

Acute Leukemia in 2026: A Therapeutic Renaissance

Brittany Knick Ragon, MD
Associate Professor of Cancer Medicine
Atrium Health Levine Cancer Institute
Wake Forest University School of Medicine

Disclosures

Advisory Board: Astellas, Bristol Myers Squibb, Syndax
Protocol Review: NMDP

Objectives

- A new era: the *therapeutic renaissance* in Acute Leukemias
- Review the evolution of Acute Myeloid Leukemia management
 - A new PARADIGM?
 - Less intensive strategies
 - Oral combinations
 - Triplet combinations
 - Novel therapeutic targets
- Chemo-free approaches to Acute Lymphoblastic Leukemia

Goals of Treatment



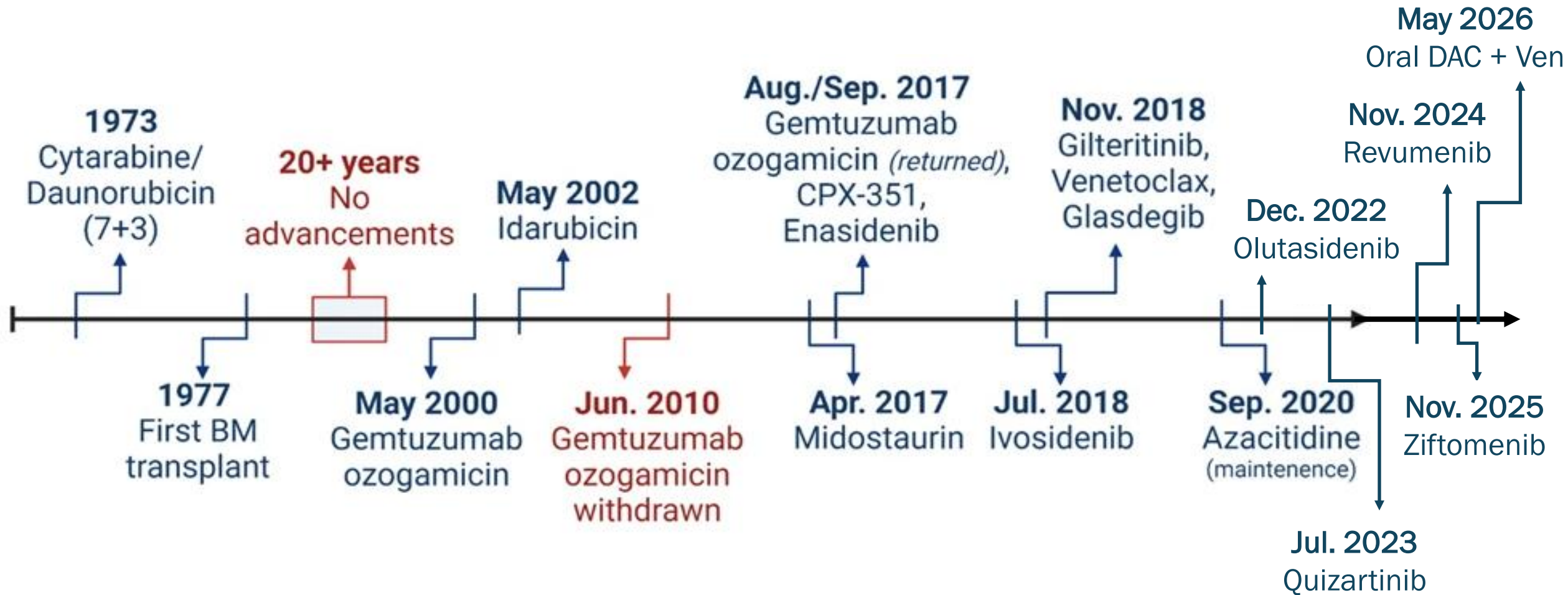
Get rid of the leukemia.



Keep the leukemia away.

*Palliation or cure?

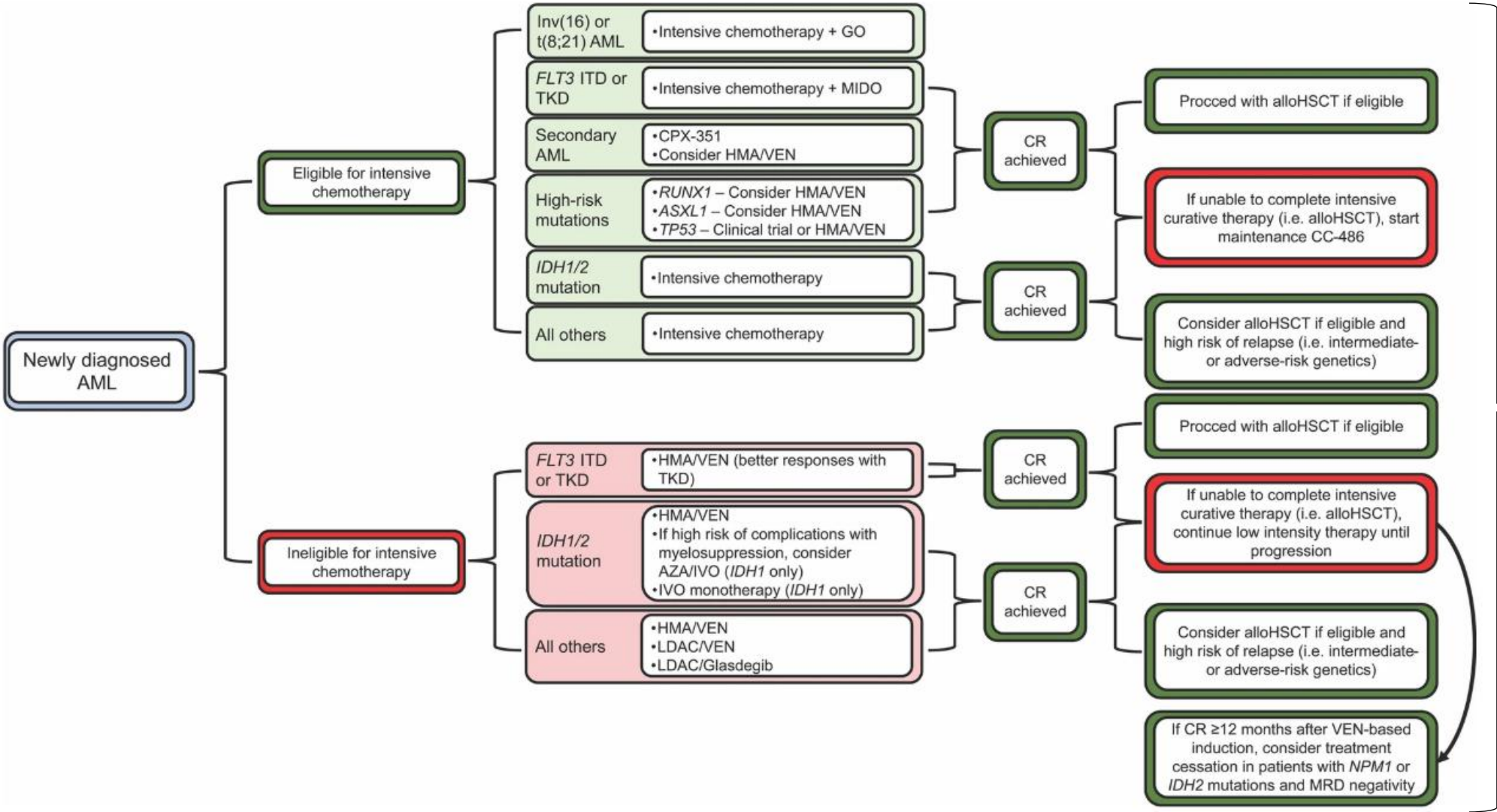
FDA Approved Therapies for AML



“Make haste, slowly”



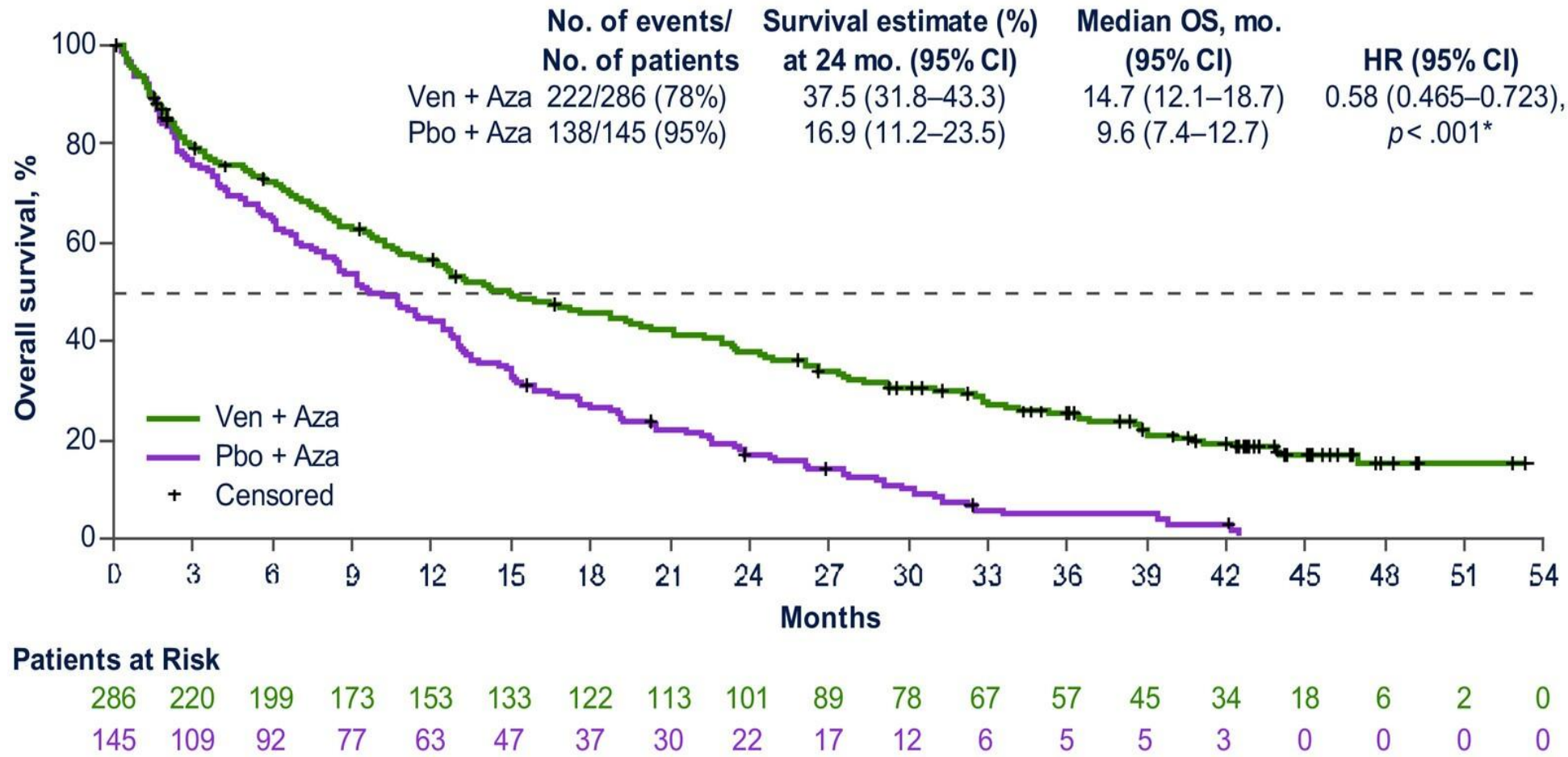
Clinical Practice Considerations in AML



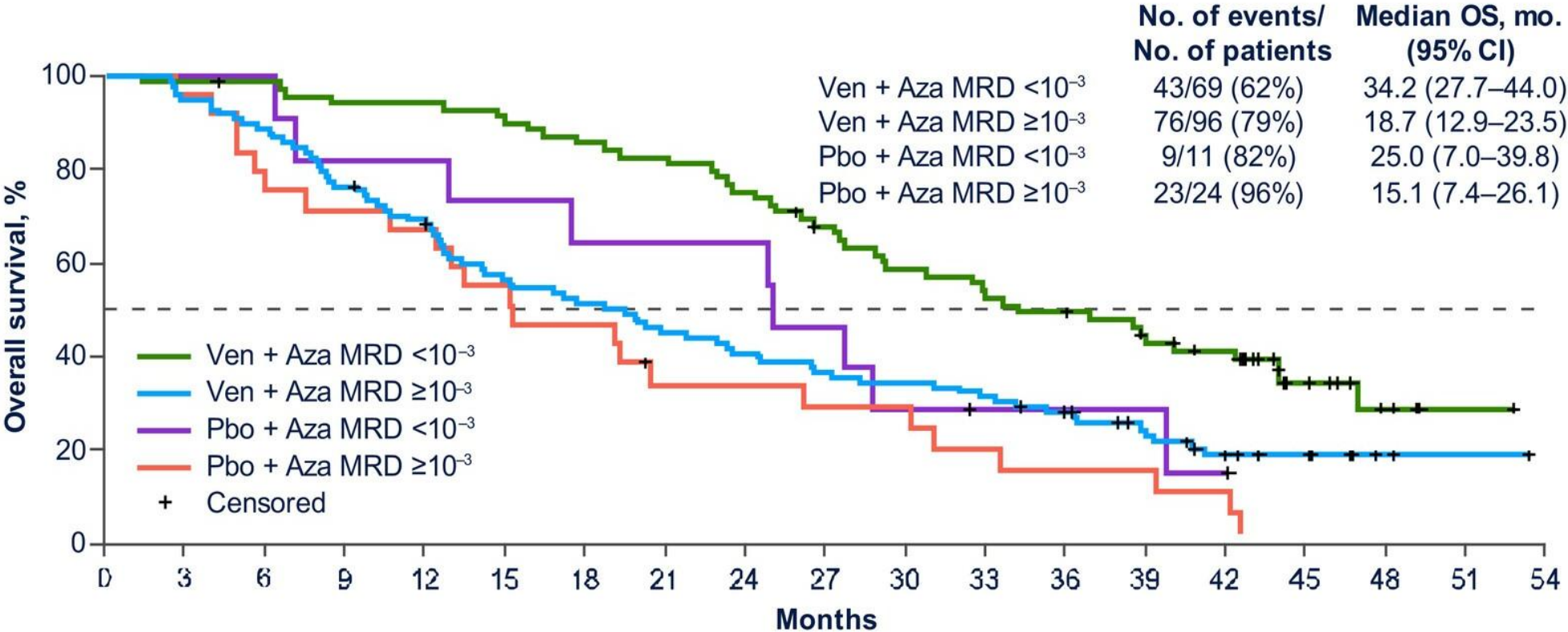
Relapsed/Refractory	
IDH1 ^{mut}	Ivosidenib Olutasidenib
IDH2 ^{mut}	Enasidenib
FLT3 ^{mut}	Gilteritinib Quizartinib
KMT2Ar	Revumenib
NPM1 ^{mut}	Revumenib Ziftomenib
CD33+	Gemtuzumab
Other	Clinical Trial Chemo HMA/LDAC ±Venetoclax

Long-Term Follow-Up of VIALE-A

All Patients



Survival by Measurable Residual Disease Status

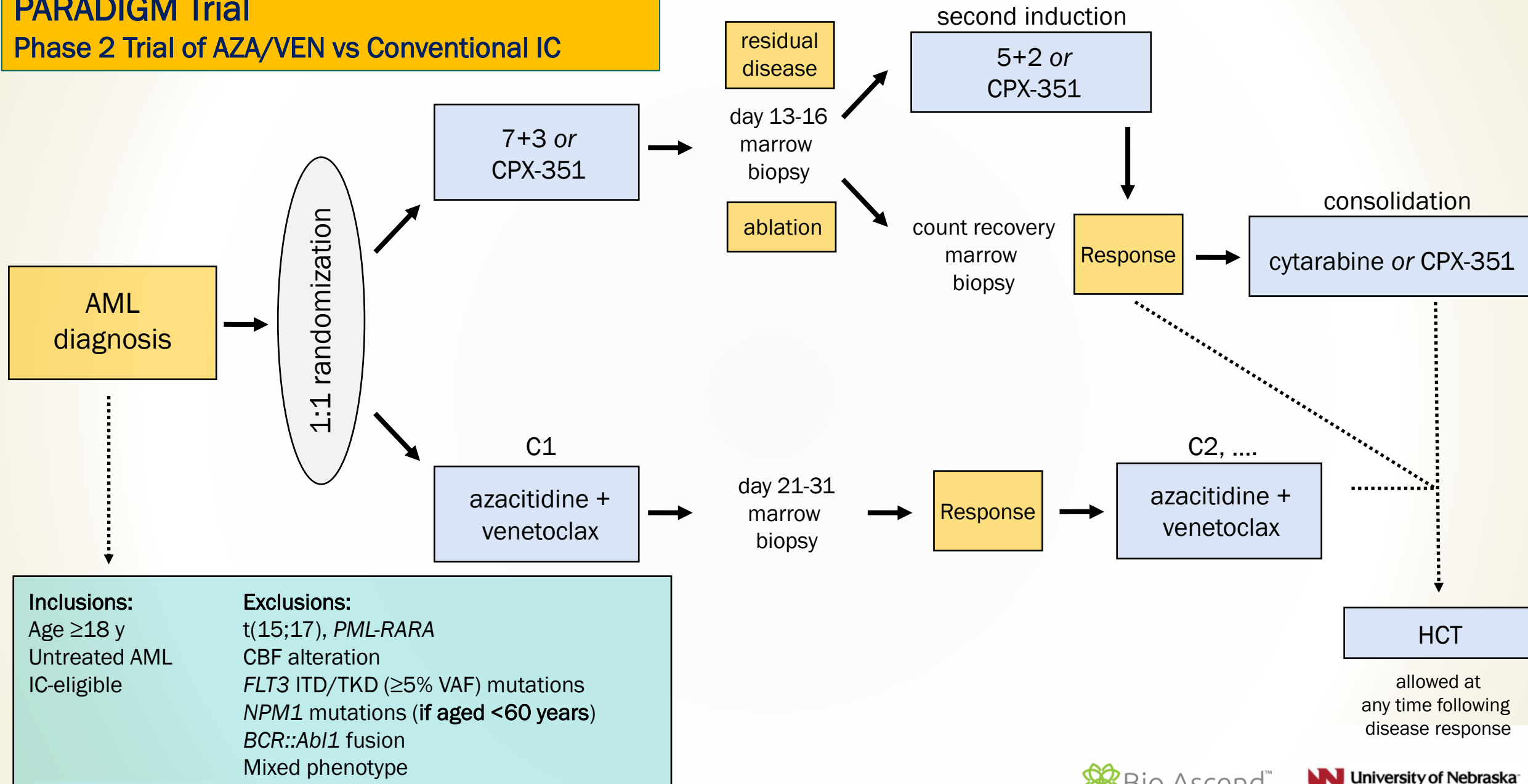


Patients at Risk

69	68	67	64	64	61	57	55	50	43	37	34	31	26	22	10	4	1	0
96	91	85	73	63	52	47	41	37	33	31	28	23	17	10	7	2	11	0
11	11	11	9	9	8	7	7	7	5	3	2	2	2	1	0			
24	23	18	17	16	13	11	7	7	6	6	4	3	3	2	0			

PARADIGM Trial

Phase 2 Trial of AZA/VEN vs Conventional IC

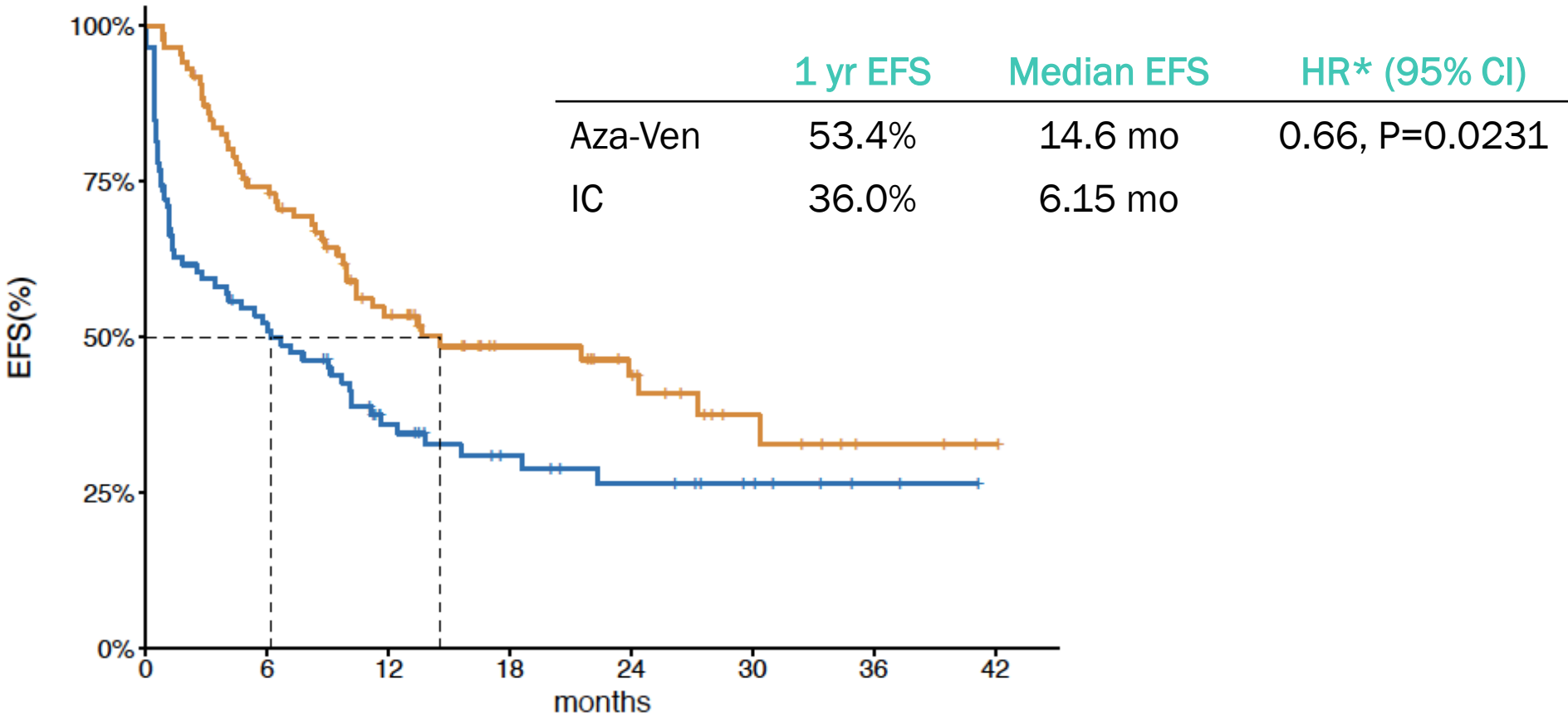


LEAD 2026: Leadership, Empowerment, and Development

PARADIGM Trial: Baseline Characteristics

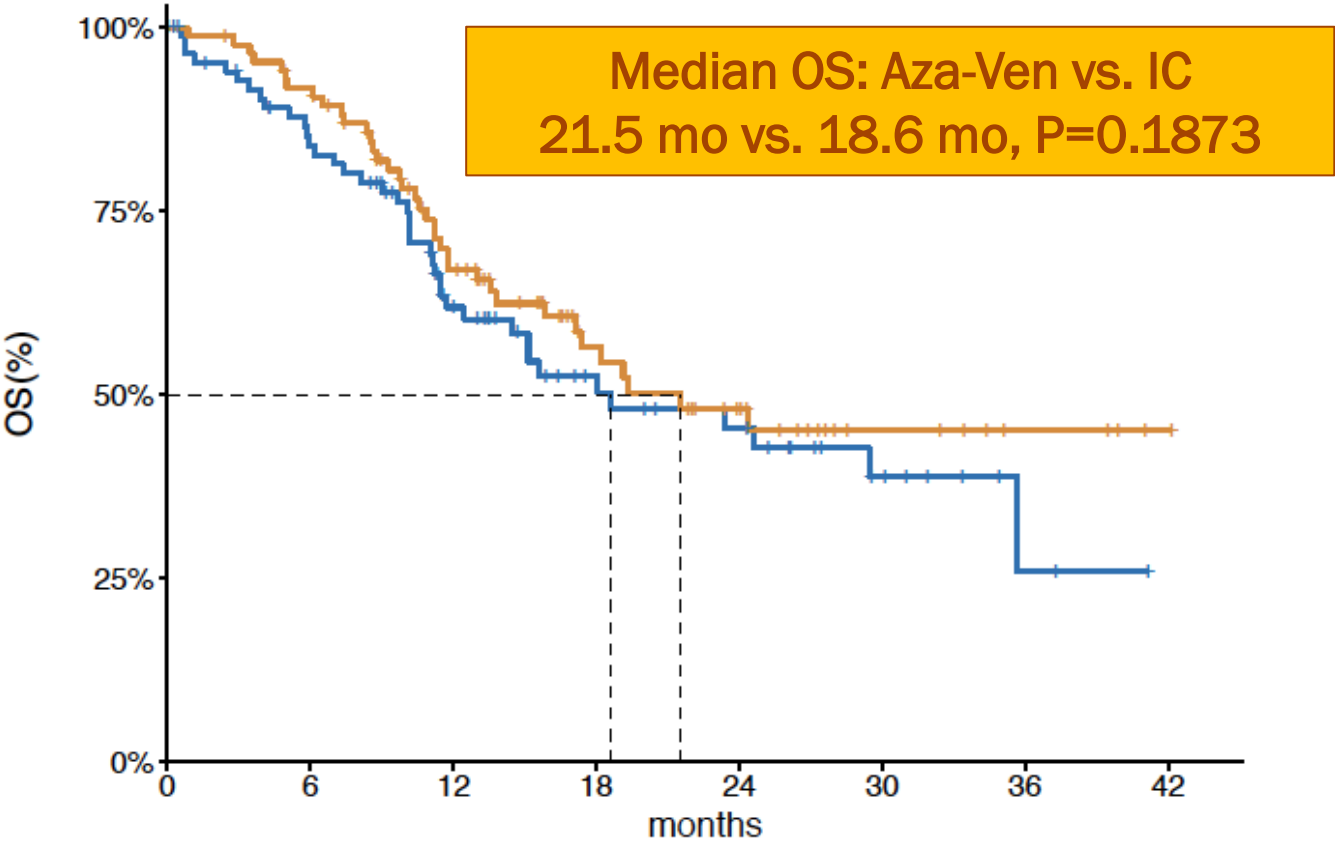
		Total	Aza-Ven	IC
		(N = 172)	(N = 86)	(N = 86)
Age (years)	Median, range	64 (23 - 79)	65 (23 - 79)	64 (28 - 79)
	Less than 65	87 (50.6)	43 (50.0)	44 (51.2)
Sex, n (%)	Male	115 (66.9)	55 (64.0)	60 (69.8)
Race, n (%)	Caucasian	134 (77.9)	65 (75.6)	69 (80.2)
	African American	10 (5.8)	5 (5.8)	5 (5.8)
	Hispanic	13 (7.6)	6 (7.0)	7 (8.1)
	Asian	15 (8.7)	10 (11.6)	5 (5.8)
ECOG, n (%)	0/1	161 (93.6)	79 (91.9)	82 (95.4)
	2	10 (5.8)	7 (8.1)	3 (3.5)
ELN 2022 risk, n (%)	Favorable	22 (12.8)	13 (15.1)	9 (10.5)
	Intermediate	26 (15.1)	15 (17.4)	11 (12.8)
	Adverse	124 (72.1)	58 (67.4)	66 (76.7)
Mutations, n (%)	NPM1	16 (9.3)	11 (12.8)	5 (5.8)
	IDH1	15 (8.7)	8 (9.3)	7 (8.1)
	IDH2	28 (16.3)	19 (22.1)	9 (10.5)
	TP53	25 (14.5)	9 (10.5)	16 (18.6)
	RUNX1	32 (18.6)	14 (16.3)	18 (20.9)
	KRAS/NRAS	32 (18.6)	17 (19.8)	15 (17.5)

PARADIGM Trial: Event-Free Survival



IC	86	43	24	15	11	7	2	0
Aza-Ven	86	62	38	23	17	8	3	1

PARADIGM Trial: Overall Survival



Patients with Relapse or Refractoriness (R/R) to Study Treatment		N (%)
IC arm (N=37)	Subsequent HMA-Ven	25 (67.6)
Aza-Ven arm (N=36)	Subsequent IC	17 (47.2)

PARADIGM Trial: Key Takeaways

Feature	Intensive Chemo	Aza-Ven
Event free survival	Shorter	Longer
Overall response rate	Lower	Higher
Early mortality	Higher	Lower
Hospitalization	Longer	Shorter
Infections	More	Fewer
Hematologic toxicity	High	Lower
Quality of life (2 wk)	Worse	Better
Transplant bridges	Fewer	More
MRD	TBD	TBD

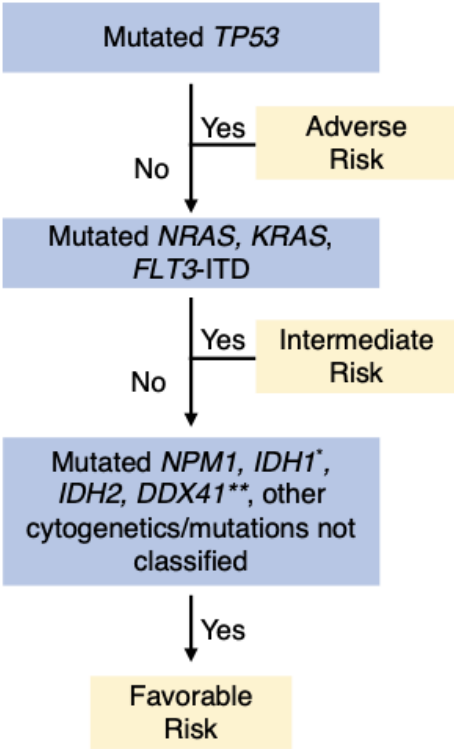
Risk Classifications Accounting for Less Intensive Therapies

ELN 2024 Risk Stratification¹

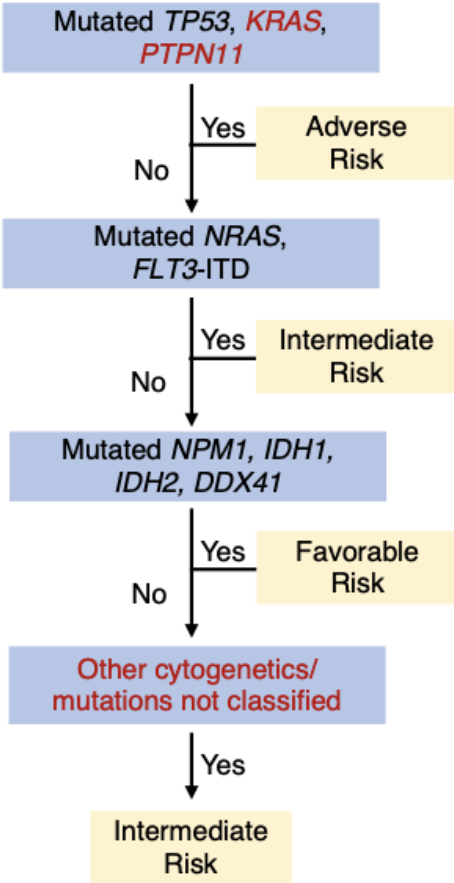
Risk category	Genetic abnormality
Favorable	Mutated <i>NPM1</i> (<i>FLT3</i> -ITD ^{neg} , <i>NRAS</i> ^{wt} , <i>KRAS</i> ^{wt} , <i>TP53</i> ^{wt}) Mutated <i>IDH2</i> (<i>FLT3</i> -ITD ^{neg} , <i>NRAS</i> ^{wt} , <i>KRAS</i> ^{wt} , <i>TP53</i> ^{wt}) Mutated <i>IDH1</i> (<i>TP53</i> ^{wt}) Mutated <i>DDX41</i> Other cytogenetic and/or molecular abnormalities (<i>FLT3</i> -ITD ^{neg} , <i>NRAS</i> ^{wt} , <i>KRAS</i> ^{wt} , <i>TP53</i> ^{wt})
Intermediate	Other cytogenetic and molecular abnormalities (<i>FLT3</i> -ITD ^{pos} and/or <i>NRAS</i> ^{mut} and/or <i>KRAS</i> ^{mut} ; <i>TP53</i> ^{wt})
Adverse	Mutated <i>TP53</i>

ELN 2024 Refined Risk Stratification²

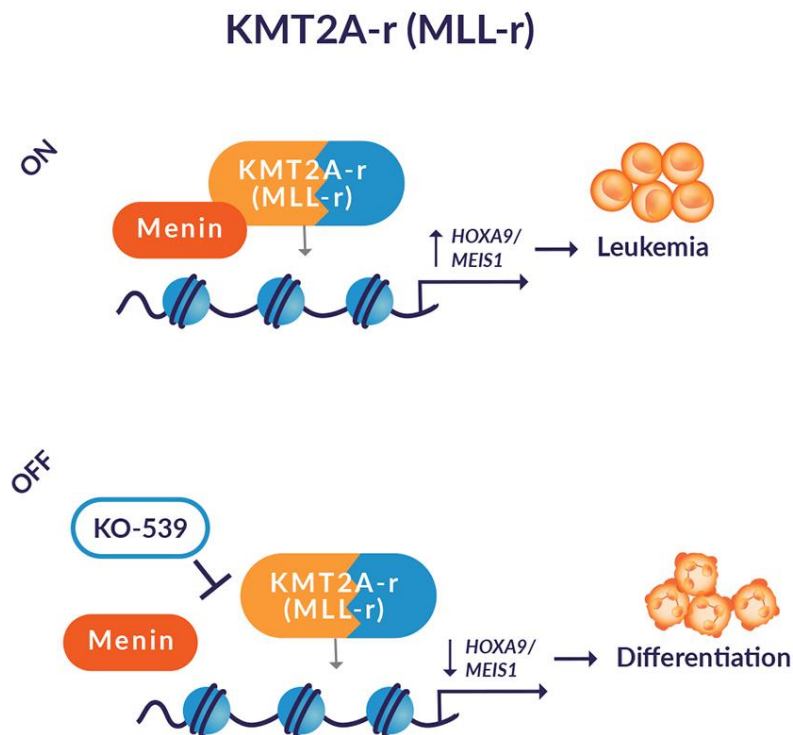
Current hierarchal ELN24 stratification



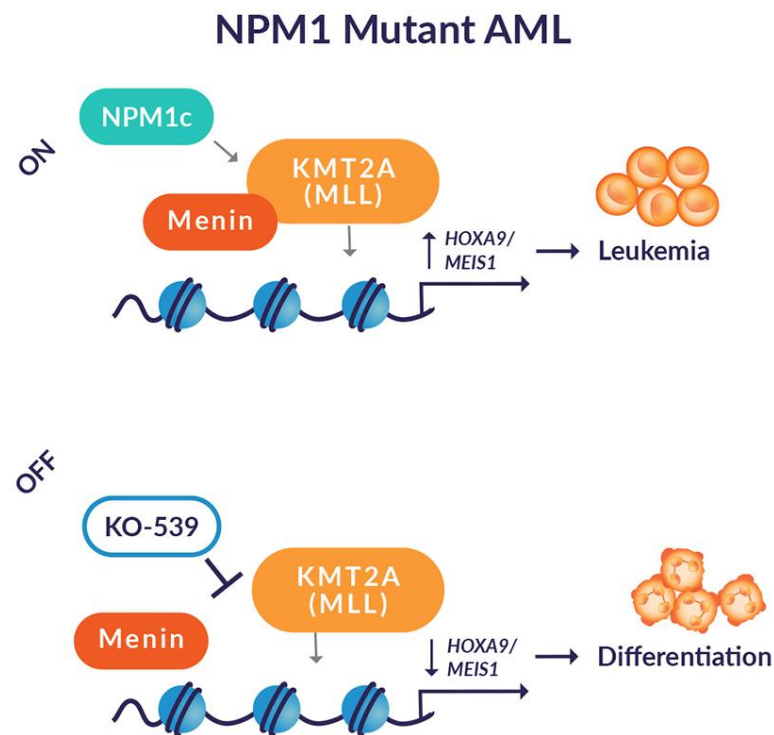
Revised hierarchal ELN24 stratification



Menin Inhibition: Targeted Therapy for Two Distinct AML Subsets



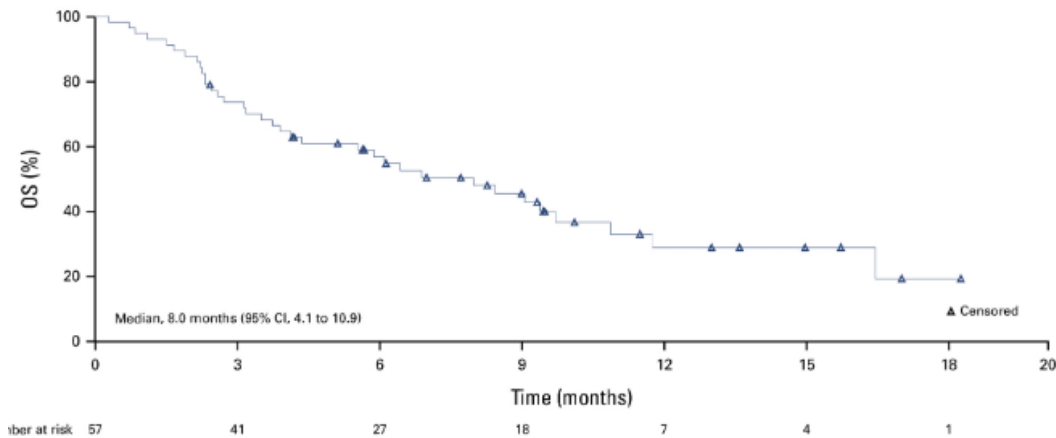
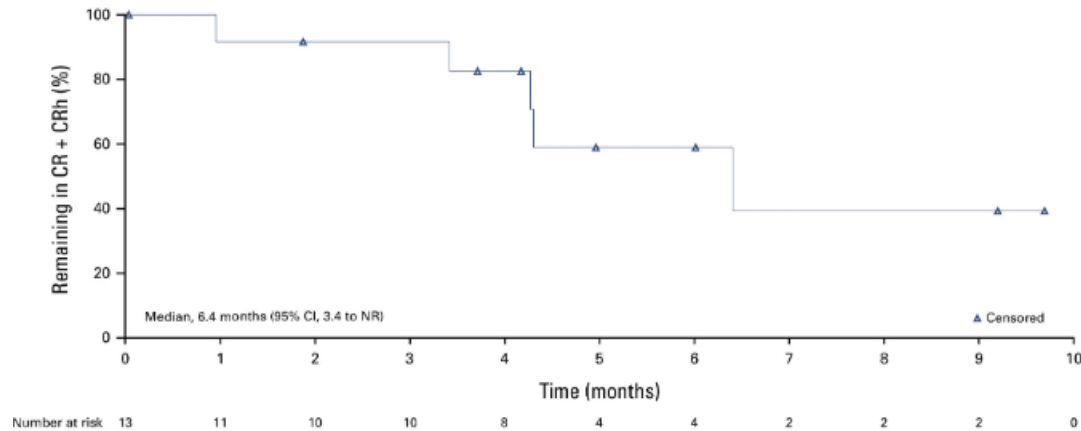
Targeting the menin-KMT2A(MLL) interaction to reverse epigenetic dysregulation in MLL-rearranged AML



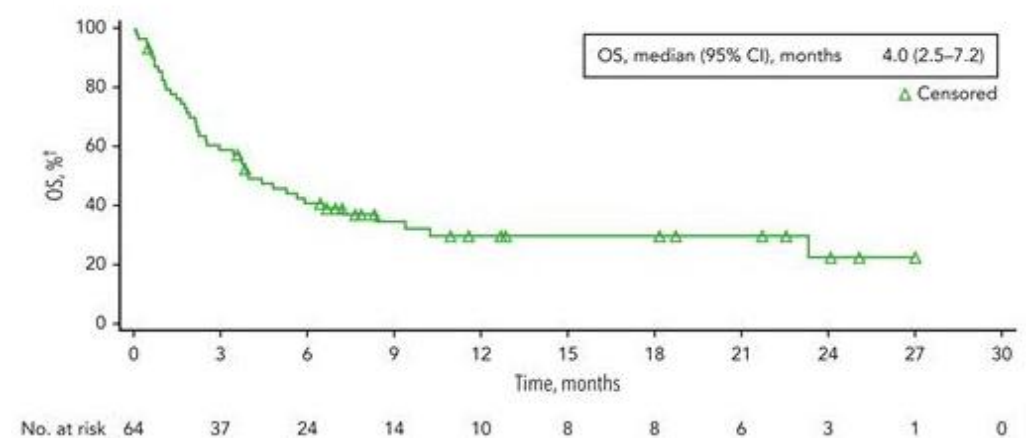
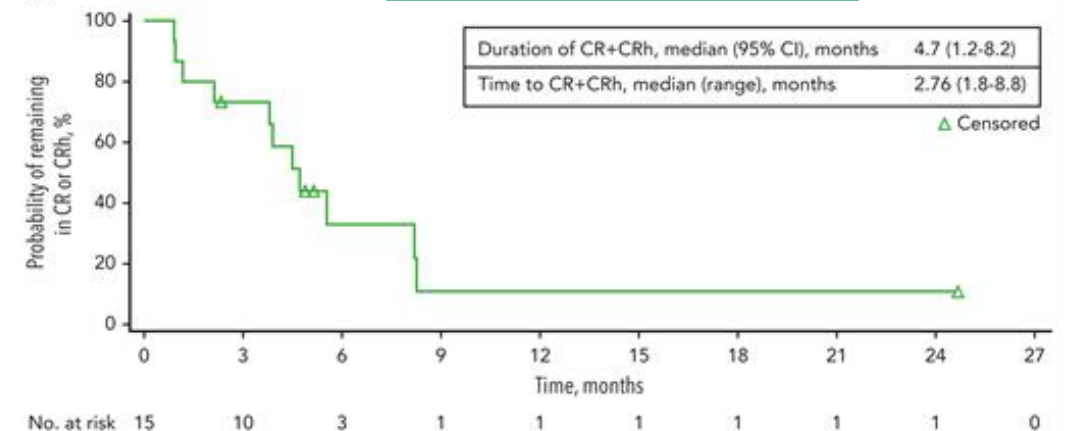
A central role for menin-KMT2A(MLL) interaction in epigenetic dysregulation in NPM1-mutant AML

AUGMENT-101: Revumenib for *KMT2A*-Rearranged and *NPM1*-mutated R/R AML

KMT2A-Rearranged



NPM1-Mutated



Intensive Chemotherapy + Menin Inhibitor Combinations in Newly Diagnosed Fit AML

	7+3 + Revumenib N=9	IC + Revumenib N=35	7+3 + Ziftomenib N=99	7+3 + Bleximenib N=24
Trial	ETCTN 10596 ¹	SNDX-5613-0708 ²	KOMET-007 ³	ALE1002 ⁴
Population	Newly Dx AML NPM1m, KMT2Ar, NUP98r	Newly Dx AML NPM1m, KMT2Ar, NUP98r	Newly Dx AML NPM1m, KMT2Ar	Newly Dx AML NPM1m, KMT2Ar
Therapeutic Dose(s)	220 mg BID; 270 mg BID Dose-adjusted with azoles	220 mg BID; 270 mg BID Dose-adjusted with azoles	600 mg QD	100 mg BID
ORR	--	97%	95%	96%
CR/CRh	--	97%	93%	75%
CR	89%	77%	88%	--
Gr. ≥ 3 QTC	0	9%	0	0
DS (any)	0	5%	4%	0

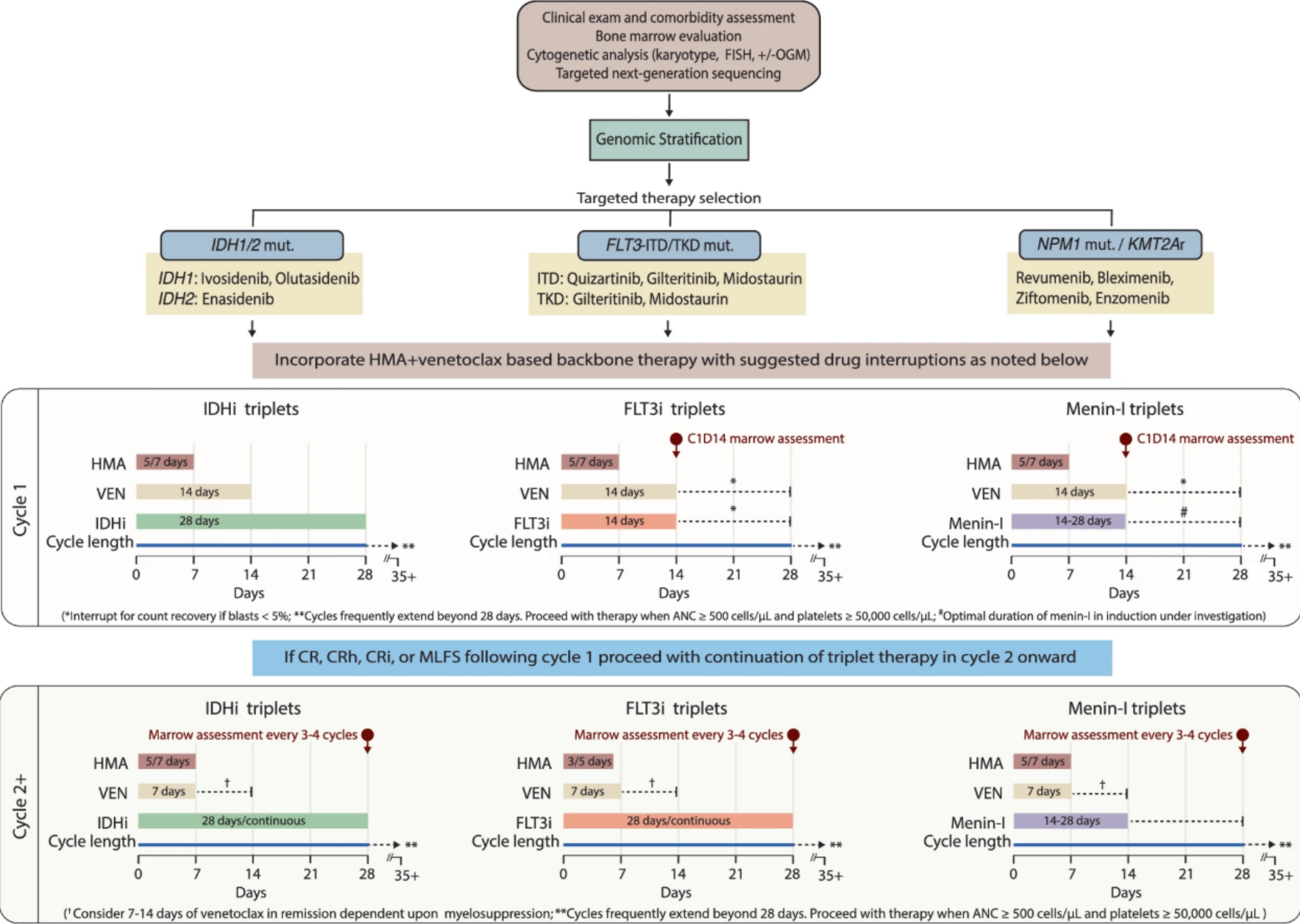
LEAD 2026: Leadership, Empowerment, and Development

1. Mims, *Blood* [ASH] 2025; 2. Aldoss, *HemaSphere* [EHA] 2026; 3. Zeidan, *HemaSphere* [EHA] 2026; 4. Dohner, *Blood* [ASH] 2025.

Azacitidine/Venetoclax + Menin Inhibitor Combinations in Newly Diagnosed Older/Unfit AML

	AZA/VEN + Revumenib (D1-28)		ASTX727/VEN + Revumenib (D1-28)		AZA/VEN + Ziftomenib (D8-28)	AZA/VEN + Bleximenib (D4-28)	
Trial	Beat AML¹		SAVE²		KOMET-007³	ALE1002⁴	
Population	Newly Dx AML ≥60 years NPM1m, KMT2Ar		Newly Dx AML or MPAL >18 years unfit NPM1m, KMT2Ar, NUP98r		Newly Dx AML >18 years unfit NPM1m	Newly Dx AML >18 years unfit NPM1m, KMT2Ar	
Therapeutic Dose(s)	220 mg BID; 270 mg BID Dose-adjusted with azoles		220 mg BID; 270 mg BID Dose-adjusted with azoles		600 mg daily	100 mg BID	
Subtype	KMT2Ar n=9	NPM1m n=34	KMT2Ar n=7	NPM1m n=14	NPM1m n=34	KMT2Ar n=4	NPM1m n=16
ORR	100%	85%	86%	86%	89%	75%	94%
CR/CRh	78%	68%	86%	79%	78%	75%	75%
CR	78%	65%	86%	71%	73%	NR	NR
Gr. ≥3 QTC	12%		0		3%	NR	
DS (any)	19%		19%		3%	NR	

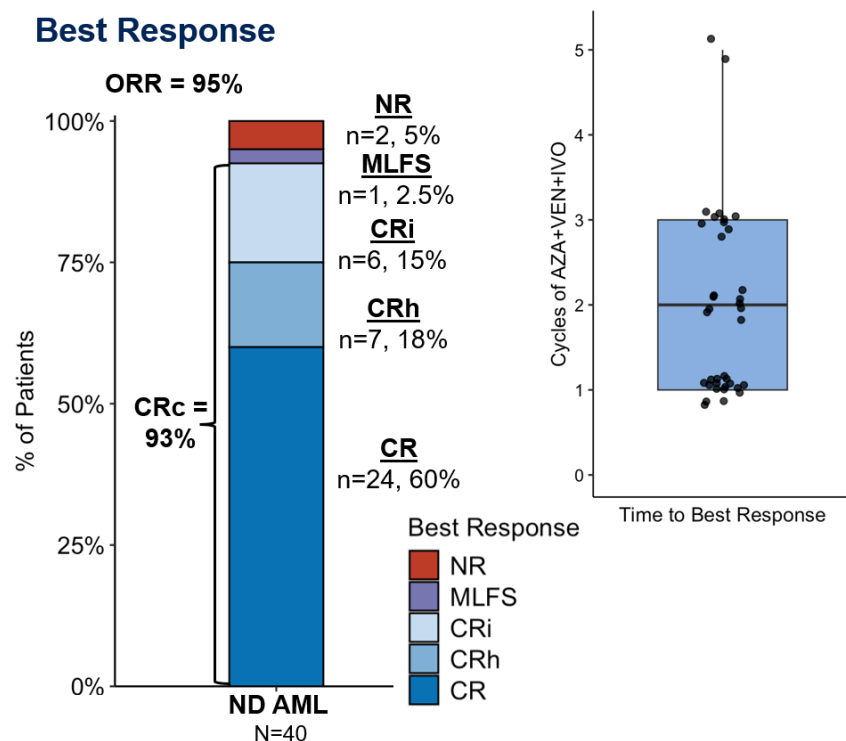
Practical Considerations for Triplet Combinations



AZA+VEN+Ivosidenib: Key Results – ASCO 2026

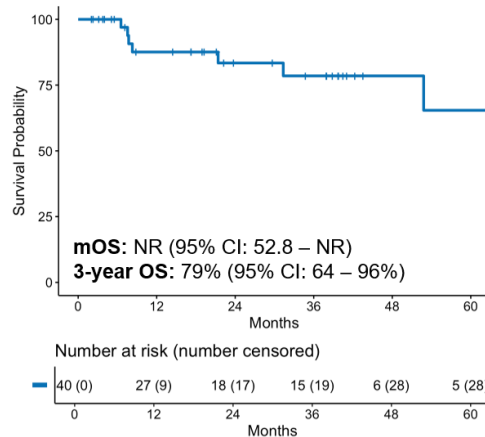
Primary Objective: Overall Response Rate

Best Response

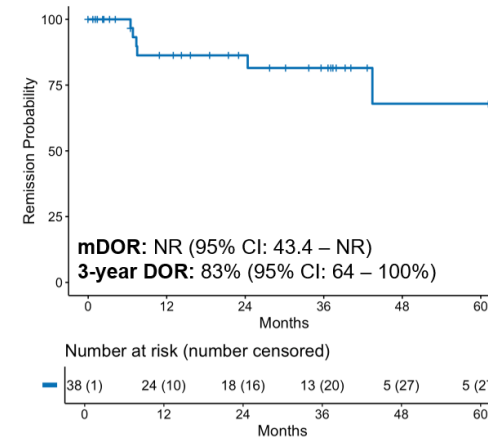


Secondary Objectives: Overall Survival, Duration of Remission, Cumulative Incidence of Relapse

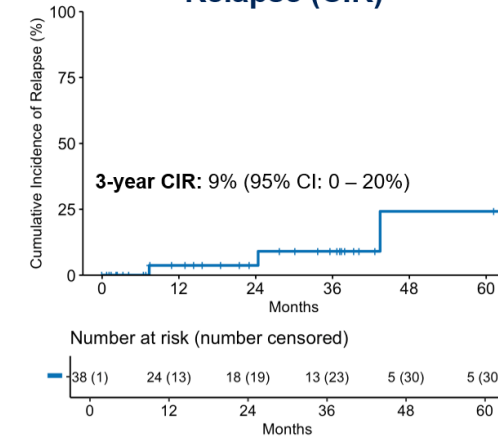
Overall Survival (OS)



Duration of Remission (DOR)



Cumulative Incidence of Relapse (CIR)



Median follow up: 35 months (95% CI: 19.3 – 40.5)

¹Censored at last known follow up

Quizartinib+Decitabine+VEN: Key Results – ASCO 2026

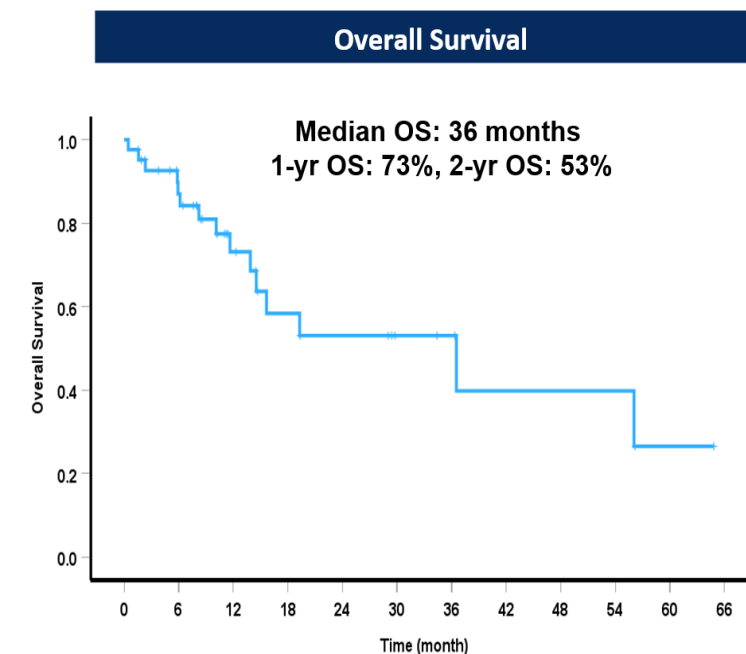
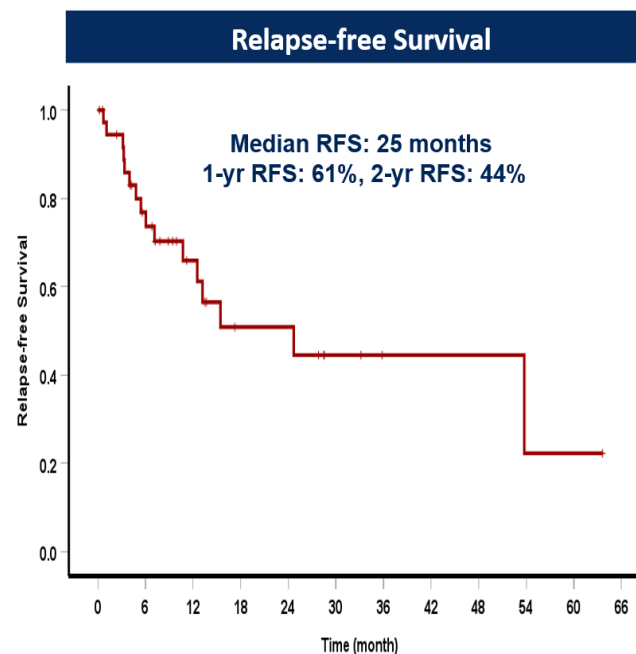
Primary Objective: Modified Composite Complete Remission

Secondary Objectives: Relapse-Free and Overall Survival in Newly Diagnosed Patients

Response*, N (%)	Newly Diagnosed Cohort (N=42)	Relapse/Refractory Cohort (N=46)
Hematologic Response		
mCRc	38 (91)	28 (61)
CR	30 (72)	5 (10)
CRi	7 (17)	8 (18)
MLFS	1 (2)	15 (33)
No response	3 (7)	17 (37)
Induction death	1 (2)	1 (2)
MRD at the end of cycle 1, N (%)		
Flow Cytometry Negative	19/31 (61)	3/25 (12)
FLT3-ITD PCR Negative	11/18 (61)	7/25 (28)
FLT3-ITD NGS Negative (< 5 x 10 ⁻⁵)	4/23 (17)	-
MRD at the end of cycle ≥2 (best), N (%)		
Flow Cytometry Negative	22/31 (71)	7/26 (27)
FLT3-ITD PCR negative	19/22 (86)	10/26 (38)
FLT3-ITD NGS Negative (< 5 x 10 ⁻⁵)	23/27 (85)	-
Bridge to bone marrow transplant	15 (36)	17 (37)

mCRc, modified composite complete remission; CRi, CR with incomplete count recovery; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; PCR, polymerase chain reaction; NGS, next generation sequencing

Musa Yilmaz, MD



Practice Change Consideration:

Chemo-Free Induction for Philadelphia chromosome–positive (Ph+) B-cell Acute Lymphoblastic Leukemia

Study	Regimen	Median Age (Years)	Complete Response	Complete Molecular Response	DFS Rate (Year)	OS Rate (Year)
CALGB 10701	Dasatinib + dexamethasone	60	95.4%	39.5%	37% (5)	48% (5)
LAL1811	Ponatinib + prednisone	66.5	95.0%	61.4%	--	88% (1)
D-ALBA	Dasatinib + blinatumomab	54	98.0%	55.0%	76% (4)	81% (4)
SWOG S1318	Dasatinib + blinatumomab	73	92.0%	55.0%	77% (3)	75% (3)
Ponatinib + Blinatumomab	Ponatinib + blinatumomab	56	93.0%	87.0%	80% (2) EFS	90% (2)

Conclusions

- Gladly welcoming the therapeutic renaissance in Acute Leukemia
 - Increased opportunities to “de-intensify” treatments
 - More oral options
 - Moving from doublets to triplets
- Treatment is shifting from age-based to biology-based
- Anticipate future treatment algorithm based on disease biology and patient preference