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DEBATES AND DIDACTICS in Hematology and Oncology

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Is Intensive Chemotherapy On Its Way Out for Frontline Treatment of AML?

Martha Arellano, MD

Professor and Associate Director, Hematology

Program Director, Hematology & Medical Oncology Fellowship

Winship Cancer Institute of Emory University

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Disclosures

SYNDAX Pharmaceuticals-advisory board

Case

65 y/o man with newly diagnosed AML, diploid karyotype, and *NPM1* mutation (VAF 30%) on rapid NGS.
ECOG = 2
PMHx: HTN, DM

How do you treat him?

?? 7+3, FLAG-Ida, HMA plus venetolax, menin inhibitor on clinical trial

HMA = hypomethylating agent

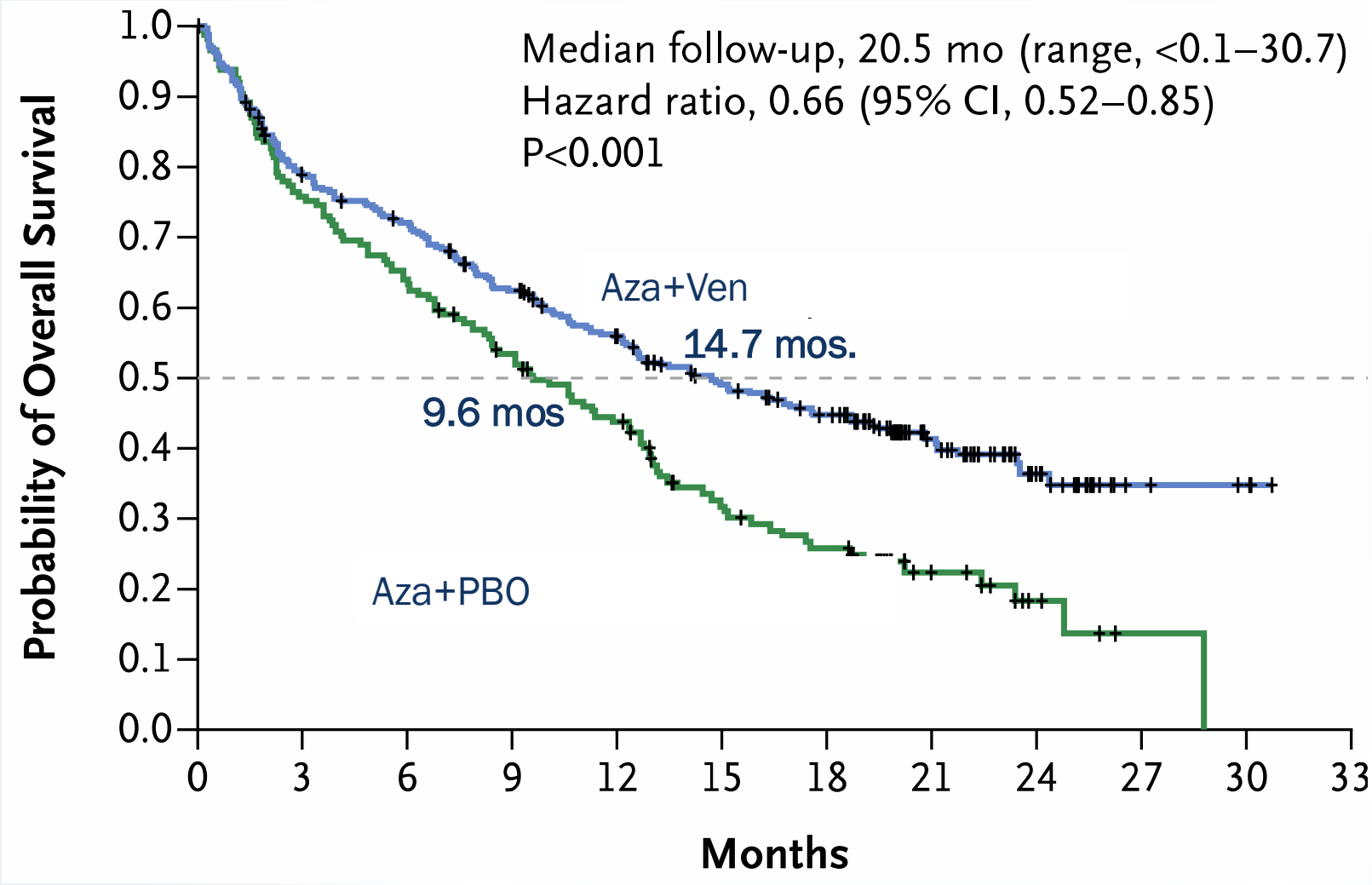
Objectives:

- Experience with azacitidine and venetoclax - Paradigm clinical trial
- Triplets combining azacitidine, venetoclax, and targeted agents
- An all-oral regimen
- Algorithm for treatment of patients with newly dx AML

Evolution of Therapeutic Discovery for Patients with AML

Image generated with help of AI, 80% M. Arellano, 20% AI

Azacitidine +/- Venetoclax for Patients with Newly dx. AML, Age ≥ 75 or with Pre-existing Conditions Precluding Induction (VIALE-A)



- CCR, 66.4% vs. 28.3%
- 30-day death,

7% (A-V) vs. 9% (A/PBO)

Aza/Ven, N= 286 vs. Aza/placebo, N= 145

Approved November 2018

CCR= composite complete remission (CR+CRi)

C.D. DiNardo, B.A. Jonas, V. Pullarkat, et al. NEJM 2020; 383: 617-29.

Real World Use of Azacitidine + Venetoclax

- 312 pts treated with Intensive chemotherapy (IC) and 488 pts treated with HMA+ venetoclax
- Overall survival for IC, 22 months vs. 10 months for HMA-Ven.
- Compared to use of IC, use of HMA-Ven was associated with:
  - older pt. age, higher performance status, and comorbidity score,
  - adverse risk disease, and lower marrow blasts,
  - treatment in community practice.
- Controlling for pre-treatment factors, survival was similar for both treatment groups (17.5 months).
- **Randomized data are needed.**

Matthews AH, Perl AE, Luger SM, et. Al. Am J Hematol. 2023 Aug;98(8):1254-1264. doi: 10.1002/ajh.26991. Epub 2023 Jun 19. PMID: 37334852; PMCID: PMC11057024.

PARADIGM- Open-label, Multicenter, Randomized Phase II Clinical Trial

Patients with newly diagnosed AML, age ≥ 18, eligible for intensive chemotherapy	
Randomization	7+3 or CPX-351 vs. Azacitidine + Venetoclax
	Both groups could continue with consolidation +/- transplantation
Exclusions	Core binding factor fusions, FLT3 mutations, NPM1 mutations (unless age ≥ 60)
Stratification	Age ≥ 65 vs < 65 and 7+3 vs CPX-351
Primary endpoint	Event-Free Survival (EFS)
Secondary endpoints	Response rates, overall survival, toxicity, MRD, hospitalization metrics, and QoL

Amir Fathi, et al. *Blood* (2025) 146 (Supplement 1): 6. https://doi.org/10.1182/blood-2025-6

PARADIGM- Patient Characteristics

Factor	Aza+Ven, N = 86	IC, N = 86	*P*-value
Median age	64	65	NS
Male	55%	60%	NS
White	65%	69%	NS
ELN22 risk:	favorable 12%, intermediate 15%, unfavorable 72%		NS

Notes:

- 172 patients at 9 US centers randomized
- Among IC arm, 54% received 7+3 and 46% received daunorubicin and cytarabine liposome (CPX-351)
- Both arms had comparable proportions of *IDH1/2*, *NPM1*, and *TP53* mutations.

Blood (2025) 146 (Supplement 1): 6.https://doi.org/10.1182/blood-2025-6

PARADIGM Results

- Median follow-up, 16 months

Outcome	Aza+Ven	IC	P-value
Overall response rate	**88%**	**62%**	**<0.001**
Composite Complete Remission	**81%**	**55%**	**<0.001**
Complete Remission	59%	50%	0.066
1-year Event-free Survival	**53%**	**39%**	**0.017**
Proceeded to transplantation	**52 (61%)**	**34 (40%)**	**0.009**
Median Overall Survival (mos)	21.5	18.6	0.1873

- No significant age effect on EFS.
- MRD-negativity at end of induction was 46.8 % for Aza-Ven and 43.6% for IC.

Composite complete remission = CR + CRh (ANC ≤ 500 and PLT ≤ 50) + CRi (ANC < 1,000 or PLT < 100k), MLFS = morphologic leukemia-free state
Overall response = CR+CRh+CRi+PR+MLFS

PARADIGM TOXICITY

Factors	IC	HMA+Ven	*P*-value
Treatment-emergent infections	20.8%	15.1%	0.04
Bleeding complications	6.3%	1.3%	0.01
30-day and 60-day mortality	3.5%, 4.7%	0%, 0%	-
Quality of life	worse	better	0.001
Symptom burden and depression	worse	better	0.019, 0.007
ICU admission	9.8%	0%	0.003
Inpatient days during initial hospitalization	36	15	<0.001
Hospital days in the 1st six months	58	41	<0.001

Gr 3-4 toxicities mostly hematological and similar across arms.

SUMMARY

Compared with intensive chemotherapy, aza-ven was associated with:

- ✓ Superior event-free survival
- ✓ Higher response rates
- ✓ Better tolerability
- ✓ Fewer hospitalizations
- ✓ Improved quality of life
- ✓ Higher likelihood of proceeding to transplantation

Blood (2025) 146 (Supplement 1): 6.https://doi.org/10.1182/blood-2025-6

Another paradigm shift…

Sabastian Sawe

- First human to break a 2:00:00 marathon (1:59:30) under race conditions. World record at the London Marathon on April 26, 2026.

- Massive **paradigm** shift in endurance sports
  New standard for elite runners

The triplets are here…

FLT3 VICEROY Trial (NCT05520567)

- Multicenter, open-label, randomized, phase 1/2, dose-ranging/expansion study
- Efficacy, safety and optimal dosing of Aza-Ven and Gilteritinib in pts. w/newly dx *FLT3*^{mut} AML, ineligible for intensive induction (≥75 y/o or younger w/comorbidities).

- Randomized 1:1 to VEN 200mg or 400mg daily with AZA (75mg/m^2/d on days 1–7) and GILT (80mg/day) on 28-day cycles
- BM bx on cycle 1 day 14 → Ven/Gilt interrupted for rest of cycle 1 if <5% blasts or ≥5% blasts and <5% cellularity.
- GCSF recommended for pts in marrow remission with ANC ≤500/µL on ≥ C1D42
- Results of phase I, **N = 44**

Parameter	VEN200	VEN400
Median age (years)	73	77
Male sex (%)	55%	54%
Lone FLT3-ITD (%)	65%	83%
Lone FLT3-TKD (%)	35%	13%

Jessica Altman, Alexander Perl, Eunice Wang, et. al. Blood, Volume 146, Supplement 1, 2025, Page 654, ISSN 0006-4971, https://doi.org/10.1182/blood-2025-654.

VICEROY (NCT05520567), Safety and efficacy, ongoing

Safety	VEN200	VEN400
DLTs	0	2
Any safety event (%)	25%	25%
Most common safety event	Febrile neutropenia (15%)	AST increased (8%)
Serious TEAEs (%)	85%	79%
Death in first 30 and 60 days	0/0	0/1

RP2D
VEN 400mg

Efficacy	VEN200	VEN400
Median follow-up (months)	14 (n=20)	12 (n=23)
Median cycles (range)	4 (1–17)	4 (1–11)
CR rate (95% CI)	70% (46–88)	65% (43–84)
CRc rate (95% CI)	90% (68–99)	91% (72–99)
Time to hematologic recovery, days	38 (31–53)	42 (29–63)
12-month OS (95% CI)	64% (39–81)	77% (54–90)
MRD <10^-4 at last visit	85% (11/13)	57% (8/14)

Jessica Altman, Alexander Perl, Eunice Wang, et. al. Blood, Volume 146, Supplement 1, 2025, Page 654, ISSN 0006-4971, https://doi.org/10.1182/blood-2025-654.

NPM1, BEAT AML, Sub-study 17

Phase I dose-escalation and expansion study of Aza-Ven and revumenib in patients age ≥ 60 years with newly diagnosed AML with *NPM1m* or *KMT2Ar* (NCT03013998). N = 43

Parameter	Result
Differentiation syndrome, n (%)	8 (19%)
QTc Fridericia prolongation, n (%)	19 (44%)
Overall response rate (ORR), % (95% CI)	88.4% (74.9–96.1); **NPM1m 85.3%; KMT2Ar 100%**
Composite CR rate, % (95% CI)	81.4% (66.6–91.6); **NPM1m 79.4%; KMT2Ar 88.9%**
Complete remission (CR) rate, % (95% CI)	67.4% (51.5–80.9); **NPM1m 65%; KMT2Ar 78%**
Median time to response was 28 days	
MRD negativity by centralized flow cytometry in 37/37 patients (100%)	

Composite complete remission (CR + CR with partial- (CRh) or incomplete hematologic recovery, CRi)

Joshua F. Zeidner et al. Azacitidine, Venetoclax, and Revumenib for Newly Diagnosed *NPM1*-Mutated or *KMT2A*-Rearranged AML. *J Clin Oncol* **43**, 2606-2615(2025). DOI:10.1200/JCO-25-00914

All-Oral Treatment for patients with Newly Diagnosed AML

- Phase 1/2 open-label, multicenter trial of oral decitabine–cedazuridine + venetoclax in pts. with newly dx AML, aged ≥ 75 years and ineligible for intensive chemotherapy.
- **Dose adjustments encouraged** in phase 2b after marrow blast clearance.
- Primary end points: venetoclax area under the curve @ 0-24 hrs and maximum observed concentration with or without decitabine–cedazuridine on days 5 & 15 of cycle 2 (phase 1–2a) and complete response (phase 2a–b).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Phase 1 (N=30)	Phase 2a (N=58)	Phase 2b (N=101)
Median age (range) — yr	78.0 (66–87)	75.0 (56–91)	78.0 (63–88)
Sex — no. (%)			
Male	16 (53)	33 (57)	61 (60)
Female	14 (47)	25 (43)	40 (40)
ECOG performance-status score — no. (%)†			
0	1 (3)	3 (5)	27 (27)
1	18 (60)	24 (41)	52 (51)
2	11 (37)	28 (48)	18 (18)
>2	0	3 (5)	3 (3)
Missing	0	0	1 (1)
Cytogenetic classification according to ELN 2017 criteria — no. (%)			
Favorable	0	2 (3)	1 (1)
Intermediate	23 (77)	40 (69)	66 (65)
Adverse	5 (17)	13 (22)	24 (24)
Test failed or missing	2 (7)	3 (5)	10 (10)
Mutation profiling according to sequencing — no. (%)‡			
TP53	NA	3 (5)	17 (17)
IDH1	NA	6 (10)	6 (6)
IDH2	NA	6 (10)	12 (12)
FLT3-ITD	NA	NA	11 (11)
KMT2A fusions	NA	2 (3)	0
NPM1	NA	8 (14)	13 (13)
KRAS	NA	3 (5)	12 (12)
NRAS	NA	6 (10)	11 (11)
NPM1/FLT3	NA	2 (3)	4 (4)
≥2 Reasons for ineligibility to receive intensive chemotherapy — no. (%)	NA	10 (17)	19 (19)

* Percentages may not total 100 owing to rounding. ELN denotes European LeukemiaNet, and NA not available.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
‡ Sequencing was performed for 50 patients in phase 2a and 96 patients in phase 2b.

Roboz GJ, Zeidan AM, Mannis GN, et al. N Engl J Med. 2026 Jun 4;394(21):2107-2116. doi: 10.1056/NEJMoa2510223. PMID: 42235013.

All-Oral Treatment for patients with Newly Diagnosed AML

Table 3. Safety Summary.

Event	Phase 1 (N=30)		Phase 2a (N=58)		Phase 2b (N=101)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)					
Any adverse event	30 (100)	26 (87)	58 (100)	53 (91)	100 (99)	99 (98)
Treatment-related adverse event*	22 (73)	19 (63)	42 (72)	37 (64)	81 (80)	73 (72)
Serious adverse event	19 (63)		45 (78)		85 (84)	
Treatment-related serious adverse event*	7 (23)		16 (28)		36 (36)	
Adverse event leading to treatment discontinuation	0		6 (10)		9 (9)	
Adverse event leading to treatment interruption	14 (47)		38 (66)		69 (68)	
Adverse event leading to dose reduction	7 (23)		5 (9)		14 (14)	
Adverse event leading to death	3 (10)		7 (12)		16 (16)	
Most frequent treatment-related adverse events*†						
Hematologic						
Anemia	6 (20)	6 (20)	15 (26)	13 (22)	33 (33)	30 (30)
Neutropenia	1 (3)	1 (3)	13 (22)	13 (22)	26 (26)	26 (26)
Febrile neutropenia	0	0	14 (24)	14 (24)	25 (25)	25 (25)
Platelet count decreased	11 (37)	11 (37)	17 (29)	17 (29)	27 (27)	25 (25)
Thrombocytopenia	2 (7)	2 (7)	6 (10)	5 (9)	22 (22)	20 (20)
Neutrophil count decreased	16 (53)	16 (53)	16 (28)	16 (28)	21 (21)	20 (20)
White-cell count decreased	5 (17)	5 (17)	17 (29)	17 (29)	15 (15)	15 (15)
Nonhematologic						
Constipation	10 (33)	1 (3)	6 (10)	0	8 (8)	0
Nausea	6 (20)	0	10 (17)	0	20 (20)	0

† Shown are events that occurred in at least 20% of the patients in any group.

All-Oral Treatment for patients with Newly Diagnosed AML

Efficacy	Phase I, N=30	Phase 2 A, N = 58	Phase 2B, N = 101
Complete response (CR) % (95%CI)	40 (23–59)	38 (26–52)	**47% (36–57)**
CR, CRh, CRi % (95% CI)	63 (44–80)	66 (52–78)	**63% (53–73)**
CR sustained at 12 mos. % (95% CI)	75 (41-91)	71 (47-86)	**75% (57-87)**
Median time to CR (range) mos.	1.9 (0.9-9.6)	2.4 (0.8-12.2)	**2.4 (0.7-15.3)**
Median overall survival mos. (95% CI)	6.8 (4.3-19.5)	14.5 (8.1-18.2)	**15.5 (7.6-could not be estimated)**

CRh, CR with partial hematologic recovery (ANC $\geq$ 500 and PLTS $\geq$ 50k)
CRi, CR with incomplete hematologic recovery (ANC $\leq$1000 or PLTS $\leq$ 100k)

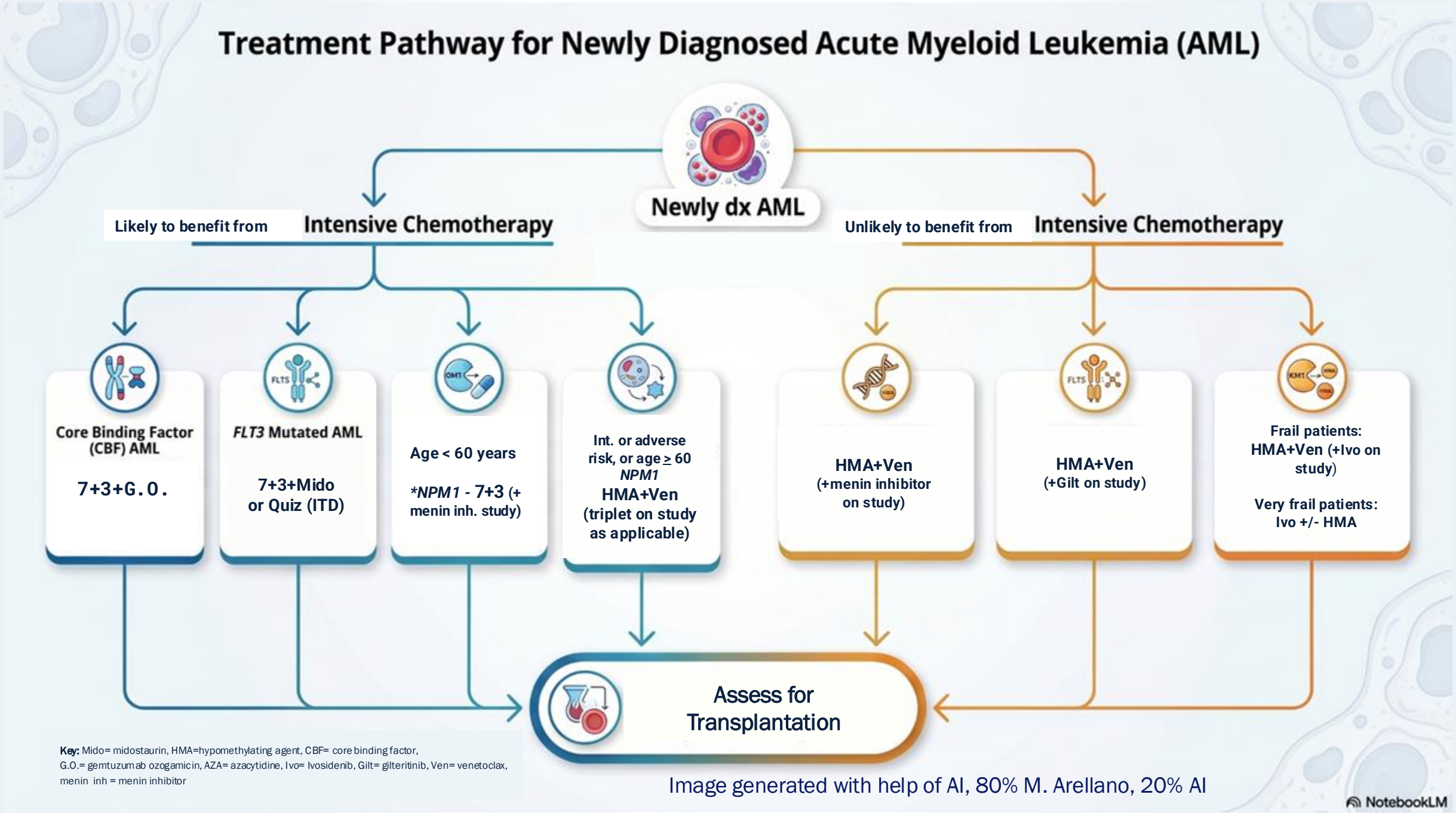
Roboz GJ, Zeidan AM, Mannis GN, et al. N Engl J Med. 2026 Jun 4;394(21):2107-2116. doi: 10.1056/NEJMoa2510223. PMID: 42235013.

Back to our patient

- Received azacitidine plus venetoclax and revumenib triplet on clinical trial.
- Developed grade 2 QTcF prolongation, managed by removing other medications known to prolong QT and dose reduction of study drug.
- Achieved MRD(-)CR after one cycle and continues treatment.

Blood (2025) 146 (Supplement 1): 6.
https://doi.org/10.1182/blood-2025-6

Treatment Pathway for Newly Diagnosed Acute Myeloid Leukemia (AML)



Key: Mido= midostaurin, HMA=hypomethylating agent, CBF= core binding factor, G.O.= gemtuzumab ozogamicin, AZA= azacytidine, Ivo= Ivosidenib, Gilt= gilteritinib, Ven= venetoclax, menin inh = menin inhibitor

Image generated with help of AI, 80% M. Arellano, 20% AI

SUMMARY

- Treatment landscape for patients with AML is changing.
- PARADIGM supports that neither patient age nor fitness alone should determine treatment decisions, rather likelihood to benefit (or not) from intensive (vs. non-intensive) chemotherapy; consider both, patient- and AML-related factors.
- Triplets with HMA-Ven backbone have the potential to increase MRD-negative, and hopefully long-lasting remissions

Blood (2025) 146 (Supplement 1): 6.https://doi.org/10.1182/blood-2025-6

Q&A

marella@emory.edu

678-886-0009