



Weill Cornell Medicine

NewYork-Presbyterian

Hypomethylating Agent + Venetoclax + X in AML: which strategy should I bet my retirement on?

**SOHO Brazil
May 8, 2025**

Gail J. Roboz, M.D.

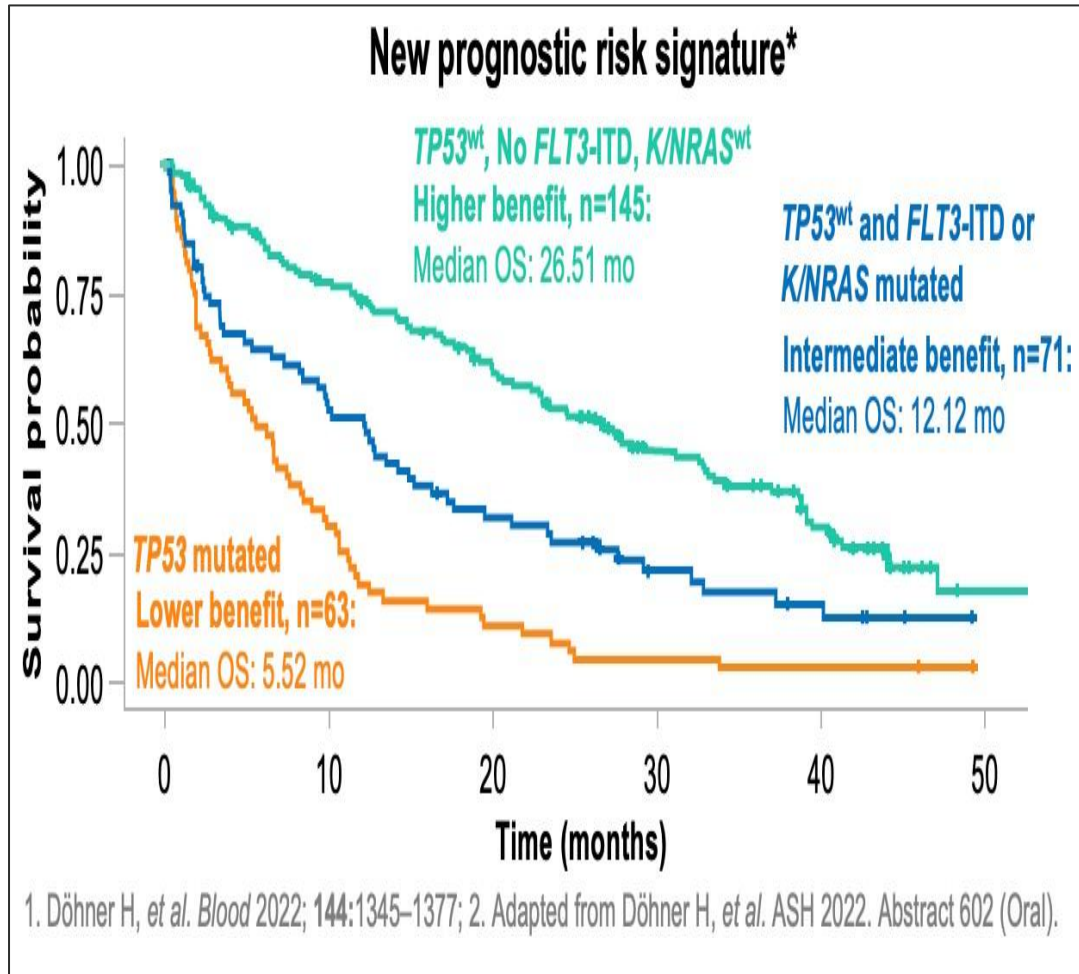
William S. Paley Professor of Medicine

Director, Clinical and Translational Leukemia Programs

DISCLOSURES OF COMMERCIAL SUPPORT

Consultancy – AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Caribou Biosciences, Celgene, Daiichi Sankyo, Ellipses Pharma, GlaxoSmithKline, Geron, Glycomimetics, Janssen, Jasper Pharmaceuticals, Jazz Pharmaceuticals, Molecular Partners, Morphosys, Novartis, Oncoprecision, Oncoverity, Pfizer, Rigel, Roche, Syndax
Research Support – Janssen

The new ELN 2024



Genetic marker	Median overall survival (months)	Reference
Favorable-risk group		
• Mutated <i>NPM1</i> (<i>FLT3-ITD</i> ^{neg} , <i>NRAS</i> ^{wt} , <i>KRAS</i> ^{wt} , <i>TP53</i> ^{wt})	39	4
• Mutated <i>IDH2</i> (<i>FLT3-ITD</i> ^{neg} , <i>NRAS</i> ^{wt} , <i>KRAS</i> ^{wt} , <i>TP53</i> ^{wt})	37	4
• Mutated <i>IDH1</i> ^a (<i>TP53</i> ^{wt})	29	6,17
• Mutated <i>DDX41</i>	>24	3,13
• AML with myelodysplasia-related gene mutations (<i>FLT3-ITD</i> ^{neg} , <i>NRAS</i> ^{wt} , <i>KRAS</i> ^{wt} , <i>TP53</i> ^{wt})	23	4
Intermediate-risk group		
• AML with myelodysplasia-related gene mutations (<i>FLT3-ITD</i> ^{pos} and/or <i>NRAS</i> ^{mut} and/or <i>KRAS</i> ^{mut} ; <i>TP53</i> ^{wt})	13	4
• Other cytogenetic and molecular abnormalities (<i>FLT3-ITD</i> ^{pos} and/or <i>NRAS</i> ^{mut} and/or <i>KRAS</i> ^{mut} ; <i>TP53</i> ^{wt})	12	4
Adverse-risk group		
• Mutated <i>TP53</i>	5-8	3,4,7,10,14-16

Dohner et al. *Blood*.2024025409.

HMA+VEN+X:

Why do we need “X” and what should its features be?

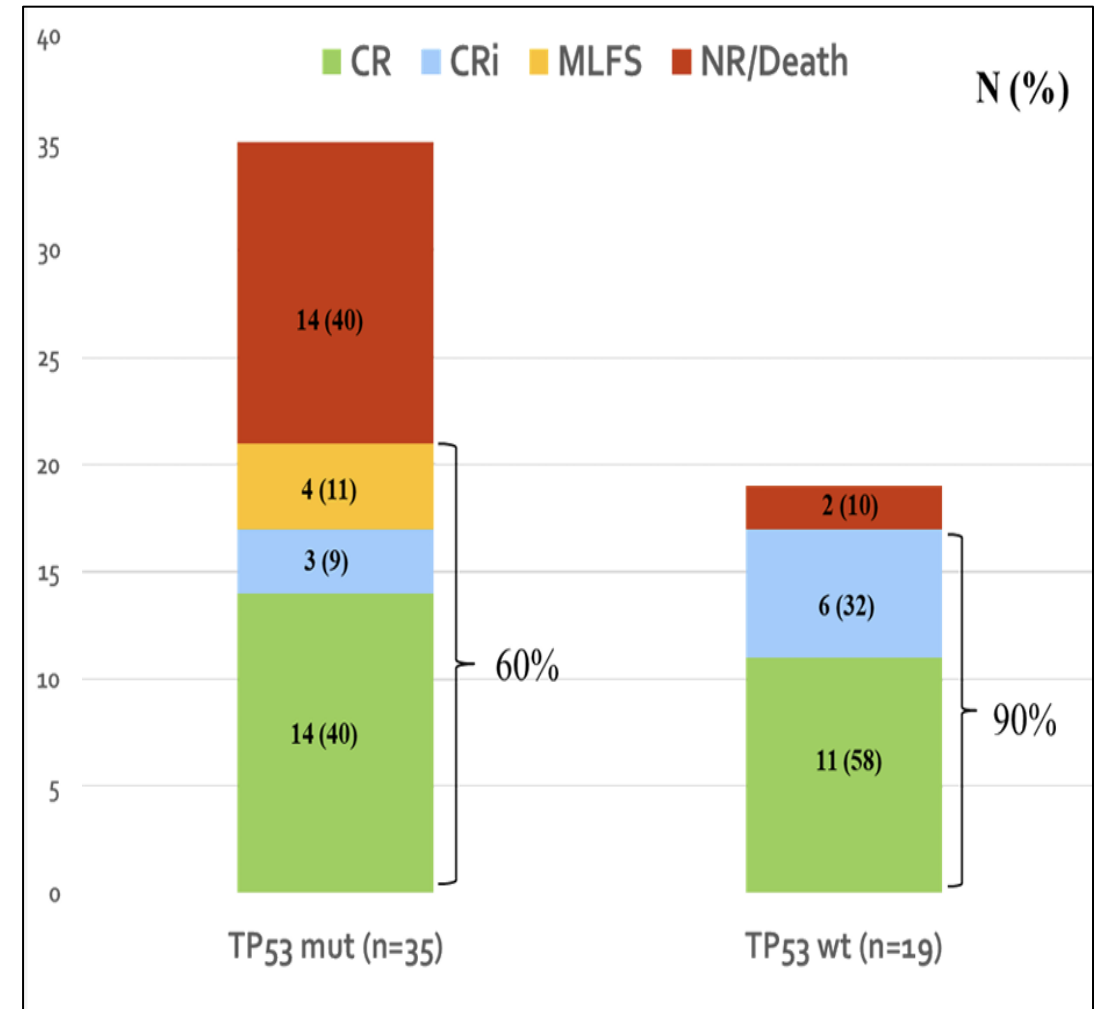
- Increase response rates
- Increase MRD- response rates
- Enhance efficacy in ELN2024 intermediate and adverse risk groups
- Preclinical synergistic/additive activity with HMA/VEN
- Limited myelosuppression
- Favorable extramedullary toxicity profile
- Feasible administration (oral preferred)



Created by GJ Roboz and MM Steinberg with DALL-E3.

What would you say about Drug X if I showed you these data for AZA+VEN+X?

Outcomes	Frontline Cohort (n=25)	
	TP53 mutated (n=14)	TP53 wild type (n=11)
ORR	12 (86)	11 (100)
CR/CRI	9 (64)	10 (91)
CR	9 (64)	7 (64)
CRI	0	3 (27)
MLFS / PR ¹	3 (21)	1 (9)
MRD neg FCM	5/9* (55)	4/9 (45)
CCyR	4/9 [‡] (44)	5/6 (83)
No response	2 (14)	0
TT 1 st response	0.7 [0.6-1.9]	0.7 [0.7-1.5]
TT Best response	1.5 [0.7-3.2]	1.1 [0.7-2.9]
Med TT ANC>500	28 (20 – 41) days	
Med TT Plt>50K	24 (18 – 41) days	
8-wk mortality	0	0



ASH 2021; Abstract #371

Daver et al. Clin Cancer Res. 2025 Apr 8.

doi: 10.1158/1078-0432.CCR-25-0229. Online ahead of print.



But look what happened in phase 3

ENHANCE-3: Venetoclax and Azacitidine Plus Magrolimab or Placebo in Untreated Acute Myeloid Leukemia (AML) Unfit for Intensive Therapy

Context of Research

- Patients with AML ineligible for intensive chemotherapy (IC) have limited treatment options
- Magrolimab (magro) is a IgG4 monoclonal antibody that blocks CD47
- The randomized, phase 3 ENHANCE-3 trial evaluated the addition of magro (magro arm) compared with placebo (control arm) when either was added to venetoclax and azacitidine in patients with untreated AML ineligible for IC

Patients and Methods (NCT05079230)

Key eligibility criteria:

- Adults with previously untreated AML
- Ineligible for IC
- ECOG PS 0-2 (≥75 years) or 0-3 (<75 years)

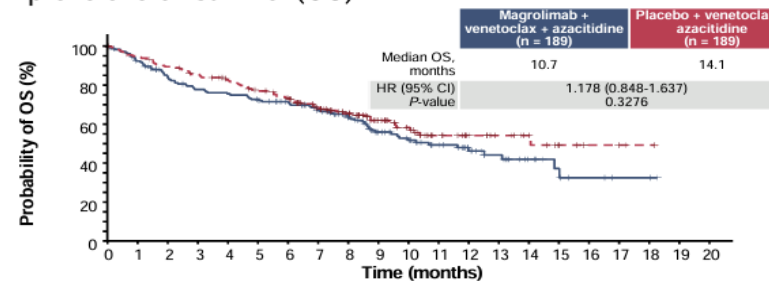
Randomization
1:1

Magrolimab +
venetoclax + azacitidine

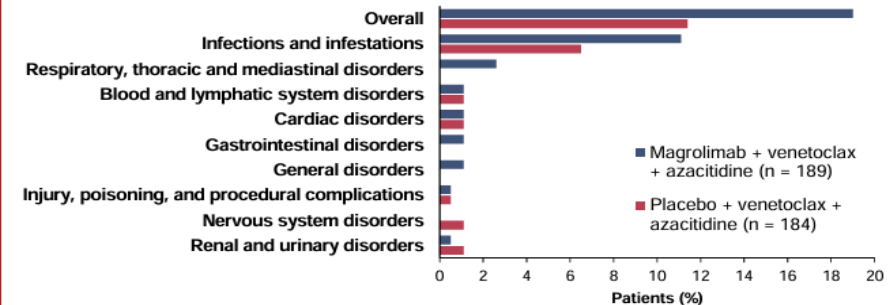
Placebo +
venetoclax + azacitidine

Main Findings

- The addition of magro (vs placebo) to venetoclax and azacitidine did not improve overall survival (OS)



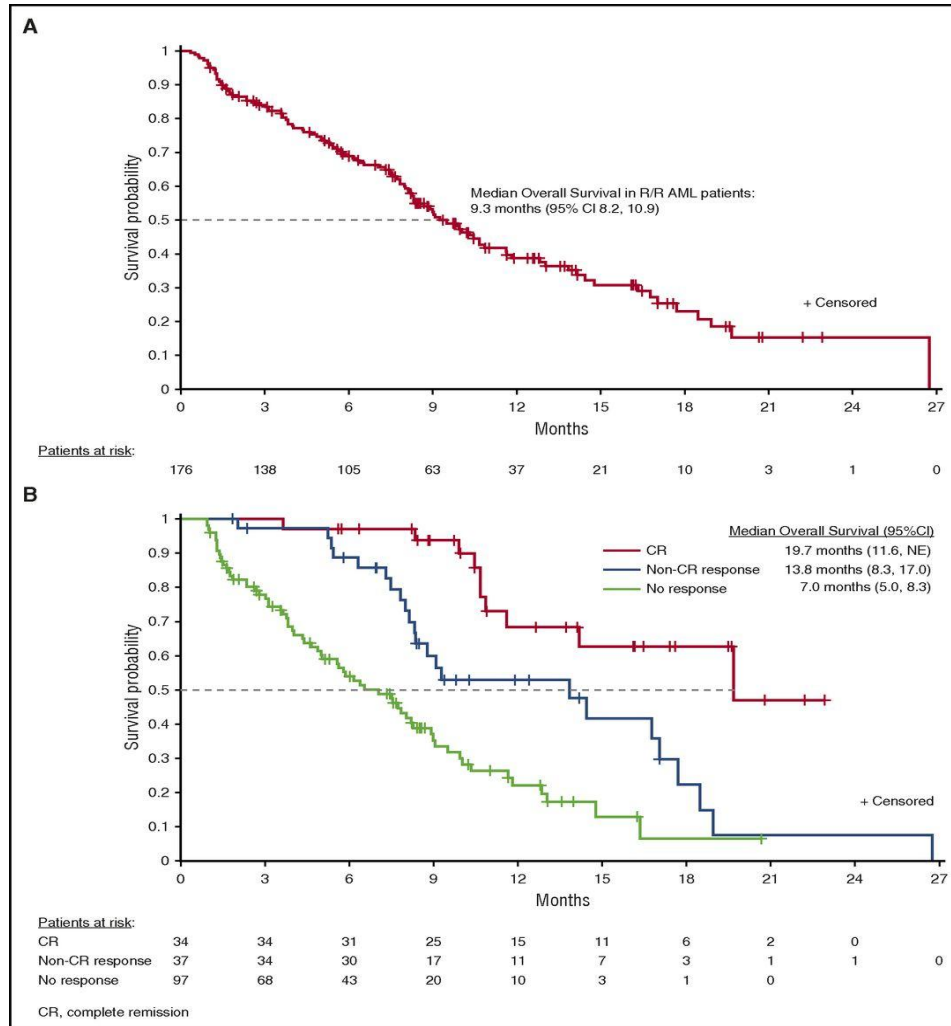
- There were more fatal adverse events in the magro arm compared with the control arm



Conclusions: In patients with previously untreated AML who were ineligible for intensive chemotherapy, the addition of magrolimab to venetoclax and azacitidine did not improve overall survival or complete remission rates and resulted in more fatal adverse events.



Enasidenib: potent, oral IDH2 inhibitor in R/R AML



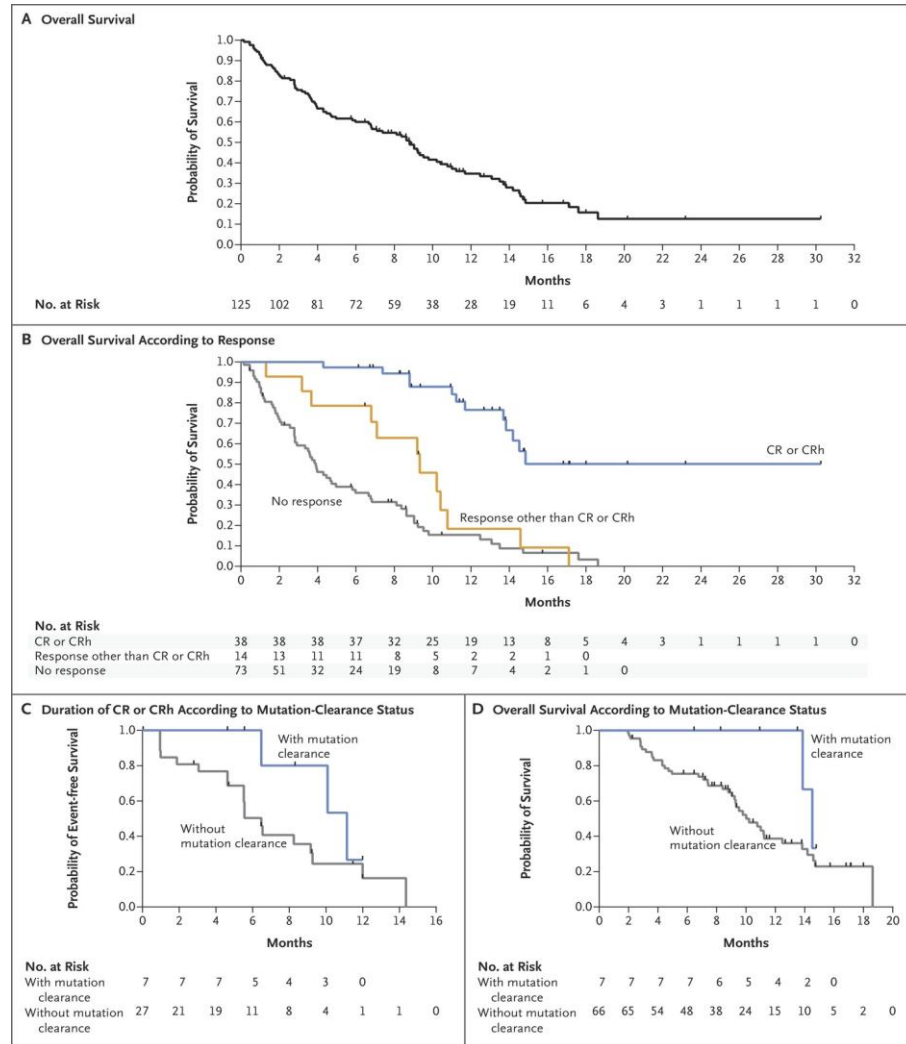
Efficacy

- ORR: 40.3%
- CR: 19.3%
- Median response duration: 5.8 mos
- Median OS R/R AML: 9.3 mos
- Median OS in CR: 19.7 mos

Enasidenib-related Adverse Events

- indirect hyperbilirubinemia (12%)
- differentiation syndrome (7%)

Ivosidenib: potent, oral IDH1 inhibitor in R/R AML



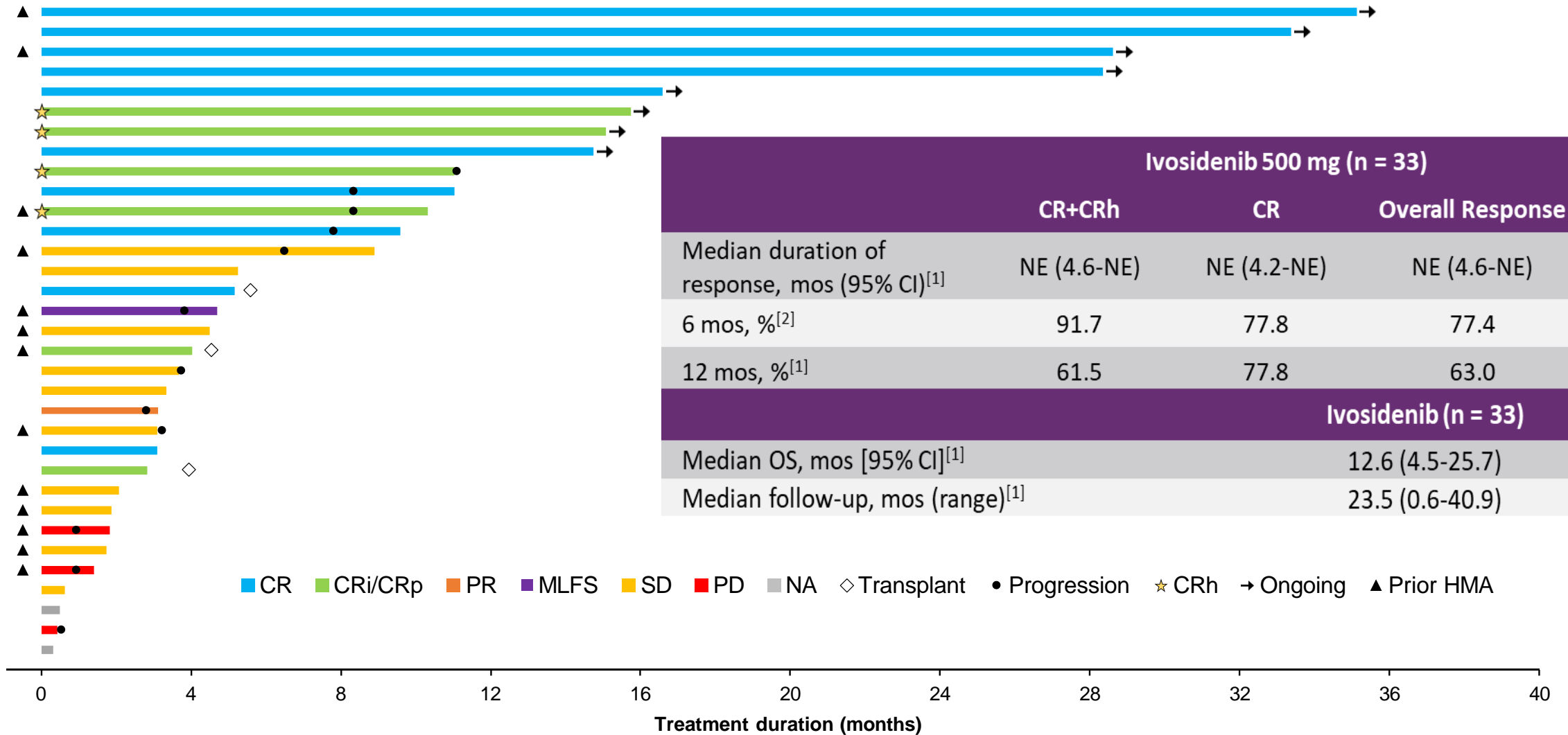
Efficacy

- ORR 41.6%, duration 6.5 mos
- CR 21.6%, duration 9.3 mos
- CR/CRh 30.4%, duration 8.2 mos
- Median OS 8.8 mos
- Median OS in CR not reached

Ivosidenib-related Adverse Events

- QT prolongation 7.8%
- IDH differentiation syndrome 3.9%
- Anemia 2.2%
- Decreased platelets 3.4%
- Leukocytosis 1.7%

Ivosidenib in Untreated *IDH1*-Mutated AML: Duration of Treatment and Best Overall Response



1. Roboz GJ. *Blood*. 2020;135:463. 2. Roboz GJ. ASH 2018. Abstr 561. Slide credit: clinicaloptions.com

Enasidenib in Untreated IDH2-Mutated AML: Duration of Treatment and Best Overall Response

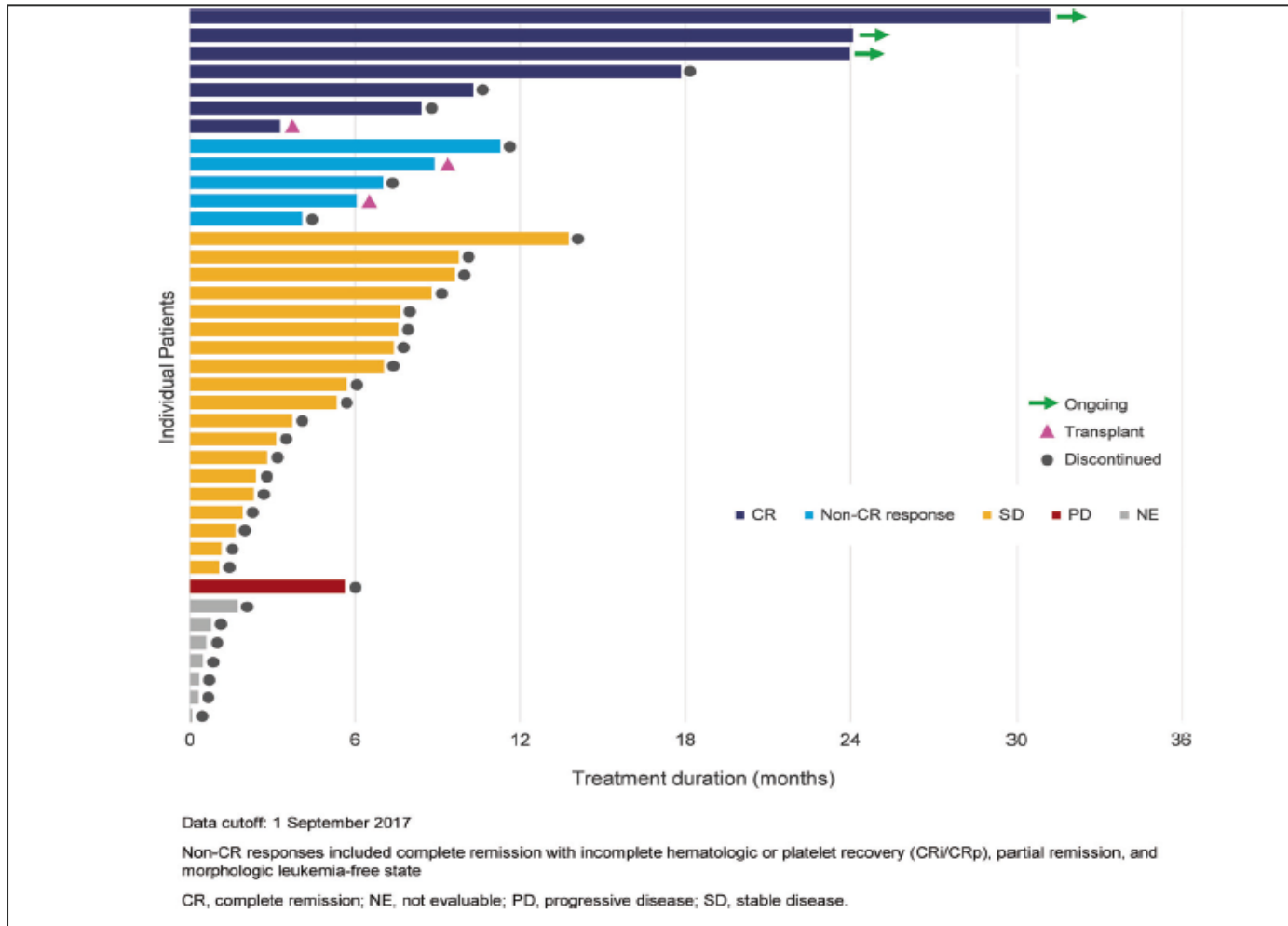
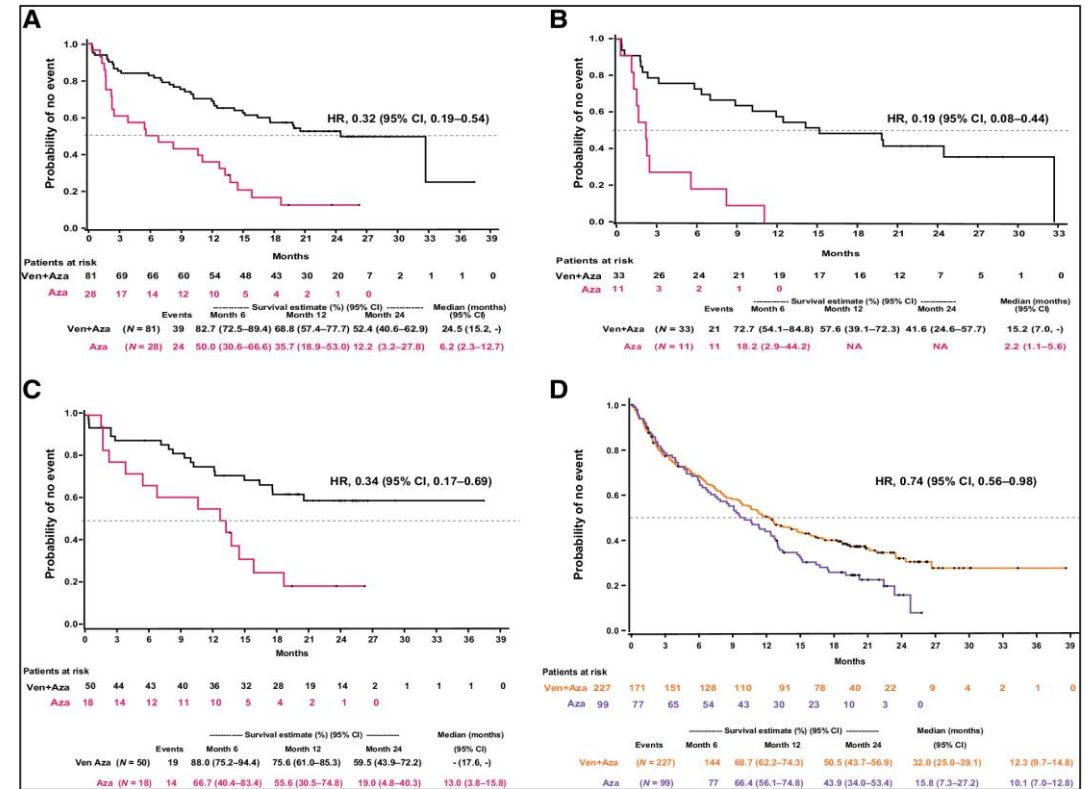
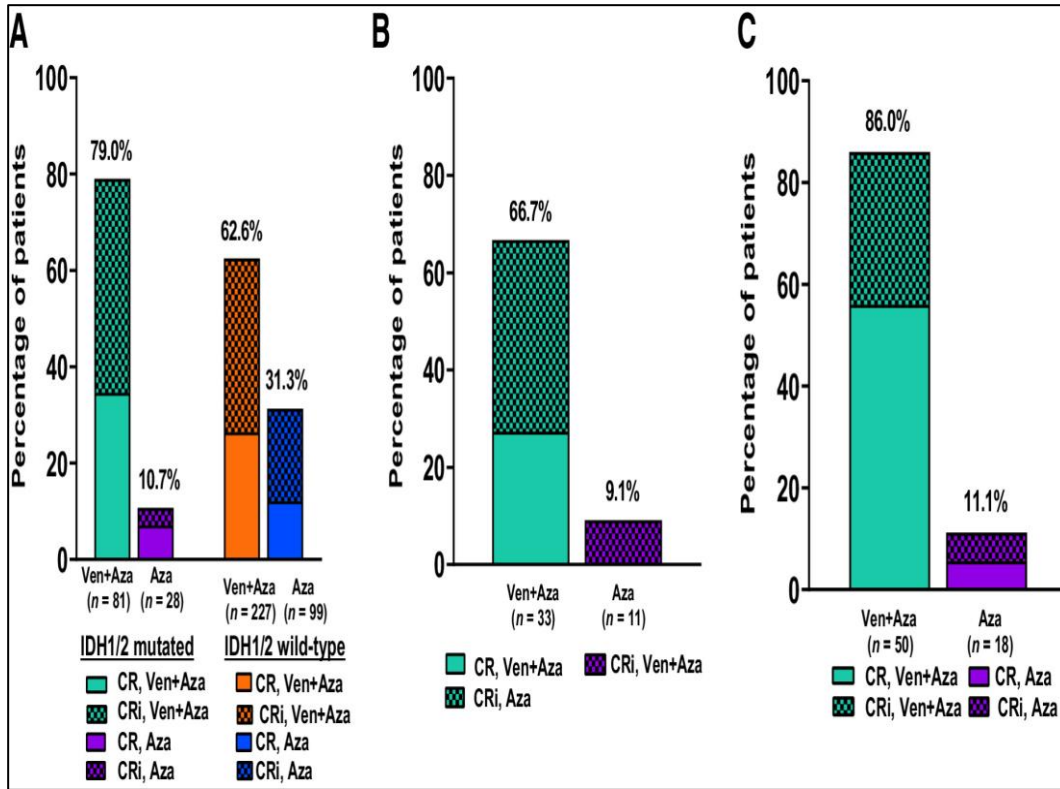


Table 3 Hematologic responses, times to response, and durations of response

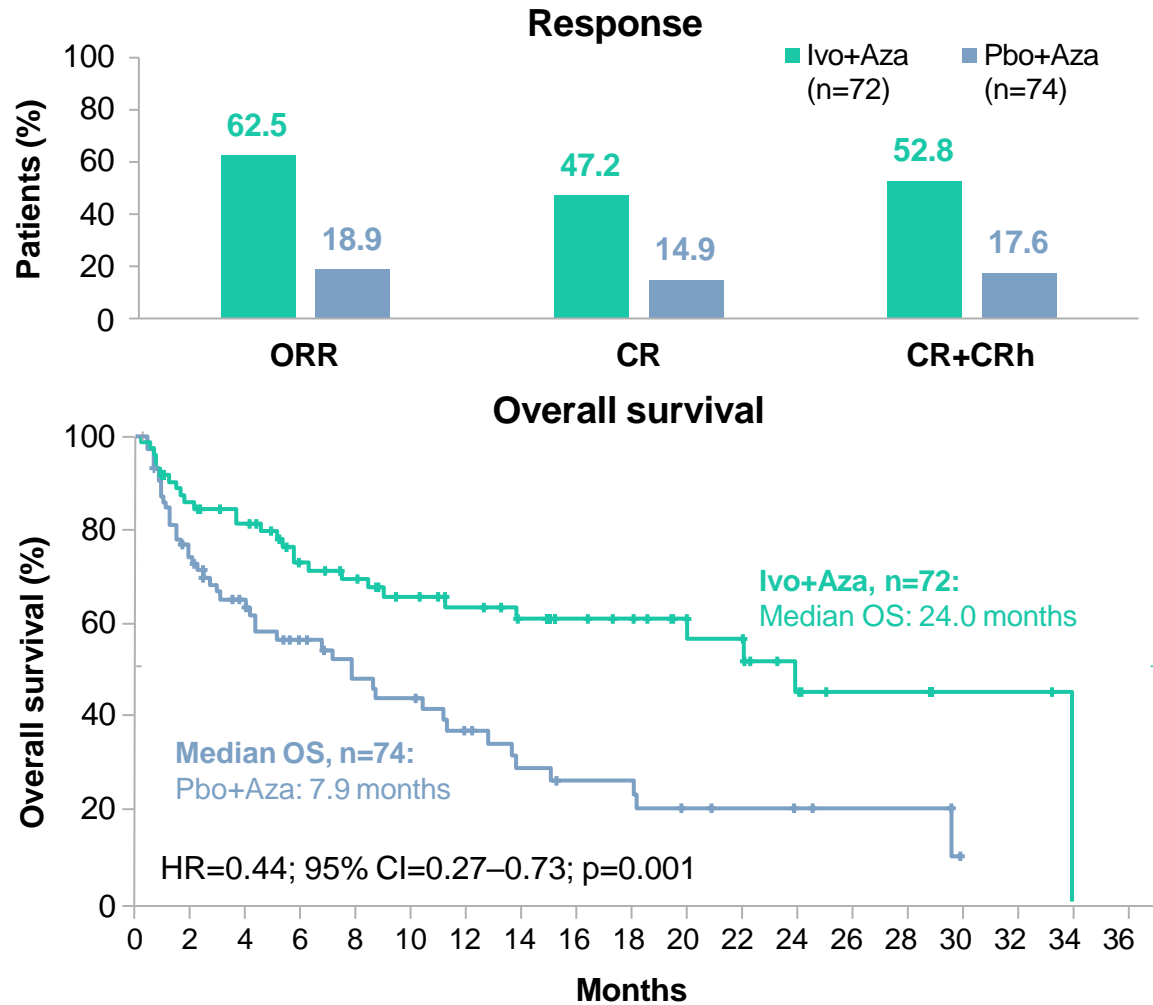
	Patients with newly diagnosed AML <i>N</i> = 39
Overall response rate (ORR), ^a <i>n</i> (%)	30.8% (12/39)
95% CI	17.0, 47.6
Best response, <i>n</i> (%)	
Complete remission (CR)	7 (18)
CR with incomplete count recovery (CRi/CRp)	1 (3)
Partial remission	2 (5)
Morphologic leukemia-free state	2 (5)
Stable disease, ^b <i>n</i> (%)	19 (49)
Disease progression, <i>n</i> (%)	1 (3)
Not evaluable, ^c <i>n</i> (%)	7 (18)
Time to first response, months, median (range)	1.9 (1.0–3.8)
Time to best response, months, median (range)	3.7 (1.0–12.9)
Duration of any response, months, median [95% CI]	NR [7.4, NR]
Time to CR, months, median (range)	5.6 (3.4–12.9)
Duration of CR, months, median [95% CI]	NR [3.7, NR]

Impact of Venetoclax and Azacitidine in Treatment-Naïve Patients with Acute Myeloid Leukemia and IDH1/2 Mutations



AGILE: Ivosidenib+Aza vs Pbo+Aza in ND *IDH1*^{mut} AML

Randomized, Ph 3 trial in patients with untreated AML and an *IDH1* mutation (N=146)

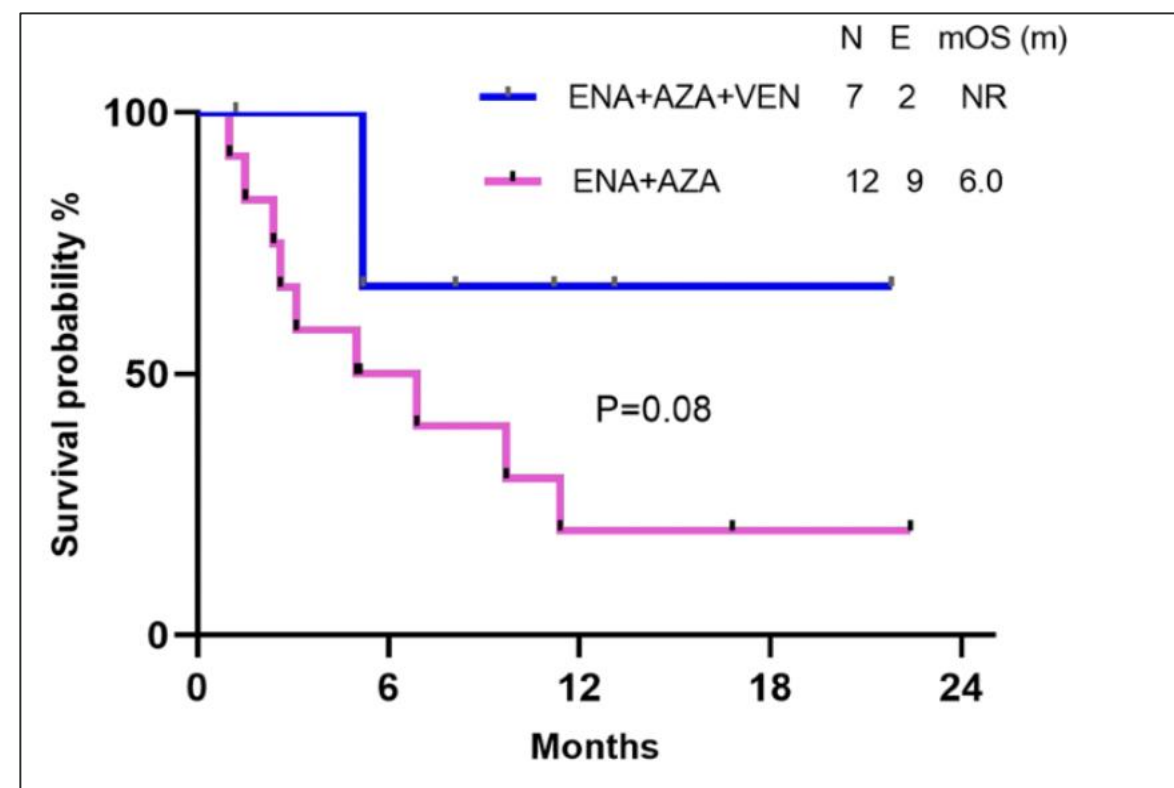
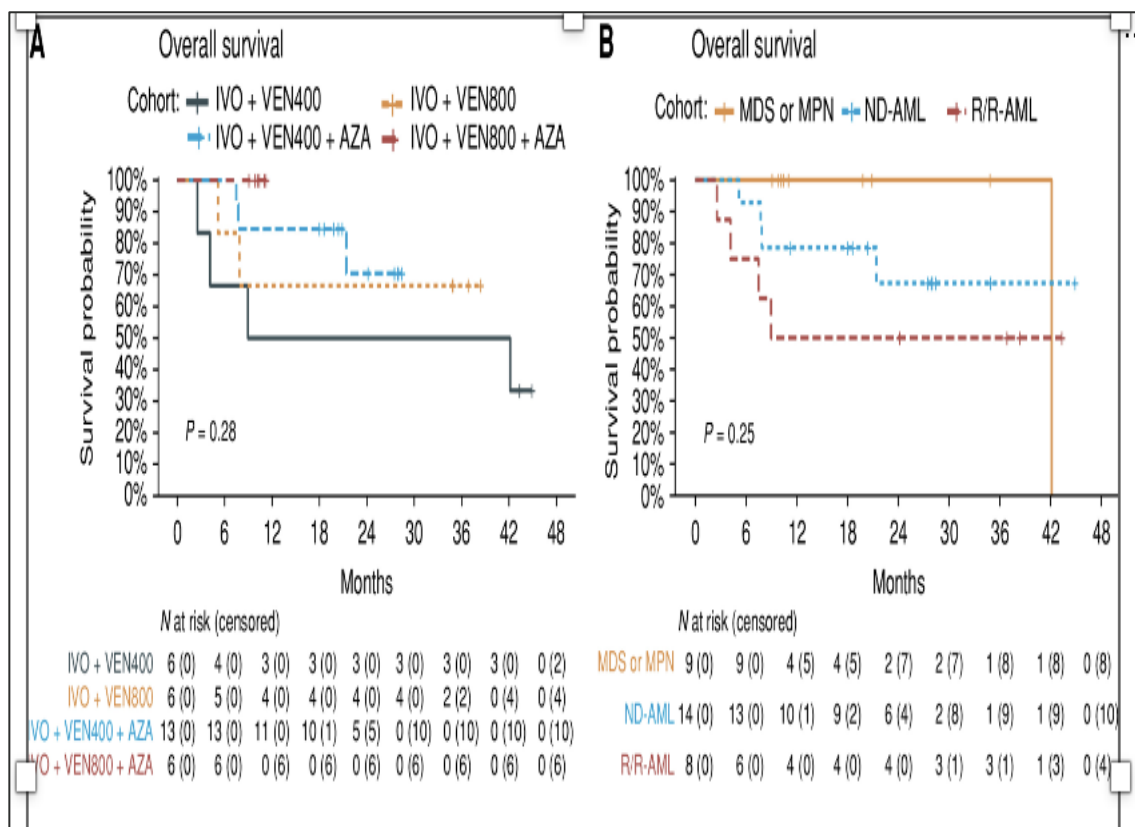


Grade ≥3 AEs in ≥20% of patients in either arm, n (%)	Ivo+Aza (n=71)	Pbo+Aza (n=73)
Hematologic AEs	50 (70)	47 (64)
Anemia	18 (25)	19 (26)
Febrile neutropenia	20 (28)	25 (34)
Neutropenia	19 (27)	12 (16)
Thrombocytopenia	17 (24)	15 (21)
Non-hematologic AEs		
Pneumonia	16 (23)	21 (29)
Infections	15 (21)	22 (30)
Other safety events, n (%)	Ivo+Aza (n=71)	Pbo+Aza (n=73)
Differentiation syndrome (any grade)	10 (14)	6 (8)
Grade ≥3	3 (4)	3 (4)
QT interval prolonged on ECG (any grade)	14 (20)	5 (7)
Grade ≥3	7 (10)	2 (3)
Discontinuation as a result of AEs	19 (27)	19 (26)

Aza, azacitidine; ECG, electrocardiography; Ivo, ivosidenib; mut, mutated; ND, newly diagnosed.

Adapted from Montesinos P, et al. *N Engl J Med* 2022; **386**:1519–1531.

Ven+Aza+IDH1/2 inhibitors



Lachowicz et al. Blood Cancer Discov. 2023;4(4):276-293.

Adapted from Daver N, et al. ASH 2022. Abstract 61 (Oral).

EVOVLE-1: IVO + AZA with or Without VEN in *IDH1*- Mutated AML

Phase III

- Pts ≥18 yrs
- Newly diagnosed AML with mutated *IDH1** ineligible for IC

* Rapid molecular screening, centrally done in Rotterdam, Oxford, Lille, Ulm / Hannover



Venetoclax/Placebo on days 1-7

until disease relapse, progression, development of unacceptable toxicity, withdrawal by subject, death, or protocol violation

Primary endpoint: Event-free survival

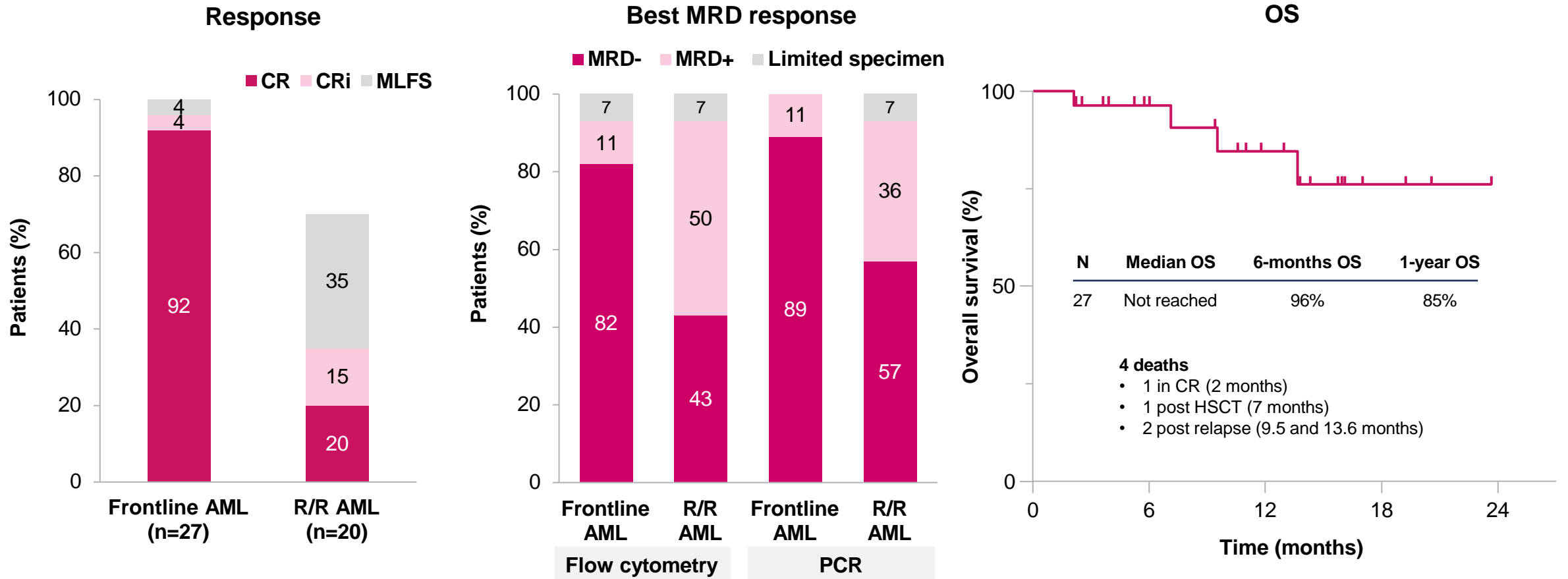
 **PI:** H. Döhner (AMLSG); Co-PIs: G. Huls (HOVON), P. Vyas (UK)

 **Start:** Q2/2025



Ven+Aza+Gilteritinib

Phase 1/2 study in IC-ineligible patients with *FLT3^{mut}* ND or R/R AML (N=47)



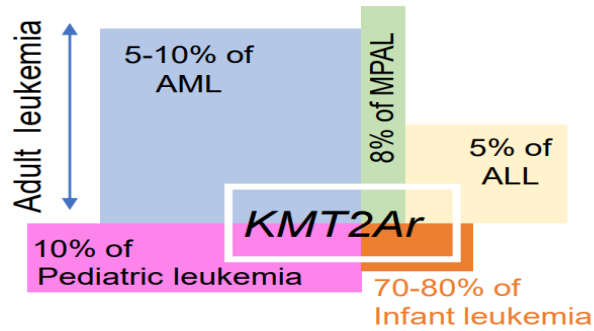
Most common Grade ≥ 3 hematologic AEs ($>10\%$ patients) were infections, febrile neutropenia, sepsis, GI bleeding, and hypotension. Myelosuppression was common but manageable with mitigation strategies

Aza, azacitidine; Gilt, gilteritinib; HSCT, hematopoietic stem cell transplantation; MLFS, morphologic leukemia-free state; mut, mutated; ND, newly diagnosed; PCR, polymerase chain reaction; Ven, venetoclax.

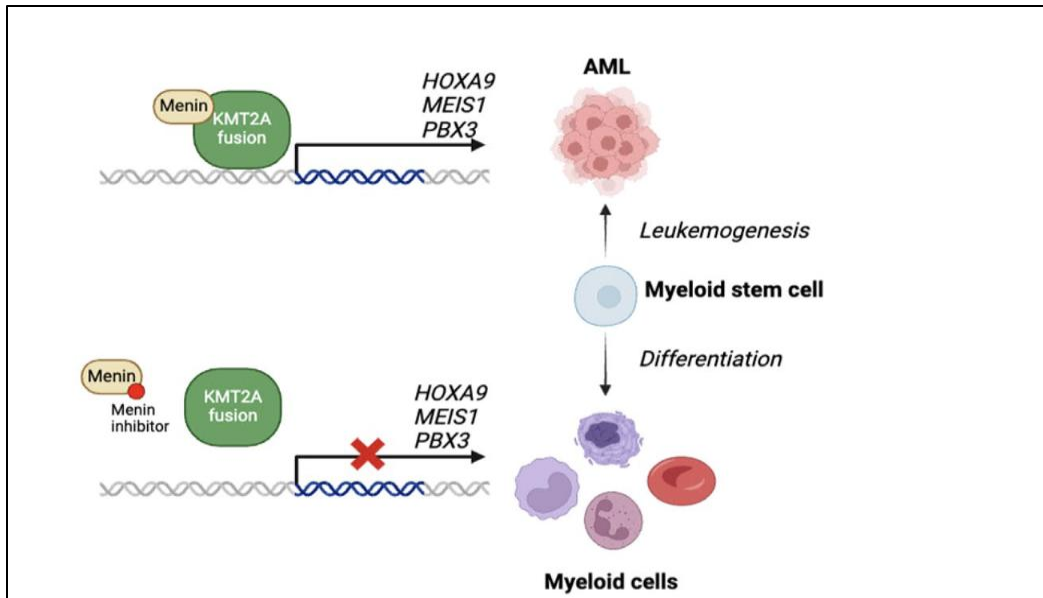
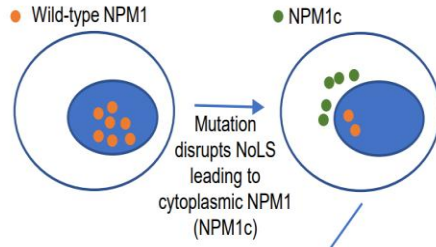
Adapted from Short N, *et al.* ASH 2022. Abstract 831 (Oral).

Menin Inhibitors in AML

KMT2Ar
 ~ 10% of Acute Leukemias
 15% of t-AML
 70% of t-AML 1-2 years following topo II Inh



NPM1c
 25-30% of AML



Agent	Reference study	Phase	Study population
Monotherapy			
Revumenib	NCT04065399 (AUGMENT-101)	2	KMT2Ar/NPM1-mutated R/R AML
Ziftomenib	NCT04067336 (KOMET-001)	2	NPM1-mutated R/R AML
JNJ-75276617	NCT04811560	1	KMT2Ar/NPM1-mutated R/R AML
DSP-5336	NCT04988555	1/2	KMT2Ar/NPM1-mutated R/R AML
BN104	NCT06052813	1/2	KMT2Ar/NPM1-mutated R/R AML
Balamenib (ZE63-0302)	Australia Clinical Trial Notification	1	Healthy volunteers
Combination therapy			
Revumenib + 3-drug reinduction or FLA	NCT05761171	2	KMT2Ar R/R AML
Revumenib + fludarabine + cytarabine	NCT05326516 (AUGMENT-102)	1	KMT2Ar/NPM1mutated/NUP98r R/R AML
Ziftomenib + venetoclax or venetoclax/azacitidine or 7 + 3	NCT05735184 (KOMET-007)	1	KMT2Ar/NPM1-mutated R/R AML
Ziftomenib + gilteritinib, FLAG-IDA or LDAC	NCT05735184 (KOMET-008)	1	KMT2Ar/NPM1-mutated R/R AML
JNJ-75276617 + venetoclax + azacitidine	NCT05453903	1b	KMT2Ar/NPM1-mutated R/R AML
Revumenib + ASTX727 + venetoclax	NCT05360160 (SAVE)	1/2	KMT2Ar/NPM1mutated/NUP98r R/R AML
DS-1594b +/- venetoclax, azacitidine or Mini-HCVD	NCT04752163	1/2	Phase 1: all R/R AML Phase 2: MLLr or NPM1-mutated

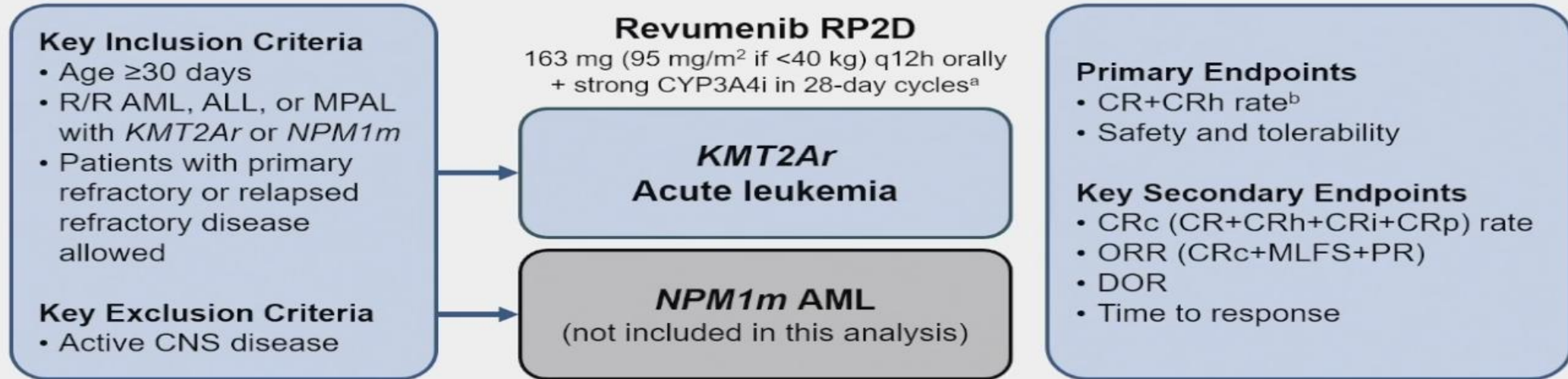
Abbreviations: FLA = fludarabine + high dose cytarabine; FLAG-IDA = fludarabine, cytarabine, G-CSF and idarubicin; LDAC = Low-dose cytarabine; mini-HCVD = cyclophosphamide and dexamethasone (50% dose reduction), no anthracycline, methotrexate (75% dose reduction), cytarabine at 0.5g/m² x 4 doses.

Inhibition of the menin-KMT2A complex downregulates HOXA9/MEIS1 and leads to differentiation of leukemic blasts.

Adapted from: Issa GC et al. Leukemia 2021 Sep;35(9):2482-2495 and Gutierrez Moore et al. Am J Hematol. 2025 Mar;100 Suppl 2:23-37.

Menin Inhibition With Revumenib for *KMT2A*-Rearranged Relapsed or Refractory Acute Leukemia (AUGMENT-101)

AUGMENT-101 Phase 2 Study Design



^aTreatment continued until lack of at least MLFS after 4 cycles, disease progression, unacceptable toxicity, or withdrawal of consent. Maintenance therapy with revumenib after allogeneic hematopoietic stem cell transplant was allowed until disease progression or unacceptable toxicity.

^bCR+CRh rate of 10% under the null hypothesis for antileukemic activity.



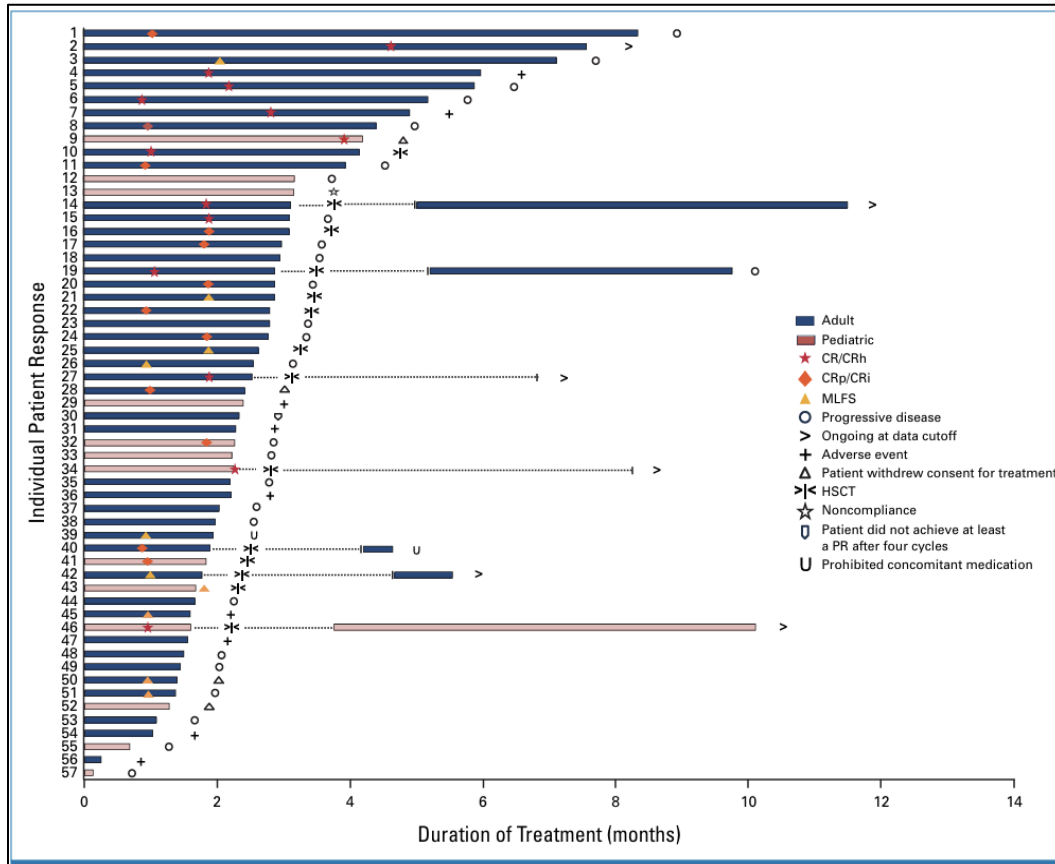
American Society of Hematology

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS, central nervous system; CR, complete remission; CRc, CR composite; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; CYP3A4i, cytochrome P450 3A4 inhibitor; DOR, duration of response; *KMT2Ar*, lysine N-methyltransferase 2A rearranged; MLFS, morphological leukemia-free state; MPAL, mixed phenotype acute leukemia; *NPM1m*, nucleophosmin 1-mutated; ORR, overall response rate; PR, partial remission; q12h, every 12 hours; RP2D, recommended phase 2 dose; R/R, relapsed/refractory

4

Menin Inhibition With Revumenib for KMT2A-Rearranged Relapsed or Refractory Acute Leukemia (AUGMENT-101)

Revumenib: oral, small molecule inhibitor of the menin-lysine methyltransferase 2A (KMT2A) interaction



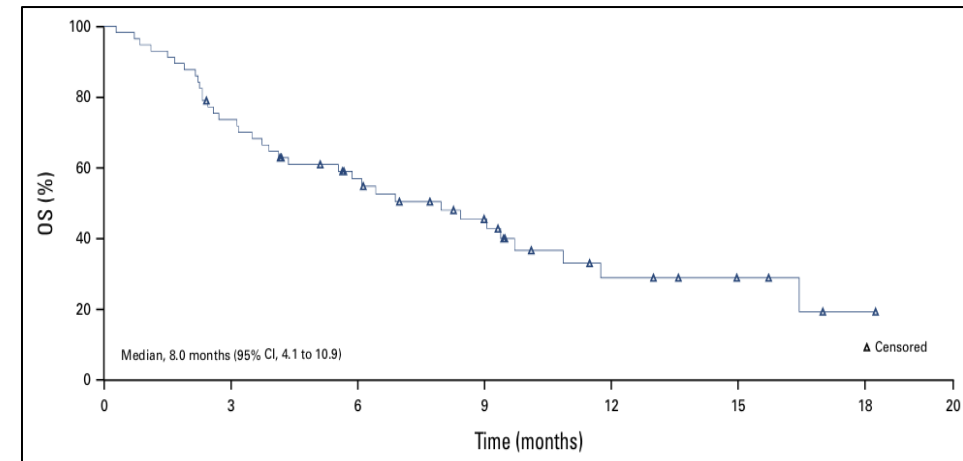
N = 94 patients (median age, 37 [1.3-75] years) Grade \geq 3

Adverse events:

febrile neutropenia (37.2%), differentiation syndrome (16.0%), and QTc prolongation (13.8%).

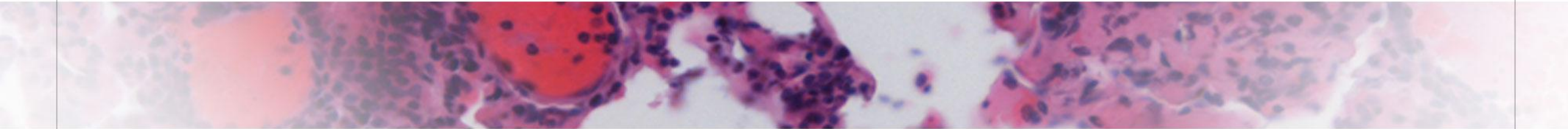
CR+CRh rate 22.8% (N=57)

ORR 63.2% (95% CI, 49.3 to 75.6), with 15 of 22 patients (68.2%) having no detectable residual disease.





American Society of Hematology
Helping hematologists conquer blood diseases worldwide



Phase I/II Study of the All-Oral Combination of Revumenib (SNDX-5613) with Decitabine/Cedazuridine (ASTX727) and Venetoclax in R/R AML (SAVE)

Ghayas C. Issa¹, Branko Cuglievan², Naval Daver¹, Courtney D. DiNardo¹, Aziz Farhat¹, Nicholas J. Short¹, David McCall², Allison Pike¹, Sheila Tan¹, Brianna Kammerer², Aimee Marshal¹, Musa Yilmaz¹, Tapan M. Kadia¹, Naveen Pemmaraju¹, Maro Ohanian¹, Hussein A. Abbas¹, Abhishek Maiti¹, Alexandre Bazinet¹, Elias Jabbour¹, Koji Sasaki¹, Gautam Borthakur¹, Guillermo Montalban-Bravo¹, Nitin Jain¹, Yesid Alvarado¹, Farhad Ravandi¹, Guillermo Garcia-Manero¹, Michael Andreeff¹, and Hagop M. Kantarjian¹

¹Department of Leukemia, ²Division of Pediatrics, The University of Texas MD Anderson Cancer Center, Houston, TX

SAVE Phase I/II Study Design

- Age ≥ 12 years
- R/R AML or Myeloid MPAL
- *KMT2Ar* or *NPM1mt* or *NUP98r*
- ECOG ≤ 2
- Adequate organ function

Revumenib (SNDX-5613)

DL 0: 113 mg

DL 1: 163 mg (**RP2D of monotherapy**)

PO Q12h D1-D28 + a strong CYP3A4i
(posaconazole or voriconazole)

ASTX727

1 tablet (35 mg decitabine and 100 mg
cedazuridine) PO daily for D1-D5

Venetoclax

400 mg target dose* with ramp up
PO D1-D14

*adjusted with azoles

D14 bone marrow for early response

Amendment: hold revumenib after D21 if D14 BM blasts $< 5\%$

Primary objectives:

- **Phase I (3+3 design)**
Safety, MTD and RP2D
- **Phase II**
Efficacy

Secondary objectives:

- Phase 2
OS, RFS, CRD, MRD

Maintenance revumenib post-
HSCT for 1 year

High response rate with SAVE in R/R AML

Best Response n (%)	All patients (N=33)	<i>KMT2Ar</i> (N=16)	<i>NPM1mt</i> (N=12)	<i>NUP98r</i> (N=5)
ORR	27 (82%)	14 (88%)	8 (67%)	5 (100%)
CR/CRh	16 (48%)	7 (44%)	6 (50%)	3 (60%)
CR	13 (39%)	6 (38%)	6 (50%)	1 (20%)
CRh	3 (9%)	1 (6%)	0	2 (40%)
CRp	4 (12%)	3 (19%)	1 (8%)	0
PR	1 (3%)	0	0	1 (20%)
MLFS	6 (18%)	4 (25%)	1 (8%)	1 (20%)
No response/NE*	6 (18%)*	2 (13%)	4 (33%)*	0
MRD neg by MFC (10^{-4}) in responders	17/26 (65%) [#]	9/13 (69%) [#]	7/7 (100%)	1/5 (20%)
<i>Within CR/CRh</i>	14/16 (88%)	7/7 (100%)	6/6 (100%)	1/3 (33%)
Proceeded to HSCT	13 (39%)	9 (56%)	2 (17%)	2 (40%)

ORR= CR+CRh+CRp+PR+MLFS. *One pt with *NPM1mt* with early death prior to response assessment. [#]One responding pt had inadequate MRD by MFC. Data Cutoff 11/18/2024

Conclusions

- The **all-oral SAVE** [revumenib (**SNDX-5613**), oral decitabine/cedazuridine (**ASTX727**) and **VENetoclax**] → acceptable safety and high efficacy in **children and adults** with R/R AML susceptible to menin inhibition
- High rates of response in heavily pretreated population
 - **ORR 82%, CR/CRh 48% → MRD-neg 88% in responders. Median DOR not reached**
 - 39% (13/33 pts) proceeded to HSCT, 7 pts resumed revumenib maintenance
 - Lower rate of DS compared to monotherapy with similar incidence of QT prolongation
- Myelosuppression, confounded by expected risk with HMA + Ven in R/R AML
- This study is now enrolling newly diagnosed patients with AML and *KMT2Ar*, *NPM1mt*, *NUP98r*, ineligible for intensive chemotherapy.

Rationale: BEAT AML Revumenib + VEN + AZA in Newly Diagnosed AML¹

Phase Ib

- Pts ≥ yrs 60
- unfit for IC
- With **frontline** *NPM1*mut or *KMT2A-r* AL

Induction (1-3 cycles)

Revumenib
DL1a or DL2a
D1-28

Aza
75 mg/m² IV/SQ QD Days
1-7

Ven
per label PO QD
Days 1-28

Antifungal
Strong CYP3A Inhibitor*

*Strong antifungal required during 1st cycle

Marrow Remission
(<5% blasts)

Morphologic evidence of AML after cycle 1 of induction

Induction Cycle 2-3

Marrow Remission
(<5% blasts)

Morphologic evidence of AML after cycle 1 of induction

Absolute Neutrophil Count (ANC) ≥0.5x10⁹/L and platelets ≥50x10⁹/L for continuation phase & each subsequent cycle

Continuation Phase
Indefinitely until progression, transplant, intolerance

Revumenib + Aza/Ven
Same doses as Induction

Antifungal
As Needed

Off Protocol Treatment

Revumenib Dose Levels

Dose Level 1a (DL 1a): 113 mg, PO Q12h (28 Days)

Dose Level 2a (DL2a): 163 mg, PO Q12h (28 Days)

- **Primary endpoint:** safety & RP2D
- **Secondary:** exploratory efficacy

- **N=26**
- **Median age:** 70 (60-85)
- ***NPM1*mut:** 65.4%
- ***KMT2A-r*:** 34.6%

AML, acute myeloid leukemia; Aza, azacitidine; DL, dose limit; IC, intensive chemotherapy; IV/SQ, intravenous/subcutaneous; mut, mutant; PO, by mouth; QD, daily; Ven, venetoclax. 1. Zeidner, J. Presented at the 2024 EHA Meeting, in Madrid, Spain from 14 June 2024. Session no. S411

Rationale: Revumenib + VEN + AZA in Newly Diagnosed AML¹

Treatment Outcomes	Escalation DL1a (n=7)	Escalation DL2a (n=6)	Expansion 0 DL2a (n=13)	All (n=26)
Best Response, no. (%)				
CR	5 (71)	5 (83)	8 (62)	18 (69)
CRh	0 (0)	1 (17)	1 (8)	2 (8)
CRi	2 (29)	0 (0)	1 (8)	3 (12)
MLFS	0 (0)	0 (0)	1 (8)	1 (4)
NE	0 (0)	0 (0)	2 (15)	2 (8)
Response Rates for Evaluable Patients?				
Composite CR (CR/CRh/CRi), no. (%)	7/7 (100)	6/6 (100)	10/11 (91)	23/24 (96)
Overall (CR/CRh/CRi/MLFS), no. (%)	7/7 (100)	6/6 (100)	11/11 (100)	24/24 (100)
MRD Negative, no. (%)	6 (86)	6 (100)	10 (91)	22 (92)
Required Only 1 Induction for marrow remission, no. (%)	7 (100)	5 (83)	9 (82)	21 (88)
On-treatment Status, no. (%)	2 (29)	1 (17)	8 (62)	11 (42)
Allo-Stem Cell Transplant, no. (%)	1 (14)	1 (17)	1 (9)	3 (13)
Relapse, no. (%)	2 (29)	1 (17)	0 (0)	3 (13)
Survival				
Death, no. (%)	1 (14)	3 (50)	2 (15)	6 (23)
30/60 Day Mortality, no. (%)	0 (0)	0 (0)	1 (8)	1 (4)
12-Month Survival Estimate, % (95% CI)*	100 (100-100)	N/A	N/A	62.2 (27.8-83.9)

EVOLVE-2¹: VEN + AZA + Revumenib vs. VEN + AZA + PBO

Phase III

- Pts ≥18 yrs
- Newly diagnosed AML with mutated *NPM1* or *KMT2A*-rearranged AML*
- **ineligible for IC**

* Rapid molecular screening, centrally done in Rotterdam, Oxford, Lille, Ulm / Hannover



 **PIs:** G. Huls (HOVON); Co-PIs: M. Kühn (AML SG), P. Vyas (UK)

 **Projected Start:** Q2/2025

ALFA
ALL Leukemia French Association

fil
FRENCH INNOVATIVE
LEUKEMIA ORGANIZATION

CETLAM
Grupo cooperativo de estudio y tratamiento
de las leucemias agudas y mielodisplasias

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

 **STUDY
AML
GROUP**

NCRI National
Cancer
Research
Institute

 **HOVON**

AML, acute myeloid leukemia; **Aza**, azacitidine; **IC**, intensive chemotherapy; **PI**, principle investigator; **PBO**, placebo; **VEN**, venetoclax

1. HO177 AML. Available at: <https://hovon.nl/en/trials/ho177>. Last accessed 14.03.2015



American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Phase 1 Results: First-in-Human Phase 1/2 Study of the Menin-MLL Inhibitor Enzomenib (DSP-5336) in Patients with Relapsed or Refractory Acute Leukemia

Joshua F. Zeidner, MD¹, Junichiro Yuda, MD, PhD², Justin M. Watts, MD³, Mark J. Levis, MD, PhD⁴, Harry P. Erba, MD, PhD⁵, Kentaro Fukushima, MD, PhD⁶, Takahiro Shima, MD, PhD⁷, Neil Palmisiano, MD, MS⁸, Eunice S. Wang, MD⁹, Uma M. Borate, MD¹⁰, Joseph Brandwein, MD¹¹, Cristina Papayannidis, MD, PhD¹², Pau Montesinos, MD, PhD¹³, Gina Keiffer, MD¹⁴, Yasushi Miyazaki, MD¹⁵, Naoko Hosono, MD, PhD¹⁶, Takayuki Ikezoe, MD, PhD¹⁷, Yoshiaki Ogawa, MD, PhD¹⁸, Timothy S Pardee, MD, PhD¹⁹, Stephen Anthony Strickland, MD²⁰, Koichi Onodera, MD²¹, Shang-Ju Wu, MD, PhD²², Melissa G Ooi, MB BCh, BAQ, MRCP(I), FRCPath, PhD²³, Emmanuel Raffoux, MD²⁴, Susana Vives, MD²⁵, Alireza Eghtedar, MD²⁶, Hongliang Cai, PhD²⁷, Curtis Allred, PhD²⁸, Bo Xu, PhD²⁹, Priya Robson²⁷, Akinobu Watanabe²⁷, Matthew Hitron, MD²⁷, Jatin Shah, MD²⁷, Hagop M. Kantarjian, MD²⁸ and Naval G. Daver, MD²⁸

¹University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC; ²National Cancer Center Hospital East, Kashihira, Japan; ³Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL; ⁴Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD; ⁵Duke Cancer Institute, Durham, NC; ⁶Osaka University Graduate School of Medicine, Suita, Japan; ⁷Kyushu University Graduate School of Medicine, Fukuoka, Japan; ⁸Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; ⁹Roswell Park Comprehensive Cancer Center, Buffalo, NY; ¹⁰The Ohio State University, Columbus, OH; ¹¹University of Alberta, Edmonton, AB, Canada; ¹²IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seragnoli", Bologna, Italy; ¹³Hospital Universitario I Politecnico, La Fe, Valencia, Spain; ¹⁴Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA; ¹⁵Hagasaki University Hospital, Nagasaki, Japan; ¹⁶University of Fukuoka, Fukuoka, Japan; ¹⁷Fukushima Medical University, Fukushima, Japan; ¹⁸Tokai University School of Medicine, Kanagawa, Japan; ¹⁹Comprehensive Cancer Center of Atrium Health Wake Forest Baptist, Winston-Salem, NC; ²⁰Sarah Cannon Research Institute, Nashville, TN; ²¹Tohoku University Graduate School of Medicine, Sendai, Japan; ²²National Taiwan University Hospital, Taipei, Taiwan; ²³National University Cancer Institute, Singapore; ²⁴Saint Louis University Hospital, AP-HP, Paris, France; ²⁵Institut Català d'Oncologia - Hospital Germans Trias i Pujol, Badalona, Spain; ²⁶Colorado Blood Cancer Institute, Denver, CO; ²⁷Sumitomo Pharma America, Inc., Marlborough, MA; ²⁸The University of Texas MD Anderson Cancer Center, Houston, TX

©2024 Sumitomo Pharma America, Inc. All rights reserved.

Differentiating Menin Inhibitors: Enzomenib Properties

	Revumenib	Ziftomenib	Bleximenib	Enzomenib
Structure*				
	Tertiary amine bond	Tertiary amine bond	Tertiary amine bond	Amide bond

*National Center for Biotechnology Information (2024). PubChem Compound Summary for CID 132212657, 138497449, 156498110, 146430058

- Beyond target engagement, chemical properties such as polar surface area, lipophilicity, and basicity may impact safety and efficacy^{1,2}
- Enzomenib was specifically and intentionally designed to have low lipophilicity and basicity, which preliminary clinical data has shown results in a low volume of distribution and minimal to no accumulation⁴

Chemical Property*	Polar Surface Area ^{1,2,3}	Lipophilicity ^{1,2}	Basicity ^{1,2}
Target Value	PSA > 75	ClogP < 3.0	Pka < 7.4
Enzomenib	89.8	2.9	6.68
Revumenib	106.9	3.13	9.27
Bleximenib	85.6	3.63	9.48
Ziftomenib	119.7	5.88	8.85

*Numeric values derived from ChemDraw based on NIH CID

- Hughes, J., et. Al (2008) Biorg Med. Chem. Lett., 18, 17, 4872-4875
- Yukawa T., Naven R. (2020) ACS Med. Chem. Lett., 11, 203-209
- The surface area of a compound associated with polar atoms

4. PK data on file, data cut: 22 Oct 2024



American Society of Hematology

Zeidner et al., #213, ASH 2024.

⇒ NewYork-Presbyterian



Weill Cornell Medicine

Conclusions

- **Menin inhibitors are not all the same**

- Enzomenib was intentionally designed to achieve chemical properties to minimize off-target toxicity

- **Enzomenib has been well tolerated with no DLTs**

- No treatment-related deaths or permanent discontinuations due to drug-related AEs

- QT interval prolongation does not appear to be a risk of enzomenib

- Low incidence of differentiation syndrome manageable without prophylaxis

- **Promising clinical activity at optimized doses (≥ 200 mg BID) in *KMT2Ar* or *NPM1m***

- *KMT2Ar*: ORR 73.3%, CR/CRh 40.0% at 300 mg BID

- *NPM1m*: ORR 58.8%, CR/CRh 47.1% at 200 mg or 300 mg BID

- 400 mg BID cohort ongoing and will be reported at a future meeting

- **The same dose of Enzomenib is used with or without azoles and there is minimal to no accumulation**

- **Combination cohorts are initiated**

- Enzomenib + Azacitidine + Venetoclax for patients with R/R *KMT2Ar* or *NPM1m* AML

- Enzomenib + Gilteritinib for patients with R/R *NPM1m* AML w/*FLT3* mutation

Zeidner et al., #213, ASH 2024.



AML Triplets: Triple the Trouble?

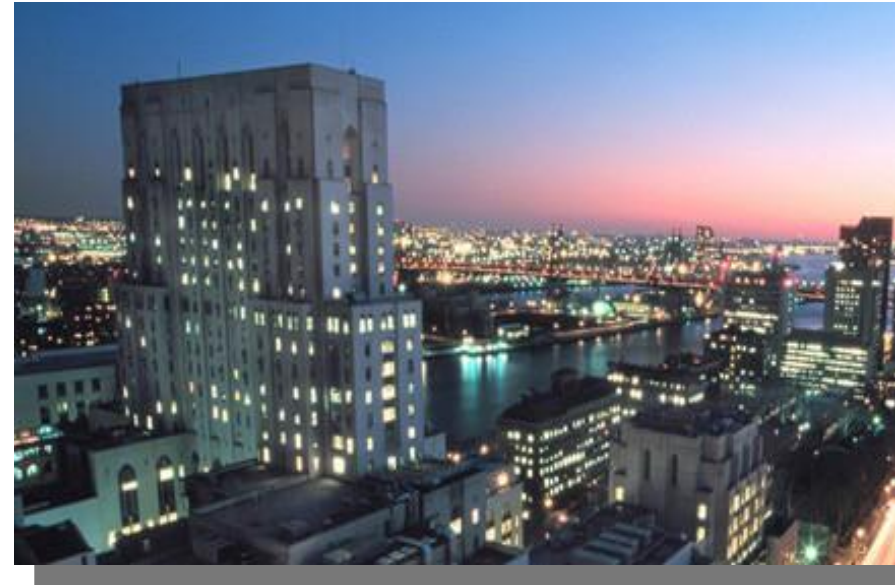
- Aza/Ven/gilt – responses better, ?OS benefit - likely
- Aza/Ven/IDHi – responses better, ?OS benefit - maybe
- Aza/ven + menin inhibitors – looks promising, but too soon to be sure
- Aza/Ven+ something new for TP53 – hopefully

-
- Which HMA?
 - Dosing and schedule are a MESS
 - Duration?? Which agents for how long?
 - Significant myelosuppression
 - Challenges in managing of concomitant medications
 - Additive extramedullary toxicities
 - Significant financial toxicity

But still, HMA/VEN triplets are here to stay.

The Weill Cornell – NY Presbyterian Leukemia Program

- Gail J. Roboz, M.D.
- Ellen K. Ritchie, M.D.
- Pinkal Desai, M.D.
- Michael Samuel, M.D.
- Justin Kaner, M.D.
- Michal Bar-Natan, M.D.
- Jonathan Canaani, M.D.
- David Helfgott, M.D.
- Tania Curcio, N.P.
- Natalie Tafel, P.A.
- Adomah Sakibia Opong, N.P.
- Michelle Vasquez, N.P.
- Rookmimi Singh, R.N.
- Maureen Thyne, P.A.
- Cassady Remy, P.A.



WCM Laboratory Collaborators:

- Monica Guzman, Ph.D.
- Olivier Elemento, Ph.D.
- Christopher Mason, Ph.D.



AA&MDSIF † MDS CLINICAL
RESEARCH CONSORTIUM

Supported by the Edward P. Evans Foundation

 **New York Presbyterian**



Weill Cornell Medicine