Practical Strategies for Managing Leukemias: Managing the Patient Who is Not Eligible for Intensive Chemotherapy and Development of Small Molecule Targeted Therapy

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Indy Rare Diseases Symposium

THE UNIVERSITY OF CHICAGO

Conflict of Interest Statement

Consulting or Advisory Role: AstraZeneca, Genentech, AbbVie, Adaptive Biotechnologies, Celgene, Pharmacyclics, CVS Health
Research Funding: AbbVie (Institutional), Syndax (Institutional), Merck (Institutional), TG Therapeutics (Institutional), Nurix (Institutional)
Expert Testimony: Apotex

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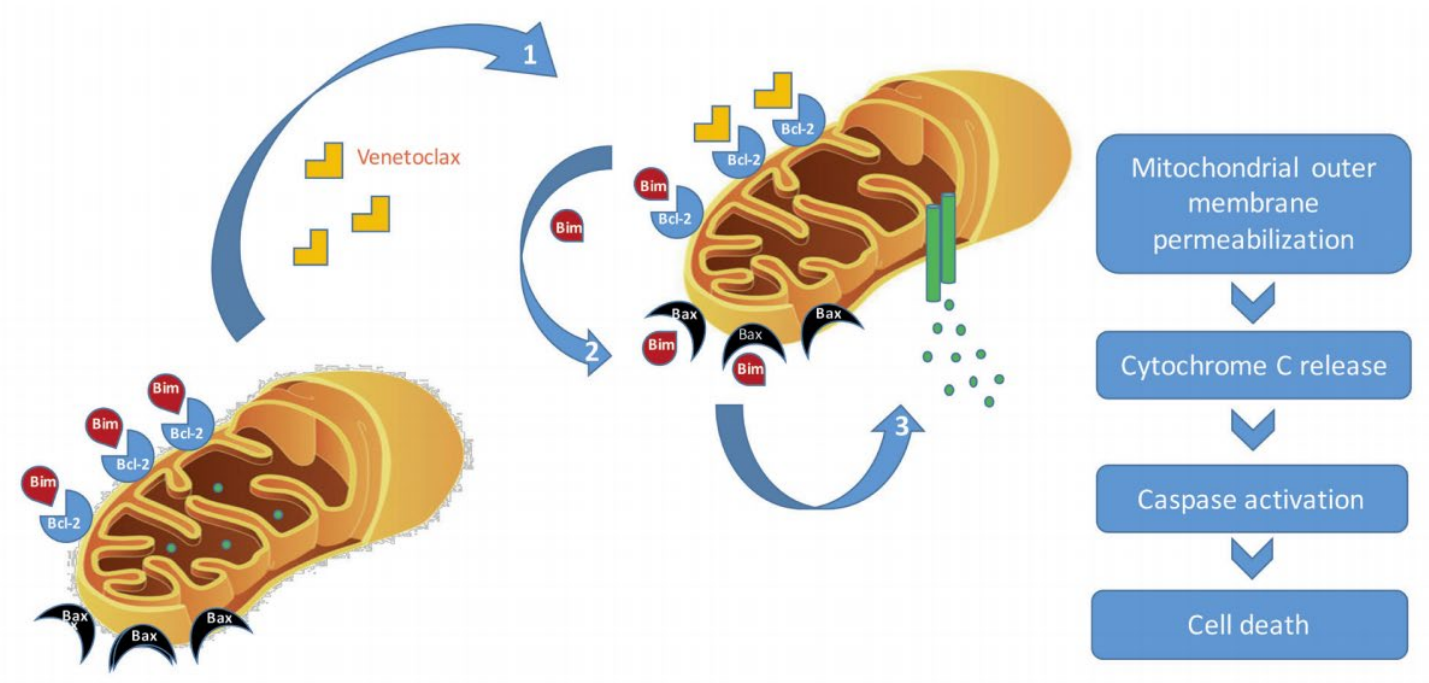
BCL-2 Inhibitor: Venetoclax



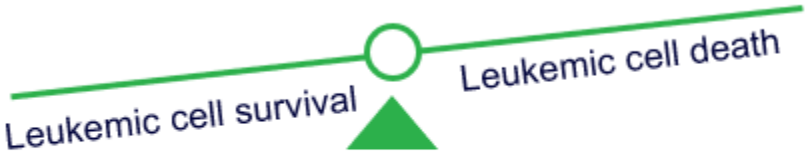
- BCL-2 stabilizes mitochondria, preventing activation of proapoptotic proteins.
- Inhibition of BCL-2 enables apoptosis.
- BCL-2 expression is elevated in high-risk MDS and AML.

Sharma P, Pollyea DA. *Curr Hematol Malig Rep* 2018;13:256-264.
Janssens A. *Belg J Hematol* 2017;8:265-271.

BCL-2 and AML

A healthy cell with **normal expression** of BCL-2 pro-survival proteins has **balanced cell survival and cell death**

An AML cell with **overexpressed** BCL-2 pro-survival proteins sequesters and prevents the activation of pro-death proteins, **enhancing leukemic cell survival**



- ~80% of AML patients overexpress BCL-2.
- Relatively limited single-agent activity (CR/Cri 19%, predominantly IDH-mutant).

Based on Plati et al, 2011; Hanahan et al, 2000; Lagadinou et al, 2013.

VIALE-A Study Design

Viale-A (NCT02993523) – Phase 3 randomized, double-blind study of VEN + AZA vs PBO + AZA in treatment-naïve patients with AML who are ineligible for standard induction therapy

Viale-a
Venetoclax Trial in AML with Azacitidine

Phase 3
1L AML Ineligible for Standard Induction

Randomized 2:1

28-day cycles

Venetoclax: 400 mg PO, daily, days 1–28
+ AZA: 75 mg/m^2 SC/IV daily, days 1–7 (N=286)

PBO: PO, daily, days 1–28
+ AZA: 75 mg/m^2 SC/IV daily, days 1–7 (N=145)

Until disease progression, unacceptable toxicity, withdrawal of consent, or meet other protocol criteria for discontinuation

Key inclusion criteria
- Ineligible for standard induction therapy
- ≥75 years
- ≥18 years with comorbidities

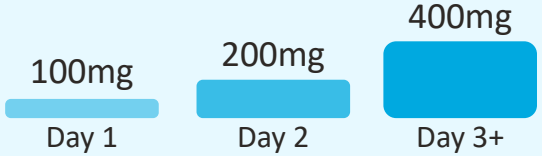
Key exclusion criteria
- Prior HMA treatment for MDS
- APL or favorable risk cytogenetics
- Active CNS involvement with AML
- Prior MPN

Primary endpoint: Overall Survival

Secondary endpoints:
- Composite CR (CR+CRi) rate
- CR rate, CR+CRh rate
- CR+CRi rate by initiation of Cycle 2
- Transfusion independence
- CR+CRi and OS in molecular subgroups
- Fatigue and GHS/QoL
- EFS

Study designed to detect a **30% reduction in mortality with 86.7% power** and a **significance level with two-sided alpha of 0.04. (HR=0.7)**

Venetoclax Ramp-Up (Cycle 1)

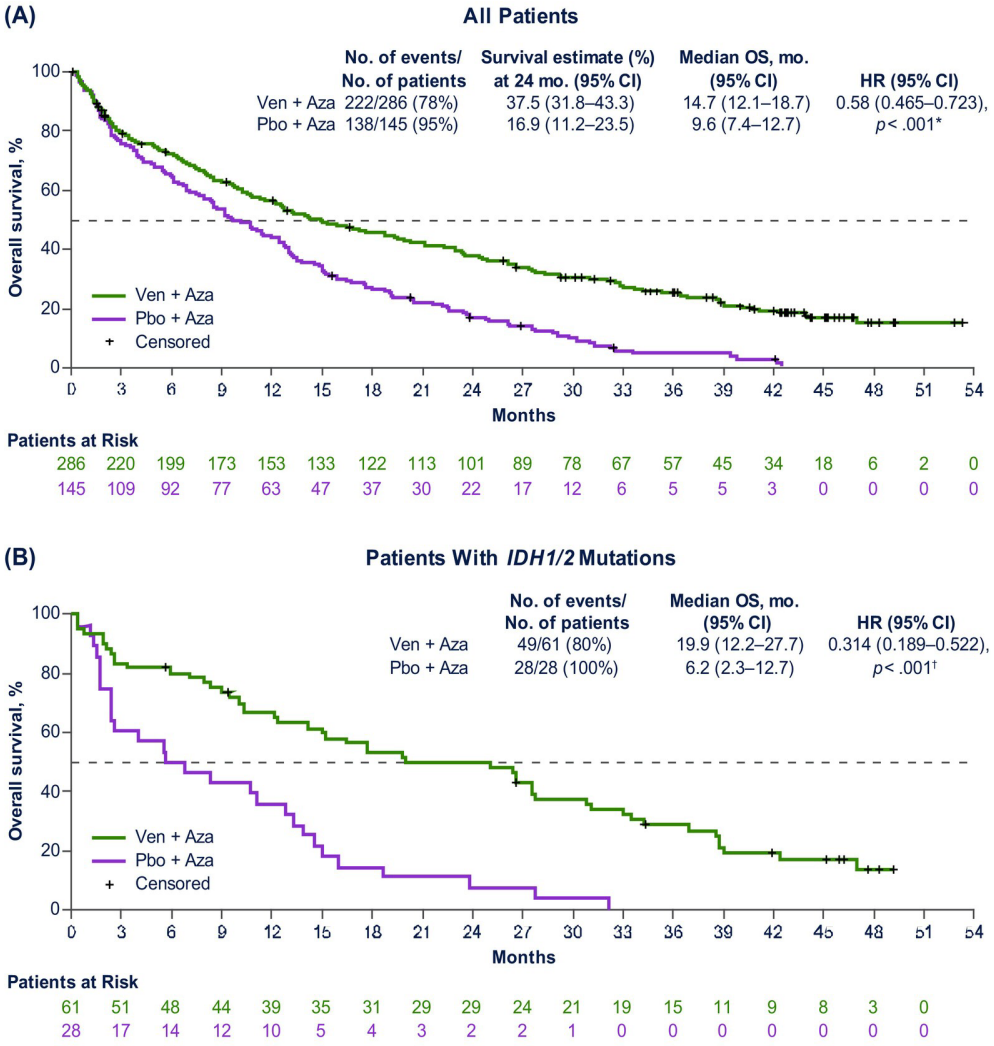


Randomization stratification
- AML cytogenetic risk (intermediate or poor)
- Age (18–<75 or ≥ 75)
- Region (US, EU, China, Japan, rest of world)

1L=First-Line. AML=Acute Myeloid Leukemia. APL=Acute Promyelocytic Leukemia. AZA=Azacitidine. CNS=Central Nervous System. CR=Complete Response. CRi=CR with Incomplete Blood Count Recovery. CRh=CR with Partial Hematologic Recovery. ECOG PS=Eastern Cooperative Oncology Group Performance Status. EFS=Event Free Survival. GHS=Global Health Status. HMA=Hypomethylating Agent. HR=Hazard Ratio. IV=Intravenous. MDS=Myelodysplastic Syndromes. MPN=Myeloproliferative Neoplasms. OS=Overall Survival. PBO=Placebo. PO=Oral. QoL=Quality of Life. SC=Subcutaneous. VEN=Venetoclax.

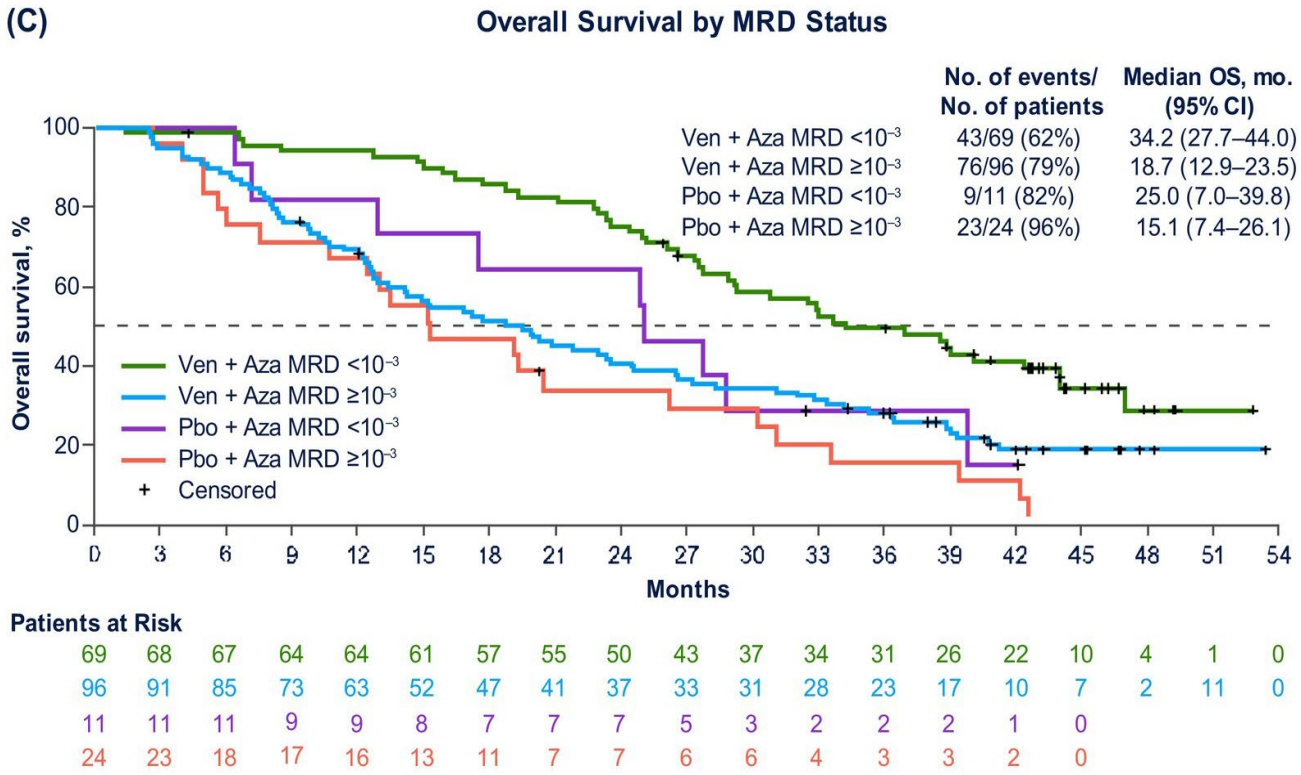
Data on File, Abbvie Inc. ABVRRTI70104.
ClinicalTrials.gov. NCT02993523 (accessed Apr 2020).
DiNardo CD, et al. Oral LB2601. 25th EHA Congress. June 11-21, 2020.

Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia



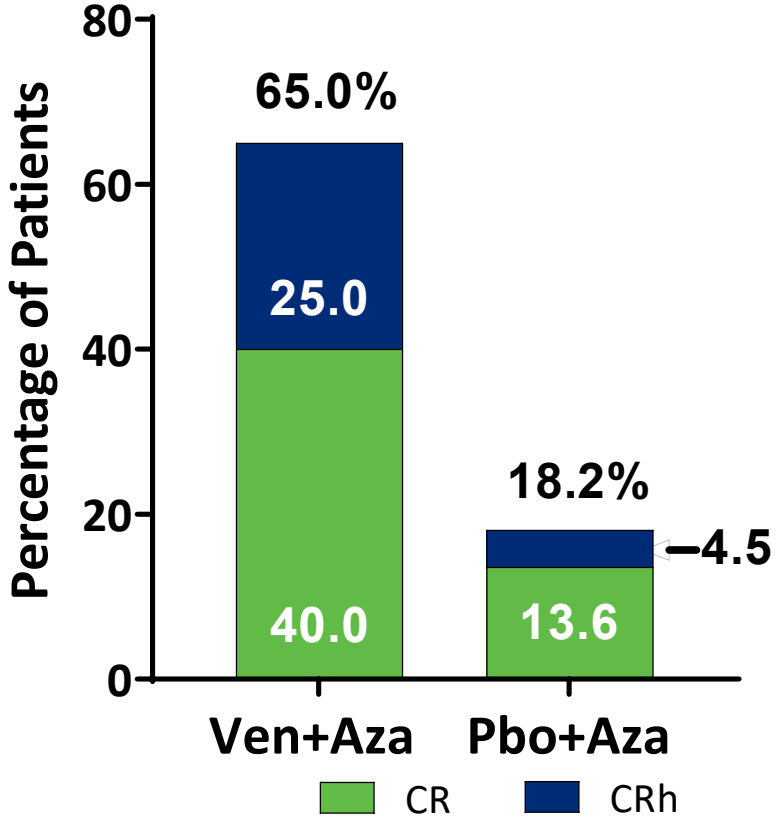
Pratz et al. American J Hematol, Volume: 99, Issue: 4, Pages: 615-624, February 2024, DOI: (10.1002/ajh.27246)

Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia



Pratz et al. American J Hematol, Volume: 99, Issue: 4, Pages: 615-624, February 2024, DOI: (10.1002/ajh.27246)

Impact of FLT3 Mutation on Outcomes after Venetoclax and Azacitidine for Patients with Treatment-Naïve Acute Myeloid Leukemia

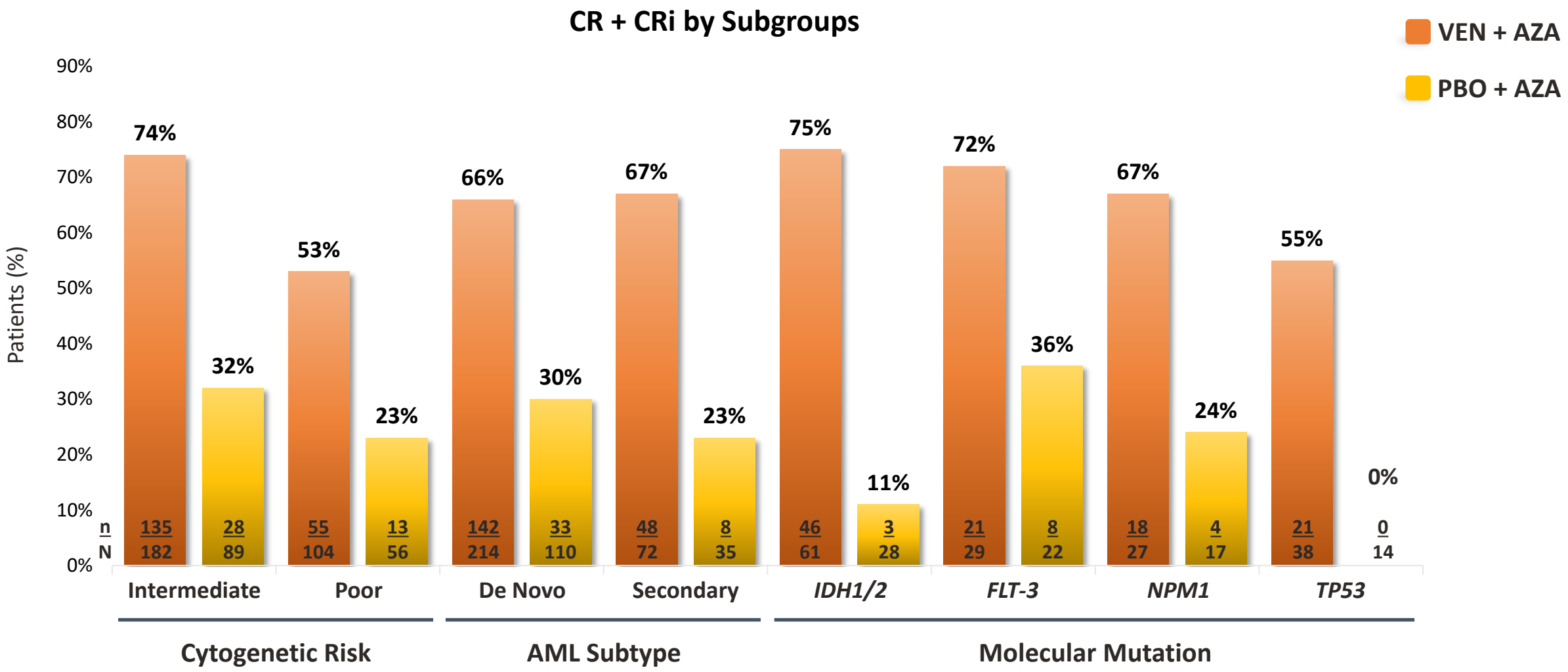


	Median Ven cycles, No. (range)	Median time to CR/CRh, months (range)	CR+CRh by initiation of cycle-2, n (%)	Median duration of CR/CRh#, months (95% CI)
Ven+Aza (n=40)	7.0 (1.0 — 31.0)	1.0 (0.8-4.8)	17 (43)	18.3 (10.1-NR)
Pbo+Aza (n=22)	5.0 (1.0 — 21.0)	3.2 (1.8-3.6)	0	15.1 (13.9-NR)

Aza: Azacitidine; CR: Complete remission; CRh: CR with partial hematologic recovery; NR: Not reached; PBO: Placebo; Ven: Venetoclax;; # Median duration of response was evaluated in responders: Ven+Aza (n=26); Pbo+Aza(n=4); CR was defined as absolute neutrophil count >10^3/µL, platelets >10^5/µL, red cell transfusion independence (TI); and bone marrow with <5% blasts;; CRh was defined as all the criteria for CR, except for neutropenia >0.5 X10^3/µL, and platelets >0.5 x 10^5 /µL; Median duration of follow-up of FLT3 mutated patients: VIALE-A (Ven+Aza: 19.9 months [range: 0-30.1]); Pbo+Aza: 20.5 months [range: 0.2-28.8]); Phase 1b (29.1 months [range: 0.4-38.6])

Konopleva et al. Clin Cancer Res. 2022;28(13):2744-2752. doi:10.1158/1078-0432.CCR-21-3405

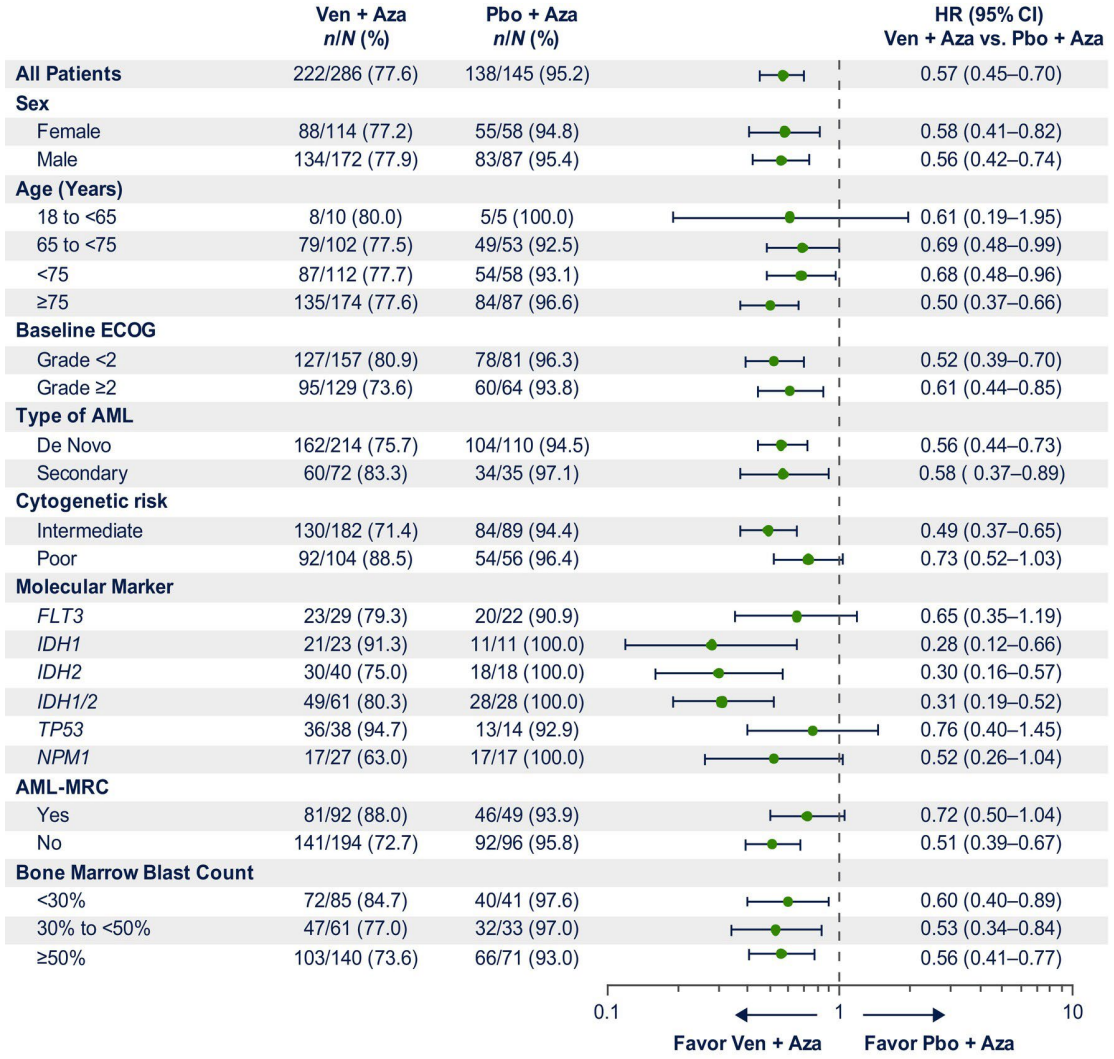
VIALE-A: Response Rates (CR+CRi) by Subgroups



- AZA=Azacitidine. CR=Complete Remission. CRi=CR with Incomplete Count Recovery. PBO=Placebo. VEN=Venetoclax.

- Data cutoff date: January 4, 2020.
- DiNardo CD, et al. Oral LB2601. 25th EHA Congress. June 11-21, 2020.

Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia



	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 et al. American J Hematol, Volume: 99, Issue: 4, Pages: 615-624, February 2024, DOI: (10.1002/ajh.27246)

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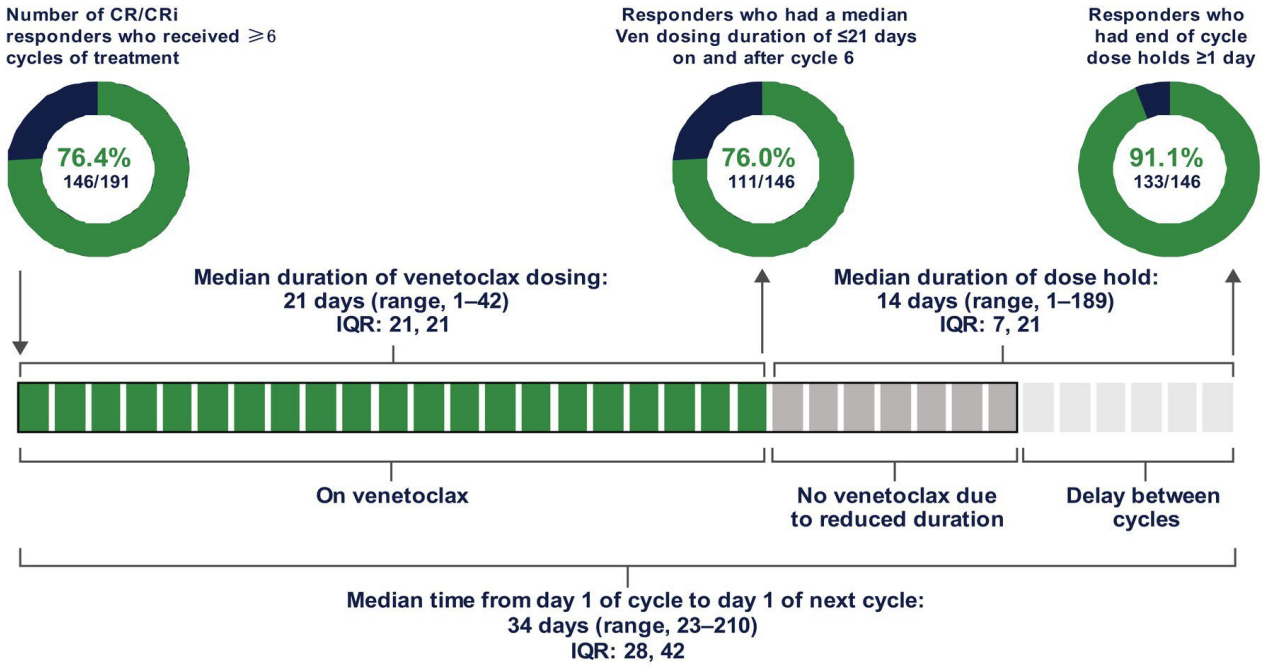

	Ven + Aza (*N* = 282)
Patients who achieved CR/CRi as best response, no. (%)	191 (68)
Median no. of cycles (range)	13 (1–46)
Responders who had ≥6 cycles, no./No. (%)	146/191 (76)

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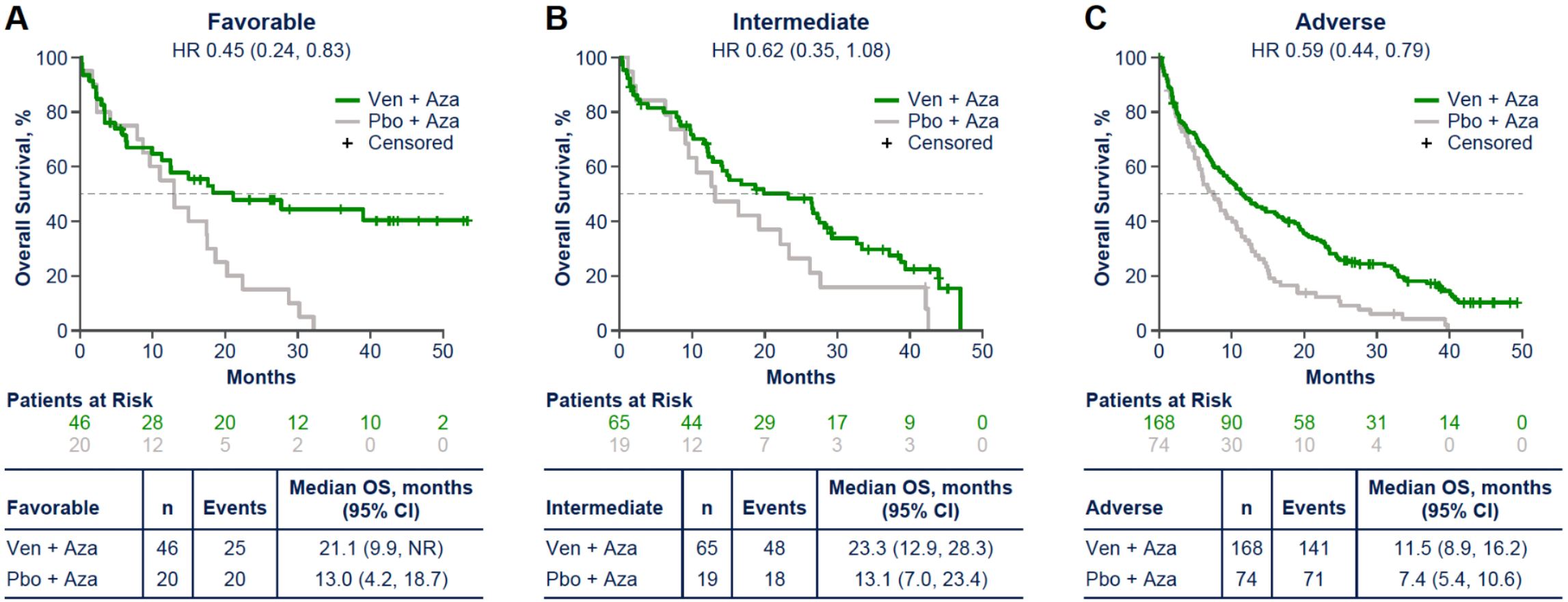
2022 ELN risk classification by genetics at initial diagnosis

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
	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;q34.1)/*DEK*::*NUP214*
	t(v;11q23.3)/*KMT2A*-rearranged
	t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*
	t(8;16)(p11;p13)/*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*, or *ZRSR2*
	Mutated *TP53*

ELN, European LeukemiaNet.
*Adapted from Döhner, *et al.*[1]

OS in patients treated with venetoclax-azacitidine or placebo-azacitidine by risk group per ELN 2017



Favorable	n	Events	Median OS, months (95% CI)
Ven + Aza	46	25	21.1 (9.9, NR)
Pbo + Aza	20	20	13.0 (4.2, 18.7)

Intermediate	n	Events	Median OS, months (95% CI)
Ven + Aza	65	48	23.3 (12.9, 28.3)
Pbo + Aza	19	18	13.1 (7.0, 23.4)

Adverse	n	Events	Median OS, months (95% CI)
Ven + Aza	168	141	11.5 (8.9, 16.2)
Pbo + Aza	74	71	7.4 (5.4, 10.6)

Döhner et al. Blood. 2024 Aug 12:blood.2024024944. doi: 10.1182

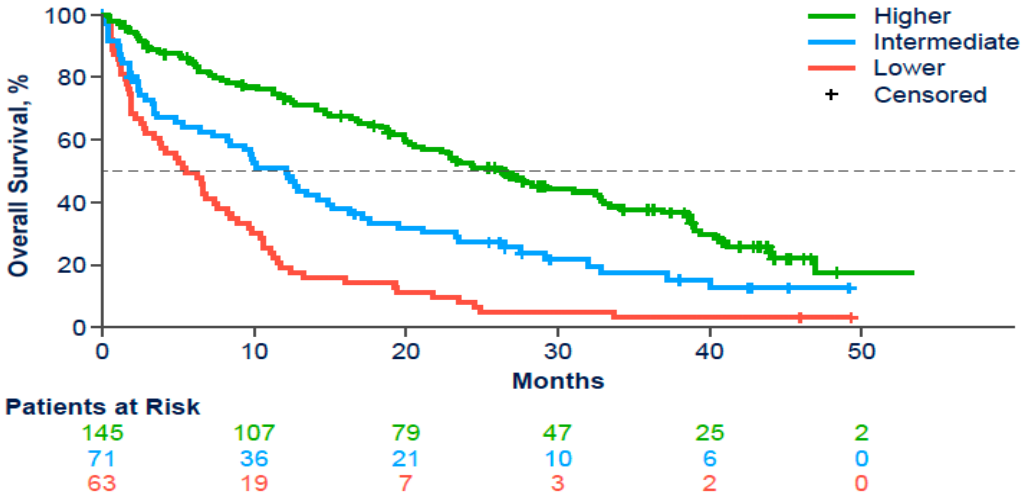
Genetic Risk Stratification and Outcomes Among Treatment-Naive Patients With Acute Myeloid Leukemia Treated With Venetoclax and Azacitidine

- While outcomes with venetoclax-azacitidine were improved across all ELN risk groups compared with placebo-azacitidine, ELN classification systems poorly discriminated venetoclax-azacitidine outcomes.
- 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.
- The median OS for the higher benefit group was26.5 months [95% CI, 20.2 to 32.7], intermediate -12.1 months [95% CI, 7.3 to 15.2], and lower benefit 5.5 months [95% CI, 2.8 to 7.6], respectively

Döhner et al. Blood. 2024 Aug 12:blood.2024024944. doi: 10.1182

Genetic Risk Stratification and Outcomes Among Treatment-Naive Patients With Acute Myeloid Leukemia Treated With Venetoclax and Azacitidine

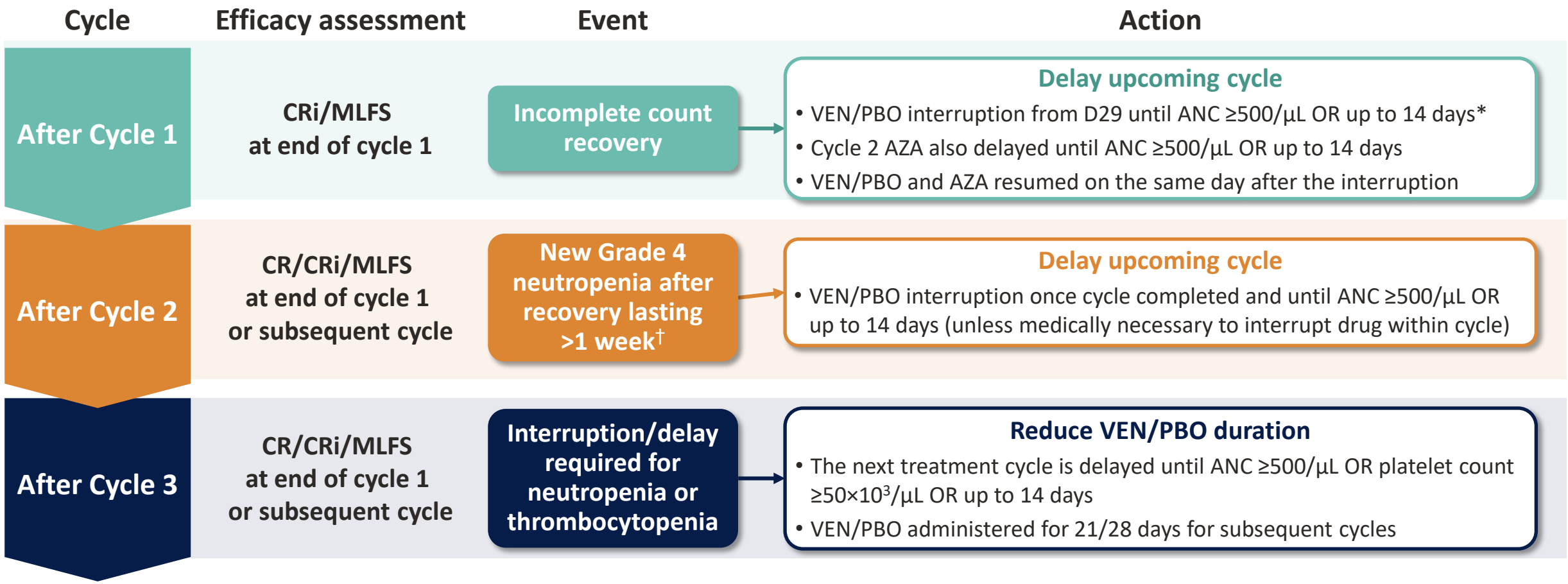
Group	Ven+Aza		
	Higher-benefit (n = 145)	Intermediate-benefit (n = 71)	Lower-benefit (n = 63)
FLT3-ITD	0	39 (54.9)	4 (6.3)
NRAS	0	28 (39.4)	5 (7.9)
KRAS	0	11 (15.5)	2 (3.2)
TP53	0	0	63 (100)



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)

Döhner et al. Blood. 2024 Aug 12:blood.2024024944. doi: 10.1182

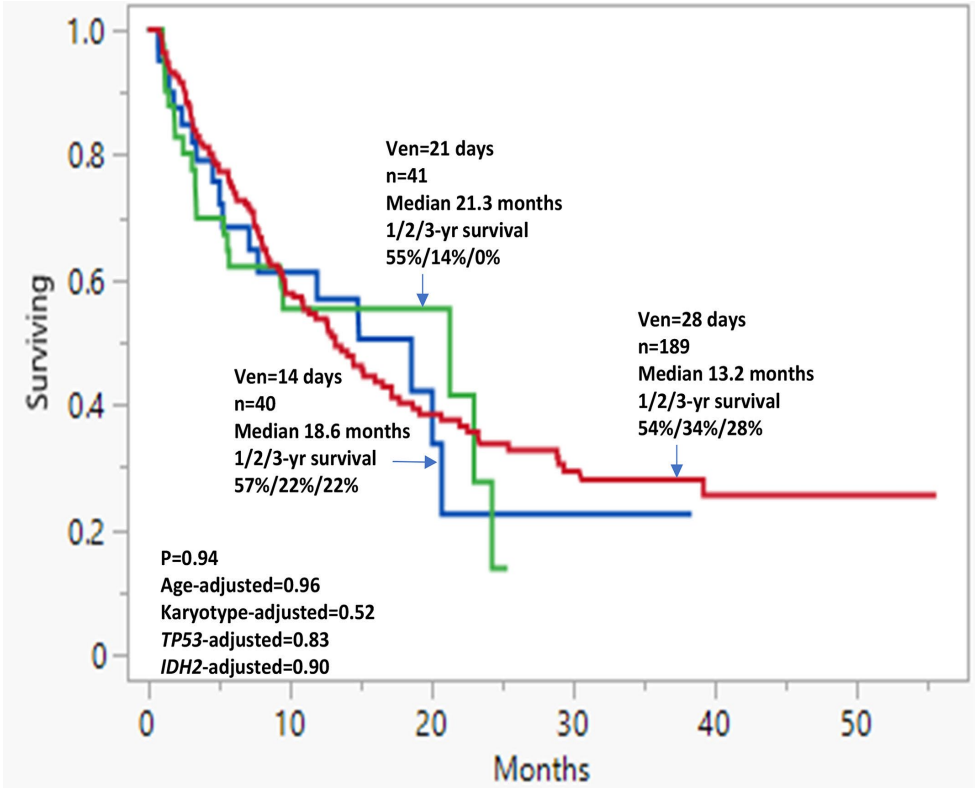
Dose Modifications for Cytopenia



*Until day 42; if no recovery by day 42, discussion between PI and the AbbVie MD required. †Unless due to underlying disease e.g. relapse.
ANC=Absolute Neutrophil Count. AZA=Azacitidine. CR=Complete Remission. CRi=CR with Incomplete Blood Count Recovery.
D=Day. MLFS=Morphologic Leukemia Free State. PBO=Placebo. VEN=Venetoclax.

DiNardo CD, et al. Oral LB2601. 25th EHA Congress. June 11-21, 2020.

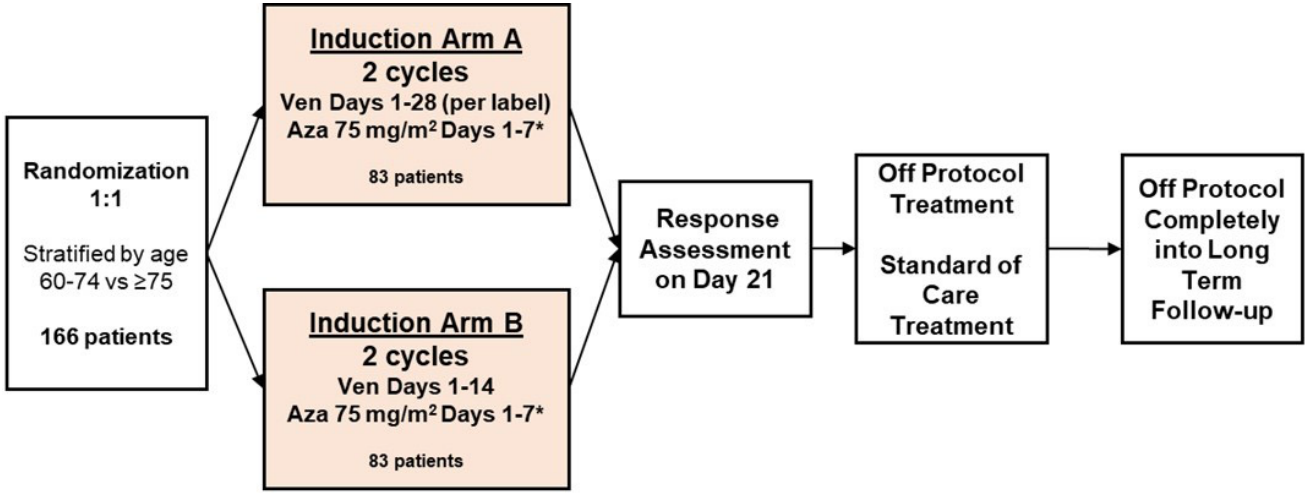
Venetoclax duration (14 vs. 21 vs. 28 days) in combination with hypomethylating agent in newly diagnosed acute myeloid leukemia: Comparative analysis of response, toxicity, and survival



CR/CRi	All patients n=270	ELN adverse Karyotype n=101	ELN non-adverse Karyotype n=169
Ven 14 days	27/40 (68%)	2/9 (22%)	25/31 (81%)
Ven 21 days	27/41 (66%)	9/15 (60%)	18/26 (69%)
Ven 28 days	117/189 (62%)	34/77 (44%)	83/112 (74%)
P-values			
Ven 14 vs 21	0.88	0.07	0.32
Ven 14 vs 28	0.50	0.19	0.44
Ven 21 vs 28	0.63	0.26	0.62

Karrar et al. American J Hematol, Volume: 99, Issue: 2, Pages: E63-E66, First published: 15 December 2023, DOI: (10.1002/ajh.27180)

BEAT AML Protocol: A Randomized Phase 2 Trial of 28-Day (Arm A) Versus 14-Day (Arm B) Schedule of Venetoclax + Azacitidine in Newly Diagnosed Acute Myeloid Leukemia Patients ≥ 60 Years



Uma M. Borate, Ying Huang, Mary F. Johnson, Joshua F. Zeidner, Ronan T. Swords, Kristin L Koenig, Eytan M. Stein, Maria R. Baer, Wendy Stock,Yazan F. Madanat, Rebecca Olin, William Blum, Gary J. Schiller, Tara L Lin, Robert L. Redner, Emily K Curran, Nyla A. Heerema, Molly Martycz, Leonard Rosenberg, Sonja Gullen, Marcus, Timothy Chen, Mona Stefanos, Ross L Levine, Brian J. Druker, Ashley Owen Yocum, Amy Burd, Alice Mims, John C. Byrd

Outcomes of Stem Cell Transplant in Older Patients With Acute Myeloid Leukemia Treated With Venetoclax + HMA Therapies

Baseline Characteristics for Patients Who Received Ven+HMA Therapies + SCT

Characteristics	N=33
Treatment regimen, n (%)	
Ven+Aza	21 (64)
Ven+Dec	12 (36)
Median age (range), y	69 (63-76)
Male	19 (58)
Bone marrow blasts ≥50%,[a] n (%)	12 (36)
AML type, n (%)	
De novo	23 (70)
Secondary	10 (30)
ECOG PS, n (%)	
0	12 (36)
1	10 (30)
2	11 (33)
NCCN cytogenetic risk category, n/N (%)	
Intermediate	20/33 (61)
Poor	12/33 (36)
ELN 2022 category,[b] n/N (%)	
Intermediate	7/30 (23)
Adverse	18/30 (60)
Baseline mutations, n/N (%)	
TP53	2/18 (11)
FLT3 (ITD or TKD)	5/20 (25)
NPM1	5/18 (28)
IDH1/2	7/20 (35)

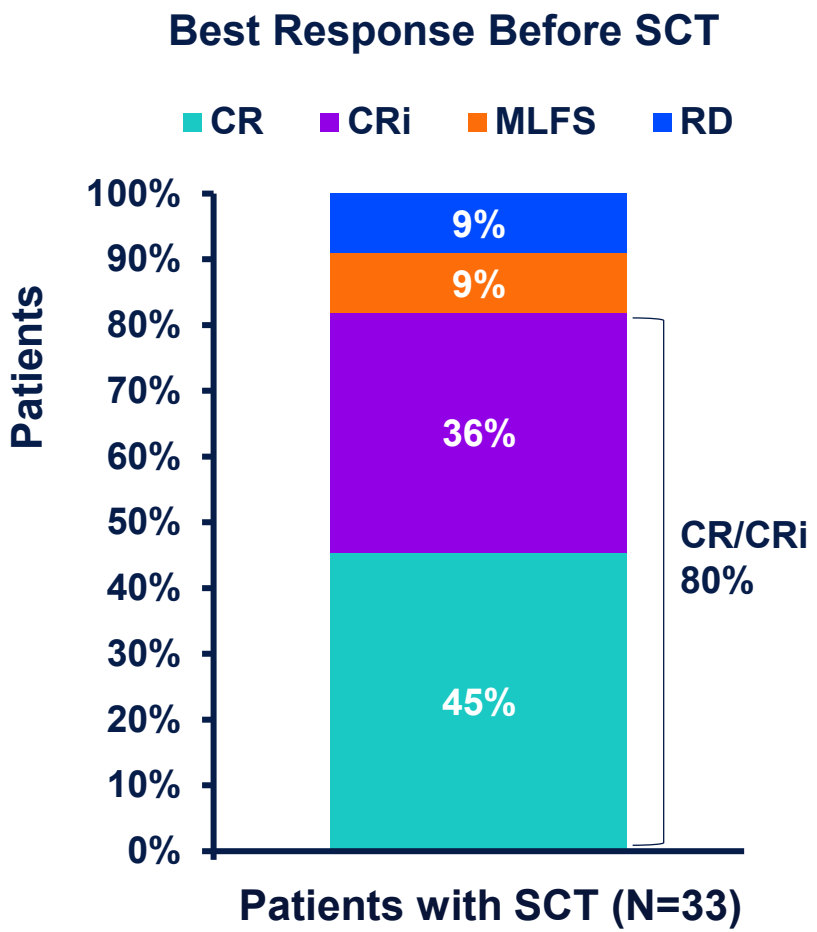
- **60% of patients** had adverse risk disease based on 2022 ELN[1] categories
- **2 patients** had *TP53* mutations

1. Döhner H, et al. *Blood*. 2022;140(12):1345-1377.

[a]At the time of study enrollment; [b]ELN classification based on 2022 ELN guidelines. ALM, acute myeloid leukemia; Aza, azacitidine; Dec, decitabine; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet; HMA, hypomethylating agent; NCCN, National Comprehensive Cancer

Outcomes of Stem Cell Transplant in Older Patients With Acute Myeloid Leukemia Treated With Venetoclax + HMA Therapies

Efficacy



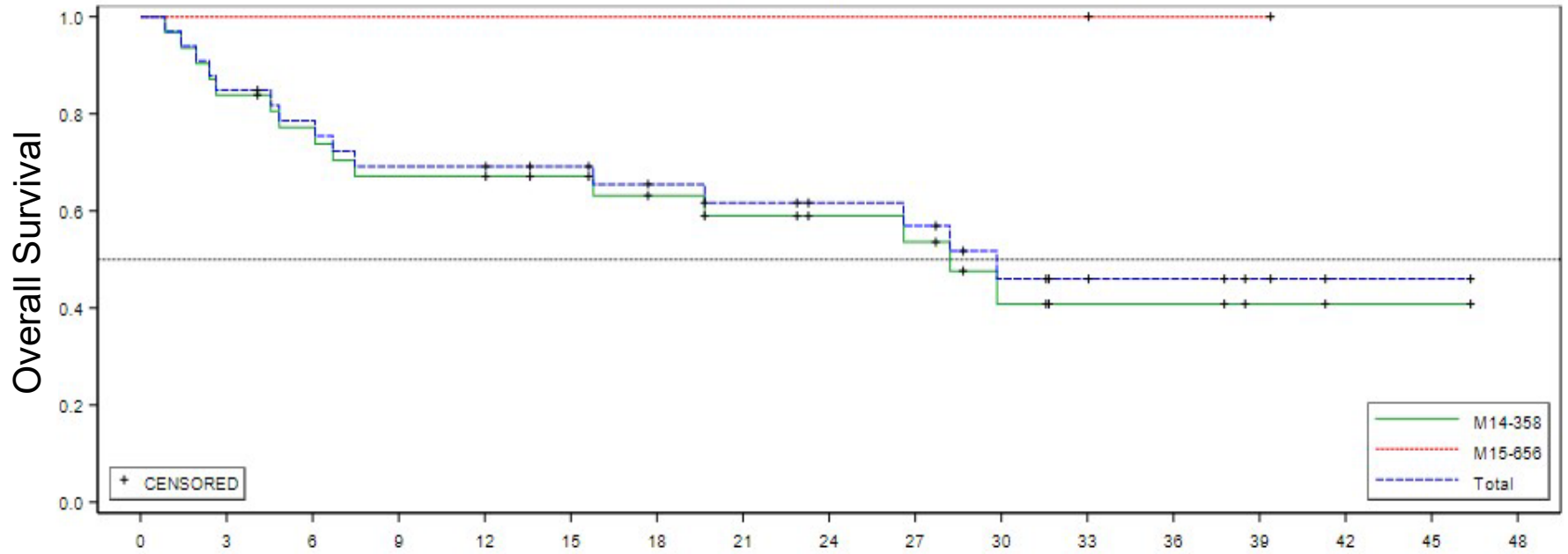
- **Median time to CR/CRi:** 1.9 months (range: 0.8–7.1)
- **2 patients** who initially had a best response of CR, CRi, or MLFS relapsed before transplant; **3 patients** had RD
- **28 patients** were in CR, CRi, or MLFS at the time of transplant
- **9 patients** had an MRD response (cutoff $<10^{-3}$ leukemia cells/leukocyte)
  - 16 patients had MRD positive disease ($\geq 10^{-3}$)
  - 8 patients were not evaluable for MRD
- PLACEHOLDER: Number of patients who had a CR or CRi and MRD response

CR, complete response; CRi, CR with incomplete blood count recovery; CRh, CR with partial hematologic recovery; MLFS, morphologic leukemia-free state; MRD, minimal residual disease; RD, resistant disease; SCT, stem cell transplantation.

Outcomes of Stem Cell Transplant in Older Patients With Acute Myeloid Leukemia Treated With Venetoclax + HMA Therapies

Efficacy

A **Overall Survival Post-transplantation**



Subjects at Risk

M14-358	31	26	23	20	20	18	15	13	11	10	6	4	4	2	1	1	0
M15-656	2	2	2	2	2	2	2	2	2	2	2	2	1	1	0	0	0
Total	33	28	25	22	22	20	17	15	13	12	8	6	5	3	1	1	0

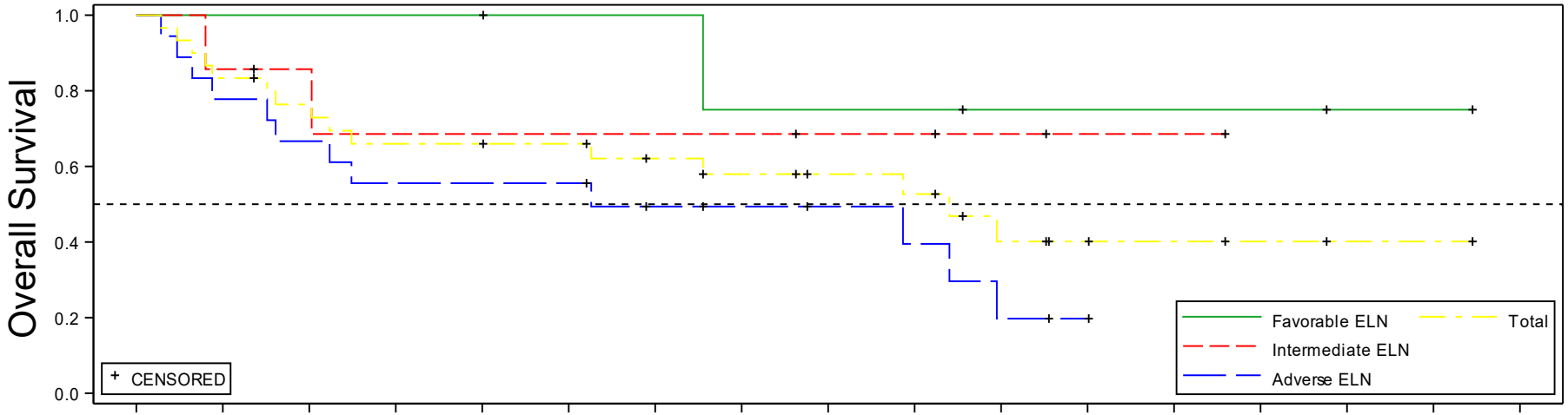
		Survival Estimate (%) (95% CI)					Median (Months)
	Events	Month 12	Month 18	Month 24	Month 36	Month 48	[95% CI]
M14-358 (N=31)	15	67.1 (47.4, 80.8)	63.1 (43.2, 77.7)	58.9 (38.8, 74.4)	40.8 (20.0, 60.7)	NA	28.2 (7.5, -)
M15-656 (N=2)	0	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	NA	-
Total (N=33)	15	69.1 (50.2, 82.1)	65.5 (46.3, 79.3)	61.6 (42.2, 76.3)	46.0 (25.6, 64.2)	NA	29.9 (15.8, -)

Outcomes of Stem Cell Transplant in Older Patients With Acute Myeloid Leukemia Treated With Venetoclax + HMA Therapies

Efficacy *(continued)*

D

Overall Survival Post-transplant by 2022 ELN Categories



Subjects at Risk

Favorable ELN	5	5	5	5	5	4	4	3	3	3	2	2	2	2	1	1	0
Intermediate ELN	7	6	5	4	4	4	4	4	3	3	2	1	1	0	0	0	0
Adverse ELN	18	14	12	10	10	10	7	6	5	4	2	1	0	0	0	0	0
Total	30	25	22	19	19	18	15	13	11	10	6	4	3	2	1	1	0

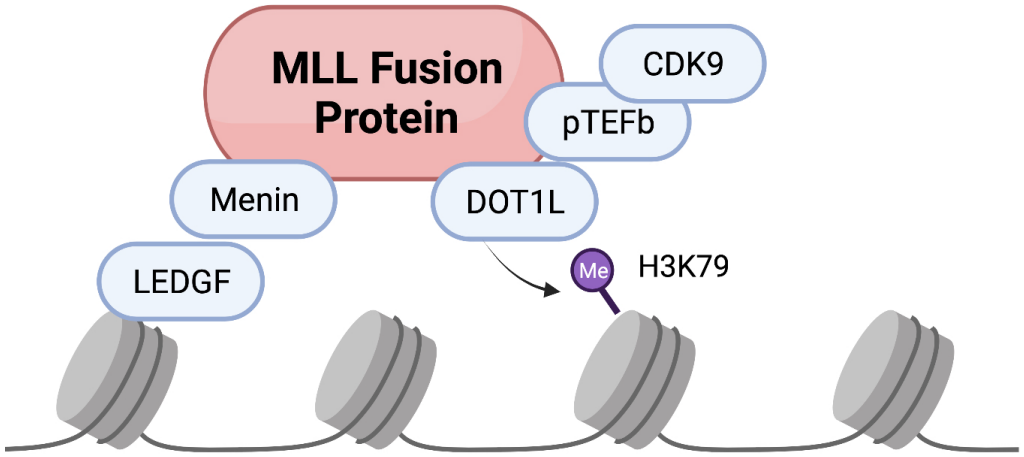
	Events	Survival Estimate (%) (95% CI) Month 12	Month 18	Month 24	Month 36	Month 48	Median (Months) [95% CI]
Favorable ELN (N=5)	1	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	75.0 (12.8, 96.1)	75.0 (12.8, 96.1)	NA	- (19.7, -)
Intermediate ELN (N=7)	2	68.6 (21.3, 91.2)	68.6 (21.3, 91.2)	68.6 (21.3, 91.2)	68.6 (21.3, 91.2)	NA	- (2.4, -)
Adverse ELN (N=18)	12	55.6 (30.5, 74.8)	49.4 (25.2, 69.7)	49.4 (25.2, 69.7)	NA	NA	15.8 (4.5, 29.9)
Total (N=30)	15	66.0 (46.0, 80.1)	62.1 (42.0, 77.0)	58.0 (37.7, 73.7)	40.1 (19.6, 60.0)	NA	28.2 (6.7, -)

ELN, European LeukemiaNet; MRD, minimal residual disease; NA, not available.

Hypomethylating Agent /Venetoclax Conclusions

- Venetoclax in combination with azacitidine or decitabine can lead to rapid and deep responses in patients with newly diagnosed AML who were ineligible for intensive chemotherapy
- Best outcomes observed in patients with IDH1, IDH2, and NPM1 mutations with azacitidine/venetoclax compared to azacitidine alone.
- Patients with TP53 mutations have a higher remission rate with azacitidine/venetoclax compared to azacitidine alone, but long term outcomes are not superior.
- The mutational status of *TP53*, *FLT3*-ITD, *NRAS*, and *KRAS* categorized patients into higher-, intermediate-, and lower-benefit groups.
- Patients who were not eligible for intensive chemotherapy and received venetoclax + hypomethylating agents followed by stem cell transplantation had a median overall survival of 2.5 years; median overall survival was not reached for those who achieved minimal residual disease response before stem cell transplantation
- These results suggest that venetoclax + hypomethylating agents can be a bridge to stem cell transplantation, which can result in long-term survival in those who are ineligible for intensive chemotherapy

AUGMENT-101: Menin Inhibitor SNDX-5613 (Revumenib) Phase 1 Study



AUGMENT-101

Best Response	Efficacy Population (N=60)
Response	
Overall response rate[1], n, (%)	32 (53%)
CR/CRh	18 (30%)
CR	12 (20%)
CRh	6 (10%)
CRp	5 (8%)
MLFS	9 (15%)
MRD^{neg}	
CRc MRD^{neg} Rate[2]	18/60 (30%)
within CR/CRh MRD^{neg} n, (%)	14/18 (78%)
within CR/CRh/CRp MRD^{neg} n, (%)	18/23 (78%)
KMT2Ar	
Overall response rate[1], n, (%)	27/46 (59%)
CR/CRh	15/46 (33%)
mNPM1	
Overall response rate[1], n, (%)	5/14 (36%)
CR/CRh	3/14 (21%)

[1]Overall Response Rate = CR+CRh+CRp+MLFS; [2]CR+CRh+CRp; MRD status assessed locally by PCR or MCF

Issa et al. Nature 2023.

KMT2A-rearranged Acute Leukemia

- Most patients relapse after chemotherapy and HSCT[1]
- In adults, remission rates after relapse (CR, 5%) and median OS (2.4 months) after ≥2 salvage therapies remain low[1]
- Outcomes in infants/children after relapse remain poor

No approved targeted therapies for *KMT2Ar* disease

OS in Adult Patients With R/R *KMT2A-r* AML After ≥3rd-Line Therapy

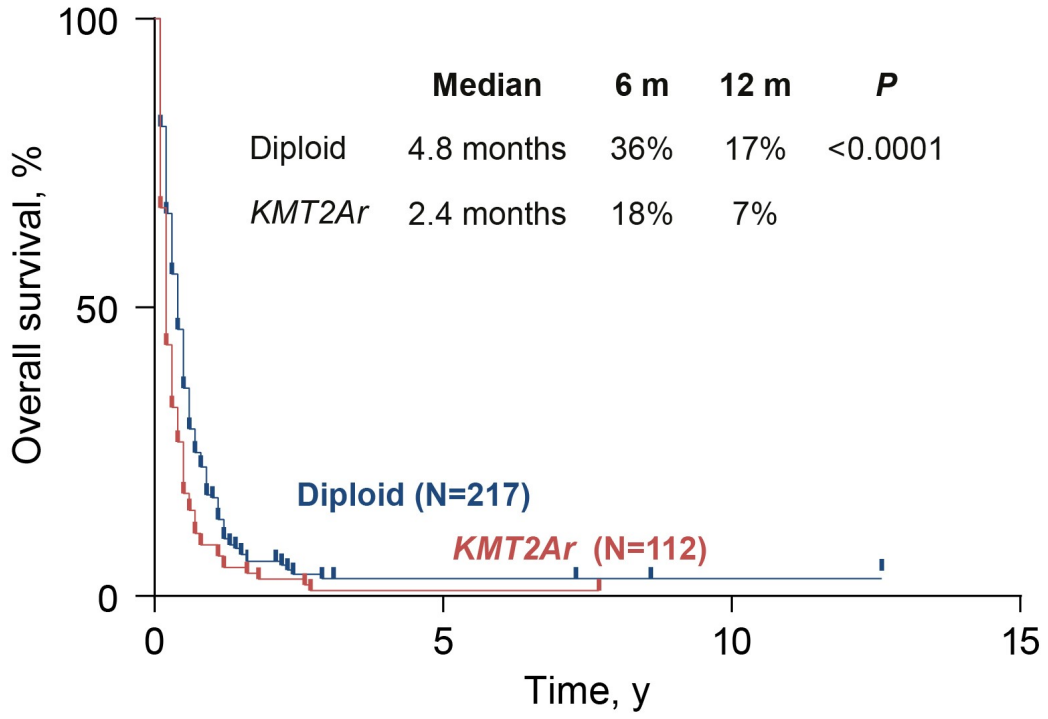


Figure reproduced from Issa GC, Zarka J, Sasaki K, et al. *Blood Cancer J*. 2021;11:162
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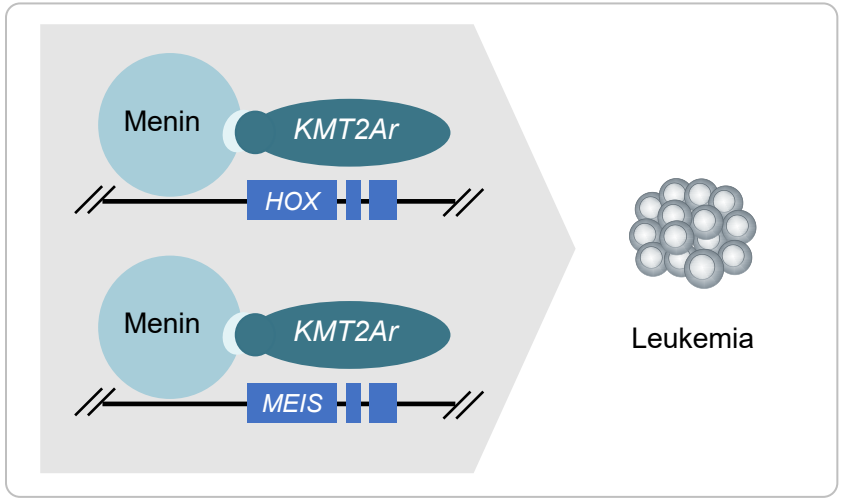
AML, acute myeloid leukemia; CR, complete remission; HSCT, hematopoietic stem cell transplant; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; OS, overall survival; R/R, relapsed/refractory.

1. Issa GC, Zarka J, Sasaki K, et al. *Blood Cancer J*. 2021;11:162.

Revumenib

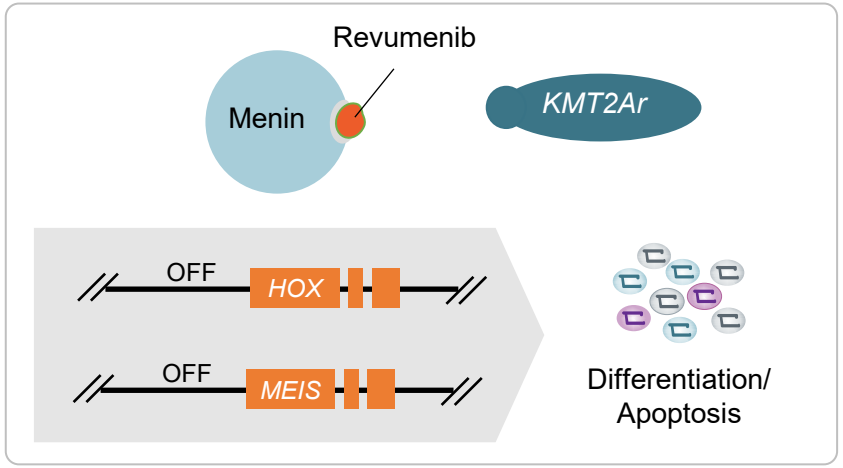
- The menin-KMT2A interaction is a key driver of leukemogenesis[1]
- In a phase 1 study of R/R *KMT2Ar* and *NPM1m* acute leukemias, revumenib demonstrated
  - Clinically meaningful responses that were consistent across subgroups[2]
  - High percentage of responders proceeding to transplant[2]
  - Manageable safety profile[2]

KMT2Ar acute leukemia



Gene transcription **ON**

Menin inhibition with revumenib



Gene transcription **OFF**

HOX, homeobox; KMT2A, histone-lysine N-methyltransferase 2A; *KMT2Ar*, KMT2A rearrangements; *MEIS*, Meis homeobox; *NPM1m*, nucleophosmin 1–mutated; R/R, relapsed/refractory.

1. Issa GC, Zarka J, Sasaki K, et al. *Blood Cancer J*. 2021;11:162. **2.** Issa GC, Aldoss I, DiPersio J, et al. *Nature*. 2023;615:920-924.

AUGMENT-101 Phase 2 Study Design

Patients aged ≥30 days with R/R acute leukemia

Revumenib RP2D

163 mg (95 mg/m^2 if body weight <40 kg) q12h oral + a strong CYP3A4i in 28-day cycles

→ ***KMT2Ar* acute leukemia**

→ ***NPM1m* AML**

Still enrolling, not included in this analysis

- **Primary endpoint**
  - CR+CRh rate
- **Key secondary efficacy endpoints**
  - CRc
  - ORR

A planned interim analysis of patients with *KMT2Ar* acute leukemia was conducted

AML, acute myeloid leukemia; CR, complete remission; CRc, CR composite (CR+CRh+CRp+CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; CYP3A4i, cytochrome P450 3A4 inhibitor; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; *NPM1m*, nucleophosmin 1–mutated; ORR, overall response rate; q12h, every 12 hours; RP2D, recommended phase 2 dose; R/R, relapsed/refractory.

Patient Demographics

Parameter	Efficacy population (n=57)	Safety population (n=94)[a]
Median age, y (range)	34.0 (1.3–75.0)	37.0 (1.3–75.0)
Age <18 y, n (%)	13 (22.8)	23 (24.5)
Age ≥18 y, n (%)	44 (77.2)	71 (75.5)
Sex, n (%)		
Female	33 (57.9)	56 (59.6)
Race, n (%)		
White	43 (75.4)	68 (72.3)
Non-White	10 (17.5)	14 (14.9)
Unknown	4 (7.0)	12 (12.8)

Data cutoff: July 24, 2023. [a]Defined as patients with *KMT2Ar* acute leukemia having received at least 1 dose of revumenib.

KMT2Ar, histone-lysine N-methyltransferase 2A rearrangements rearrangements.

Baseline Characteristics

Parameter	Efficacy population (n=57)	Safety population (n=94)[a]
Leukemia type, n (%)		
AML	49 (86.0)	78 (83.0)
ALL	7 (12.3)	14 (14.9)
MPAL/Other	1 (1.8)	2 (2.1)
Disease status at baseline, n (%)		
Primary refractory	14 (24.6)	18 (19.1)
Refractory relapse[b]	32 (56.1)	54 (57.4)
Untreated relapse	11 (19.3)	22 (23.4)
Number of prior lines of therapy, median (range)	2 (1–11)	2 (1–11)
1, n (%)	17 (29.8)	25 (26.6)
2, n (%)	14 (24.6)	28 (29.8)
≥3, n (%)	26 (45.6)	41 (43.6)
Prior HSCT, n (%)	26 (45.6)	47 (50.0)

Data cutoff: July 24, 2023. [a]Defined as patients with *KMT2Ar* acute leukemia having received at least 1 dose of revumenib. [b]Defined as disease unresponsive to most recent salvage treatment.

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplant; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; MPAL, mixed phenotype acute leukemia.

Response to Revumenib

Parameter	Efficacy population (n=57)
ORR, n (%)	36 (63.2)
CR+CRh rate, n (%)	13 (22.8)
95% CI	12.7–35.8
P value, 1-sided	0.0036
CRc	25 (43.9)
95% CI	30.7–57.6
Negative MRD status[a]	
CR+CRh	7/10 (70.0)
CRc	15/22 (68.2)

Parameter	Efficacy population (n=57)
Best response, n (%)	
CR	10 (17.5)
CRh	3 (5.3)
CRi	1 (1.8)
CRp	11 (19.3)
MLFS	10 (17.5)
PR	1 (1.8)
PD	4 (7.0)
No response	14 (24.6)
Other[b]	3 (5.3)

Data cutoff: July 24, 2023. [a]MRD done locally; not all patients had MRD status reported. [b]Includes patients without postbaseline disease assessment.

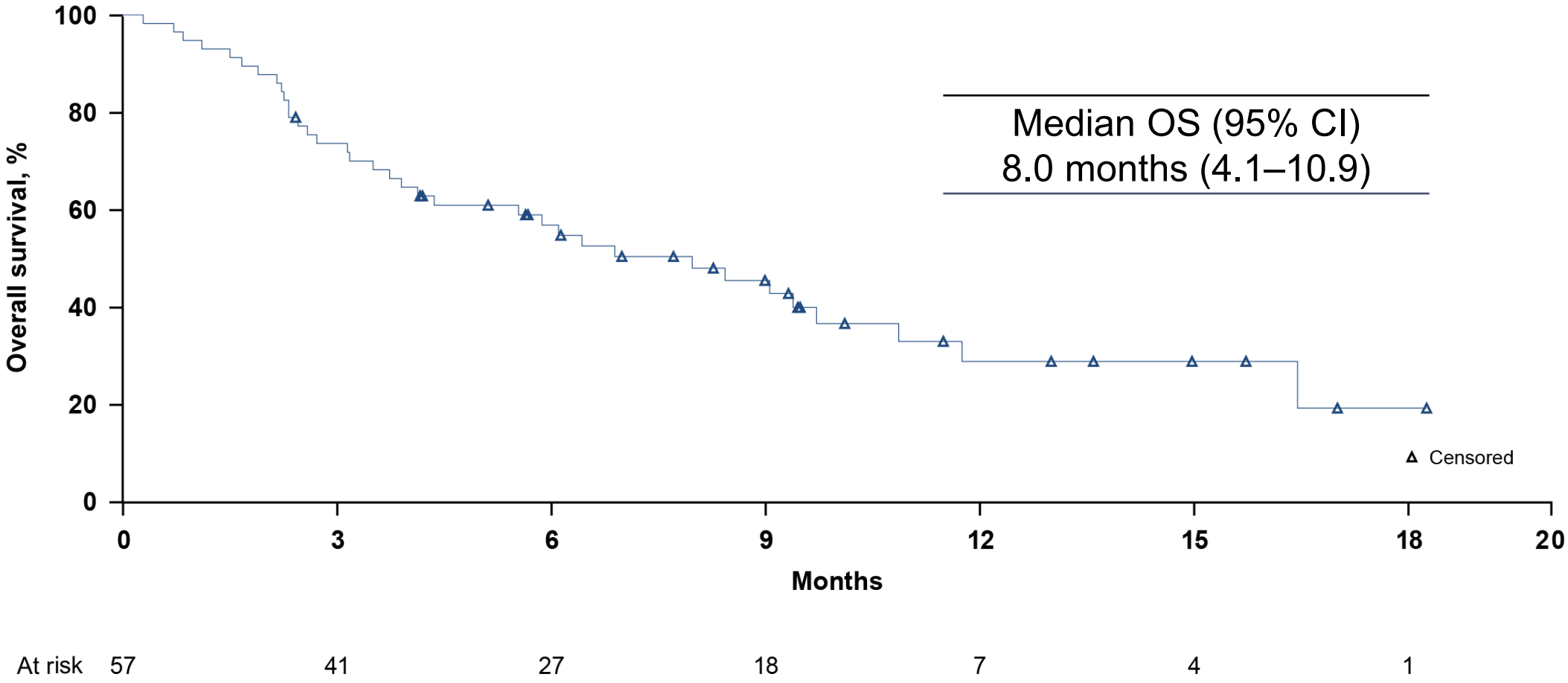
CR, complete remission; CRc, composite CR (CR+CRh+CRp+CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphological leukemia-free state; MRD, minimal residual disease; ORR, overall response rate (CRc+MLFS+PR); PD, progressive disease; PR, partial remission.

Responses Observed Across *KMT2A* Rearrangements

KMT2A rearrangement/ translocation	Summary of ORR		Summary of CR+CRh rate	
	n/N	ORR (95% CI)	n/N	CR+CRh rate (95% CI)
9;11	10/11	90.9 (58.7–99.8)	2/11	18.2 (2.3–51.8)
11;19	7/13	53.8 (25.1–80.8)	2/13	15.4 (1.9–45.4)
10;11	5/7	71.4 (29.0–96.3)	2/7	28.6 (3.7–71.0)
6;11	5/7	71.4 (29.0–96.3)	2/7	28.6 (3.7–71.0)
4;11	2/2	100.0 (15.8–100.0)	0/2	0 (0.0–84.2)
1;11	0/2	0 (0.0–84.2)	0/2	0 (0.0–84.2)
Unknown KMT2A fusion partner	5/13	38.5 (13.9–68.4)	4/13	30.8 (9.1–61.4)
Other translocations	2/2	100.0 (15.8–100.0)	1/2	50.0 (1.3–98.7)

CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; KMT2A, histone-lysine N-methyltransferase 2A; ORR, overall response rate (CR+CRh+CRp+CRi+MLFS+PR); PR, partial remission.

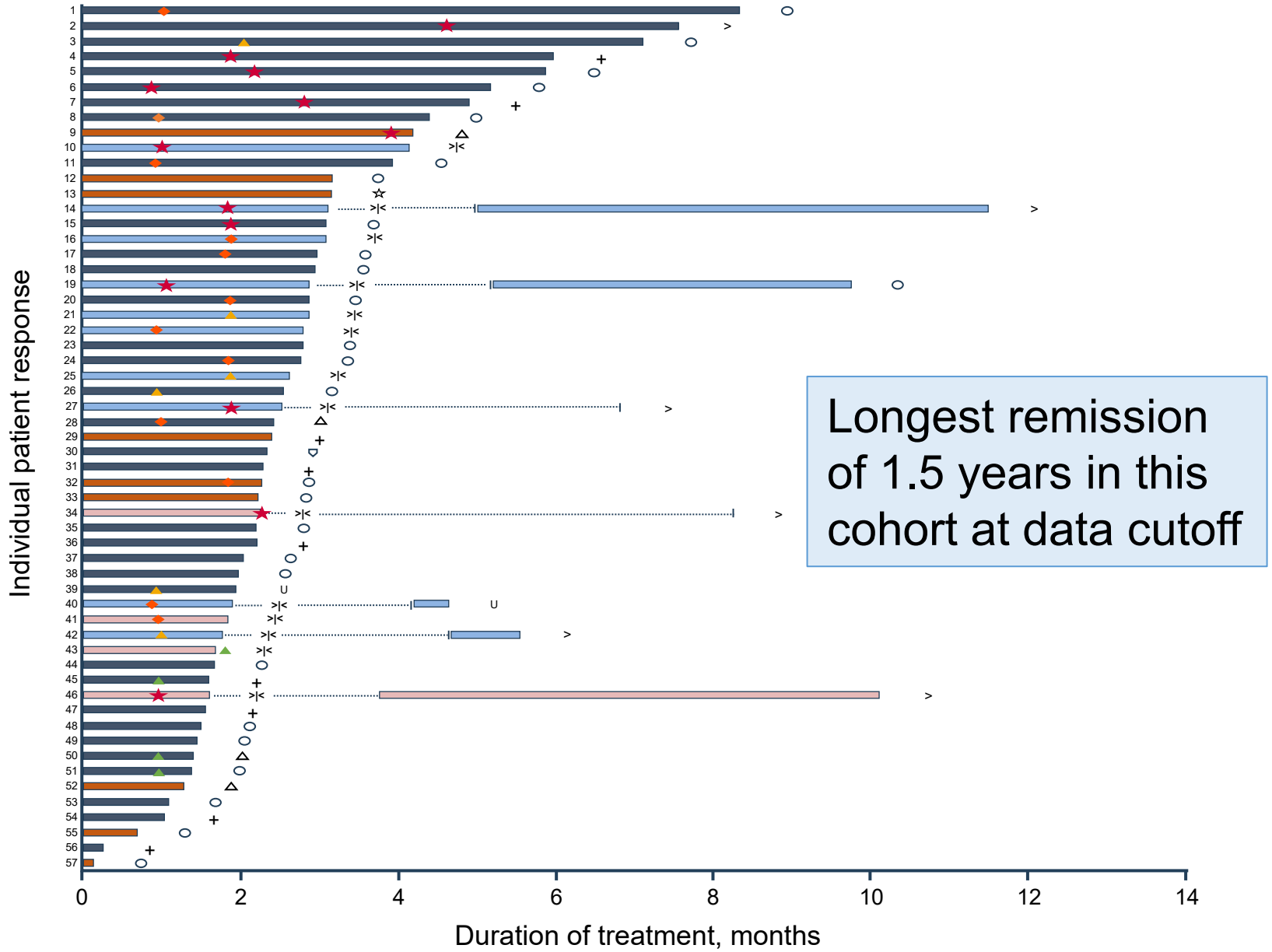
Overall Survival



OS, overall survival.

Duration of Treatment

- Adult
- Adult, underwent HSCT
- Pediatric
- Pediatric, underwent HSCT
- CR/CRh
- CRp/CRi
- MLFS
- Progressive disease
- Ongoing at data cutoff
- Adverse event
- Subject withdrew consent for treatment
- HSCT
- Noncompliance
- Patient did not achieve at least a PR after 4 cycles
- Prohibited concomitant medication



Longest remission of 1.5 years in this cohort at data cutoff

CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; HSCT, hematopoietic stem cell transplant; MLFS, morphological leukemia-free state; NR, not reached; PR, partial remission.

Duration of Treatment

Parameter	Patients achieving CR+CRh (n=13)
Median time to CR+CRh, months (range)	1.87 (0.9–4.6)
Median duration of CR+CRh, months (95% CI)	6.4 (3.4–NR)
Proceeded to HSCT, n (%)	14/36 (38.9)
Proceeded to HSCT in CR or CRh	6/14 (42.9)
Proceeded to HSCT in MLFS or CRp	8/14 (57.1)
Restarted revumenib post HSCT, n (%)	7/14 (50.0)

Data cutoff: July 24, 2023.

CR, complete remission; CRh, CR with partial hematologic recovery; CRp, CR with incomplete platelet recovery; HSCT, hematopoietic stem cell transplant; MLFS, morphological leukemia-free state; NR, not reached.

Revumenib Safety Profile

All terms	Safety population (n=94)[a] TEAEs	TRAEs
Any grade, n (%)	93 (98.9)	77 (81.9)
≥Grade 3, n (%)	86 (91.5)	51 (54.3)
Serious AE, n (%)	72 (76.6)	35 (37.2)
AEs leading to:		
Dose reduction	9 (9.6)	8 (8.5)
Discontinuation	12 (12.8)	6 (6.4)
Death	14 (14.9)	4 (4.3)

Data cutoff: July 24, 2023. [a]Defined as patients with *KMT2Ar* acute leukemia having received at least 1 dose of revumenib.

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Revumenib Safety Profile

Any grade TEAEs that occurred in ≥25% patients

All terms, n (%)	Safety population (n=94)[a]
Nausea	42 (44.7)
Febrile neutropenia	36 (38.3)
Diarrhea	33 (35.1)
Vomiting	29 (30.9)
Differentiation syndrome	26 (27.7)
Hypokalemia	26 (27.7)
Epistaxis	25 (26.6)
QTc prolongation	24 (25.5)

Grade ≥3 TEAEs that occurred in ≥10% patients

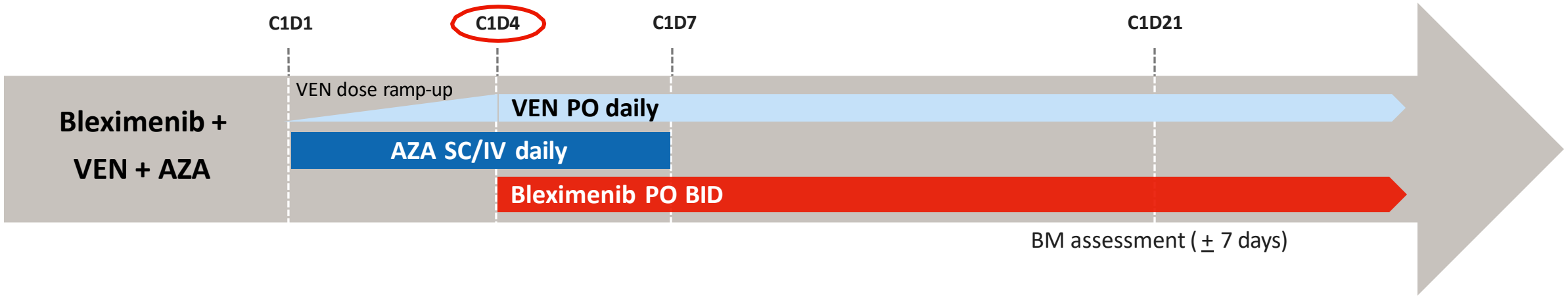
All terms, n (%)	Safety population (n=94)[a]
Febrile neutropenia	35 (37.2)
Decreased neutrophil count	15 (16.0)
Decreased white blood cell count	15 (16.0)
Decreased platelet count	14 (14.9)
Anemia	17 (18.1)
Differentiation syndrome	15 (16.0)
QTc prolongation	13 (13.8)
Sepsis	11 (11.7)
Hypokalemia	10 (10.6)

Data cutoff: July 24, 2023. [a]Defined as patients with *KMT2Ar* acute leukemia having received at least 1 dose of revumenib.

No patients discontinued due to differentiation syndrome, QTc prolongation, or cytopenias

KMT2Ar, histone-lysine N-methyltransferase 2A rearrangements; TEAE, treatment-emergent adverse event.

Bleximenib (JNJ-75276617) Phase 1b Combination Trial in R/R AML: Dosing Schedule



Key Considerations for Dosing

- 28-day treatment cycles
- VEN and AZA administration guided by the approved label
  - Bleximenib does not impact VEN exposures
  - Bleximenib exposure in combination similar to monotherapy
- Bleximenib given BID continuously from C1D4
- Isavuconazole primary antifungal of choice, when indicated
- Hydroxyurea and steroids for DS prophylaxis and treatment permitted

AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; C, Cycle; D, Day; DS, differentiation syndrome; IV, intravenous; PO, by mouth; R/R, relapsed/refractory; SC, subcutaneous; VEN, venetoclax.

Presented by AH Wei at the European Hematology Association (EHA) 2024 Hybrid Congress; June 13–16, 2024; Madrid, Spain

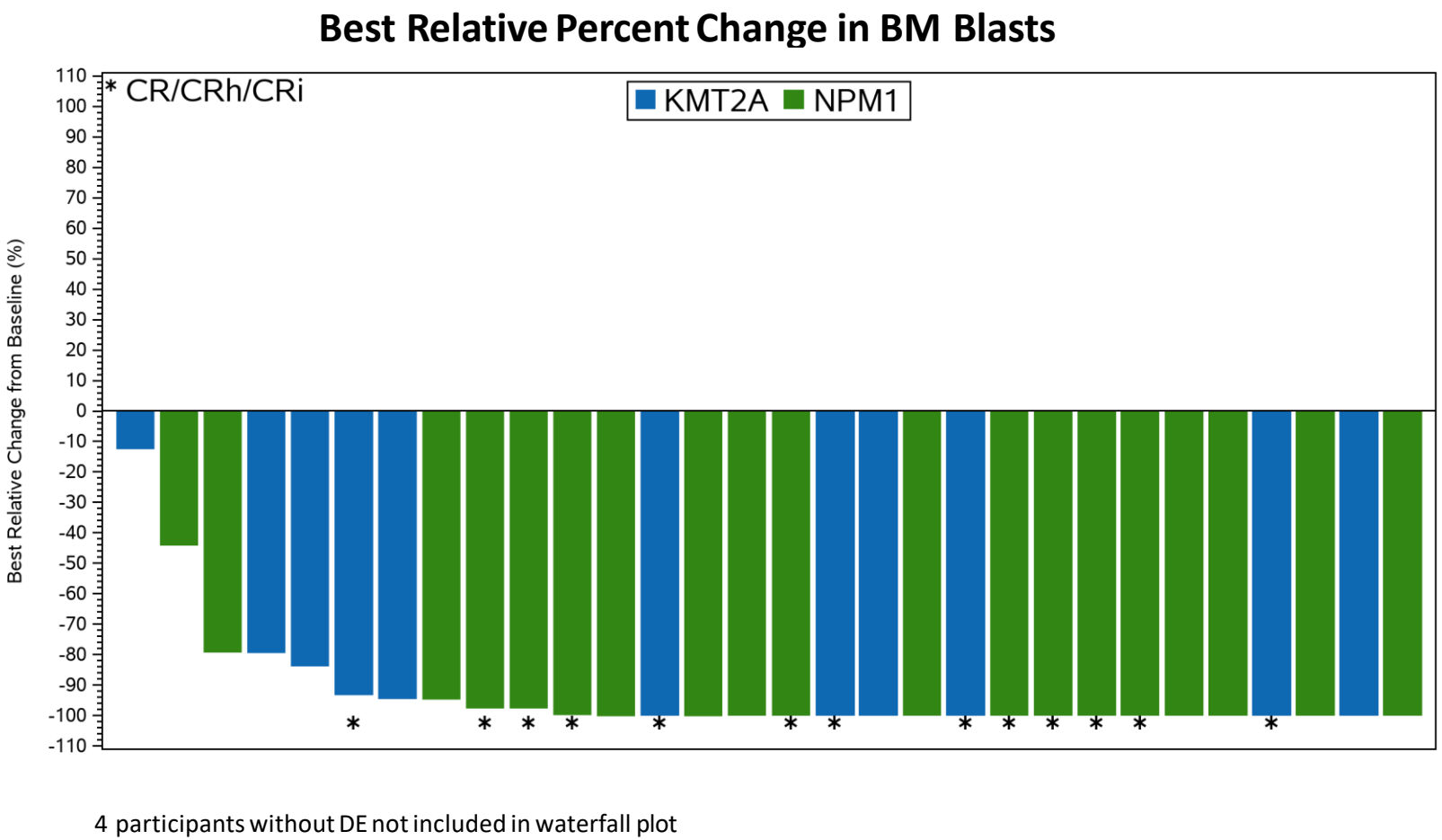
Bleximenib Combination with AZA/VEN

- **Phase 1b study demonstrates the combinability of bleximenib with standard doses of VEN and AZA in R/R AML with *KMT2A* or *NPM1* alterations**
- **Bleximenib combination therapy well tolerated (n=60)**
  - DS observed in 3% (2 participants; G3 & G5/DLT)
  - No bleximenib related events of QT prolongation or TLS
- **Preliminary clinical activity observed in *KMT2Ar* and *NPM1*m R/R AML**
  - Efficacy population (n=34; ≥50 mg BID): ORR 79%; CR/CRh/CRi 41%
  - In participants with prior VEN exposure (n=17): ORR 65%; CR/CRh/CRi 29%
- **Phase 1 dose escalation ongoing to identify RP2D**
  - Exploration of bleximenib in combination with AML directed therapies ongoing in this study (**NCT05453903**):
    - *Newly diagnosed fit AML: bleximenib + '7+3'; newly diagnosed unfit AML (bleximenib + VEN + AZA) participants*
    - *Doublet combinations (bleximenib + VEN or AZA) in relapsed/refractory cohorts*

AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; CR, complete remission; CRh, complete remission with partial hematologic recovery; DLT, dose-limiting toxicity; DS, differentiation syndrome; G, Grade; *KMT2A*, histone-lysine N-methyltransferase 2A; *KMT2Ar*, rearrangement of histone-lysine N-methyltransferase 2A; *NPM1*, nucleophosmin 1; *NPM1*m, nucleophosmin 1 mutations; ORR, overall response rate; R/R, relapsed/refractory; RP2D, recommended Phase 2 dose; TLS, tumor lysis syndrome; TRAE, treatment-related adverse event; VEN, venetoclax.

Presented by AH Wei at the European Hematology Association (EHA) 2024 Hybrid Congress; June 13–16, 2024; Madrid, Spain

Bleximenib (JNJ-75276617) Phase 1b Combination Trial in R/R AML: Change in Leukemic Burden (N=34)



4 participants without DE not included in waterfall plot

- **34 participants in efficacy population**
  - 13 *KMT2Ar*
  - 21 *NPM1*m
- **All participants with observed reduction in leukemic burden**
- **93% of participants with ≥50% reduction in BM blasts**
- **Reductions observed in both *KMT2Ar* or *NPM1*m**

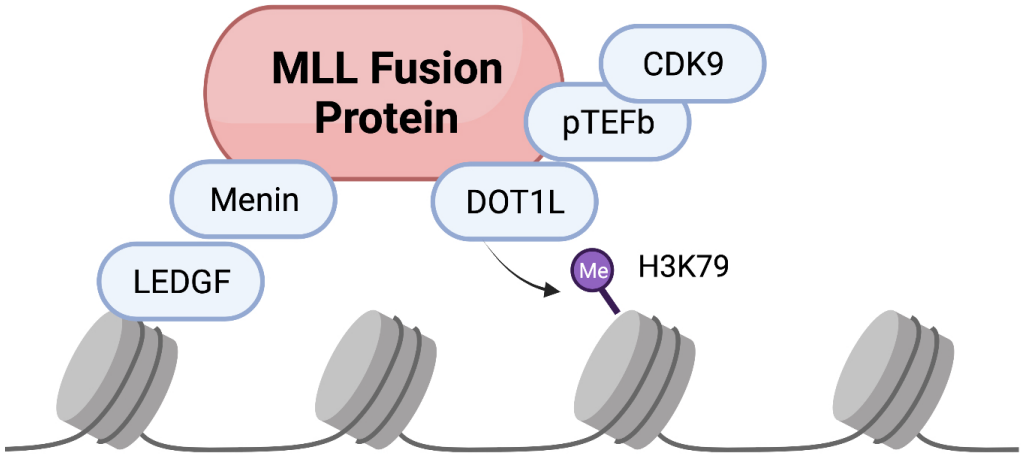
Data cut-off: May 7, 2024.

Bars are only presented for participants where measurable change from baseline was available; each bar represents a unique participant.

AE, adverse event; AML, acute myeloid leukemia; BM, bone marrow; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; DE, disease evaluation; *KMT2Ar*, rearrangement of histone-lysine N-methyltransferase 2A; *NPM1*m, nucleophosmin 1 mutations; PD, progressive disease; R/R, relapsed/refractory.

Presented by AH Wei at the European Hematology Association (EHA) 2024 Hybrid Congress; June 13–16, 2024; Madrid, Spain

AUGMENT-101: Menin Inhibitor SNDX-5613 (Revumenib) Phase 1 Study



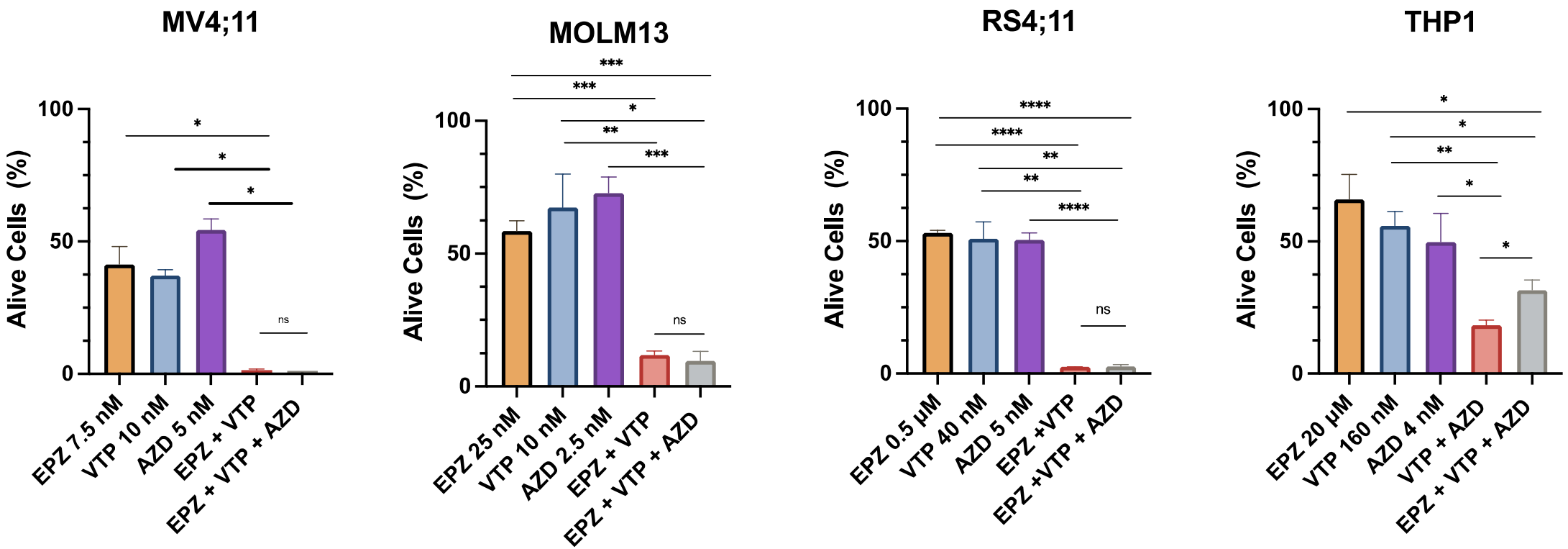
AUGMENT-101

Best Response	Efficacy Population (N=60)
Response	
Overall response rate[1], n, (%)	32 (53%)
CR/CRh	18 (30%)
CR	12 (20%)
CRh	6 (10%)
CRp	5 (8%)
MLFS	9 (15%)
MRD^{neg}	
CRc MRD^{neg} Rate[2]	18/60 (30%)
within CR/CRh MRD^{neg} n, (%)	14/18 (78%)
within CR/CRh/CRp MRD^{neg} n, (%)	18/23 (78%)
KMT2Ar	
Overall response rate[1], n, (%)	27/46 (59%)
CR/CRh	15/46 (33%)
mNPM1	
Overall response rate[1], n, (%)	5/14 (36%)
CR/CRh	3/14 (21%)

[1]Overall Response Rate = CR+CRh+CRp+MLFS; [2]CR+CRh+CRp; MRD status assessed locally by PCR or MCF

1. Chandrasekharappa et al. Science 1997.
2. Yokoyama et al. Cell 2005.
3. Krivstov et al. Cancer Cell 2019
4. Issa et al. Nature 2023.

Three-drug combinations of menin, DOT1L, and CDK9 inhibitors



Menin Inhibitor Conclusions

- Menin inhibitors are effective and safe in pediatric and adult patients with R/R *KMT2A*-rearranged and NPM1-mutated leukemia.
- Durable MRD-negative remissions were observed in responders.
- Differentiation syndrome occurs with menin inhibitors.
- Discontinuations and dose reductions due to TRAE or TEAEs were low.
- Combination therapies with AZA/VEN are promising.
- A New Drug Application for revumenib in *KMT2A*-rearranged leukemia has been initiated under the FDA Real-Time Oncology Review program based on these data.

KMT2Ar, histone-lysine N-methyltransferase 2A rearrangements; MRD, minimal residual disease; *NPM1m*, mutated nucleophosmin 1; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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- Aysenur Esen
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