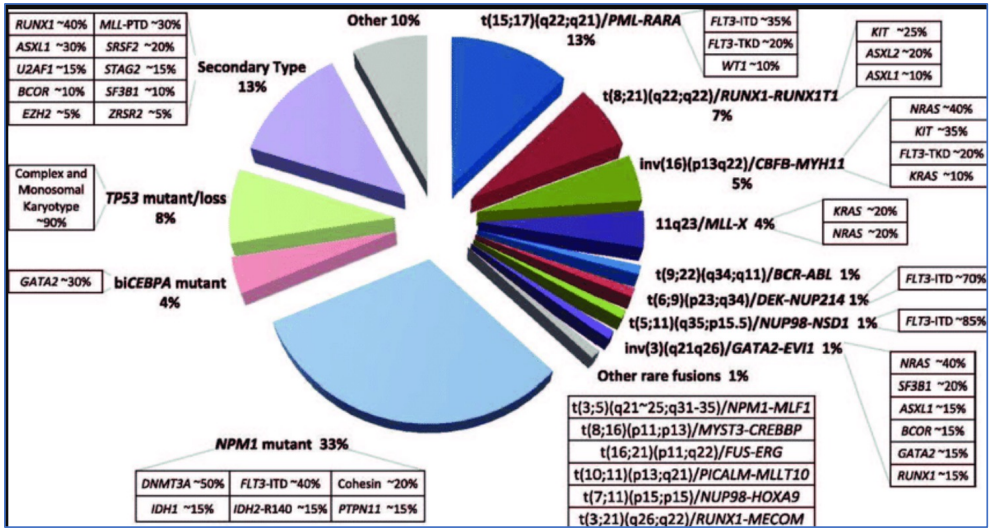
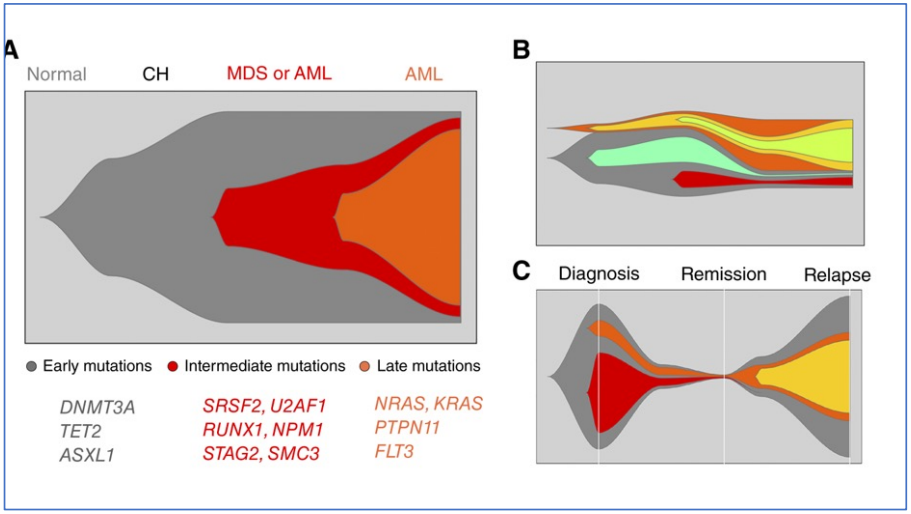
Highlights nella leucemia mieloide acuta

F. Ferrara (Napoli)

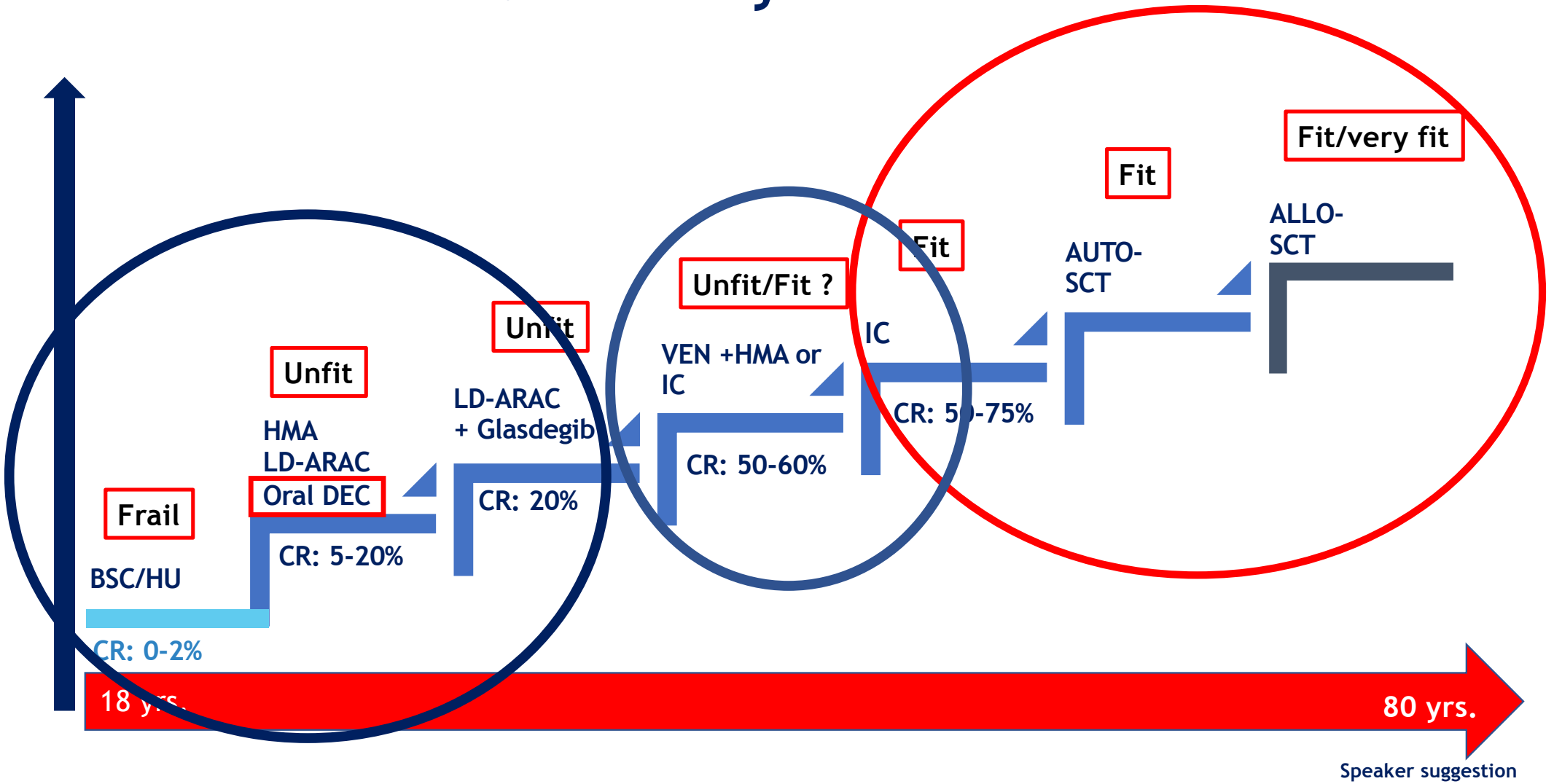
Molecular complexity of AML



Hierarchical complexity of AML

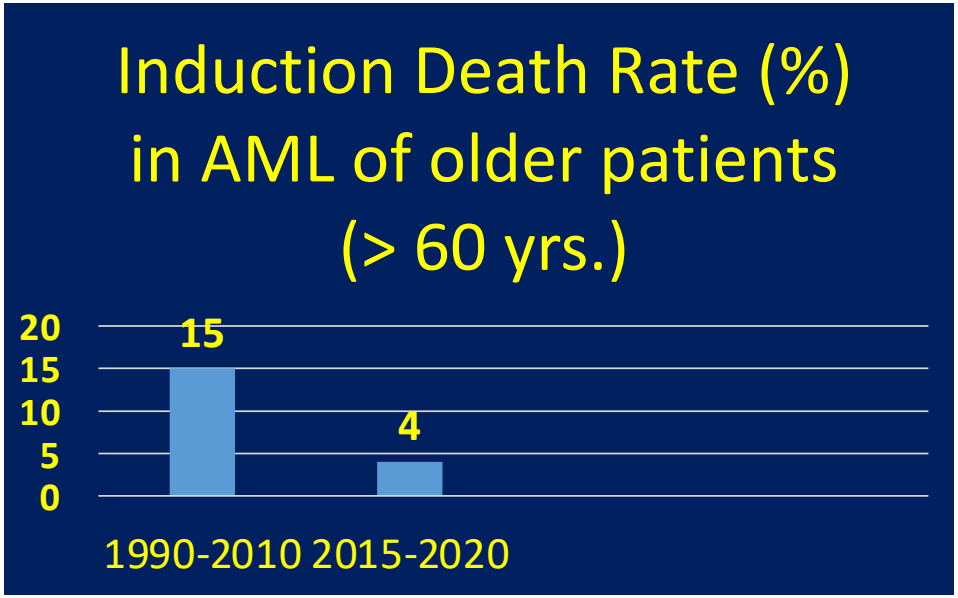


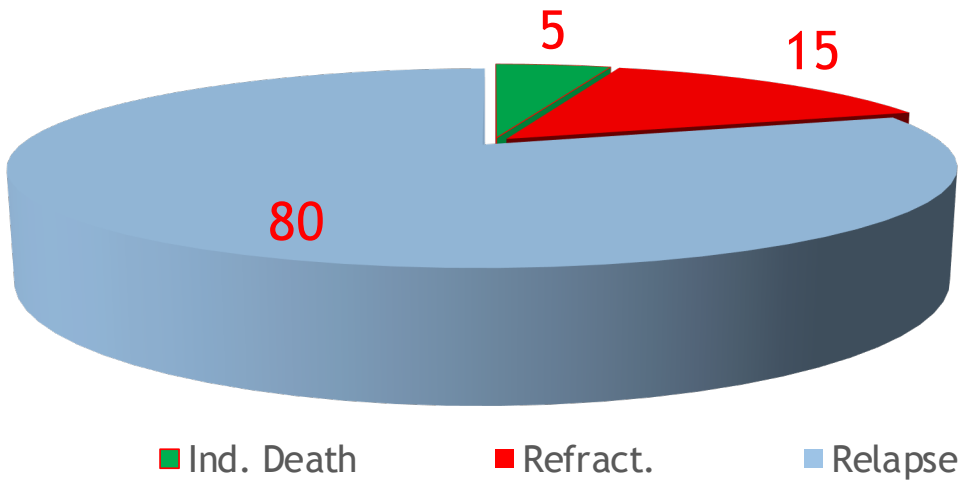
AML: intensity of treatment



Speaker suggestion

Failure in AML (%)





Better supportive care

Improved patients selection

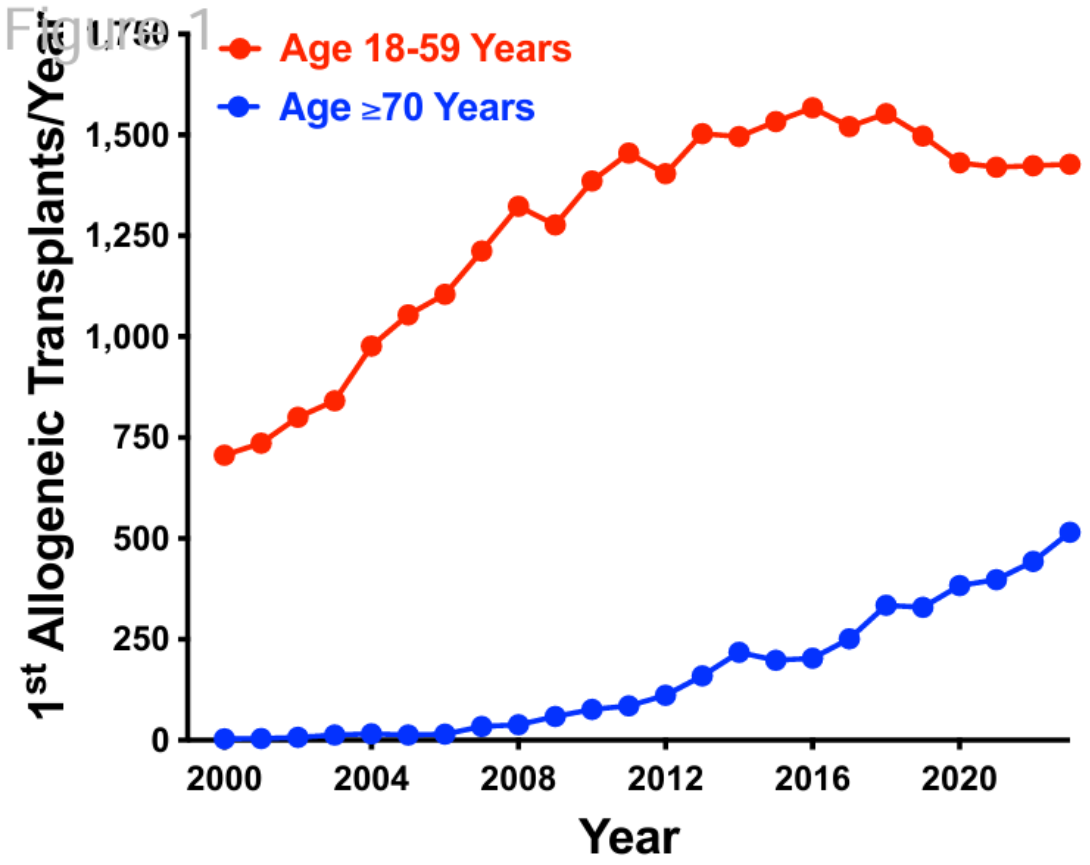
Speaker's experience

Outcomes with intensive treatment for acute myeloid leukemia: an analysis of two decades of data from the HARMONY Alliance

Characteristics	Total n=5359 (100%)	1997-2001 n=1127	2002-2006 n=1294	2007-2011 n=1821	2012-2016 n=1117	*p*
Age, median (range)	53 (18-85)	55 (17-84)	51 (15-85)	53 (16-86)	55 (17-85)	
<60 years, n (%) 60-69, n (%) ≥70 years, n (%)	3745 (69.8) 1229 (22.9) 385 (7.2)	689 (61.1) 307 (27.2) 131 (11.6)	1012 (78.2) 206 (16) 76 (5.8)	1312 (72) 403 (22.1) 106 (5.9)	732 (65.5) 313 (28) 72 (6.5)	< 0.0001 < 0.0001 < 0.0001
Intensive regimens <70 years ≥70 years	 4974 (92.82) 385 (7.18)	 996 (88.4) 131 (11.6)	 1218 (94.2) 76 (5.8)	 1715 (94.1) 106 (5.9)	 1045 (93.5) 72 (6.5)	 < 0.0001 < 0.0001
Early death ≤ 14 days ≤ 30 days ≤ 60 days	 96 (1.79%) 232 (4.33%) 435 (8.12%)	 34 (3.01%) 71 (6.3%) 147 (13.04%)	 22 (1.7%) 57 (4.4%) 105 (8.11%)	 31 (2.7%) 76 (4.17%) 130 (7.14%)	 9 (0.81%) 28 (2.5%) 53 (4.74%)	 0.0002 < 0.0001 < 0.0001

Sobas et al, Haematologica 2024

Annual number of HCTs in patients 70 years and older with AML



Walter RB et al Blood. 2024

Stratification of risk in AML

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]

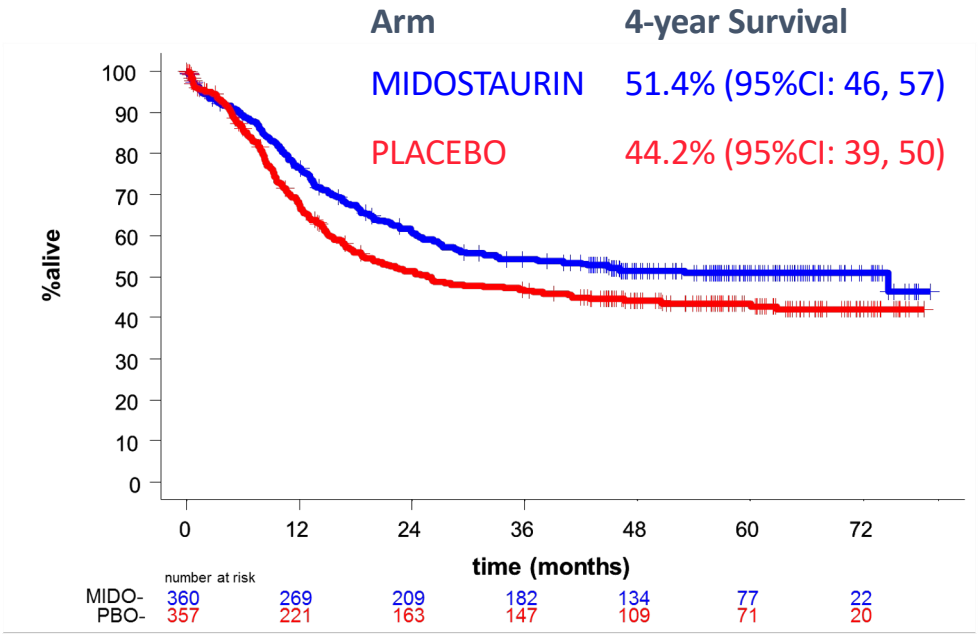
No allogenic transplant in CR1
Evaluate molecularly MRD

MRD oriented ?

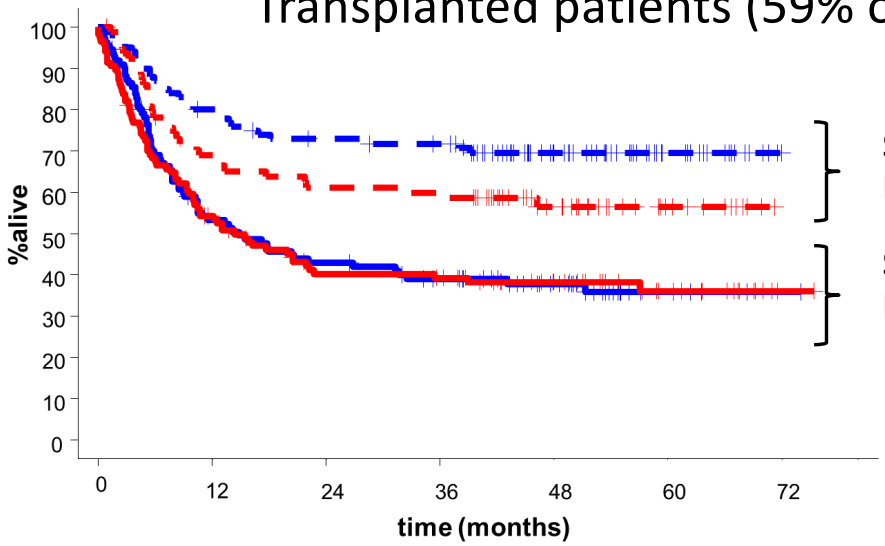
***Allogenic transplant* in CR1**
In adverse risk no role for MRD

Dohner H et al, Blood 2022

Survival on Midostaurin



Transplanted patients (59% of enrolled)



	MIDO (N=360)	PBO (N=357)	p *
CR by day 60	212 (59%)	191 (53%)	0.15
CR in induction/consolidation	239 (66%)	211 (59%)	0.045
Time to CR, median (range)	37 days (20-99)	36 days (20-112)	

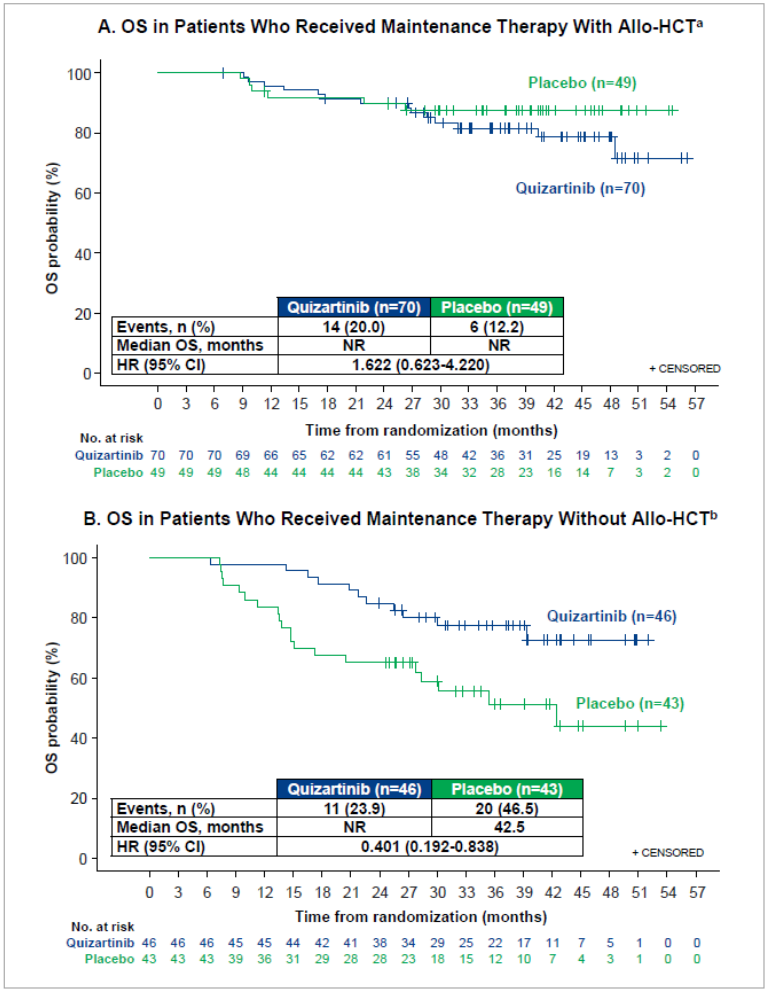
RATIFY/C10603

Stone RM, et al. *N Engl J Med.* 2017;377(5):454-464

Results: OS in Patients Who Received Maintenance by Allo-HCT and by Treatment Arm

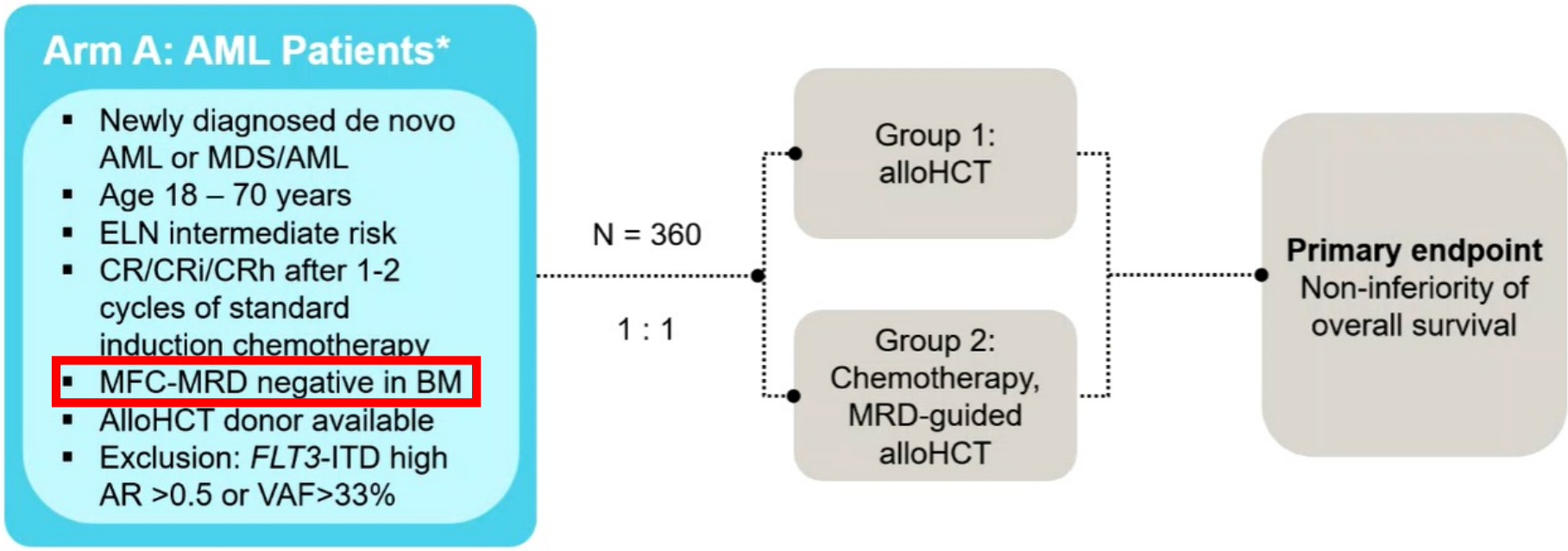
- Among 119 patients who underwent allo-HCT before receiving maintenance, a survival difference between arms was not demonstrated (**Figure 6A**)
  - The number of transplanted patients proceeding to maintenance was different between arms (71.4% with quizartinib vs 55.1% with placebo; **Figure 5**)
  - The number of OS events is limited, accounting for 16.8% of the 119 patients
  - The 95% CI of the HR is wide (at 0.623-4.220)
- Among 89 patients who received maintenance without prior allo-HCT, quizartinib provided an OS benefit over placebo with a 60% reduction in the risk of death (**Figure 6B**)
  - The number of patients in the 2 arms was similar, with a similar proportion of patients without allo-HCT in both arms proceeding to maintenance (**Figure 5**), and the number of OS events accounts for 34.8% of the 89 patients (**Figure 6B**)

Figure 6. OS in Patients Who Received Maintenance by Allo-HCT and by Treatment Arm



[a]Includes protocol-specified allo-HCT. [b]There were 6 patients who underwent allo-HCT during maintenance (4 in the quizartinib arm and 2 in the placebo arm); these 6 patients are included in this plot.
Allo-HCT, allogeneic hematopoietic cell transplantation; CI, confidence interval; HR, hazard ratio; NE, not estimable; No, number; NR, not reached; OS, overall survival.

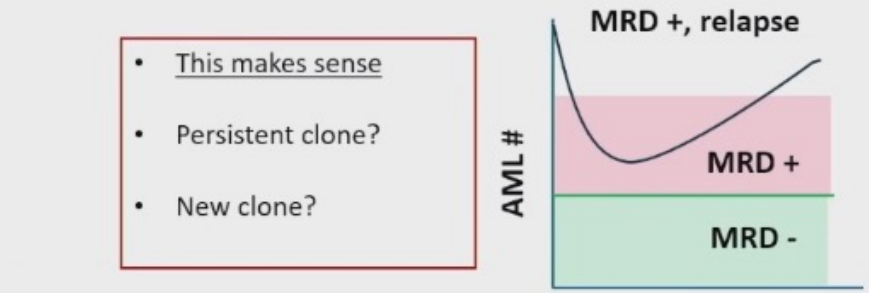
Randomized trial of chemo vs alloHCT in MRD negative ELN intermediate risk patients: RESOLVE trial



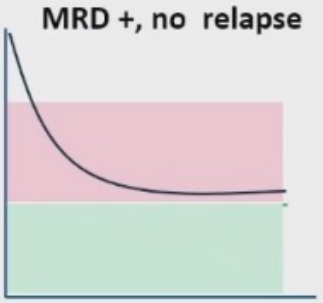
*only key inclusion criteria are shown, refer to the protocol for the full list of in- and exclusion criteria

Resolve MRD guided treatment
Funded by the European Union
MHH Hannover Medical School

Four possible states of MRD and relapse

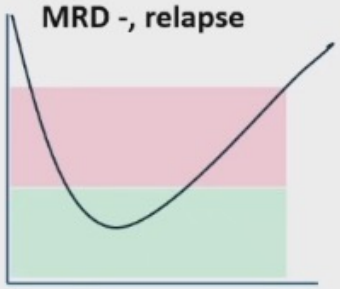


- This makes sense
- Persistent clone?
- New clone?

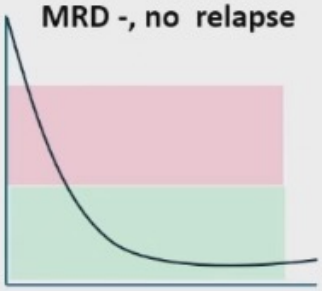


- Some clones more" tolerable?"
- Persistence of "CHIP" mutations?
- Mutation in lymphoid lineage?
- GVL?

AML #



- Need a better test?
- Clonal evolution and loss of markers?
- New clone?

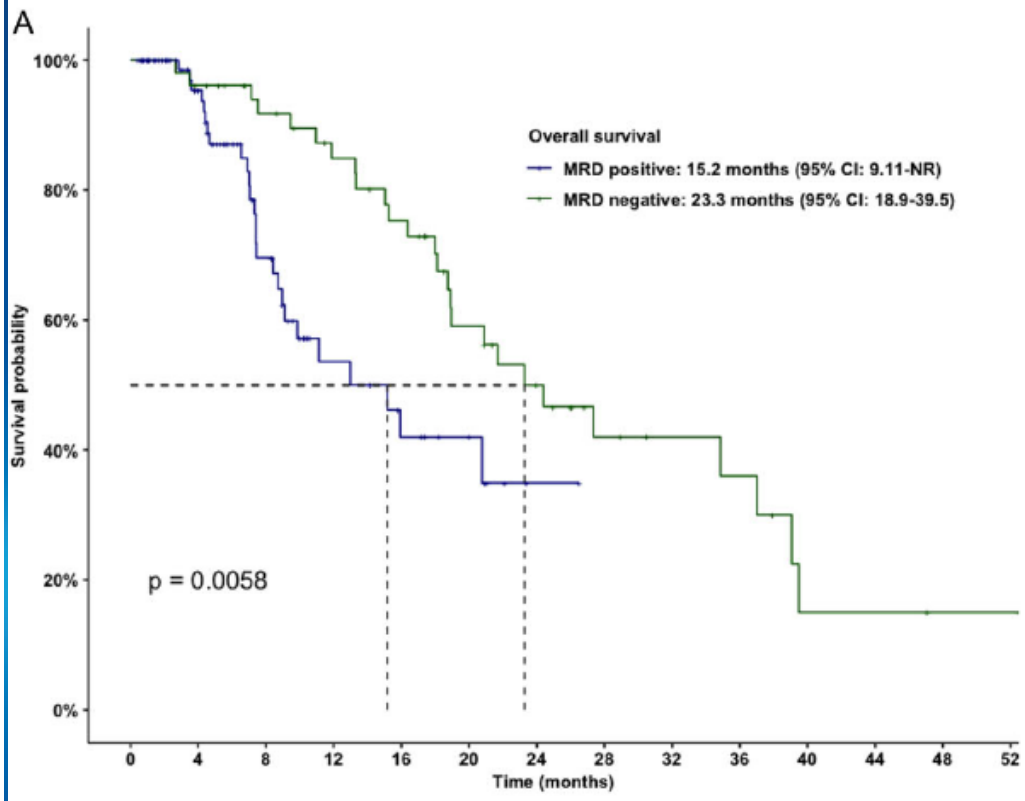


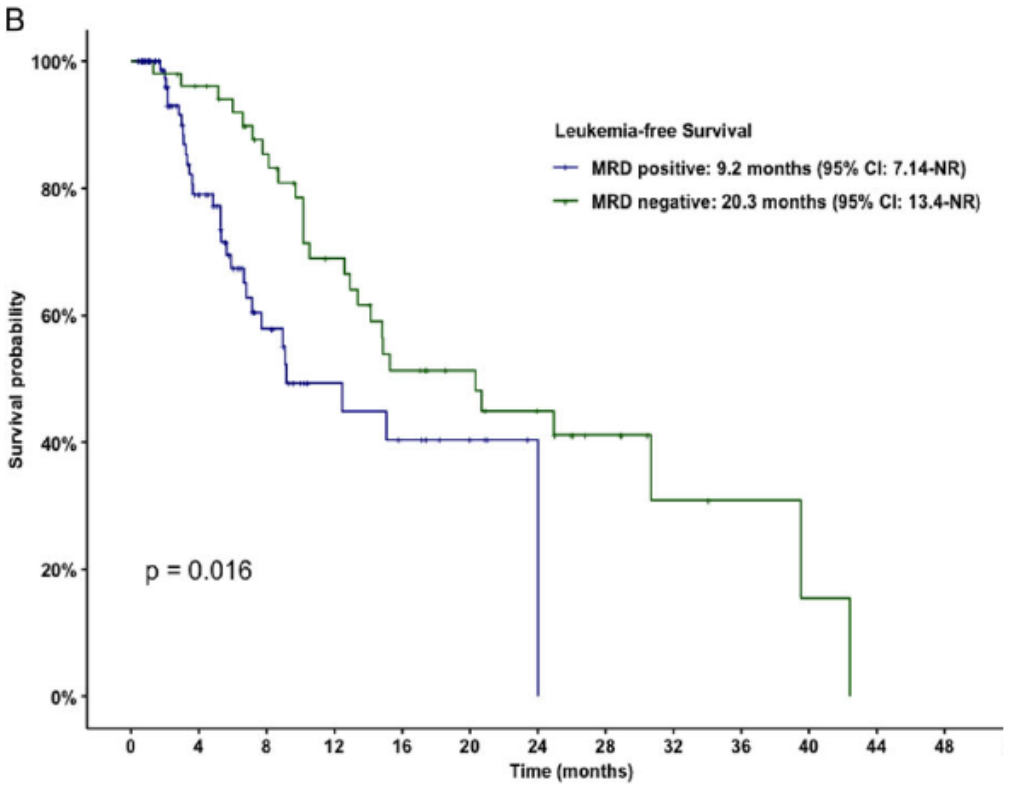
- This makes sense

TIME

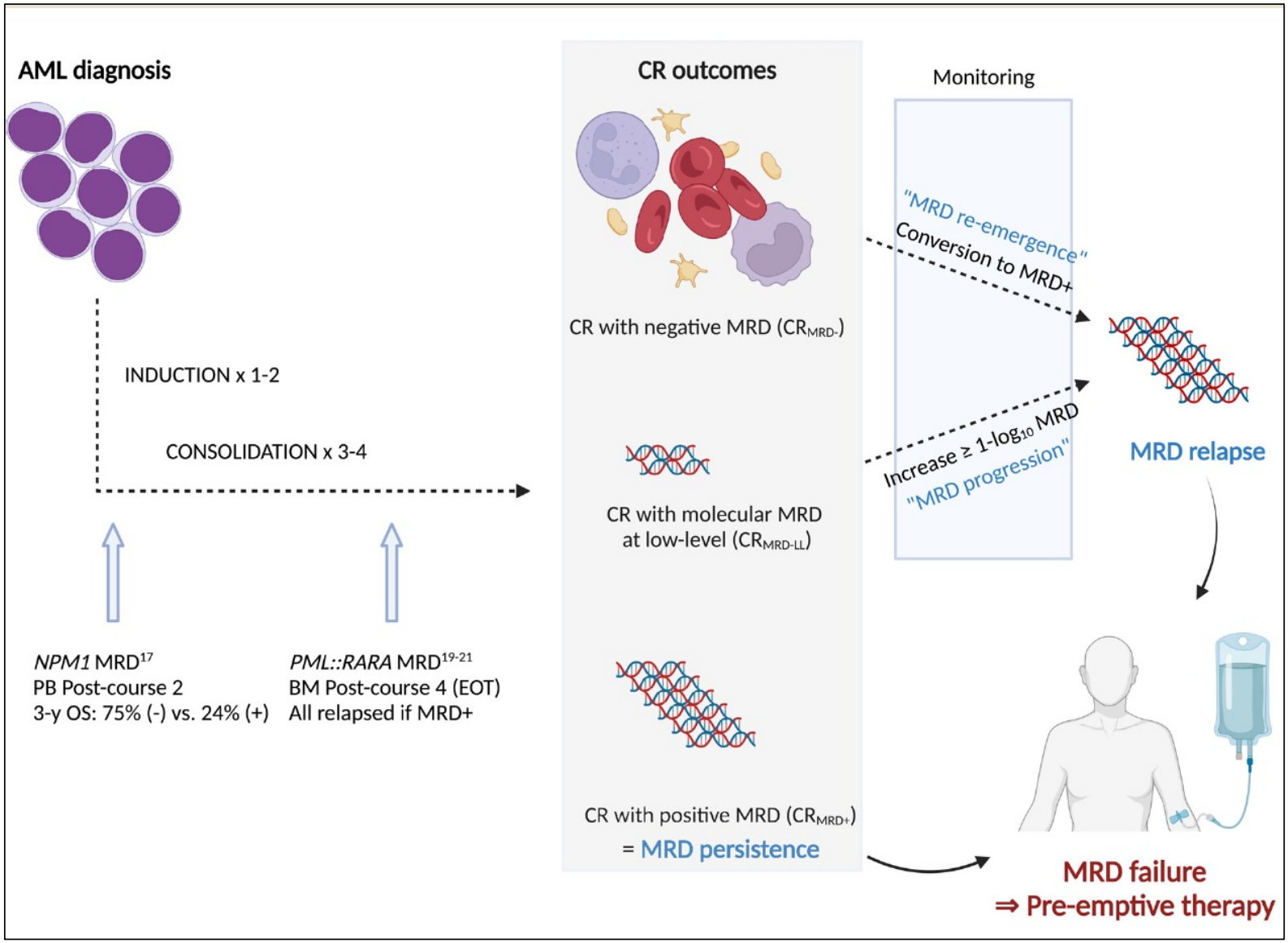
VEN/HMA treatment

Correspondence

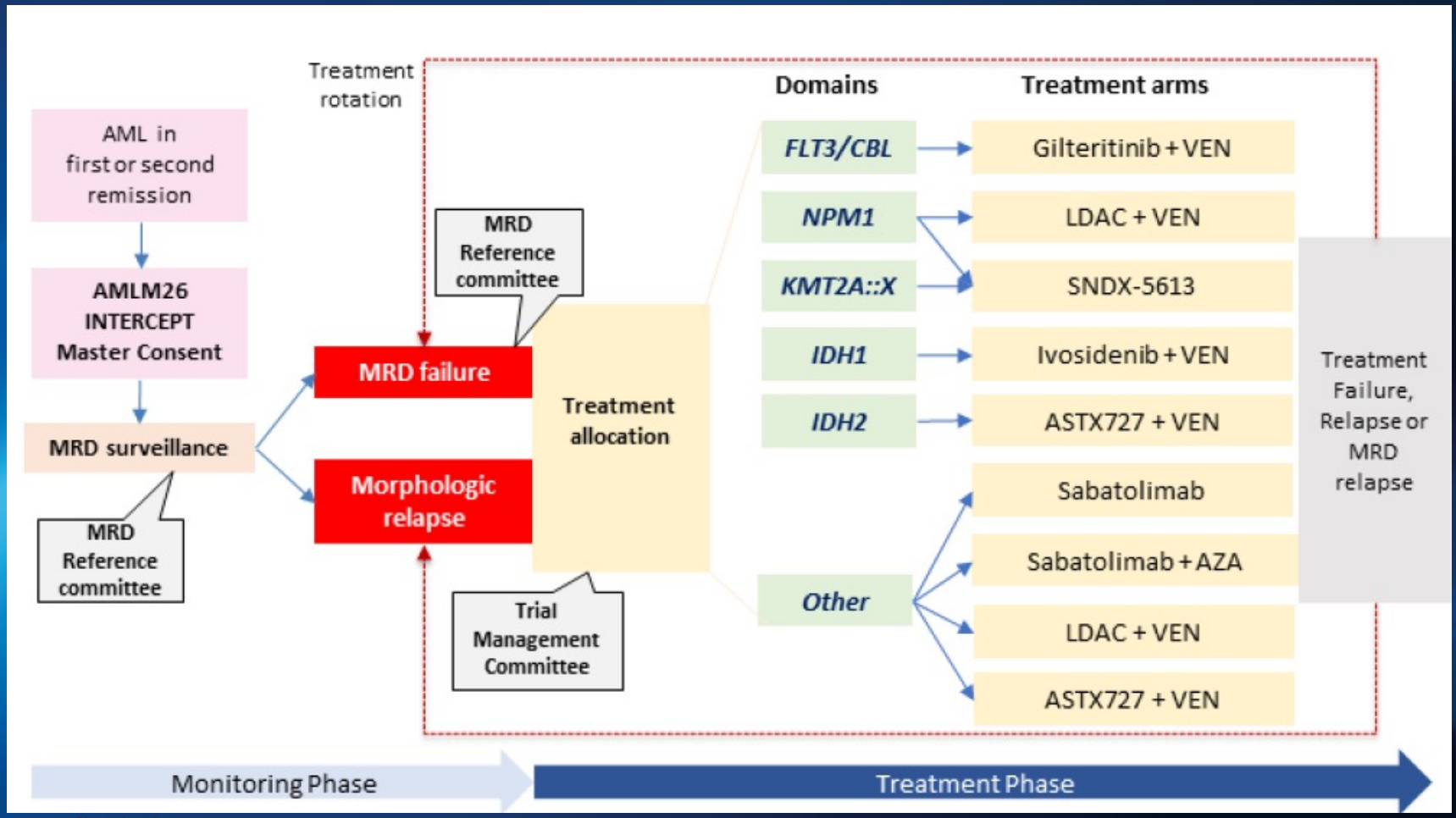




Jimenez-Vicente et al, BCJ, 2025

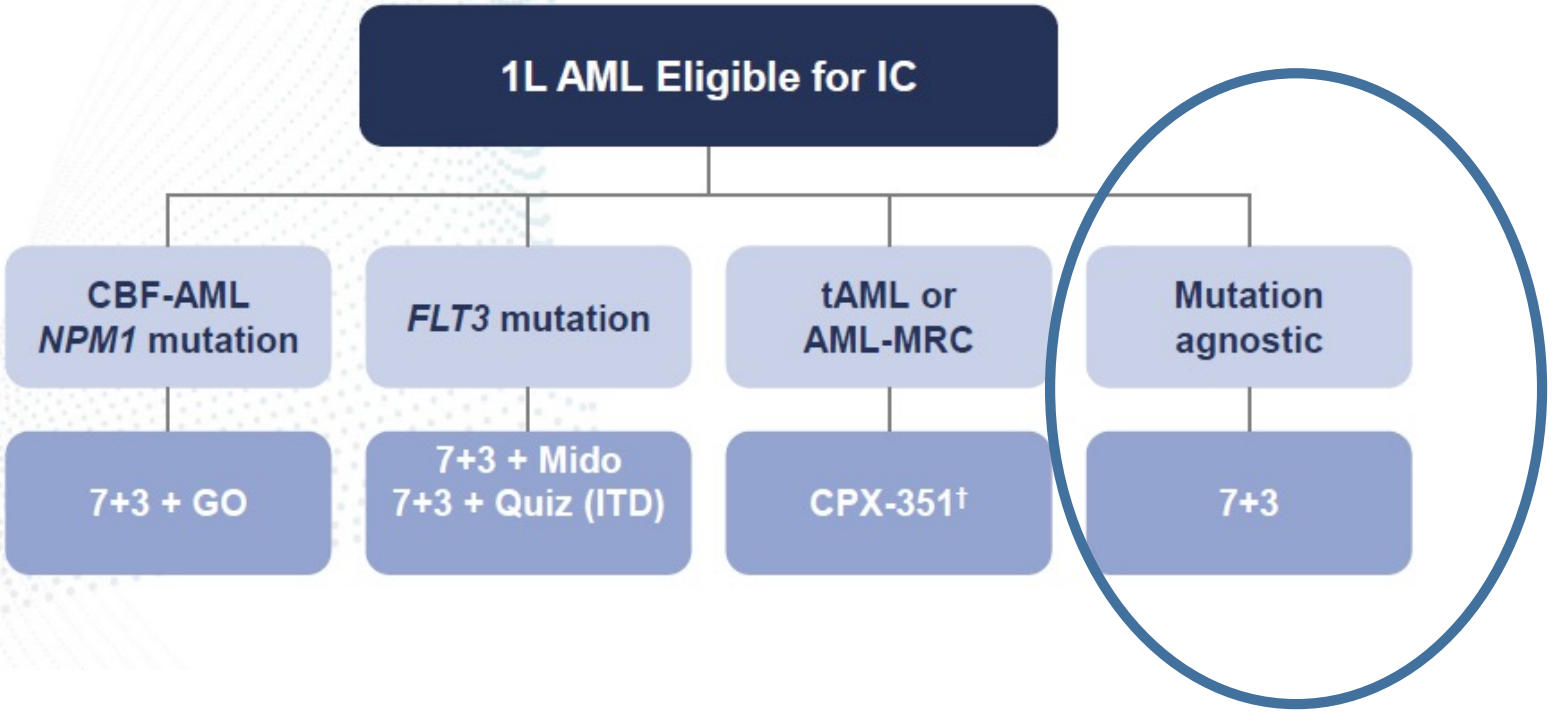

AML diagnosis
INDUCTION x 1-2
CONSOLIDATION x 3-4
NPM1 MRD[17]
PB Post-course 2
3-y OS: 75% (-) vs. 24% (+)
PML::RARA MRD[19-21]
BM Post-course 4 (EOT)
All relapsed if MRD+
CR outcomes
CR with negative MRD (CR_{MRD-})
CR with molecular MRD at low-level (CR_{MRD-LL})
CR with positive MRD (CR_{MRD+})
= MRD persistence
Monitoring
"MRD re-emergence"
Conversion to MRD+
Increase ≥ 1-log_{10} MRD
"MRD progression"
MRD relapse
MRD failure
⇒ Pre-emptive therapy

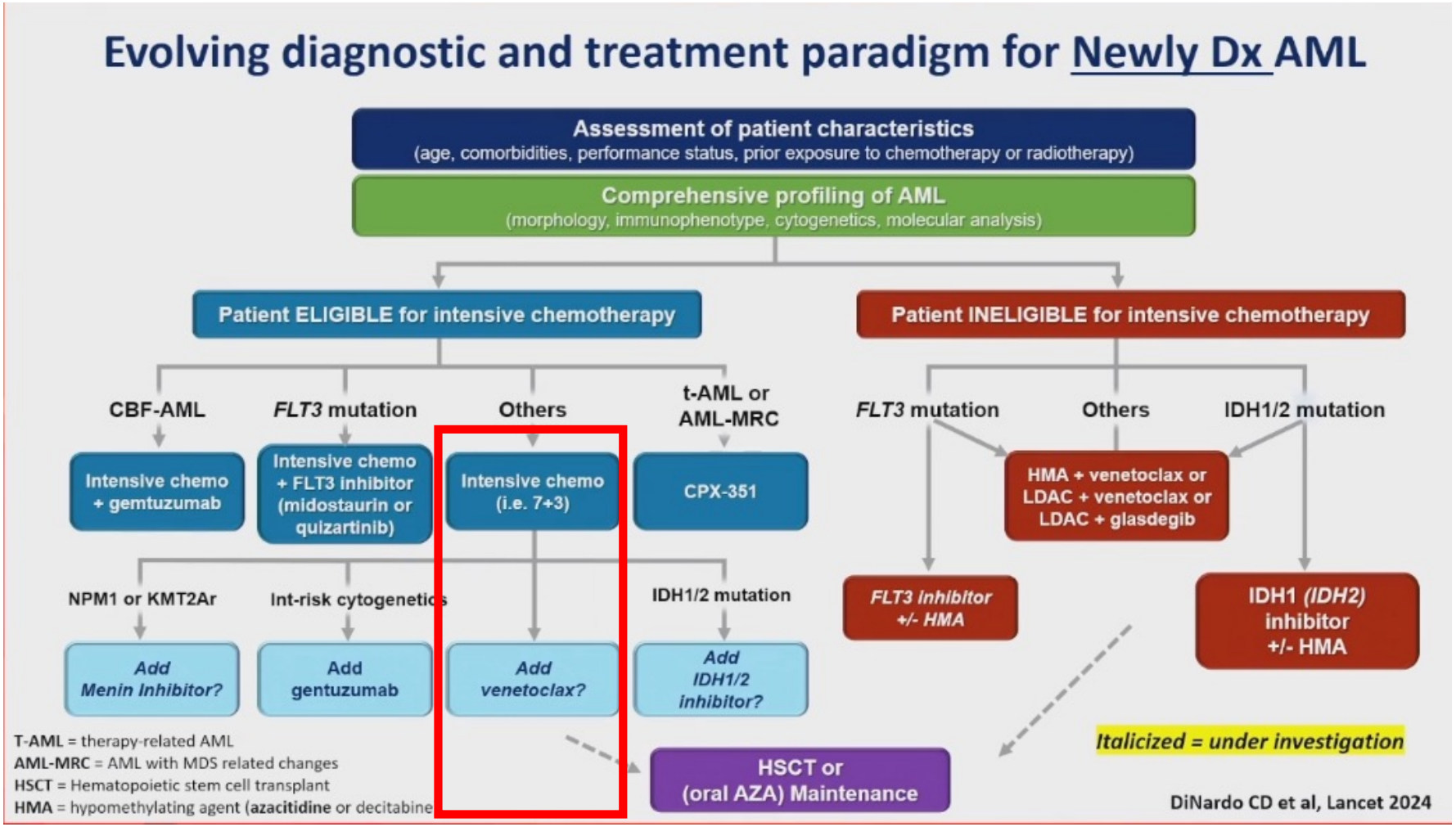
AMLM26 INTERCEPT for MRD-directed therapy in AML.



Si precisa che è rimborsata dal SSN la sola combinazione venetoclax+azacitidina in pazienti affetti da AML non precedentemente trattati,non eleggibili a chemioterapia intensiva;sabatolimab non è approavto per il trattamendo della LMA; in italia gli inibiori della menina non sono approvati pe ril trattamento della LAM;in Italia è rimborsata dal SSN la sola combinazione ivosidenib+azacitidina per i pazienti affetti da AML non precedentemente trattata,non elegibili a chemioterapia intensiva

Induction options





Si precisa che in italia gli inibitori della menina non sono approvati per il trattamento della AML RR;in Italia è rimborsata dal SSN la sola combinazione ivosidenib+azacitidina per i pazienti affetti da AML non precedentemente trattata,non elegibili a chemioterapia intensiva; in Italia è rimborsata dal SSN la sola combinazione venetoclax+azacitidina in pazienti affetti da AML non precedentemente trattati,non eleggibili a chemioterapia intensiva

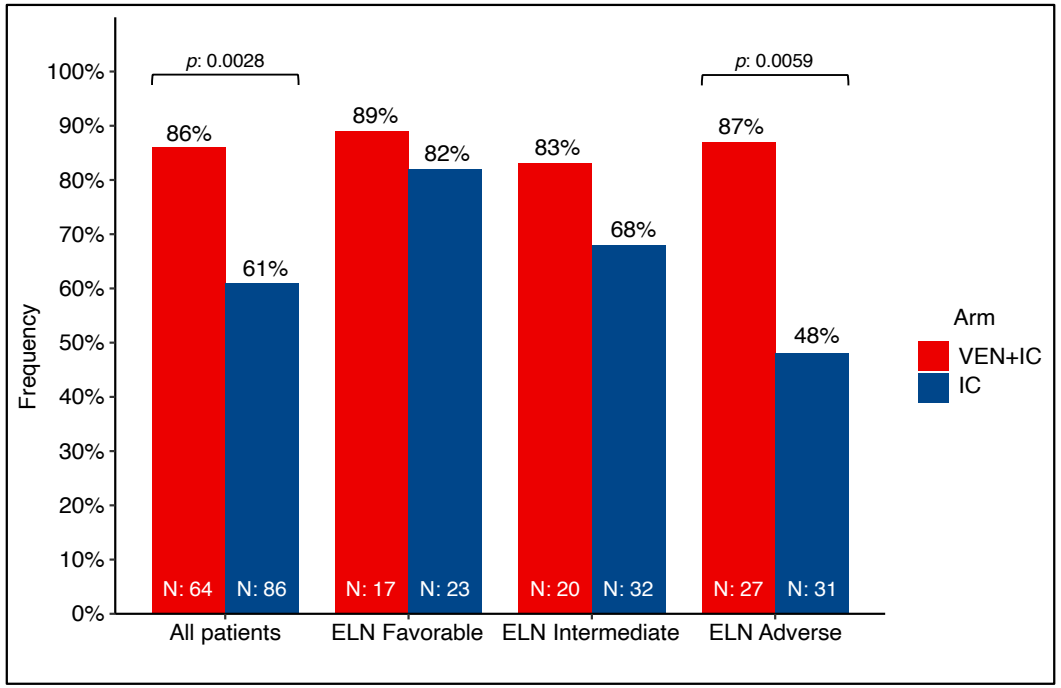
.

VEN + IC in AML: MRD-Negative Response Rates and SCT Rates

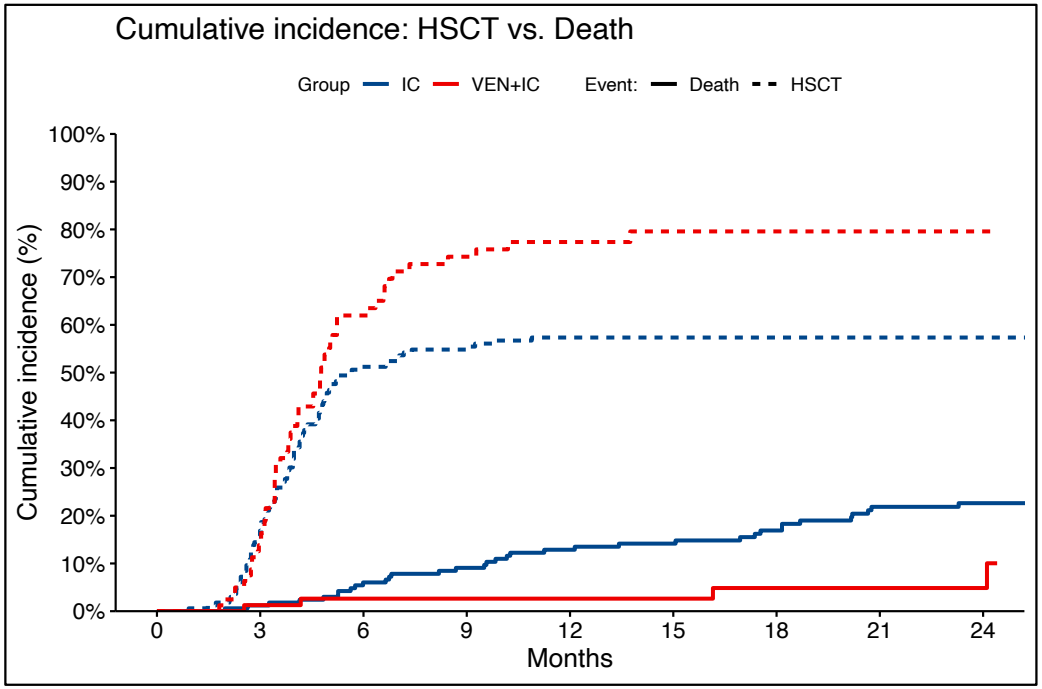
VEN + IC compared with IC resulted in
- **Earlier responses**
- **Increased overall response rate**
- **Increase in MRD-negative CR rates**
- **Increase in MRD-negative CR rates in ELN adverse risk**

VEN + IC compared with IC resulted in increased alloHSCT incidence and lower incidence of death
- **AlloHSCT VEN + IC 79% vs IC 57%; *P* = .012**
- **Early death VEN + IC 5% vs IC 26%; *P* = .018**

MRD-Negative Response Rates Between Cohorts



AlloHSCT Rates Between Cohorts



Lachowiez CA, et al. *Lancet Haematol*. 2022;9:e350-e360.

Final Analysis for the Primary End-Point of Gimema AML1718, 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

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

Marconi G, et al.

ASH 2023

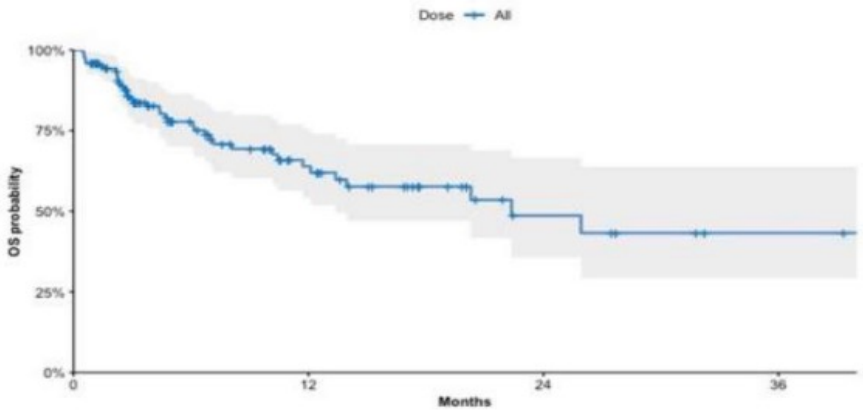
- 124 patients, median age 55 yrs (18-66)
- ELN 2017 : 67 patients (54%) INTERMEDIATE, 57 patients (46%) HIGH-RISK
- Median OS was 22.4 months (95% confidence interval [C.I.] 13.4 months - not reached, Figure 1), with a 12-month OS probability of 64%
- With a median follow-up of 10 months, 60 patients (49%) underwent (HSCT) in CR, and 1 patient underwent HSCT in partial remission.

Table 1: Response assesment after 1 induction with V-FLAI

	Arm			
Characteristic	Overall, N = 124	SRI-C1+P1-C1 VEN 400mg, N = 28	SRI-C2+P1-C2 VEN 600mg, N = 29	Part 2 VEN 400mg, N=67
CR	80 (64.5%)	15 (53.6%)	23 (79.3%)	42 (62.7%)
CRp	7 (5.6%)	5 (17.9%)	1 (3.5%)	1 (1.5%)
CRi	6 (4.8%)	1 (3.6%)	1 (3.5%)	4 (6.0%)
PR	7 (5.6%)	3 (10.7%)	1[1] (3.5%)	3 (4.5%)
SD[2]	12 (9.7%)	2 (7.1%)	2 (7.0 %)	8 (12.0%)
Not tested	12 (9.7%)	2 (7.1%)	1 (3.5%)	9 (13.4%)
CRR	**93 (74.9%)**	**21 (75%)**	**25 (86.2%)**	**47 (70.0%)**

[1] 1 patient obtained PR after 1st induction and CR after 2nd V-FLAI
[2] 4 patietns died before C1D28 and are counted as within SD
SRI-C1: safety run-in cohort 1; SRI-C2: safety run-in cohort 2; P1-C1: part 1 cohort 1; P1-C2: part 1 cohort 2; 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 (CR+CRp+CRi).

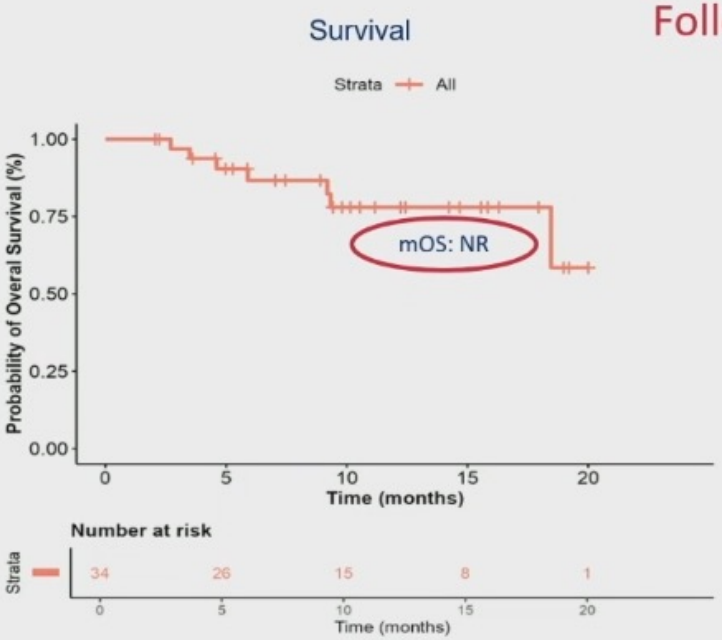
Figure 1: overall survival probability

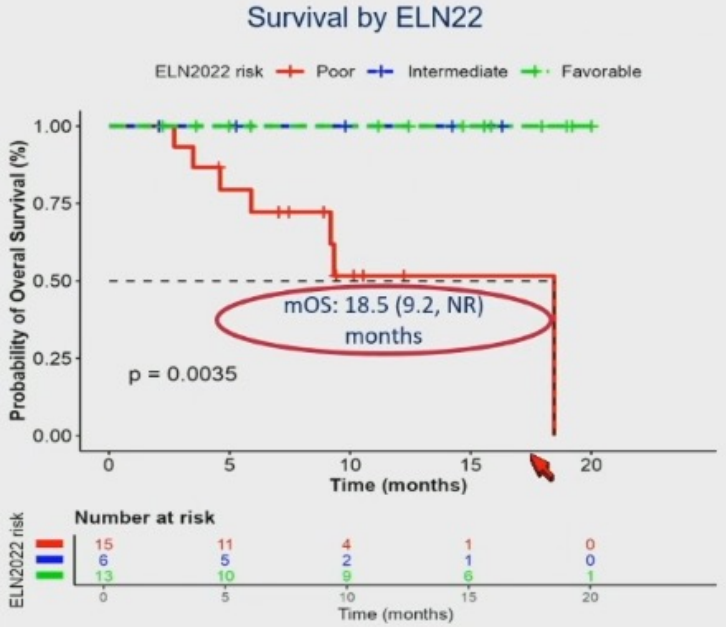


Blood (2023) 142 (Supplement 1): 1536

3 + 7 + VEN

Follow-up





- With a median follow-up time of 9.6 (2-20) months:
  - median DoR, EFS (mEFS) and OS (mOS) were not reached
- 10 pts (29%) have undergone transplant in CR1
- At DOC 27/29 responding pts (93%) were alive and 22/29 (76%) remained in continuous MRD-neg CR

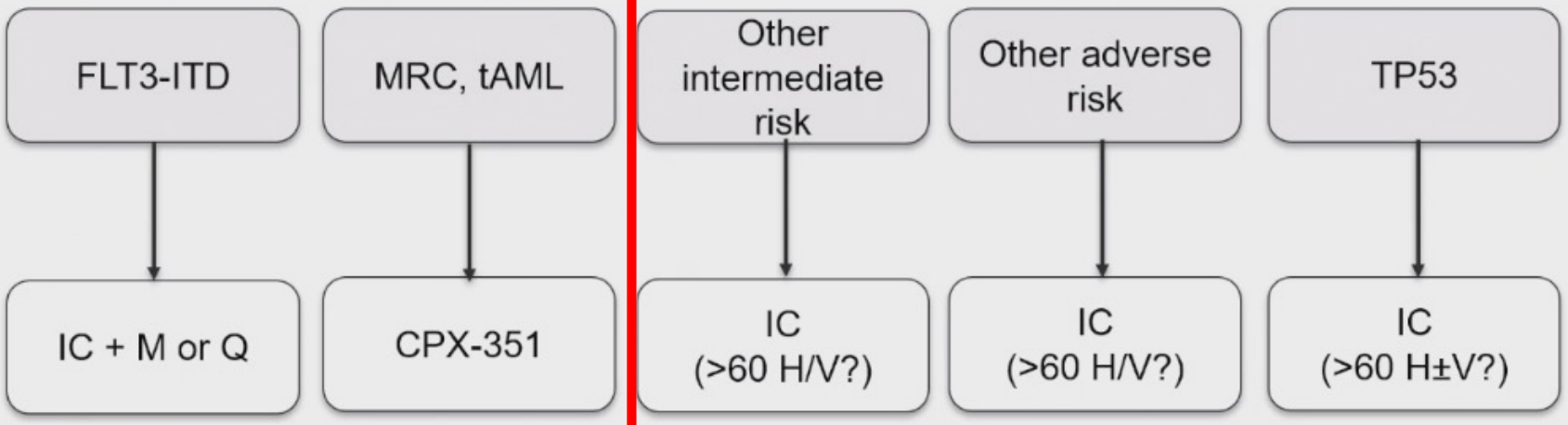
American Society *of* Hematology

Mantzaris et al, ASH, 2024

Intensive induction regimens

Regimen name	Backbone	Venetoclax target dose	Venetoclax duration	Notes
5+2 + VEN	Cytarabine 100 mg/m^2 days 1–5 Idarubicin 12 mg/m^2 days 2–3	Venetoclax 50–600 mg	Days –6–7	Ramp up to goal dose over days –6 to 0, continue at goal days 1–7
7+3 + VEN	Cytarabine 100 mg/m^2 days 1–7 Daunorubicin 60 mg/m^2 days 1–3	Venetoclax 400 mg	Days 4–11	Ramp up: 100 mg day 4 200 mg day 5, 400 mg days 6–11
CPX-351 + VEN	Cytarabine 100 mg/m^2 days 1, 3, and 5 Daunorubicin 44 mg/m^2 days 1, 3, and 5	Venetoclax 300 mg	Days 2–8	
FLAG-Ida + VEN	Fludarabine 30 mg/m^2 days 2–6 Cytarabine 1.5 g/m^2 days 2–6 Idarubicin 8 mg/m^2 for ND or 6 mg/m^2 for R/R days 4–6 G-CSF 5 µg/kg days 1–7	Venetoclax 400 mg	Days 1–7	
CLIA + VEN	Cladribine 5 mg/m^2 days 1–5 Cytarabine 1.5 g/m^2 for age <60 or 1 g/m^2 for age 60 years or greater days 1–5 Idarubicin 10 mg/m^2 days 1–3	Venetoclax 400 mg	Days 2–8	Idarubicin reduced to 2 days for age >60

Induction treatment for ELN intermediate and adverse risk patients



ITD – internal tandem duplication
MRC – myelodysplasia-related changes
tAML – therapy-related AML

IC – intensive chemotherapy (e.g. daunorubicin or idarubicin, cytarabine, ± fludarabine/cladribine
M – midostaurin
Q – quizartinib
H/V – Hypomethylating agent/venetoclax

Si precisa che è rimborsata dal SSN la sola combinazione venetoclax+azacitidina in pazienti affetti da AML non precedentemente trattati,non eleggibili a chemioterapia intensiva

ASSESSING ROLE OF COMORBIDITIES IN TREATMENT SELECTION FOR OLDER PATIENTS WITH ACUTE MYELOID LEUKEMIA

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1. NewYork-Presbyterian/Weill Cornell Medical Center, New York, New York

Weill Cornell Medicine

AIM

We aimed to investigate comorbidities in older AML patients to understand whether clinical decisions in treatment choice (IC with CPX-351 or 7+3 vs non-IC with HMA+V) and transplant decision correlated with FS and HCT-CI, respectively.

METHODS

- This is a multicenter retrospective study drawing from 4 U.S. academic medical centers (Weill Cornell, Moffitt, MSKCC, Northwestern).
- Eligibility included pts aged 60-75 who received CPX-351, 7+3 (both IC), or HMA+V (non-IC) as frontline treatment for AML from 2013-2022.
- The Ferrara score was assessed prior to induction Rx and HCT-CI post-induction, prior to possible transplant.
- To evaluate the association between individual Ferrara criteria and selection of frontline AML Rx, the chi-square or Fisher's exact test were used, and Wilcoxon rank-sum test was performed on total HCT-CI score for transplant decision.
- For the primary (binary) outcome variable of selection status of frontline AML Rx, multivariable logistic regression analysis was performed to evaluate the effect of FS on selection of frontline AML Rx.
- Survival analyses were conducted using the Kaplan-Meier method. Only patients with higher risk disease receiving upfront CPX-351 or HMA-V were included in this analysis. Survival probabilities were compared using log-rank tests.

Table 1: Baseline patient characteristics.

	IC N = 191	HMA-V N = 98	P value
Male, n (%)	109 (57.1)	58 (59.2)	0.73
Median age (range)	67.2 (64.0-71.3)	70.2 (67.4-72.6)	**<0.001**
CHF with EF<50%, n (%)	3 (1.57)	7 (7.22)	**0.03**
Pulmonary disease, n (%)	5 (2.62)	13 (13.3)	**<0.001**
On hemodialysis and >60 years old or uncontrolled renal neoplasm	0 (0)	0 (0)	N/A
Liver disease	1 (0.52)	0 (0)	1.00
Active resistant infection at time of AML diagnosis, n (%)	2 (1.05)	5 (5.10)	**0.04**
Psychiatric illness	1 (0.52)	0 (0)	1.00
ECOG ≥ 3	2 (1.05)	5 (5.10)	**0.04**
Ferrara scores			
0	177 (92.7)	71 (74.0)	**<0.001**
1-2	14 (7.33)	25 (26.0)	**<0.001**
Adverse 2017 ELN risk	93 (49.0)	76 (77.6)	**<0.001**
Prior myeloid malignancy	107 (56.0)	59 (60.2)	0.50
Prior HMA Treatment	34 (17.8)	11 (11.2)	0.31

Patients who received HMA-V were more likely to be older, have higher Ferrara scores, and have CHF, pulmonary disease, active infection, higher ECOG, and adverse ELN risk.

Table 2: Ferrara score and its components predicted likelihood of receiving lower intensity treatment.

Variable	OR	95% CI	P value
Ferrara score 1-2 vs 0	4.45	2.19-9.05	**<0.0001**
CHF or EF<50%	5.88	1.48-23.36	**0.01**
Pulmonary disease	5.35	1.79-15.98	**0.003**
Active resistant infection	2.83	0.47-17.11	0.26
ECOG ≥ 3	4.68	0.85-25.91	0.08

A higher Ferrara score, CHF diagnosis, and active pulmonary disease at induction predicted likelihood of HMA-V treatment.

Table 3: Patient age and adverse ELN risk also predicted likelihood of receiving lower intensity treatment.

Variable	Odds ratio	95% CI	P value
Ferrara score 1-2 vs 0	6.06	2.60-14.11	**<0.0001**
Age at diagnosis	1.16	1.08-1.25	**<0.0001**
TP53 Mutation present	1.66	0.81-3.42	0.17
ELN 2017 adverse risk	2.67	1.38-5.17	**0.004**
Prior myeloid malignancy	1.09	0.48-2.46	0.84
Prior HMA therapy	0.33	0.11-0.98	0.18

Treatment decision was most influenced by Ferrara score, age, and ELN risk.

Grenet et al, ASH 2024

Table 4: Transplant decisions differed in those receiving intensive vs non-intensive induction.

	IC	HMA-V	P value
Pts undergoing HSCT	54.7%	18.6%	**<0.001**
Achieved CR/CRi before HSCT (N=177)	69.4%	31.1%	**<0.001**

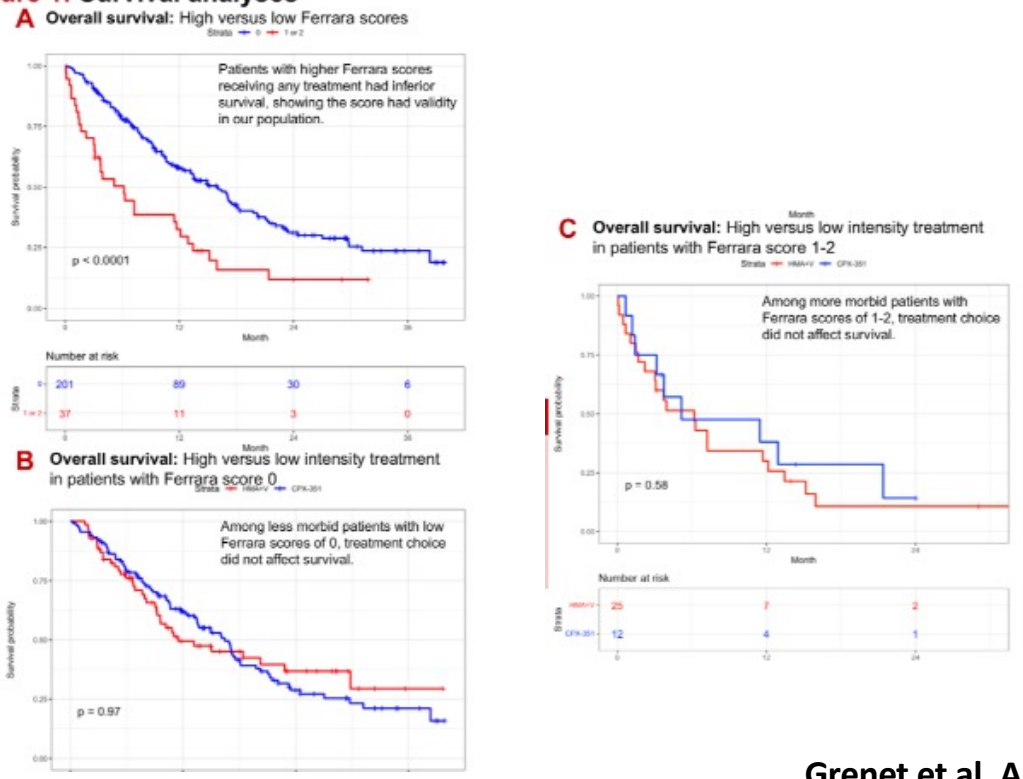
Those who received HMA-V were less likely to undergo transplant. This difference could not be explained by CR/CRi rates.

Table 7: Ferrara score at diagnosis predicted eventual transplant.

Variable	Odds ratio	95% CI	P value
Ferrara score 1-2 vs 0	0.19	0.07-0.54	**0.002**
Age at diagnosis	0.84	0.78-0.90	**<0.0001**
TP53 mutation present	0.40	0.17-0.94	**0.04**
ELN 2017 adverse risk	0.58	0.32-1.06	0.08
Prior myeloid malignancy	1.30	0.58-2.90	0.52
Prior HMA therapy	0.31	0.11-0.93	0.13

Patients with higher vs lower Ferrara scores at the time of diagnosis were less likely to be transplanted (15.4% vs 47.0%,

Figure 1: Survival analyses



CONCLUSIONS

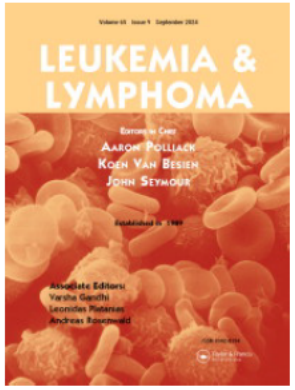
- Ferrara criteria is correlated with upfront AML treatment choice.
- A significant proportion of HMA+V treated pts had a Ferrara score of 0, and adverse biological risk did not always explain the treatment choice.
- While current clinical trials continue to use these criteria for determination of IC vs. non-IC eligibility, Ferrara score does not reflect all the factors that influence treatment selection in the real world.
- Higher Ferrara score can predict worse outcomes in general, but not necessarily outcomes after receiving IC versus non-IC.
- Non-IC pts received significantly less transplants compared to IC pts even in CR and with equivalent HCT-CI scores. This decision may have been strongly affected by their fitness at the time of presentation rather than after induction.

Grenet et al, ASH 2024

12. (consensus not reached) Adverse genetic/cytogenetic profiles are not a contraindication to IC in older fit patients [LoE IV; GoR B]

PANEL RECOMMENDATION: Although an agreement was not reached, 67% of the panelists concurred that no clear contraindications exist to treating adverse risk, older, fit patients with adverse-risk profiles using IC.
The lack of consensus on this issue stems from unsatisfactory results when treating patients with adverse risk with either intensive or non-intensive approaches. The authors agree on the necessity to implement treatment strategies for this patient population.

Venditti et al, Blood Adv, 2025



Leukemia & Lymphoma

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ilal20

Venetoclax-based treatment in acute myeloid leukemia: an unexpected bonus on the path to allogeneic hematopoietic stem cell transplant?

Tarantini et al, 2024

Table 3. Currently reported studies utilizing HMA-VEN for remission induction prior to allogeneic SCT

Study	Type	Participating sites	Number of patients	12-month NRM (%)	12-month CIR	12-month RFS (%)	12-month OS (%)	Relapse (%)/median LFS (month)	OS (months)
Pasvolsky et al[35]	Retrospective	Multicenter	24	19.1		58	63		
Winters et al[36]	Retrospective	Single center	29			66.1	74.5		
Pollyea et al[37,38]	Retrospective	Single center	21	11		80			NR
Kennedy et al[39,40]	Retrospective	Multicenter	88	17	18		73		
Nizamuddin et al[41]	Retrospective	Single center	36					39/11.2	25.4
Rautenberg et al[42]	Retrospective	Single center	26			67	81		NR

CIR, cumulative index of relapse; NR, not reached; NRM, onrelapse mortality; RFS, relapse free survival; LFS, leukemia free survival.

ASH 2023, Ed. Program

Real-world outcomes of newly diagnosed AML treated with venetoclax and azacitidine or low-dose cytarabine in the UK NHS

Short title: venetoclax for AML in the UK

Key points

1. Outcomes of patients treated with venetoclax-based non-intensive therapies across > 50 NHS hospitals mirror those seen in clinical trials
2. Current mutation based prognostic systems are inadequate. Collaborative efforts are needed to establish a definitive prognostic scheme

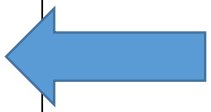
Othman et al, Blood Neoplasia, 2024

Si precisa che in Italia è rimborsata dal SSN la sola combinazione venetoclax+azacitidina in pazienti non precedentemente trattati e non eleggibili a chemioterapia intensiva

Table 2

Remission and outcome

Characteristic	Azacitidine N = 587	Low-dose cytarabine N = 67
Best response		
Complete remission	272 (47%)	38 (58%)
Complete remission with incomplete hematologic recovery	114 (20%)	10 (15%)
Morphologic leukemia-free state	21 (3.7%)	0 (0%)
Partial remission	61 (11%)	1 (1.5%)
Refractory disease	62 (11%)	11 (17%)
Death prior to response assessment	44 (7.7%)	6 (9.1%)
Missing	13	1
Day 30 mortality	5%	6%
Day 60 mortality	8%	7%
Allogeneic transplant	35 (6.0%)	4 (6.0%)
In CR1	32 (5.5%)	3 (4.5%)
Overall survival		
Median survival (months)	13.6 (95% CI 11.7 – 15.1)	10.9 (95% CI 8.8 - 20.2)
12-month survival	54%	46%



Othman et al, Blood Neoplasia, 2024

1514 Real World Outcome of Unfit Patients with Acute Myeloid Leukemia Treated with the Combination Venetoclax Plus Hypomethylating Agents in the Gimema AML2320 Observational Trial

Total: 188 patients from 30 Italian centers

Eleven (6%) pts were submitted to an allogeneic stem cell transplant after having received 4 courses of VEN+HMA and being in CR/CRi.

Venditti et al, ASH, 2023

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 13, 2020 VOL. 383 NO. 7

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

C.D. DiNardo, B.A. Jonas, V. Pullarkat, M.J. Thirman, J.S. Garcia, A.H. Wei, M. Konopleva, H. Döhner, A. Letai, P. Fenaux, E. Koller, V. Havelange, B. Leber, J. Esteve, J. Wang, V. Pejsa, R. Hájek, K. Porkka, Á. Illés, D. Lavie, R.M. Lemoli, K. Yamamoto, S.-S. Yoon, J.-H. Jang, S.-P. Yeh, M. Turgut, W.-J. Hong, Y. Zhou, J. Potluri, and K.W. Pratz

433 randomized

Two patients in the azacitidine–venetoclax group and 1 patient in the azacitidine–placebo group underwent transplantation after discontinuing azacitidine–venetoclax or azacitidine–placebo

How to select patients who are candidate to VEN/HMA ?

Table 3. Operation criteria to define unfitness to intensive chemotherapy in AML

1.	An age older than 75 years
2.	Congestive heart failure or documented cardiomyopathy with an EF $\leq$50%
3.	Documented pulmonary disease with DLCO $\leq$65% or FEV1 $\leq$65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
4.	On dialysis and age older than 60 years or uncontrolled renal carcinoma
5.	Liver cirrhosis Child B or C, or documented liver disease with marked elevation of transaminases (>3 times normal values) and an age older than 60 years, or any biliary tree carcinoma or uncontrolled liver carcinoma or acute viral hepatitis
6.	Active infection resistant to anti-infective therapy
7.	Current mental illness requiring psychiatric hospitalization, institutionalization or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
8.	ECOG performance status $\geq$3 not related to leukemia
9.	Any other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy

Abbreviations: AML, acute myeloid leukemia; DLCO, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; EF, ejection fraction; FEV1, forced expiratory volume in 1 s.

Table 4. Operational criteria to define unfitness to non-intensive chemotherapy in AML

1.	Refractory congestive heart failure
2.	Documented pulmonary disease with DLCO $\leq$65% or FEV1 $\leq$65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
3.	Liver cirrhosis Child B or C or acute viral hepatitis
4.	Active infection resistant to anti-infective therapy
5.	Current mental illness requiring psychiatric hospitalization, institutionalization or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
6.	Uncontrolled neoplasia

Abbreviations: AML, acute myeloid leukemia; DLCO, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; EF, ejection fraction; FEV1, forced expiratory volume in 1 s.

Ferrara et al, Leukemia, 2013

blood

American Society of Hematology
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Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

How I Treat patients with AML using azacitidine and venetoclax

- The published experience for allo-HCT after AZA-VEN remains limited, with current data indicating the proportion transplanted after AZA-VEN ~10-17% and the median time from initial therapy to transplant ~5 months.

- In our practice, we consider HCT in patients up to the age of 75 years with good performance status, intact organ function and strong social/logistic supports, with each patient evaluated on a case-by-case basis.

Wei & Daver, Blood, 2024

Table 2. Prospective studies evaluating younger, fit patients eligible for IC compared to AZA-VEN

Study	Phase	Type	Therapy	Key inclusion	Key exclusion
NCT04801797	II	Randomized	• IC • AZA-VEN	• Age 18+ • ECOG ≤2	• *FLT3* • Age <60 with *NPM1* mutated • Favorable risk
NCT03573024	II	Single arm	• AZA-VEN	• Age 18–59 • ECOG ≤2 • Adverse risk	• Willing to receive IC
NCT05554393 (MyeloMATCH)	II	Randomized	• 7+3 • 7+3 + VEN • AZA-VEN	• Age 18–59 • ECOG 0–3	• Favorable and adverse risk by ELN 2017 criteria • *FLT3-ITD/TKD* • Secondary or therapy-related AML
NCT05554406 (MyeloMATCH)	II	Randomized	• CPX-351 • 7+3 • AZA-VEN • 7+3+ VEN • CPX-351 + VEN	• Age 18–59 • ECOG 0–3 • Adverse risk per ELN 2017 criteria	• Favorable or intermediate risk • *FLT3- ITD/TKD*

ASH 2023, Ed. Program

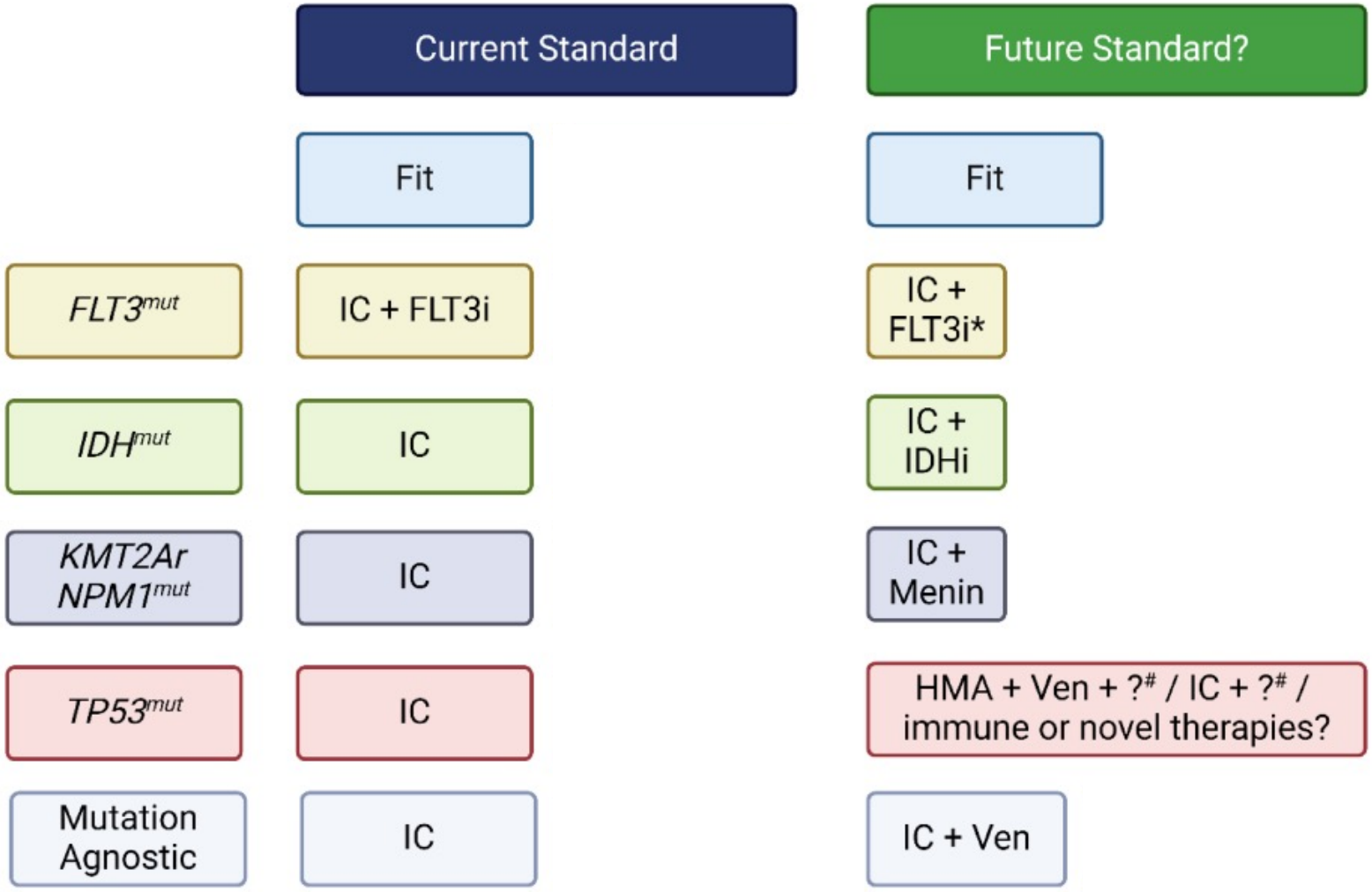
Journal of
Clinical Medicine

MDPI

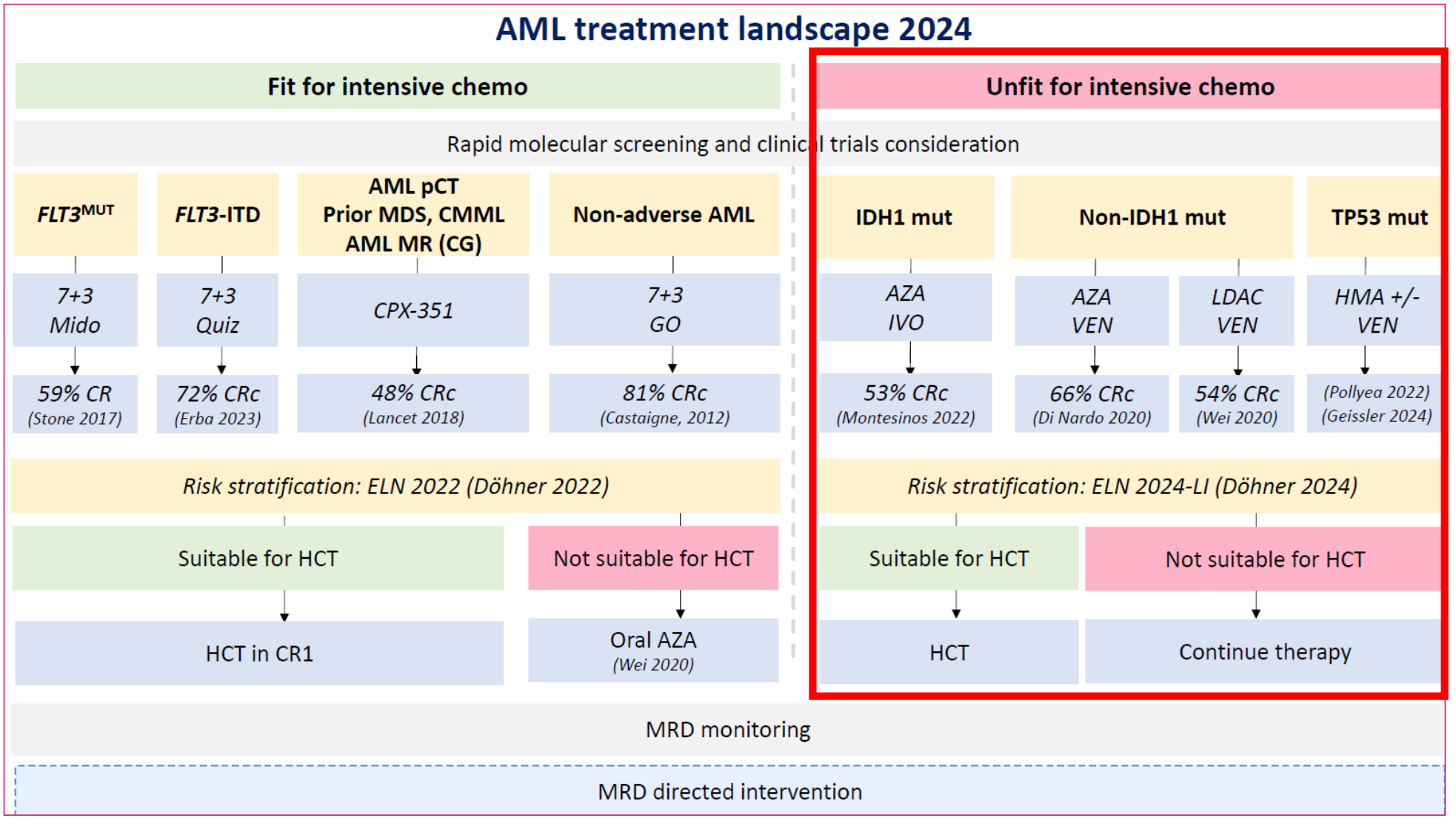
Review

Intensive Chemotherapy Versus Venetoclax-Based Regimens in Elderly Patients with Acute Myeloid Leukemia: Is the Chemotherapy Era Ending?

Farina et al, 2025



Speaker suggestion

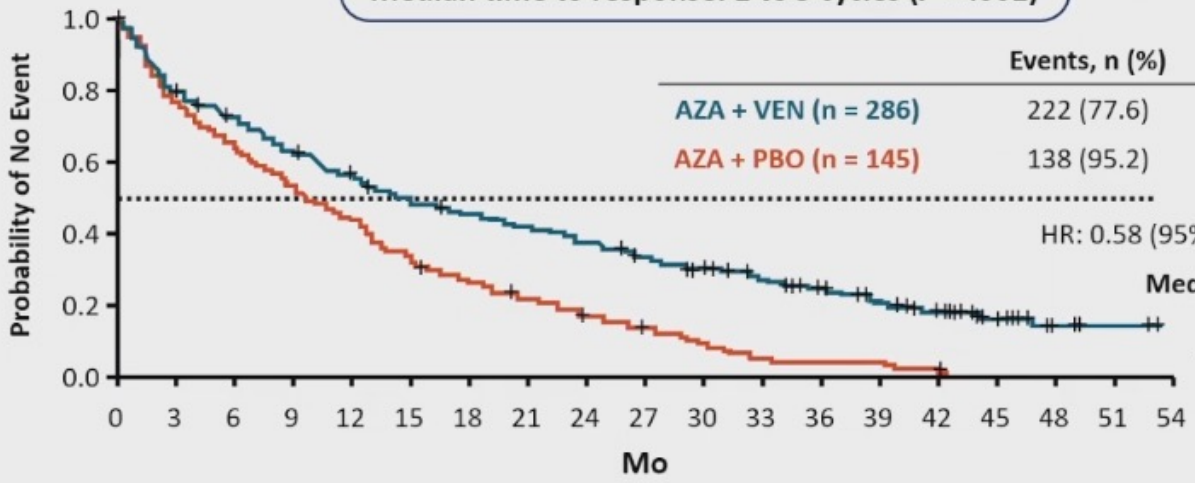

AML treatment landscape 2024
Fit for intensive chemo
Unfit for intensive chemo
Rapid molecular screening and clinical trials consideration
FLT3MUT
FLT3-ITD
AML pCT
Prior MDS, CMML
AML MR (CG)
Non-adverse AML
IDH1 mut
Non-IDH1 mut
TP53 mut
7+3
Mido
7+3
Quiz
CPX-351
7+3
GO
AZA
IVO
AZA
VEN
LDAC
VEN
HMA +/-
VEN
59% CR
(Stone 2017)
72% CRc
(Erba 2023)
48% CRc
(Lancet 2018)
81% CRc
(Castaigne, 2012)
53% CRc
(Montesinos 2022)
66% CRc
(Di Nardo 2020)
54% CRc
(Wei 2020)
(Pollyea 2022)
(Geissler 2024)
Risk stratification: ELN 2022 (Döhner 2022)
Risk stratification: ELN 2024-LI (Döhner 2024)
Suitable for HCT
Not suitable for HCT
Suitable for HCT
Not suitable for HCT
HCT in CR1
Oral AZA
(Wei 2020)
HCT
Continue therapy
MRD monitoring
MRD directed intervention

Long-Term VIALE-A Follow Up of AZA + VEN

CR rate: 36.7% vs 17.9% (*P* < .001)

CR/CRi rate: 66.4% vs 28.3% (*P* < .001)

Median time to response: 1 vs 3 cycles (*P* < .001)



	Events, n (%)	Median OS, months (95% CI)
AZA + VEN (n = 286)	222 (77.6)	**14.7 (12.1–18.7)**
AZA + PBO (n = 145)	138 (95.2)	**9.6 (7.4-12.7)**

HR: 0.58 (95% CI: 0.47-0.72); *P* <.001

Median follow-up: 43.2 mo

\+ Censored

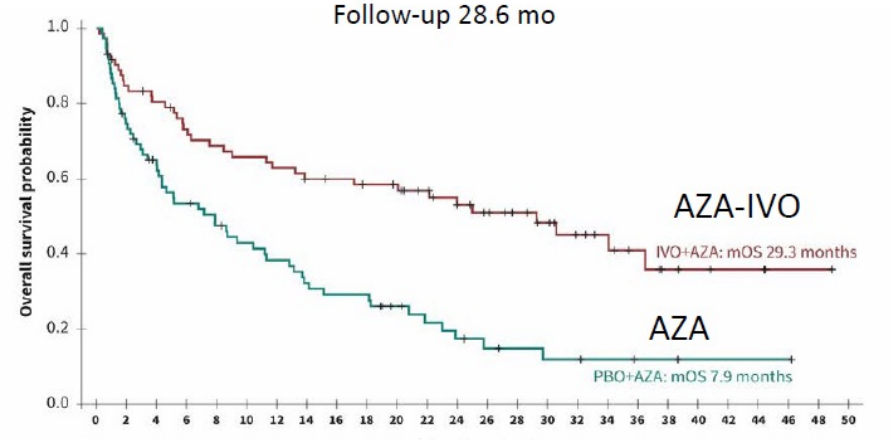
Patients at Risk, n

AZA + PBO	145	109	92	77	63	47	37	30	22	17	12	6	5	5	3	0			
AZA + VEN	286	220	199	173	153	133	122	113	101	89	78	67	57	45	34	18	6	2	0

Pratz K et al, AJH 2024

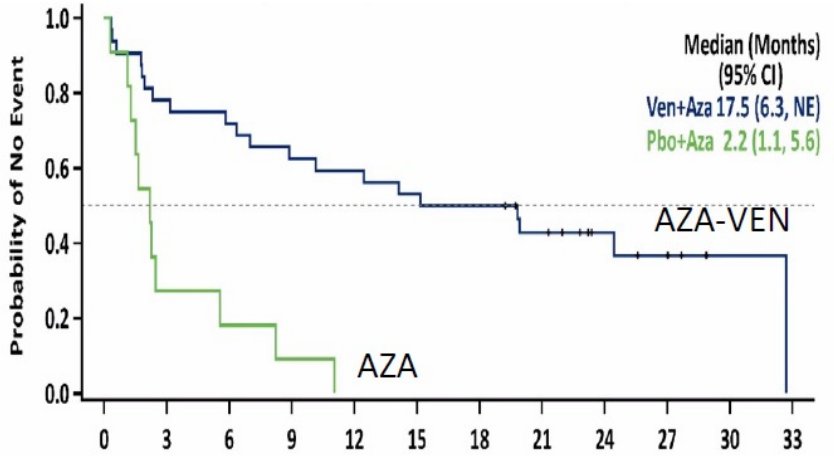
Less intensive options for *IDH1* mutant AML

Outcome	AZA-IVO (n=72)	AZA (n=74)
CR	**47%**	15%
CR/CRh	53%	18%
Median OS	**29.3 mo**	7.0 mo
Time to CR	2.1 mo	3.7 mo
Feb neut	27.8%	33.8%



De Botton, ASCO 2023

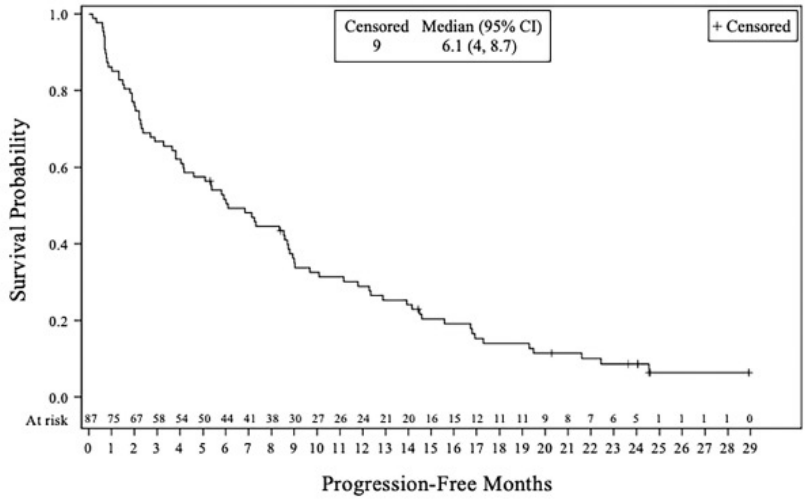
Outcome	AZA-VEN (n=32)	AZA (n=11)
CR	28%	0
CR/CRh	59%	9.1%
Median OS	17.5 mo	2.2 mo
Time to CR	**1.2 mo**	3.4 mo
Feb neut	29.6%	14.3%



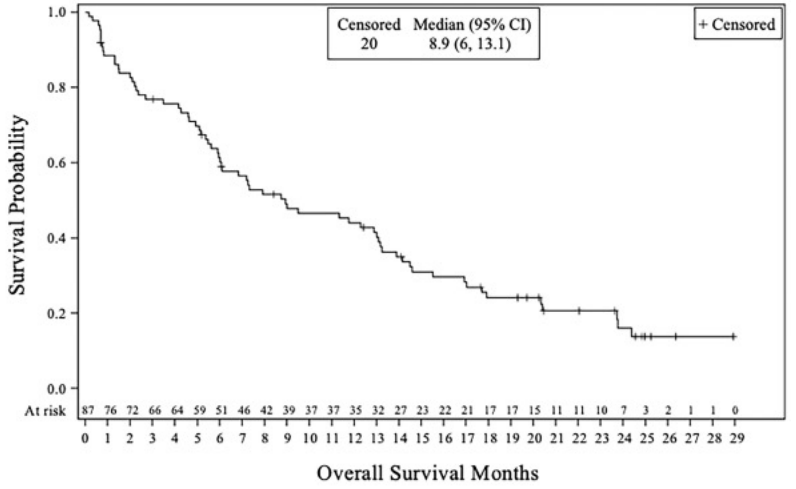
Pollyea, et al, Clin Cancer Res. 2022

Oral Decitabine/Cedazuridine vs Intravenous decitabine for AML: final results of a randomized, crossover, registration enabling Pharmacokinetics study (phase 3 study)

Progression Free Survival

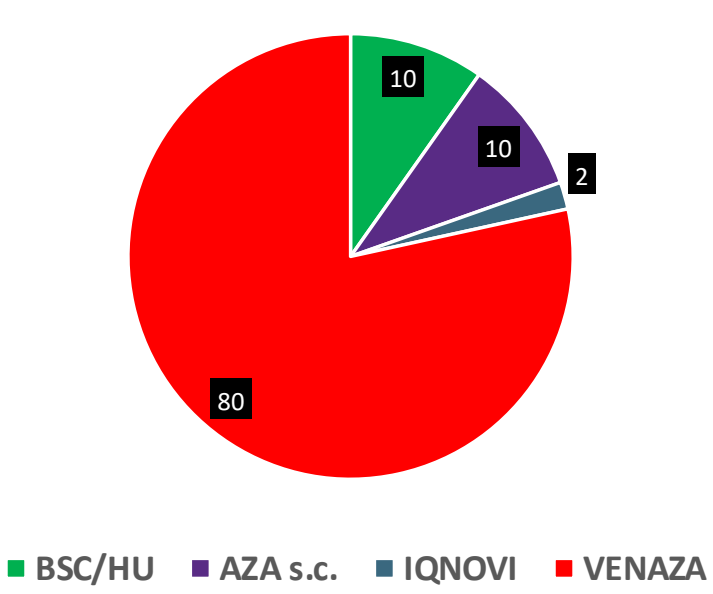


Overall Survival

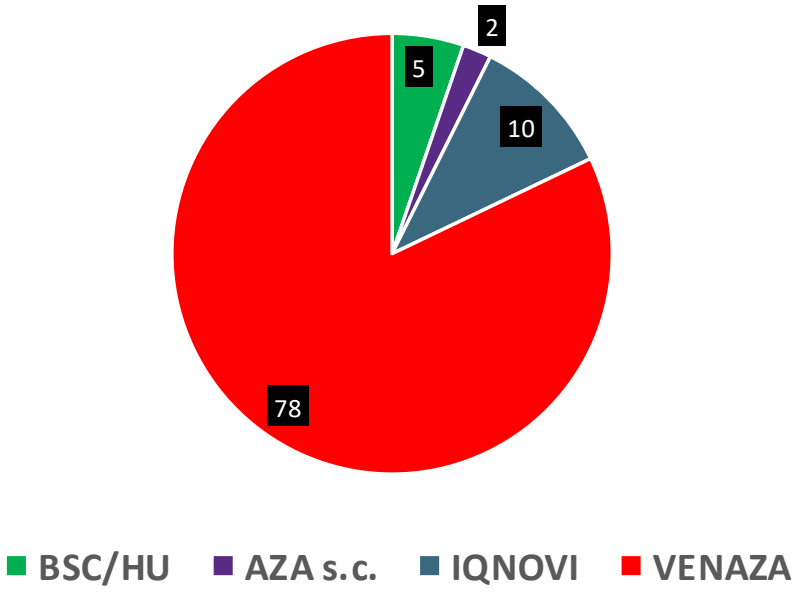


Geissler K *et al*. Br J Haematol. 2024;00:1–12

TODAY

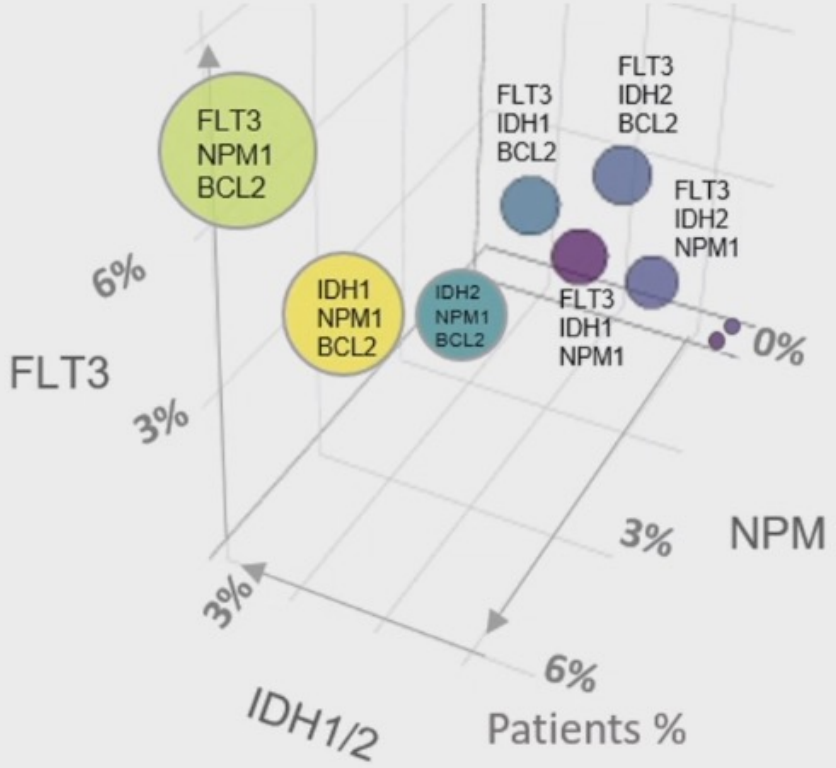


TO MORROW



Speaker’s opinion

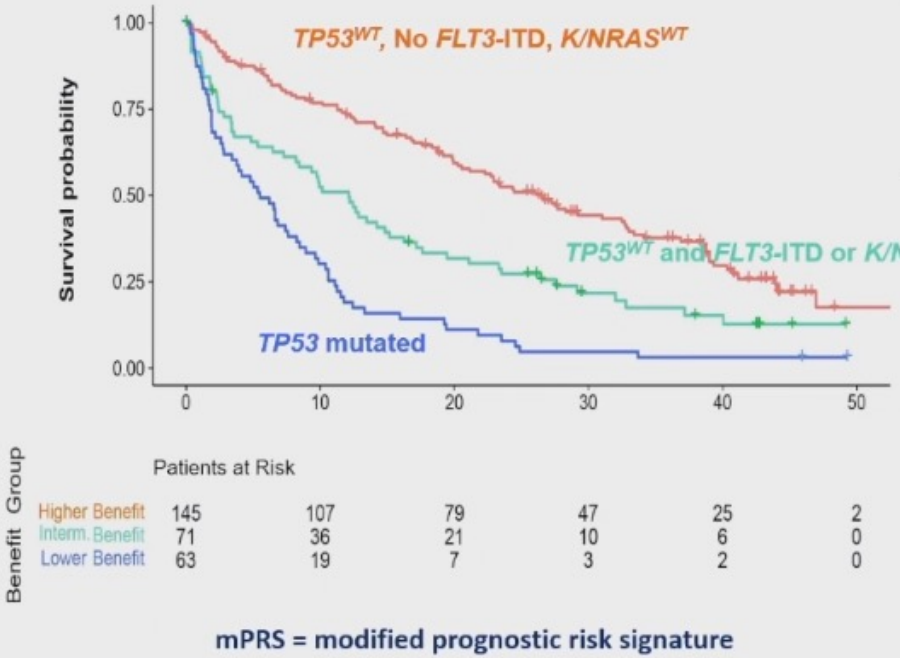
Outlook: Chemo-free combination treatments and oral



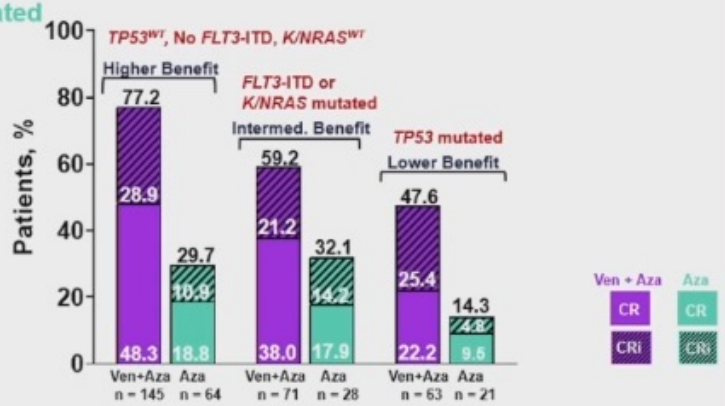
Based on 725 patients

Patients receiving Ven+Aza are **better characterized** by three molecularly-defined subgroups

"mPRS Score"



Ven + Aza (N = 279)	n	Events	Median OS, months (95% CI)
Higher Benefit	145	96	**26.51** (20.24, 32.69)
Intermediate Benefit	71	57	**12.12** (7.26 – 15.15)
Lower Benefit	63	61	**5.52** (2.79 – 7.59)

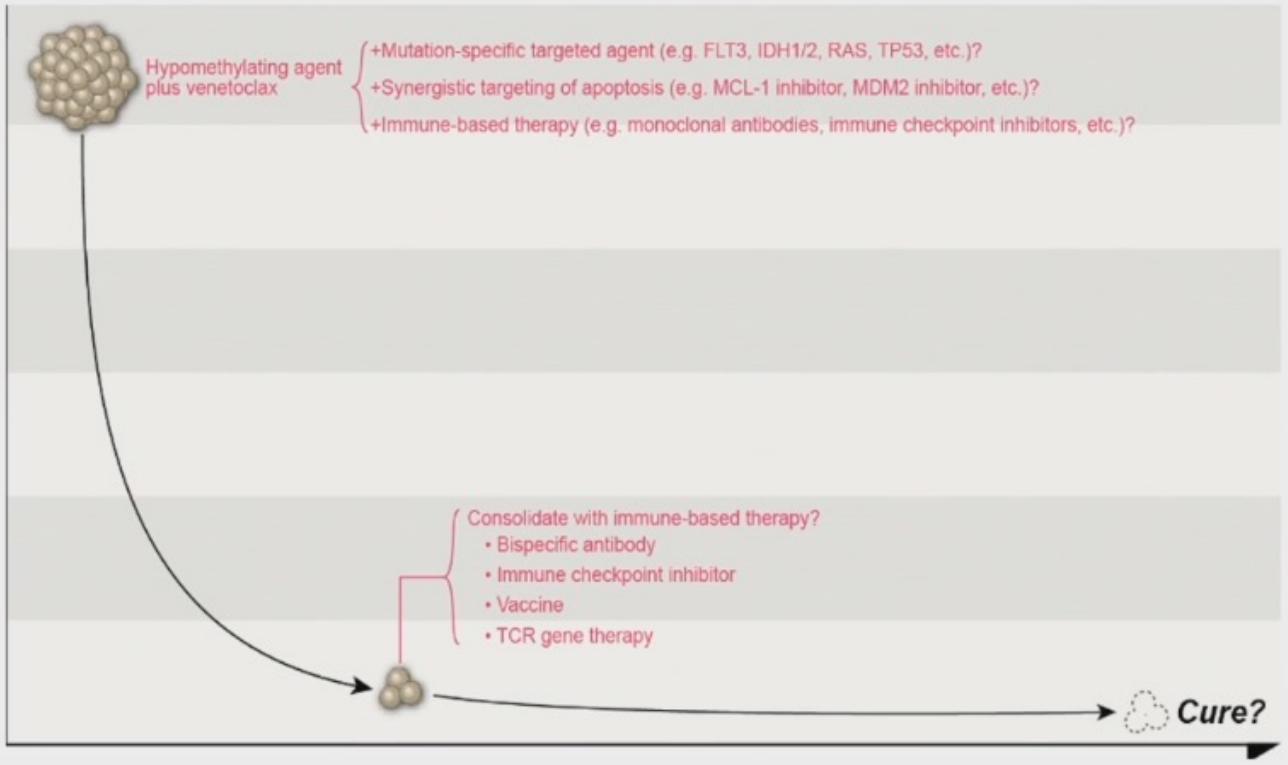


mPRS = modified prognostic risk signature

Dohner H et al, Blood 2024

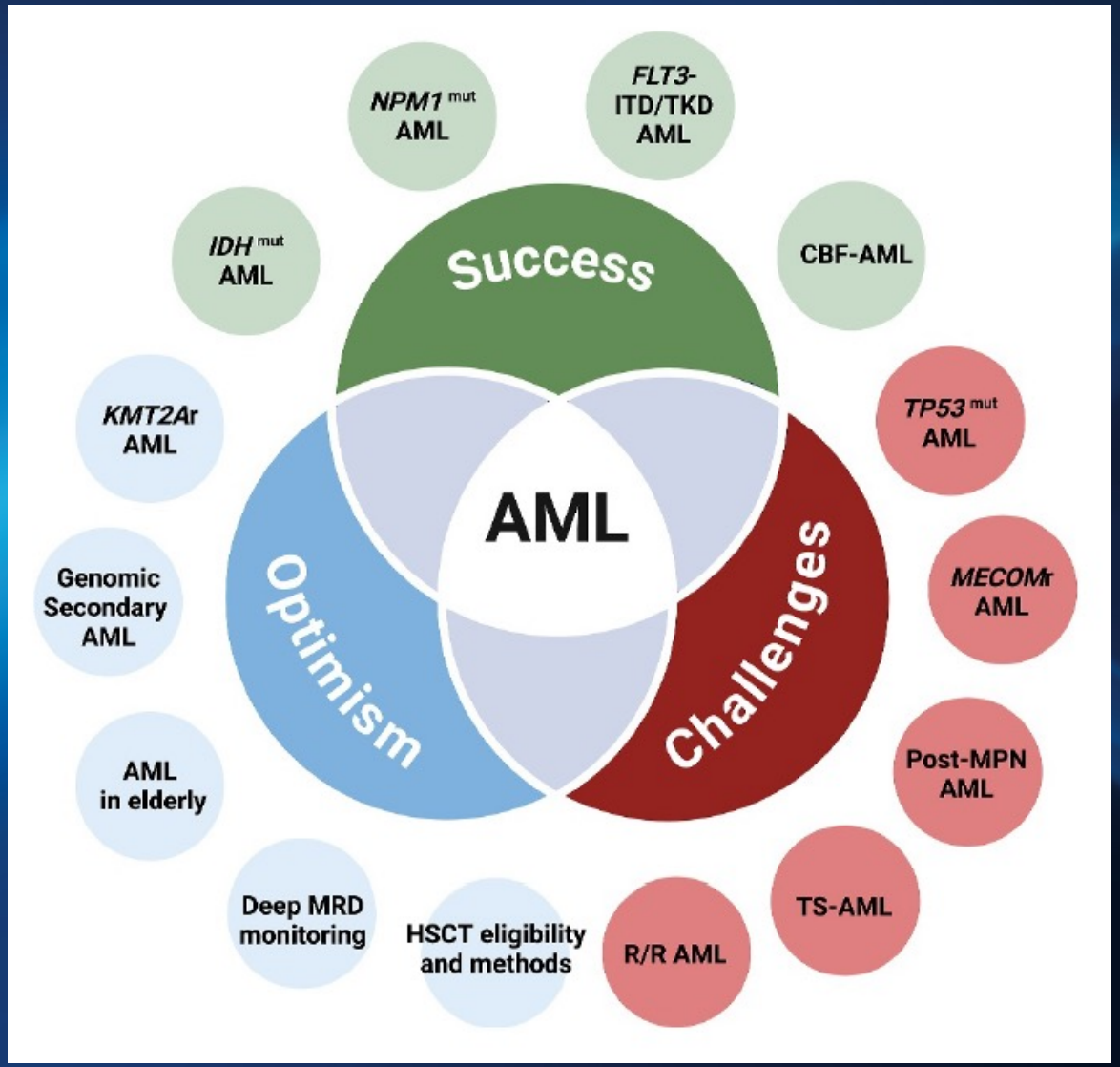
HMA + VEN + Novel Agent "Triplet" Strategy

- Quizartinib
- Gilteritinib
- Ivosidenib
- Olutasidenib
- Enasidenib
- Menin I's
- Tuspetinib
- Gemtuzumab
- SL-401
- IMGN-632
- EP0042
- ADI-PEG 20
- CDK9 inhibitors
- Selinexor
- Sabatolimab
- Cusatuzumab
- Many many others…



As Per ClinicalTrials.gov

Short N et al, Cancer Discov 2020


NPM1 mut AML
FLT3-ITD/TKD AML
IDH mut AML
CBF-AML
KMT2Ar AML
TP53 mut AML
Genomic Secondary AML
MECOMr AML
AML in elderly
Post-MPN AML
Deep MRD monitoring
HSCT eligibility and methods
R/R AML
TS-AML
Success
Optimism
Challenges
AML