Year in Review: Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Oncology

Menin Inhibitors in Acute Myeloid Leukemia

A CME/MOC-Accredited Live Webinar

Thursday, March 26, 2026
5:00 PM – 6:00 PM ET

Faculty

Amir Fathi, MD
Eunice S Wang, MD

Moderator

Neil Love, MD

RTP Year in Review 2026

Faculty

Amir Fathi, MD
Director, Leukemia Program
Massachusetts General Hospital
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Eunice S Wang, MD
Chief, Leukemia/Benign Hematology Service
Professor of Oncology, Department of Medicine
Roswell Park Comprehensive Cancer Center
Buffalo, New York

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

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Commercial Support

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Dr Love — Disclosures

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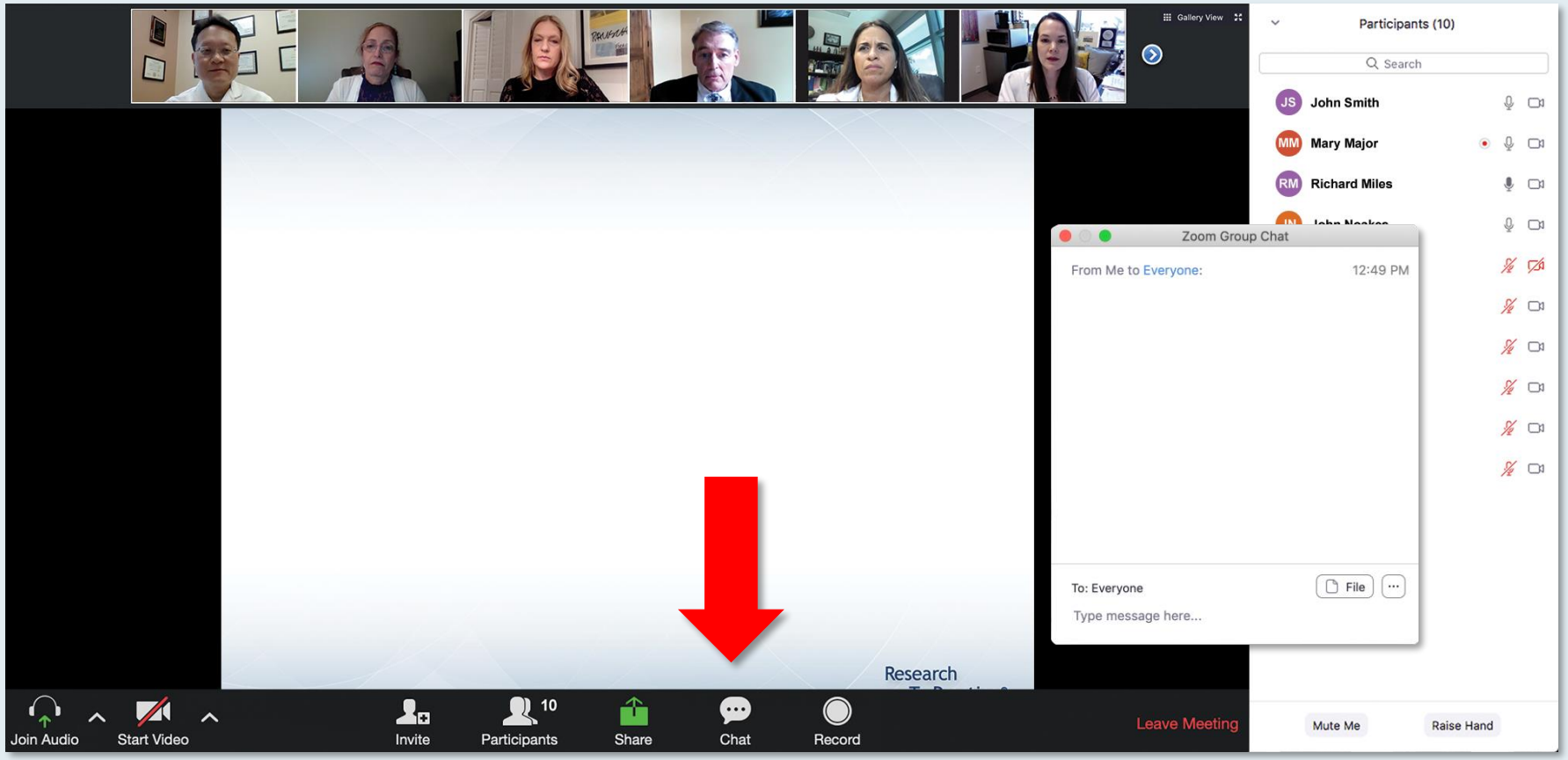

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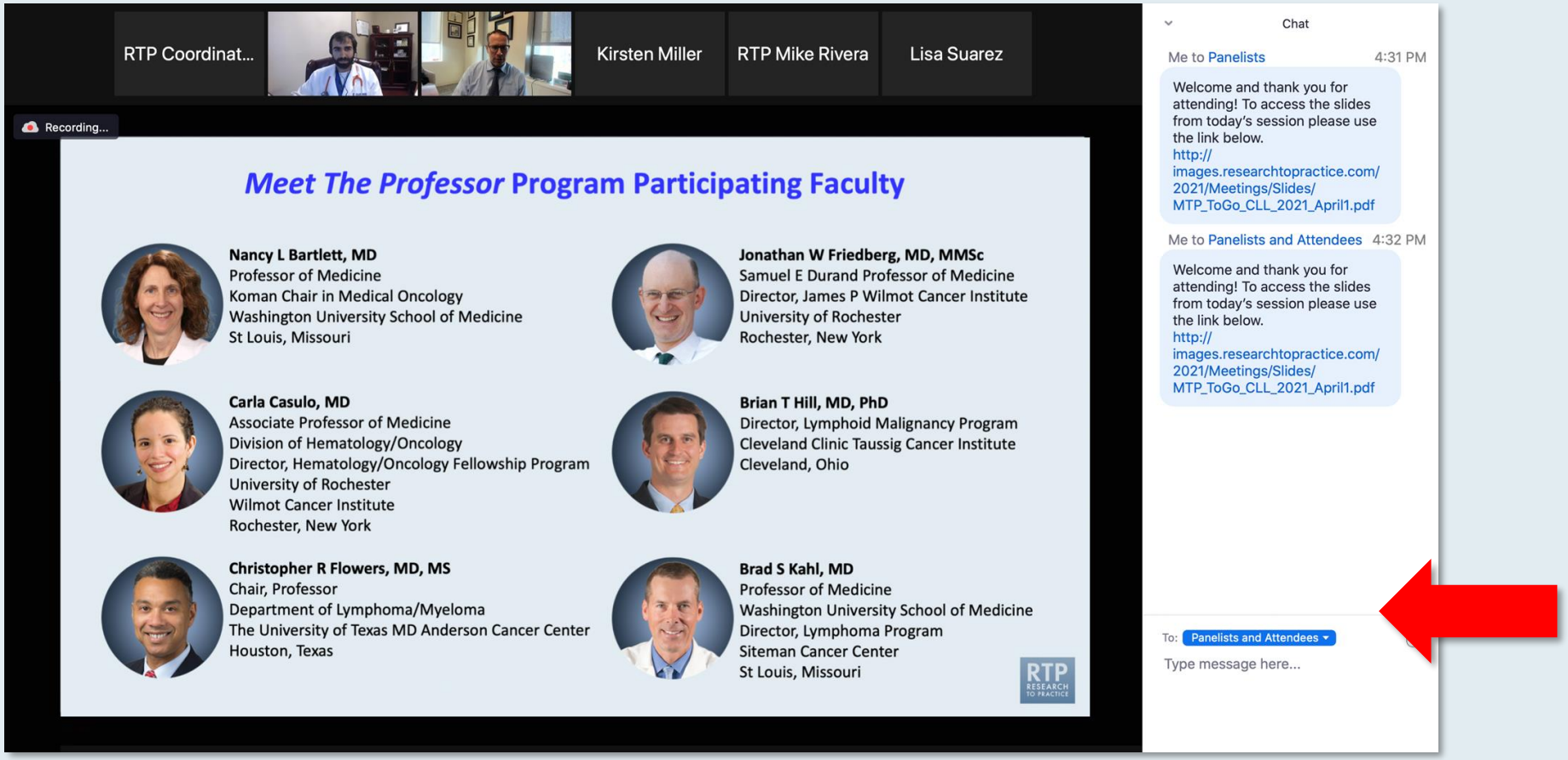

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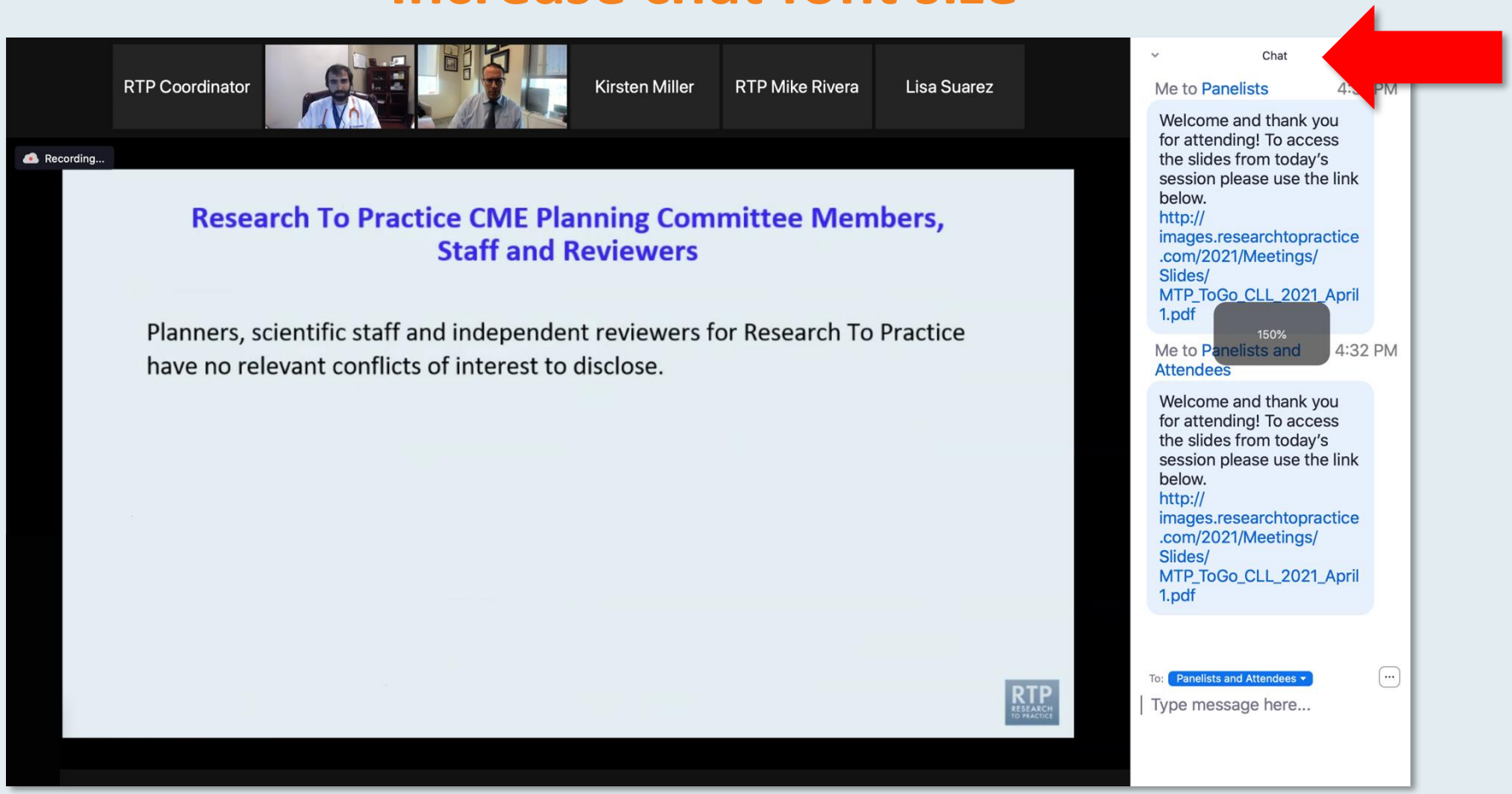

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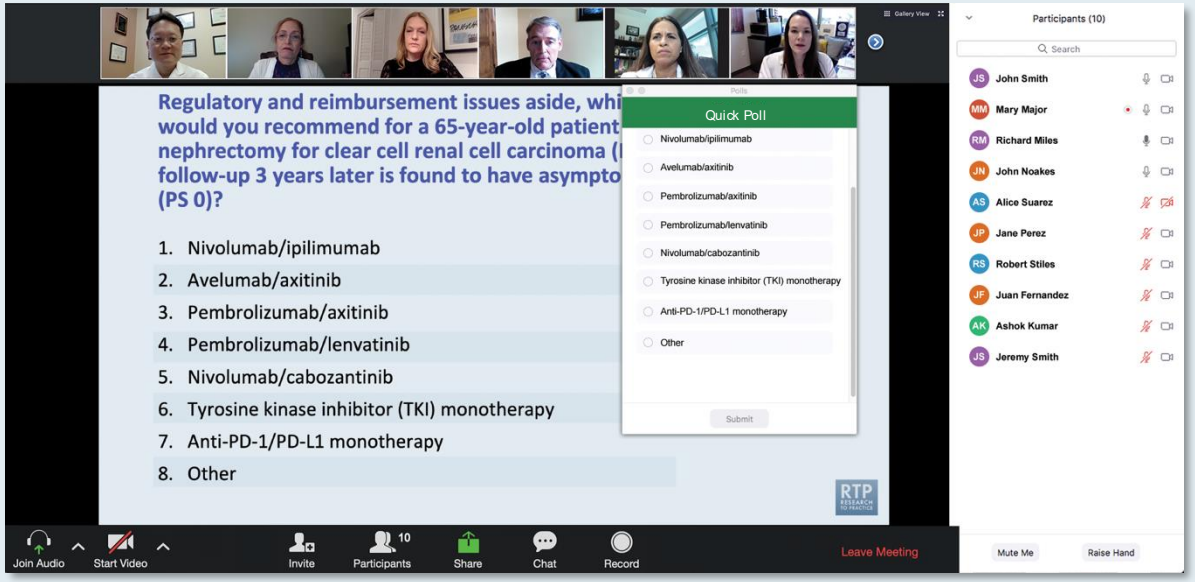

Acute Myeloid Leukemia — An Interview with Ghayas Issa, MD, on the Role of Menin Inhibitors

GHAYAS ISSA, MD
THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

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HER2-Positive Gynecologic Cancers

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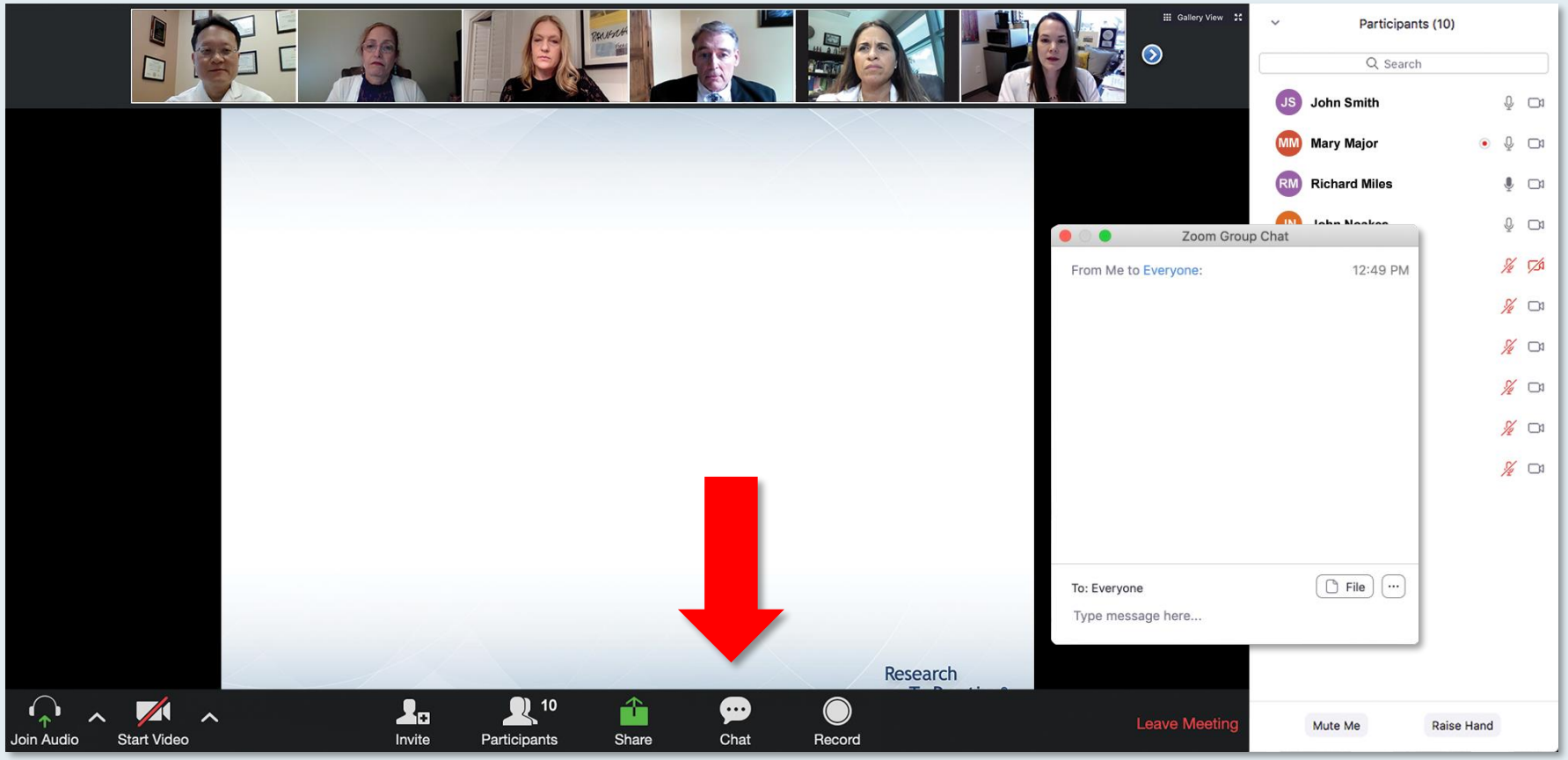

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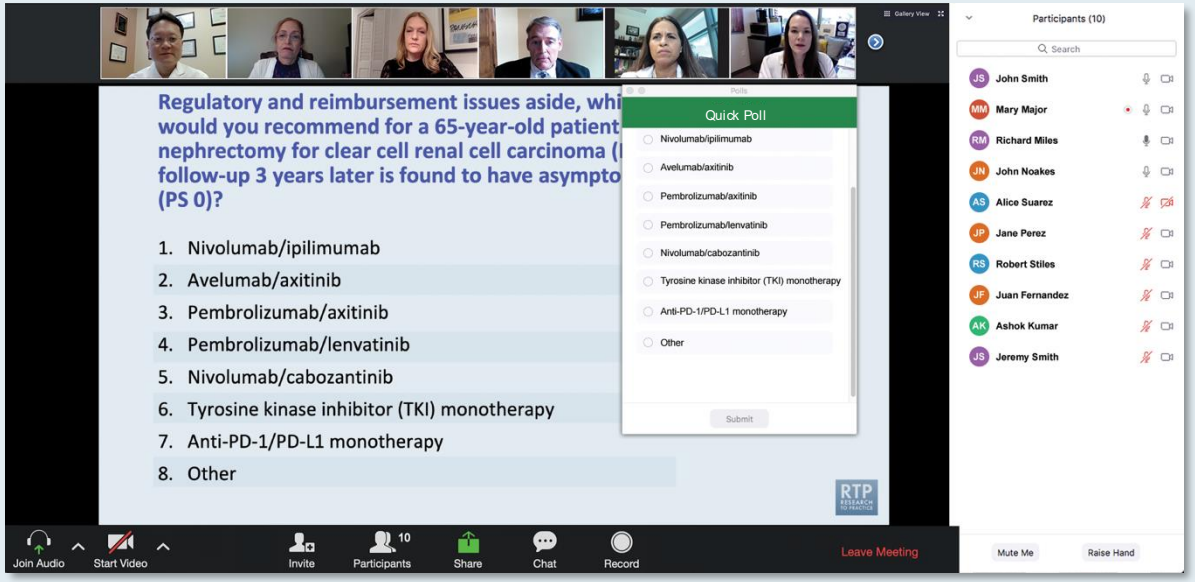

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Year in Review: Biology Underlying the Utility of Menin Inhibitors in Acute Leukemias: Use of These Agents as Monotherapy

Eunice S. Wang MD
Roswell Park Comprehensive Cancer Center
March 2026

Year in Review: Menin Inhibitors in Combination

Amir T. Fathi, MD
Director, Leukemia Program, MGB Cancer Institute
Professor of Medicine, Harvard Medical School

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Key Datasets

Eunice S Wang, MD

- Navarro-Vicente I et al. **Real world outcomes** in a series of 417 adult patients with **KMT2A (MLL) gene rearranged acute myeloid leukemia**. EHA 2025;Abstract S147.
- Huether R et al. **Detection of KMT2A partial tandem duplication (PTD)** in AML by **whole genome sequencing (WGS):** Addressing limitations of traditional techniques in the era of **revumenib** approval. ASCO 2025;Abstract 6532.
- Wang E at al. **Ziftomenib in relapsed or refractory NPM1-mutated AML**. *J Clin Oncol* 2025;43(31):3381-90.
- Aldoss I et al. **Updated results and longer follow-up** from the **AUGMENT-101 phase 2** study of **revumenib** in patients with **relapsed or refractory (R/R) *KMT2Ar* acute leukemia**. EHA 2025;Abstract PS1473.
- Arellano ML et al. Patients with **relapsed or refractory R/R) nucleophosmin 1-mutated (NPM1m) acute myeloid leukemia (AML): Updated results** from the **phase 2 AUGMENT-101** study. EHA 2025;Abstract PS1467.
- Issa G et al. **Revumenib activity** in patients with **acute leukemia with *NUP98r*: Results** from the **AUGMENT-101 phase 1** study. EHA 2025;Abstract PS1501.
- Daver N et al. **Monotherapy update** from **phase 1 portion in phase1/2 trial** of the **menin-MLL inhibitor enzomenib (DSP-5336)** in patients with **relapsed or refractory acute leukemia**. ASH 2025;Abstract 763.
- Shukla N et al. **Detection of MEN1 resistance mutations** in **cell-free DNA** from **acute leukemia** patients **treated with menin inhibitors**. ASH 2025;Abstract 938.

Key Datasets

Amir Fathi, MD

- Issa G et al. **Ziftomenib in combination with venetoclax and azacitidine** in **relapsed/refractory NPM1-m or KMT2A-r acute myeloid leukemia: Updated phase 1a/b safety and clinical activity** results from **KOMET-007**. ASH 2025;Abstract 764.
- Roboz G et al. **Ziftomenib in combination with venetoclax and azacitidine** in **newly diagnosed NPM1-m acute myeloid leukemia: Phase 1b results** from **KOMET-007**. ASH 2025;Abstract 766.
- Erba H et al. **Ziftomenib combined with intensive induction chemotherapy (7+3)** in **newly diagnosed NPM1-M or KMT2A-R acute myeloid leukemia (AML): Updated phase 1a/b results** from **KOMET-007**. EHA 2025;Abstract S136.
- Zeidner JF et al. **Azacitidine, venetoclax, and revumenib** for **newly diagnosed NPM1-mutated or KMT2A-rearranged AML.** *J Clin Oncol* 2025;43(23):2606-15.
- Jen W-Y et al. **Phase II** study of the **all-oral combination of revumenib (SNDX-5613)** with **decitabine/cedazuridine (ASTX727)** and **venetoclax (SAVE)** in **newly diagnosed AML**. ASH 2025;Abstract 47.
- Wei AH et al. **RP2D determination of bleximenib in combination with VEN + AZA: phase 1b** study in **ND & R/R AML with KMT2A/NPM1 alterations**. EHA 2025;Abstract S137.

Key Datasets

Amir Fathi, MD (continued)

- Döhner H et al. **Bleximenib in combination with intensive chemotherapy**: A **Phase 1b** study in **newly diagnosed acute myeloid leukemia with KMT2A or NPM1 alterations**. ASH 2025;Abstract 5199.
- Watts J et al. **Preliminary data** from the **ongoing phase 1** study of the **menin-MLL inhibitor enzomenib (DSP-5336)** in combination with venetoclax and azacitidine in patients with **relapsed or refractory acute myeloid leukemia**. ASH 2025;Abstract 765.

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- Biomarker evaluation in first-line therapy
- Biology of KMT2A rearrangements (KMT2Ar) and NPM1 mutations (NPM1m)
- Mechanism of action of menin inhibitors
- Efficacy indirectly compared to other targetable mutations
- Other alterations (NUP98R)
- Mechanism of resistance

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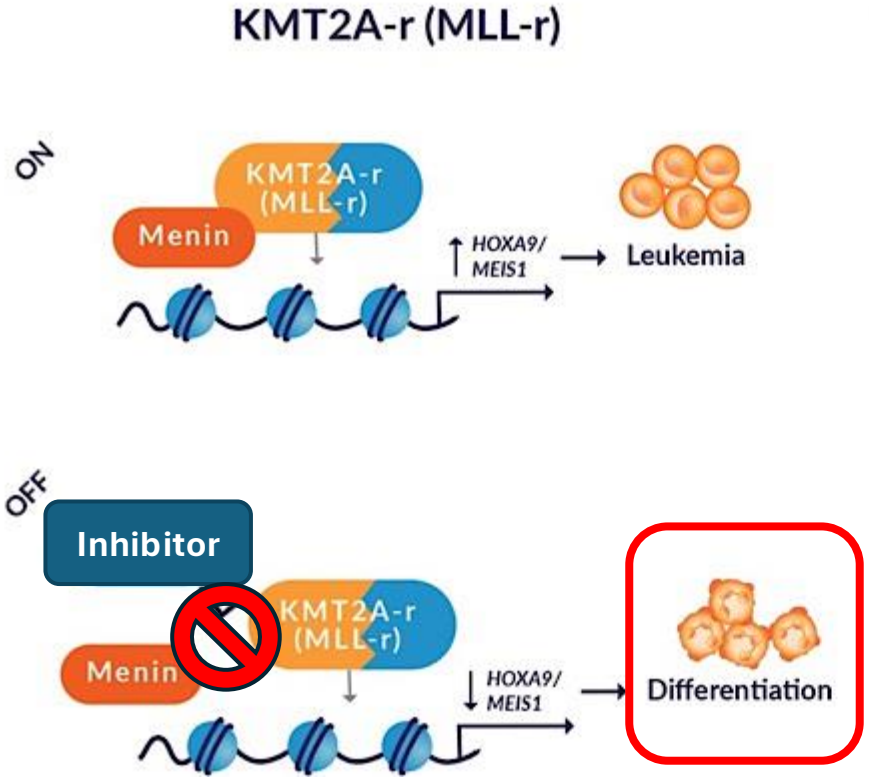
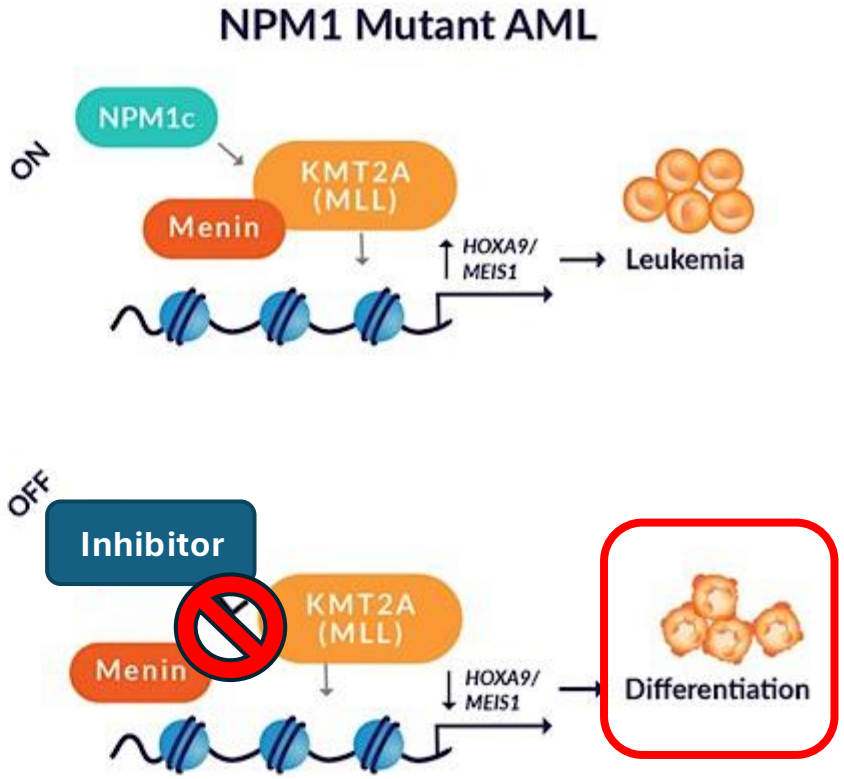
Menin Inhibitor Induced Differentiation: On target effect



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

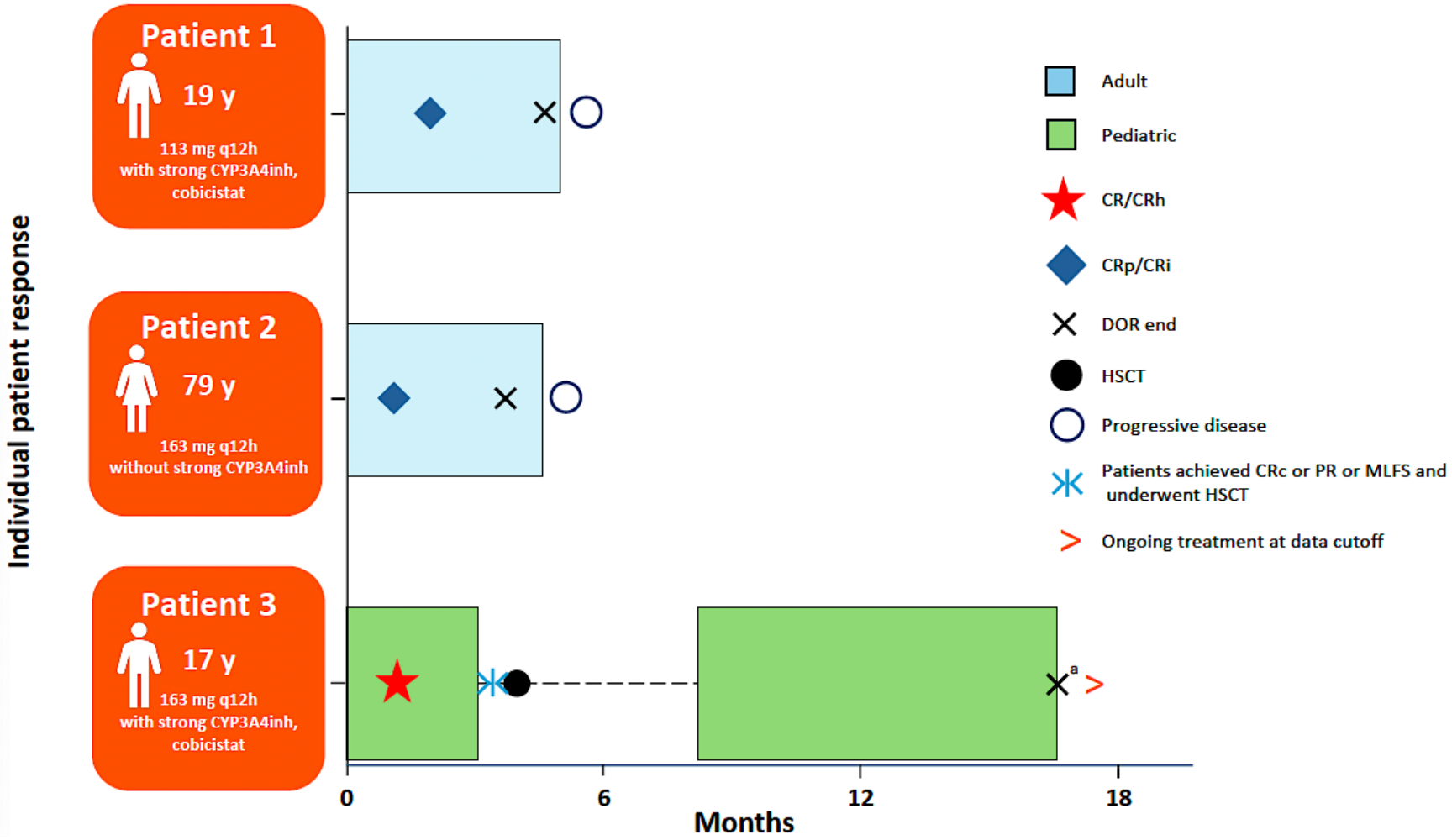
Kühn MW, *et al. Cancer Discov.* 2016;6(10):1166-1181 | Thorsteinsdottir U, *et al. Mol Cell Biol.* 2001;21(1):224-234 | Patel SS, *et al. Curr Hematol Malig Rep.* 2020;15(4):350-359 | Brunetti L, *et al. Cancer Cell.* 2018;34(3):499-512

Issa G et al. REVUMENIB ACTIVITY IN PATIENTS WITH ACUTE LEUKEMIA WITH NUP98R: RESULTS FROM THE AUGMENT-101 PHASE 1 STUDY. EHA 2025;Abstract PS1501.

Three out of five patients with R/R NUP98r AML achieved morphological remission on revumenib monotherapy (113-163 mg BID-TID)

Duration of response was 2.8, 2.8 and 15.6 months (underwent HSCT)

Adverse events:
Gr 3 decreased LVEF
Gr 2 paresthesia
Gr 1 dysgeusia, alopecia



Shukla N et al. Detection of MEN1 resistance mutations in cell-free DNA from acute leukemia patients treated with menin inhibitors. ASH 2025;Abstract 938.

- High-sensitivity research NGS assay **MSK-ACCESS-MEN1** includes probes to all MEN1 exons for cell-free DNA interrogation in hematologic cancers
- MSK-ACCESS-MEN1 identified:
  - an emerging *MEN1* M322I mutation in cfDNA from a patient with *KMT2A*-rearranged AML who had received 14 cycles of revumenib with an MRD-negative BM remission. At the time of cfDNA collection, she remained transfusion independent without evidence of relapse. She subsequently relapsed 3 months later with identification of the *MEN1* M322I mutation.
- **Incorporation of cfDNA monitoring for MEN1 resistance mutations into clinical protocols for menin inhibitor therapy is warranted**

Year in Review:
Menin Inhibitors in Acute Myeloid Leukemia

MODULE 1: Menin Inhibitor Monotherapy

- Approved agents: Revumenib, ziftomenib
- Agents in development: Bleximenib, enzomenib
- Toxicity: QTc prolongation

Conclusions

The emergence of menin inhibitors:

- Effective, safe agents with activity in multiply R/R *NPM1*-m, *KMT2A*-r AML
- Differentiation syndrome as a class effect – requires close vigilance.
- Limited durability of response as monotherapy.

The promise of combinations:

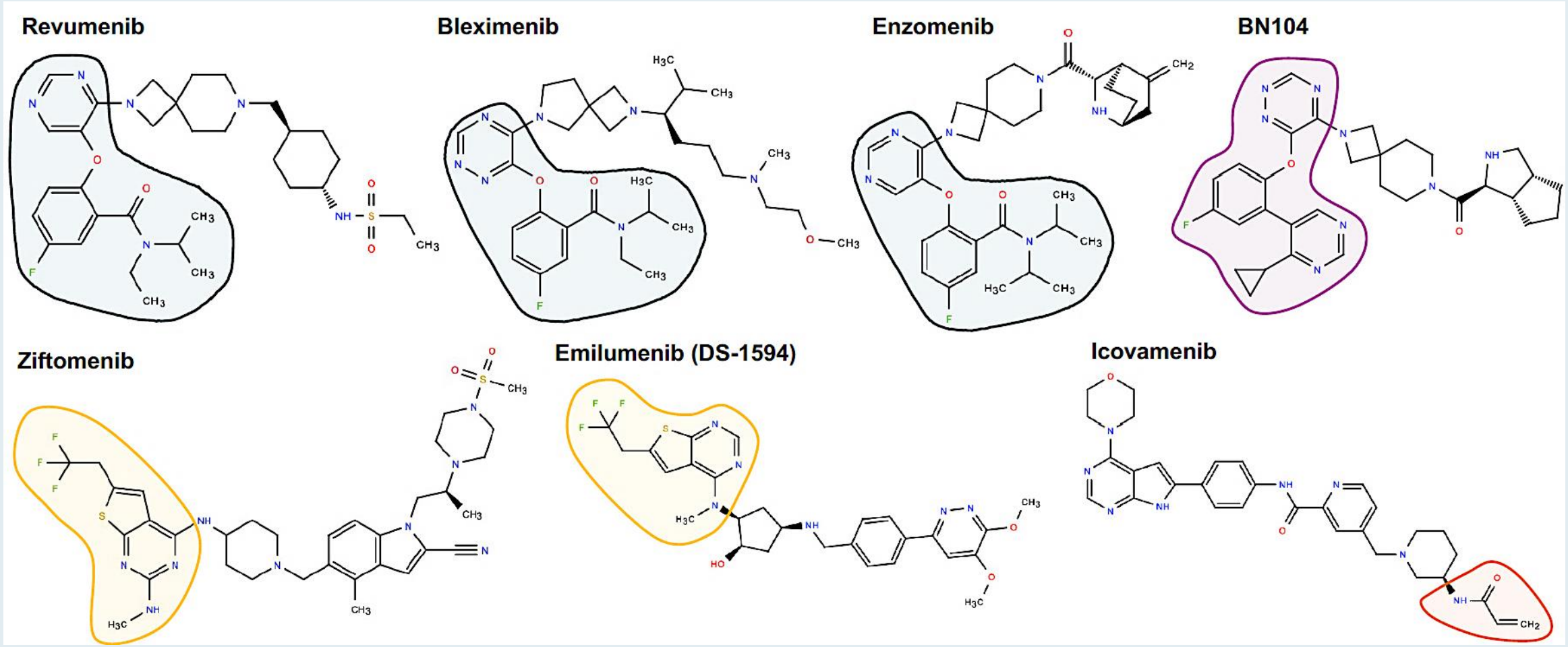
- Studies reveal promise in combination with HMA-ven and induction chemotherapy
- High response rates and promising durability of response, particularly in the frontline setting.
- Will likely mitigate risk of DS.
- Potential for all-oral regimens

Multiple phase 3 studies under way:

- KOMET-017
- REVEAL / EVOLVE-2
- cAMeLOt

Courtesy of Amir Fathi, MD

Menin Inhibitor Structures



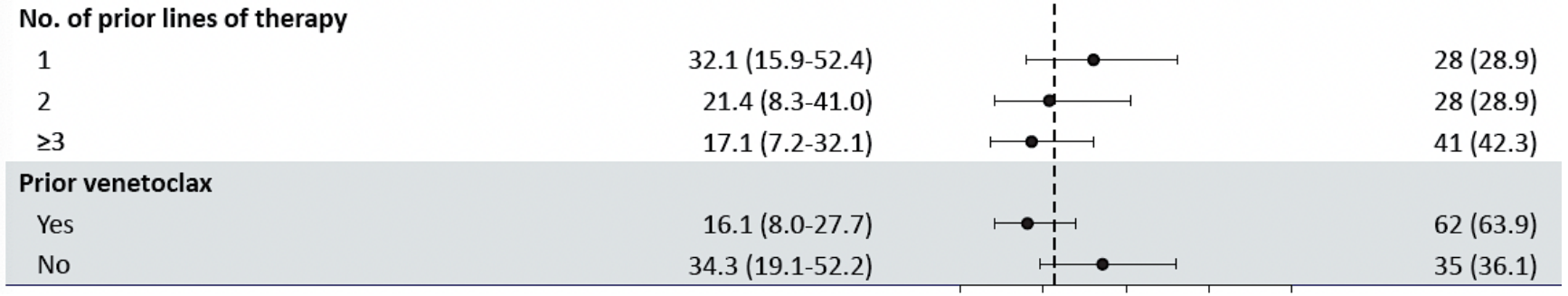
Issa G et al. *Blood Cancer Discov* 2025;6(6):547-60.

Aldoss I et al. UPDATED RESULTS AND LONGER FOLLOW-UP FROM THE AUGMENT-101 PHASE 2 STUDY OF REVUMENIB IN PATIENTS WITH RELAPSED OR REFRACTORY (R/R) KMT2AR ACUTE LEUKEMIA. EHA 2025; Abstract PS1473.

Parameter	Efficacy population (n=97)[a]
ORR, n (%)	**62 (63.9)**
CR+CRh rate, n (%)	22 (22.7)
95% CI	14.8-32.3
CRc rate, n (%)	41 (42.3)
95% CI	32.3-52.7
Negative MRD status, n/N (%)[b]	
CR+CRh	11/18 (61.1)
CRc	21/36 (58.3)

Median duration of CR/CRh = 6.4 mos 1.9-NR)
Time to first response = 1 month (0.9-3.1 mos)
Time to CR/CRh= 2 months (0.9-4.6 mos)

Out of 62 responders, 21 (34%) proceeded to HSCT
Decreased responses associated with prior lines of therapy and prior venetoclax



Aldoss I et al. UPDATED RESULTS AND LONGER FOLLOW-UP FROM THE AUGMENT-101 PHASE 2 STUDY OF REVUMENIB IN PATIENTS WITH RELAPSED OR REFRACTORY (R/R) KMT2AR ACUTE LEUKEMIA. EHA 2025; Abstract PS1473.

	Safety population (N=116)[a]	
All terms	**DS**	**QTc prolongation**
Any grade TEAE, n (%)	31 (26.7)	34 (29.3)
Grade 3	16 (51.6)	15 (44.1)
Grade 4	1 (3.2)	0
Grade 5	0	0
Dose interruptions	9 (29.0)	14 (41.2)
Dose reductions	0	4 (11.8)
Treatment discontinuations	0	0
Time to initial onset, days, median (range)	10 (3-41)	8 (1-72)
Duration of initial event, days, median (range)	12 (3-31)	1 (1-8)

- QTc prolongation was manageable, and most patients with grade 3 events were able to continue treatment in ≤1 day

Arellano ML et al. PATIENTS WITH RELAPSED OR REFRACTORY (R/R) NUCLEOPHOSMIN 1-MUTATED (NPM1M) ACUTE MYELOID LEUKEMIA (AML): UPDATED RESULTS FROM THE PHASE 2 AUGMENT-101 STUDY. EHA 2025;Abstract PS1467.

Parameter	Efficacy population (n=77)[a]
ORR, n (%)	37 (48.1)
CR + CRh rate, n (%)	20 (26.0)
95% CI	16.6-37.2
CRc rate, n (%)	25 (32.5)
95% CI	22.2-44.1
MRD-negative status, n/n (%)[b]	
CR + CRh[c]	12/19 (63.2)
CRc[d]	13/23 (56.5)

Median time to first CR/CRh = 2.8 (0.9-8.8) months
Median duration of CR/CRh = 4.7 (2.1-8.2) months
Median OS= 4.8 (3.4-8.4) months

Five patients out of 77 proceeded to HSCT

Arellano ML et al. PATIENTS WITH RELAPSED OR REFRACTORY (R/R) NUCLEOPHOSMIN 1-MUTATED (NPM1M) ACUTE MYELOID LEUKEMIA (AML): UPDATED RESULTS FROM THE PHASE 2 AUGMENT-101 STUDY. EHA 2025;Abstract PS1467.

Differentiation syndrome	Safety population (N=84)[a]
All grade, n (%)	16 (19.0)[b]
Grade ≥3, n (%)[c]	11 (13.1)
Time to initial onset, days, median (range)	10 (4-34)
Duration, days, median (range)	14.5 (3-57)
Associated treatment changes, n (%)	
Dose interruption	7 (8.3)
Dose reduction	0
Discontinuation	1 (1.2)

QTc prolongation	Safety population (N=84)[a]
All grade, n (%)	36 (42.9)
Grade ≥3, n (%)[c]	19 (22.6)
Time to initial onset, days, median (range)	8 (1-84)
Duration, days, median (range)	4 (1-14)
Associated treatment changes, n (%)	
Dose interruption	18 (21.4)
Dose reduction	8 (9.5)
Discontinuation	1 (1.2)

Wang E at al. Ziftomenib in Relapsed or Refractory NPM1-Mutated AML. J Clin Oncol 2025;43(31):3381-90.

Response Rate

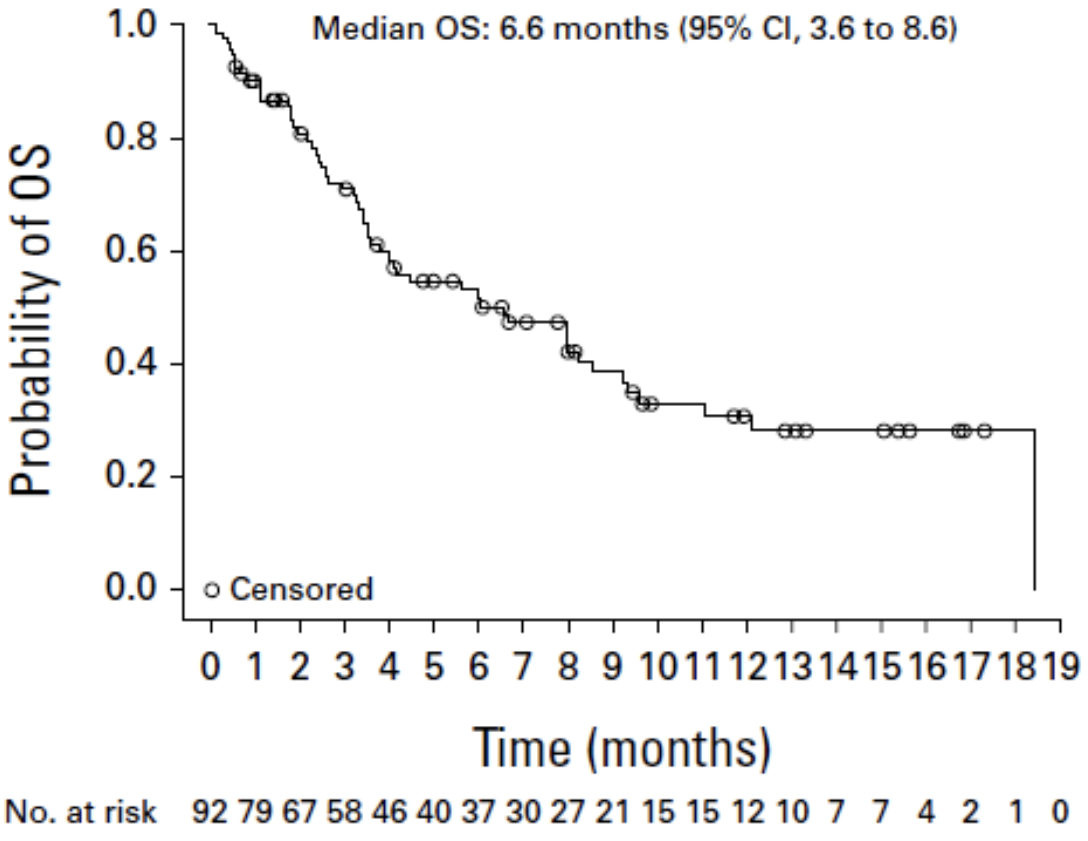
Response	Ziftomenib 600 mg QD (N=92)
ORR	30 (33%)
CR/CRh	20 (22%)
CR	13 (14%)
CRh	7 (8%)
Med Time to ORR	1.9 (0.8-3.7 mos)
Med DOR	4.6 (2.8-7.4 mos)
MRD negativity	14/25 (56%)

Adverse events/Safety

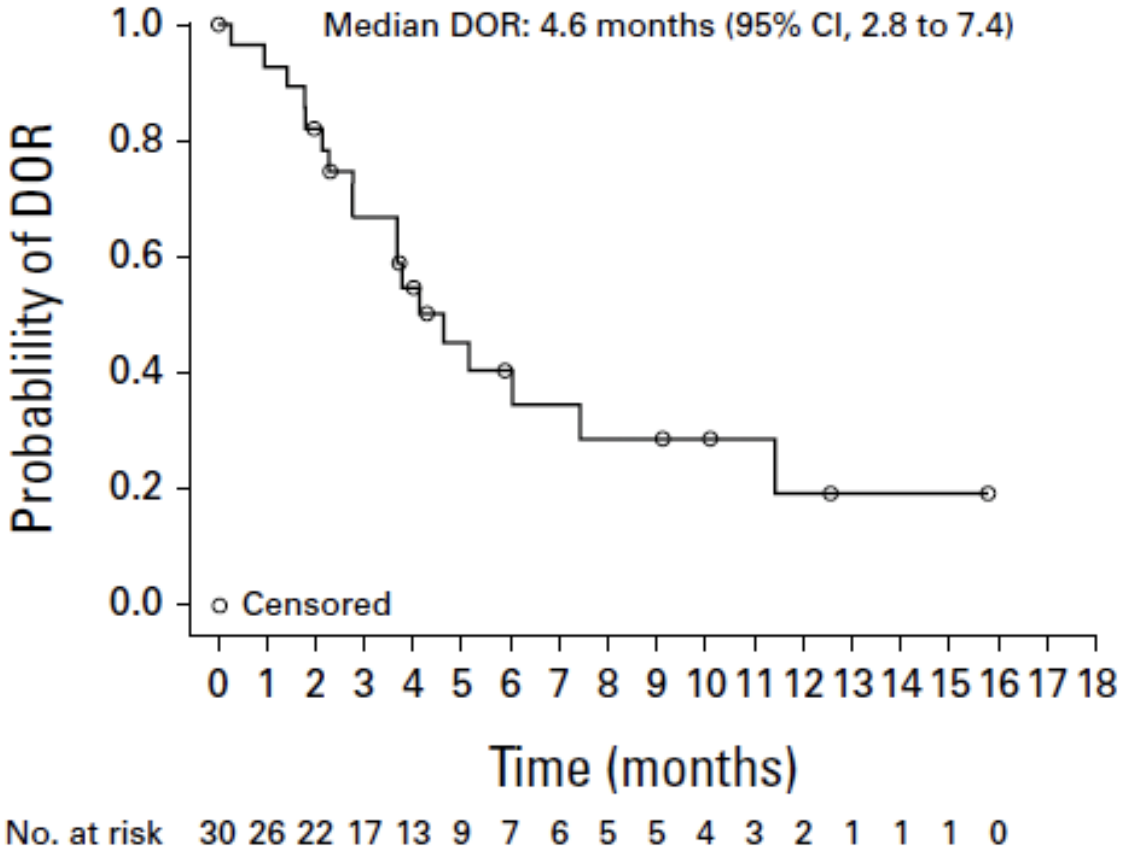
Event	Any Grade, No. ( )	Grade 3, No. ( )
Any adverse event	92 (100)	86 (93)
Hematologic adverse events		
Febrile neutropenia	24 (26)	24 (26)
Anemia	20 (22)	18 (20)
Thrombocytopenia	18 (20)	18 (20)
Platelet count decreased	14 (15)	14 (15)
Neutropenia	13 (14)	13 (14)
Nonhematologic adverse events		
Diarrhea	26 (28)	1 (1)
Differentiation syndrome	23 (25)	14 (15)[a]
Nausea	23 (25)	1 (1)
Peripheral edema	23 (25)	0
Hypokalemia	22 (24)	12 (13)
Pruritus	21 (23)	0

Wang E at al. Ziftomenib in Relapsed or Refractory NPM1-Mutated AML. J Clin Oncol 2025;43(31):3381-90.

Overall survival

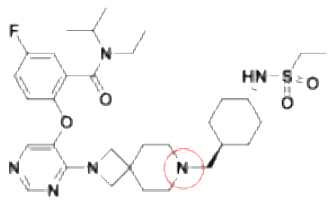
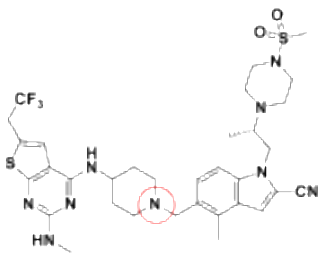
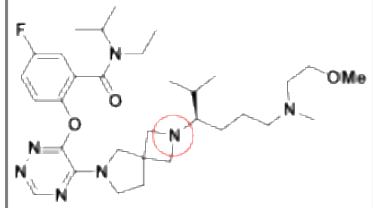
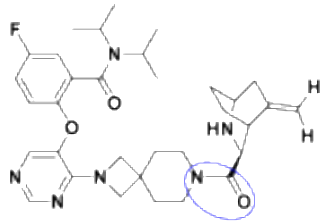


Duration of Response



Daver N et al. Monotherapy update from Phase 1 portion in Phase1/2 trial of the menin-MLL inhibitor enzomenib (DSP-5336) in patients with relapsed or refractory acute leukemia. ASH 2025;Abstract 763.

Menin inhibitors are not the same with differences in chemical structure and physiochemical 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

- Each menin inhibitor has a different chemical structure and different physiochemical properties such as polar surface area, lipophilicity, and basicity that may impact safety and efficacy[1,2]
- Enzomenib was specifically and intentionally designed to have low lipophilicity and basicity, which preliminary clinical data from the ongoing phase 1 trial has shown results in rapid clearance and minimal to no accumulation[3]

1. Hughes J et al. Bioorg Med Chem Lett. 2008 Sep 1;18(17):4872-5.
2. Yukawa T, Naven R. ACS Med Chem Lett. 2020 Jan 29;11(2):203–209.
3. Zeidner et al. ASH 2024;Abstract 213

Enzomenib Monotherapy: Response Rates in R/R AML

KMT2Ar AL (n = 39)

- Dose optimization is complete evaluating 200, 300 and 400 mg po bid
- Optimal RP2D as monotherapy is 300 mg po bid (n=15)
- At RP2D
  - Overall Response rate (CR/CRh/CRi/MLFS) 73.3%
  - Composite CR rate (CR/CRh/CRi) 60%
  - CR + CRh rate 40%

NPM1m AML (n = 25)

- Dose optimization is ongoing at 200, 300 and 400 mg po bid and initial activity is similar across dose levels

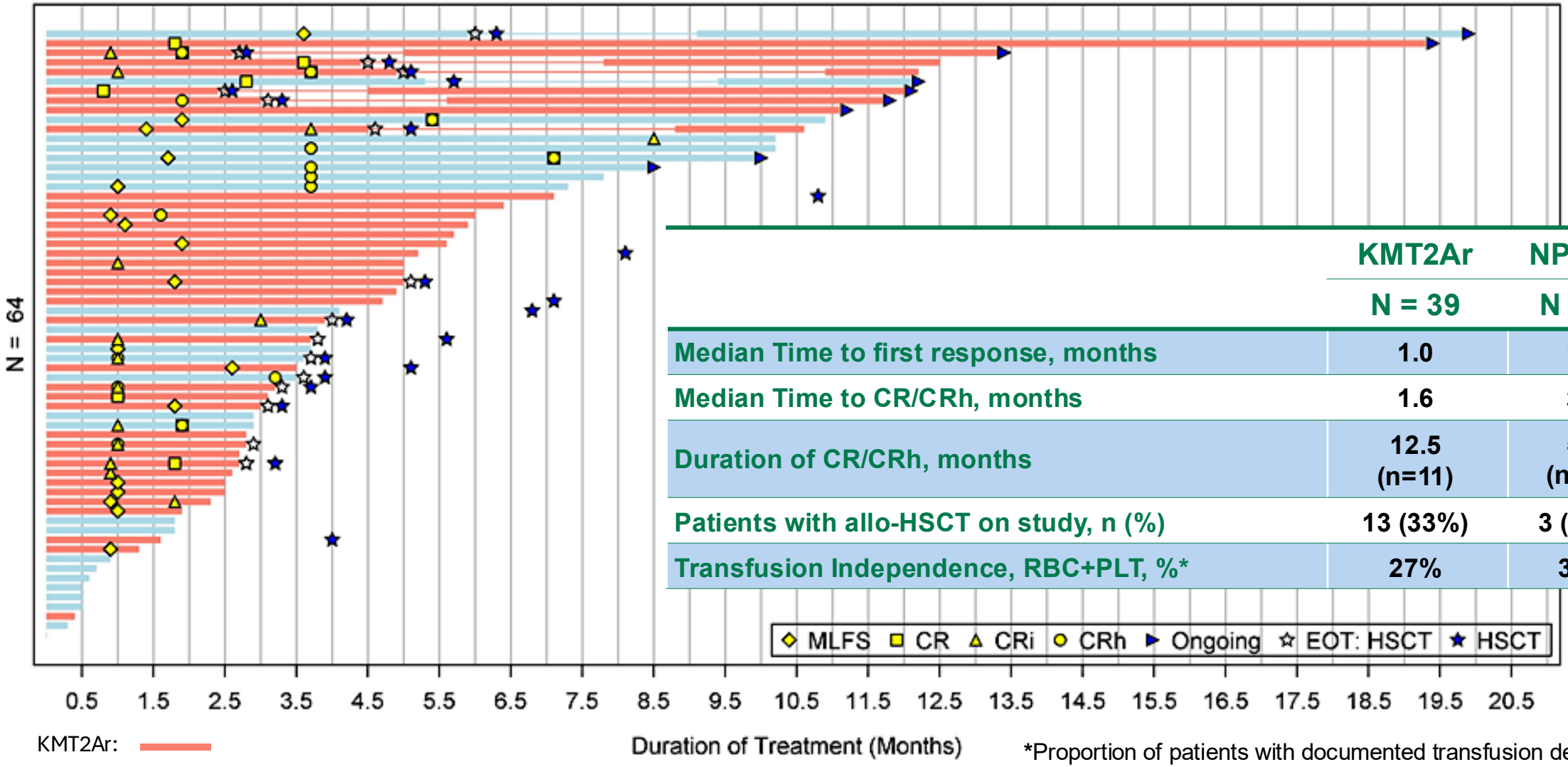
	NPM1m		
Response Category* * Pts who achieved CRh and CRi or MLFS were counted as CRh	**200 mg BID (n = 10)**	**300 mg BID (n = 7)**	**400 mg BID (n = 8)**
Overall Response rate (CR/CRh/CRi/MLFS)	**60% (6/10)**	**57.1% (4/7)**	**37.5% (3/8)**
Composite CR rate (CR/CRh/CRi)	**50% (5/10)**	**42.9% (3/7)**	**37.5% (3/8)**
CR/CRh rate	**50% (5/10)**	**42.9% (3/7)**	**37.5% (3/8)**

- Of 95 total patients with KMT2Ar or NPM1m, the efficacy analysis population (n = 64) did not include those who received < 200 mg BID enzomenib (n = 16), had prior menin inhibitor treatment (n = 11), and who had bone marrow blasts < 5% (n = 4)

Daver N et al. ASH 2025;Abstract 763

Study ongoing, data cutoff 04 OCT 2025

Enzomenib: Responses in R/R AML are Durable



	KMT2Ar	NPM1m
	N = 39	N = 25
Median Time to first response, months	1.0	1.8
Median Time to CR/CRh, months	1.6	3.7
Duration of CR/CRh, months	12.5 (n=11)	5.7 (n=11)
Patients with allo-HSCT on study, n (%)	13 (33%)	3 (12%)
Transfusion Independence, RBC+PLT, %*	27%	38%

*Proportion of patients with documented transfusion dependence for RBC or PLT at baseline that had transfusion independence for both RBC and PLT on study prior to HSCT

Daver N et al. ASH 2025;Abstract 763

Study ongoing, data cutoff 04 OCT 2025

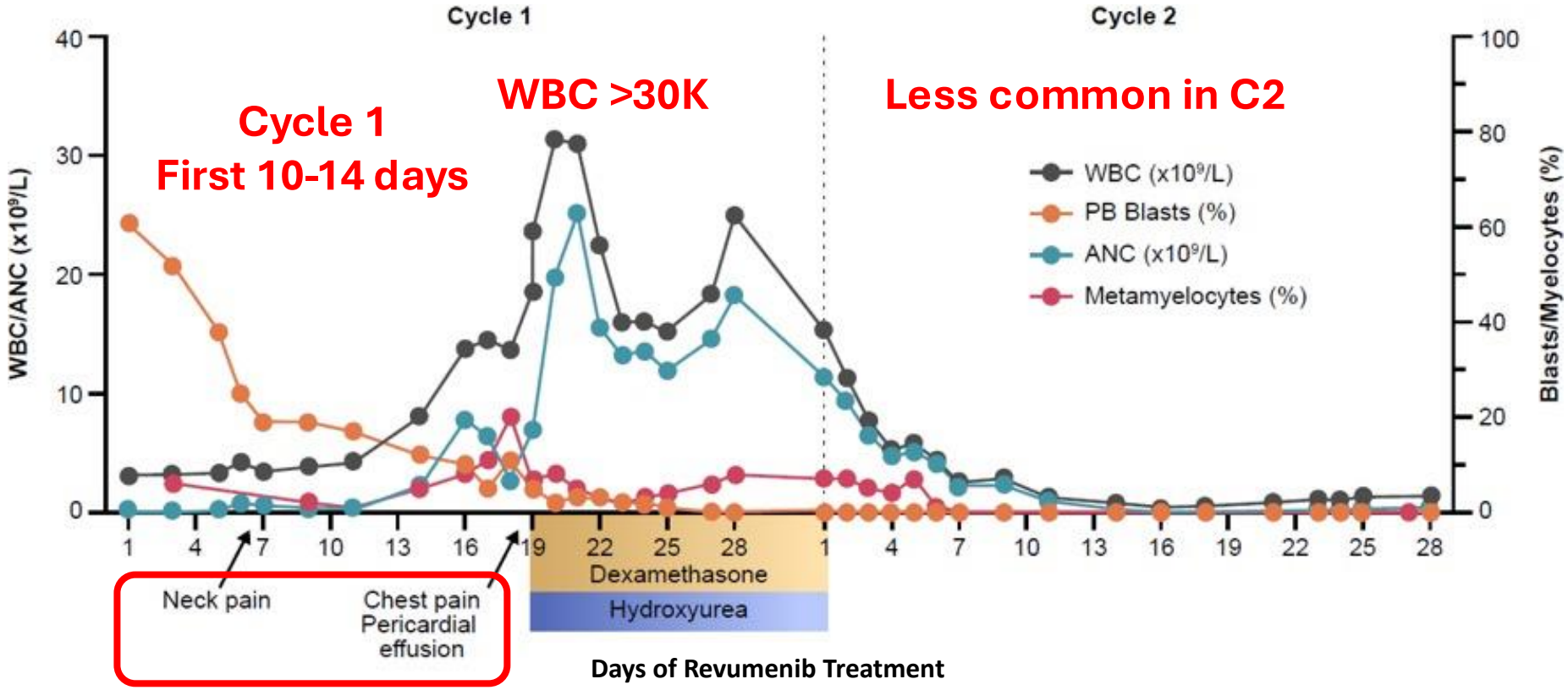
Year in Review:
Menin Inhibitors in Acute Myeloid Leukemia

MODULE 2: Differentiation Syndrome

- Distinguishing characteristics
- Clinical presentation, grading and timing
- Prevention and management
- Correlation with tumor burden, type of alteration and type of menin inhibitor

Case: Revumenib induced DS in *KMT2Ar* AML patient

- 71-year-old with *KMT2Ar* AML relapsed after an allogeneic stem cell transplant
- Received revumenib at 339 mg PO q12h (Arm A), and achieved CRh, MRD negative remission



Issa G et al ASH 2022;Abstract 376

Revumenib: Black Box warning for Differentiation Syndrome

- **Differentiation Syndrome:** Revumenib can cause fatal or life-threatening differentiation syndrome (DS). Symptoms of DS, including those seen in patients treated with revumenib, include fever, dyspnea, hypoxia, peripheral edema, pleuropericardial effusion, acute renal failure, rash, and/or hypotension.

- In clinical trials, DS occurred in 60 (25%) of 241 patients treated with revumenib at the recommended dosage for relapsed or refractory acute leukemia. Among those with a *KMT2A* translocation, DS occurred in 33% of patients with acute myeloid leukemia (AML), 33% of patients with mixed-phenotype acute leukemia (MPAL), and 9% of patients with acute lymphoblastic leukemia (ALL); DS occurred in 18% of patients with *NPM1m* AML. DS was Grade 3 or 4 in 12% of patients and fatal in 2 patients. The median time to initial onset was 9 days (range 3-41 days). Some patients experienced more than 1 DS event. Treatment interruption was required for 7% of patients, and treatment was withdrawn for 1%.

Revumenib product insert (2025)

Ziftomenib-induced DS (23%) in *NPM1*m R/R AML

Ziftomenib-Related AEs in ≥ 5% of All Patients

Event, n (%)	Ziftomenib RP2D 600 mg QD			
	Phase 2 (N = 92)		Pooled Phase 1b/2 (N = 112)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any ziftomenib-related AE	64 (70)	37 (40)	77 (69)	45 (40)
Hematologic AEs				
Anemia	5 (5)	5 (5)	6 (5)	6 (5)
Neutropenia	6 (7)	6 (7)	6 (5)	6 (5)
Nonhematologic AEs				
Differentiation syndrome	**22 (24)**	**14 (15)[a]**	**26 (23)**	**15 (13)[a]**
Pruritus	15 (16)	0	16 (14)	0
Nausea	8 (9)	0	13 (12)	0
Diarrhea	8 (9)	0	10 (9)	2 (2)
Alanine aminotransferase increased	6 (7)	2 (2)	7 (6)	2 (2)
Decreased appetite	5 (5)	0	6 (5)	0

[a]No patients had Grade 4–5 differentiation syndrome.

*All 3 patients were on additional medications associated with QTc prolongation: 2 patients had electrolyte abnormalities and 1 patient had prior diagnosis of atrial fibrillation.

Ziftomenib was well tolerated, with a safety profile consistent with previous studies, including:

- **Differentiation syndrome: Overall 26 pts (23%)**
- **15 (13%) Grade 3 DS**
- **No Grade 4–5 DS events**
- **3% pts discontinued due to ziftomenib-related AEs**

Wang ES et al JCO 2025

Ziftomenib: Black Box Warning for Differentiation Syndrome

Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells. Symptoms of differentiation syndrome, including those seen in patients treated with ziftomenib, may include fever, hypoxia, joint pain, hypotension, dyspnea, rapid weight gain or peripheral edema, pleural or pericardial effusions, acute kidney injury, and rashes.

In the clinical trial, differentiation syndrome occurred in 29 (26%) of 112 patients with relapsed or refractory AML with an *NPM1* mutation who were treated with ziftomenib at the recommended dosage. Differentiation syndrome was Grade 3 in 13% and fatal in two patients. In broader evaluation of all patients with any genetic form of AML treated with ziftomenib monotherapy in clinical trials, differentiation syndrome occurred in 25% of patients. Four fatal cases of differentiation syndrome occurred out of 39 patients with *KMT2A*-rearranged AML treated with ziftomenib. ziftomenib is not approved for use in patients with *KMT2A*-rearranged AML.

In the 112 patients with an *NPM1* mutation, differentiation syndrome was observed with and without concomitant hyperleukocytosis, in as early as 3 days and up to 46 days after ziftomenib initiation. The median time to onset was 15 days. Two patients experienced more than one differentiation syndrome event. Treatment was interrupted and resumed in 15 (13%) patients, while it was permanently discontinued in 2 (2%) patients.

Ziftomenib prescribing information, November 2025.

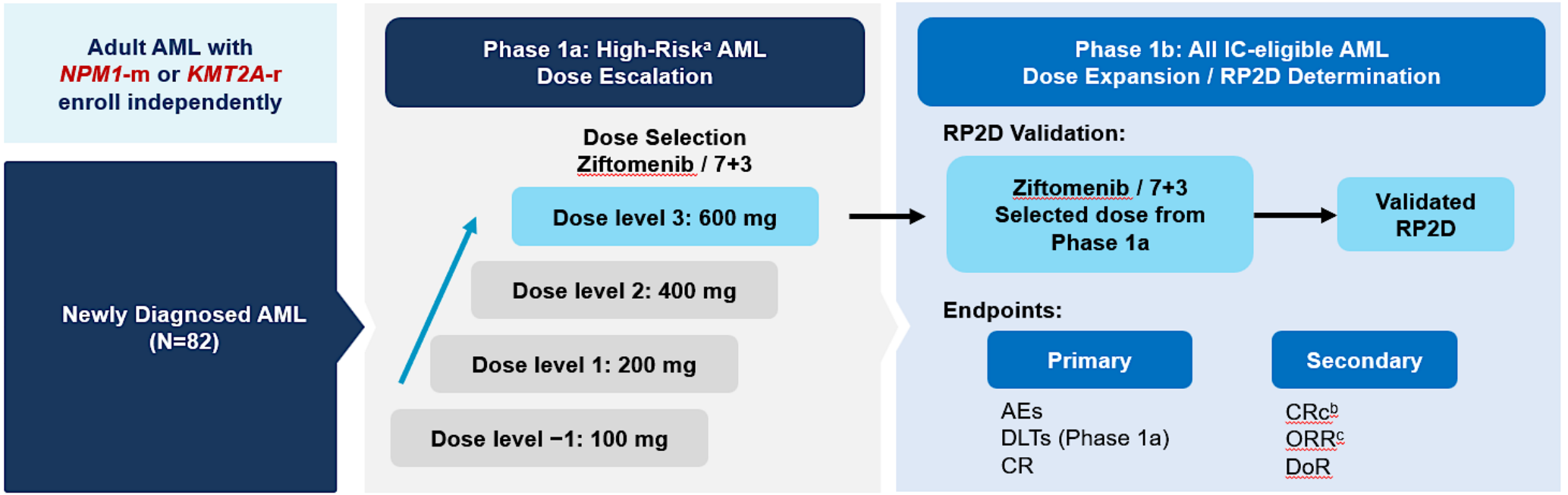
Year in Review:
Menin Inhibitors in Acute Myeloid Leukemia

MODULE 3: Menin Inhibitor Combination Approaches

- Intensive chemotherapy (7 + 3)
- HMA/venetoclax:
  - All oral

KOMET-007: Ongoing Combination Trial of Ziftomenib in Newly Diagnosed AML

Ziftomenib / 7+3 Combination



- Ziftomenib started on Cycle 1 Day 8 and administered continuously thereafter. Cytarabine administered on Cycle 1 Days 1–7; daunorubicin on Cycle 1 Days 1–3; re-induction cycles allowed based on bone marrow biopsy results
- Here we present updated safety and clinical activity in all newly diagnosed AML patients treated at the ziftomenib RP2D of 600 mg QD in combination with standard doses of 7+3 across phase 1a/b

[a]High-risk is defined as *KMT2A*-r AML, or *NPM1*-m with adverse-risk cytogenetics per ELN criteria, age ≥60 yrs and/or treatment-related AML regardless of age. [b]CR, CRh, or CRi. [c]CRc or MLFS.
AE, adverse event; CR / CRh / CRi, complete remission with full / partial / incomplete hematologic recovery; CRc, composite complete remission; DLT, dose limiting toxicity; DoR, duration of remission; IC, intensive chemotherapy; MLFS, morphologic leukemia-free state; QD, once daily; ORR, objective response rate; RP2D, recommended phase 2 dose.

Erba H, et al. EHA, 2025;Abstract S136.

KOMET-007: Clinical Activity in All Response-Evaluable[a] 1L Patients (N=71)

n (%)	*NPM1*-m 600 mg (n=44)	*KMT2A*-r 600 mg (n=27)	All Patients 600 mg (N=71)
CRc	**41 (93)**	**24 (89)**	**65 (92)**
ORR	**43 (98)**	**24 (89)**	**67 (94)**
CR	37 (84)	20 (74)	57 (80)
CRh	1 (2)	0	1 (1)
CRi	3 (7)	4 (15)	7 (10)
MLFS	2 (5)	0	2 (3)
PR	0	0	0
NR	1 (2)	2 (7)	3 (4)
NE	0	1 (4)	1 (1)
CR MRD-negativity, n/N (%)[b]	**24/34 (71)**	**14/16 (88)**	**38/50 (76)**
CRc MRD-negativity, n/N (%)[b]	**26/38 (68)**	**15/18 (83)**	**41/56 (73)**
Median time to CR MRD-negativity, weeks (range)	4.7 (2–17)	4.4 (3–12)	4.5 (2–17)
Median time to CRc MRD-negativity, weeks (range)	4.7 (2–17)	4.1 (3–12)	4.3 (2–17)

[a]Patients who had ≥1 response assessment or who had died.
[b]Among evaluable responders tested for MRD per local assay (NGS, RT-qPCR, FISH, flow cytometry). Preliminary central testing also shows concordance with local MRD-negative rates.

Data cutoff: Mar 21, 2025.
Per ELN 2022: CR / CRh / CRi, complete remission with full / partial / incomplete hematologic recovery; CRc, composite complete remission; FISH, fluorescence in situ hybridization; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; NE, not evaluable; NGS, next-generation sequencing; NR, no response; ORR, objective response rate; PR, partial remission; RT-qPCR, quantitative reverse transcription polymerase chain reaction.

Erba H, et al. EHA, 2025; Abstract S136.

5199

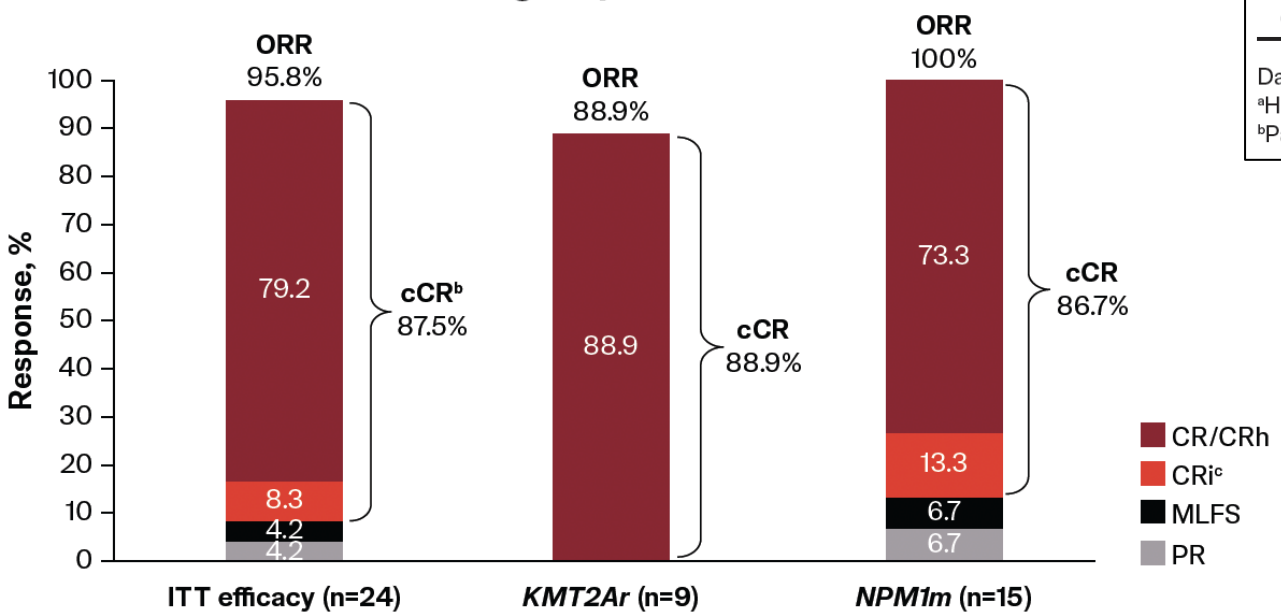
Bleximenib in Combination With Intensive Chemotherapy: A Phase 1b Study in Newly Diagnosed Acute Myeloid Leukemia With *KMT2A* or *NPM1* Alterations

Outcome	
MRD negativity[a]	80% (12 of 15 participants with evaluable samples)
Median event-free survival[b]	NR[c]

Time, median (range), days	N=22[b]
From day 1 of induction to platelet count recovery (≥50 × 10^9/L)[a]	31.5 (22.0–71.0)
From day 1 of induction to neutrophil count recovery (≥0.5 × 10^9/L)[a]	30.0 (25.0–69.0)

Data cutoff: October 2025.
[a]Hematologic parameters over time are shown in **Supplementary Figure 2**.
[b]Participants who received bleximenib 100 mg BID and achieved cCR (comprising CR, CRh, and CRi)

Figure 3: Best overall response in the ITT efficacy population[a] and *KMT2Ar* and *NPM1m* subgroups



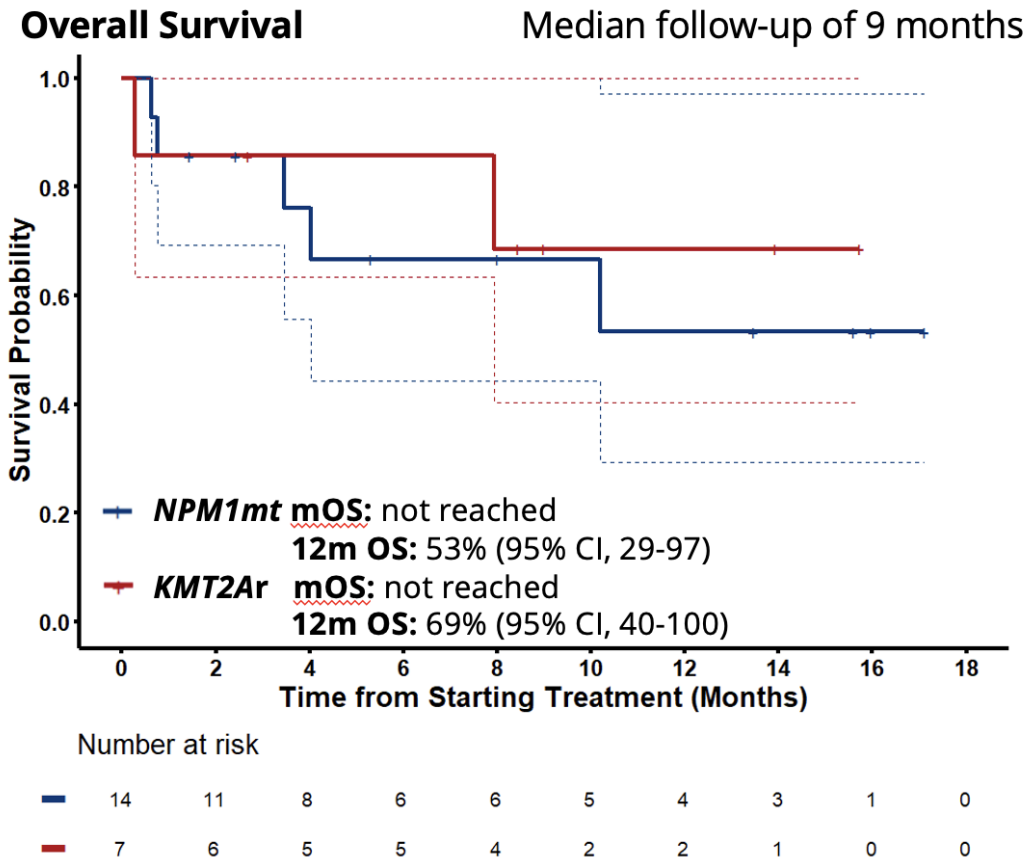
Dohner H, et al. ASH, 2025;Abstract 5199.

All Oral Triplet Regimens

Phase II study of the all-oral combination of revumenib with decitabine/cedazuridine and venetoclax (SAVE) in newly diagnosed AML

Wei-Ying Jen, Courtney D. DiNardo, Nicholas J. Short, Aziz Farhat, Georgina El Hajjar, Baili Zhang, Dzifa Yawa Duose, Naval G. Daver, Tapan M. Kadia, Branko Cuglievan, Kelly S. Chien, Nitin Jain, Hussein A. Abbas, Abhishek Maiti, Jayastu Senapati, Elias Jabbour, Guillermo Montalban-Bravo, Yesid Alvarado, Sanam Loghavi, Farhad Ravandi, Michael Andreeff, Guillermo Garcia-Manero, Hagop M. Kantarjian and Ghayas C. Issa

Best Response	All patients (N=21)	*NPM1mt* (N=14)	*KMT2Ar* (N=7)
ORR	18 (86%)	12 (86%)	6 (86%)
CR/CRh	17 (81%)	11 (79%)	6 (86%)
CR	16 (76%)	10 (71%)	6 (86%)
CRh	1 (5%)	1 (7%)	0
CRp	1 (5%)	1 (7%)	0
MLFS	0	0	0
Early death (30-day)	2 (10%)	2 (10%)	0
Not evaluable*	1 (5%)	0	1 (14%)
MRD neg by MFC (10^{-4})	18 (86%)	12 (86%)	6 (86%)
Within responders	18 (100%)	12 (100%)	6 (100%)



Jen W, et al. ASH, 2025;Abstract 47.

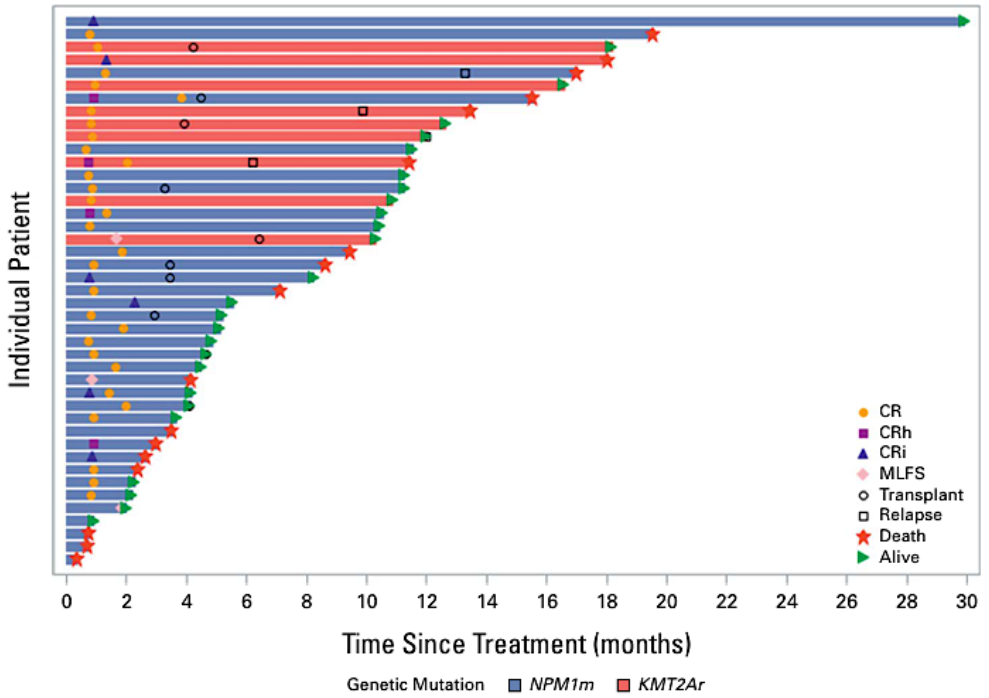
MENi-Triplet (Revumenib)

Azacitidine, Venetoclax, and Revumenib for Newly Diagnosed *NPM1*-Mutated or *KMT2A*-Rearranged AML

Joshua F. Zeidner, MD[1]; Tara L. Lin, MD[2]; Rina Li Welkie, MPH[3]; Emily Curran, MD[4]; Kristin Koenig, MD[3]; Wendy Stock, MD[5]; Yazan F. Madanat, MD[6]; Ronan Swords, MD, PhD[7]; Maria R. Baer, MD[8]; William Blum, MD[9]; Eytan M. Stein, MD[10]; Rebecca L. Olin, MD, MSc[11]; Gary Schiller, MD[12]; Angela Nichols, MSN[1]; Olatoyosi Odenike, MD[5]; Elie Traer, MD, PhD[7]; Curtis Lachowiez, MD[7]; Vu H. Duong, MD, MSc[8]; Michael J. Hochman, MD[9]; Sheng F. Cai, MD, PhD[10]; Catherine Smith, MD[11]; Mona Stefanos, MBChB[3]; Molly Martycz, MSc[3]; Ying Huang, MSc[3]; Len Rosenberg, PhD[13]; Sonja Marcus, MPH[13]; Timothy L. Chen, PhD[3]; Ashley O. Yocum, PhD[13]; Brian J. Druker, MD[7]; Ross L. Levine, MD[10]; Uma Borate, MBBS[3]; John C. Byrd, MD[4]; and Alice S. Mims, MD[3]

Characteristic	All		
	KMT2Ar (n = 9)	*NPM1m* (n = 34)	All (N = 43)
Age, years, median (range)	67 (60-81)	73.5 (61-92)	70 (60-92)
Age ≥75 years, No. (%)	1 (11.1)	16 (47.1)	17 (39.5)
Sex, No. (%)			
Female	4 (44.4)	19 (55.9)	23 (53.5)
Race, No. (%)			
Black	1 (11.1)	0 (0.0)	1 (2.3)
Other	1 (11.1)	2 (5.9)	3 (7.0)
Unknown	0 (0.0)	4 (11.8)	4 (9.3)
White	7 (77.8)	28 (82.4)	35 (81.4)
Ethnicity, No. (%)			
Not Hispanic	8 (88.9)	33 (97.1)	41 (95.4)
Unknown	1 (11.1)	1 (2.9)	2 (4.7)
ECOG performance status, No. (%)			
0	2 (22.2)	3 (8.8)	5 (11.6)
1	6 (66.7)	19 (55.9)	25 (58.1)
2	1 (11.1)	12 (35.3)	13 (30.2)
WBC, 10^9/L, median (range)	5.0 (1.2-14.3)	3.2 (0.7-18.8)	3.2 (0.7-18.8)
Platelets, 10^9/L, median (range)	37 (12-124)	59 (7-874)	54 (7-874)
Bone marrow blast (%), median (range)	78 (55-84)	54 (15-95)	60 (15-95)
Albumin, g/L, median (range)	36 (28-42)	31 (3-40)	32 (3-42)
LDH, U/L, median (range)	210 (144-434)	283 (141-1,130)	272 (141-1,130)
ELN 2017 risk, No. (%)			
Favorable	0 (0.0)	23 (67.7)	23 (53.5)
Intermediate	0 (0.0)	10 (29.4)	10 (23.3)
Adverse	9 (100.0)	1 (2.9)	10 (23.3)
ELN 2024 risk, No. (%)			
Favorable	5 (55.6)	17 (50.0)	22 (51.2)
Intermediate	3 (33.3)	17 (50.0)	20 (46.5)
Adverse	1 (11.1)	0 (0.0)	1 (2.3)
NRAS mutation, No. (%)[a]			
Present	3 (33.3)	6 (18.2)	9 (21.4)
KRAS mutation, No. (%)[a]			
Present	2 (22.2)	3 (9.1)	5 (11.9)
FLT3-ITD mutation, No. (%)			
Present	0 (0.0)	11 (32.4)	11 (25.6)

Clinical Outcomes	All		
	KMT2Ar (n = 9)	*NPM1m* (n = 34)	All (N = 43)
Best response, No. (%)			
CR	7 (77.8)	22 (64.7)	29 (67.4)
CRh	0 (0.0)	1 (2.9)	1 (2.3)
CRi	1 (11.1)	4 (11.8)	5 (11.6)
MLFS	1 (11.1)	2 (5.9)	3 (7.0)
Not evaluable	0 (0.0)	5 (14.7)	5 (11.6)
ORR, % (95% CI)			
CR/CRh/CRi/MLFS	100 (66.4 to 100)	85.3 (68.9 to 95.1)	88.4 (74.9 to 96
CRc rate, % (95% CI)			
CR/CRh/CRi	88.9 (51.8 to 99.7)	79.4 (62.1 to 91.3)	81.4 (66.6 to 91
Response-evaluable CRc rate,[a] % (95% CI)			
CR/CRh/CRi	88.9 (51.8 to 99.7)	93.1 (77.2 to 99.2)	92.1 (78.6 to 98
Flow MRD negative, No. (% of tested)	9 (100.0)	28 (100.0)	37 (100.0)
NPM1m MRD negative, No. (% of tested)	NA	8 (30.7)	8 (30.7)
Allo stem-cell transplant, No. (%)	3 (33.3)	7 (20.6)	10 (23.2)



Zeidner JF, et al. J Clin Oncol, 2025.

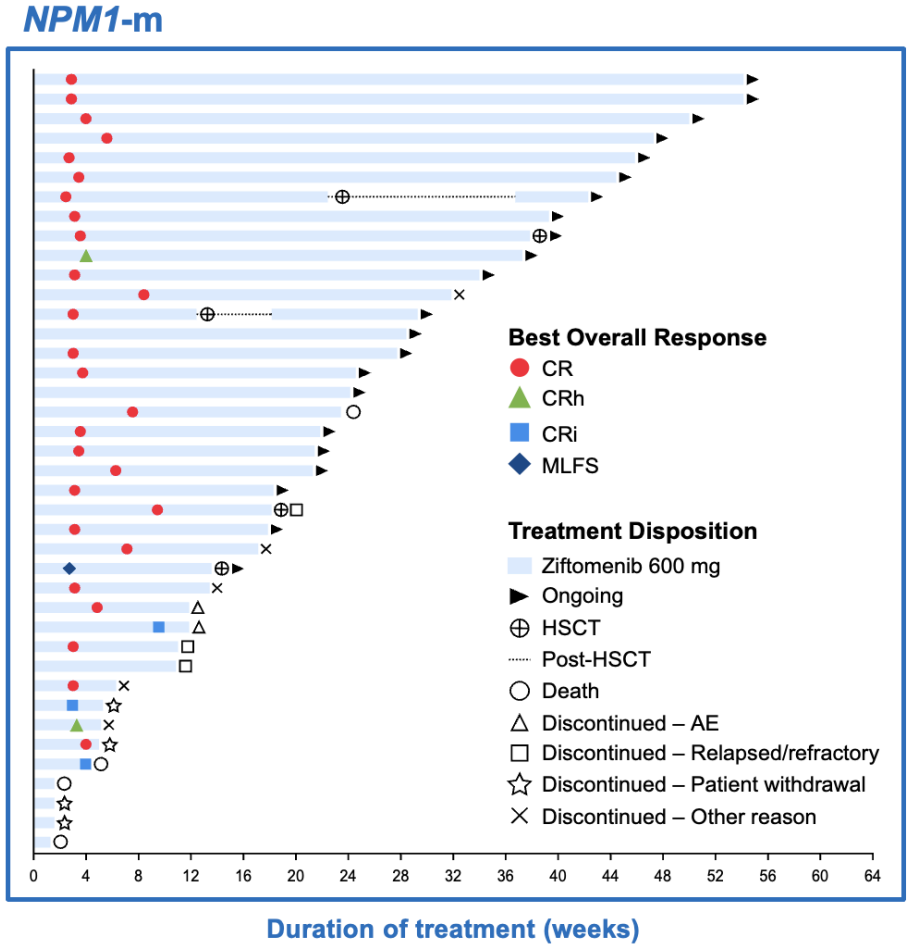
MENi-Triplet (Ziftomenib)

Ziftomenib in Combination with Venetoclax and Azacitidine in Newly Diagnosed *NPM1*-m Acute Myeloid Leukemia: Phase 1b Results from KOMET-007

Gail J. Roboz, MD[1], Eunice S. Wang, MD[2], Amir T. Fathi, MD[3], Harry Erba, MD, PhD[4], Keith W. Pratz, MD[5], Guru Subramanian Guru Murthy, MD, MS[6], Leonard C. Alsfeld, MD[7], James S. Blachly, MD[8], Kiran Naqvi, MD[9], Ghayas C. Issa, MD[10], Ayman Qasrawi, MD[11], Stephen A. Strickland, MD[12], Neil D. Palmisiano, MDMS[13], Jessica K. Altman, MD[14], Cecilia Arana Yi, MD[15], Grerk Sutamtewagul, MD[16], Yazan F. Madanat, MD[17], Suresh Kumar Balasubramanian, MD[18], Christine M. McMahon, MD[19], Hongling Zhang, MS[20], Tianle Chen, PhD[20], Marcie Riches, MD[20], Daniel Corum, PhD[20], Mollie Leoni, MD[20], Amer M. Zeidan, MBBS, MHS[21]

Clinical Activity[a] of Ziftomenib with Ven/Aza: Newly Diagnosed AML

n (%)	*NPM1*-m, 600 mg (N=37)
CRc	32 (86)
Median time to first CRc, weeks (range)	3.4 (2.4–9.6)
ORR	33 (89)
CR	27 (73)
CRh	2 (5)
CRi	3 (8)
MLFS	1 (3)
PR	0 (0)
NR	1 (3)
NE[b]	3 (8)



Roboz GJ, et al. ASH, 2025;Abstract 766.

Clinical Activity[a] of Ziftomenib with Ven/Aza: R/R AML

n (%)	*NPM1*-m, 600 mg (N=48)	*KMT2A*-r, 600 mg (N=32)
CRc	23 (48)	9 (28)
Median time to first CRc, weeks (range)	3.9 (2.7–15.6)	4.0 (2.6–18.9)
ORR	31 (65)	13 (41)
CR	13 (27)	2 (6)
CRh	6 (13)	5 (16)
CRi	4 (8)	2 (6)
MLFS	7 (15)	4 (13)
PR	1 (2)	0
NR	13 (27)	17 (53)
NE[b]	4 (8)	2 (6)
MRD negativity rate[c], n/N (%)	12/20 (60)	3/7 (43)
Median time to first MRD negativity, weeks (range)	8.8 (2.9–21.4)	8.1 (7.7–18.9)

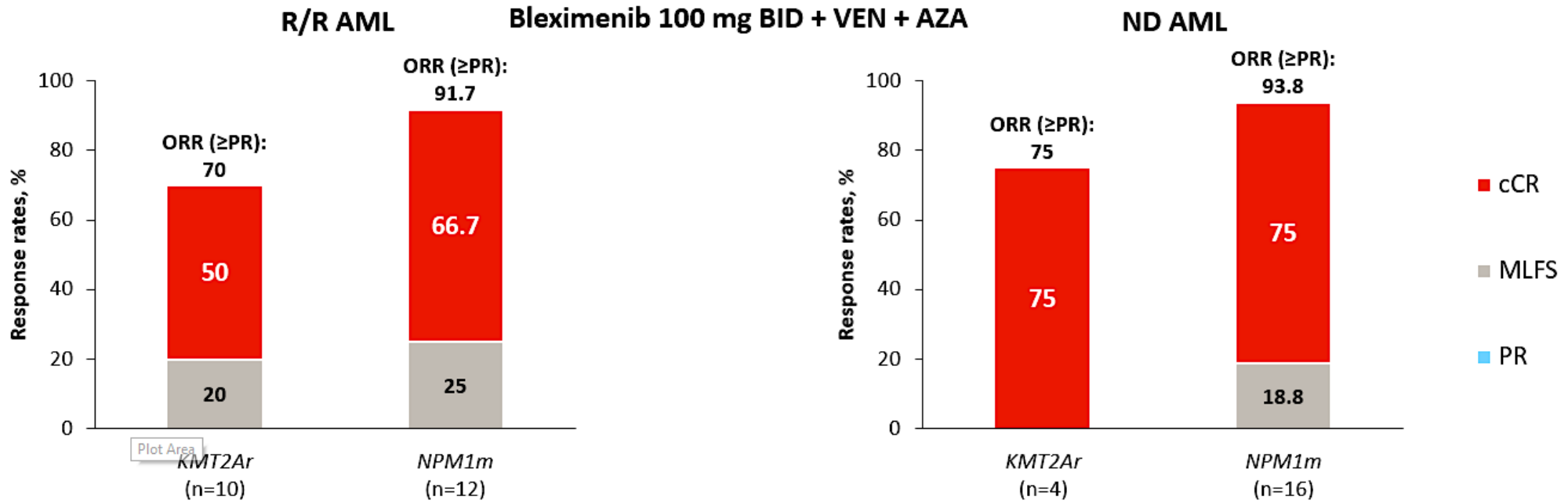
- For *NPM1*-m, CR/CRh rates were 46% (13/28), 42% (5/12), and 14% (1/7) for patients with 1, 2, and ≥3 prior lines of therapy, respectively

[a]In patients with ≥1 response assessment or had died. [b]Not evaluable (1 *NPM1*-m) or not done (3 *NPM1*-m, 2 *KMT2A*-r). [c]Locally assessed among CRc responders (NGS, RT-qPCR, FISH, flow cytometry)
Data cutoff: Sep 24, 2025. CR / CRh / CRi, complete remission with full / partial / incomplete hematologic recovery; CRc, composite complete remission; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; NE, not evaluable; NR, no response; ORR, objective response rate; PR, partial response

Issa G, et al. ASH, 2025;Abstract 764.

Bleximenib in Combination with VEN + AZA in R/R or ND AML

Efficacy in *KMT2Ar* and *NPM1m*



cCR is a composite score of CRi/CRh/CR.

Key observations

- Responses observed in both *KMT2Ar* and *NPM1m* participants
- No acquired *MEN1* resistance mutations were identified in 19 R/R pts with available on-treatment samples, with a mean of 275 days on treatment

Responses of participants with an underlying diagnosis of AML are based upon modified ELN 2017 recommendations (Dohner 2017, Bloomfield 2018) or modified ELN 2022 recommendations (Dohner 2022).

Data cut-off date: May 7, 2025. AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; CR, complete response; CRh, CR with partial haematological recovery; CRi , complete remission with incomplete recovery; ELN, European LeukemiaNet; *KMT2A,* Histone-lysine N-methyltransferase 2A; *KMT2Ar, KMT2A* rearranged; MLFS, morphologic leukemia-free state; ND, newly diagnosed; *NPM1,* nucleophosmin 1; *NPM1m*, *NPM1*-mutated; ORR, overall response rate; PR, partial response; pt, participant; R/R, relapsed/refractory; VEN, venetoclax.

Presented by AH Wei at EHA 2025; June 12 2025; Milan, Italy

Wei A, et al. EHA, 2025;Abstract S137.

Bleximenib in Combination with VEN + AZA in R/R or ND AML

Adverse Events of Clinical Interest with Menin Inhibition

AE, regardless of relatedness	Any Grade			Grade ≥3		
	50 mg BID (n=45)	100 mg BID (n=49)	All-dosed (N=125)	50 mg BID (n=45)	100 mg BID (n=49)	All-dosed (N=125)
Differentiation syndrome, n (%)	5 (11)	2 (4)	7 (6)	3 (7)	2 (4)	5 (4)
QTc prolongation, n (%)	2 (4)	3 (6)	5 (4)	0	0	0

Key observations

- With implementation of safety mitigation measures*, low rates of DS were observed; one Grade 5 event in R/R
- No QTc prolongation signal identified
  - All reported QTc prolongation events were Grade 1; no bleximenib dose interruptions or reductions required

Data cut-off date: May 7, 2025
*Protocol-specified guidance, including study drug interruption, use of prophylactic steroids and hydroxyurea in select participants considered at high-risk for the development of severe DS, and staggered initiation of bleximenib dosing on C1D4 have been implemented as safety measures to mitigate and manage the risk of DS.
AE, adverse event; AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; C, cycle; D, day; DS, differentiation syndrome; ND, newly-diagnosed; QTc, corrected QT interval; R/R, relapsed/refractory; VEN, venetoclax.

Presented by AH Wei at the 2025 Pan Pacific Leukemia Conference; July 15–18, 2025; Lahaina, Hawaii

Wei A, et al. EHA, 2025;Abstract S137.

Clinical Activity –Responses Observed with Enzomenib/Aza/Ven in R/R AML

The study is ongoing with patients still early in treatment; the pre-specified efficacy analysis population includes:

- ≥ 5% blasts in bone marrow at baseline
- Completed 56 days ***or*** permanently discontinued (i.e., early discontinuations are *included* in the efficacy analysis)

Patients were not included if they were on treatment in Cycle 1 or Cycle 2 (n = 9 and n = 2, respectively) or if they did not have measurable disease in the bone marrow (bone marrow blasts < 5%, n = 3)

	Enzo 140 mg BID + Aza/Ven 100 mg No azole in C1 (n = 4)	Enzo 200 mg BID + Aza/Ven 100 mg No azole in C1 (n = 6)	Enzo 300 mg BID + Aza/Ven 100 mg No azole in C1 (n = 8)	Enzo 300 mg BID + Aza/Ven 50-100 With azole in C1 (n = 8)	Total (n = 26)
Objective Response (CR/CRh/CRi/MLFS)*	100% (4/4)	83% (5/6)	62.5% (5/8)	80% (6/8)	77% (20/26)
Composite CR (CR/CRh/CRi)	50% (2/4)	50% (3/6)	50% (4/8)	50% (4/8)	50% (13/26)

*Per ELN 2017: CR / CRh / CRi, complete remission with full / partial / incomplete hematologic recovery; MLFS, morphological leukemia-free state; Patients who achieved CRi or MLFS and CRh were counted as CRh

Study ongoing, data cutoff 04 OCT 2025

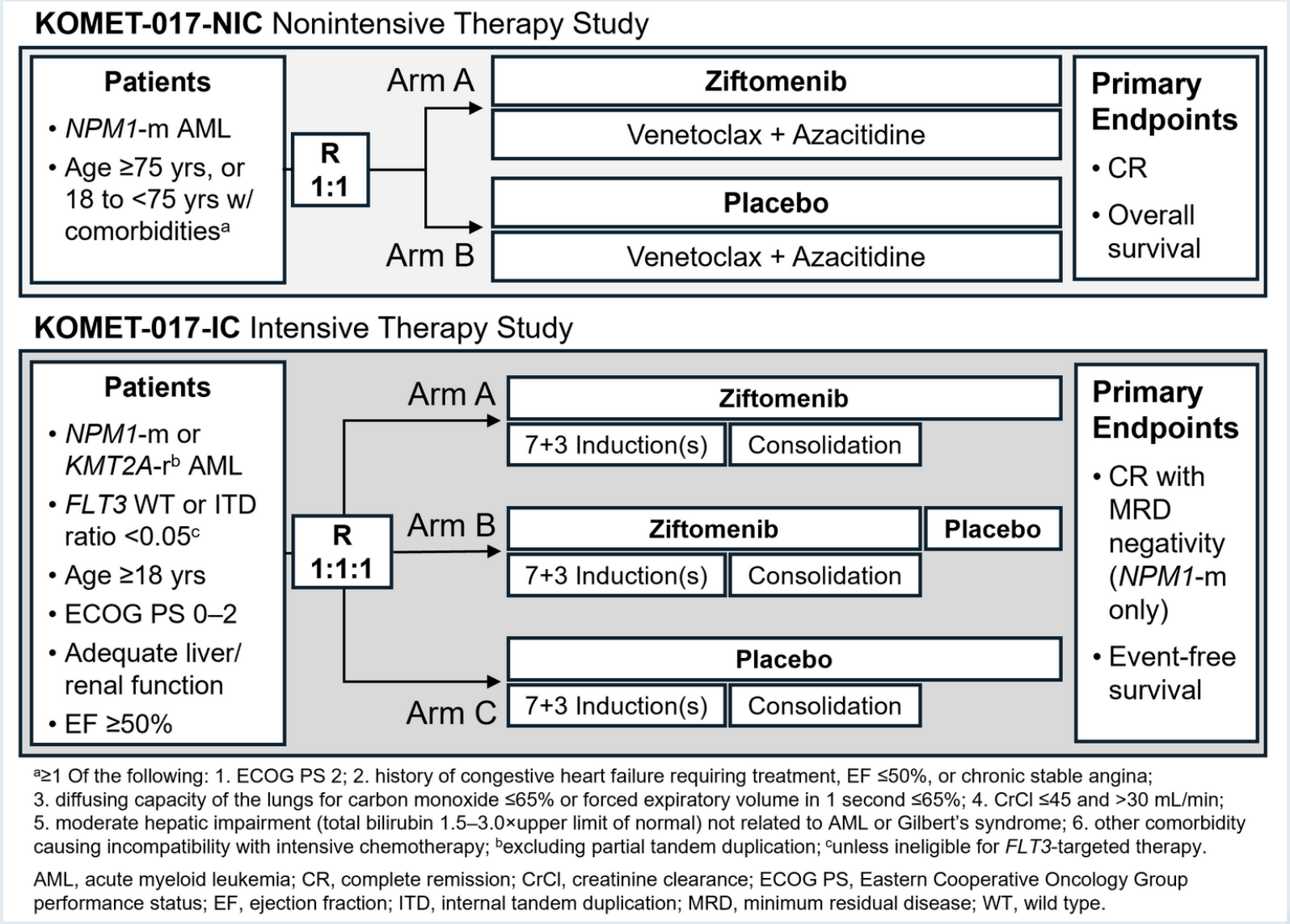
Watts J, et al. ASH, 2025;Abstract 765.

Year in Review:
Menin Inhibitors in Acute Myeloid Leukemia

MODULE 4: Future Directions

- Ongoing trials:
  - KOMET-017
  - REVEAL/EVOLVE-2
  - cAMeLot
  - HOVON 181

KOMET-017: Ongoing Phase III Trial Designs

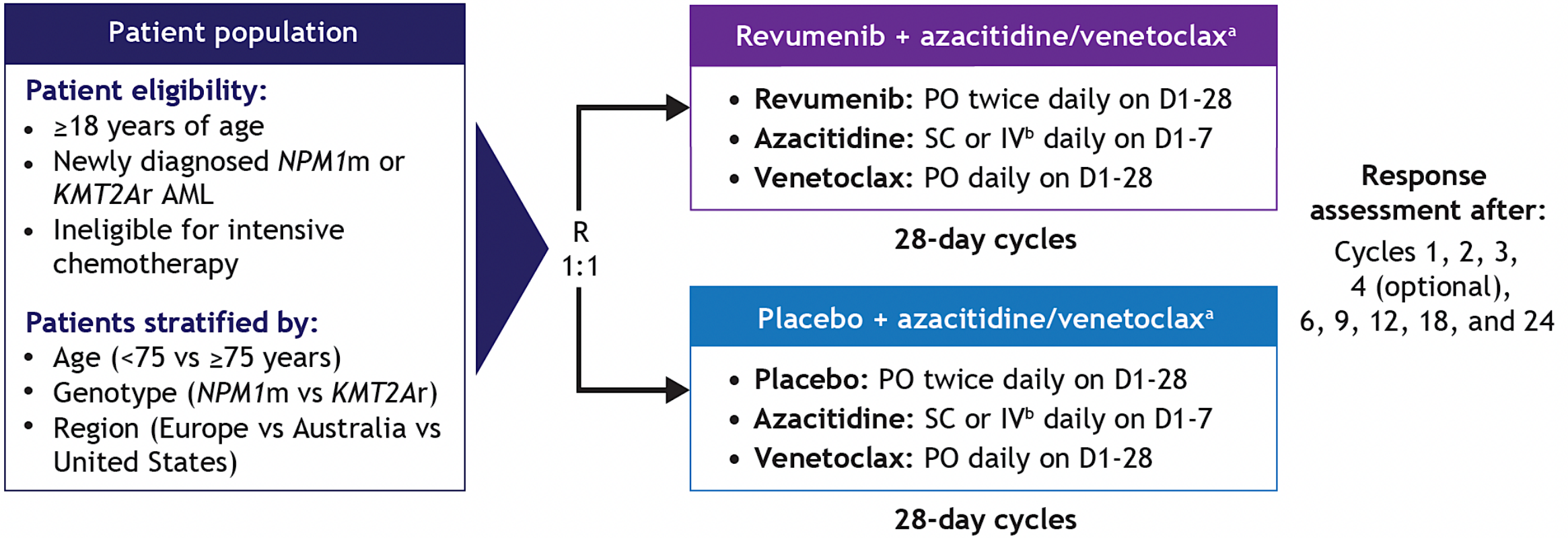


[a]≥1 Of the following: 1. ECOG PS 2; 2. history of congestive heart failure requiring treatment, EF ≤50%, or chronic stable angina; 3. diffusing capacity of the lungs for carbon monoxide ≤65% or forced expiratory volume in 1 second ≤65%; 4. CrCl ≤45 and >30 mL/min; 5. moderate hepatic impairment (total bilirubin 1.5–3.0×upper limit of normal) not related to AML or Gilbert's syndrome; 6. other comorbidity causing incompatibility with intensive chemotherapy; [b]excluding partial tandem duplication; [c]unless ineligible for *FLT3*-targeted therapy.

AML, acute myeloid leukemia; CR, complete remission; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; EF, ejection fraction; ITD, internal tandem duplication; MRD, minimum residual disease; WT, wild type.

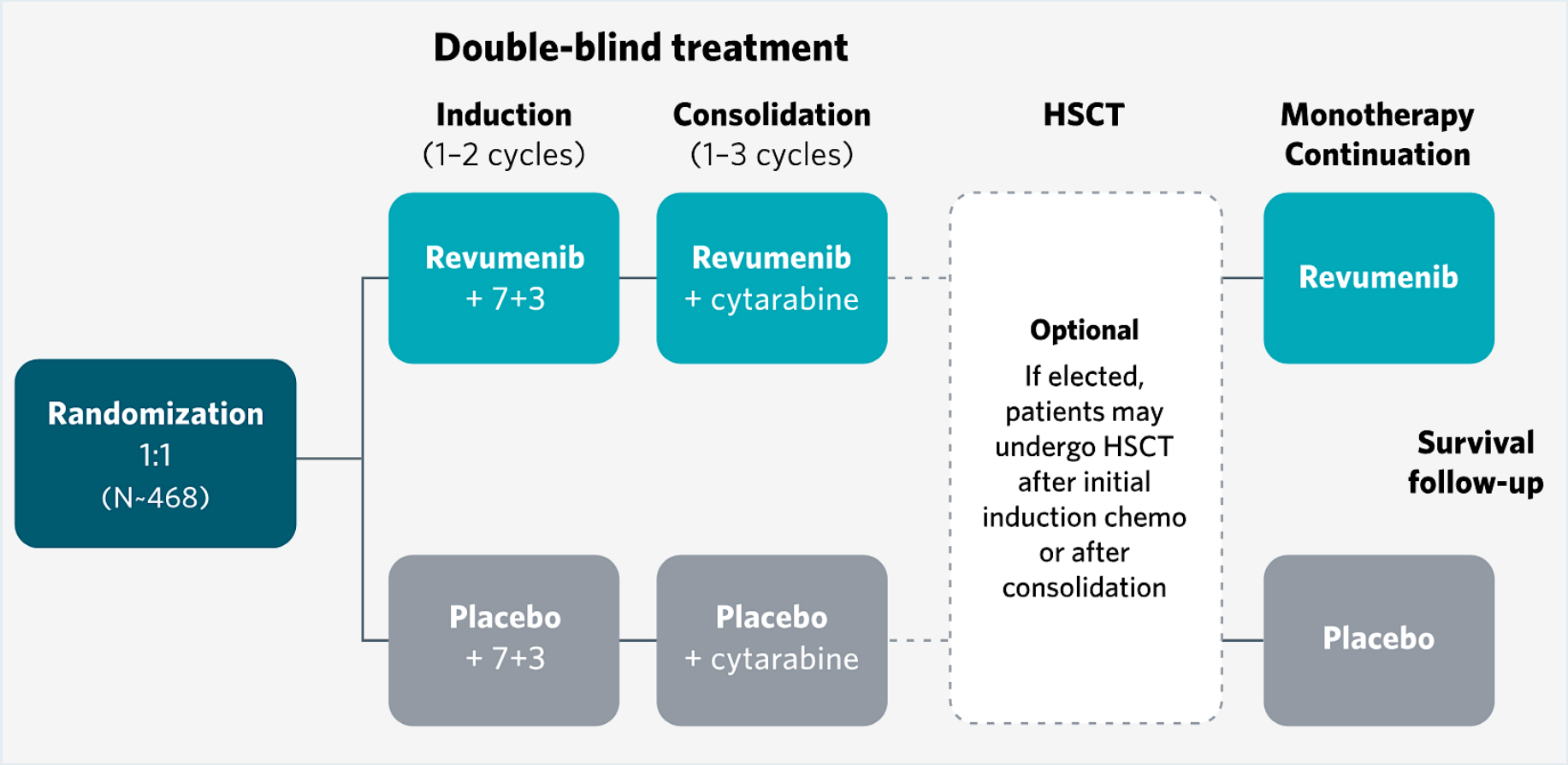
Zeidan AM et al. EHA 2025;Abstract PB2573.

EVOLVE-2: Ongoing Phase III Trial Design



Huls G et al. European School of Hematology International Conference on Acute Myeloid Leukemia 2025; Poster.

REVEAL-ND NPM1: Ongoing Phase III Trial Design



Eligibility: Newly diagnosed, previously untreated *NPM1*-mutated AML

Primary endpoints: Event-free survival, MRD complete remission rate

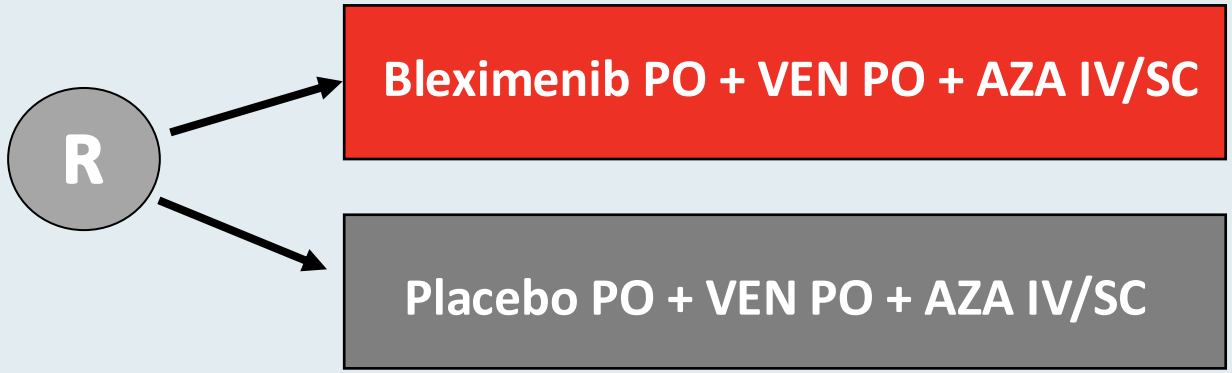
https://revealtrialaml.com

cAMeLot-2: Ongoing Phase III Trial Design

Eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • ND *KMT2Ar* or *NPM1m* AML[a] • Ineligible for IC[b] • Adequate hepatic and renal function	• Diagnosis of acute promyelocytic leukemia (APL) • Known active leukemic involvement of the CNS • Active infectious hepatitis • Significant cardiac disorder ≤6 months prior to randomization

[a]≥10% bone marrow blasts per 2022 International Consensus Classification criteria.
[b]Based on: [a] ≥75 years and ineligible per physician's discretion, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, or [b] ≥18 to <75 years with ≥1 of the following comorbidities: ECOG PS of 2; severe cardiac or pulmonary disorder; renal impairment; comorbidity that, in the investigator's opinion, makes the participant unsuitable for IC.

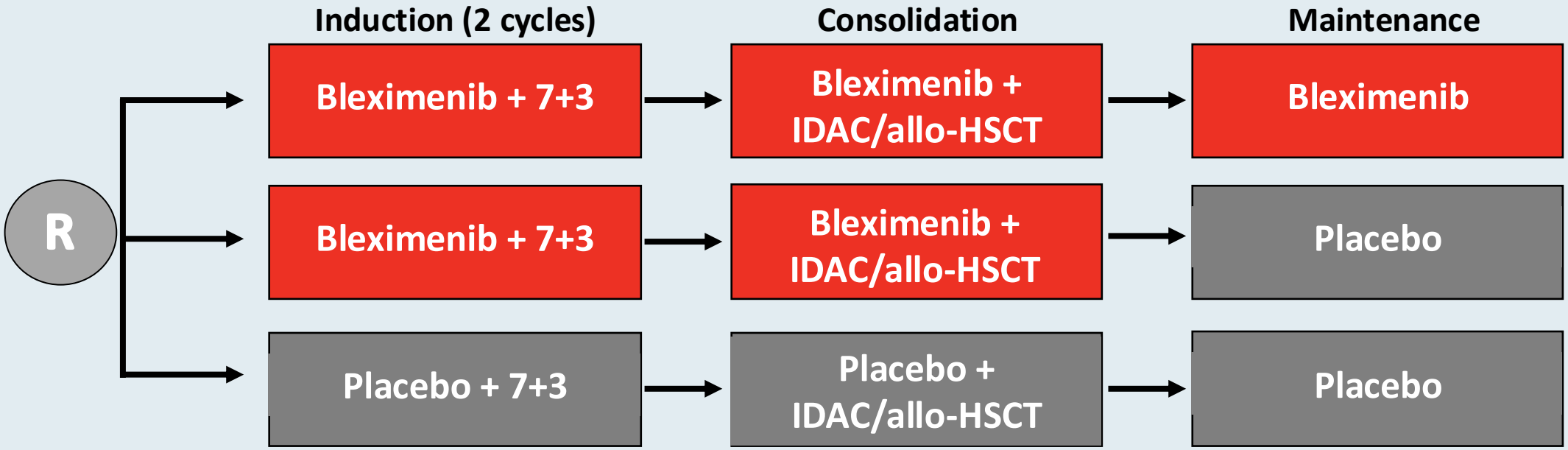


Primary Endpoints: % complete remission and OS

Jabbour E et al. ASH 2025;Abstract 3429.

HOVON 181 AML/AMLSG 37-25: Ongoing Phase III Trial Design

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • ND *KMT2Ar* or *NPM1m* AML[a] • Eligible for IC • ECOG PS ≤2 • Adequate hepatic and renal function	• Prior chemotherapy for AML • Known active leukemic involvement of the CNS • Prior solid organ transplantation • Active infectious hepatitis • Significant cardiac disorder ≤6 months prior to randomization



Primary endpoint: Event-free survival

Raajmakers M et al. ASH 2025;Abstract 1654.

Conclusions

The emergence of menin inhibitors:

- Effective, safe agents with activity in multiply R/R *NPM1*-m, *KMT2A*-r AML
- Differentiation syndrome as a class effect – requires close vigilance.
- Limited durability of response as monotherapy.

The promise of combinations:

- Studies reveal promise in combination with HMA-ven and induction chemotherapy
- High response rates and promising durability of response, particularly in the frontline setting.
- Will likely mitigate risk of DS.
- Potential for all-oral regimens

Multiple phase 3 studies under way:

- KOMET-017
- REVEAL / EVOLVE-2
- cAMeLOt

Courtesy of Amir Fathi, MD

Year in Review:
Menin Inhibitors in Acute Myeloid Leukemia

INTRODUCTION: Overview — Biopharmacologic Considerations

MODULE 1: Menin Inhibitor Monotherapy

MODULE 2: Differentiation Syndrome

MODULE 3: Menin Inhibitor Combination Approaches

MODULE 4: Future Directions

MODULE 5: PARADIGM — Randomized Phase II Trial

RTP Year in Review 2026

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Introduction to:

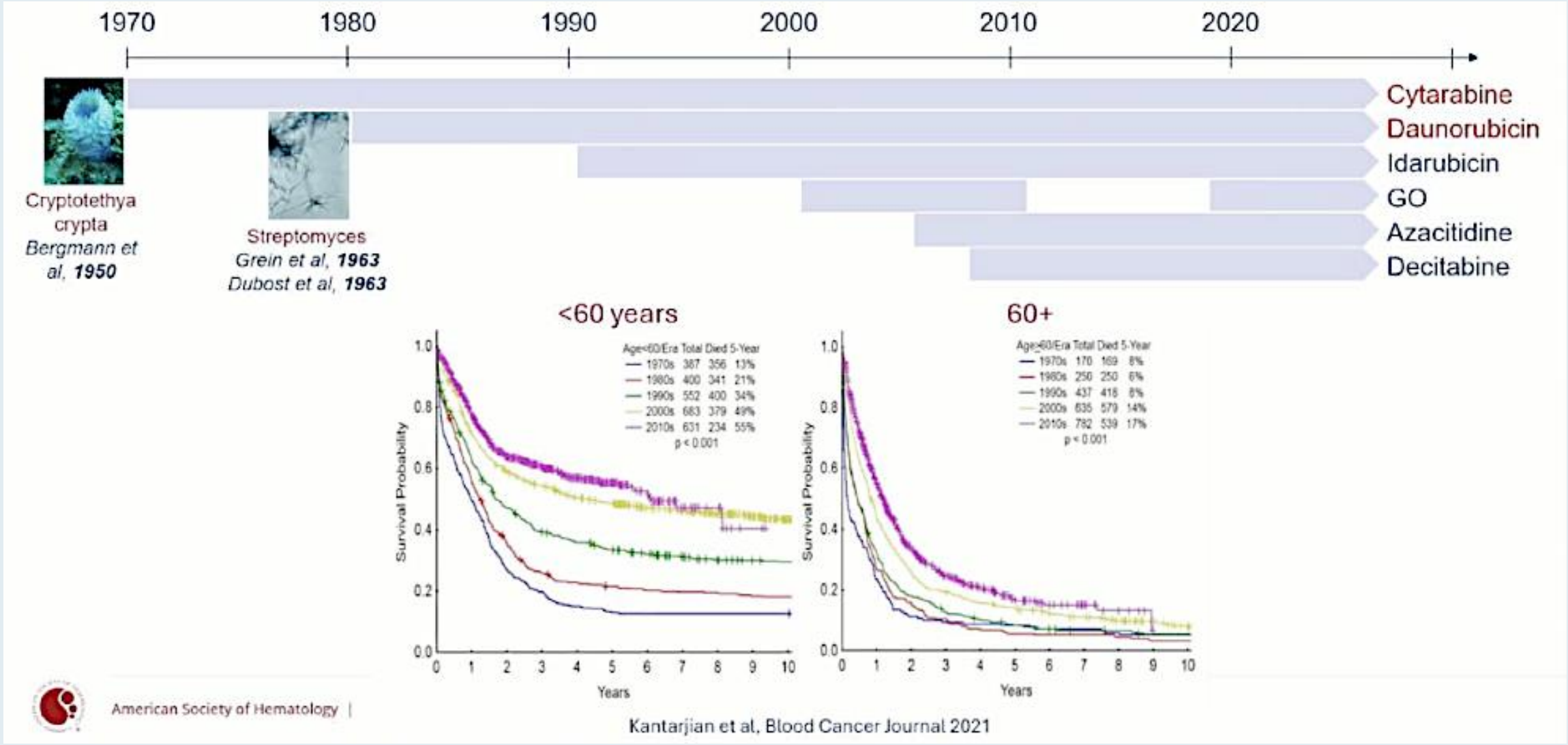
Results from paradigm - a phase 2 randomized multi-center study comparing azacitidine and venetoclax to conventional induction chemotherapy for newly diagnosed fit adults with acute myeloid leukemia

Andrew H. Wei, MBBS PhD

Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Australia
Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

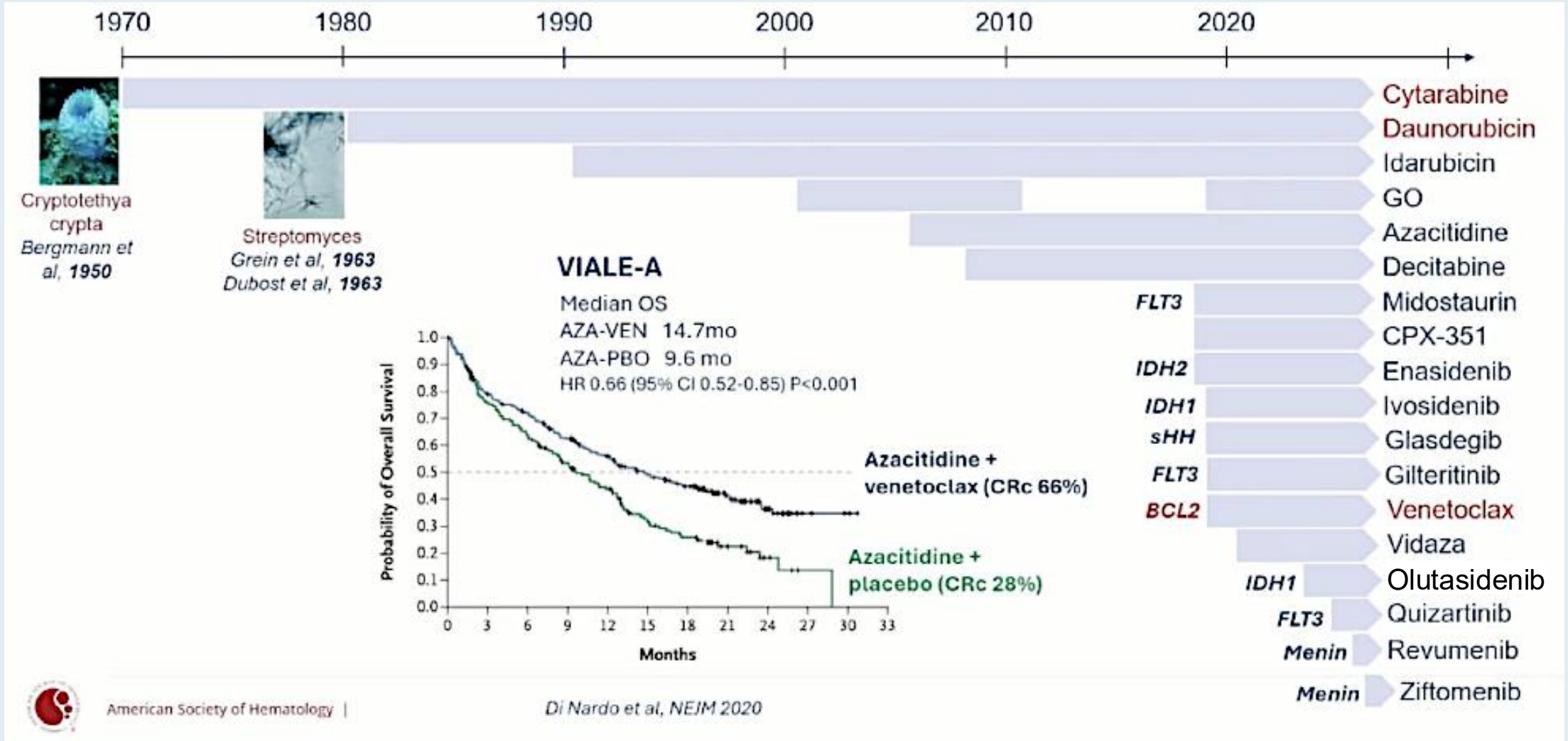
Wei AL et al. ASH 2025.

Evolution of Approved AML Therapies



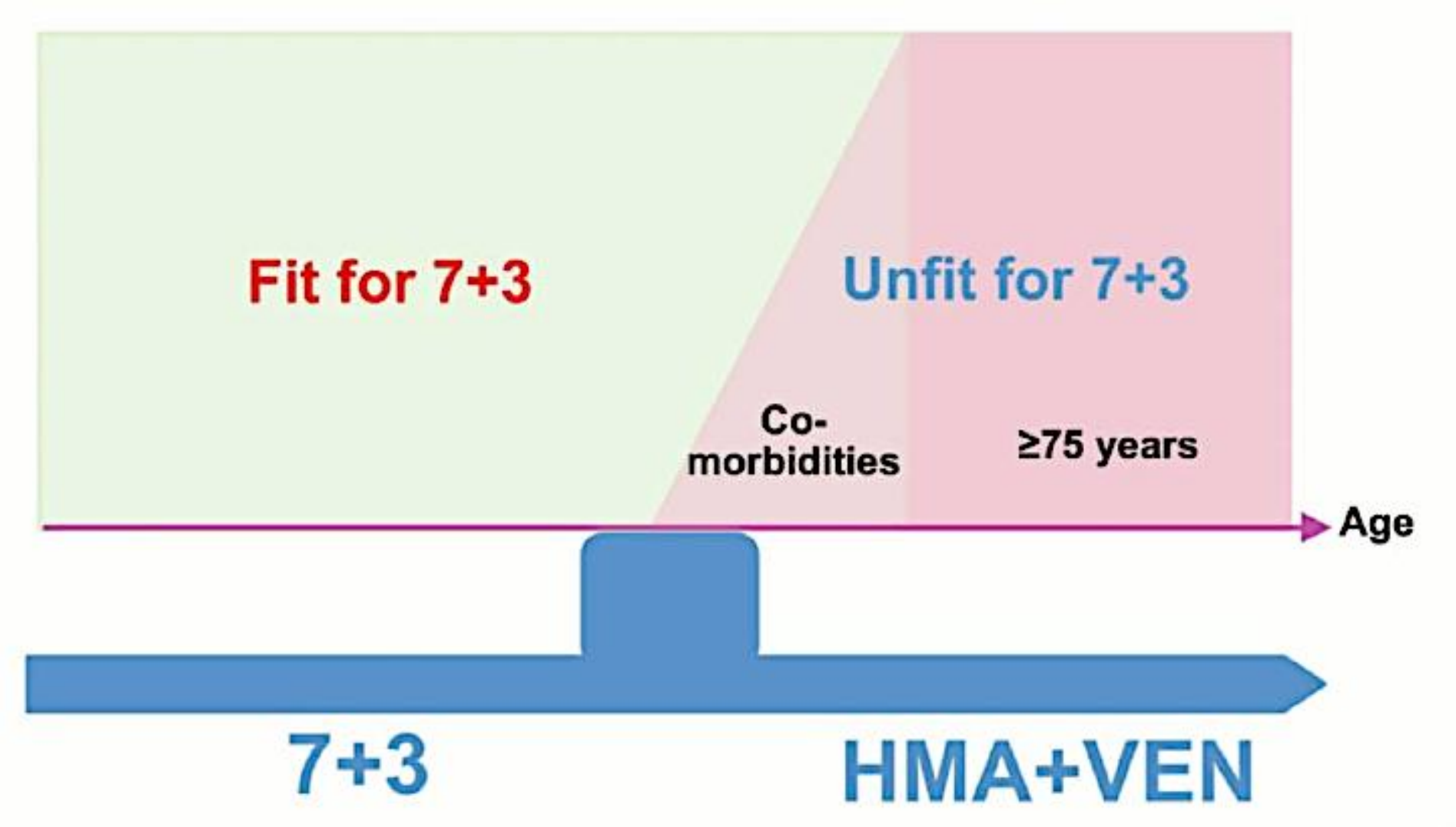
Wei AL et al. ASH 2025.

Evolution of Approved AML Therapies (Continued)



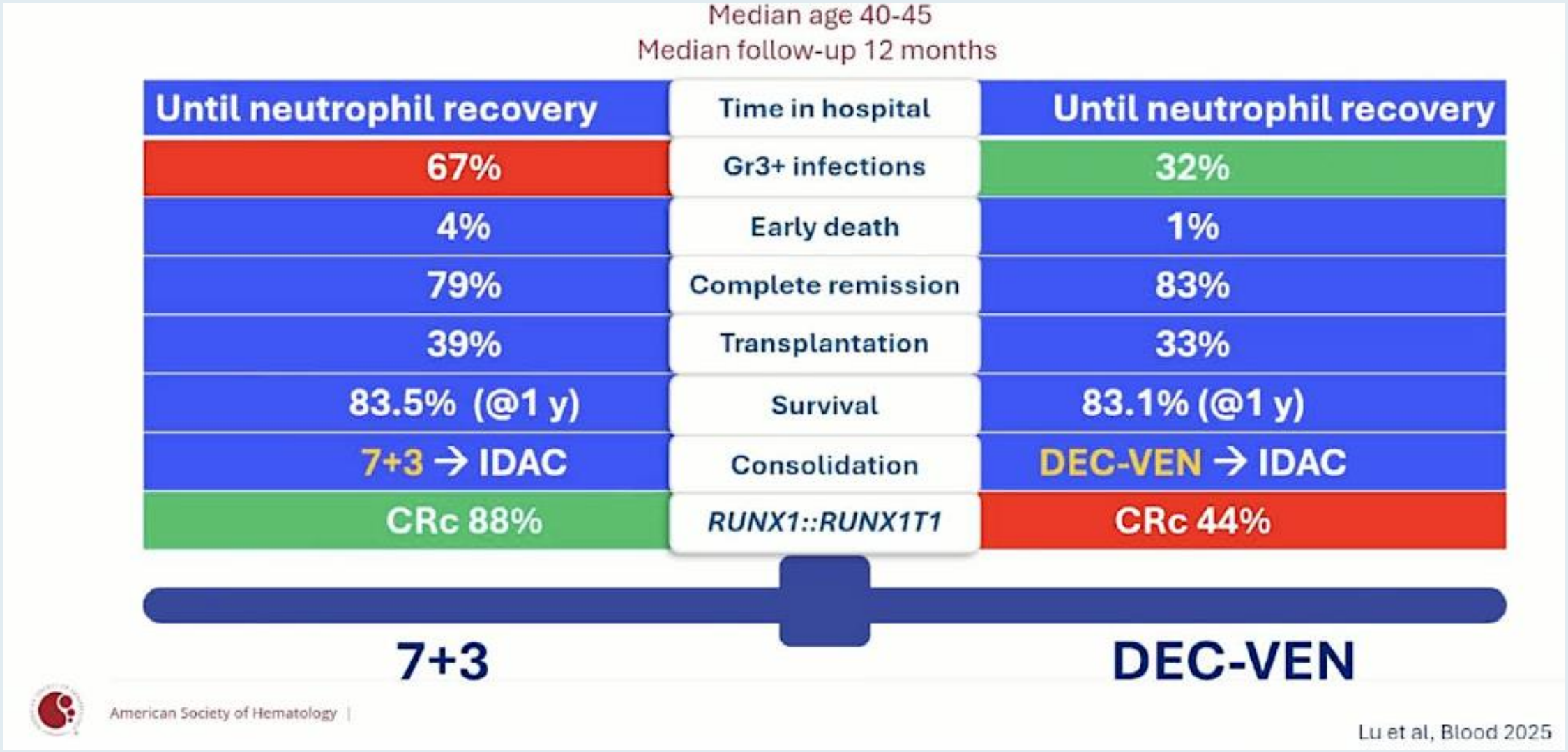
Wei AL et al. ASH 2025.

Established AML Dogma



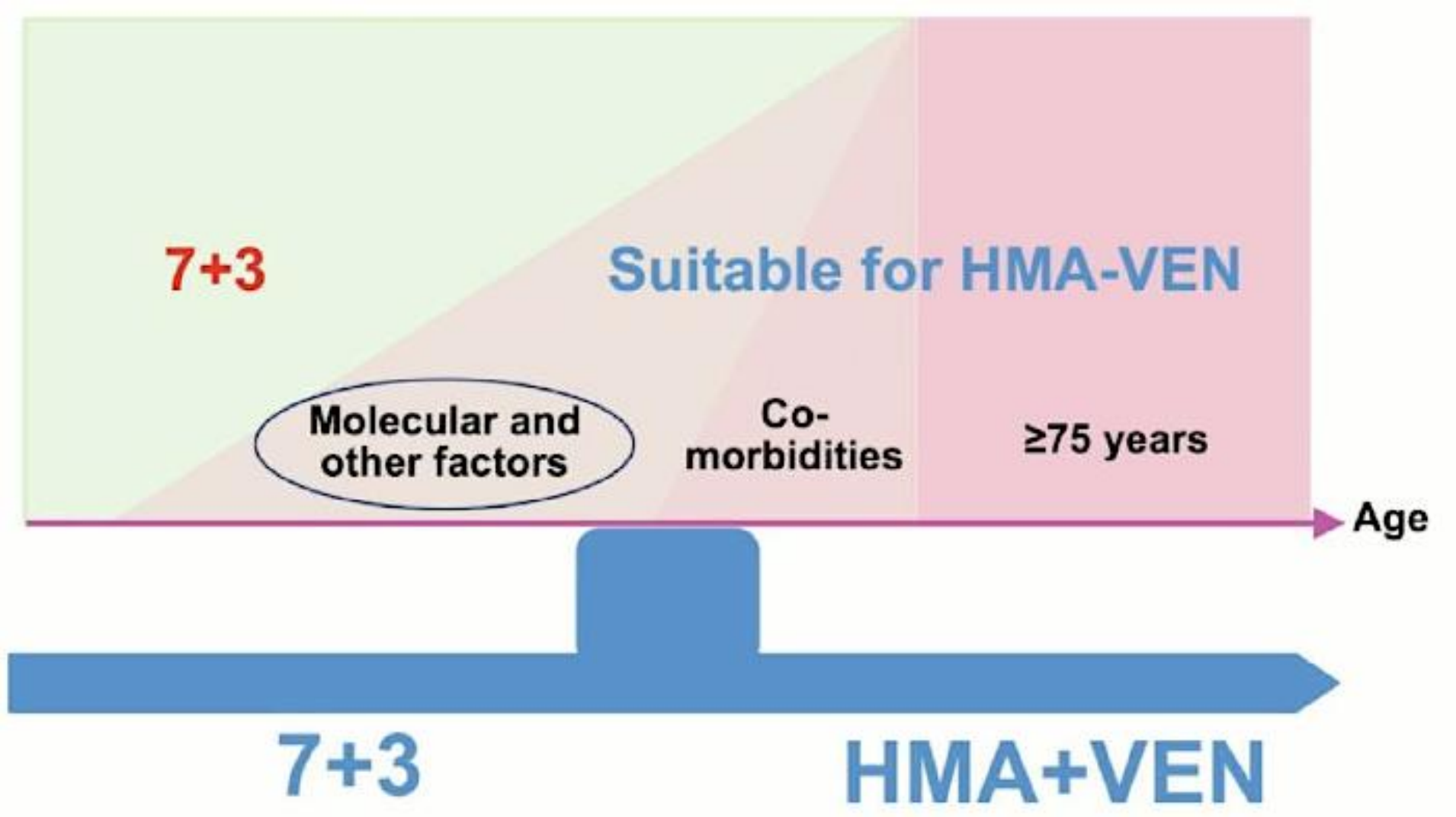
Wei AL et al. ASH 2025.

Could a Fit Patient Receive Less-Intensive AML Therapy?



Wei AL et al. ASH 2025.

PARADIGM Trial



Wei AL et al. ASH 2025.

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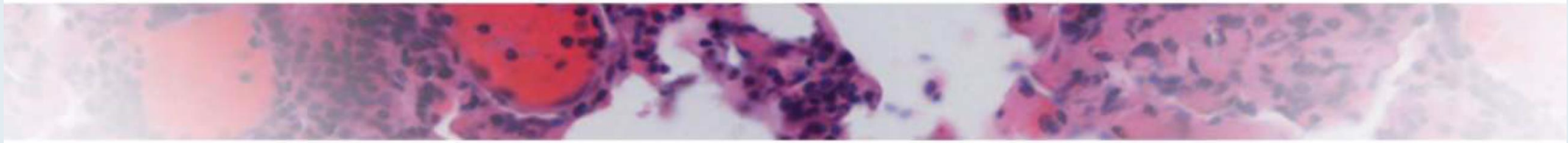
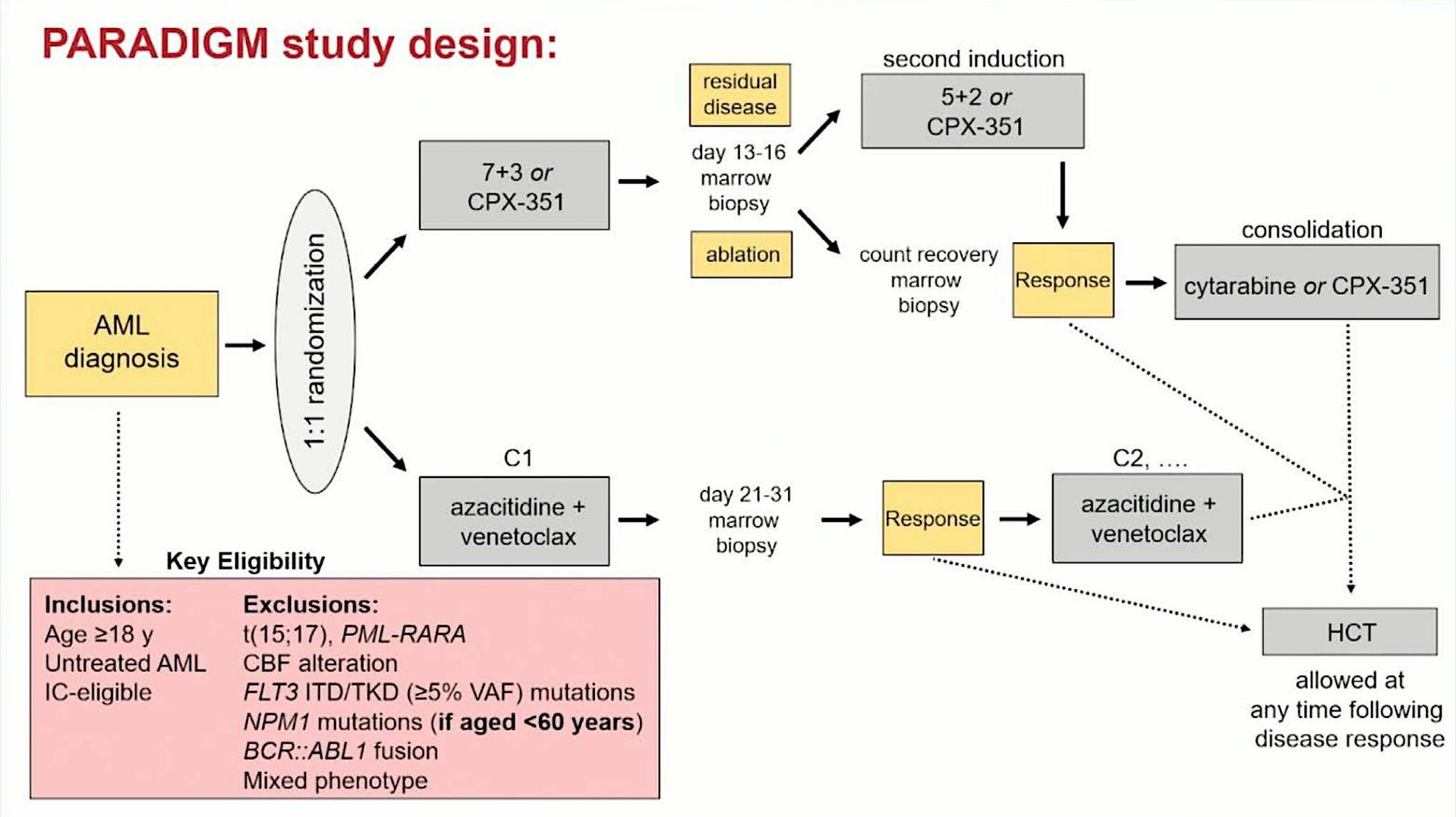


Results from PARADIGM - A phase 2 randomized multi-center study comparing azacitidine and venetoclax to conventional induction chemotherapy for newly diagnosed fit adults with AML

Amir T. Fathi[1], Alexander E. Perl[2], Geoffrey G. Fell[3], Brian A. Jonas[4], Brittany K. Ragon[5], Alice S. Mims[6], Uma Borate[6], Gabriel N. Mannis[7], Karen Quillen[8], Maximilian Stahl[3,9], Paul Koller[10], Andrew S. Artz[10], Monzr M. Al Malki[10], Guido Marcucci[10], Mary Linton B. Peters[8], Timothy A Graubert[1], Peter Westervelt[1], Philip C. Amrein[1], Hanno R. Hock[1], Andrew M. Brunner[1], Gabriela Hobbs[1], Rupa Narayan[1], Michelle H. Lee[1], Brandon J. Aubrey[1], Alyssa L. Watson[1], Richard Hao[1], Shilton Dhaver[1], Michael R. Grunwald[5], Yi-Bin Chen[1], Andrew H. Matthews[2], Brent L. Wood[11], Chris S. Hourigan[12], Donna S. Neuberg[3], Areej El-Jawahri[1], Ibrahim Aldoss[10]

Fathi AT et al. ASH 2025;Abstract 6.



IC = induction chemotherapy; HCT = hematopoietic cell transplant

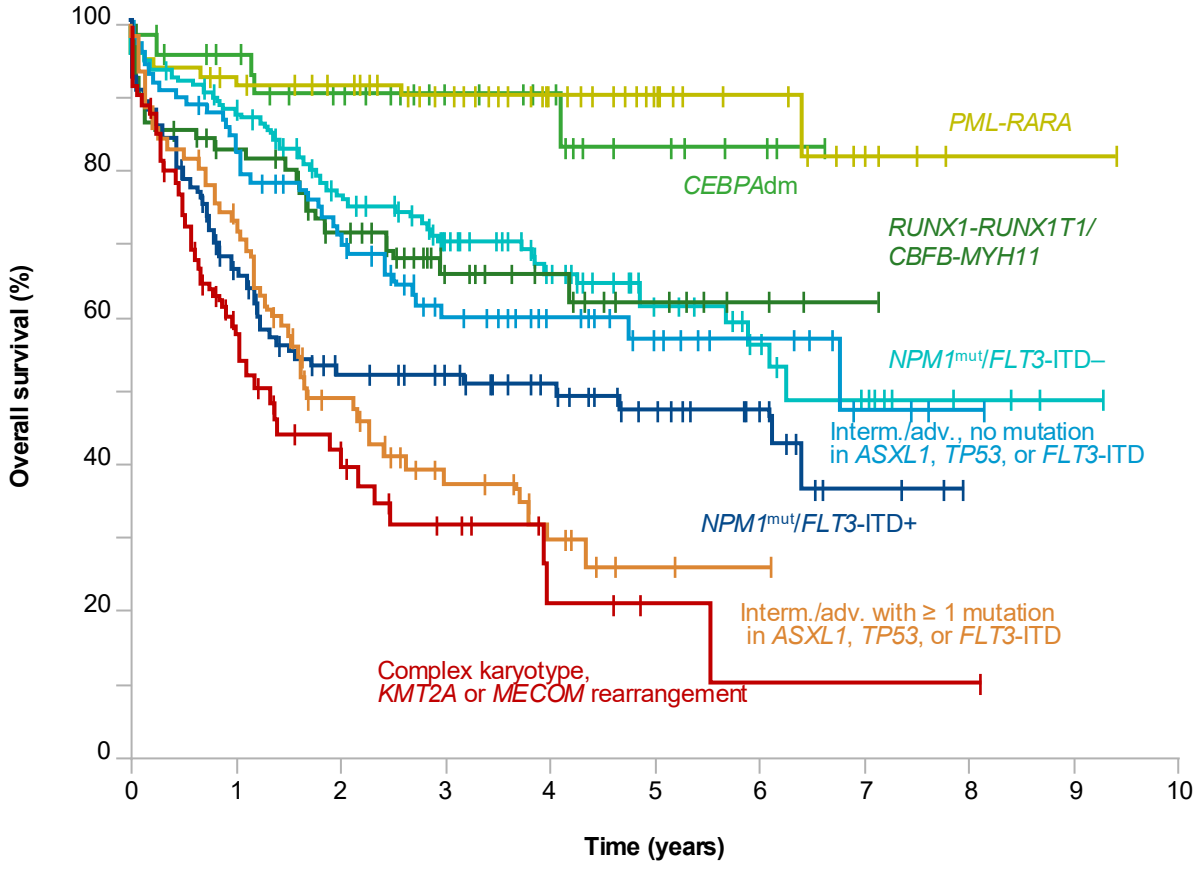
Fathi AT et al. ASH 2025;Abstract 6.

Outcomes with IC vary significantly based on AML biology

EUROPEAN LEUKEMIA NET 2022[1]

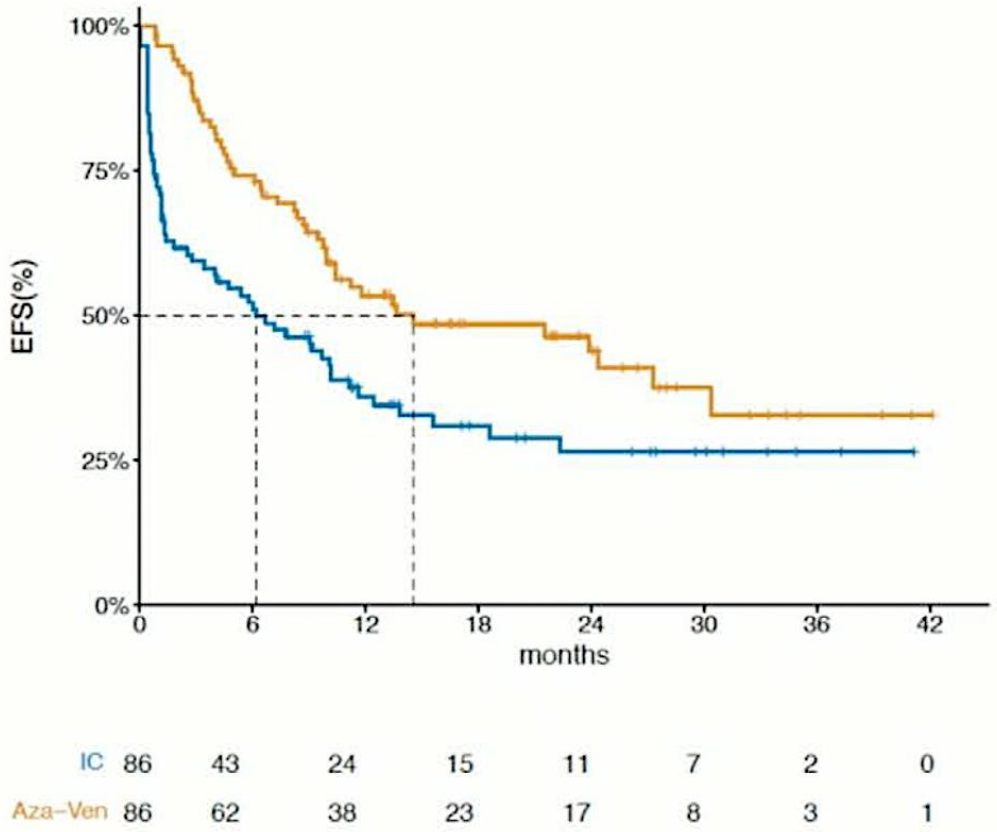
Favorable	• t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11* • Mut *NPM1* w/o *FLT3*-ITD • bZIP in-frame mut *CEBPA*
Intermediate	• Mut *NPM1* with ***FLT3*-ITD** • Wt *NPM1* with ***FLT3*-ITD** • t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A* • Cytogenetic and/or molecular
Adverse	• t(6;9)(p23.3;q34.1)/*DEK::NUP214* • t(v;11q23.3)/*KMT2A*-rearr • t(9;22)(q34.1;q11.2)/*BCR::ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2,MECOM(EVI1)* • t(3q26.2;v)/*MECOM(EVI1)*-rearr • –5 or del(5q); –7; –17/abn(17p) • Complex/monosomal karyotype • Mut *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1,* or *ZRSR2* • Mut *TP53*

OS in Patients Aged < 60 Years With *de Novo* AML* (N = 867)[2]



*** This population of patients had been treated with standard intensive chemotherapy.** ELN, European LeukemiaNet. 1. Döhner H et al. *Blood*. 2022;144(12):1345-1377. 2. Adapted from Haferlach C et al. *Blood*. 2016;128:286.

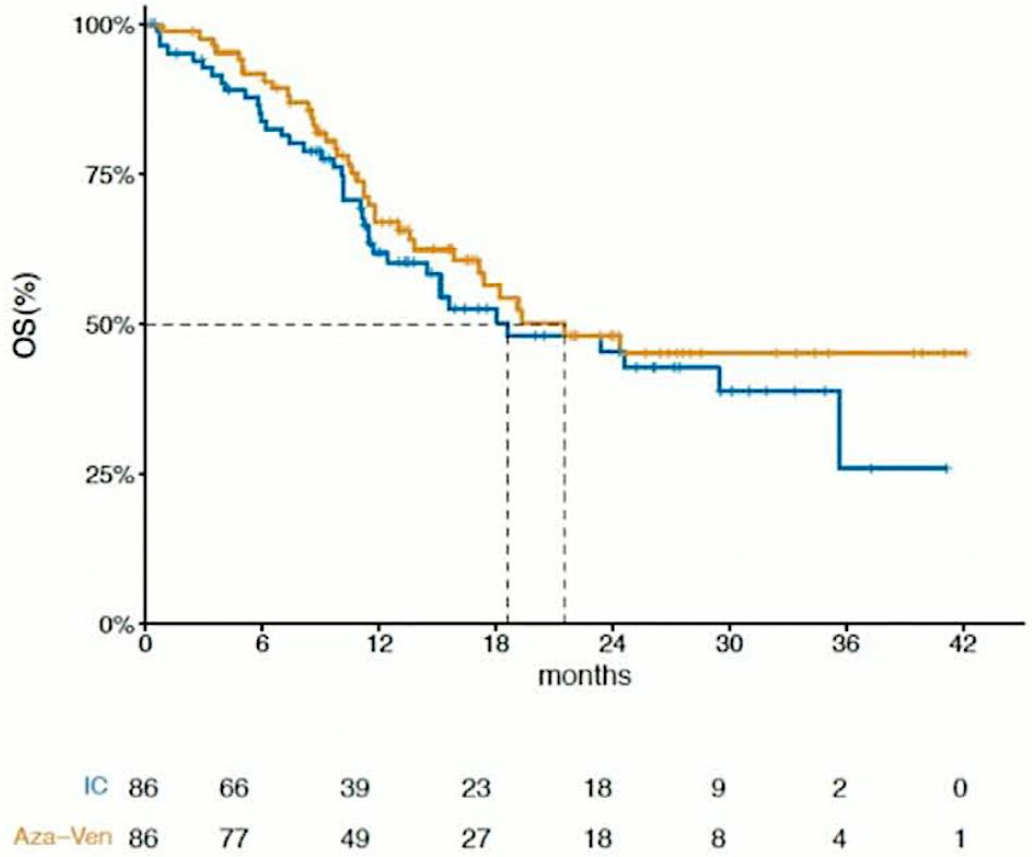
PARADIGM Primary Endpoint: Event-Free Survival (EFS)



- Median EFS of 14.6 for Aza-Ven vs 6.15 months for IC (P=0.0021).
- One-year EFS was 53.4% for Aza-Ven vs 36.0% for IC.
- The HR for a univariate Cox model was 0.57 (P=0.0022).
- After adjustment for variables in a multivariable model, the effect of Aza-Ven remained protective for EFS (HR:0.66; P=0.0231).

Fathi AT et al. ASH 2025;Abstract 6.

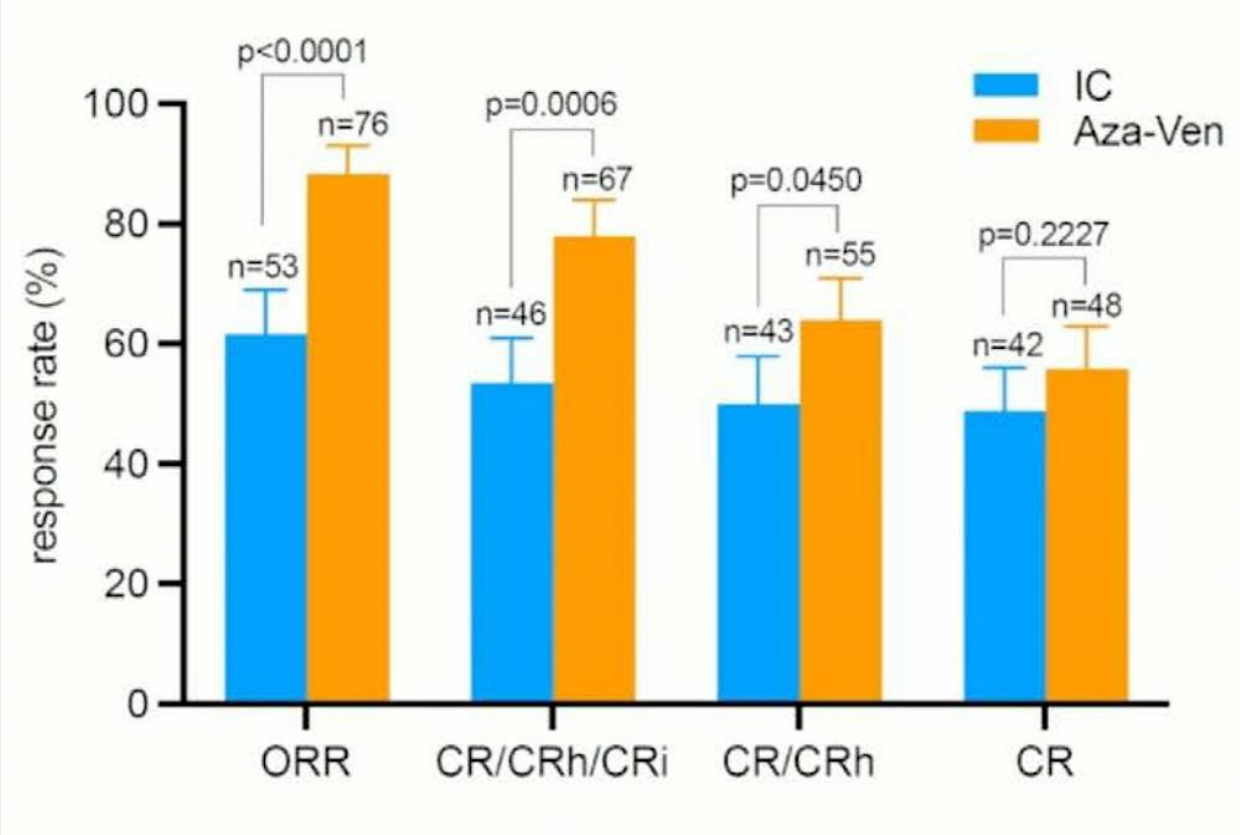
PARADIGM Secondary Endpoint: Overall Survival (OS)

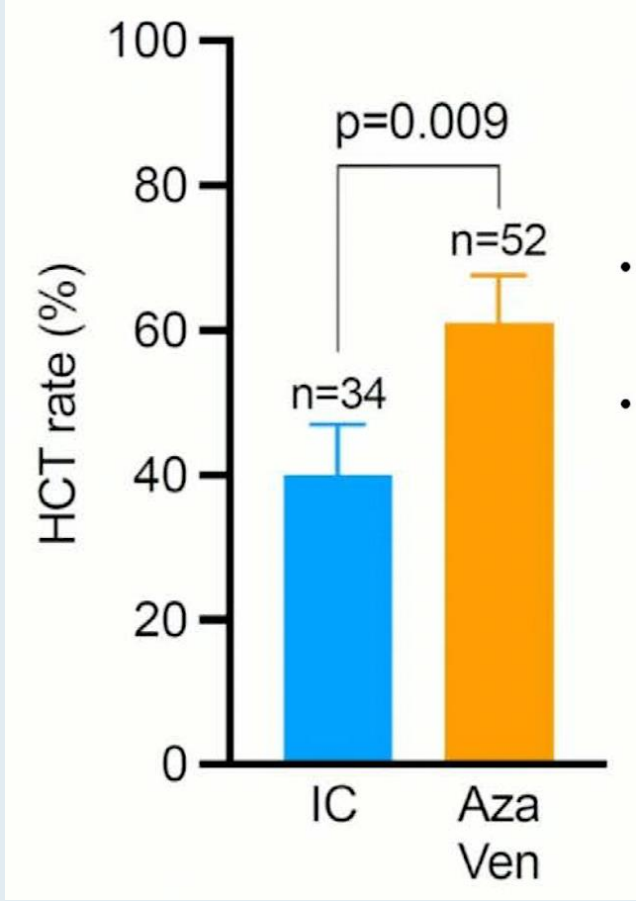


- The median OS was 21.5 months for Aza-Ven vs 18.6 months for IC (log rank, P = 0.1873).

Fathi AT et al. ASH 2025;Abstract 6.

PARADIGM: Clinical Activity and Transplant





- Transplant had a significant protective effect for EFS.
- After adjustment for HCT in univariable and multivariable models for EFS, effect of Aza-Ven remained protective (HR:0.67; P=0.0302).

Fathi AT et al. ASH 2025;Abstract 6.

PARADIGM: Safety and Tolerability

Toxicities (n (%))	IC				Aza-Ven			
	Grade 3	Grade 4	Grade 5	≥ Grade 3	Grade 3	Grade 4	Grade 5	≥ Grade 3
Febrile neutropenia	51 (62.2)	1 (1.2)	0 (0.0)	52 (63.4)	46 (53.5)	3 (3.5)	0 (0.0)	49 (57.0)
Platelet count decreased	3 (3.7)	47 (57.3)	0 (0.0)	50 (58.1)	8 (9.3)	38 (44.2)	0 (0.0)	46 (53.5)
Anemia	35 (40.7)	3 (3.5)	0 (0.0)	38 (46.3)	34 (39.5)	1 (1.2)	0 (0.0)	35 (40.7)
Neutrophil count decreased	1 (1.2)	39 (47.6)	0 (0.0)	40 (48.8)	1 (1.2)	48 (55.8)	0 (0.0)	49 (57.0)
White blood cell decreased	0 (0.0)	20 (24.4)	0 (0.0)	20 (24.4)	2 (2.3)	24 (27.9)	0 (0.0)	26 (30.2)
Lymphocyte count decreased	9 (11.0)	8 (9.8)	0 (0.0)	17 (20.7)	11 (12.8)	6 (7.0)	0 (0.0)	17 (19.8)
Lung infection	11 (15.6)	2 (2.4)	2 (2.4)	15 (18.3)	12 (14.0)	0 (0.0)	0 (0.0)	12 (14.0)
Sepsis	10 (12.2)	2 (2.4)	0 (0.0)	12 (14.6)	5 (5.8)	1 (1.2)	0 (0.0)	6 (7.0)
Anorexia	12 (14.6)	0 (0.0)	0 (0.0)	12 (14.6)	4 (4.7)	0 (0.0)	0 (0.0)	4 (4.7)
Hypoxia	7 (8.5)	2 (2.4)	0 (0.0)	9 (11.0)	4 (4.7)	0 (0.0)	0 (0.0)	4 (4.7)

Grade ≥3 treatment-emergent adverse events in ≥10% of patients

Fathi AT et al. ASH 2025;Abstract 6.

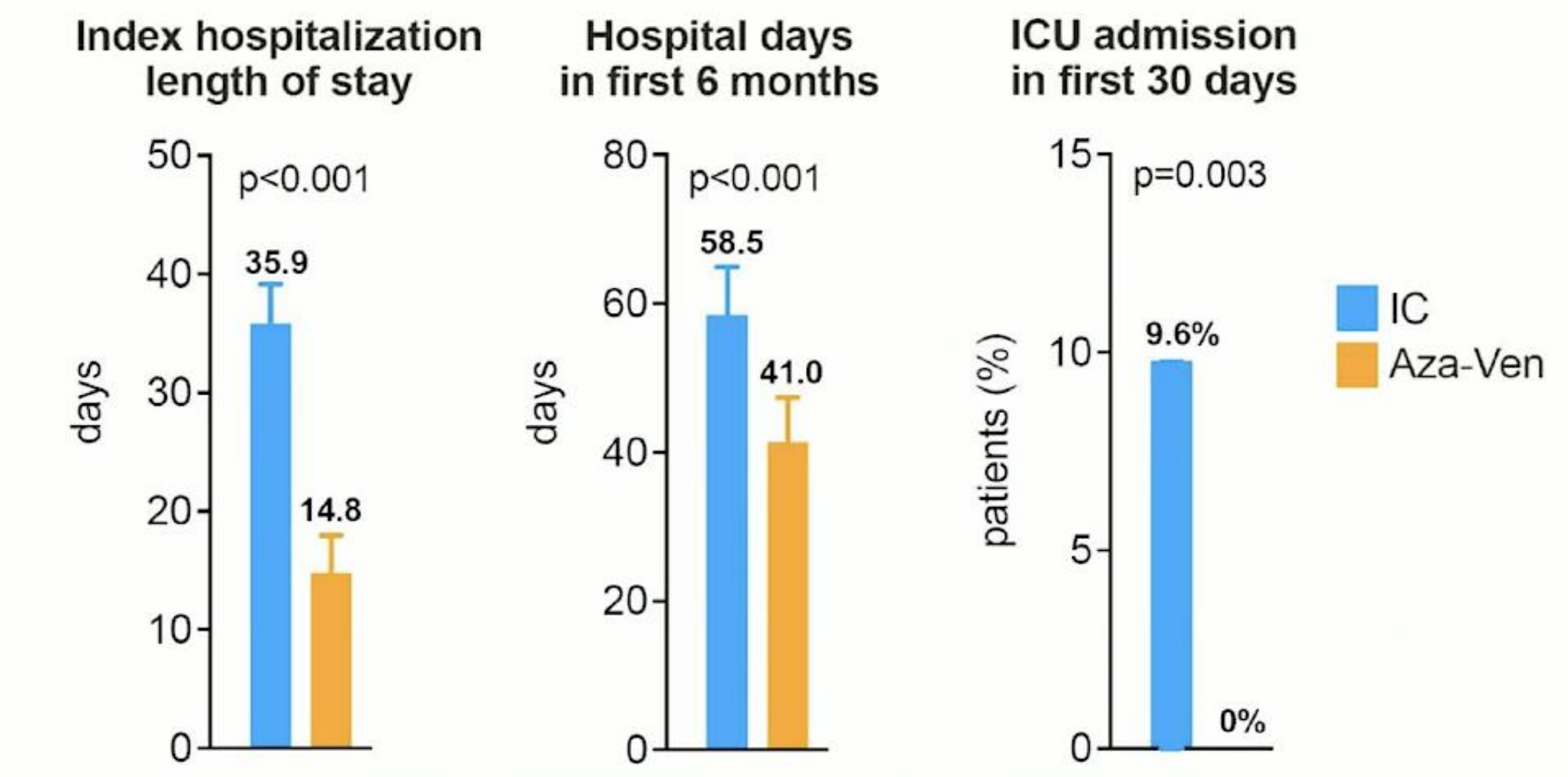
PARADIGM: Patient-Reported Outcomes (PROs)

PROs at Week-2	Aza-Ven (95%CI)	IC (95%CI)	P-Value
QOL (FACT-Leukemia)	126.1 (121.9 – 130.3)	115.4 (110.7 – 120.2)	**0.001**
Anxiety Symptoms (HADS)	4.3 (3.6 – 5.0)	4.6 (3.8 – 5.4)	0.565
Depression Symptoms (HADS)	4.8 (4.0 – 5.6)	6.9 (6.0 – 7.9)	**0.0007**
Symptom Burden (ESAS)	22.2 (18.7 – 26.6)	28.6 (24.6 – 32.6)	**0.0186**

FACT = Functional assessment of cancer treatment
HADS = Hospital anxiety and depression scale
ESAS = Edmonton symptom assessment system

Fathi AT et al. ASH 2025;Abstract 6.

Healthcare Utilization



Wei AL et al. ASH 2025; Discussant.

PARADIGM: Conclusions

- The study met its primary endpoint in this IC-eligible population.
- Aza-Ven improves EFS versus conventional IC.
- Aza-Ven leads to higher rates of OR and CCR, when compared to IC.
- A greater proportion of Aza-Ven patients successfully proceeded to HCT following response on trial.
- Aza-Ven was associated with less early mortality, improved QOL and symptom burden during initial therapy, with less time in the hospital and ICU.
- These data support the use of Aza-Ven in functionally fit patients with intermediate or adverse-risk, *FLT3*-wildtype AML.

Fathi AT et al. ASH 2025;Abstract 6.

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Oncology

Oral SERDs for Breast Cancer

A CME/MOC-Accredited Live Webinar

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RTP Year in Review 2026

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