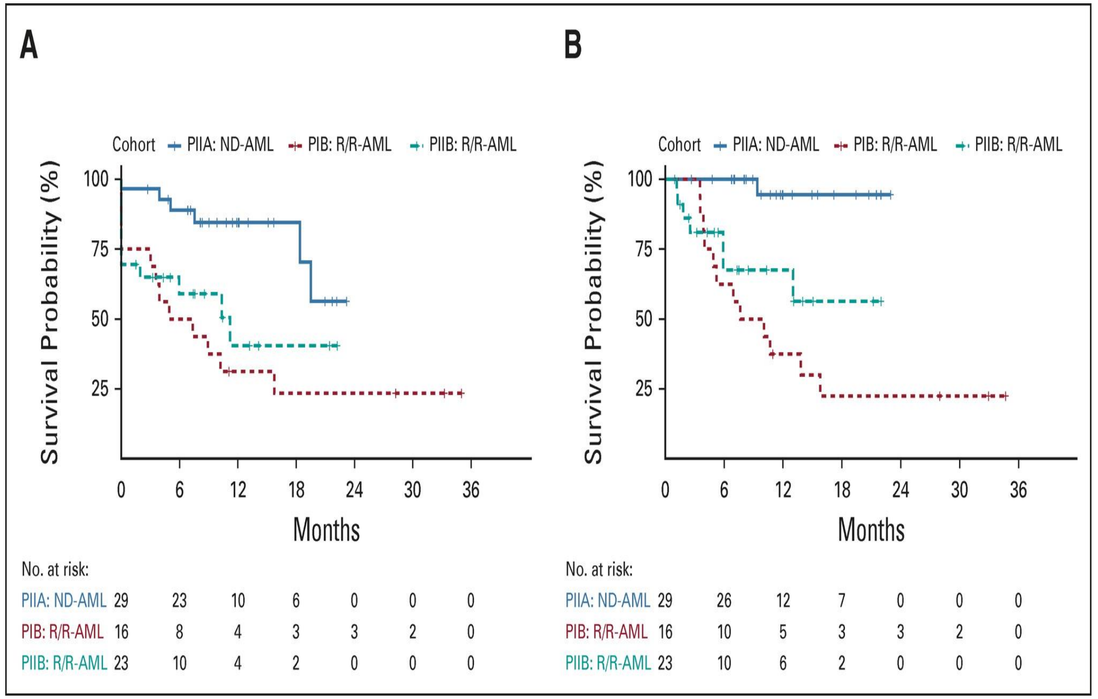
Number of patients: 103

	CR/CRi, n (%)	P
All patients treated	61 (59)	
AML subtype		
t-AML	19 (70)	.01
MRC-AML	40 (55)	
With/without prior MDS	15 (44)/46 (68)	.14
With/without CMML	2 (22)/59 (63)	.03
Hyperleukocytosis		
Presence/absence	7 (13)/47 (87)	.21
HMA experience		
Prior HMA	4 (22)	.001
No prior HMA	56 (69)	
Karyotype (presence/absence)		
Complex karyotype	17 (49)/44 (66)	.09
Monosomal karyotype	11 (39)/50 (68)	.009
Chromosome 5 abnormalities	13 (46)/48 (65)	.09
Chromosome 7 abnormalities	15 (47)/46 (66)	.07
Chromosome 17 abnormalities	6 (43)/55 (63)	.16
2017 ELN genetic risk stratification		
Favorable	2 (100)	.26
Intermediate	25 (66)	
Adverse	33 (54)	
Lindsley's classifier		
De novo/pan-AML	18 (86)	.009
Secondary-type-mutation AML	20 (56)	
TP53-mutated AML	9 (41)	
Mutation status (mutated/nonmutated)		
TP53	9 (41)/35 (66)	.04
ASXL1	9 (53)/37 (67)	.28
RUNX1	12 (57)/27 (66)	.50
EVI1	1 (17)/50 (63)	.03
FLT3-ITD	6 (67)/53 (60)	.72
FLT3-TKD	3 (50)/56 (60)	.62
NPM1	4 (57)/55 (59)	.92
Functional group (presence/absence of mutation)		
Epigenetic modifications	24 (59)/22 (69)	.37
Spliceosome complex	14 (61)/32 (64)	.80
Signaling and kinase pathway	16 (55)/30 (68)	.26
Cohesin complex	6 (60)/40 (63)	.83
Transcription factors	17 (61)/29 (64)	.75

Edmond Chiche E et al, Blood Adv, 2021

Venetoclax Combined With FLAG-IDA Induction and Consolidation in Newly Diagnosed and Relapsed or Refractory Acute Myeloid Leukemia





68 patients (median age 46 years [range, 20-73]) have been enrolled.
Forty-one percent of ND-AML had sAML, ts-AML, or t-AML. European LeukemiaNet (ELN) risk across PIB, PIIA, and PIIB cohorts was favorable in 37.5%, 17%, and 26% of patients; intermediate in 12.5%, 45%, and 13%; and adverse in 50%, 38%, and 61%.

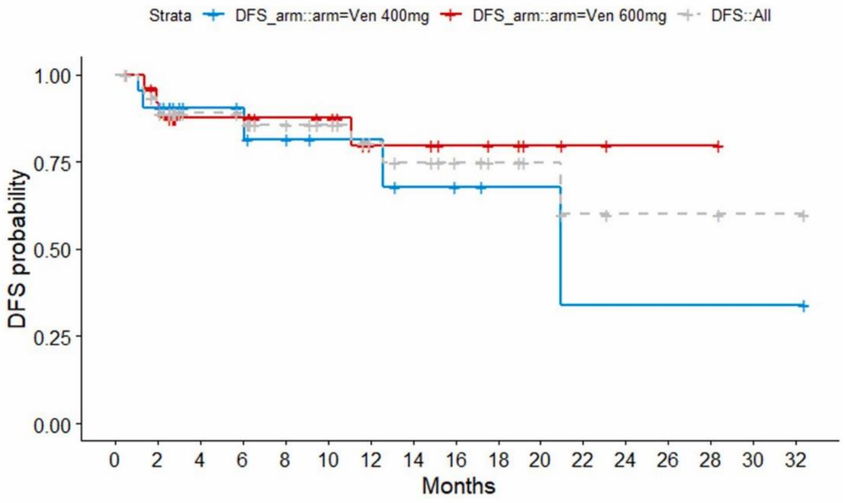
DiNardo C et al, J Clin Oncol. 2021 Sep 1;39(25):2768-2778

Table 1: Response assesment after induction

		Arm		
Characteristic	Overall, N = 57	Ven 400mg, N = 28	Ven 600mg, N = 29	p-value[1]
CR	38 (70%)[2]	15 (58%)	23 (82%)[2]	0.19
CRp	7 (13%)	6 (23%)	1 (3.6%)	
CRi	2 (3.7%)	1 (3.8%)	1 (3.6%)	
PR	3 (5.6%)	2 (7.7%)	1 (3.6%)	
SD	4 (7.4%)	2 (7.7%)	2 (7.1%)	
CRR	**48 (84%)[2]**	**22 (79%)**	**26 (90%)[2]**	**0.30**

[1]Fisher's exact test
[2]1 patient obtained PR after 1st induction and CR after 2nd V-FLAI

VEN: venetoclax; CR: complete response; CRp: complete response without full platelet recovery; CRi: complete response without platelet and neutrophils recovery; PR: partial response; SD: stable disease; CCR: cumulative complete remission.



Marconi G et al, ASH 2022

GIMEMA AML1718 Part 1: Planned Interim Analysis of a Safety Run-in and Phase 2 Open-Label Study of Venetoclax, Fludarabine, Idarubicin and Cytarabine (V-FLAI) in the Induction Therapy of Non Low-Risk Acute Myeloid Leukemia

Results:

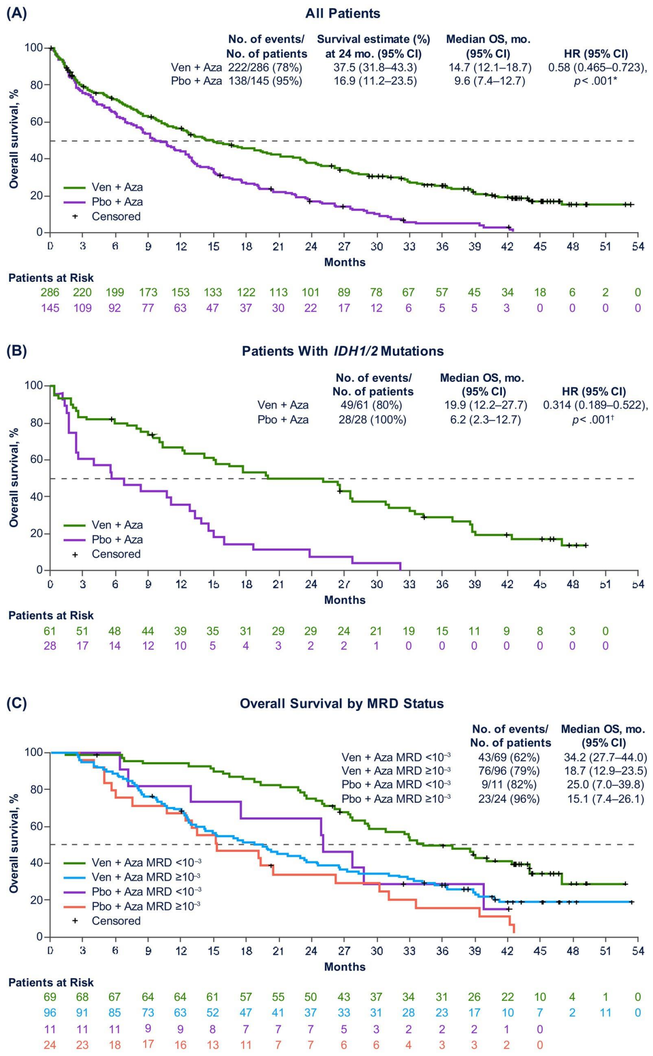
57 patients; 28 patients received V-FLAI with VEN 400 mg and 29 patients V-FLAI with VEN 600 mg. Median age of 54 years (18 - 65); 32 (56%) and 25 (44%) were at intermediate- and high-risk according to ELN2017 category, respectively;

Complete remission: 48/57 patients (84%). 74% of patients were measurable residual disease (MRD) negative after induction (67% in ven 400 mg, and 78% in ven 600 mg arm).

With a median follow-up of 10.5 months, 28 patients (49%) received HSCT in CR, of which 20 (80%) in MRD negative CR; median overall survival (OS) was not reached; probability of 12-month OS was 76% (71.5% for VEN 400 mg and 76.5% for VEN 600 mg. Median disease-free survival was not reached (figure 1).

Conclusions: V-FLAI administration was associated with a high and promising CR rate and prolonged OS duration in an intermediate- and high-risk population, without any safety signals. Preliminary MRD analysis revealed deep responses in most of the patients that translated to favorable 1-year survival.

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia (VIALE-A Study): long-term follow-up



	Ven + Aza *n/N* (%)	Pbo + Aza *n/N* (%)	HR (95% CI) Ven + Aza vs. Pbo + Aza
All Patients	222/286 (77.6)	138/145 (95.2)	0.57 (0.45–0.70)
Sex			
Female	88/114 (77.2)	55/58 (94.8)	0.58 (0.41–0.82)
Male	134/172 (77.9)	83/87 (95.4)	0.56 (0.42–0.74)
Age (Years)			
18 to <65	8/10 (80.0)	5/5 (100.0)	0.61 (0.19–1.95)
65 to <75	79/102 (77.5)	49/53 (92.5)	0.69 (0.48–0.99)
<75	87/112 (77.7)	54/58 (93.1)	0.68 (0.48–0.96)
≥75	135/174 (77.6)	84/87 (96.6)	0.50 (0.37–0.66)
Baseline ECOG			
Grade <2	127/157 (80.9)	78/81 (96.3)	0.52 (0.39–0.70)
Grade ≥2	95/129 (73.6)	60/64 (93.8)	0.61 (0.44–0.85)
Type of AML			
De Novo	162/214 (75.7)	104/110 (94.5)	0.56 (0.44–0.73)
Secondary	60/72 (83.3)	34/35 (97.1)	0.58 (0.37–0.89)
Cytogenetic risk			
Intermediate	130/182 (71.4)	84/89 (94.4)	0.49 (0.37–0.65)
Poor	92/104 (88.5)	54/56 (96.4)	0.73 (0.52–1.03)
Molecular Marker			
FLT3	23/29 (79.3)	20/22 (90.9)	0.65 (0.35–1.19)
IDH1	21/23 (91.3)	11/11 (100.0)	0.28 (0.12–0.66)
IDH2	30/40 (75.0)	18/18 (100.0)	0.30 (0.16–0.57)
IDH1/2	49/61 (80.3)	28/28 (100.0)	0.31 (0.19–0.52)
TP53	36/38 (94.7)	13/14 (92.9)	0.76 (0.40–1.45)
NPM1	17/27 (63.0)	17/17 (100.0)	0.52 (0.26–1.04)
AML-MRC			
Yes	81/92 (88.0)	46/49 (93.9)	0.72 (0.50–1.04)
No	141/194 (72.7)	92/96 (95.8)	0.51 (0.39–0.67)
Bone Marrow Blast Count			
<30%	72/85 (84.7)	40/41 (97.6)	0.60 (0.40–0.89)
30% to <50%	47/61 (77.0)	32/33 (97.0)	0.53 (0.34–0.84)
≥50%	103/140 (73.6)	66/71 (93.0)	0.56 (0.41–0.77)

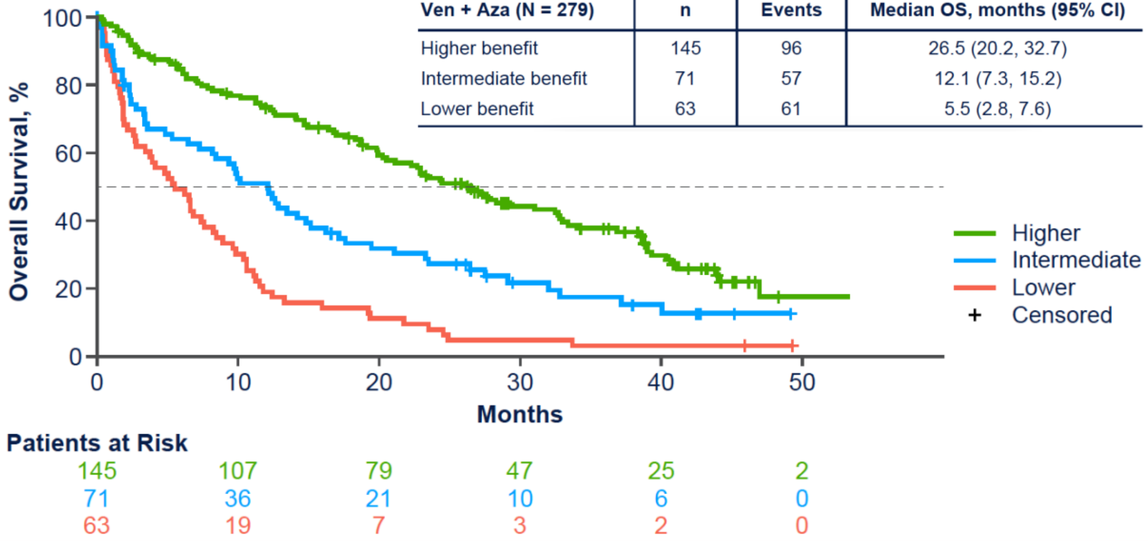
Pratz KW et al, Am J Hematol. 2024 Apr;99(4):615-624.

Genetic Risk Stratification and Outcomes Among Treatment-Naive Patients With AML Treated With Venetoclax and Azacitidine

Outcomes with Venetoclax-Azacitidine by Genetic Risk in Newly Diagnosed AML

In this post hoc pooled analysis, ELN 2017 and 2022 classification systems and a 4-gene signature developed by a bioinformatic algorithm were assessed as potential prognostic frameworks for risk stratification of outcomes with venetoclax-azacitidine in newly diagnosed AML

Ven + Aza (N = 279)	n	Events	Median OS, months (95% CI)
Higher benefit	145	96	26.5 (20.2, 32.7)
Intermediate benefit	71	57	12.1 (7.3, 15.2)
Lower benefit	63	61	5.5 (2.8, 7.6)



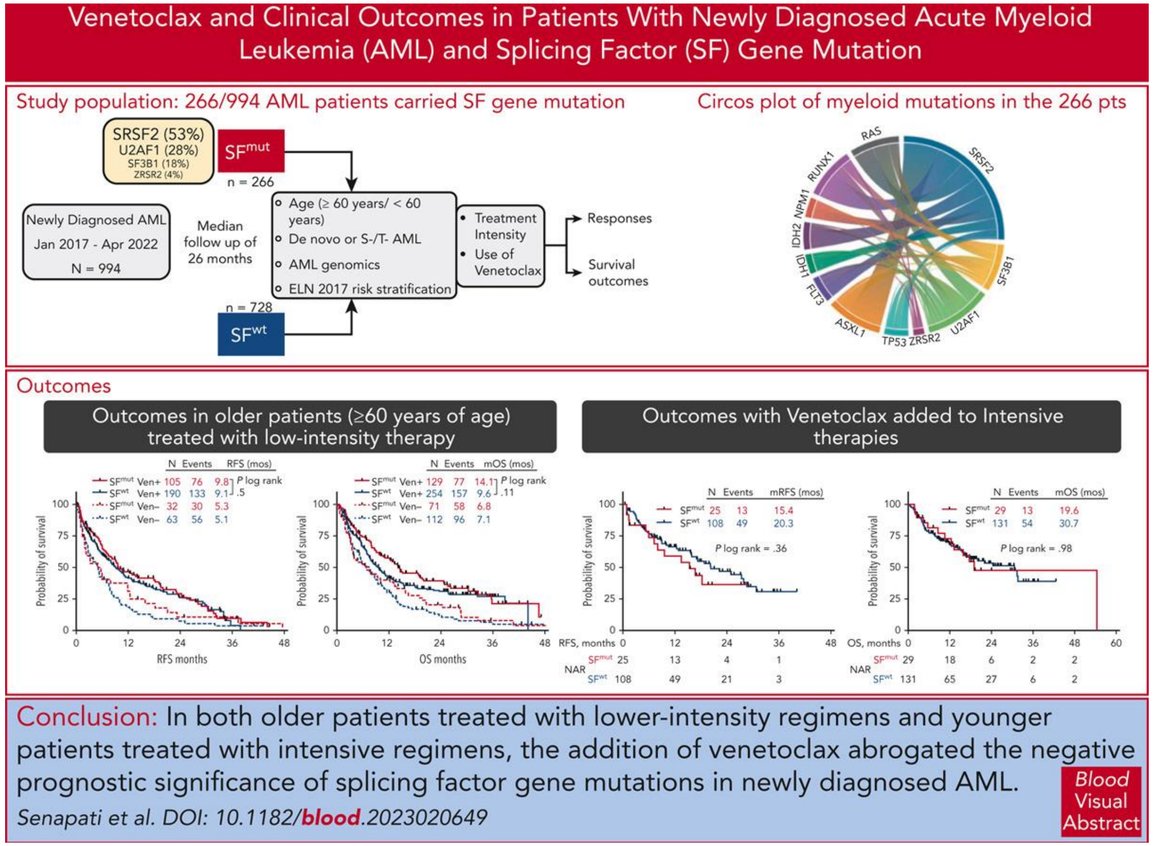
Conclusions: Although ELN 2017 and 2022 classification systems failed to discriminate outcomes, the application of a bioinformatic algorithm identified a 4-gene prognostic risk classifier (*FLT3*-ITD, *KRAS*, *NRAS*, and *TP53*) that successfully differentiated outcomes among patients with newly diagnosed AML treated with venetoclax-azacitidine.

By applying a bioinformatic algorithm, new molecular signatures were derived differentiating OS outcomes with venetoclax-azacitidine; the mutational status of TP53, FLT3-ITD, NRAS, and KRAS categorized patients into higher-, intermediate-, and lower-benefit groups (52%, 25%, and 23% of patients, respectively), each associated with a distinct median OS (26.5 months, 12.1 months, and 5.5 months, respectively).

- ELN prognostic classifiers do not provide clinically meaningful risk stratification of OS outcomes for patients with AML treated with venetoclax-azacitidine.
- TP53, FLT3-ITD, NRAS, and KRAS mutation status allows classification of these patients into three risk groups with distinct differences in median OS.

Dohner H et al, Blood. 2024 Aug 12:blood.2024024944

Venetoclax abrogates the prognostic impact of splicing factor gene mutations in newly diagnosed acute myeloid leukemia



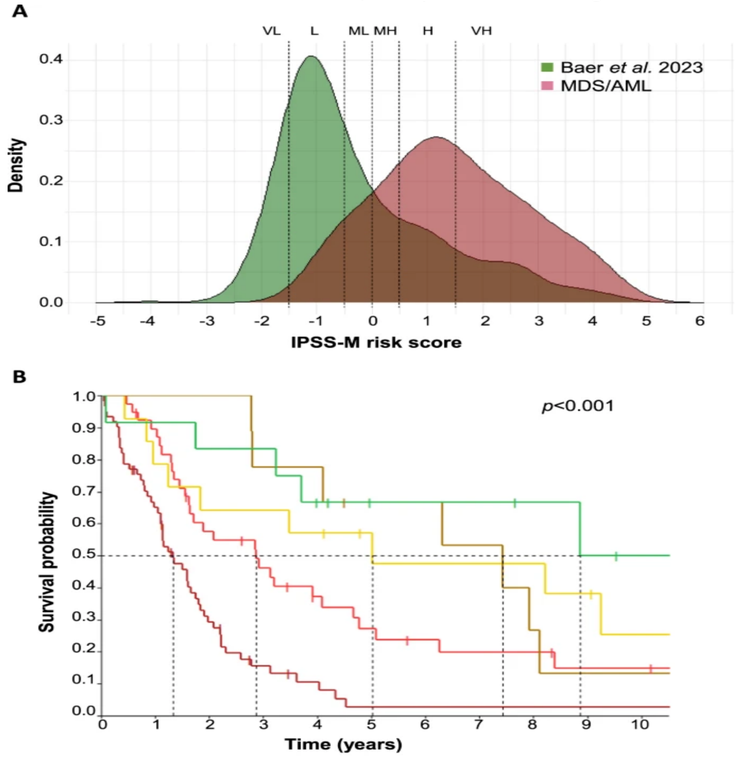
Key Points

- Splicing factor gene mutations are enriched in older patients with AML and in those with secondary AML.
- The use of venetoclax with LI or intensive therapies abrogates any negative prognostic impact of these mutations on survival.

Senapati J et al, Blood (2023) 142 (19): 1647–1657

Risk assessment according to IPSS-M is superior to AML ELN risk classification in MDS/AML overlap patients defined by ICC

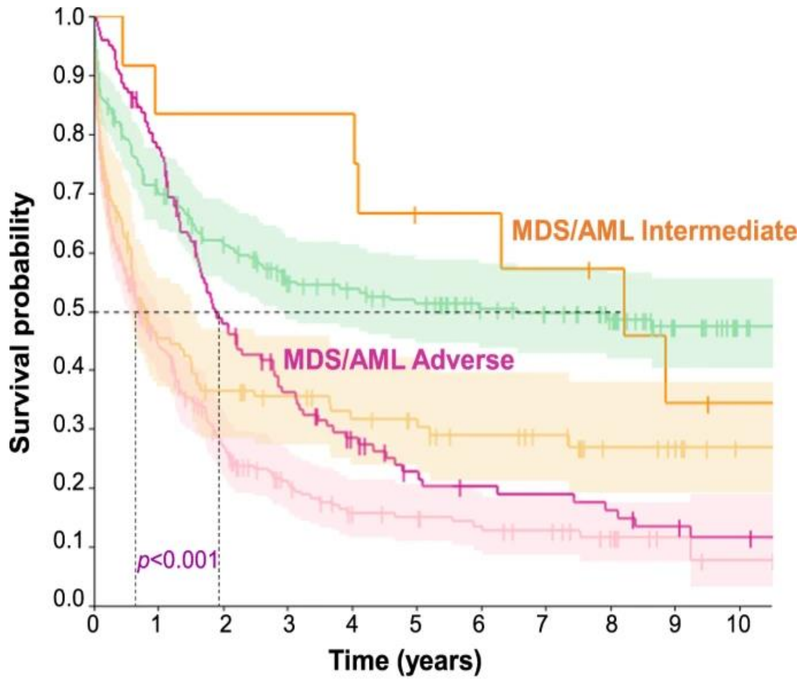
Risk-stratification of MDS/AML patients according to IPSS-M



C

Category	n	MDS/AML, median OS	Baer *et al.*, median OS	Bernard *et al.*, median OS
Very low	0	NA	9.5	10.6
Low	12	8.9	6.9	6.0
Moderate low	9	7.4	6.1	4.6
Moderate high	14	5.0	3.4	2.8
High	40	2.9	2.8	1.8
Very high	62	1.3	1.2	1.0
Total	**137**	**2.1**	5.7	4.7
Median age (years)		**74**	73	72

Risk-stratification of MDS/AML patients according to ELN 2022 guidelines



Category	n	MDS/AML, median OS	AML control, median OS
Favorable	0	NA	6.6
Intermediate	12	8.2	0.8
Adverse	125	1.9	0.7
Total	**137**	**2.1**	**1.3**
Median age (years)		**74**	**69**

Key points:
For MDS/AML patients, MDS-based risk assessment according to IPSS-M is fully applicable with comparable OS data to a real-world MDS cohort despite a skewing towards high-risk categories.
In contrast, AML-based risk classification according to ELN 2022 guidelines is not applicable for MDS/AML.
The classification of nearly all patients as adverse risk due to their MR-associated genetic profile is not meaningful.

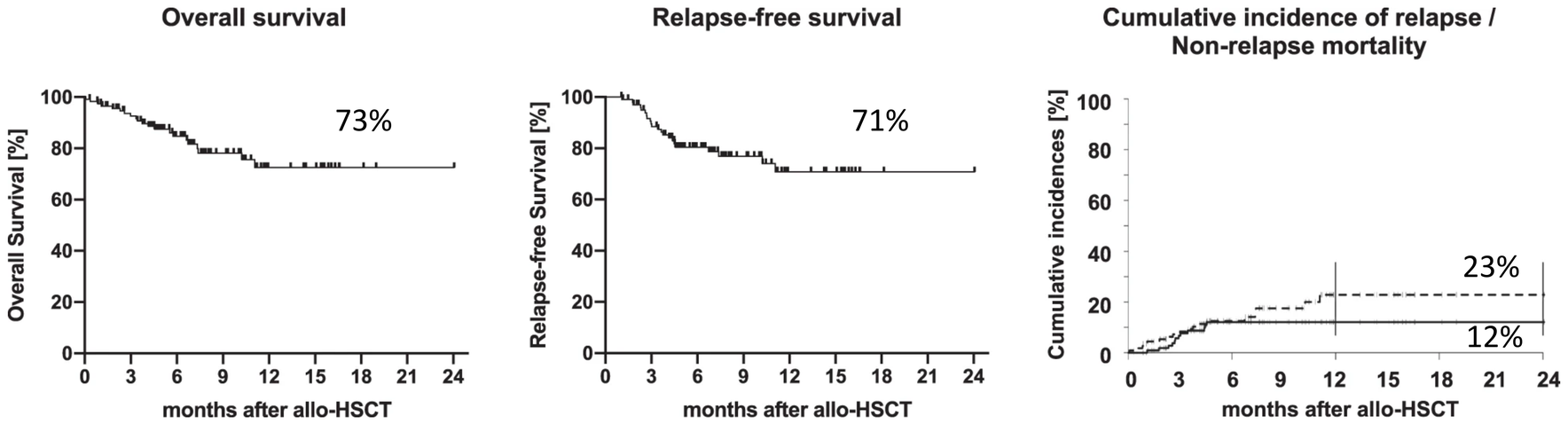
Conclusion:
If MDS/AML patients were to be included into AML studies, development of a specific risk assessment for MDS/AML other than ELN 2022 would be needed.

The better survival of MDS/AML patients compared to adverse risk AML despite more intensive therapy in the latter and higher age in the former (74 vs. 69 years in our cohort) raises substantial concerns about a potential justification of a general inclusion of MDS/AML patients in a clinical trial designed for adverse risk AML.

Huber S et al, Leukemia volume 37, pages2138–2141 (2023)

Real-world experience of CPX-351 as first-line treatment for patients with acute myeloid leukemia: outcome of the transplant cohort

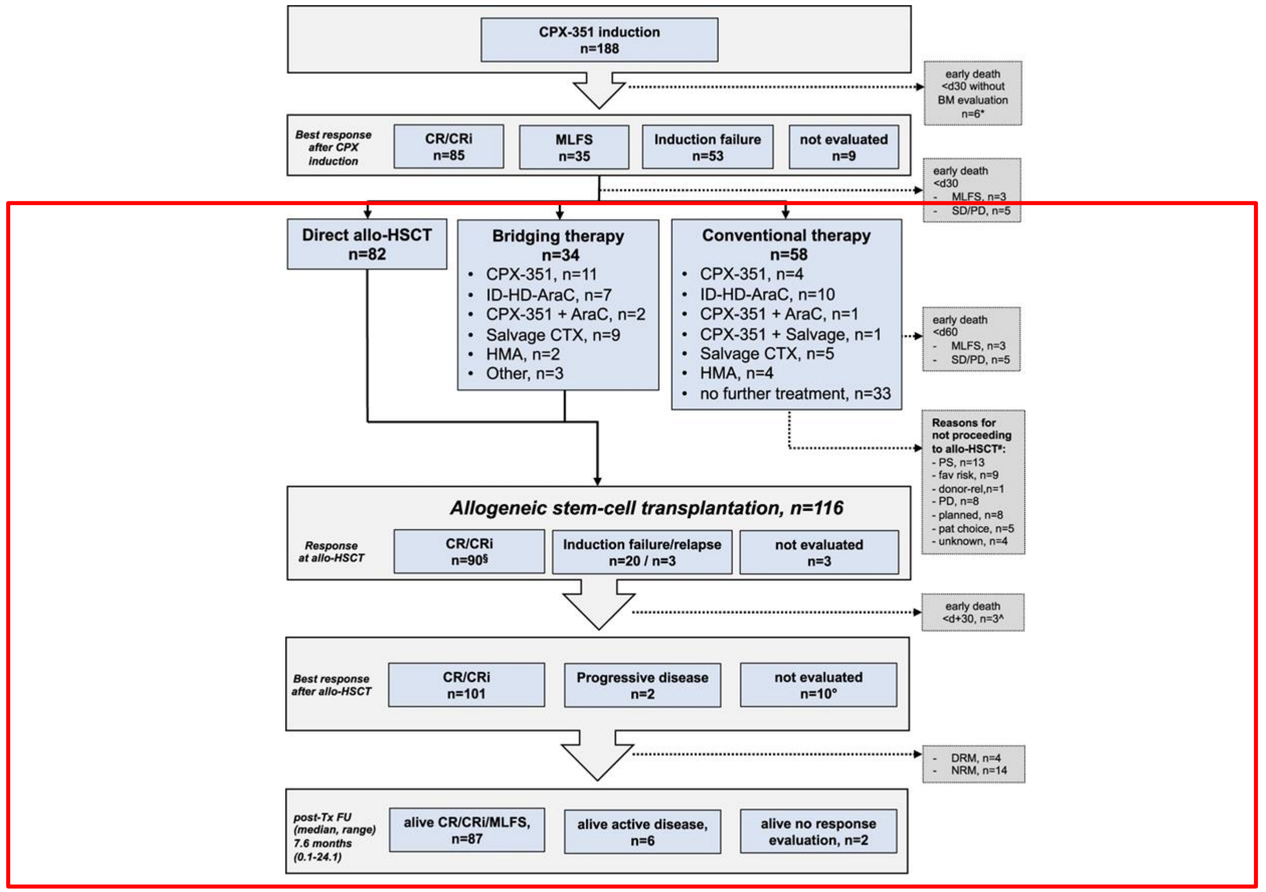
Median follow-up: 7.6 months



With a median FU of 7.6 months (range: 0.1–24.1 months) estimated 2-year OS, RFS, CIR, and NRM probabilities of the entire cohort were 73%, 71%, 23%, and 12%, respectively.

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

Real-world experience of CPX-351 as first-line treatment for patients with acute myeloid leukemia: outcome of the transplant cohort



*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

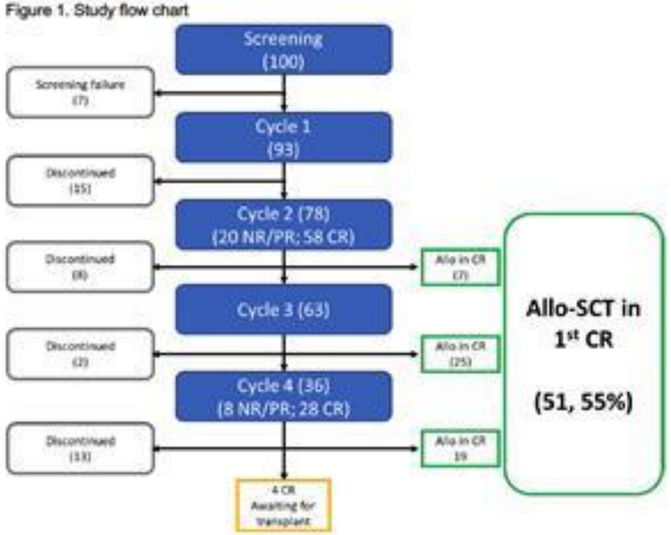
Rautenberg C et al, Blood Cancer Journal,, volume 11, 164, October 2021

Venetoclax plus decitabine as a bridge to allogeneic haematopoietic stem-cell transplantation in older patients with acute myeloid leukaemia (VEN-DEC GITMO): final report of a multicentre, single-arm, phase 2 trial

Table 1

	Overall (93)
AML subtype	
Therapy-related or MRC AML	48 (52%)
AML, NOS	32 (34%)
AML, others	13 (14%)
Sex	
Male	50 (54%)
Median age, y (range)	68.5 (60.2-74.6)
ECOG	
0	54 (58%)
1-2	39 (42%)
FIL unfit	19 (20%)
HCT-CI high risk class (3+)	18 (20%)
Median Hb, g/dl (range)	8.7 (6.8-13.9)
Median WBC, x109/L (range)	3.35 (0.21-57.06)
Median platelet count, x109/L (range)	53 (7-493)
Peripheral blasts, % (range)	8 (0-94)
BM blasts, % (range)	40 (8-99)
Cytogenetics on 86 evaluable	
abnormal karyotype	40 (47%)
normal karyotype	46 (53%)
Molecular data on 90 evaluable	
FLT3-ITD mutation	20 (22.2%)
NPM1-mutated	10 (11.1%)

Figure 1. Study flow chart

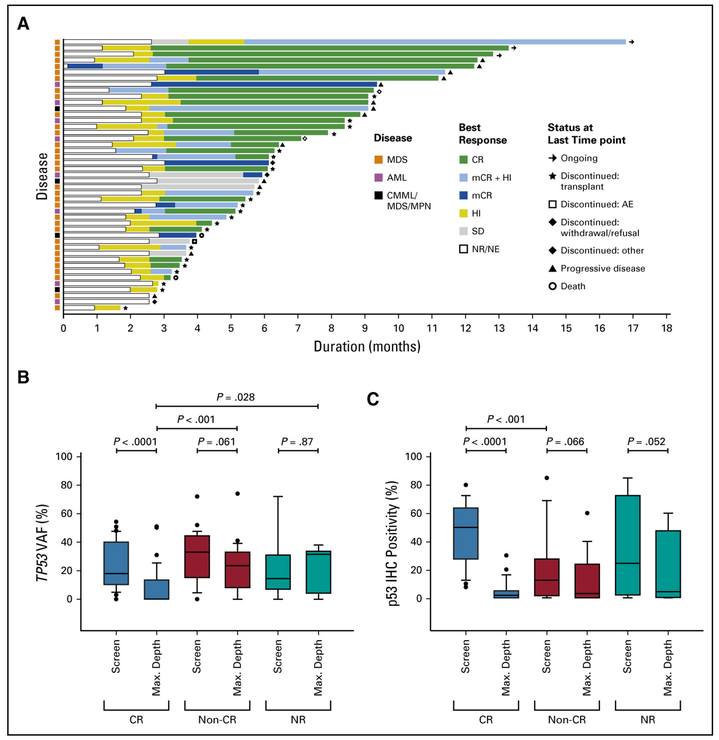


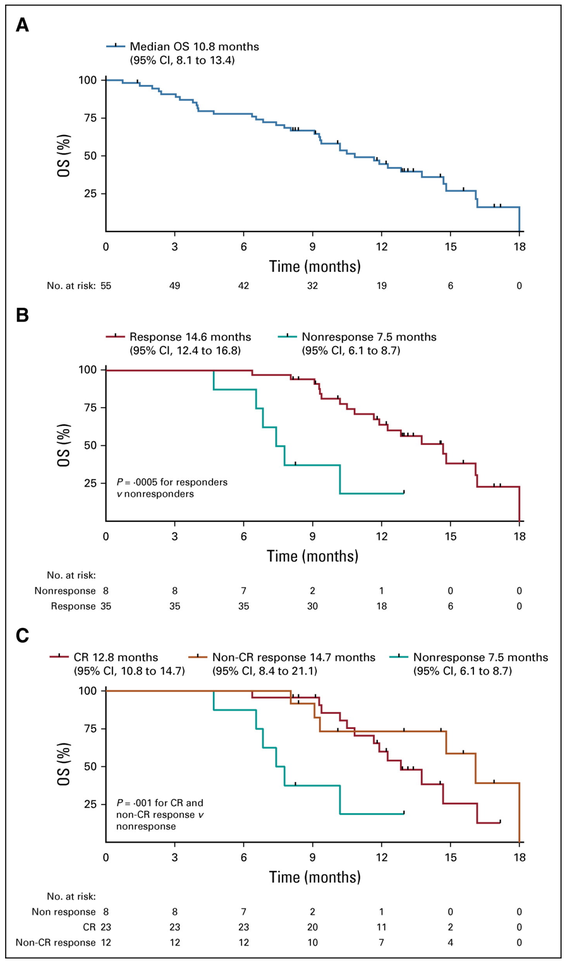
93 patients were enrolled and started venetoclax plus decitabine induction (44 [47%] at intermediate risk and 49 [53%] at high risk).
The median age was 68·5 (IQR 60·3-74·7).
The median follow-up was 236 days (IQR 121-506).
64 (69%) of 93 patients reached complete remission and 53 (57%) underwent allogeneic HSCT in complete remission.
53 (83%) of 64 with a complete remission underwent allogeneic HSCT.

Adverse events (grade ≥3) occurred in 49 (53%) of 93 patients. The most common adverse events were infections (including pneumonia, bacterial sepsis, and SARS-CoV-2 causing seven deaths among 28 [57%] of 49 patients), neutropenia (17 [35%]), thrombocytopenia (two [4%], including one fatal CNS bleeding), and cardiac events (four [8%], including one fatal heart failure).

Russo D et al, Lancet Haematol. 2024 Sep 20:S2352-3026(24)00241-2

Eprenetapopt (APR-246) and Azacitidine in TP53-Mutant MDS and oligoblastic AML





RESULTS

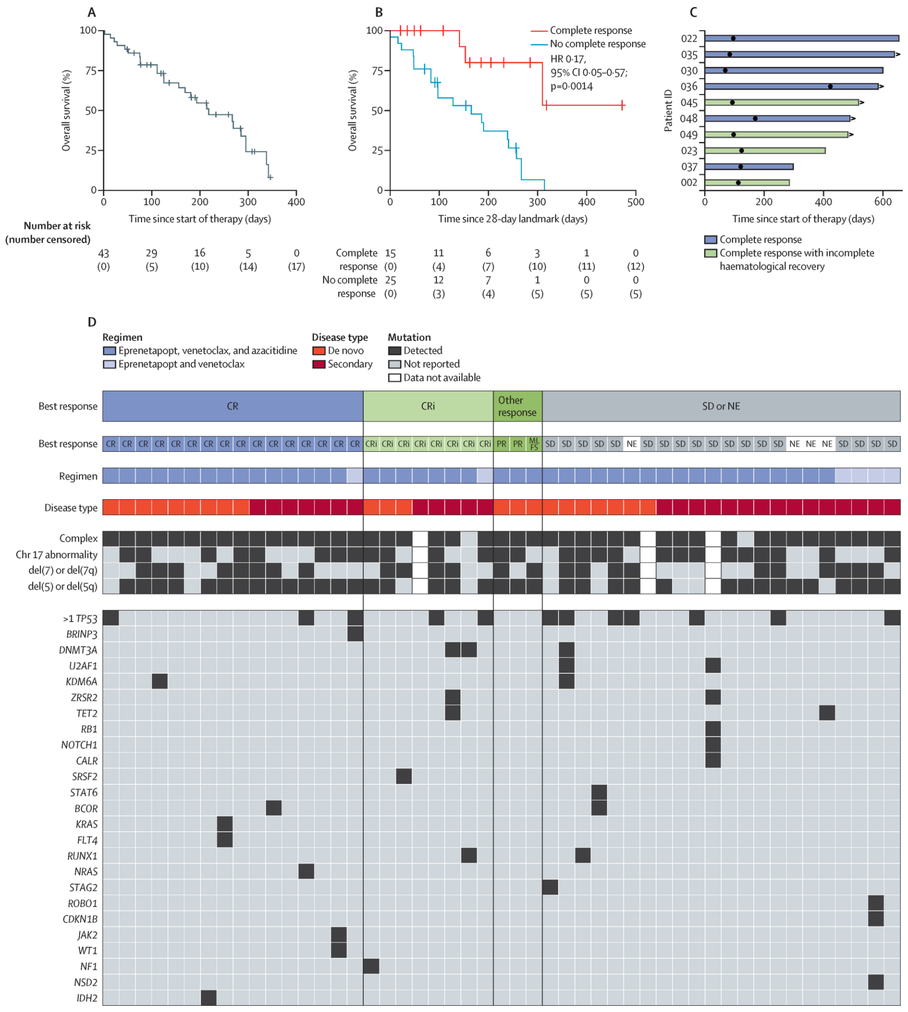
55 patients (40 MDS, 11 AML with 20-30% blasts, and four MDS/myeloproliferative neoplasms)
ORR: 71%
CR: 44%.
The overall response rate and CR rate for patients with AML was 64% (n = 7) and 36% (n = 4), respectively.
Median overall survival: 10.8 months with significant improvement in responding versus nonresponding patients (14.6 *v* 7.5 months; *P* = .0005).
19/55 (35%) patients underwent allogeneic SCT with a median overall survival of 14.7 months.
Good safety profile

CONCLUSION

Combination treatment with eprenetapopt and azacitidine is well-tolerated yielding high rates of clinical response and molecular remissions in patients with *TP53*-mutant MDS and oligoblastic AML.

Sallman DA et al, J Clin Oncol. 2021 May 10;39(14):1584-1594.

Eprenetapopt combined with venetoclax and azacitidine in TP53-mutated acute myeloid leukaemia: a phase 1, dose-finding and expansion study



Key points

49 patients with ND AML (median age: 67 year).

Treatment: eprenetapopt and venetoclax with or without azacitidine

The median follow-up: 9·5 months (IQR 6·1–11·5).

No dose-limiting toxicities

Treatment-related serious adverse events: 27%

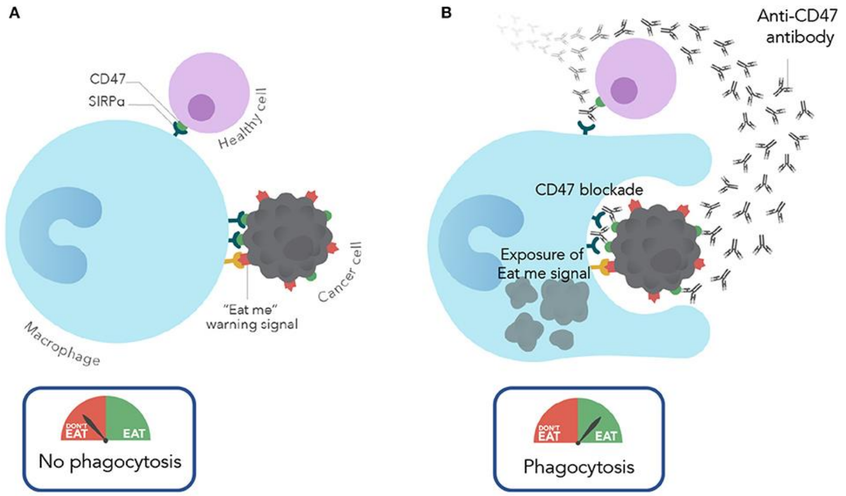
ORR: 64% (25/39)

CR: 38% (15/39)

Eprenetapopt and venetoclax with azacitidine had an acceptable safety profile and encouraging activity, supporting further evaluation of this combination in the treatment of TP53-mutated AML.

Manero G et al, Lancet Haematol. 2023 Apr;10(4):e272-e283.

Phase II study of azacitidine, venetoclax and magrolimab for newly diagnosed and relapsed/refractory AML



Magrolimab (Hu5F9-G4) is an antibody blocking CD47, a macrophage immune checkpoint and “don’t eat me” signal on cancers
Magrolimab induces tumor phagocytosis and eliminates LSCs. Azacitidine (AZA) synergizes with magrolimab by inducing “eat me” signals on leukemic blasts, thereby enhancing phagocytosis.

Chao MP et al, Front. Oncol., 22 January 2020

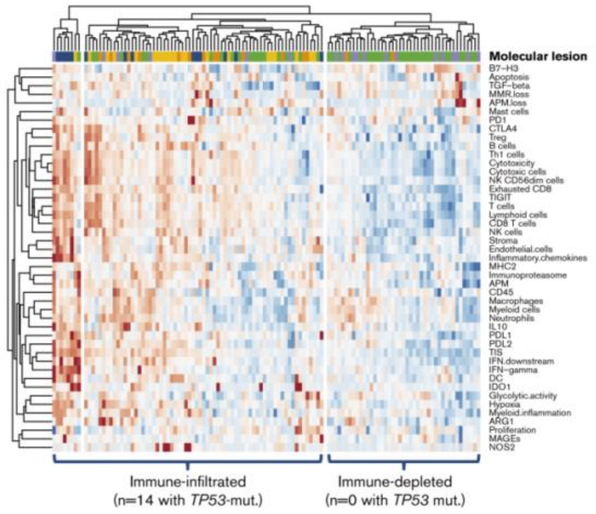
43 ND and 36 R/R patients

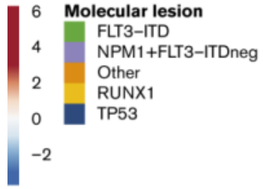
De novo AML: CR rate was 46% in patients with mutated *TP53* and 55% in those with wild-type *TP53*. Among patients with secondary AML, the CR rates were 40% and 60%, respectively. The median duration of response was not reached regardless of *TP53* status. The 12-month overall survival (OS) rate was 83% in patients with wild-type *TP53* and 53% in *TP53* mut.

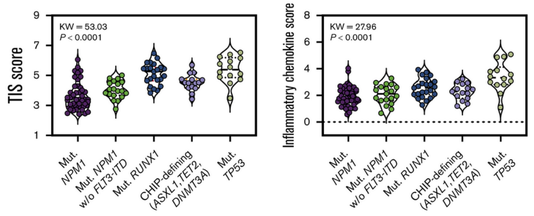
R/R AML: 18 patients were previously exposed to venetoclax and 18 were venetoclax-naïve. The CR rate was 19% overall, 0% in the venetoclax-exposed cohort, and 39% in the venetoclax-naïve. The median relapse-free survival was 3.1 months in the exposed cohort and 7.5 months in the naïve cohort. The median OS was 3.1 months and 5.6 months, respectively.

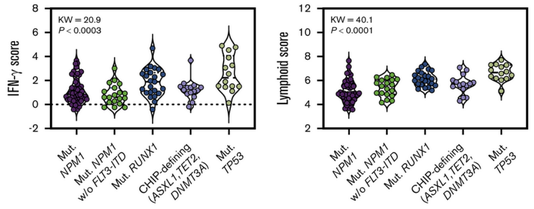
Daver N, et al, ASH 2022

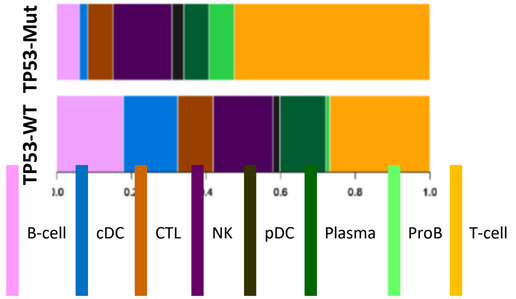
*TP53*mut AML patients show an inflammatory and immunosuppressive microenvironment

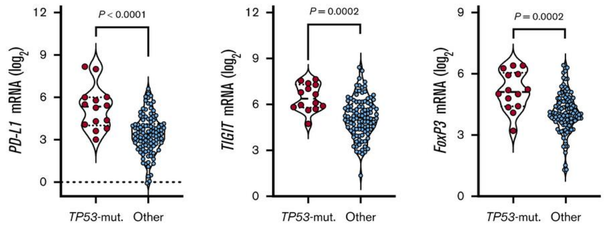




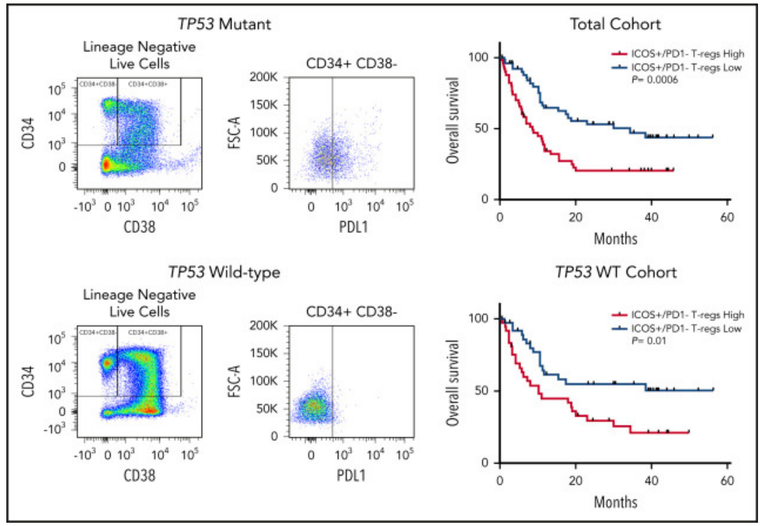


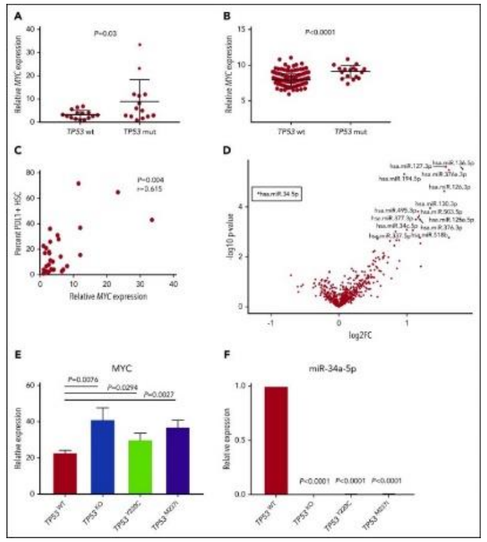






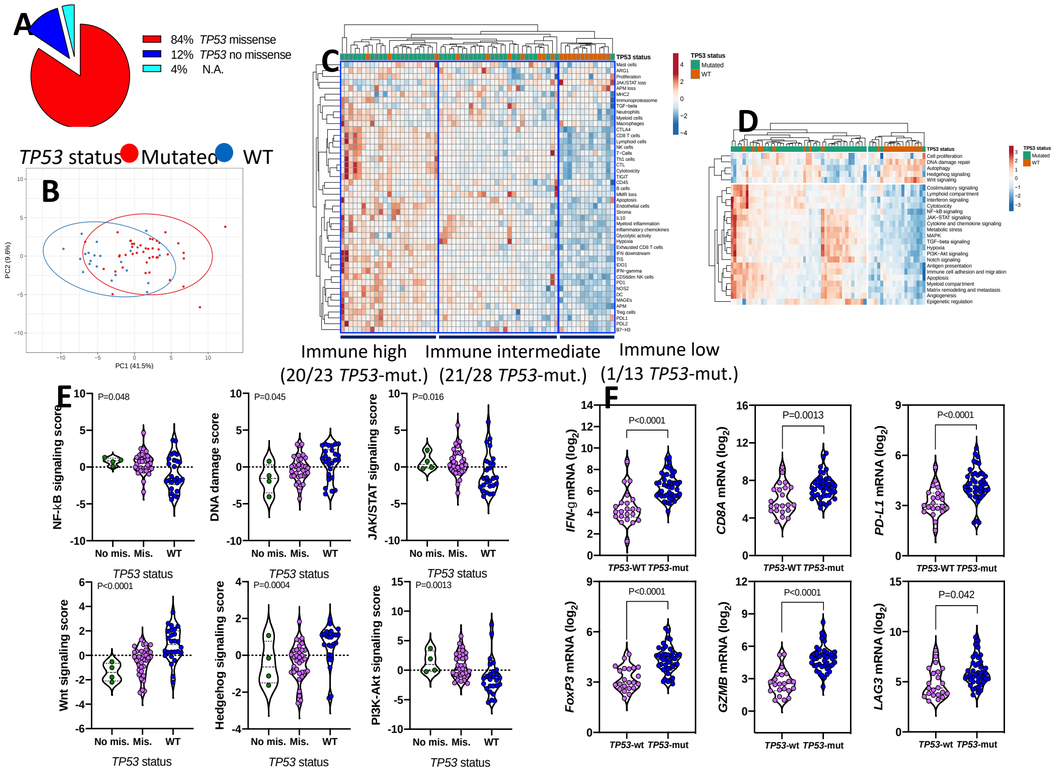
Vadakekolathu J . Blood Adv. 2020



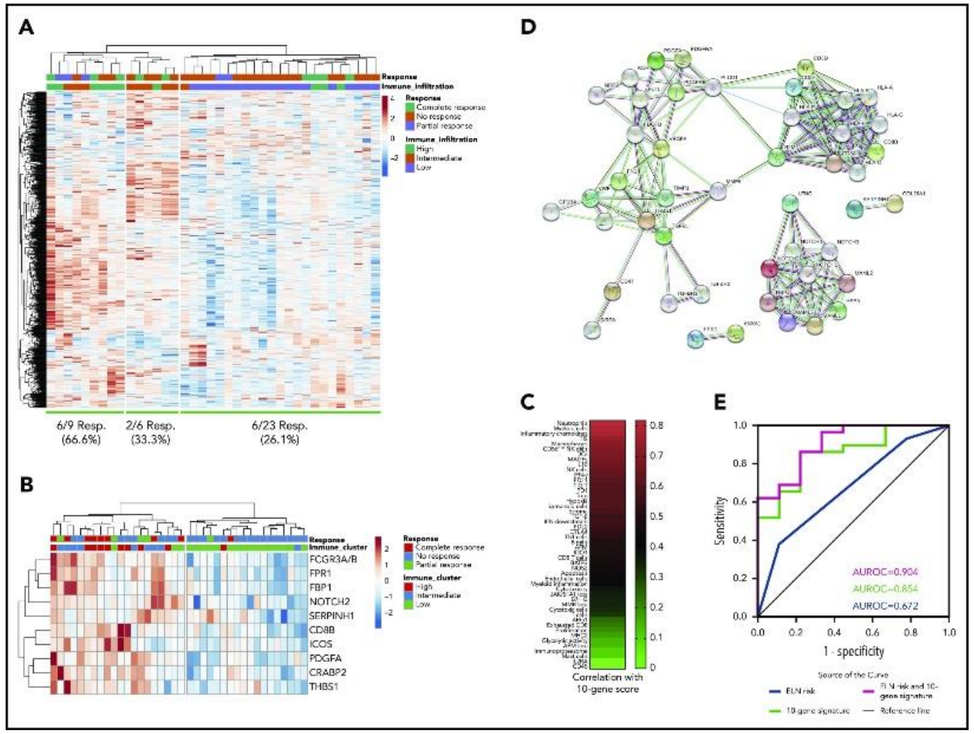


Sallman D et al,
Blood. 2020 10;136(24):2812-2823

TP53 abnormalities correlate with immune infiltration and associate with response to flotetuzumab immunotherapy in AML



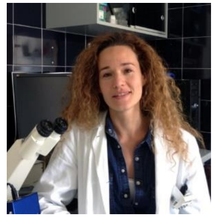
Vadakekolathu J et al, Blood Adv. 2020 Oct 27;4(20):5011-5024



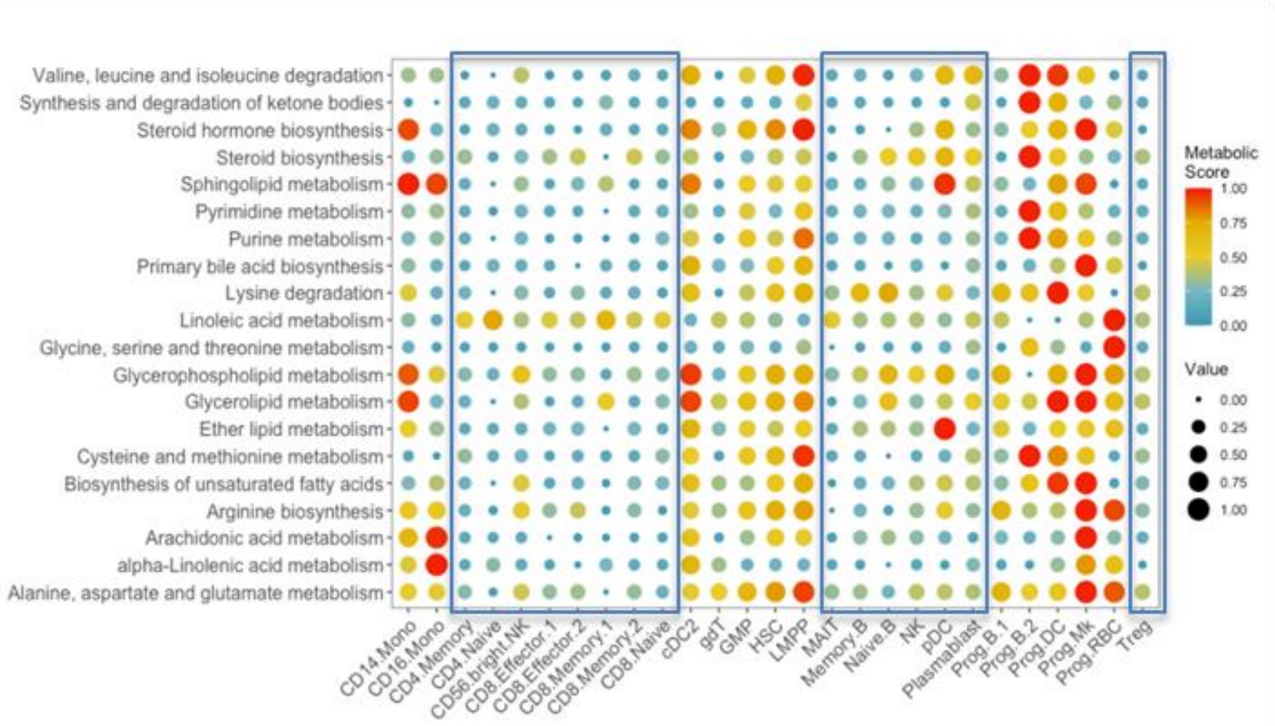
Uy GL et al, Blood. 2021 Feb 11; 137(6): 751–762.

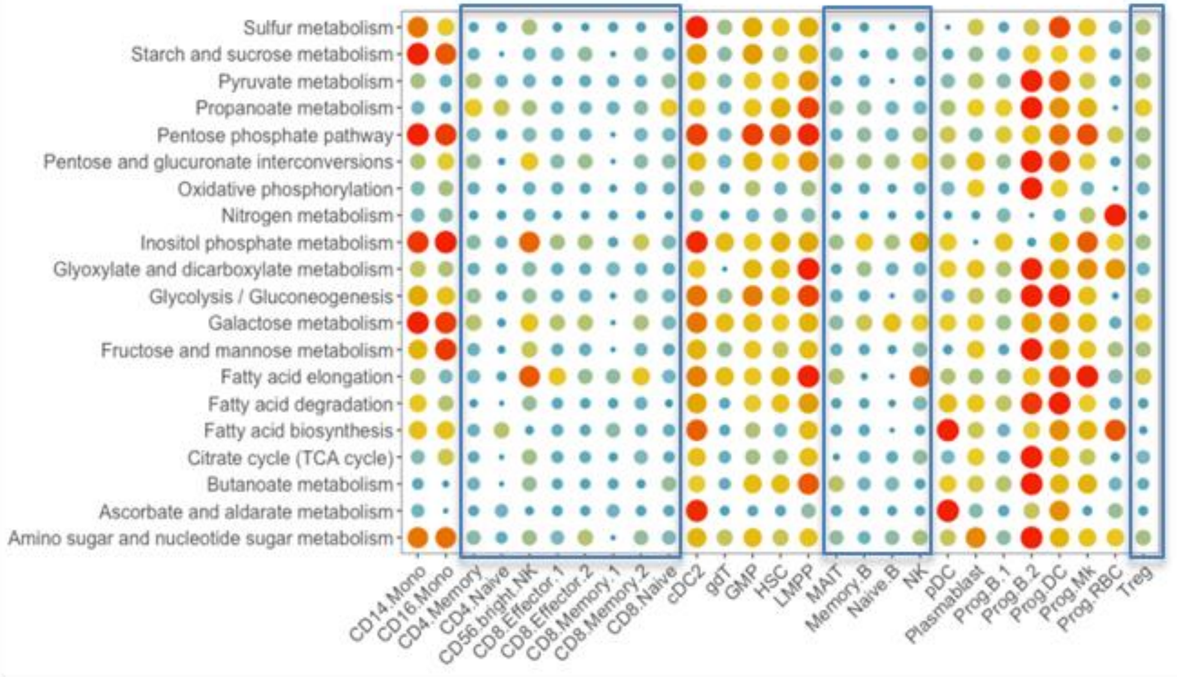
A 10-gene immune signature predicts response to flotetuzumab with greater accuracy than the ELN risk classifier.

The lymphoid compartment is “metabolically off" in TP53 mutant AML patients



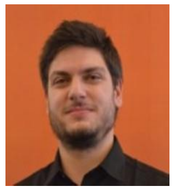
Valentina Salvestrini



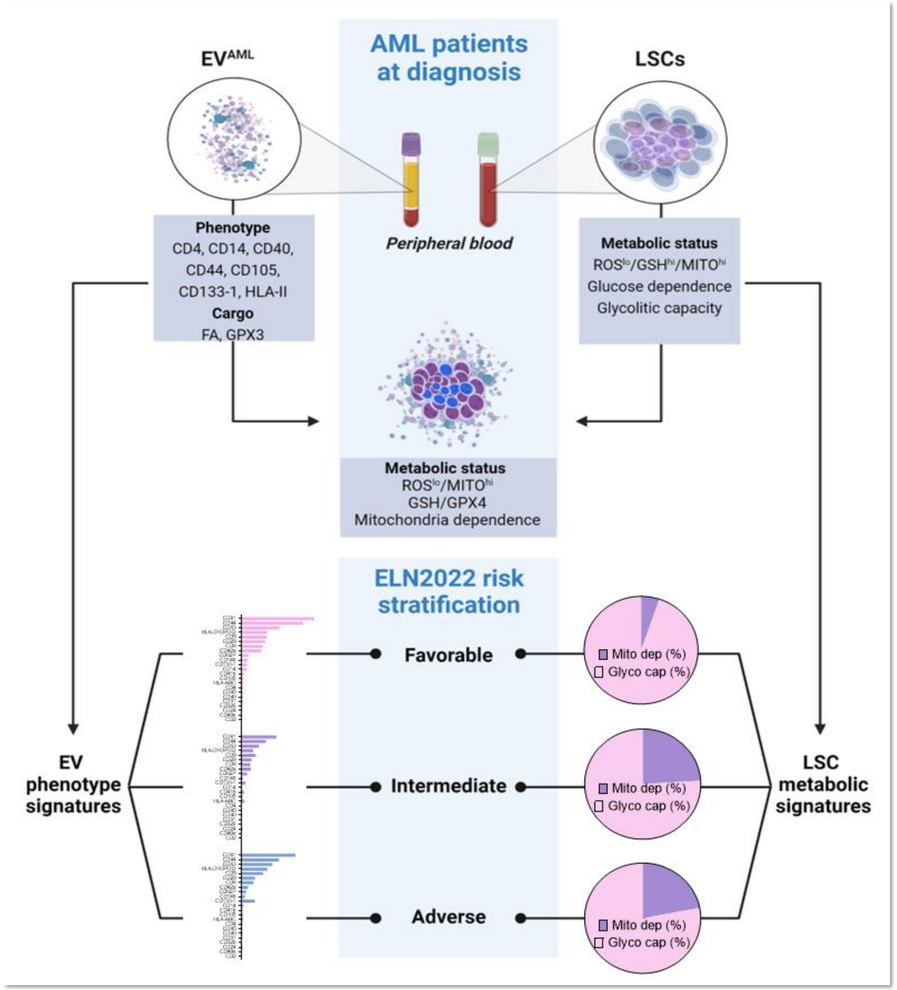


Salvestrini V et al. manuscript in preparation.

Parallel single-cell metabolic analysis and extracellular vesicle profiling reveal novel vulnerabilities with prognostic significance in acute myeloid leukemia



Dorian Forte



- ✓ AML CD34+ cells displayed low ROS levels with both high glutathione (GSH) levels and mitochondrial functionality
- ✓ AML CD34+ cells at diagnosis are highly dependent on glucose oxidation (contrary to immune cell subsets) and prone to exploit glycolysis for energy.
- ✓ The phenotype of circulating EVs from AML patients shows high expression for stem cell markers such as CD44 and CD133-1
- ✓ EVAML partially modulates the redox metabolism of CD34+ LSC-like cells through GSH/GPX4 axis
- ✓ Quantitative lipidomic analysis of EVs may support risk stratification for AML
- ✓ EVAML improve the engraftment of human cell line MOLM-13

Forte D et al, Nature Communications, in press

Conclusions

- There is no standard of care for AML evolving from MDS.
- The recurrent theme for secondary AML is the poor outcomes to available chemotherapy and the need to pursue HSCT for prolonged OS.
- Newer classification systems such as IPSS-M, ICC, and WHO 2022 have incorporated disease biology, specifically molecular information, into routine diagnostic, thus changing the way we look at this entity.
- Most of the available evidence for therapy consists of subset analyses, extrapolations of larger studies, and retrospective single institute experiences.
- Enrolling patients with the newly defined biological and clinical subsets in well-designed multi-center clinical trials should be prioritized and are essential to improving treatment outcomes.

Seragnoli Institute (Director: Prof. M. Cavo)
Acute Leukemia and MDS Group

Laboratory
Valentina Salvestrini
Marilena Ciciarello
Darina Ocadlikova
Dorian Forte
Karyna Volkava
Federico Pasini
Ismael Polanco Sanchez

Clinical Team
Stefania Paolini
Sarah Parisi
Cristina Papayannidis
Chiara Sartor
Gianluca Cristiano
Jacopo Nanni
Federico Zingarelli
Andrea Davide Romagnoli
Federica Ardizzoia
Caterina Azzimondi

Study coordinators
Miriam Fogli
Francesco Ingletto
Manuel Cella
Antonella Pagano
Ottavia Iotti

Collaborators:
Roberto Maria Pellegrino
(University of Perugia)

Sabina Sangaletti
Mario Colombo
(INT Milan)

Sharham Kordasti
King's College, London

Jayakumar Vadakekolathu,
Sergio Rutella
(Nottingham Trent University, UK)

Maura Rossi, Claudio Agostinelli, Elena Sabattini
(IRCCS AOU Bologna)

Francesco Fabbri, Giorgia Simonetti
(IRST Meldola)

ALMA IDEA Junior grant

ASH/Bigi memorial award 2019