Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Acute Myeloid Leukemia

A CME-Accredited Friday Satellite Symposium Preceding the 67th ASH Annual Meeting

Friday, December 5, 2025

7:30 AM – 9:30 AM ET

Faculty

Harry Paul Erba, MD, PhD

Amir Fathi, MD

Tara L Lin, MD, MS

Alexander Perl, MD

Eytan M Stein, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

Harry Paul Erba, MD, PhD
Director, Leukemia Program
Professor in the Department of Medicine
Member of the Duke Cancer Institute
Duke University School of Medicine
Durham, North Carolina

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

Tara L Lin, MD, MS
Professor, Hematologic Malignancies
and Cellular Therapeutics
University of Kansas Medical Center
Kansas City, Kansas

Alexander Perl, MD
Associate Professor of Medicine
Perelman School of Medicine
Member, Leukemia Program
Abramson Cancer Center
University of Pennsylvania
Philadelphia, Pennsylvania

Eytan M Stein, MD
Chief, Leukemia Service
Director, Program for Drug Development
in Leukemia
Associate Attending Physician
Leukemia Service, Department of Medicine
Memorial Sloan Kettering Cancer Center
New York, New York

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Contributing Clinical Investigators

Jorge Cortes, MD
Director, Georgia Cancer Center
Augusta University
Augusta, Georgia

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

Courtney D DiNardo, MD, MSCE
Professor, Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Dr Erba — Disclosures
Faculty

Consulting Agreements	AbbVie Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Daiichi Sankyo Inc, Gilead Sciences Inc, GlycoMimetics Inc, Incyte Corporation, Jazz Pharmaceuticals Inc, Kura Oncology, Novartis, Pfizer Inc, Servier Pharmaceuticals LLC, Stemline Therapeutics Inc, Sumitomo Pharma America
Contracted Research	AbbVie Inc, Agios Pharmaceuticals Inc, ALX Oncology, Amgen Inc, Aptose Biosciences Inc, Ascentage Pharma, Daiichi Sankyo Inc, Forma Therapeutics, Gilead Sciences Inc, GlycoMimetics Inc, ImmunoGen Inc, Jazz Pharmaceuticals Inc, Kura Oncology, MacroGenics Inc, Novartis, Oryzon, PTC Therapeutics, Sumitomo Pharma America, Taiho Oncology Inc
Speakers Bureaus	AbbVie Inc, Bristol Myers Squibb, Incyte Corporation, Jazz Pharmaceuticals Inc, Servier Pharmaceuticals LLC, Syndax Pharmaceuticals
Study IRCs	AbbVie Inc (Chair, VIALE-A and VIALE-C)
Study Steering Committee Chairs	Bristol Myers Squibb (AML Registry), Daiichi Sankyo Inc (QuANTUM-First and QuANTUM-Wild)
Study Steering Committees	GlycoMimetics Inc, Kura Oncology, Sumitomo Pharma America
Nonrelevant Financial Relationships	Fortrea

Dr Fathi — Disclosures
Faculty

Consulting Agreements	AbbVie Inc, Astellas, AstraZeneca Pharmaceuticals LP, Autolus, Bristol Myers Squibb, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Kura Oncology, Pfizer Inc, Prelude Therapeutics, Remix Therapeutics, Rigel Pharmaceuticals Inc, Schrödinger, Servier Pharmaceuticals LLC, Syndax Pharmaceuticals, Takeda Pharmaceuticals USA Inc, Thermo Fisher Scientific
Contracted Research	AbbVie Inc, Bristol Myers Squibb, Kura Oncology, Servier Pharmaceuticals LLC

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Dr Lin — Disclosures
Faculty

Consulting Agreements	Daiichi Sankyo Inc, Jazz Pharmaceuticals Inc, Johnson & Johnson, Servier Pharmaceuticals LLC, Syndax Pharmaceuticals
Contracted Research	Aptevo Therapeutics, Bio-Path Holdings Inc, Cardiff Oncology, CicloMed, Cleave Biosciences, Jazz Pharmaceuticals Inc, Kura Oncology, Lin BioScience
Data and Safety Monitoring Boards/Committees	Sumitomo Pharma America

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Dr Perl — Disclosures
Faculty

Advisory Committees	AbbVie Inc, Astellas, Daiichi Sankyo Inc, Johnson & Johnson, Rigel Pharmaceuticals Inc, Stemline Therapeutics Inc, Syndax Pharmaceuticals
Consulting Agreements	Astellas, Daiichi Sankyo Inc, Foghorn Therapeutics, Syndax Pharmaceuticals
Contracted Research	AbbVie Inc, Astellas, Daiichi Sankyo Inc, Syndax Pharmaceuticals
Data and Safety Monitoring Boards/Committees	Foghorn Therapeutics
Nonrelevant Financial Relationships	Beat AML LLC

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Dr Stein — Disclosures
Faculty

Consulting Agreements	AbbVie Inc, Astellas, Cullinan Therapeutics, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Janssen Biotech Inc, Kura Oncology, Servier Pharmaceuticals LLC, Syndax Pharmaceuticals
Contracted Research	Astellas, Bristol Myers Squibb, Servier Pharmaceuticals LLC, Syndax Pharmaceuticals
Stock Options — Private Companies	Auron Therapeutics

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Dr Cortes — Disclosures
Survey Participant

Consulting Agreements	Ascentage Pharma, Bio-Path Holdings Inc, Novartis, Pfizer Inc, Sun Pharmaceutical Industries Ltd, Syndax Pharmaceuticals, Takeda Pharmaceuticals USA Inc, Terns Pharmaceuticals
Contracted Research	Ascentage Pharma, Bio-Path Holdings Inc, CytoAgents, Kura Oncology, Novartis, Pfizer Inc, Sun Pharmaceutical Industries Ltd, Terns Pharmaceuticals
Stock Options/Stock — Public Companies	Bio-Path Holdings Inc

Dr DiNardo — Disclosures
Survey Participant

Advisory Committees	Astellas, Bristol Myers Squibb, Kura Oncology
Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Genmab US Inc, Molecular Partners, Rigel Pharmaceuticals Inc, Servier Pharmaceuticals LLC
Contracted Research	AbbVie Inc, Astex Pharmaceuticals, Auron Therapeutics, Remix Therapeutics, Rigel Pharmaceuticals Inc, Servier Pharmaceuticals LLC, SillaJen, SystImmune Inc

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Dr Wang — Disclosures
Survey Participant

Advisory Boards	AbbVie Inc, Blueprint Medicines, Cullinan Therapeutics, Daiichi Sankyo Inc, Dark Blue Therapeutics, Johnson & Johnson, Kite, A Gilead Company, Kura Oncology, Novartis, QIAGEN, Rigel Pharmaceuticals Inc, Ryvu Therapeutics, Schrödinger, Servier Pharmaceuticals LLC, Syndax Pharmaceuticals, Takeda Pharmaceuticals USA Inc
Consulting Agreements	Kura Oncology, Menarini Group
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Speakers Bureaus	Astellas, Pfizer Inc
Nonrelevant Financial Relationships	UpToDate

Dr Love — Disclosures

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Cases from the Community
Investigators Discuss Available Research Guiding the Selection of Therapy for Patients with Chronic Lymphocytic Leukemia

A CME-Accredited Friday Satellite Symposium Preceding the 67th ASH Annual Meeting

Friday, December 5, 2025
11:30 AM – 1:30 PM ET

Faculty

Matthew S Davids, MD, MMSc
Bita Fakhri, MD, MPH
Professor Constantine Tam, MBBS, MD
Jennifer Woyach, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Expert Second Opinion
Investigators Discuss the Optimal Management of Myelofibrosis and Systemic Mastocytosis

A CME-Accredited Friday Satellite Symposium Preceding the 67th ASH Annual Meeting

Friday, December 5, 2025

3:15 PM – 5:15 PM ET

Faculty

Professor Claire Harrison
Andrew T Kuykendall, MD
Stephen T Oh, MD, PhD
Jeanne Palmer, MD
Raajit K Rampal, MD, PhD

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

Expert Second Opinion
Investigators Discuss the Role of Novel Treatment Approaches in the Care of Patients with Follicular Lymphoma and Diffuse Large B-Cell Lymphoma

A CME-Accredited Friday Satellite Symposium Preceding the 67th ASH Annual Meeting

Friday, December 5, 2025

7:00 PM – 9:00 PM ET

Faculty

Nancy L Bartlett, MD
John P Leonard, MD
Matthew Matasar, MD
Loretta J Nastoupil, MD
Professor Pier Luigi Zinzani

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

CASES FROM THE COMMUNITY
Investigators Discuss the Role of Antibody-Drug Conjugates in the Management of Triple-Negative and HR-Positive Metastatic Breast Cancer

Part 1 of a 3-Part CME Satellite Symposium Series

Tuesday, December 9, 2025

7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)

Faculty

Javier Cortés, MD, PhD

Professor Peter Schmid, FRCP, MD, PhD

Rita Nanda, MD

Priyanka Sharma, MD

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

CASES FROM THE COMMUNITY
Investigators Discuss the Optimal Management of HER2-Positive Breast Cancer

Part 2 of a 3-Part CME Satellite Symposium Series

Wednesday, December 10, 2025

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Professor Giuseppe Curigliano, MD, PhD
Nadia Harbeck, MD, PhD
Ian E Krop, MD, PhD
Nancy U Lin, MD
Joyce O'Shaughnessy, MD

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

CASES FROM THE COMMUNITY
Investigators Discuss the Optimal Role of Endocrine-Based and Other Strategies in the Management of HR-Positive Breast Cancer

Part 3 of a 3-Part CME Satellite Symposium Series

Thursday, December 11, 2025

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Angela DeMichele, MD, MSCE
Komal Jhaveri, MD, FACP, FASCO
Erica Mayer, MD, MPH, FASCO
Hope S Rugo, MD
Seth Wander, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss Available Research Guiding the Management of Relapsed/Refractory Multiple Myeloma — What Happened at ASH 2025?

A CME/MOC-Accredited Live Webinar

Monday, December 15, 2025

5:00 PM – 6:00 PM ET

Faculty

Sagar Lonial, MD, FACP, FASCO

María-Victoria Mateos, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Practical Perspectives on the Current and Future Management of Immune Thrombocytopenia — What Happened at ASH 2025?

A CME/MOC-Accredited Live Webinar

Tuesday, December 16, 2025

5:00 PM – 6:30 PM ET

Faculty

Hanny Al-Samkari, MD

Francesco Zaja, MD

Additional faculty to be announced

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

Practical Perspectives on the Current Role of Bispecific Antibodies in the Management of Lymphoma — What Happened at ASH 2025?

A CME/MOC-Accredited Live Webinar

Wednesday, December 17, 2025
5:00 PM – 6:00 PM ET

Faculty

Michael Dickinson, MD
Laurie H Sehn, MD, MPH

Moderator

Neil Love, MD

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Grand Rounds

CME/MOC-Accredited Interactive Series

Through April 2026

Three Series

Optimizing Treatment for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

Optimizing the Use of Novel Therapies for Patients with Diffuse Large B-Cell Lymphoma

Optimizing Therapy for Patients with Hormone Receptor-Positive Localized Breast Cancer

Host a 1-hour session at your institution:
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Save The Date

Fifth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, April 24 to 26, 2026

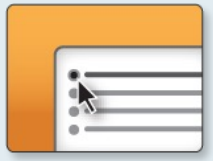
The Ritz-Carlton Orlando, Grande Lakes | Orlando, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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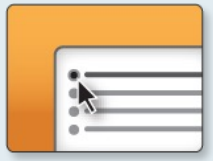
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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RTP Playlist with Neil Love, MD

BREAST CANCER

Dr Hope Rugo: Interview (28 min)

SMALL CELL LUNG CANCER

Drs Stephen Liu and Charles Rudin: Cases (58 min)

GASTROESOPHAGEAL CANCER

Drs Geoffrey Ku and Zev Wainberg: Cases (61 min)

PROSTATE CANCER

Drs Emmanuel Antonarakis and Karim Fizazi: Year in Review (60 min)

ENDOMETRIAL AND OVARIAN CANCER

Dr Shannon Westin: Interview (52 min)

NEUROENDOCRINE TUMORS

Drs Simron Singh and Jonathan Strosberg: Meeting (50 min)

NON-HODGKIN LYMPHOMA

Drs Jeremy Abramson, Joshua Brody, Christopher Flowers, Ann LaCasce and Tycel Phillips: Meeting, cases (59 min)

CHRONIC LYMPHOCYTIC LEUKEMIA

Drs Jennifer Brown and Paolo Ghia: Year in Review (59 min)

ACUTE MYELOID LEUKEMIA

Dr Jorge Cortes: Interview (43 min)

MULTIPLE MYELOMA

Drs Natalie Callander and Sagar Lonial: Patient videos (59 min)

IMMUNE THROMBOCYTOPENIA

Drs Hanny Al-Samkari, James Bussel and Nichola Cooper: Think Tank (117 min)

OCULAR TOXICITES IN ONCOLOGY

Dr Neel Pasricha: Interview (54 min)

Feedback (Please!)
DrNeilLove@ResearchToPractice.com

RTP Playlist with Neil Love, MD

Webinar for patients and families on relapsed multiple myeloma with Drs Natalie Callander and Sagar Lonial.

Relapsed Multiple Myeloma: Where We Were, Where We Are (4 min)

Common Questions from the Beginning (5 min)

Choosing Treatment Options (4 min)

Clinical Research Trials (6 min)

Neuropathy (5 min)

Chimeric Antigen Receptor (CAR) T-Cell Therapy (6 min)

Bispecific Antibodies (8 min)

Antibody-Drug Conjugates: Belantamab Mafadotin (8 min)

Interacting with the Oncology Team (5 min)

Other Questions (4 min)

Recording of Entire Webinar (62 min)

Feedback (Please!)
DrNeilLove@ResearchToPractice.com

ASH and SABCS RTP Video Participants

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ASH and SABCS RTP Participating Faculty

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Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Acute Myeloid Leukemia

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Tara L Lin, MD, MS

Alexander Perl, MD

Eytan M Stein, MD

Moderator

Neil Love, MD

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Agenda

Module 1: Up-Front Therapy for Older Patients with Acute Myeloid Leukemia (AML) — Dr Lin

Module 2: Selection of Therapy for Younger Patients with AML without a Targetable Mutation; Promising Investigational Strategies — Dr Perl

Module 3: Role of FLT3 Inhibitors in AML Management — Dr Erba

Module 4: Incorporation of IDH Inhibitors into the Care of Patients with AML — Dr Fathi

Module 5: Current and Future Role of Menin Inhibitors in the Treatment of AML — Dr Stein

Agenda

Module 1: Up-Front Therapy for Older Patients with Acute Myeloid Leukemia (AML) — Dr Lin

Module 2: Selection of Therapy for Younger Patients with AML without a Targetable Mutation; Promising Investigational Strategies — Dr Perl

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Module 4: Incorporation of IDH Inhibitors into the Care of Patients with AML — Dr Fathi

Module 5: Current and Future Role of Menin Inhibitors in the Treatment of AML — Dr Stein

Up-Front Therapy for Older Patients with Acute Myeloid Leukemia

Tara L. Lin, MD

Professor of Medicine
Director, Acute Leukemia Program
Medical Director, Clinical Trials Office
Division of Hematologic Malignancies & Cellular Therapeutics

The University of Kansas Cancer Center

Treatment decision-making for older patients with AML

- What is “old” for AML?
- How do we determine fitness?

- Disease biology to determine optimal treatment
- Incorporation of targeted agents
- Shared decision making with the patient

- What if “intensive therapy” isn’t better than less intensive?
- Clinical trial design less focused on age vs fitness

What is OLDER AML?

Latest ASH Guidelines for Older Adults – age 55+

Trials of less intensive therapy – age 75

Does AGE matter – or is age just one tool in assessing FITNESS?

Why fitness assessment is important

- Guides treatment choice
- Predicts treatment tolerance
- Assessment of toxicity/tolerance/efficacy of new treatments

- Encouraged *to take the time* to perform a comprehensive assessment

How do we assess fitness for intensive therapy?

- Age
- Performance status
- Medical comorbidities

Ferrara Criteria

1.	An age older than 75 years
2.	Congestive heart failure or documented cardiomyopathy with an EF ≤50%
3.	Documented pulmonary disease with DLCO ≤65% or FEV1 ≤65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
4.	On dialysis and age older than 60 years or uncontrolled renal carcinoma
5.	Liver cirrhosis Child B or C, or documented liver disease with marked elevation of transaminases (>3 times normal values) and an age older than 60 years, or any biliary tree carcinoma or uncontrolled liver carcinoma or acute viral hepatitis
6.	Active infection resistant to anti-infective therapy
7.	Current mental illness requiring psychiatric hospitalization, institutionalization or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
8.	ECOG performance status ≥3 not related to leukemia
9.	Any other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy

Leukemia **volume 27**, pages 997–999 (2013)

How **should** we assess fitness?

- Age
- Performance status
- Medical comorbidities
- **Geriatric assessment**

- **Comprehensive:** age, PS, comorbidities AND functional capacity
- **Dynamic** – at multiple stages of treatment
- **Specific** – in the context of specific treatments
- **Not a binary FIT/UNFIT determination**

REVIEW ARTICLE

blood advances

Fitness assessment in acute myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet

Table 4. Timing for fitness/genetic determination

Statement	Recommendations: timing for fitness/genetic determination	LoE	GoR	LoA
14	Because the time to treatment start does not seem to affect short- and long-term outcomes, comprehensive fitness and biological assessment should be conducted before starting therapy.	IV	B	96%
15	Fitness level attribution should be performed after appropriate supportive therapy when general condition impairments are suspected to be due to disease burden rather than preexisting conditions.	IV	B	81%
16	Fitness improvement/worsening should be assessed dynamically throughout therapy in responding and nonresponding patients to modulate treatment intensity as appropriate.	IV	B	100%
17	Biological reassessment should be performed at disease relapse to assist the choice of salvage therapy.	I	A	100%

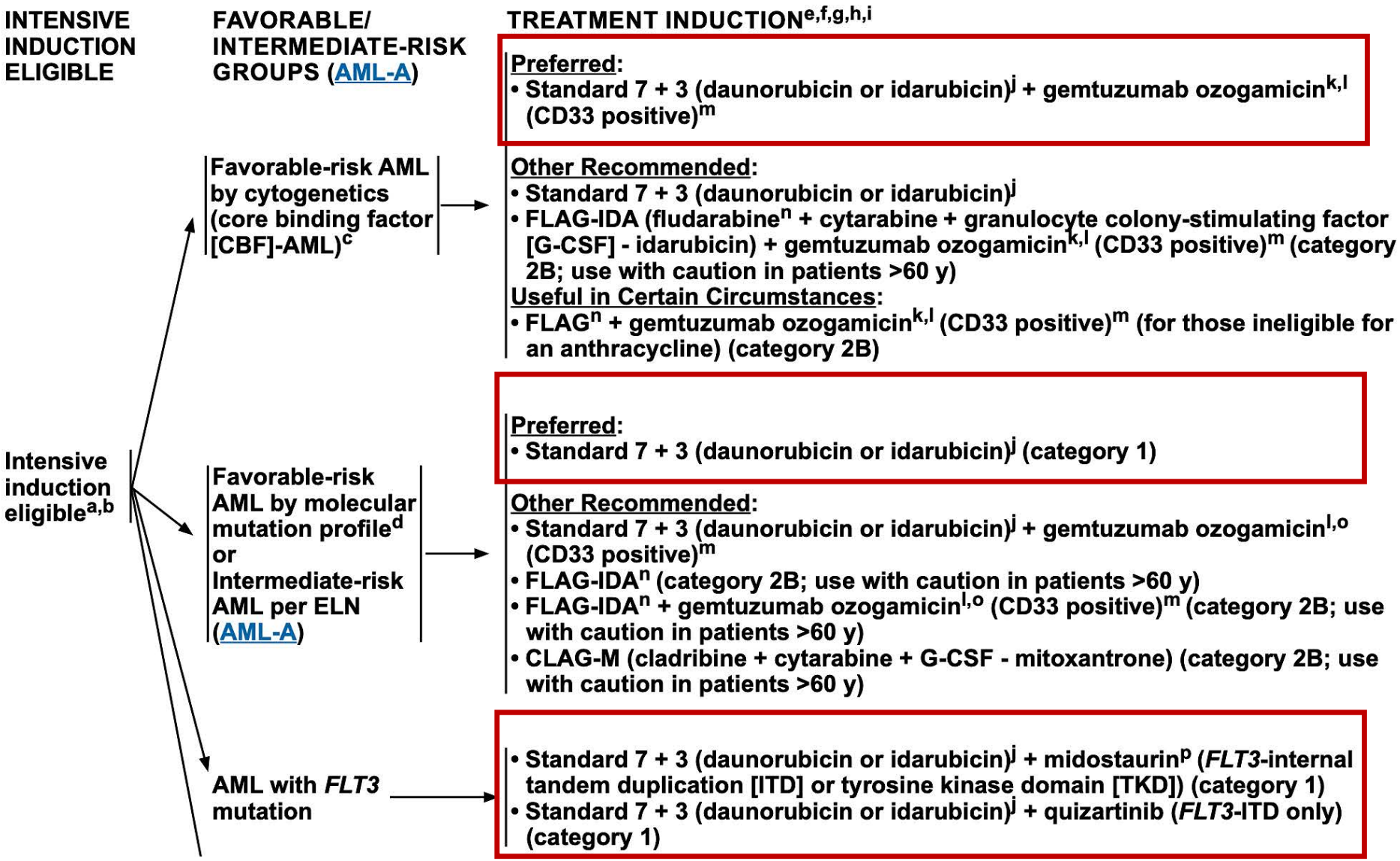
Blood Adv (2025) 9 (9): 2207–2220.

Table 5. Available tools for comprehensive geriatric assessment

Tool	Aim	Number of items	Completion time	Score range	Interpretation	Level of priority
Activities of daily living	Measuring functional basic activity of daily living in older patients	6	5-10 min	0-6	Higher score corresponds to higher level of functional activity	***
Instrumental activities of daily living	Measuring elaborate functional activities in older patients	8	5-10 min	0-8 (women) 0-5 (men)	Higher score corresponds to higher level of functional activity	**
MMSE	Evaluating cognitive function in clinical practice patients	30	5-10 min	0-30	MMSE score ≤23 is indicative of cognitive impairment	***
Geriatric depression scale	Rating depression in older individuals	15	5 min	0-15	0-4: normal 5-8: mild depression 9-11: moderate depression 12-15: severe depression	***
Mini nutritional assessment	Evaluating nutritional status	30	10-15 min	0-30	24-30: normal nutritional status 17-23.5: risk for malnutrition <17: malnourished patient	**
Time to get up and go	Evaluating gait and balance	1	<5 min	1-5	>3: patient at risk of falling	*
ACE-27	Evaluating comorbidity index in patients with cancer	27	>20 min	None, mild, moderate, and severe	In the cases in which ≥2 moderate ailments occur in different organ systems or disease groupings, the overall comorbidity score is designated as severe	*

Blood Adv (2025) 9 (9): 2207–2220.

Disease Biology + Fitness to Guide Treatment



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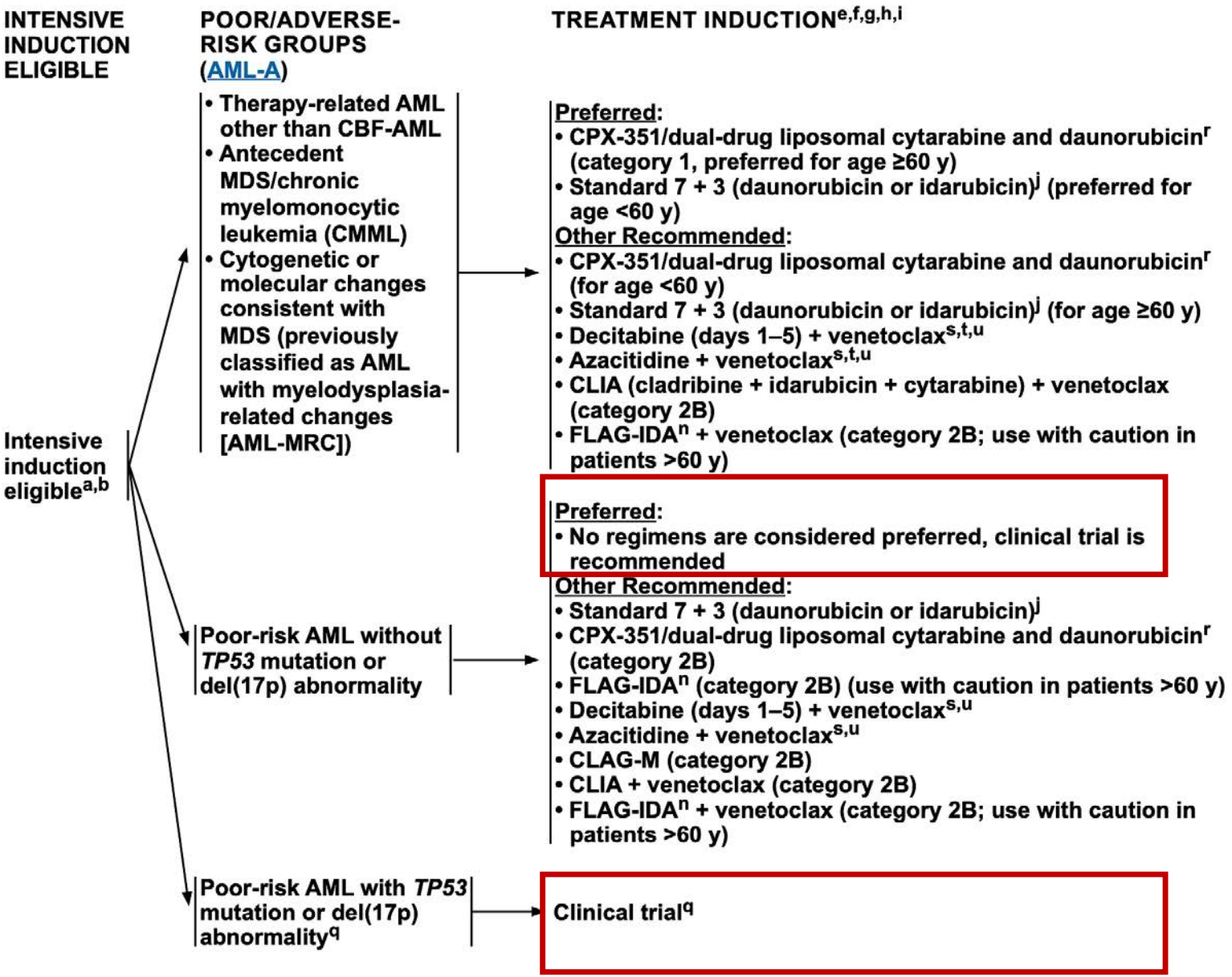
Disease Biology + Fitness to Guide Treatment



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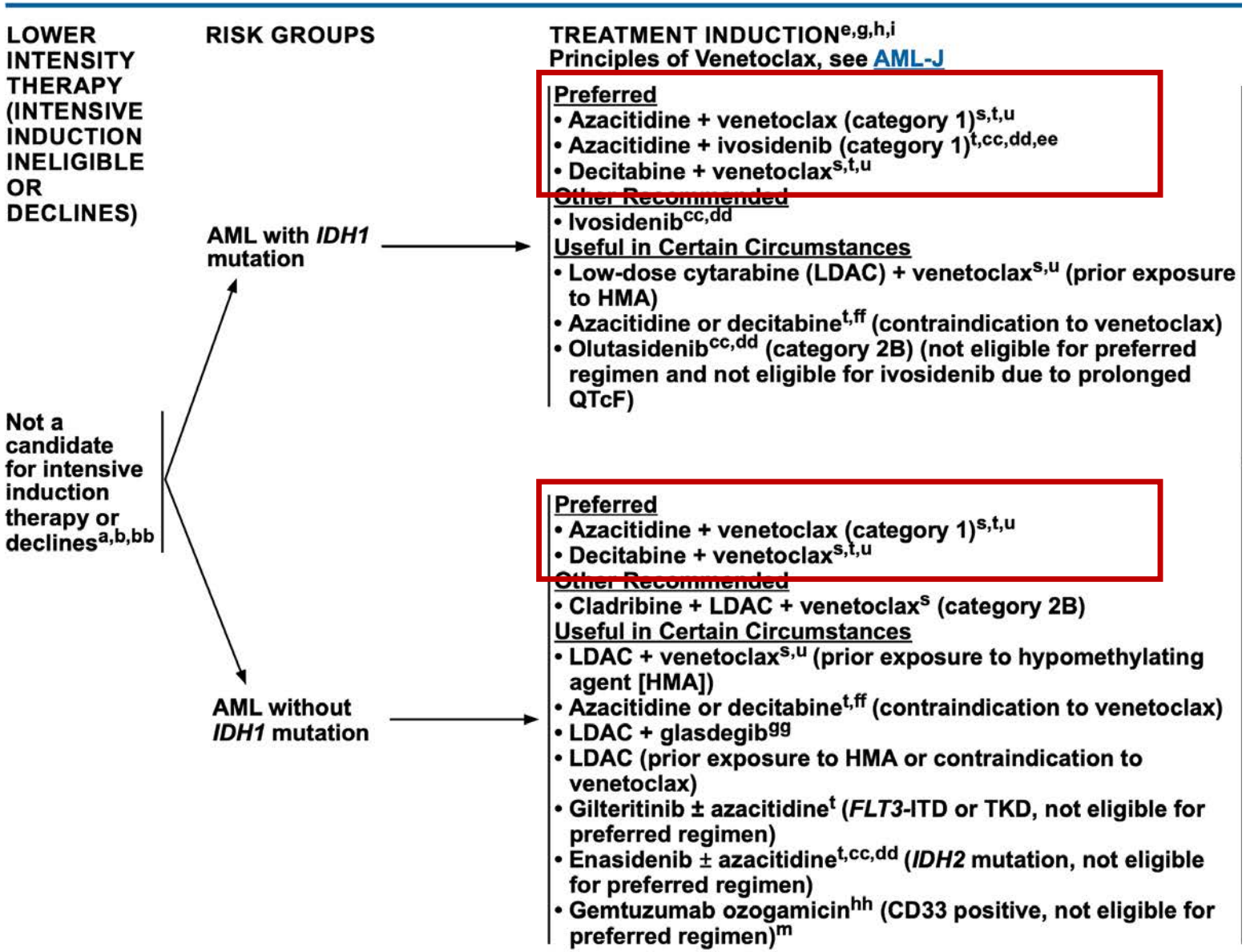
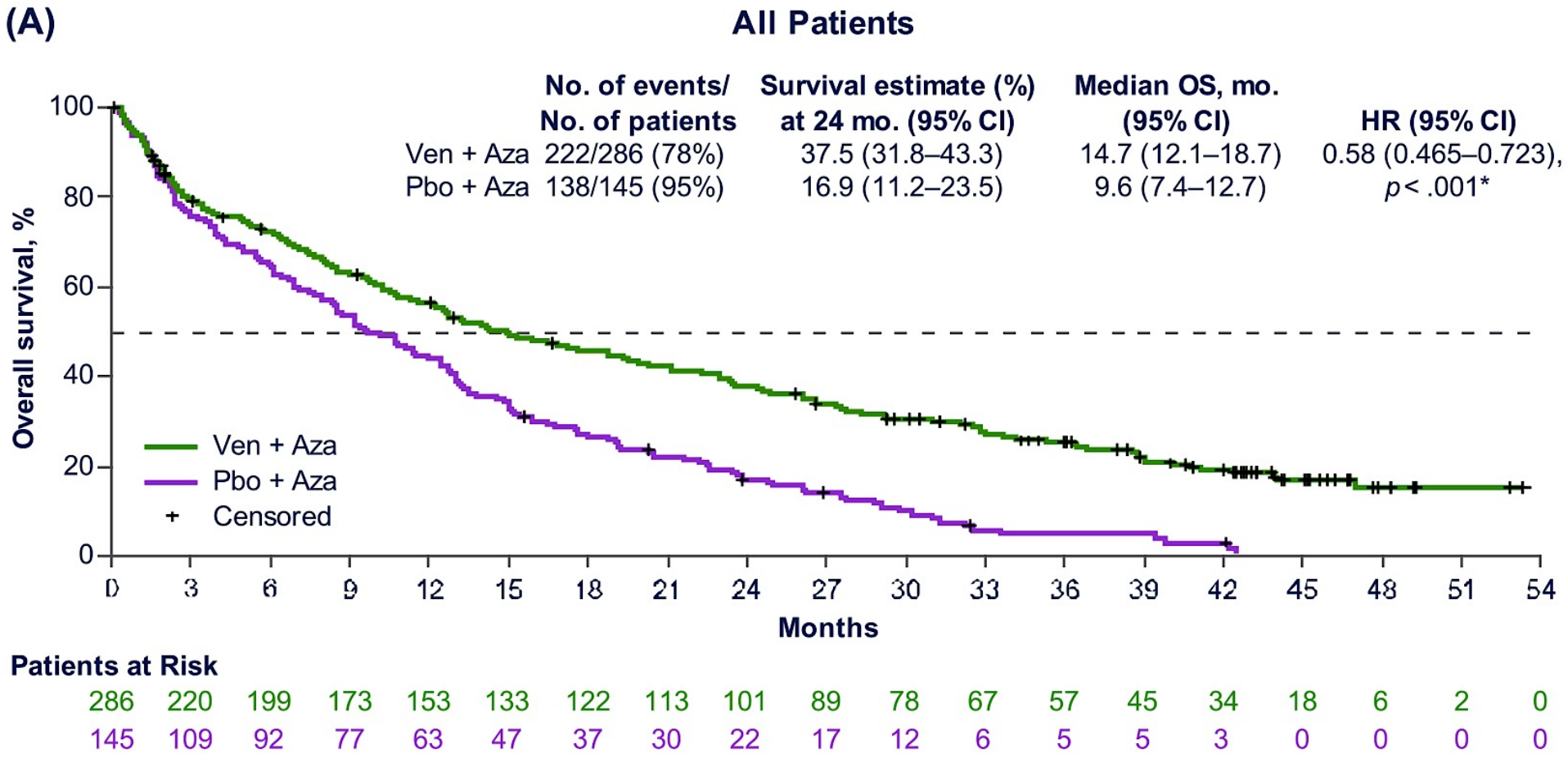
Disease Biology + Fitness to Guide Treatment



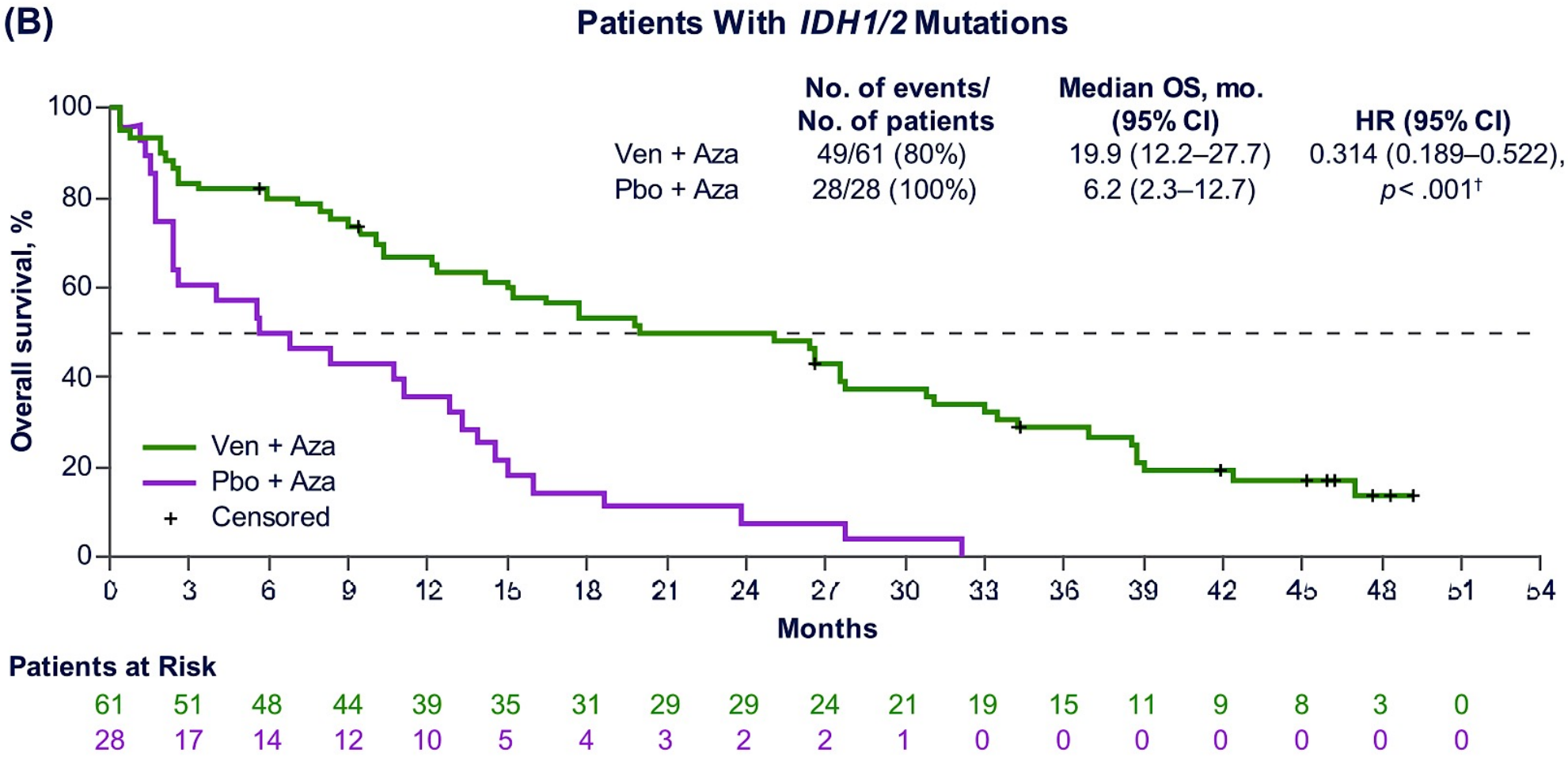
https://www.nccn.org

VIALE-A long-term follow-up



Pratz KW et al. Am J Hematol. 2024;99:615–624.

VIALE-A long-term follow-up



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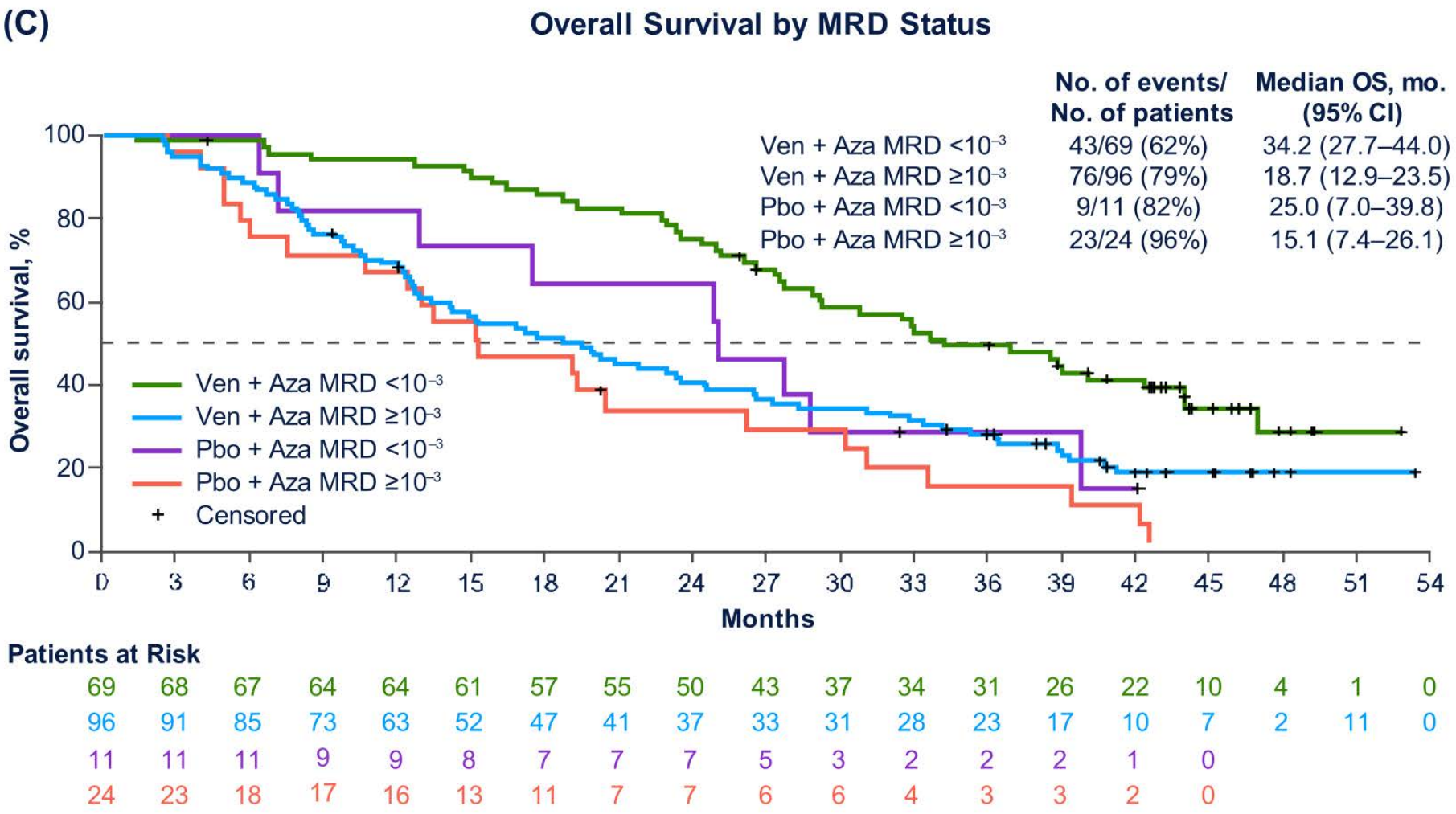
VIALE-A long-term follow-up



Pratz KW et al. Am J Hematol. 2024;99:615–624.

VIALE-A long-term follow-up

Serious treatment-emergent adverse events in ≥ 5% of patients in either arm

Adverse event, no. (%)	Venetoclax-Azacitidine N=283	Placebo-Azacitidine N=144
Any serious adverse event, no. (%)	242 (86)	111 (77)
Hematologic serious adverse event	121 (43)	29 (20)
Febrile neutropenia	88 (31)	15 (10)
Anemia	19 (7)	9 (6)
Infection	172 (61)	67 (47)
Pneumonia	55 (19)	35 (24)
Sepsis	20 (7)	12 (8)

Pratz KW et al. Am J Hematol. 2024;99:615–624.

How I Treat Patients with Acute Myeloid Leukemia Using Azacitidine and Venetoclax

General considerations

- ❑ If deemed unfit for intensive chemotherapy, assess likely benefit from AZA-VEN (ELN 2024: LI risk)
- ❑ Consider inpatient management for patients at risk of prolonged neutropenia until neutrophil recovery

Minimize TLS risk

- ❑ Assess for high-risk TLS features e.g. *IDH2* mutation, elevated WBC, LDH, uric acid, impaired renal function
- ❑ Reduce baseline WBC to <15 × 10^9/L (<10 × 10^9/L if *IDH2* mutation)
- ❑ TLS prophylaxis and monitoring. Inpatient initiation of therapy for patients at increased risk
- ❑ If concurrent CYP3A4 inhibitor use planned, adjust venetoclax ramp-up and plateau dose during cycle 1

Neutropenic phase

- ❑ If inpatient: align antimicrobial management with intensive chemotherapy practice
- ❑ If outpatient: antimicrobial prophylaxis during severe neutropenia
- ❑ Close monitoring and aggressive management of infections

Response assessment in C1 (days 21-28)

- ❑ If blast clearance, interrupt venetoclax
- ❑ Consider G-CSF if neutrophil count < 0.5 × 10^9/L after confirming response
- ❑ If persistent disease, proceed to cycle 2

Subsequent cycles

- ❑ Allow sufficient time for optimal neutrophil (≥1 × 10^9/L) and platelet (≥100 × 10^9/L) recovery
- ❑ If recovery delayed (>42 days):
  - ❑ Shorten venetoclax duration
  - ❑ Increase inter-cycle interval
  - ❑ Reduce AZA dose

Abbreviations: AZA, azacitidine; ELN, European LeukemiaNet; VEN, venetoclax; LDH, lactate dehydrogenase; G-CSF, granulocyte colony-stimulating factor; LI, lower intensity; TLS, tumor lysis syndrome; WBC, white blood cell count

Conclusions: Increased exposure to venetoclax (dose and duration) enhances antileukemic efficacy, but also the risk of damage to hematopoietic stem and progenitor cells. The aim of therapy is to deliver an optimal rather than excessive dose of venetoclax to maximize the safety and clinical benefit of therapy.

*Wei et al. DOI: 10.1182/**blood**.2024024009*

blood Visual Abstract

Blood (2025) 145 (12): 1237–1250.

Management of common toxicities

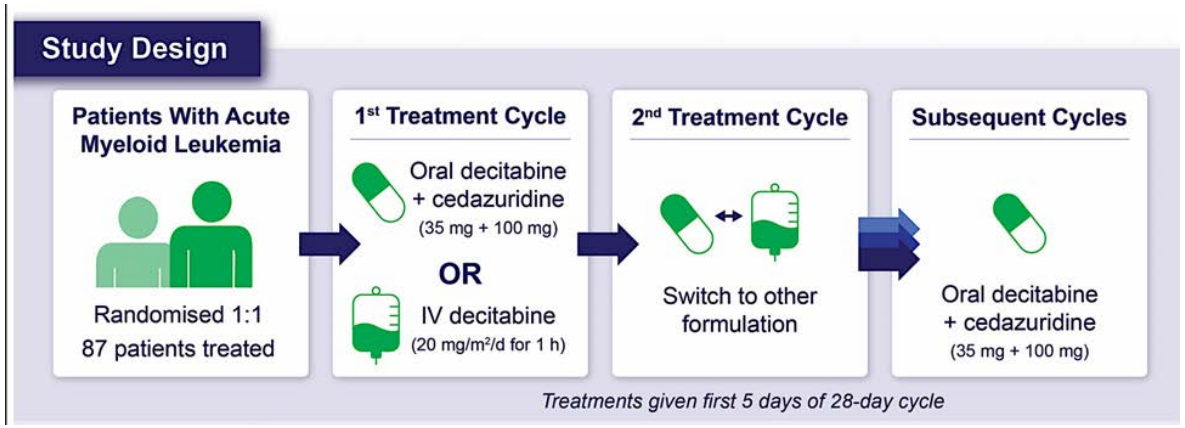
- Tumor Lysis
  - Prevention with IVF, allopurinol
  - Electrolyte monitoring, telemetry as needed

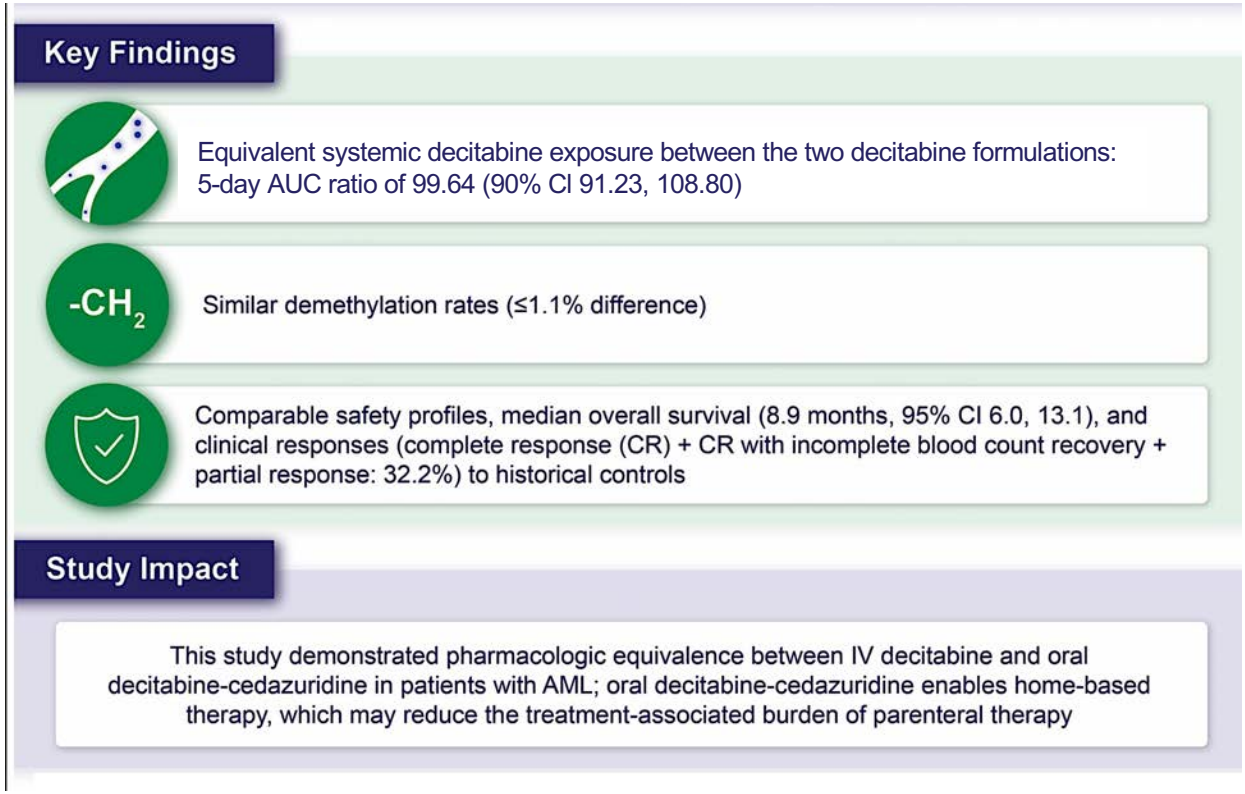
- Cytopenias
  - Appropriate ven dose for anti-fungal
  - G-CSF if blast clearance and delayed ANC recovery
  - Start next cycle when ANC >1000 and platelets >50-100
  - Reduce duration of ven
  - Cycles q6 weeks

- Febrile neutropenia/infections
  - Appropriate prophylaxis
  - Information for emergency management of fever

Blood (2025) 145 (12): 1237–1250.

Phase III ASCERTAIN-AML





Geissler K, et al. Br J Haematol. 2024;205(5):1734–1745.

2025 ASCO® ANNUAL MEETING

An All-Oral Regimen of Decitabine-Cedazuridine Plus Venetoclax in Patients With Newly Diagnosed Acute Myeloid Leukemia Ineligible for Intensive Induction Chemotherapy: Results From a Phase 2 Cohort of 101 Patients

Amer M. Zeidan,[1] Elizabeth A. Griffiths,[2] Courtney D. DiNardo,[3] Gabriel N. Mannis,[4] Pau Montesinos,[5] Montserrat Arnan,[6] Michael R. Savona,[7] Olatoyosi Odenike,[8] James K. McCloskey,[9] Harsh V. Amin,[10] Amir T. Fathi,[11] Teresa Bernal del Castillo,[12] Gabriela Rodríguez-Macías,[13] Jane Liesveld,[14] Annie P. Im,[15] Aram Oganesian,[16] Qing Xu,[16] Margit Dijkstra,[16] Harold Keer,[16] Gail J. Roboz[17]

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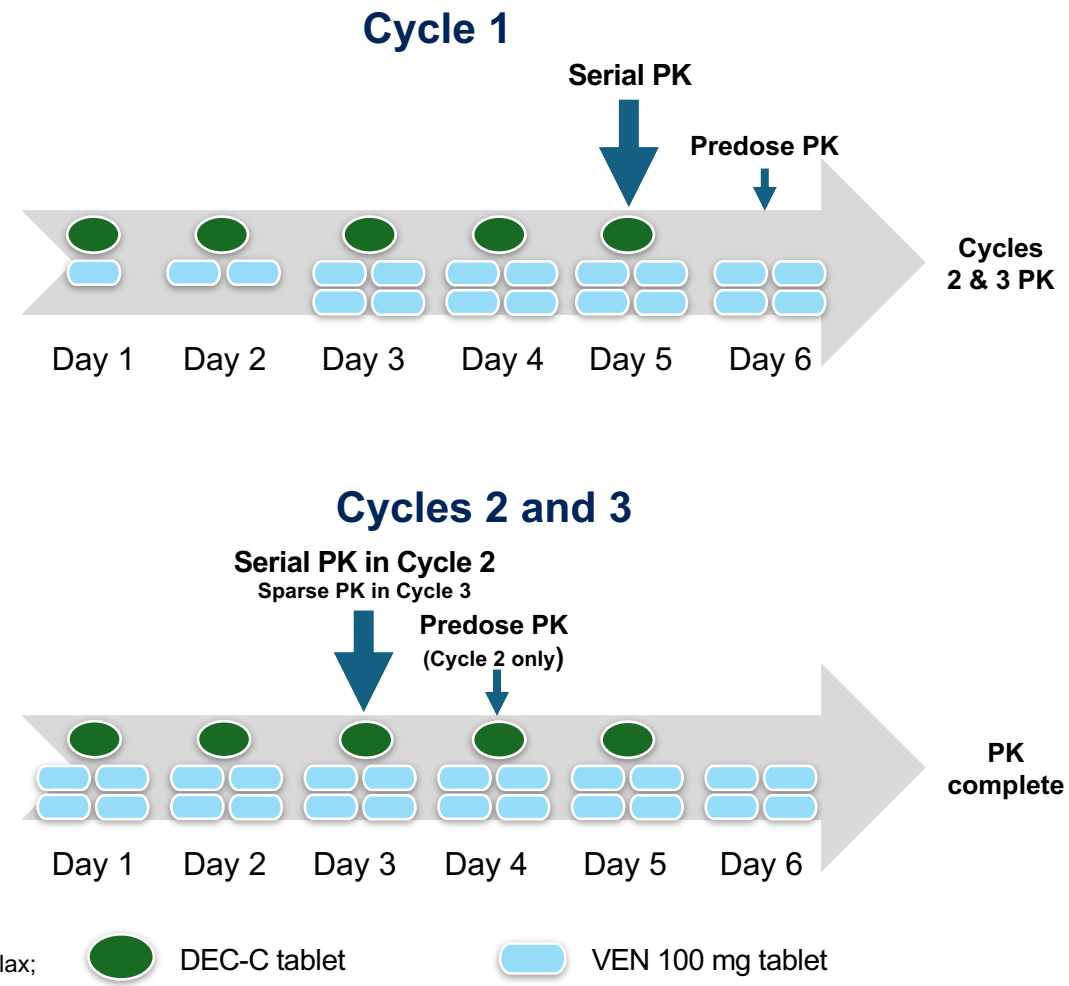
ASCERTAIN-V: Methods

Trial Schema: Phase 2 Part B

Cycle 1 (28-day cycle)	Patients (n=101)
Dosing	
Day 1	DEC-C + VEN 100 mg (ramp up)
Day 2	DEC-C + VEN 200 mg (ramp up)
Days 3–5	DEC-C + VEN 400 mg
Days 6–28	VEN 400 mg

Cycles 2 and 3 (28-day cycle)	Patients (n=101)
Dosing	
Days 1–5	DEC-C + VEN 400 mg
Days 6–28	VEN 400 mg

Continue treatment until disease progression, unacceptable toxicity, or patient is withdrawn from study



ASCERTAIN-V, AStx727-07: decitabine + CEdazuRidine TreAtment In Newly diagnosed AML adding Venetoclax; DEC-C, decitabine-cedazuridine; PK, pharmacokinetics; VEN, venetoclax.

ASCERTAIN-V: Results

Patient Baseline Characteristics

Characteristic	Patients (n=101)
Median (range) age, years	78 (63–88)
Patients aged ≥75 years, n (%)	82 (81.2)
Male, n (%)	61 (60.4)
ECOG PS,[a] n (%)	
0	27 (26.7)
1	52 (51.5)
≥2	21 (20.8)
Cytogenetic classification by ELN 2017, n (%)[a]	
Favorable	32 (31.7)
Intermediate	34 (33.7)
Adverse	30 (29.7)
Mutation profiling (at baseline) by NGS, n (%)[b]	
TP53	17 (16.8)
IDH1	6 (5.9)
IDH2	12 (11.9)
FLT3	12 (11.9)
NPM1	13 (12.9)

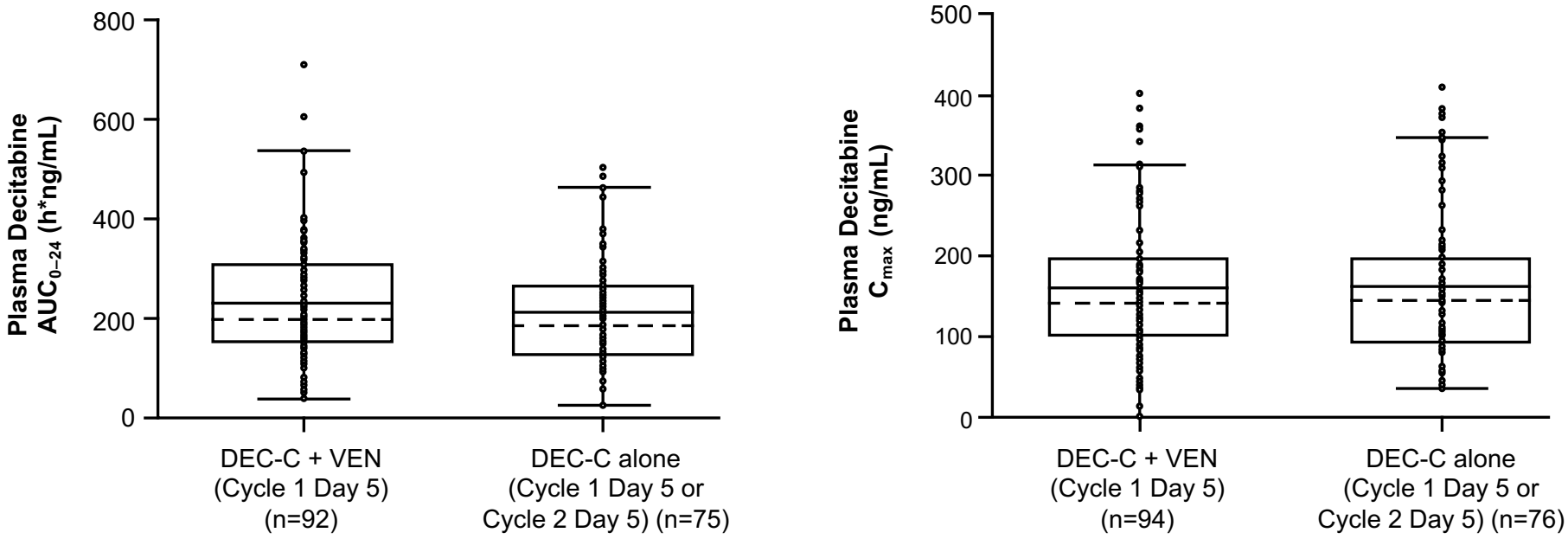
[a]Excludes patients with missing data. [b]NGS testing was performed for 96 patients in phase 2 Part B.
ASCERTAIN-V, AStx727-07: decitabine + CEdazuRidine TreAtment In Newly diagnosed AML adding Venetoclax; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European Leukemia Net; NGS, next-generation sequencing.

ASCERTAIN-V: Results

Pharmacokinetics

- PK data confirmed no drug-drug interactions between DEC-C and VEN
- Decitabine (shown here) and cedazuridine PK were not affected by VEN

Drug-Drug Interaction Box Plots of Plasma Decitabine Parameters ($AUC_{0–24}$ and C_{max}): Phase 2b

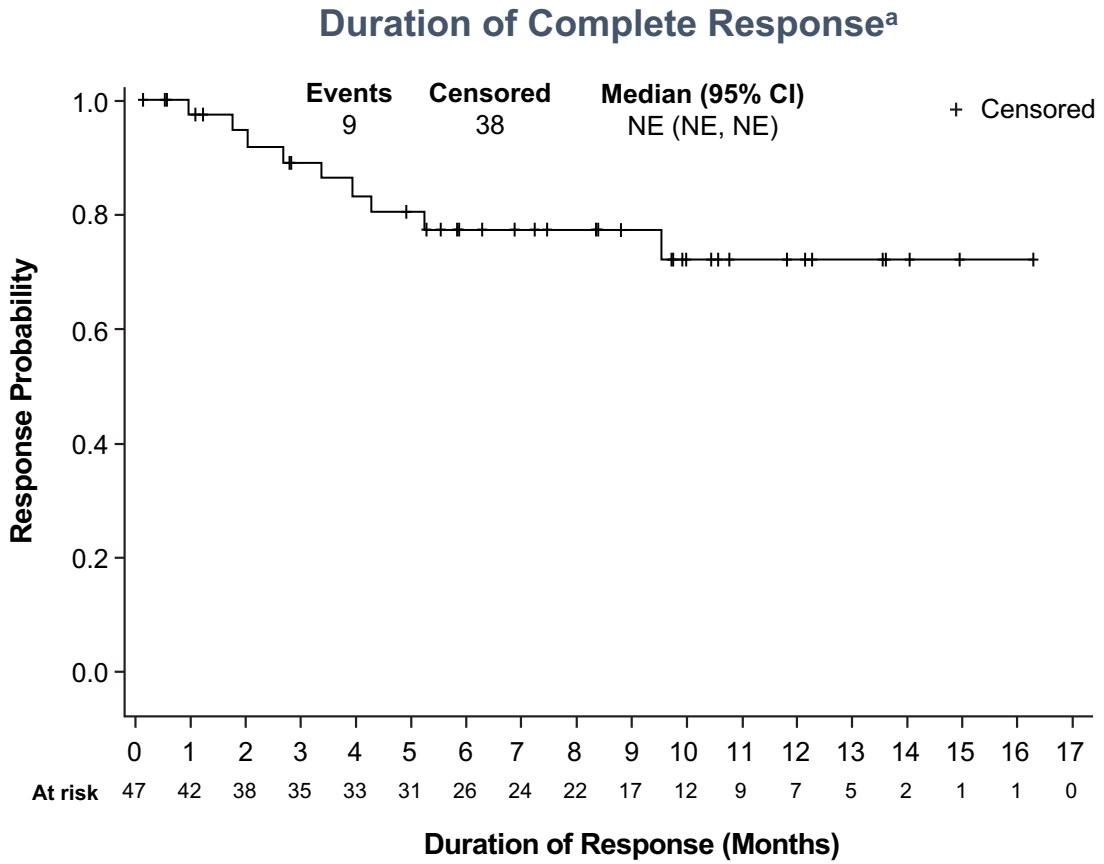


Open circles represent individual data. Line within the box represents the mean and the dotted line represents the median. The whiskers show the lowest data value still within 1.5 IQR of the lower quartile, and the highest value still within 1.5 IQR of the upper quartile, where IQR is the interquartile range (the difference between the third and first quartiles, the middle 50%).
ASCERTAIN-V, AStx727-07: decitabine + CEdazuRidine TreAtment In Newly diagnosed AML adding Venetoclax; $AUC_{0–24}$, area under the curve from 0 to 24 hours; C_{max}, maximum concentration; DEC-C, decitabine-cedazuridine; IQR, interquartile range; PK, pharmacokinetic; VEN, venetoclax.

ASCERTAIN-V: Results

Best Overall Response and Duration of Response

	Patients (n=101)
Best overall response, %	
CR,% (95% CI)	46.5 (36.5, 56.7)
CRi, %	16.8
CRh, %	5.0
CR/CRi (95% CI)	63.4 (53.2, 72.7)
CR/CRh (95% CI)	51.5 (41.3, 61.6)
Median time to complete response, months	2.4
CR duration, %[a]	
Responders continuing CR at 6 months	80.0
Responders continuing CR at 12 months	75.3
Median duration of follow-up, months	11.2



The clinical cutoff date for phase 2 was September 30, 2024.
[a]Median CR duration was not reached.
ASCERTAIN-V, AStx727-07: decitabine + CEdazuRidine TreAtment In Newly diagnosed AML adding Venetoclax; CI, confidence interval; CR, complete response; CRh, complete response with partial hematologic recovery; CRi, complete response with incomplete hematologic recovery; NE, not estimable.

ASCERTAIN-V: Results

- Dose reductions in venetoclax were common in later cycles
- Grade ≥3 AEs were reported in 98.0% of patients
  - febrile neutropenia (49.5%)
  - anemia (38.6%)
  - neutropenia (35.6%)
- Grade 2 nausea in 20%
- 30- and 60-day mortality rates were 3.0% and 9.9%, respectively

Conclusions

- Rapidly changing AML treatment landscape
- Traditional concepts of “fit” and ”unfit” are no longer appropriate
- Intensive therapy may not always be the preferred treatment backbone
- Comprehensive fitness assessment and disease biology should guide initial treatment decisions

- Data of all oral therapy with decitabine-cedazuridine plus venetoclax is encouraging (although not without questions of compliance)
- Personalized approach and shared decision-making with our patients is key to realizing the benefits of these newer therapies

Investigator Survey Results

Regulatory and reimbursement issues aside, what initial treatment would you generally recommend for an 80-year-old patient with AML and no actionable mutations who was not eligible for intensive chemotherapy?

 Dr Erba	Azacitidine + venetoclax
 Dr Fathi	HMA + venetoclax
 Dr Lin	Azacitidine + venetoclax
 Dr Perl	Azacitidine + venetoclax
 Dr Stein	Azacitidine + venetoclax
 Dr Cortes	Azacitidine + venetoclax
 Dr DiNardo	HMA + venetoclax
 Dr Wang	Azacitidine + venetoclax

HMA = hypomethylating agent

RTP RESEARCH TO PRACTICE

In general, in what situations, if any, are you partnering oral decitabine (decitabine/cedazuridine) with venetoclax for patients with AML to whom you've decided to administer HMA/venetoclax as initial treatment?

 Dr Erba	Eligible for initial therapy as an outpatient, no infection or DIC, reliable/compliant and able to rapidly obtain oral decitabine/cedazuridine
 Dr Fathi	When more convenient, so often
 Dr Lin	Rarely used outside of a trial; patients who live far away, patients in remission with stable counts/doses who want to travel or live part of the year away from the center
 Dr Perl	I am not generally recommending this off study due to lack of insurance reimbursement and concern for dosing modification challenges in later cycles
 Dr Stein	I do this for cycle 2 and beyond in patients who have achieved a remission
 Dr Cortes	Currently only in clinical trials
 Dr DiNardo	I think this should be the preferred approach. I typically start oral decitabine with cycle #2 (due to reimbursement and obtainment purposes)
 Dr Wang	Achieving benefit from ven/aza but not able to continue to come daily for aza therapy

DIC = disseminated intravascular coagulation

RTP RESEARCH TO PRACTICE

In general, for a patient with AML who is receiving HMA/venetoclax, on how many days do you administer venetoclax during cycle 1 of therapy?
In general, for a patient with AML who is receiving HMA/venetoclax, when do you perform the first bone marrow biopsy?

	Venetoclax administration	First bone marrow biopsy
 Dr Erba	21 days	Day 21
 Dr Fathi	Plan for 28 days	Day 21-23
 Dr Lin	21 days	Day 21
 Dr Perl	21 days	Day 21
 Dr Stein	28 days	Day 21-28
 Dr Cortes	Plan for 28 days	Day 21
 Dr DiNardo	21 days	Day 24-28
 Dr Wang	21 days	Day 21

What is a major toxicity other than cytopenias that you've observed in patients with AML receiving an HMA/venetoclax combination?

 Dr Erba	TLS, hypoxia with pulmonary infiltrates, fungal pneumonia
 Dr Fathi	Not much. Some have GI toxicity. Heart toxicity can be seen but is quite rare
 Dr Lin	GI symptoms in about 30%; rarely joint pain requiring steroids
 Dr Perl	Myelosuppression, infection and GI toxicity; bleeding and mucositis are rare
 Dr Stein	Rarely, patients (often monocytic) can develop a CRS-like syndrome
 Dr Cortes	Nothing of significance
 Dr DiNardo	Neutropenic infections — especially during the first 2 cycles
 Dr Wang	Not seeing any other significant toxicities

TLS = tumor lysis syndrome; CRS = cytokine release syndrome

In what situations, if any, would you currently offer venetoclax-based first-line therapy to a younger, fit patient with AML?

 Dr Erba	Adverse-risk AML as defined by ELN 2022
 Dr Fathi	HMA and venetoclax is acceptable in younger, fit patients with intermediate- or adverse-risk, FLT3-WT AML
 Dr Lin	Clinical trial or adverse-risk disease (eg, TP53, complex cytogenetics)
 Dr Perl	Adverse-risk AML as defined by ELN 2022
 Dr Stein	In a patient with adverse-risk genetics
 Dr Cortes	On clinical trials only at the moment
 Dr DiNardo	ELN 2022 unfavorable disease (complex cytogenetics, MDS-associated mutations, etc)
 Dr Wang	Adverse-risk cytogenetics and/or TP53-mut AML

ELN = European LeukemiaNet; WT = wild type; MDS = myelodysplastic syndromes

RTP RESEARCH TO PRACTICE

What effect, if any, do you expect the plenary presentation of the PARADIGM trial (azacitidine and venetoclax versus conventional induction chemotherapy for fit patients with newly diagnosed AML) will have on current clinical management?

 Dr Erba	More oncologists will adopt ven/HMA for ELN 2022 adverse-risk disease
 Dr Fathi	HMA and venetoclax is acceptable in younger, fit patients with intermediate- or adverse-risk, FLT3-WT AML
 Dr Lin	Many will adopt this, especially for intermediate/high-risk AML proceeding to transplant. This will impact ongoing/planned clinical trials and potentially adjust control arms away from 7 + 3
 Dr Perl	Much less 7 + 3 will be given for ELN 2022 adverse-risk AML and perhaps generally in patients who plan to proceed to transplant in CR1
 Dr Stein	More physicians will use aza/ven for patients with adverse risk around the age of 60-65 and above
 Dr Cortes	I expect some use in general practice but not full adoption. It may allow for more patients treated in the community
 Dr DiNardo	In the US, I think it will lead to a substantial increase in the number of patients “induced” with HMA + ven, often in their local community practice
 Dr Wang	May lead to clinicians offering fit patients with adverse-risk AML induction with HMA/ven instead of SOC 7 + 3

SOC = standard of care

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Up-Front Therapy for Older Patients with Acute Myeloid Leukemia (AML) — Dr Lin

Module 2: Selection of Therapy for Younger Patients with AML without a Targetable Mutation; Promising Investigational Strategies — Dr Perl

Module 3: Role of FLT3 Inhibitors in AML Management — Dr Erba

Module 4: Incorporation of IDH Inhibitors into the Care of Patients with AML — Dr Fathi

Module 5: Current and Future Role of Menin Inhibitors in the Treatment of AML — Dr Stein

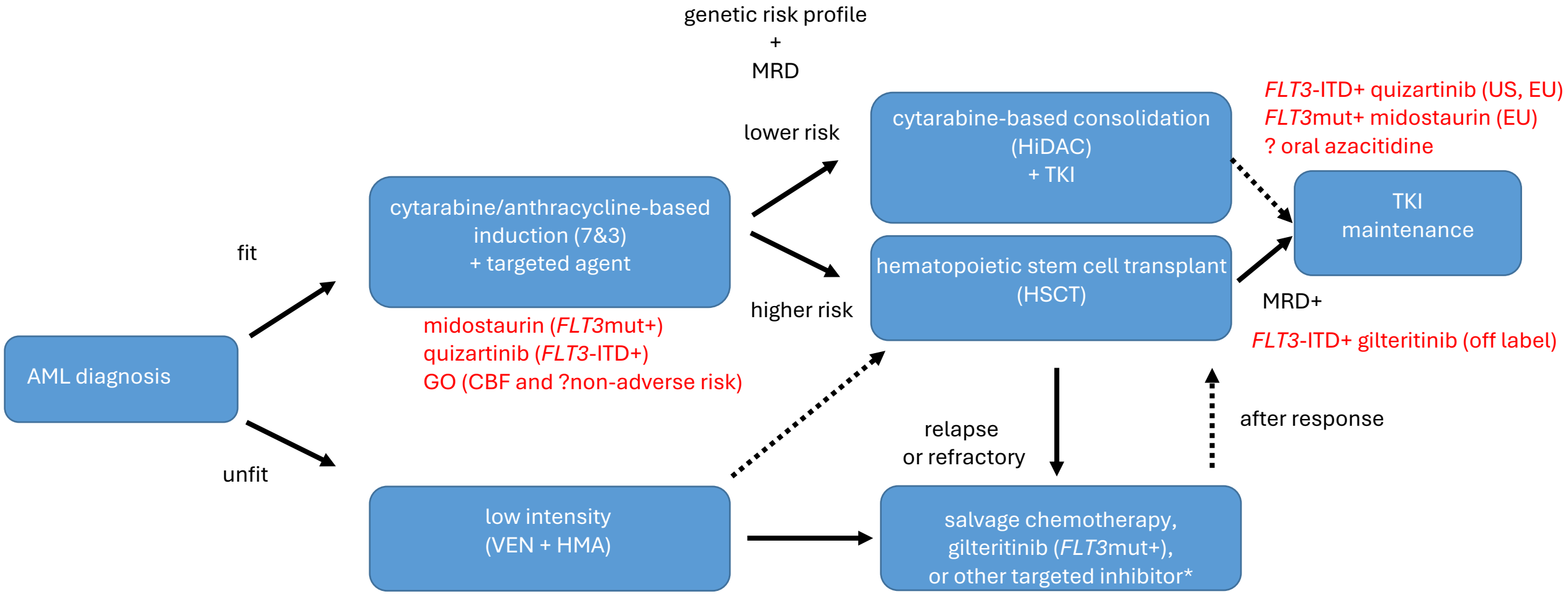
Selection of Therapy for Younger Patients with AML without a Targetable Mutation; Promising Investigational Strategies

Alexander Perl, MD
Leukemia Program, Abramson Cancer Center
Associate Professor
University of Pennsylvania, Perelman School of Medicine

Research To Practice ASH Friday Satellite
December 5, 2025

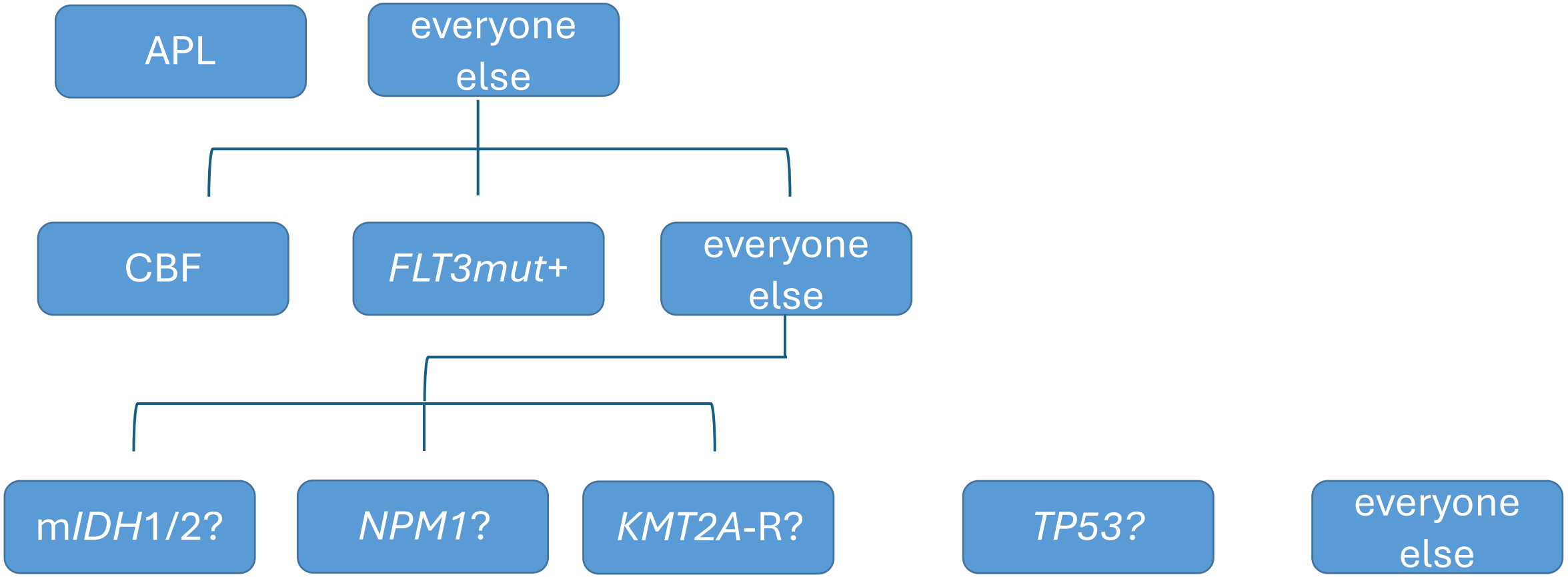
Penn
University of Pennsylvania

The current treatment approach for AML

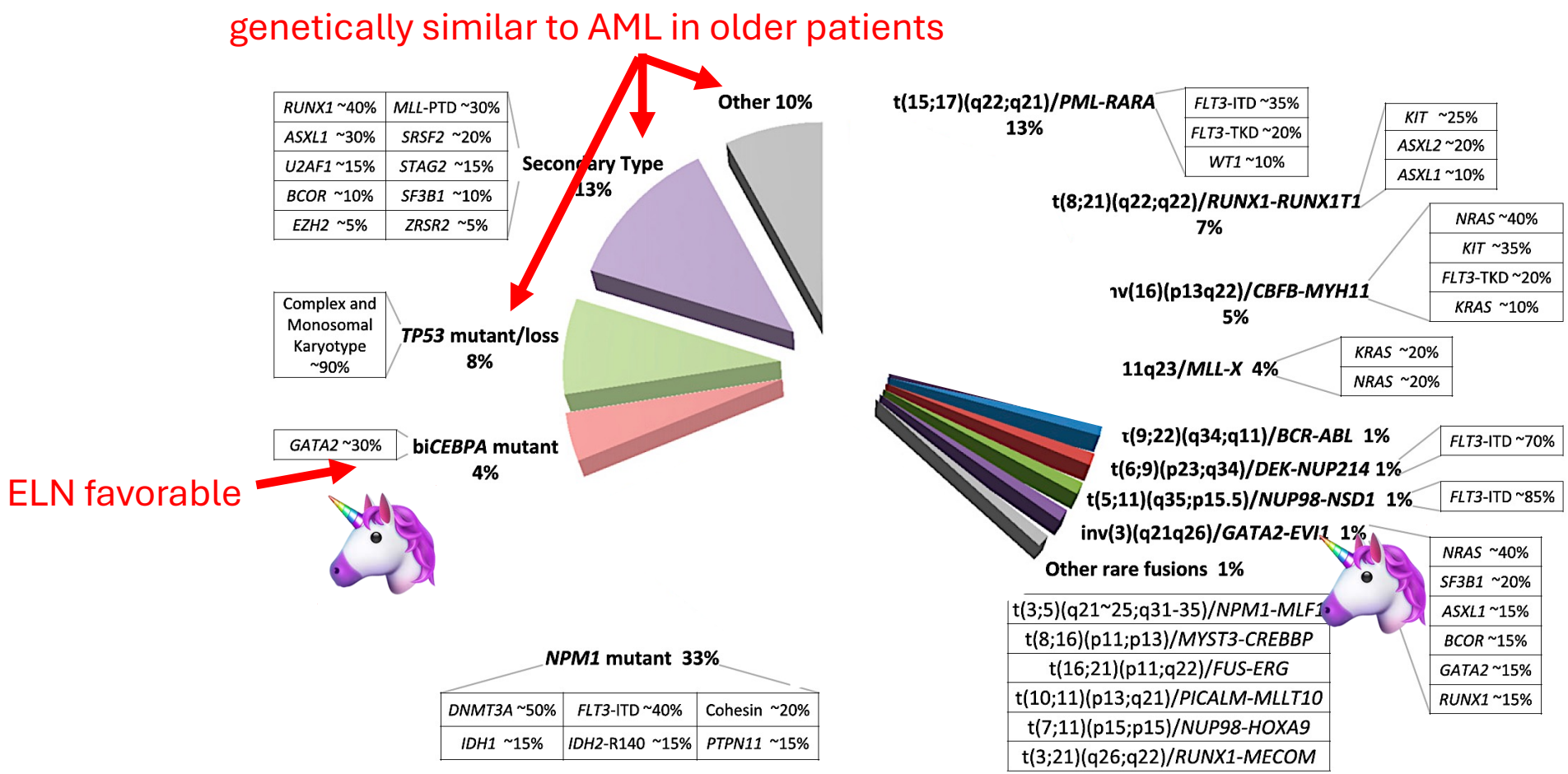


*other approved targeted agents in R/R AML: enasidenib (*IDH2*+), ivosidenib or olutasidenib (*IDH1*+), revumenib or ziftomenib (*KMT2A*-R and/or *NPM1*+)

Marker Negative—how do we define this?!?



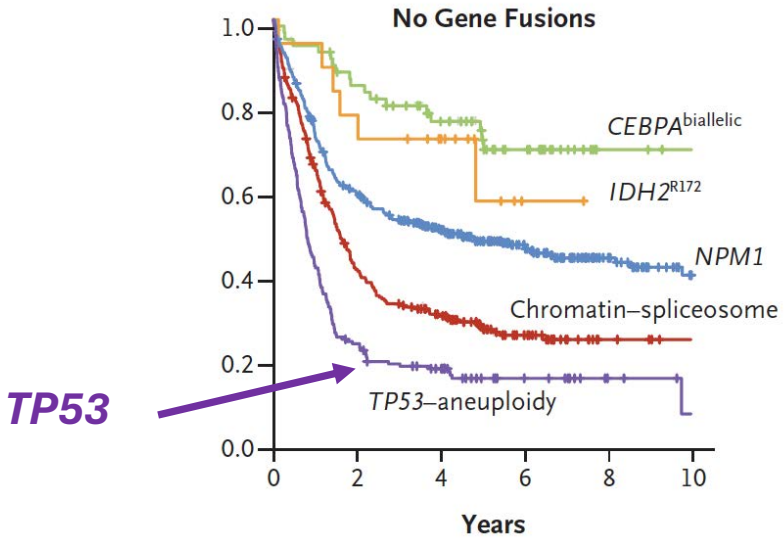
Which AML subsets really need 7&3 alone?



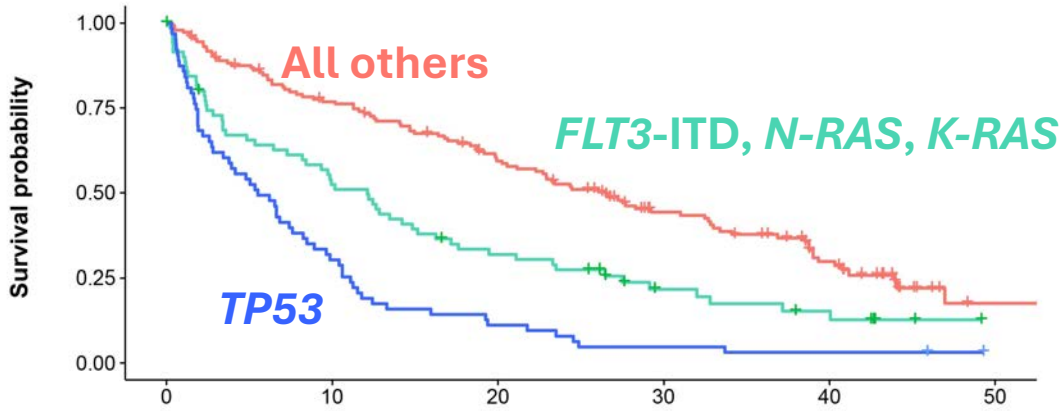
Grimwade D, et al. Blood. 2016 Jan 7;127(1):29-41

AML with mutated *TP53*

Intensive chemotherapy



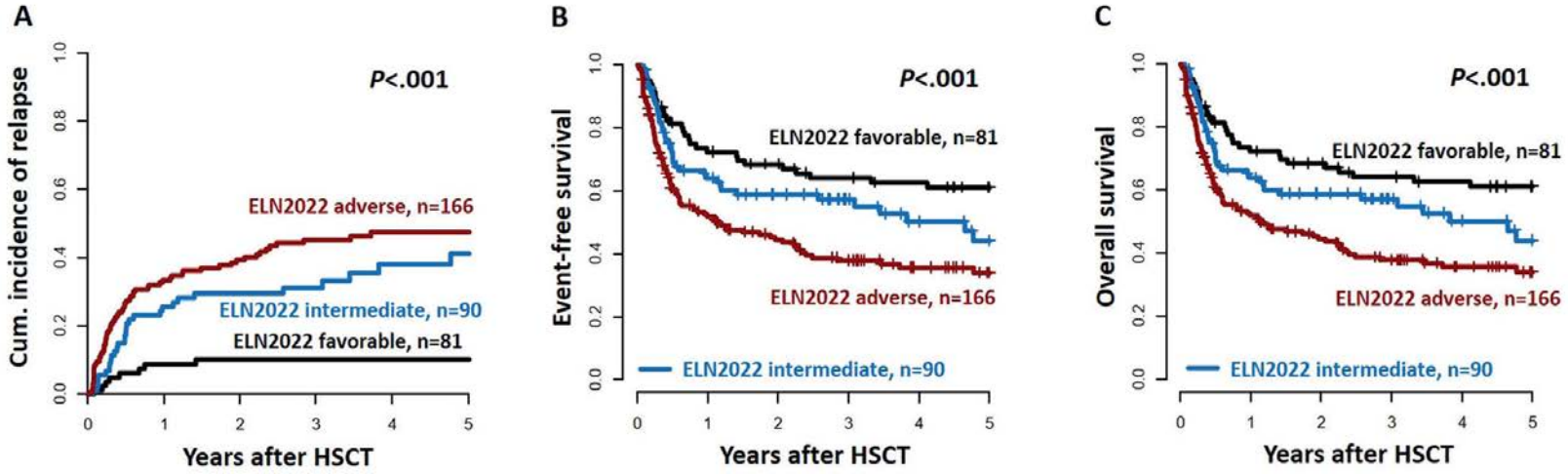
Venetoclax + azacitidine



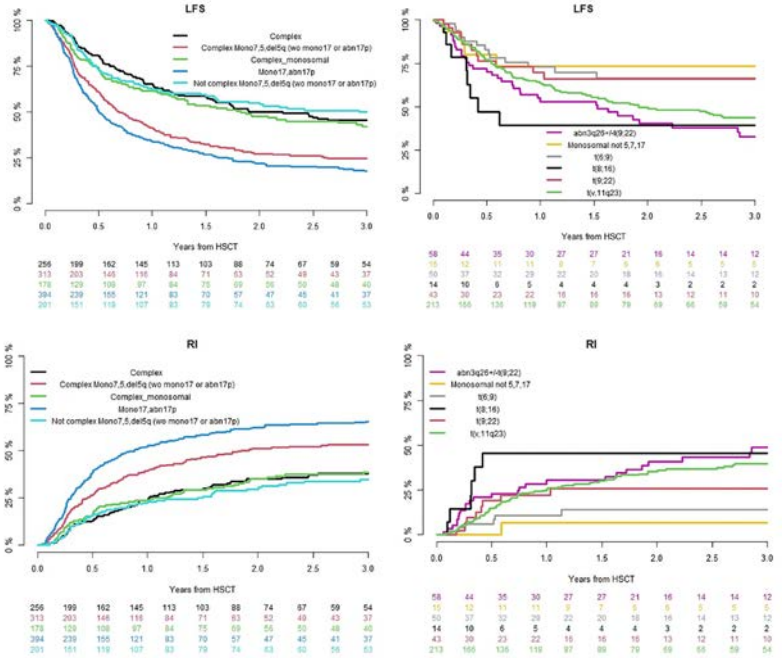
- Most *TP53* AML data come from older patients
  - no satisfactory treatment approach has been identified
  - *TP53*+ identifies patients with poor survival to 7&3 as well as ven/aza
  - transplant for TP53 consistently shows poor LFS and OS
  - no targeted agent has improved the OS of *TP53*+ AML
- *TP53*mut+ AML has strong association with complex karyotype and autosomal monosomies, esp. Chr 5 & 7
  - del5q and abnormal 17p also associated with *TP53* mutation
  - when the above karyotype is seen and/or if VAF is >25%, prognosis is even worse

Papaemmanuil E, et al. N Engl J Med. 2016 Jun 9;374(23):2209-2221.
Döhner H, et al. Blood. 2024 Nov 21;144(21):2211-2222

HSCT for Intermediate/Adverse Risk AML

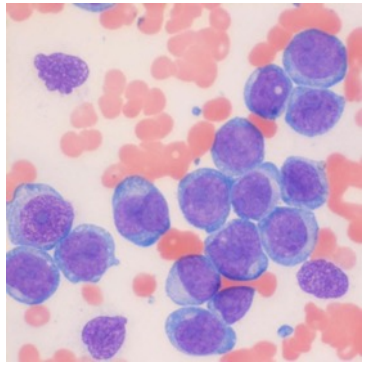


- Transplant is the preferred strategy for non-favorable risk AML
  - widening donor options & improved GVHD prevention/treatment
  - best frontline = whatever is most likely to bridge to HSCT
- Recent EBMT retrospective registry (n=1735, median age 56) shows diverse outcomes of HSCT for ELN2022 adverse cytogenetic risk
  - cure rate ~50% for most
  - worse LFS/OS if complex karyotype or monosomal with del5q, -5, -7, or abnormal 17p
- Data on HMA/VEN vs. IC prior to HSCT to be presented at ASH 2025 (Claiborne J, et al. Sat 12/6/25 #44 9:45-10AM)



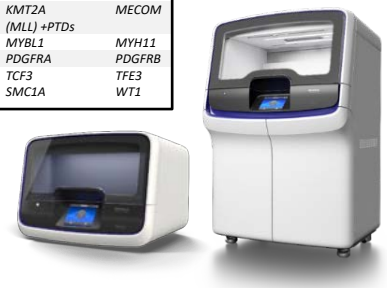
Jentzch M, et al. Blood Cancer J. 2022 Dec 19;12(12):170
Bazarbachi A, et al. Am J Hematol. 2025 Aug;100(8):1374-1386.

NCI Precision Medicine Initiative: MyeloMATCH



Newly diagnosed AML

DNA hotspots				
ABL1	*ANKRD26*	*BRAF*	*CBL*	*CSF3R*
DDX41	*DNMT3A*	*FLT3*	*GATA2*	*HRAS*
IDH1	*IDH2*	*JAK2*	*KIT*	*KRAS*
MPL	*MYD88*	*NPM1*	*NRAS*	*PPM1D*
PTPN11	*SETBP1*	*SF3B1*	*SMC1A*	*SMC3*
SRSF2	*U2AF1*	*WT1*		
DNA Full Gene				
ASXL1	*BCOR*	*CALR*	*CEBPA*	*ETV6*
EZH2	*IKZF1*	*NF1*	*PHF6*	*PRPF8*
RB1	*RUNX1*	*SH2B3*	*STAG2*	*TET2*
TP53	*ZRSR2*			
RNA Fusion Driver Genes				
ABL1	*ALK*	*BCL2*	*BRAF*	*CCND1*
CREBBP	*EGFR*	*ETV6*	*FGFR1*	*FGFR2*
FUS	*HMGA2*	*JAK2*	*KMT2A (MLL) +PTDs*	*MECOM*
MET	*MLLT10*	*MLLT3*	*MYBL1*	*MYH11*
NTRK3	*NUP214*	*NUP98*	*PDGFRA*	*PDGFRB*
RARA	*RBM15*	*RUNX1*	*TCF3*	*TFE3*
BAALC	*MECOM*	*MYC*	*SMC1A*	*WT1*



- Platform: Ion Torrent™ Genexus™ System
  - 45 DNA genes and 35 fusion driver genes
  - Includes 28/30 (93.3%) genes mutated with >=3% frequency in AML.
  - Includes 36/50 (72%) genes mutated with >1% frequency in AML.
  - Includes 779 unique fusions reported in AML
  - Can detect FLT3-ITD up to 120bp
- Can detect all genetic alterations needed for
  - WHO classification of AML, except inv 3
  - NCCN/ELN risk stratification, except inv 3

- 3-day genotyping/risk stratification
- Rational allocation to randomized trial with novel agents
  - targeted agent when present
  - genetic risk-specific if not
- Trial registration for all stages of therapy
- Correlative science in top academic labs including flow MRD and Twinstrand NGS MRD

http://imagebank.hematoloqv.org/image/61433/aml-circulating-blasts

Master Screening and Reassessment Protocol (MSRP)

Initial treatments for newly diagnosed patients

Tier 1 Treatment Trials

Older Adult
MDS
Young Adult

MSRP Reassessment 1

Trials designed to evaluate patients in CR using MRD-based assignments

or

Tier 2 Treatment Trials (MRD)

Older Adult
MDS
Young Adult

MSRP Reassessment 2

Trials designed to evaluate patients using MRD-based assignments

or

Tier 3 Treatment Trials (Transplant/Cellular Therapy)

Transplant/ Cellular Therapy

MSRP Reassessment 3

Participants with low disease burden states: trials designed to validate clinical utility of NGS and other assays

Tier 4 Treatment Trials (NGS)

Clinical Utility
Assay Validation
studies

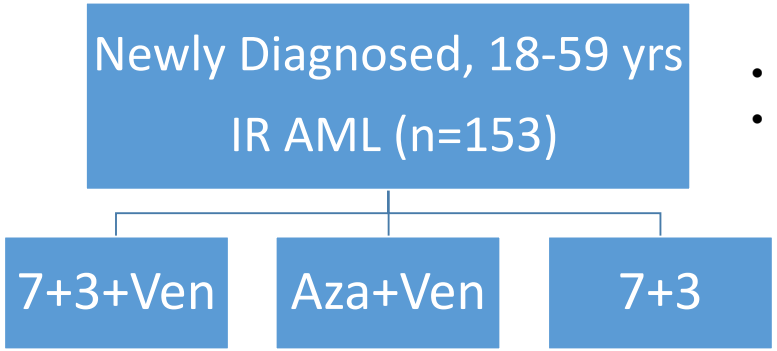
High Disease Burden

Low Disease Burden

Slide courtesy of Harry Erba, MD, PhD

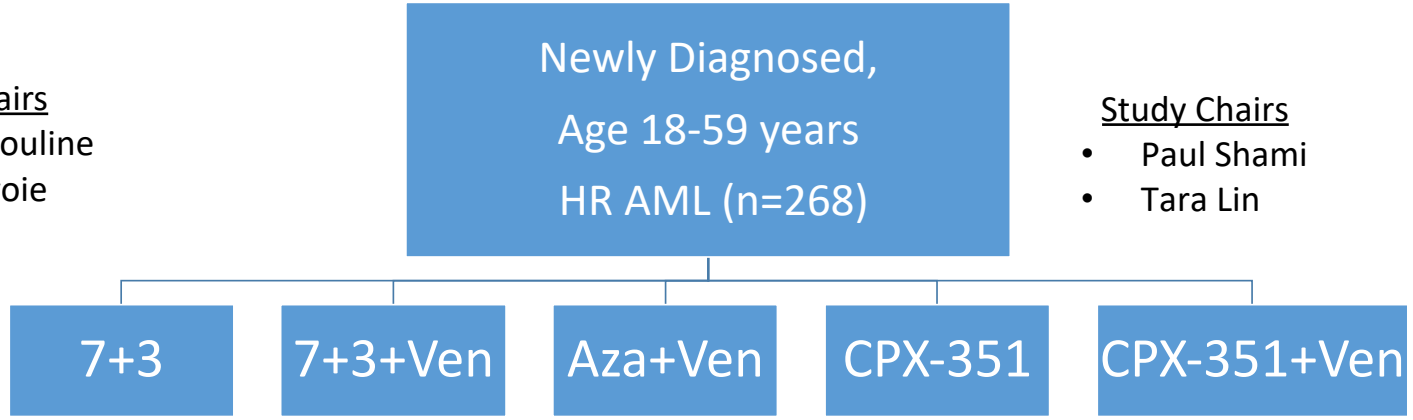
Myelomatch “marker negative” studies

Intermediate Risk AML: MM1YA-CTG01



Study Chairs
- Sarit Assouline
- Lynn Savoie

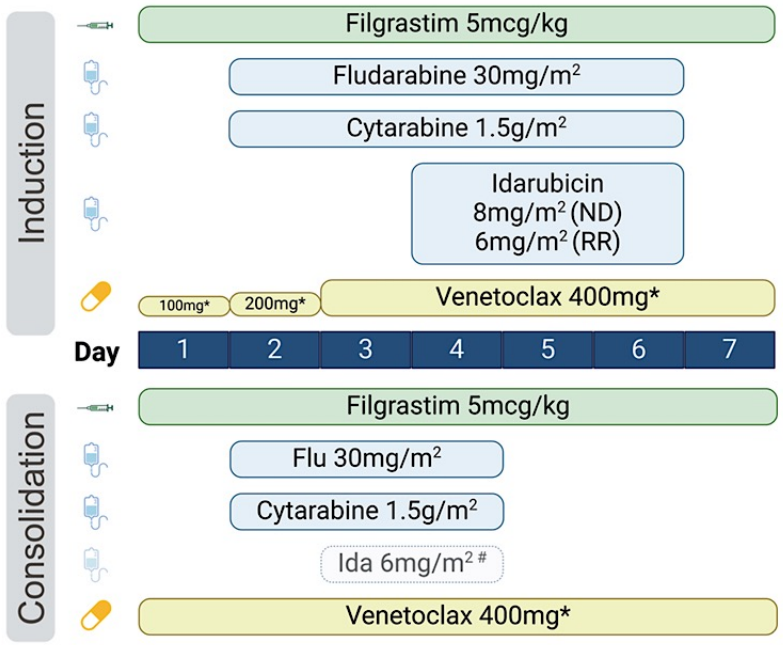
High Risk AML: MM1YA-S01

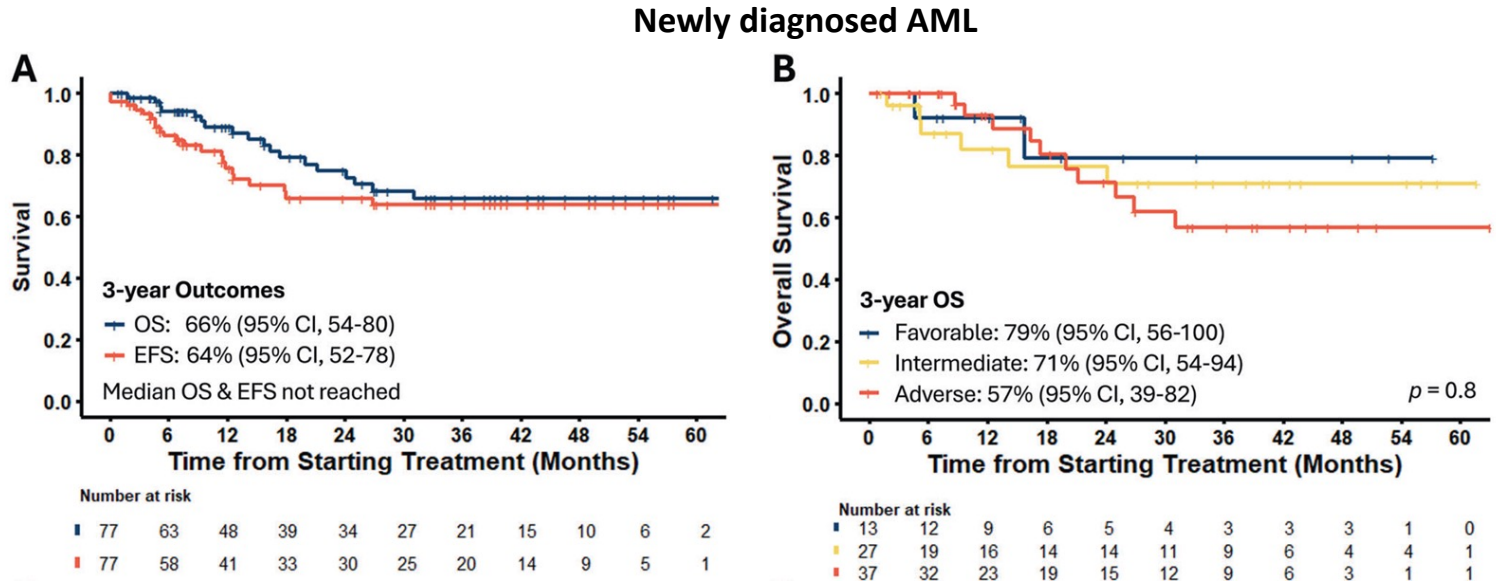


Study Chairs
- Paul Shami
- Tara Lin

ASH 2025: first randomized study to compare IC to ven + IC or VEN + HMA: Fang Q, et al. #650 Sun. 12/7 4:45-5PM

VEN-FLAG-IDA



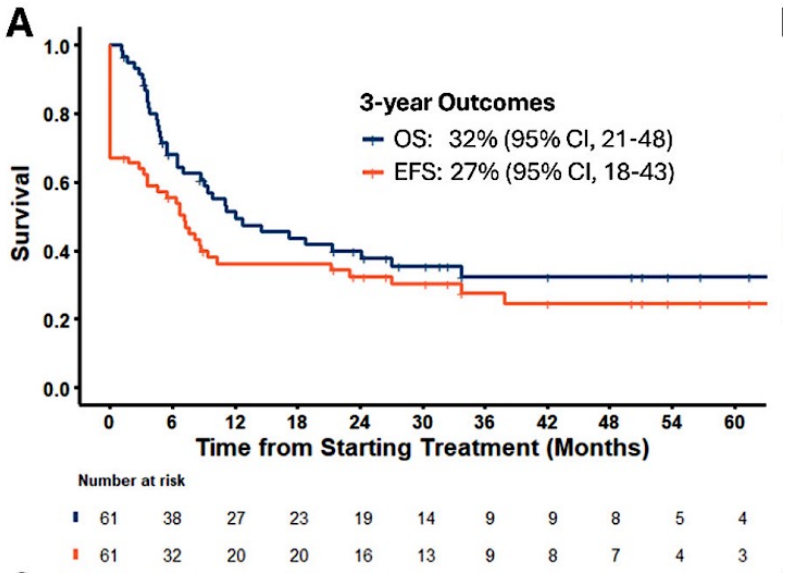


- highly intensive regimen, best suited for younger adults
  - e.g. age <40, very fit
- Very high CRc (95%) and flow MRD(-) CR rates (90% of CRc) in ND AML
  - prolonged thrombocytopenia very common (C2 and onward)
- no obvious survival differences by ELN2022
  - 64% of patients transplanted in CR1
  - but also no long-term survivors reported among *TP53*+ or *MECOM*-rearranged (combined n= 10)

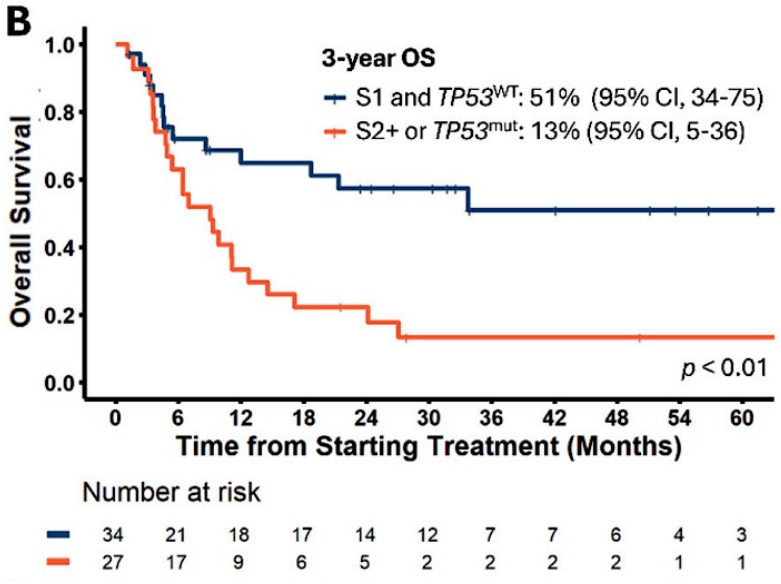
DiNardo CD, et al. Leukemia 2025 Apr;39(4):854-863

VEN-FLAG-IDA – R/R AML

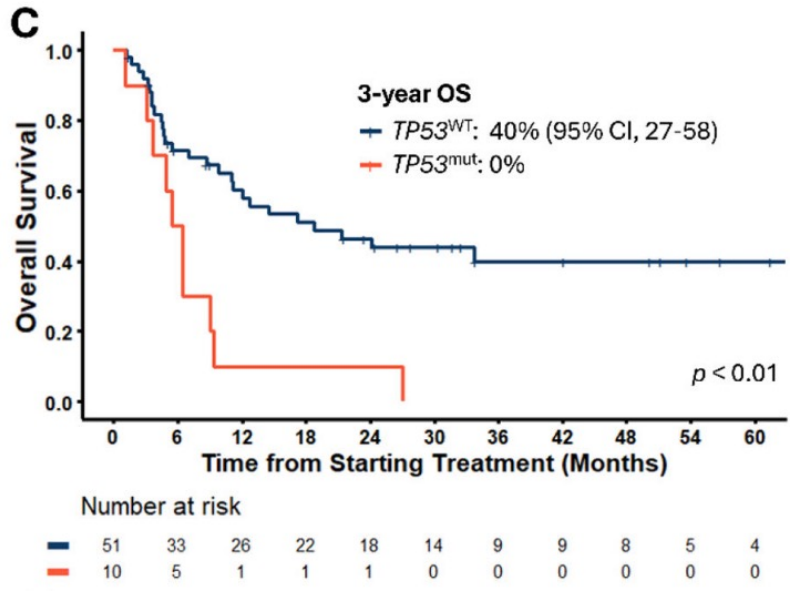
All Patients



Salvage Number/TP53 Status



$TP53^{WT}/TP53^{mut}$

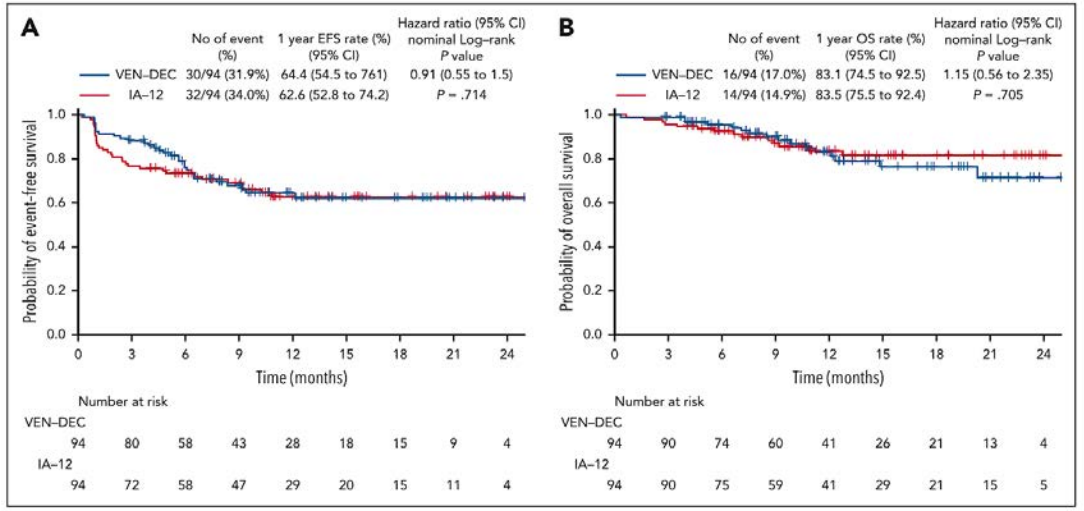


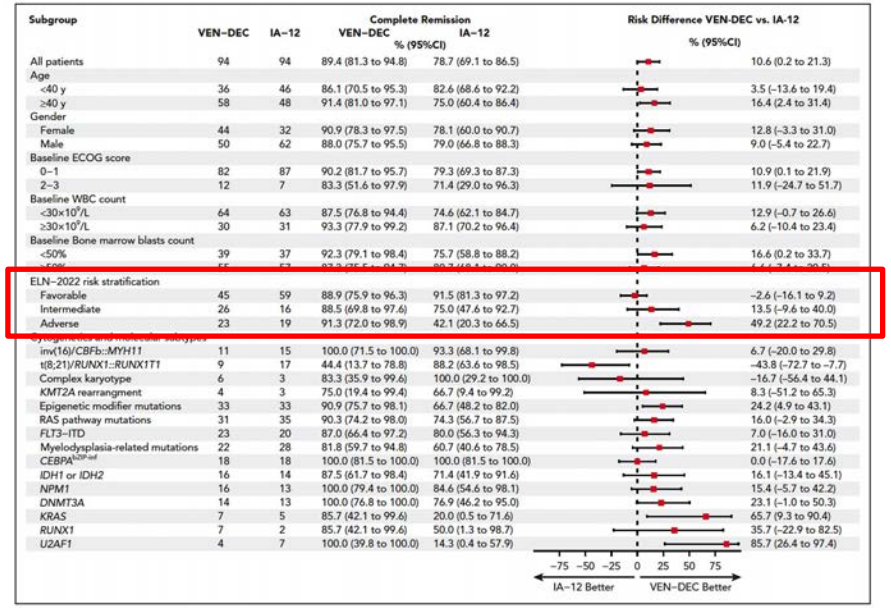
- OS of first salvage TP53-WT was similar to frontline therapy
- In the RR cohort, CRc=64%, and CRc=74% for first salvage TP53-WT patients

DiNardo CD, et al. Leukemia 2025 Apr;39(4):854-863

Prospective comparison of HMA-VEN and IC

Variable	VEN-DEC group (n = 94)		IA-12 group (n = 94)		Treatment difference (95% CI)*	P Value
	No./total no.	% (95% CI)	No./total no.	% (95% CI)	% points	
Best response for induction therapy						
CRc	84/94	89 (81-95)	74/94	79 (69-87)	10.6 (0.2-21.3)	.0021†
CR	78/94	83 (74-89)	74/94	79 (69-87)	4.3 (7.1-15.6)	—
CRi	6/94	6 (3-13)	0	—	6.4 (2.3-13.2)	—
MRD negative‡	67/84	80 (70-88)	56/74	76 (64-85)	4.1 (−8.9 to 17.3)	.085†
Overall remission	89/94	95 (88-98)	90/94	96 (90-98)	−1.1 (−8.2 to 5.8)	1.0§
Median time to first remission (95% CI), d	43 (39.9-46.1)		38 (35.3-40.7)		—	.26‖





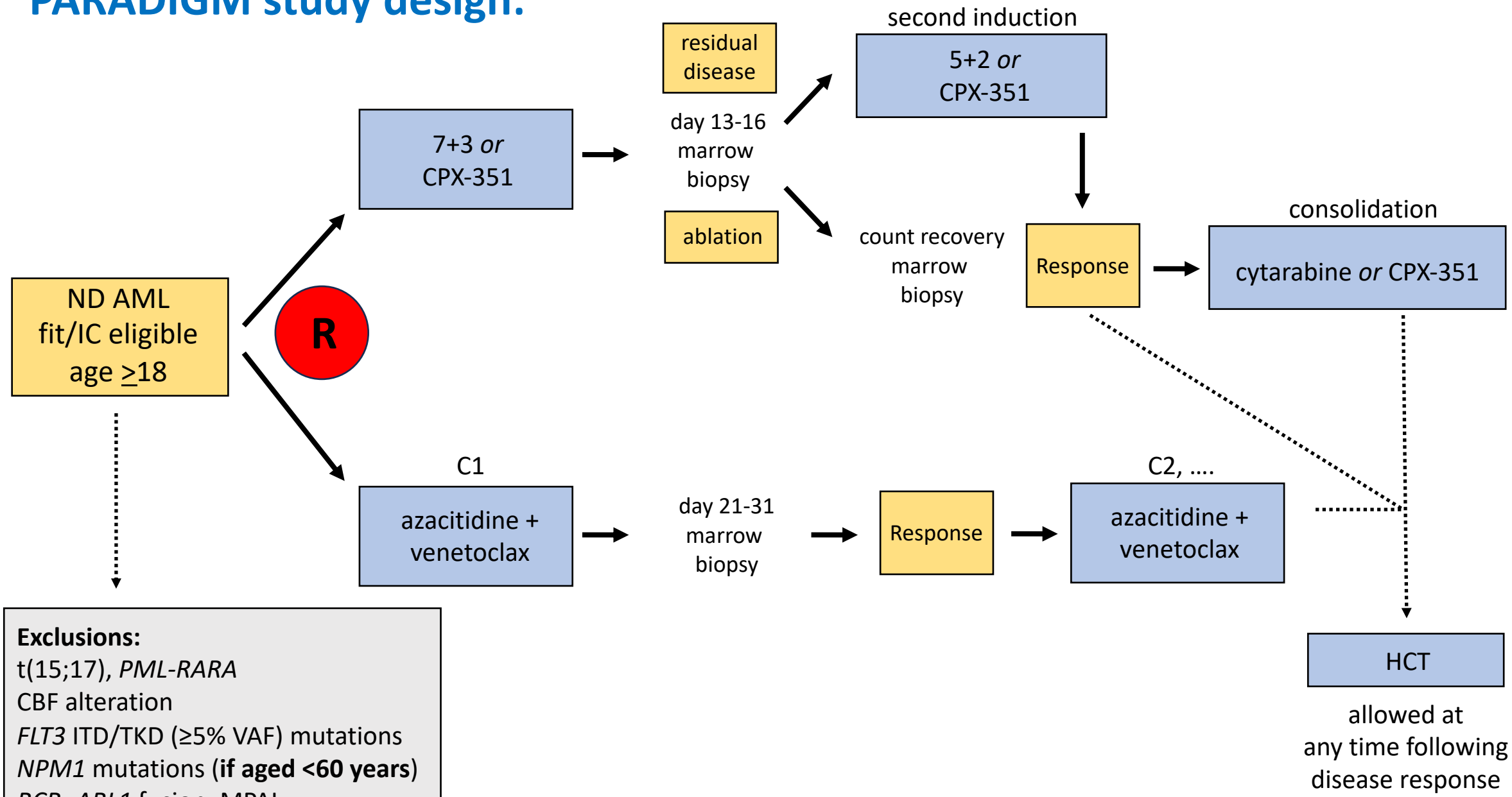
- 188 fit adults with ND AML age 18-59 (all genotypes)
- randomized 1:1 to ven + decitabine (5 days) x 1-2 cycles vs. 7&3 (ida/ara) x 1-2
  - both arms consolidated with HiDAC (2 gm/m2 x 6 doses for 1-4 cycles)

- Primary endpoint: CRc rate after induction (non-inferiority design)
  - CRc rate higher with ven + decitabine (p=0.021);
  - CR, MRD(-), and CR1 transplantation rates similar

- Safety/tolerability favors ven-decitabine over IC
  - early mortality (ven-dec 1% vs IC 4%)
  - ≥Gr3 infections (ven-decitabine 30% vs IC 67%, p<0.01)
  - less ≥Gr3 thrombocytopenia (13 vs. 19 days); similar days of ≥Gr3 neutropenia

Lu J, et al. Blood 2025 May 29;145(22):2645-2655

PARADIGM study design:



Exclusions:
t(15;17), *PML-RARA*
CBF alteration
FLT3 ITD/TKD (≥5% VAF) mutations
NPM1 mutations (**if aged <60 years**)
BCR::ABL1 fusion, MPAL
prior HMA

ASH 2025 Plenary session, Fathi AT, et al. #6 12/7 3:45-4PM

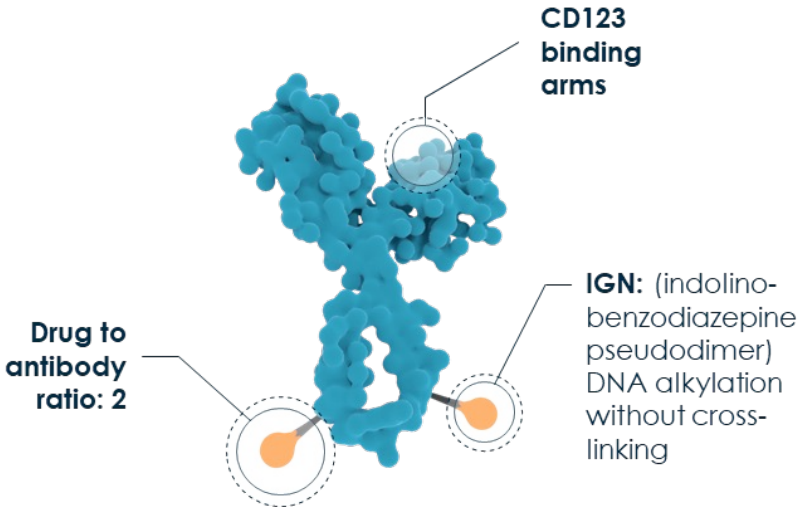
NCT04801797

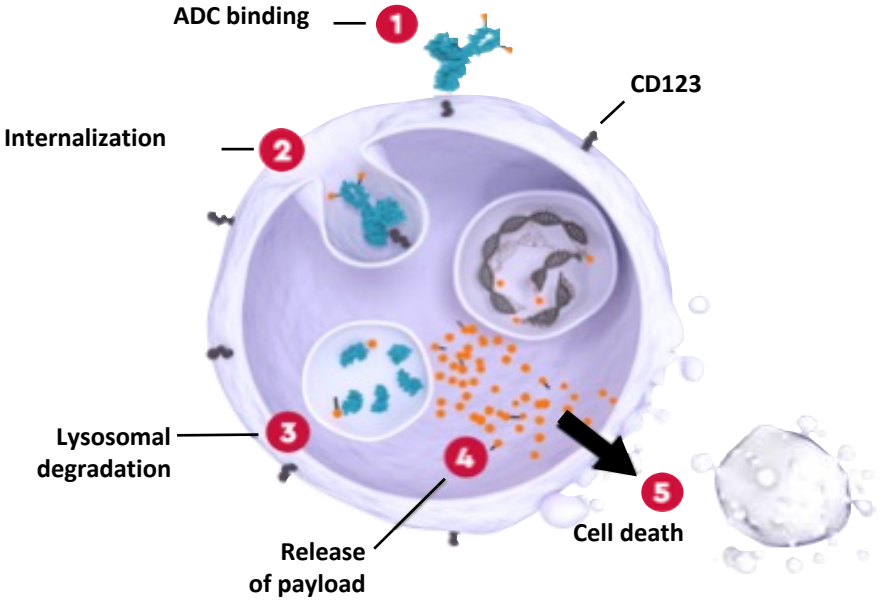
PARADIGM Results:

- As of 7/25/2025, 172 patients (pts) at 9 US centers were randomized to aza-ven (n=86) or IC (n=86)
- Intent-to-treat analysis:
  - ORR (OR=CR+CRh+CRi+PR+MLFS) was significantly higher in the aza-ven arm (88% vs 62%; P<0.001)
  - CCR (CR+CRh+CRi) was significantly higher in the aza-ven arm (81% vs 55%; p<0.001)
  - CR rates for aza-ven and IC were not significantly different (59% vs 50%; p=.066)
- Primary EFS endpoint (median follow-up 16 months):
  - 1-year EFS was 53% for the aza-ven arm and 39% for the IC arm (HR 0.61; p=0.017)
- Procession to HCT following response from protocol therapy differed across arms (p=0.009)
  - 52 (61%) pts on aza-ven arm and 34 (40%) pts on IC arm
- Grade 3/4 lung infections and sepsis occurred in 12% and 7% of aza-ven, and 15% and 11% of IC pts
- 30- and 60-day mortality rates on the aza-ven arm were both 0%, vs 3.5% and 4.7% in the IC arm, respectively

ASH 2025 Plenary session, Fathi AT, et al. #6 12/7 3:45-4PM

Pivekimab sunirine (PVEK) in AML





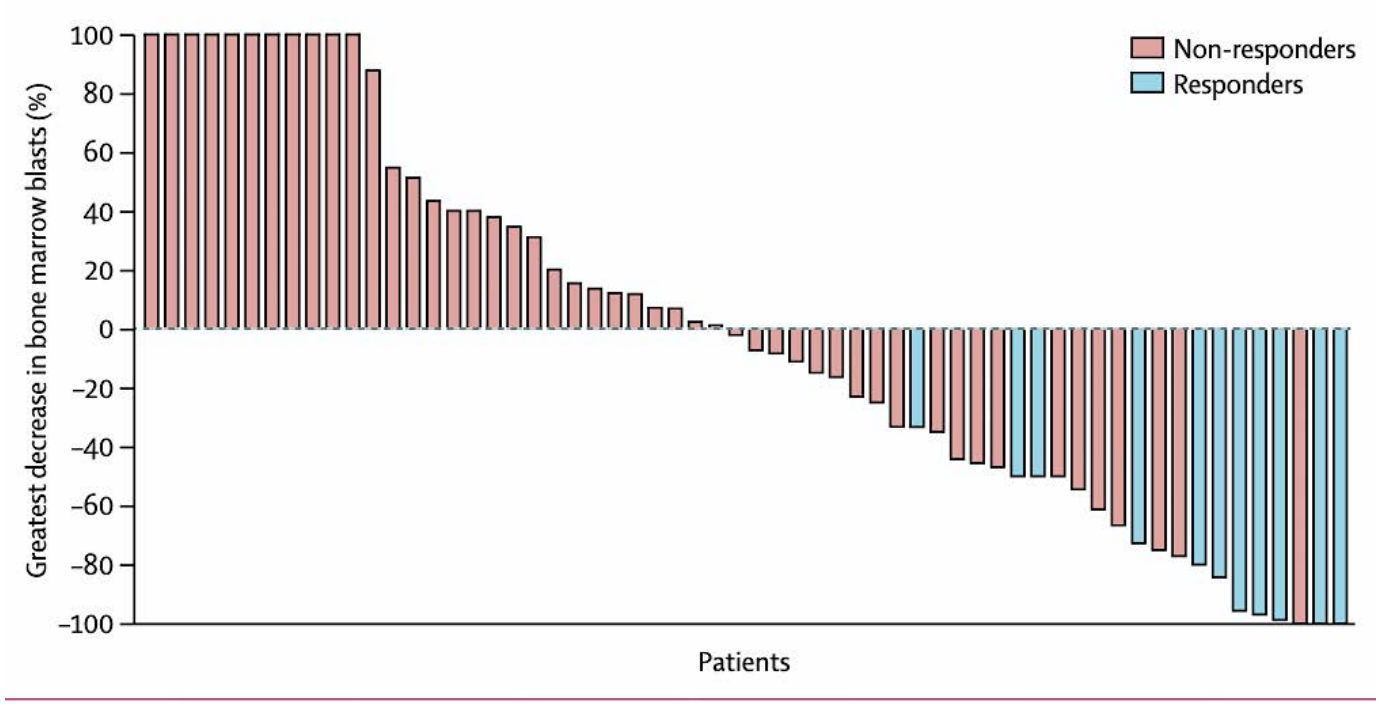
- ADC targeting CD123 (IL-3Rα)
- >90% of AML samples overexpress CD123
- single agent data in R/R AML show clinical activity without substantial myelosuppression (CR/CRi/CRp= 16%)
  - thrombocytopenia was the only Gr≥3 AE seen in ≥10% of patients
  - small risk of VOD/SOS (2/68=3% during ph1)
  - Gr1-2 peripheral edema common (25% in Ph1) but not capillary leak syndrome
- Ongoing studies:
  - ND unfit/older patients with VEN/AZA (Daver N, et al. ASH 2025 #651, Sunday 12/7 5-5:15PM)
  - ND in fit adults with ELN 2022 adverse risk AML combined with FLAG-IDA (Appelbaum J, et al. ASH 2025 #3422 Sunday 12/7 poster session)
  - frontline or R/R BPDCN (Pemmaraju N, et al. ASH 2025 #5195 Monday 12/8 poster session)

figure courtesy of Naval Daver

Daver NG, et al. *Lancet Oncol.* 2024 Mar;25(3):388-399.

Pivekimab sunirine (PVEK) in AML

Response in Patients Receiving Schedule A (once every 3 weeks, on day 1 of a 3-week cycle)



	All participants in schedule A* (n=68)	Recommended phase 2 dose cohort (n=29)
Overall response rate, n (%; 95% CI)	11 (16%; 8–27)	6 (21%; 8–40)
Best overall response†		
Complete remission	2 (3%)	1 (3%)
Complete remission with partial haematological recovery	2 (3%)	1 (3%)
Complete remission with incomplete recovery	4 (6%)	3 (10%)
Morphological leukaemia-free state	2 (3%)	1 (3%)
Partial remission	1 (1%)	0
Stable disease	35 (51%)	17 (59%)
Progressive disease	16 (24%)	5 (17%)
Composite complete remission rate, n (%; 95% CI)	8 (12%; 5–22)	5 (17%; 6–36)
Median duration of remission, months	2·0 (1·0–3·6)	2·6 (0·7–NE)
Median duration of composite complete remission, months	2·2 (1·0–3·6)	2·3 (1·6–NE)

Daver NG, et al. *Lancet Oncol.* 2024 Mar;25(3):388-399.

Pivekimab sunirine (PVEK) with VEN/AZA in ND AML

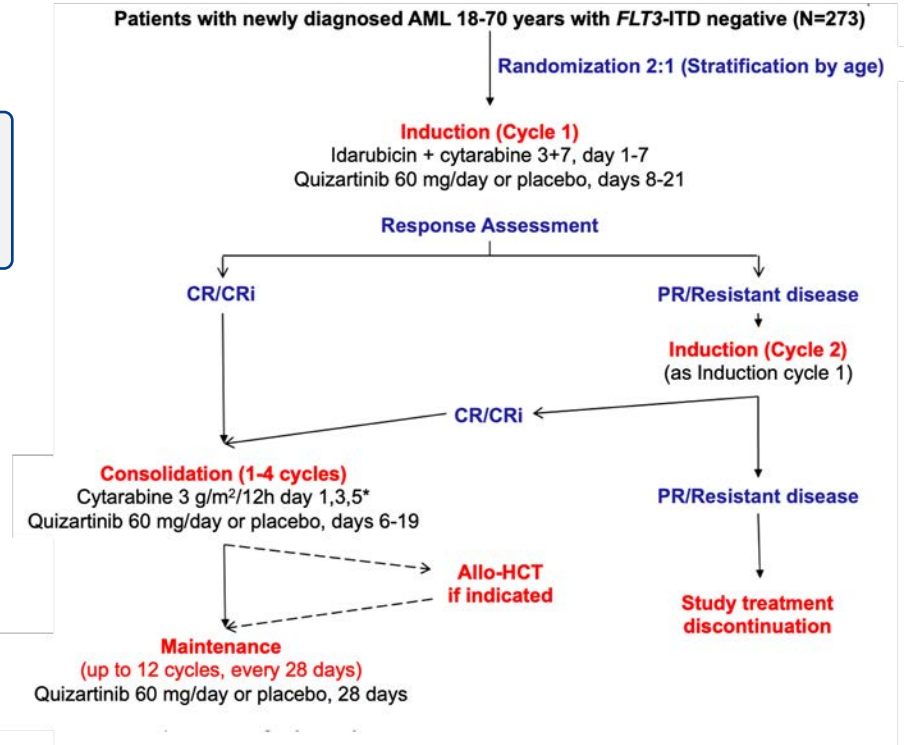
- Dose expansion phase of an ongoing, Phase 1b/2 study of 1L PVEK+VEN+AZA in unfit adults with AML deemed CD123-positive by investigator
- Unfit pts were aged ≥75 years (yr), or aged <75 yr with ECOG PS score 2–3, or ≥1 defined comorbidity
- Pts received PVEK (0.045 mg/kg, intravenous [IV]) on D7 and VEN (400 mg equivalent, oral) daily in a 28-D cycle (cohort 1 received ≥14 D of VEN; cohort 2 received 28 D of VEN) and AZA (up to 75 mg/m2, subcutaneous or IV) on D1–7
- With a median follow-up of 10 mo:
  - CR: 63.3%
  - CR/CRi: 79.6%
  - CR/CRh: 73.5%
- Of pts who achieved CR or CR/CRi with an MRD-evaluable sample, 92% (23/25) and 90% (27/30) achieved flow cytometry MRD negativity (<0.1%) respectively
- The most common (≥50% of pts) any grade treatment-emergent adverse events (AEs) were neutropenia/neutrophil count decreased and thrombocytopenia/platelet count decreased (both 69%); constipation (61%); and peripheral edema (51%)

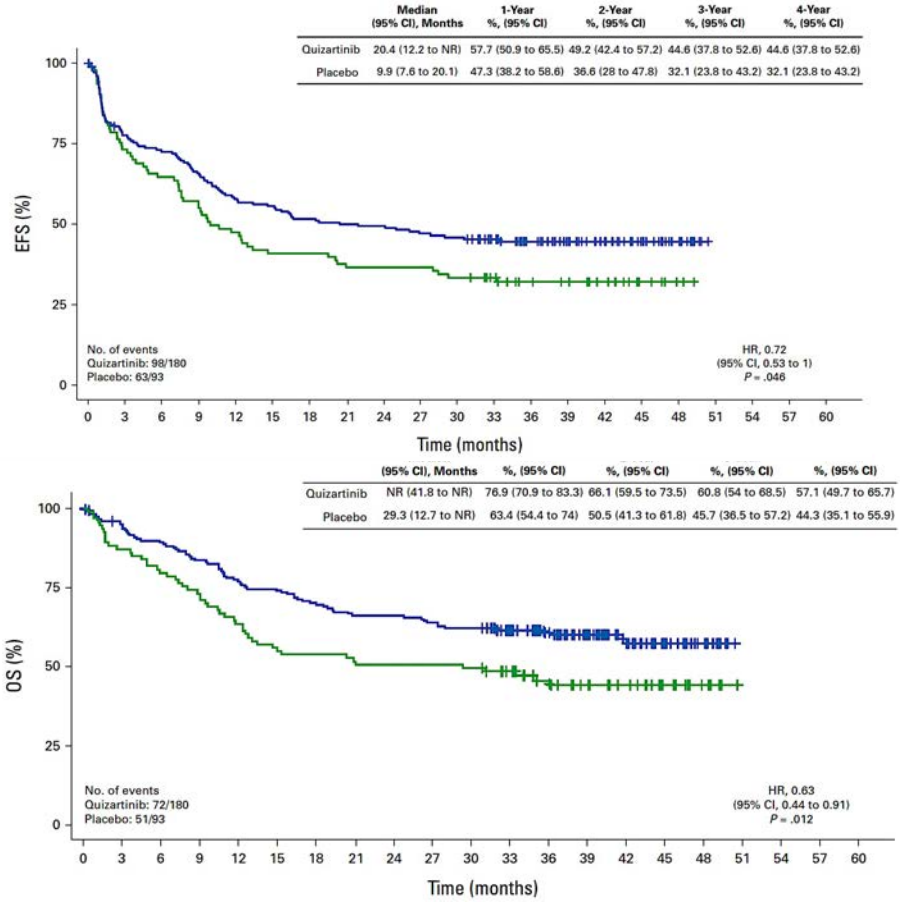
Daver N, et al. ASH 2025 #651, Sunday 12/7 5-5:15PM

QuiWI study

- 18-70 years of age
- ECOG <3
- Newly diagnosed *FLT3*-ITD negative AML (ratio <0.03)
- *FLT3*-ITD centrally screened (PCR)
- Patients begin 7+3 chemotherapy during screening

Selected endpoints
- **Primary endpoint**: EFS
- **Secondary endpoints**: OS, CR/CRc, Safety
- **Exploratory endpoints**: RFS, DoCR





- median f/u= 39 months
- EFS and OS significantly longer with quizartinib
  - Principal group benefitted: *NPM1*+ (quiz 3-year OS = 90% vs. 71%)
  - No survival benefit in ELN adverse group
  - OS benefit over placebo maintained even among patients who did not receive HSCT
- Phase 3 now underway (Quantum Wild, NCT06578247)

Montesinos P, et al. *J Clin Oncol* 2025 (epub, online)

Conclusions

- Rapid integrated genomics now risk stratify patients within days
  - NCI Myelomatch program brings this approach to the masses

- If no molecular therapeutic target is found, prognosis is dependent upon:
  - presence of favorable markers (e.g CEBPA bZIP in-frame indel mutations)
  - absence of *TP53* mutation
  - The ultimate goal is HSCT for non-favorable risk patients and/or patients who remain MRD+ after 2 cycles of IC or up to 4 cycles of aza/ven

- Several novel approaches show promise:
  - adding venetoclax to HMA or intensive (or highly intensive) chemotherapy
  - novel ADCs (PVEK) or signaling inhibitors (quizartinib) may achieve similar gains to much more intensive regimens and warrant prospective randomized comparisons

Investigator Survey Results

Regulatory and reimbursement issues aside, which initial treatment would you generally recommend for a 35-year-old patient with AML and a TP53 mutation with a variant allele frequency (VAF) of 55% and complex karyotype who was eligible for intensive chemotherapy?

 Dr Erba	Decitabine + venetoclax
 Dr Fathi	HMA + venetoclax (no preference for HMA)
 Dr Lin	Azacitidine + venetoclax
 Dr Perl	Azacitidine + venetoclax
 Dr Stein	Azacitidine + venetoclax
 Dr Cortes	Azacitidine + venetoclax
 Dr DiNardo	Oral decitabine (decitabine/cedazuridine) + venetoclax
 Dr Wang	HMA + venetoclax (no preference for HMA)

Regulatory and reimbursement issues aside, what initial treatment would you generally recommend for a 55-year-old patient with intermediate-risk secondary AML and no actionable mutations who was eligible for intensive chemotherapy?

 Dr Erba	CPX-351
 Dr Fathi	CPX-351 or HMA + venetoclax
 Dr Lin	CPX-351
 Dr Perl	Azacitidine + venetoclax
 Dr Stein	CPX-351
 Dr Cortes	CPX-351
 Dr DiNardo	If this patient has not received a prior HMA or ven regimen, then I would prioritize oral decitabine (decitabine/cedazuridine) + ven, followed by ASCT
 Dr Wang	CPX-351

RTP RESEARCH TO PRACTICE

Would you use venetoclax-based therapy for a younger, fit patient whose disease had relapsed after 7+3 chemotherapy followed by ASCT? If yes, what would you most likely combine with venetoclax?

 Dr Erba	Yes, azacitidine or FLAG-IDA
 Dr Fathi	Yes, decitabine or oral decitabine (decitabine/cedazuridine)
 Dr Lin	Yes, azacitidine
 Dr Perl	Yes, azacitidine
 Dr Stein	Yes, azacitidine
 Dr Cortes	Yes, HMA
 Dr DiNardo	Yes, oral decitabine (decitabine/cedazuridine)
 Dr Wang	Yes, azacitidine (+ targeted therapy if applicable)

RTP RESEARCH TO PRACTICE

What future role do you see for pivekimab sunirine in the management of AML?

 Dr Erba	As an option in relapsed disease unless survival benefit is demonstrated for treatment-naïve disease in transplant-ineligible patients, then in combination with ven/HMA
 Dr Fathi	Intriguing data with HMA/ven for intermediate, adverse-risk, non-P53-mutated disease
 Dr Lin	Preliminary data in R/R setting are encouraging; it may be used in patients without an actionable mutation in combination with ven/aza
 Dr Perl	Early data suggest activity in patients with high CD123 expression. An advantage of the drug appears to be its tolerability and lack of myelosuppression
 Dr Stein	None
 Dr Cortes	It could be a valuable adjunct, but I expect the benefit to possibly be modest
 Dr DiNardo	Possibly in combination with HMA + ven for younger patients prior to ASCT
 Dr Wang	Up-front therapy with ven/aza

RTP RESEARCH TO PRACTICE

What future role do you see for chimeric antigen receptor T-cell therapy in the management of AML?

 Dr Erba	An option for relapsed/refractory disease only in clinical trials
 Dr Fathi	Challenge remains overlapping targets between leukemic and normal marrow precursors, and related toxicities
 Dr Lin	Still a significant challenge, not sure we have the right targets, may need to be planned in tandem with alloSCT if CAR T is ablative
 Dr Perl	It is uncertain if it will ever be tolerable, safe, and active in AML. The biggest challenge is finding a tumor-specific antigen that is not shared with normal hematopoietic elements
 Dr Stein	Minimal role in 2025
 Dr Cortes	Good potential once an approach is identified with a more leukemia-specific target
 Dr DiNardo	As maintenance or MRD-directed therapy
 Dr Wang	Relapsed/refractory AML or MRD eradication maybe post-transplant (?)

alloSCT = allogeneic stem cell transplant

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Up-Front Therapy for Older Patients with Acute Myeloid Leukemia (AML) — Dr Lin

Module 2: Selection of Therapy for Younger Patients with AML without a Targetable Mutation; Promising Investigational Strategies — Dr Perl

Module 3: Role of FLT3 Inhibitors in AML Management — Dr Erba

Module 4: Incorporation of IDH Inhibitors into the Care of Patients with AML — Dr Fathi

Module 5: Current and Future Role of Menin Inhibitors in the Treatment of AML — Dr Stein

FLT3 Inhibitors for Previously Untreated Acute Myeloid Leukemia

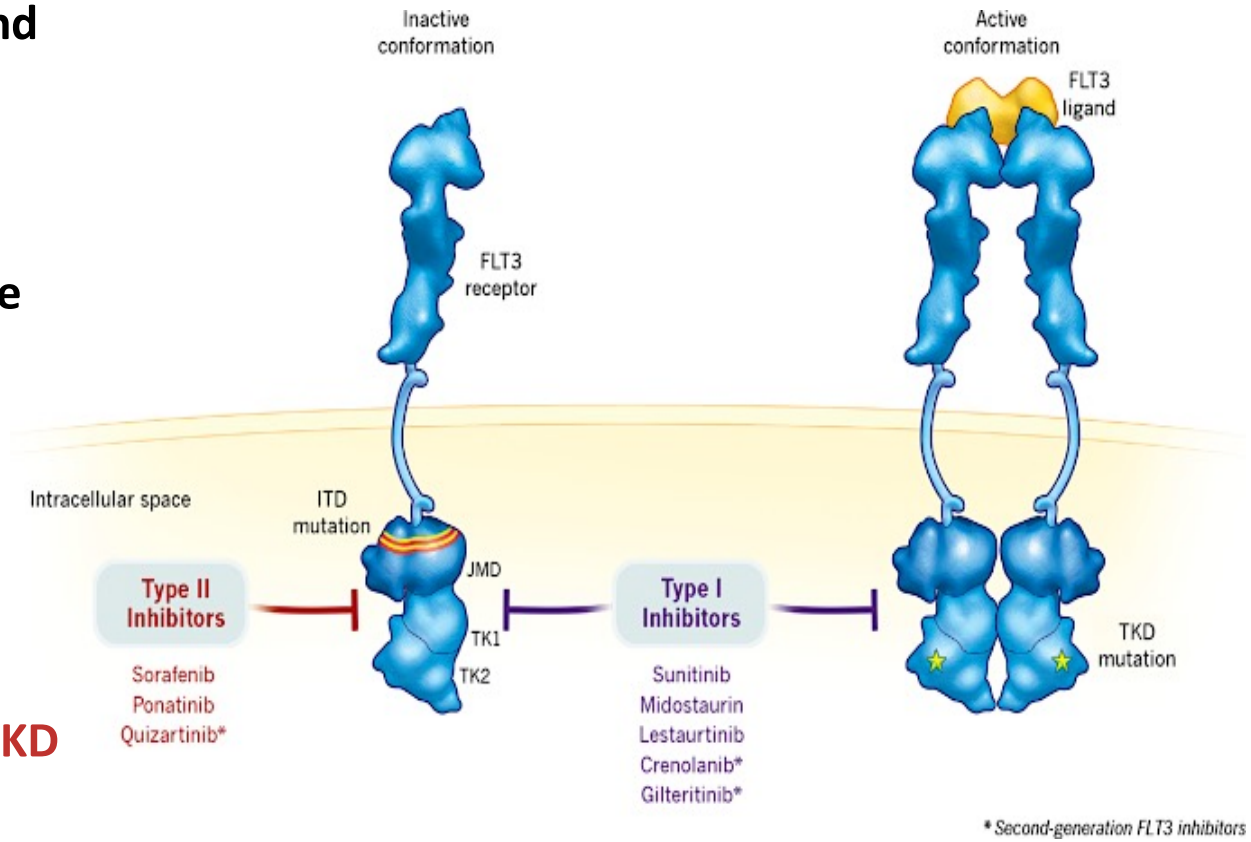
Harry P. Erba, MD, PhD
Professor, Department of Medicine
Director, Leukemia Program
Duke University
Durham, NC

DukeHealth

FLT3 Inhibitors: Mechanism of Action

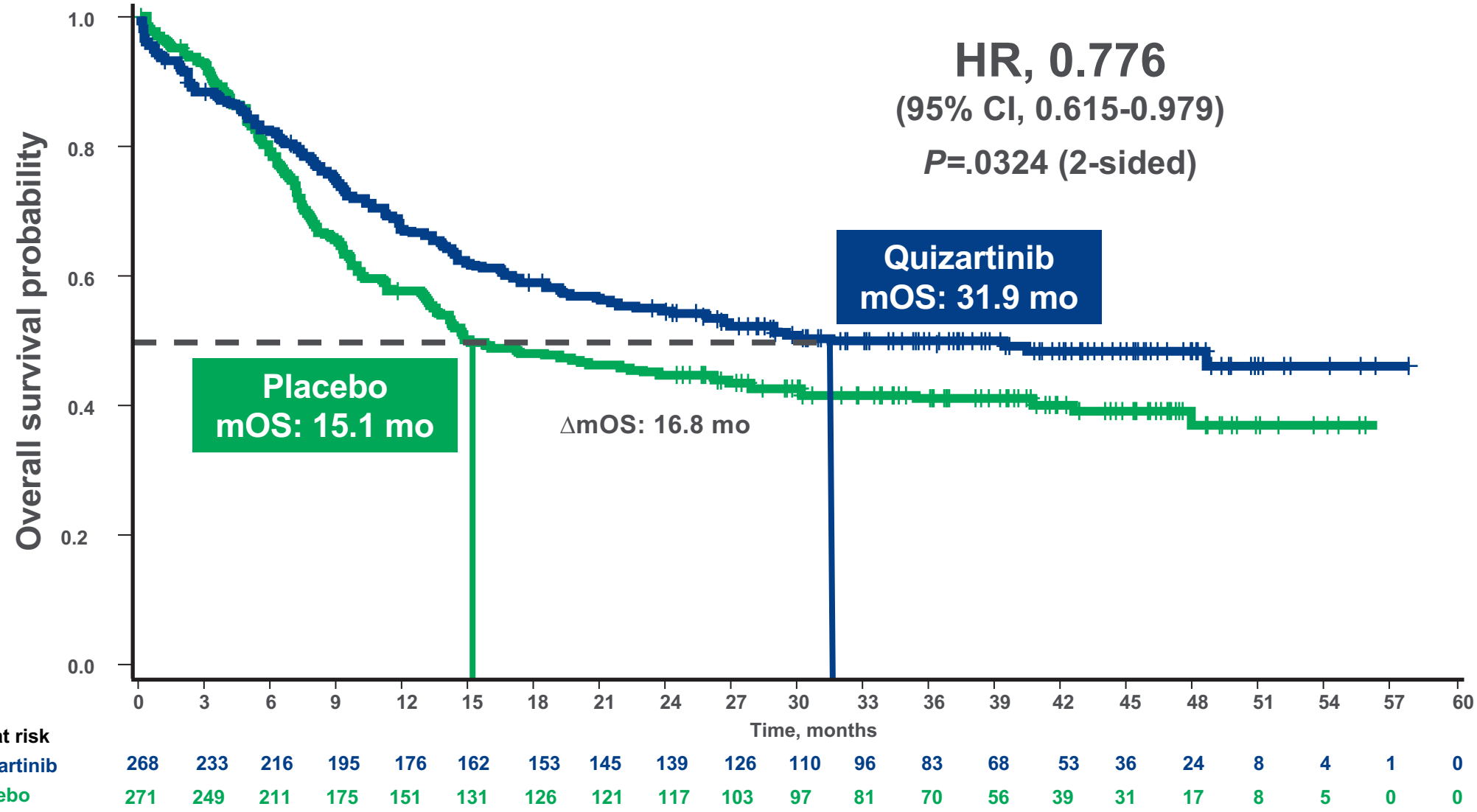
- **ATP-binding site inhibition:**
  - **FLT3 inhibitors competitively inhibit ATP binding to the FLT3 receptor, preventing its autophosphorylation and activation[1,2]**
- **Type I inhibitors (e.g., midostaurin, gilteritinib)**
  - **Bind to both active and inactive conformations of the FLT3 receptor[1,2]**
  - **Active against ITD and TKD mutations[3]**
- **Type II inhibitors (e.g., quizartinib, sorafenib)**
  - **Bind specifically to the inactive FLT3 conformation[1,2]**
  - **Prevent activity of ITD mutations but do not target TKD mutations[3]**

Mechanisms of Type I and Type II FLT3 Inhibitors in Targeting *FLT3* Mutations[3]



1. Cerchione C, et al. *Expert Rev Hematol*. 2021;14:851-865. 2. Negotei C, et al. *J Clin Med*. 2023;12:6429.
3. Daver N, et al. *Leukemia*. 2019;33:299-312.

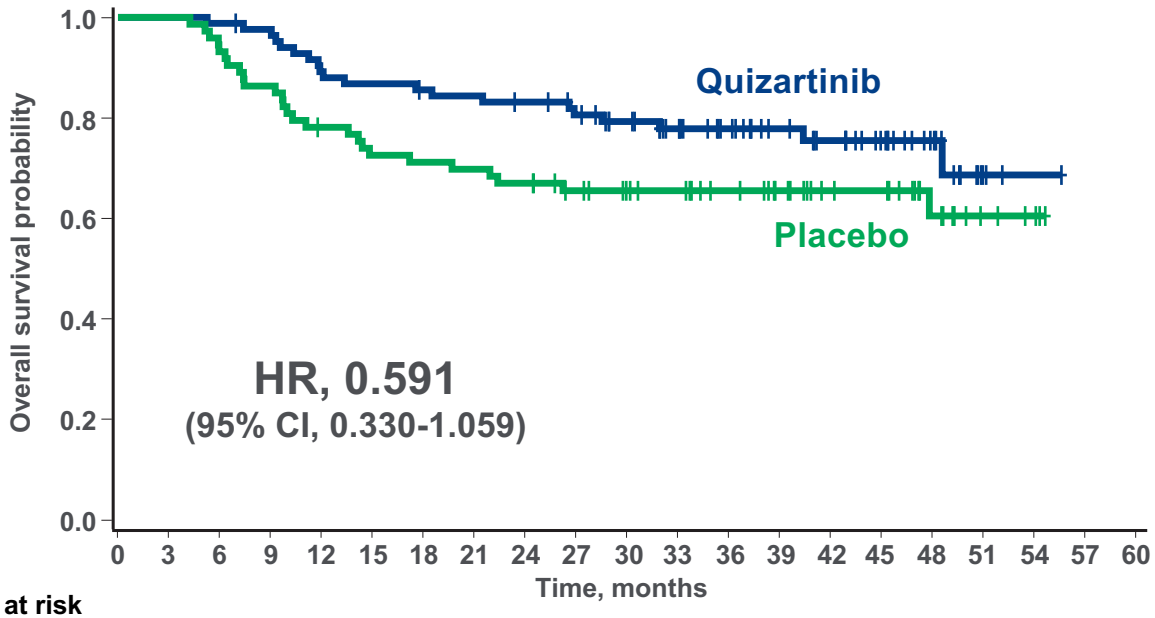
QuANTUM-First Primary Endpoint: Overall Survival



Erba HP, et al. *Lancet* 2023; 401(10388): 1571-1583

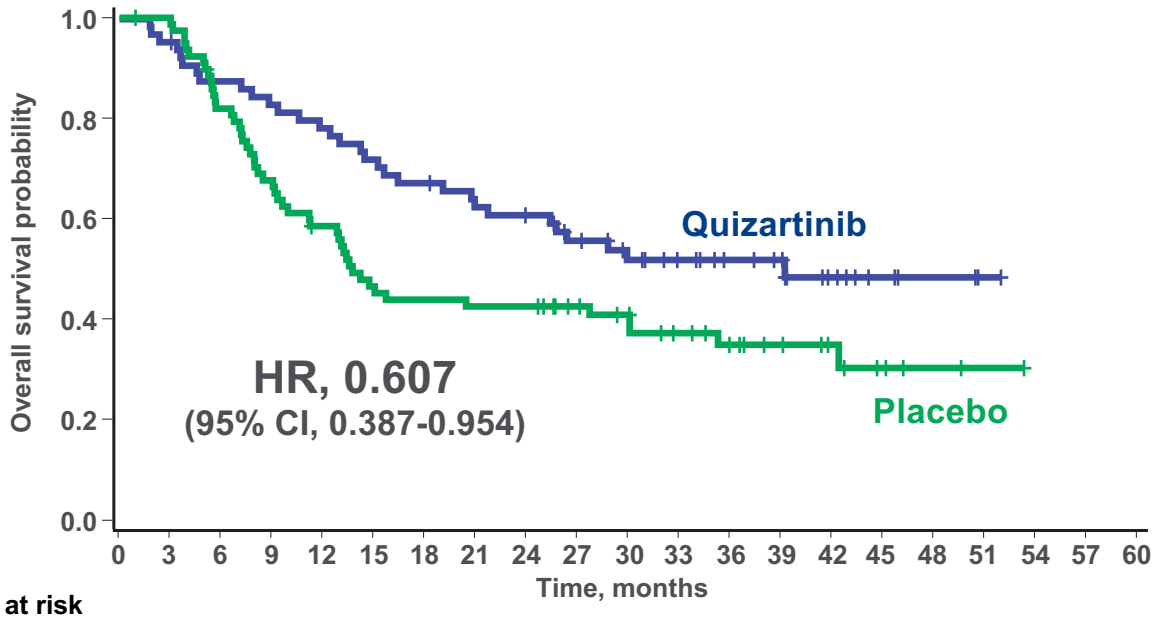
QuANTUM-First: Overall Survival in Patients Who Achieved CR

Patients With CR Who Received Allo-HCT in CR1



No. at risk																					
Quizartinib	84	84	83	81	74	72	70	69	67	63	57	50	42	34	29	22	14	3	1	0	0
Placebo	73	73	68	63	56	52	51	50	48	43	39	37	32	27	21	20	12	5	3	0	0

Patients With CR NOT Receiving Allo-HCT in CR1



No. at risk																					
Quizartinib	63	60	54	51	48	44	41	37	35	30	25	21	17	15	9	5	3	1	0	0	0
Placebo	77	76	61	50	42	33	31	30	30	25	22	17	14	10	7	4	2	1	0	0	0

Erba HP, et al. *Lancet* 2023; 401(10388): 1571-1583

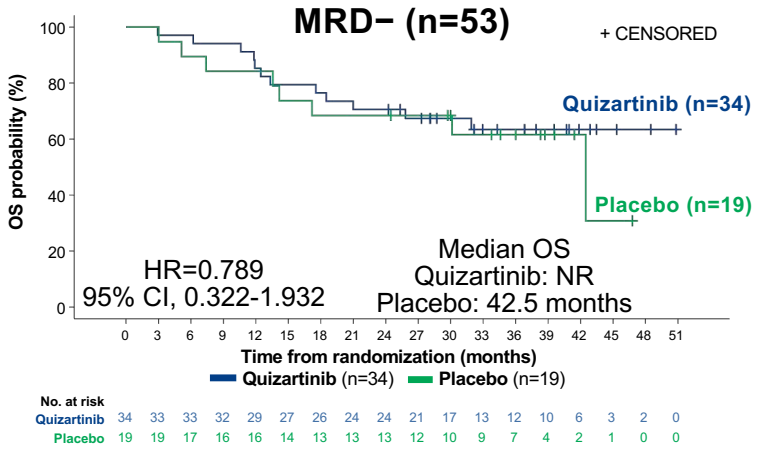
Elimination of MRD by *FLT3* ITD NGS MRD Assay in QuANTUM-First Trial by Treatment Course

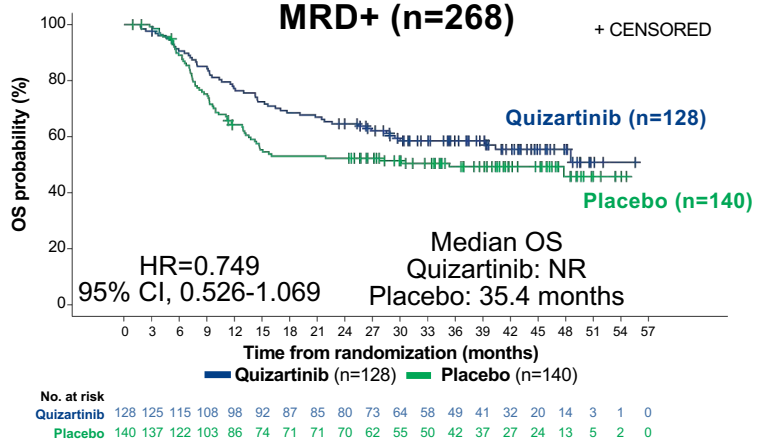
	CRc After Induction		After 2 Cycles of CTx		After Last Consolidation Cycle	
	QUIZ	PLAC	QUIZ	PLAC	QUIZ	PLAC
Patients with non-detectable MRD, %	22.8	11.9	31.7	21.7	55.8	41.2
Nominal *P* value	0.0122		0.0609		0.0089	

Perl A, et al. ASH 2023;Abstract 832

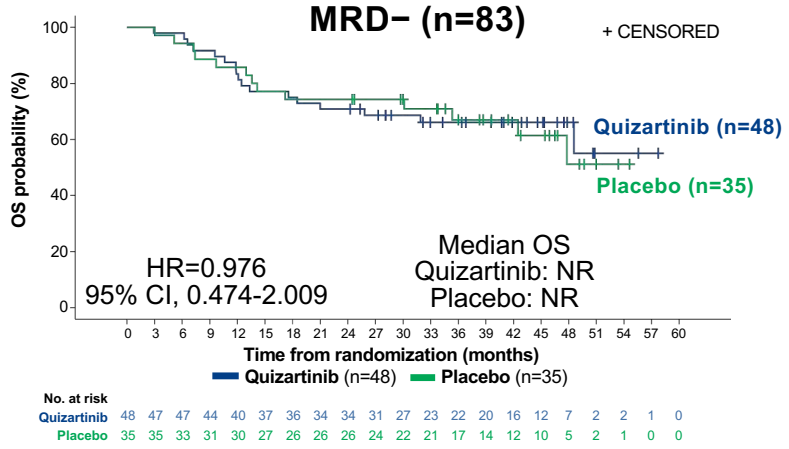
FLT3-ITD MRD Reduction Predicts Survival Across Therapy

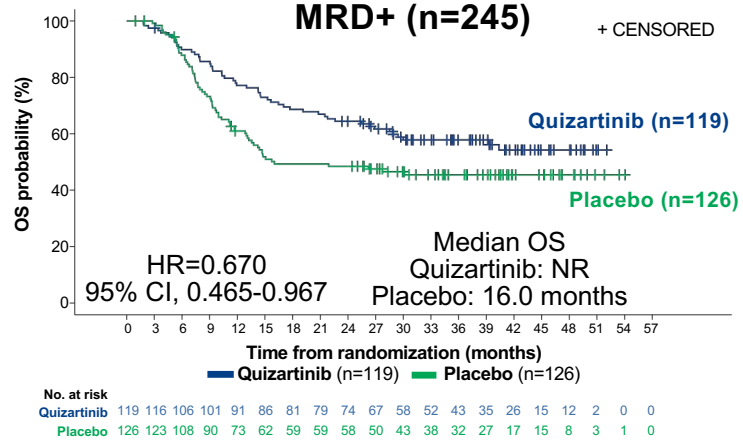
CRc After Induction
(1 or 2 cycles)



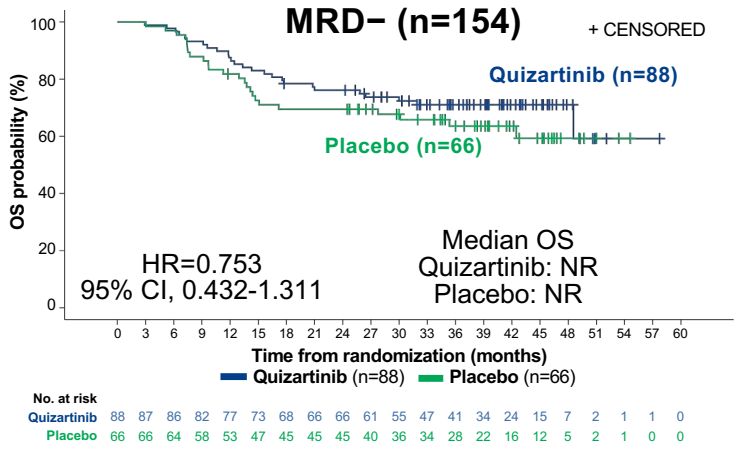


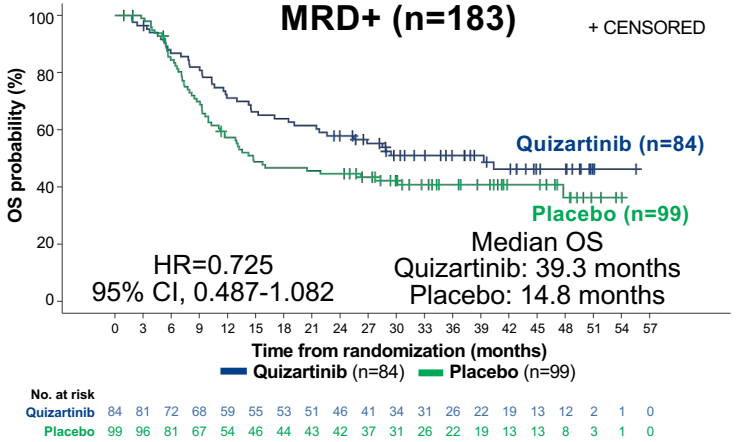
After 2 Cycles of CTx
(CRc after induction × 2 cycles or
CRc after induction #1 + consolidation #1)





After Last Consolidation Cycle
(up to 4 cycles)

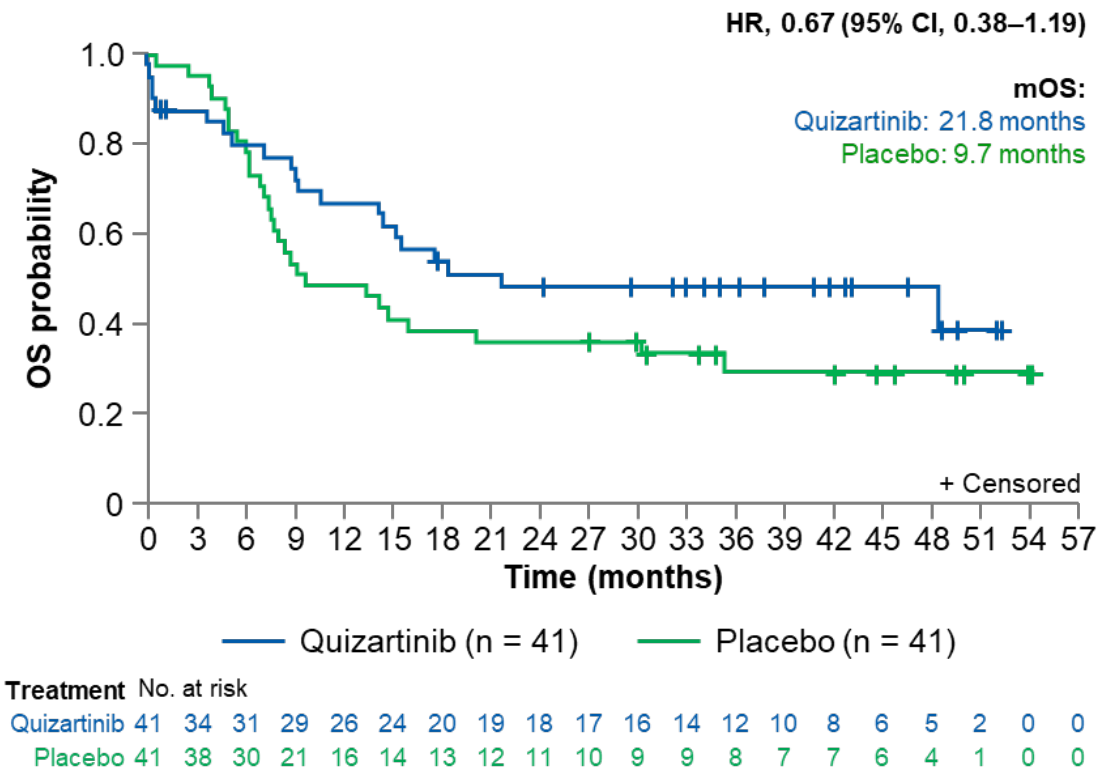




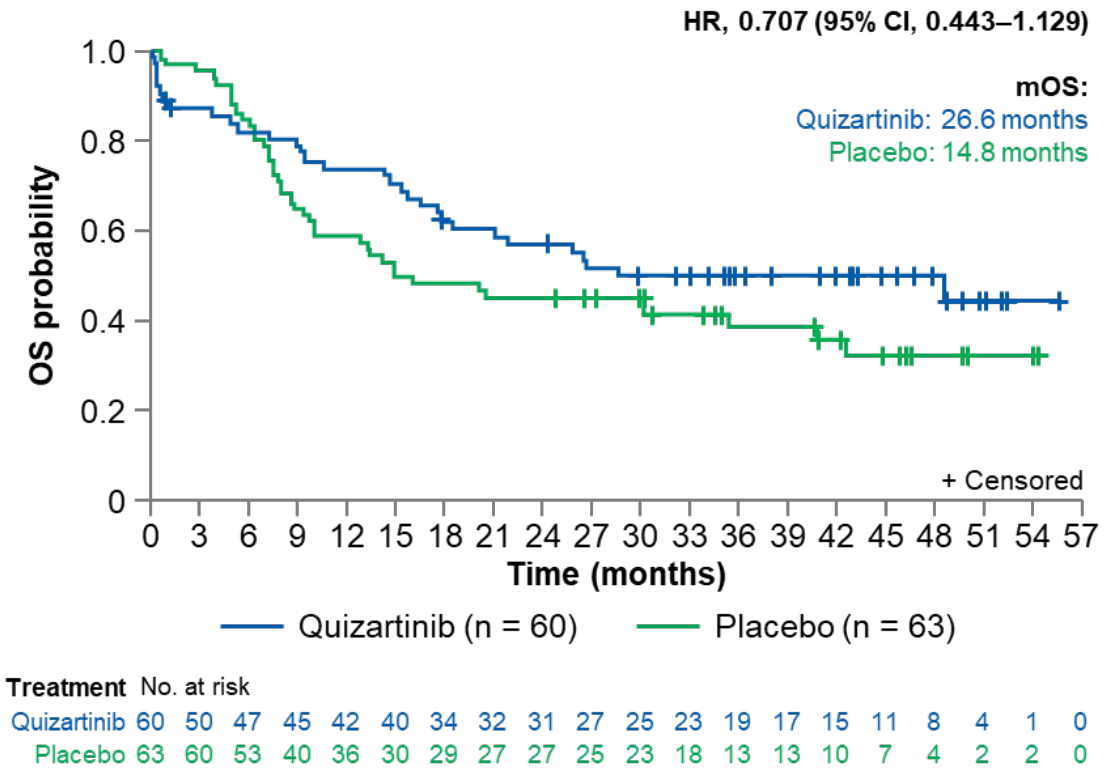
Levis MJ, et al. *Blood Adv.* 2025;bloodadvances.2025016444; Perl A, et al. ASH 2023;Abstract 832

Effect of Co-mutations on Overall Survival of *FLT3* ITD + AML Patients Age ≥ 60 Years Treated with IC with Quizartinib vs Placebo

***NPM1* and *DNMT3A* mutations**



NPM1* and ≥ 1 mutation in *DNMT3A*, *TET2*, *WT1*, *IDH1*, or *IDH2



Montesinos P and Levis M. Manuscript in Preparation, 2025; Levis M, et al. ASH 2024;Abstract 848

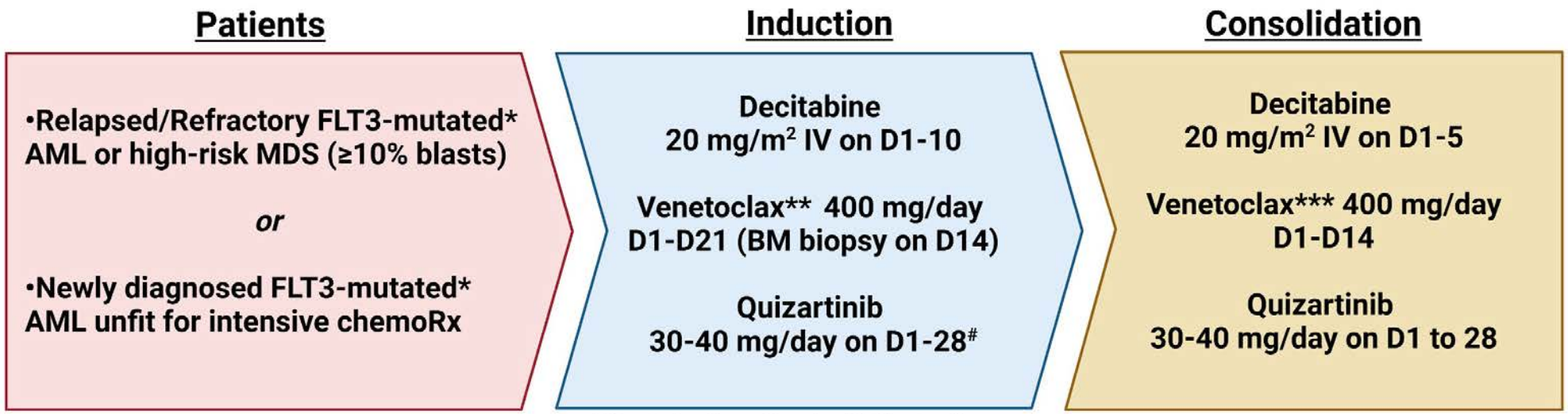
Decitabine + Venetoclax + Quizartinib for FLT3-ITD Mutated AML

Primary Objective:

- To establish RP2D of quizartinib in combination with DAC + VEN in pts with FLT3m AML

Secondary Objective:

- To determine complete remission (CR), CR with incomplete count recovery (CRi), minimal residual disease (MRD), and overall survival (OS)



*FLT3-ITD with/without TKD mutations allowed

**Venetoclax discontinued on D14 in pts with BM blasts ≤5% or hypoplastic BM
Amendment - reduced quizartinib to 14 days in C1

Up to 12 cycles. ***Venetoclax duration reduced to 14 > 10 >7 days in subsequent cycles for pts in CR based on count recovery durations. Quizartinib dose reduced to 14 days in pts with prolonged count recovery

***Amendment (November 2023): Decitabine 5 days in cycle 1, quizartinib D1-D21 (BM biopsy on day14)**

Decitabine + Venetoclax + Quizartinib for *FLT3*-ITD Mutated AML

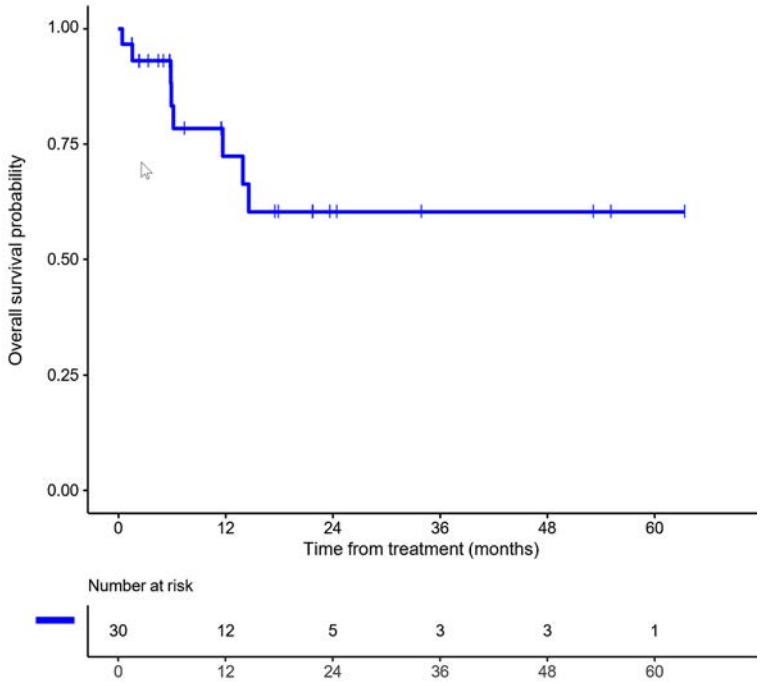
Response*, N (%)	Newly Diagnosed Cohort (N=30) N (%), Median [Range]
Hematologic Response	
CRc (composite CR)	28 (94)
CR	21 (70)
CRi	7 (24)
MLFS	0
No response	1 (3)
Induction death	1 (3)
MRD Response, EOC1, N (%)	
Flow cytometry negative	14/24 (58)
FLT3 PCR negative	11/18 (61)
MRD Response, best, N (%)	
Flow cytometry negative	18/26 (69)
FLT3 PCR negative	18/21 (86)
Bridge to ASCT	9 (30)

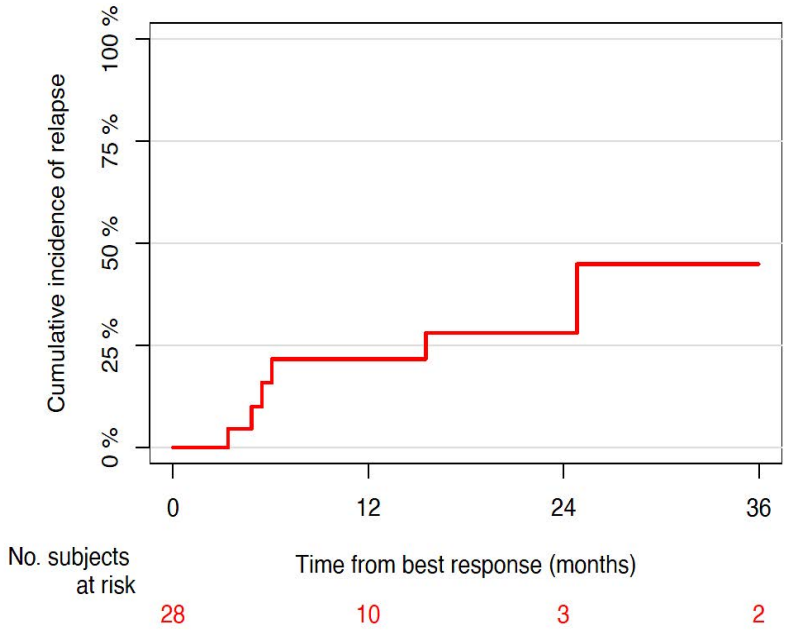
Median time to ANC >500/mcL: 38 days [18-56]
Median time to ANC >1000/mcL: 40 days [19-67]

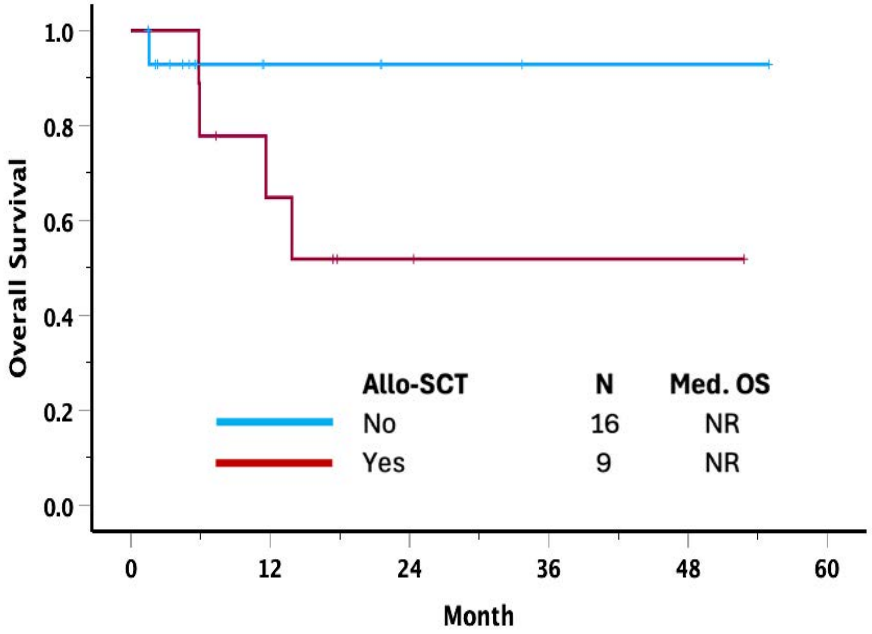
Median time to PLT >50,000/mcL: 35 days [16-71]
Median time to PLT >100,000/mcL: 39 days [18-105]

Yilmaz M, et al. EHA 2025;Abstract S142

Decitabine + Venetoclax + Quizartinib for *FLT3*-ITD Mutated AML







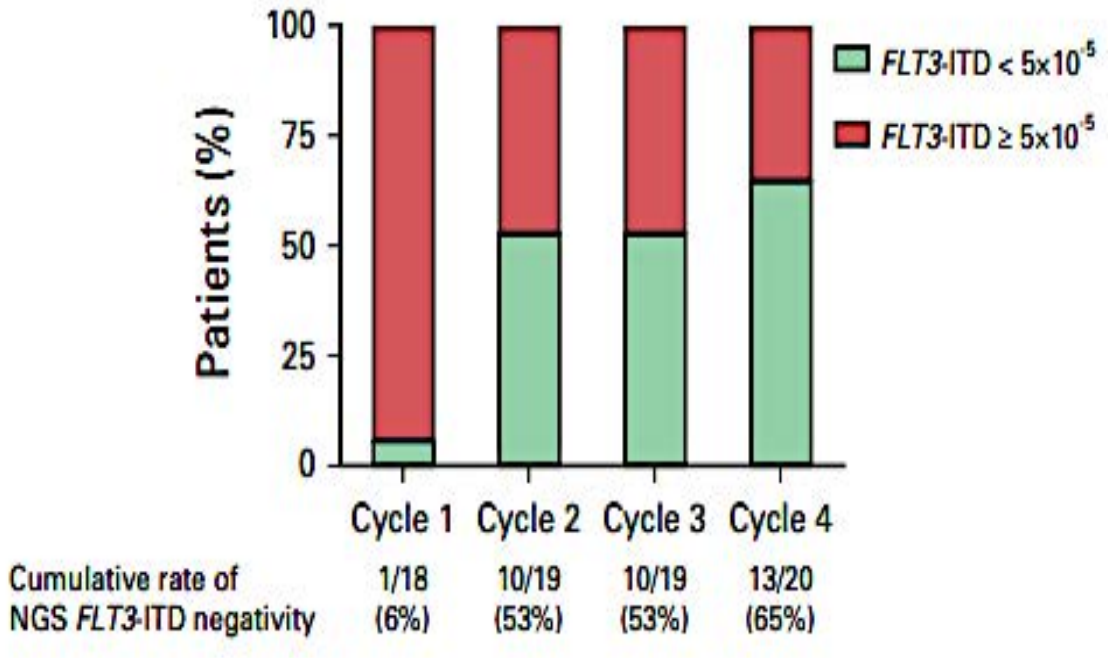
Median OS: NR (median follow up 17 months)

1-yr OS: 72%, 2-yr OS: 60%

Yilmaz M, et al. EHA 2025;Abstract S142

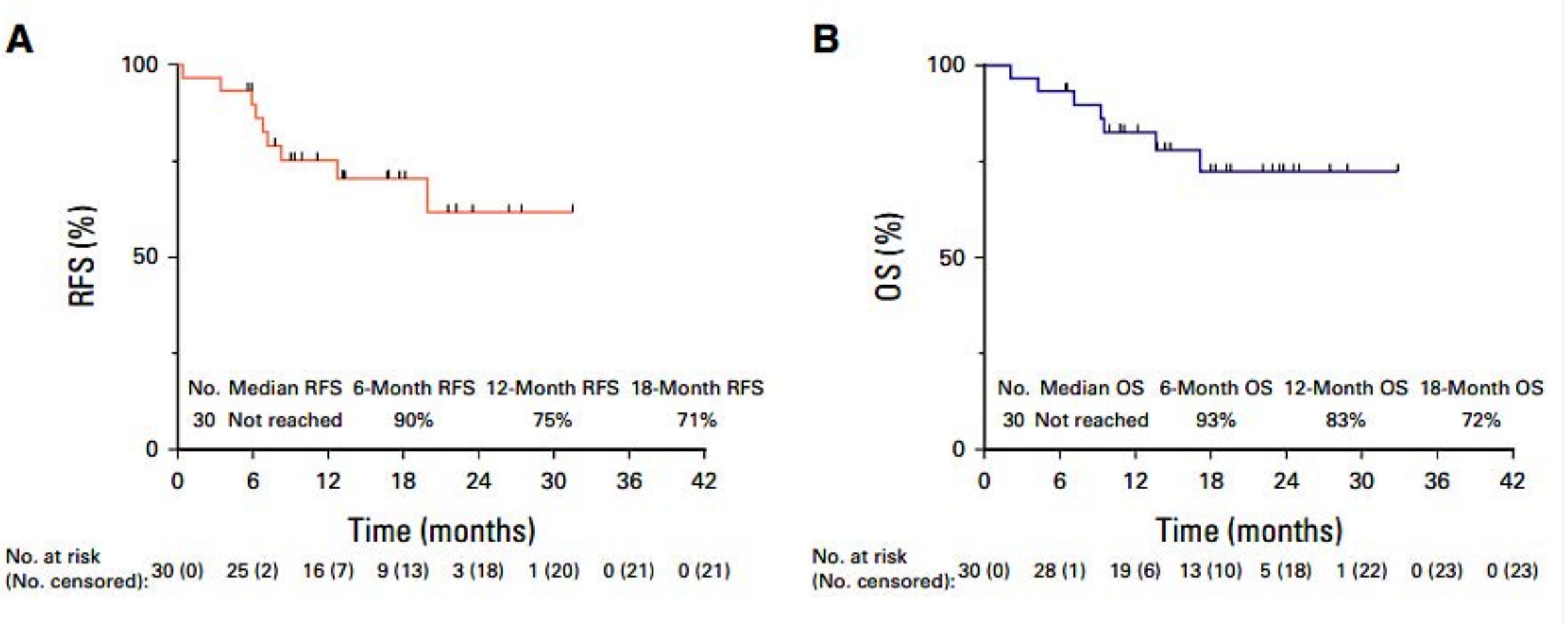
Phase II Study of AZA/VEN/GILT in ND *FLT3*m AML: Response and Rate of *FLT3*-ITD Negativity Across Treatment Cycle

Hematologic Response	Frontline Cohort (n = 30)
mCRc (CR/Cri/MLFS), no. (%)	30 (100)
CR	27 (90)
CRi	2 (6)
MLFS	1 (4)
PR	0
No response	0



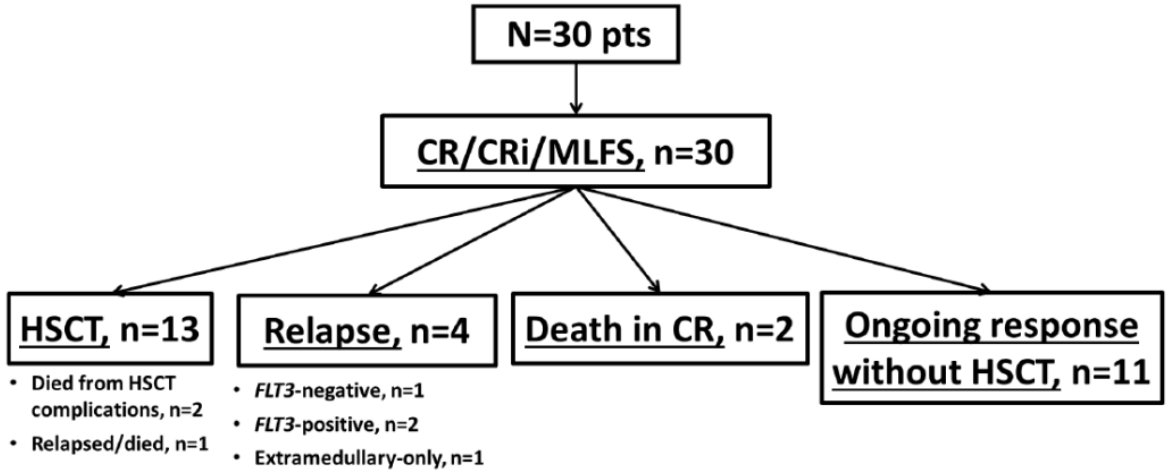
Short N, et al. *J Clin Oncol.* 2024;42:1499-1508

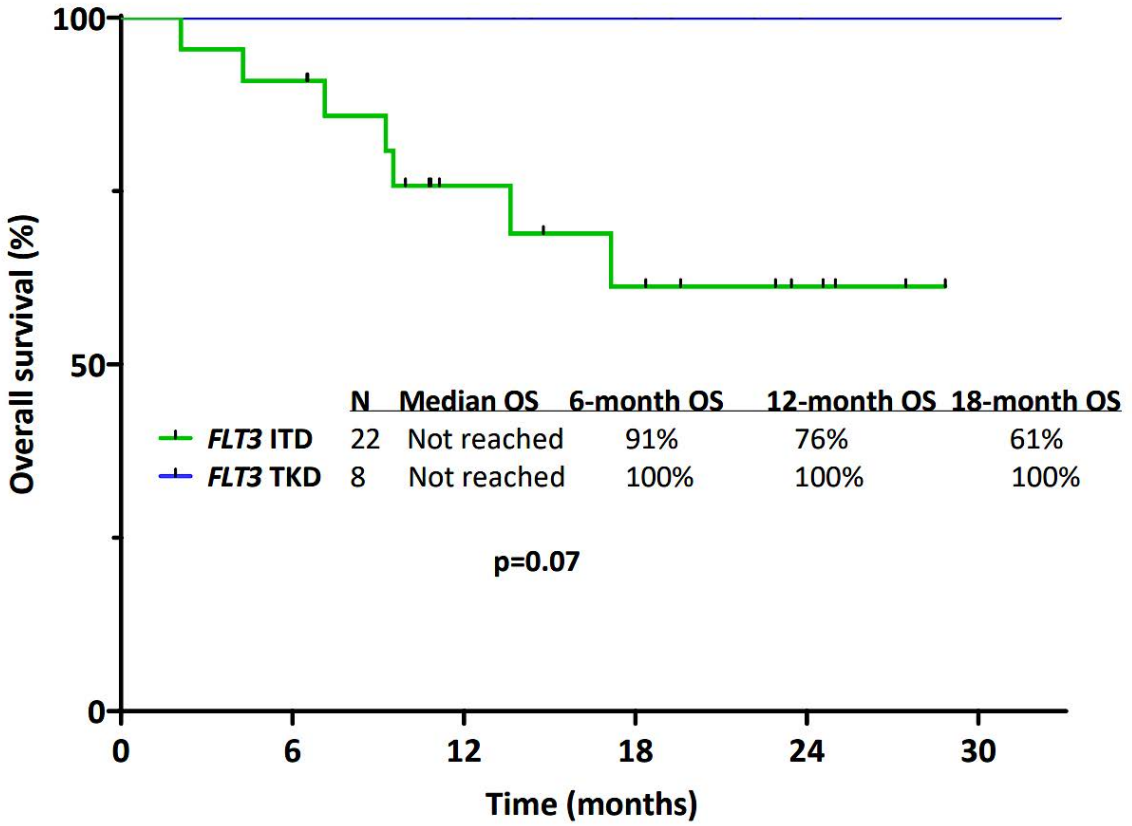
Azacitidine, Venetoclax, and Gilteritinib for *FLT3* Mutated AML (Median follow up 19 months)



Short N, et al. *J Clin Oncol.* 2024;42:1499-1508

Azacitidine, Venetoclax, and Gilteritinib for Previously Untreated *FLT3* Mutated AML





Short N, et al. *J Clin Oncol.* 2024;42:1499-1508

Quizartinib Monotherapy in Relapsed/Refractory AML

	Cohort 1		Cohort 2	
	FLT3-ITD positive (n=112)	*FLT3*-ITD negative (n=44)	*FLT3*-ITD positive (n=136)	*FLT3*-ITD negative (n=40)
Best response				
Composite complete remission	63 (56%)	16 (36%)	62 (46%)	12 (30%)
Complete remission	3 (3%)	2 (5%)	5 (4%)	1 (3%)
Complete remission with incomplete platelet recovery	4 (4%)	1 (2%)	2 (1%)	1 (3%)
Complete remission with incomplete haematological recovery	56 (50%)	13 (30%)	55 (40%)	10 (25%)
Partial remission	23 (21%)	4 (9%)	39 (29%)	6 (15%)
No response	20 (18%)	17 (39%)	24 (18%)	16 (40%)
Unknown	6 (5%)	7 (16%)	11 (8%)	6 (15%)
Overall response†	86 (77%)	20 (45%)	101 (74%)	18 (45%)
Composite complete remission after one cycle	34/63 (54%)	6/16 (38%)	39/62 (63%)	8/12 (67%)

135 mg daily (men)
90 mg daily (women)

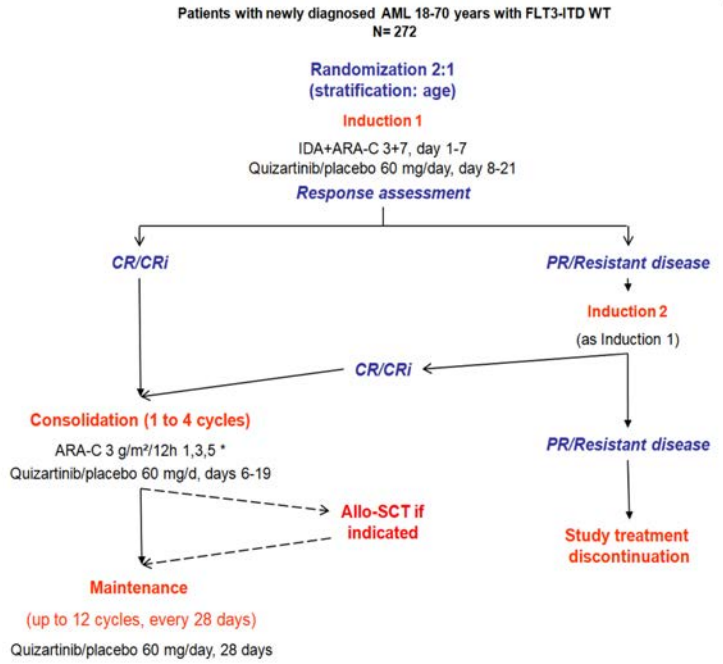
***FLT3* ITD negative =**
VAF ≤ 10%

Cohort 1: ≥ 60 years old, CR1 < 1 year or refractory to first line therapy
Cohort 2: ≥ 18 years old, relapsed/refractory following one salvage or HSCT

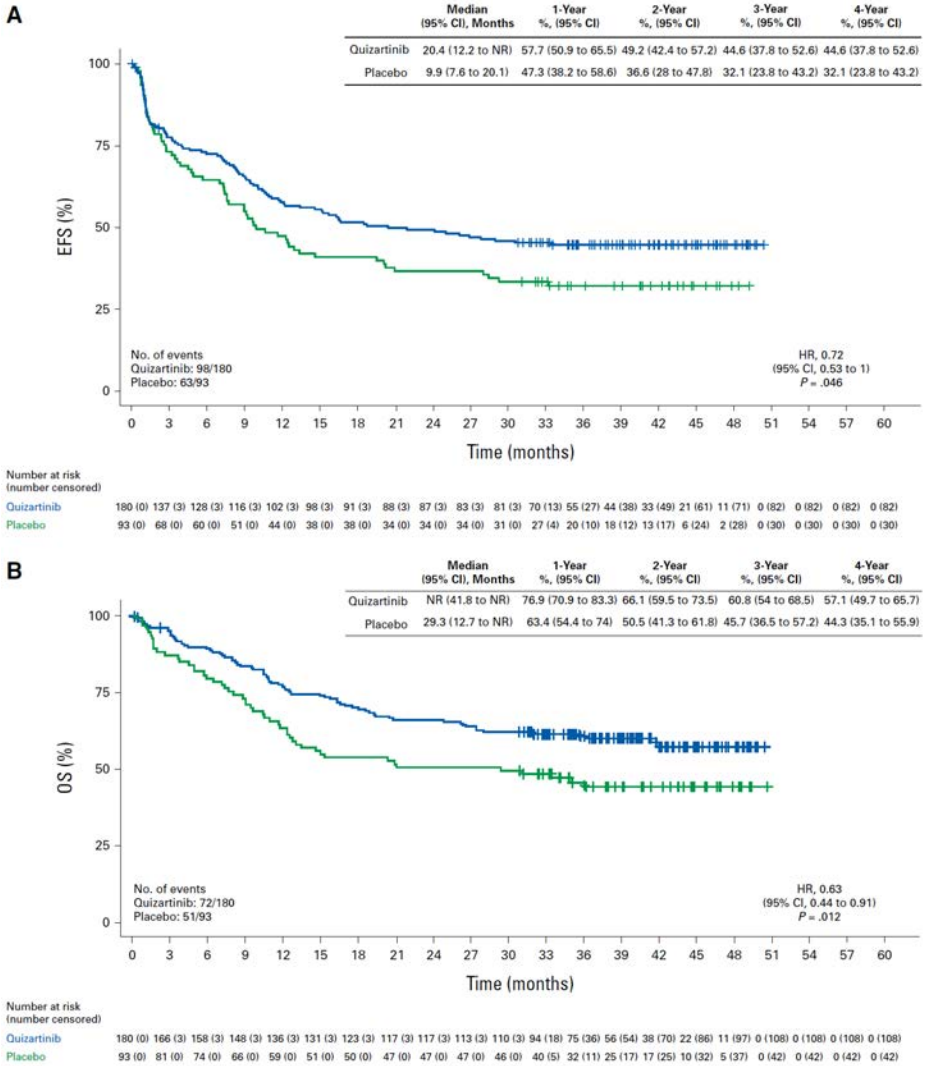
Cortes J, et al. *Lancet Oncol.* 2018;19:889-903.

Quizartinib for Newly Diagnosed *FLT3*-ITD Negative AML: Phase II QUIWI Trial

- Safety run-in phase: open-label cytarabine 200 mg/m^2 (days 1-7), Idarubicin 12 mg/m^2 (days 1-3) Quizartinib 60 mg/d x 14 days (30mg with strong CYP3A inhibitor)



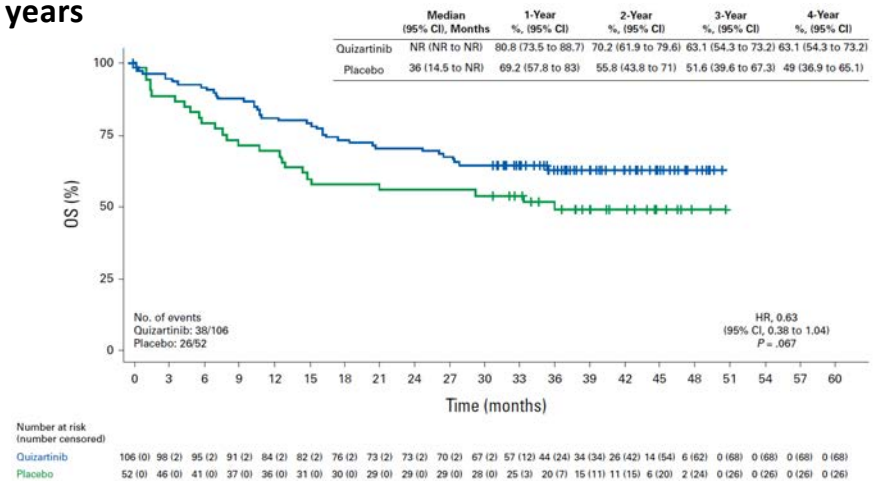
- Enrollment: September 2019 – November 2021
- Age: 18-70 years of age
- Performance status: ECOG <3
- Newly diagnosed *FLT3*-ITD negative AML (ratio <0.03)
- *FLT3*-ITD centrally screened (capillary electrophoresis)
- Patients begin 7+3 chemotherapy during screening



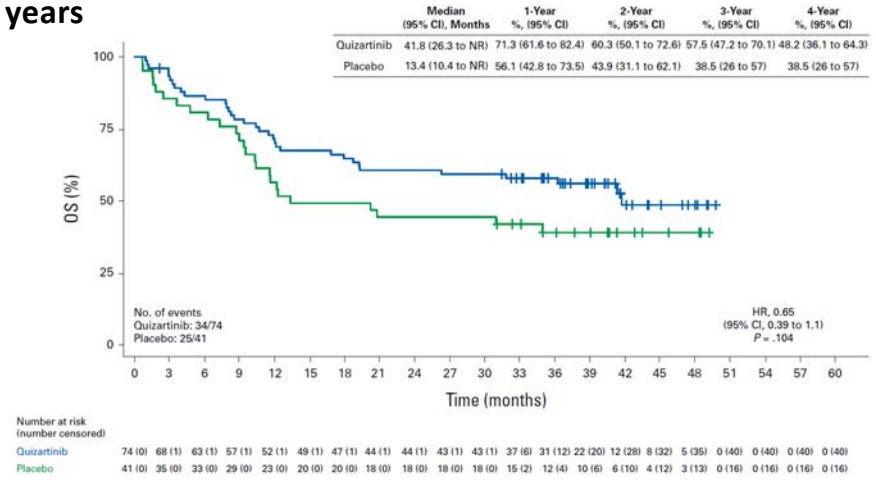
Montesinos P, et al. *J Clin Oncol*. 2025 Oct 13:JCO2501841.

Quizartinib for Newly Diagnosed *FLT3*-ITD Negative AML: Overall Survival by Age and Allo HSCT

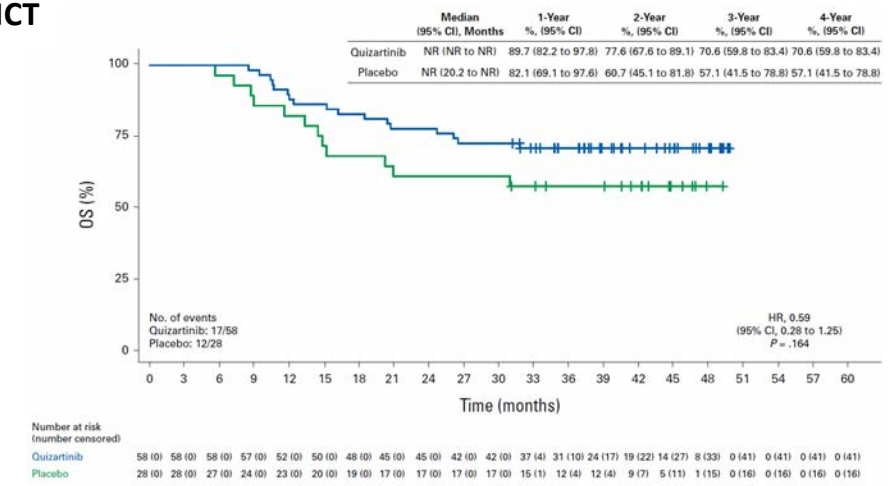
Age < 60 years



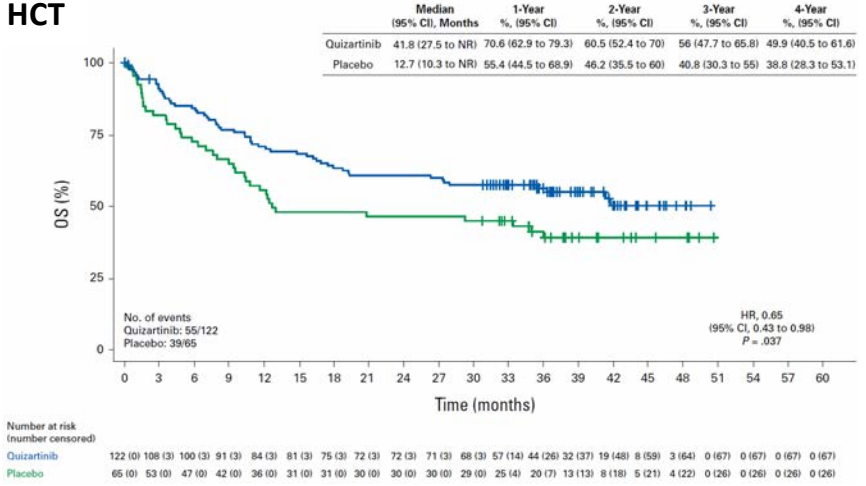
Age ≥ 60 years



Allo HCT



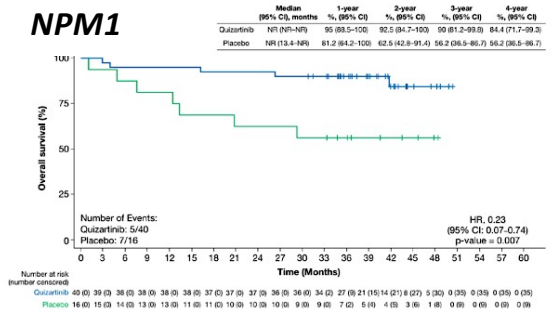
No Allo HCT



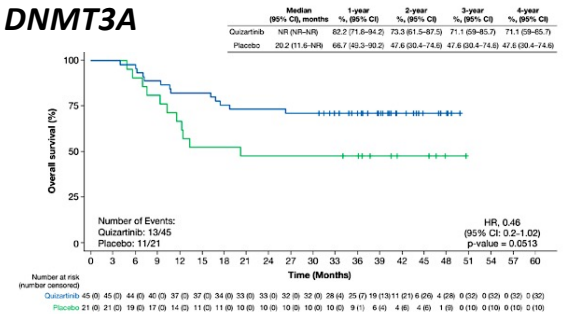
Montesinos P, et al. *J Clin Oncol*. 2025 Oct 13:JCO2501841.

Quizartinib for Newly Diagnosed *FLT3*-ITD Negative AML: Overall Survival by Mutation and ELN 2022 Risk Stratification

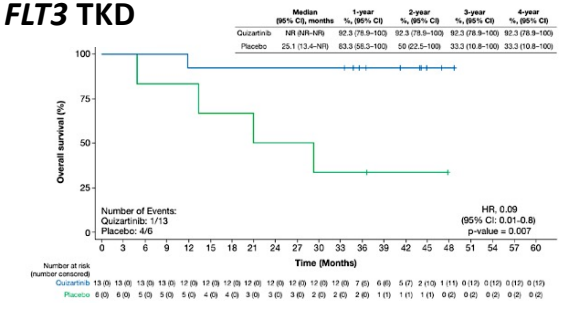
NPM1



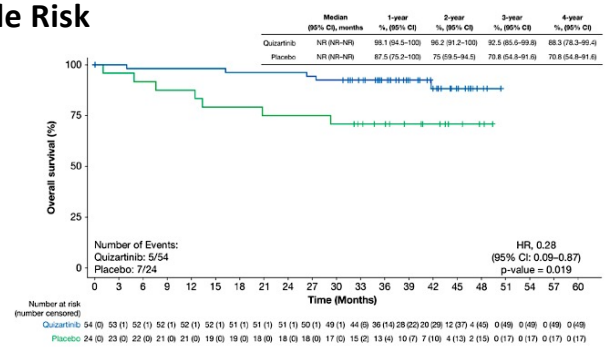
DNMT3A



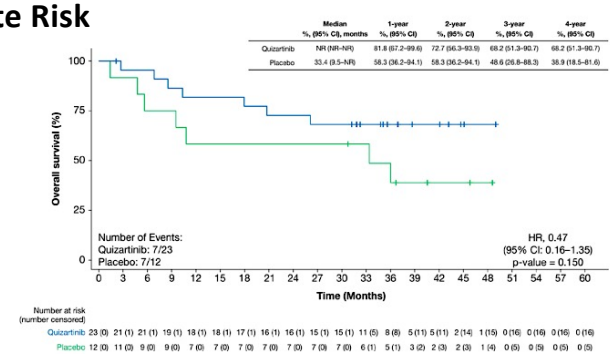
***FLT3* TKD**



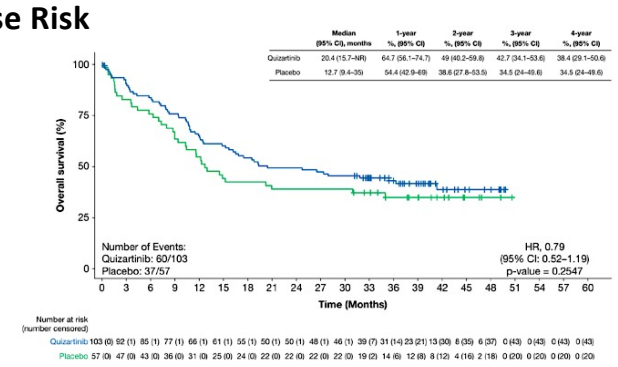
ELN 2022 Favorable Risk



ELN 2022 Intermediate Risk



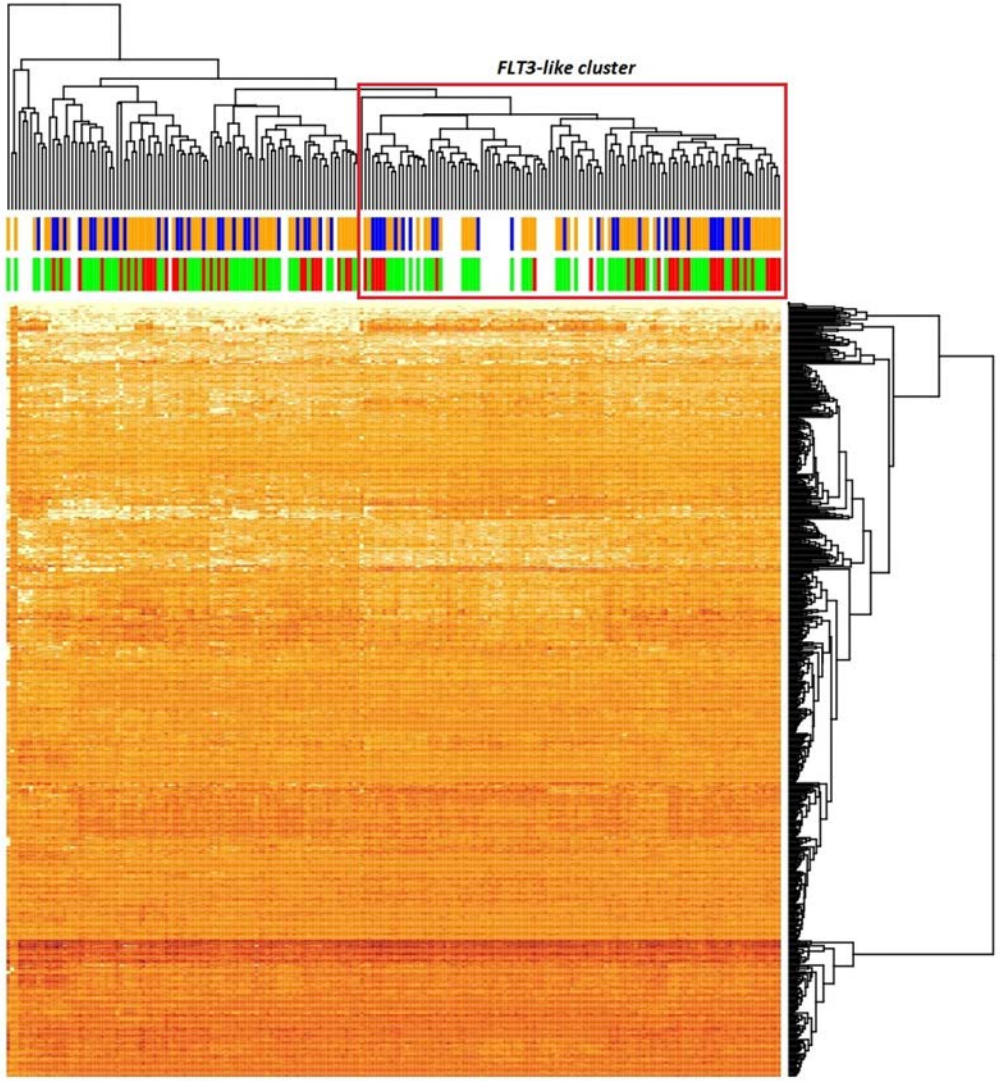
ELN 2022 Adverse Risk



Montesinos P, et al. *J Clin Oncol*. 2025 Oct 13:JCO2501841.

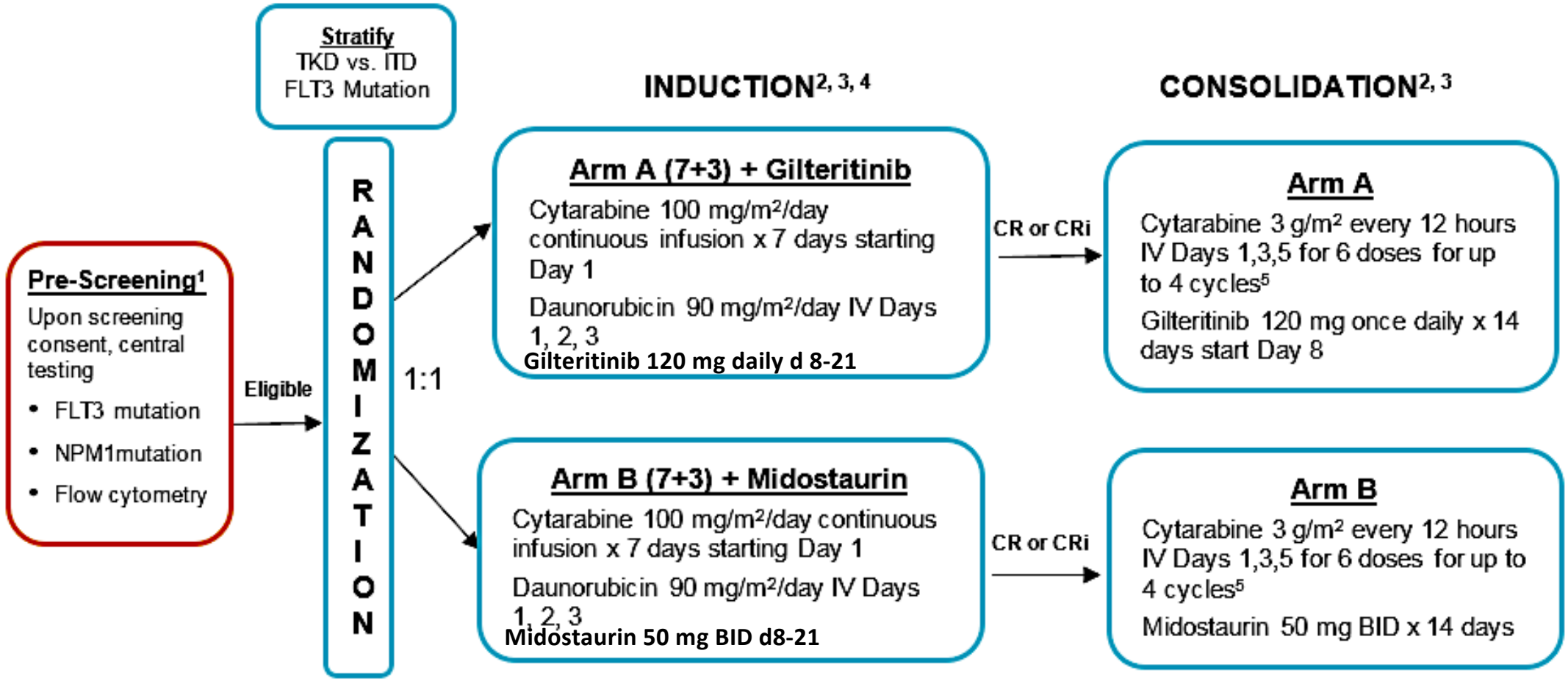
Overview of the FLT3-like Clusters in QUIWI Trial

Overview of the FLT3-like signature
FLT3-like Cases: ➢ Account for 49.67% of FLT3-ITD negative patients. ➢ Characterized by a gene expression signature similar to *FLT3*-ITD positive cases. **Non-FLT3-like Cases:** ➢ Constitute 50.33% of *FLT3*-ITD negative patients lacking the FLT3-like gene expression signature.



Mosquera Orgueira A, et al. ASH 2023;Abstract 974.

Induction and Consolidation Chemotherapy with Gilteritinib or Midostaurin



Luger S, et al. ASH 2024;Abstract 221.

PrECOG 0905: Induction and Response

177 newly diagnosed adults ages 18-70 years with, *FLT3* ITD+ or TKD+ AML were eligible and treated

- Arm A (Gilteritinib) 90, Arm B (Midostaurin) 87
  - 5 (5.6%) vs 6 (6.9%) received 2 cycles induction
- CRc (Gilteritinib) 85.6% vs 72.4% (Midostaurin), p=0.042
- Allo HSCT in CR1: Gilteritinib Arm A 60.0% vs Midostaurin Arm B 45.9%

	Arm A (Gilteritinib) N=90	Arm B (Midostaurin) N=87	Overall (N=177)
CR	68 (75.6%)	57 (65.5%)	125 (70.6%)
CRi	9 (10%)	6 (6.9%)	15 (8.5%)
CRc	77 (85.6%)	63 (72.4%)	137 (79.3%)
No Response	13 (14.4%)	24 (27.6%)	37 (20.9%)

Six color flow cytometry performed after induction to assess MRD negative remission (10^{-4})

FC MRD post induction	Arm A (Gilteritinib) N=90	Arm B (Midostaurin) N=87	Overall (N=177)
MRD positive, not in CR or dropped out/unknown	32 (35.6%)	35 (40.2%)	67 (37.9%)
MRD negative CRc	58 (64.4%)	52 (59.8%)	110 (62.1%)

Luger S, et al. ASH 2024;Abstract 221.

PrECOG 0905: *FLT3* Mutation MRD Post-induction

- For ITD*:* LOD 10^{-4} by PCR followed by NGS
- For TKD*:* LOD 10^{-2} by PCR followed by capillary electrophoresis

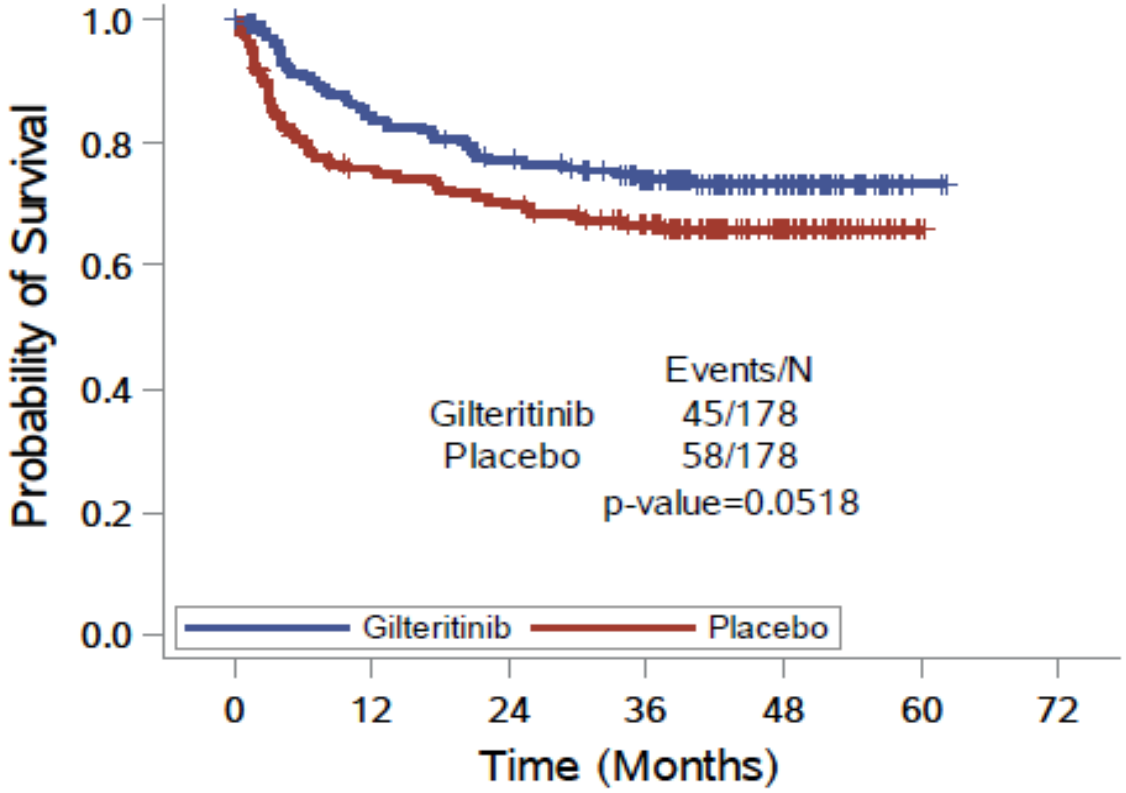
MRD regardless of remission status	Arm A (Gilteritinib) N=90	Arm B (Midostaurin) N=87	Overall N=177
MRD negative	36 (40.0%)	46 (52.9%)	82 (46.3%)
MRD positive	39 (43.3%)	28 (32.3%)	67 (37.9%)
Dropped Out/Unknown	15 (16.7%)	13 (14.9%)	28 (15.8%)

- *FLT3*m negative CRc post induction
- 40% Gilteritinib (A) vs 47.1% Midostaurin (B), p=0.366

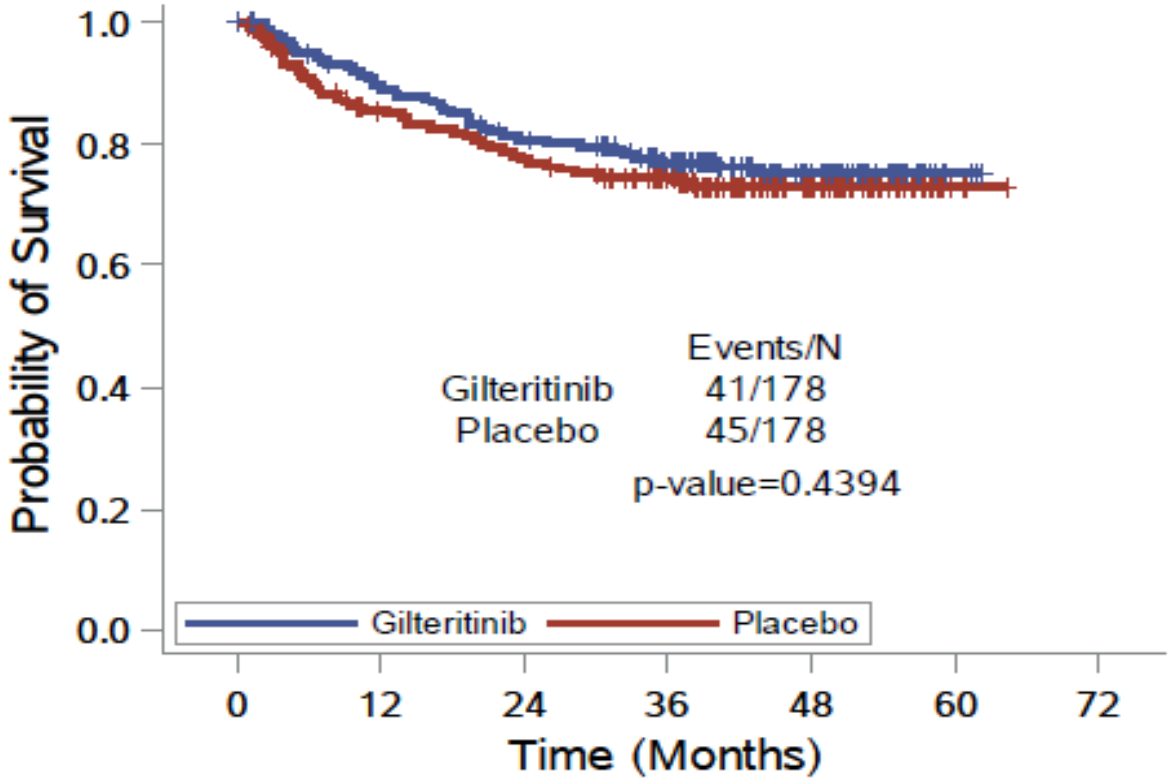
Luger S, et al. ASH 2024;Abstract 221.

BMT-CTN 1506 (MORPHO): Efficacy Outcomes

Primary objective:
Relapse-free survival
HR = 0.679 (0.459-1.005)



Key secondary objective:
Overall survival
HR = 0.846 (0.554-1.293)

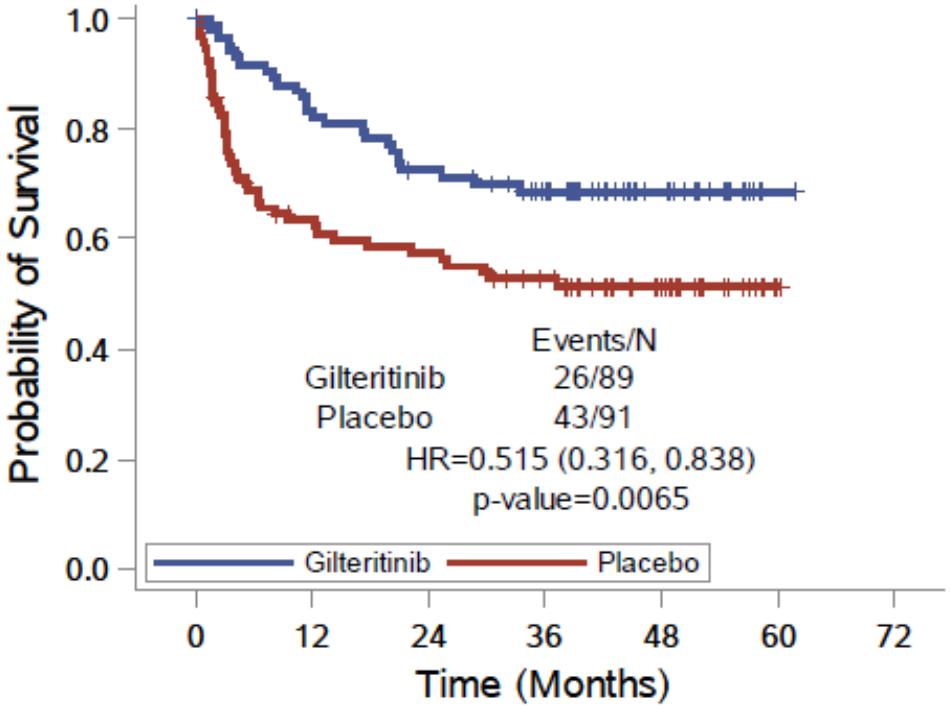


Levis MJ, et al. *J Clin Oncol.* 2024;42:1766-1775

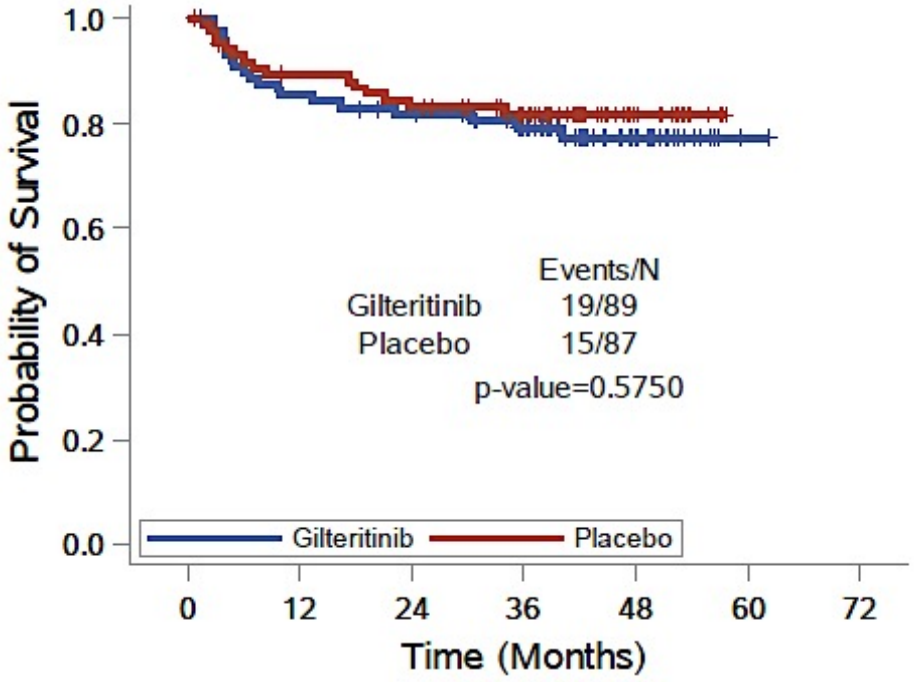
BMT CTN
Blood & Marrow Transplant Clinical Trials Network

MORPHO: Effect of detectable MRD6 on RFS by study arm

RFS
MRD+



RFS
MRD-



Levis MJ, et al. *J Clin Oncol.* 2024;42:1766-1775

BMT CTN
Blood & Marrow Transplant Clinical Trials Network

MORPHO: Drug-related Grade 3 or higher treatment emergent adverse events

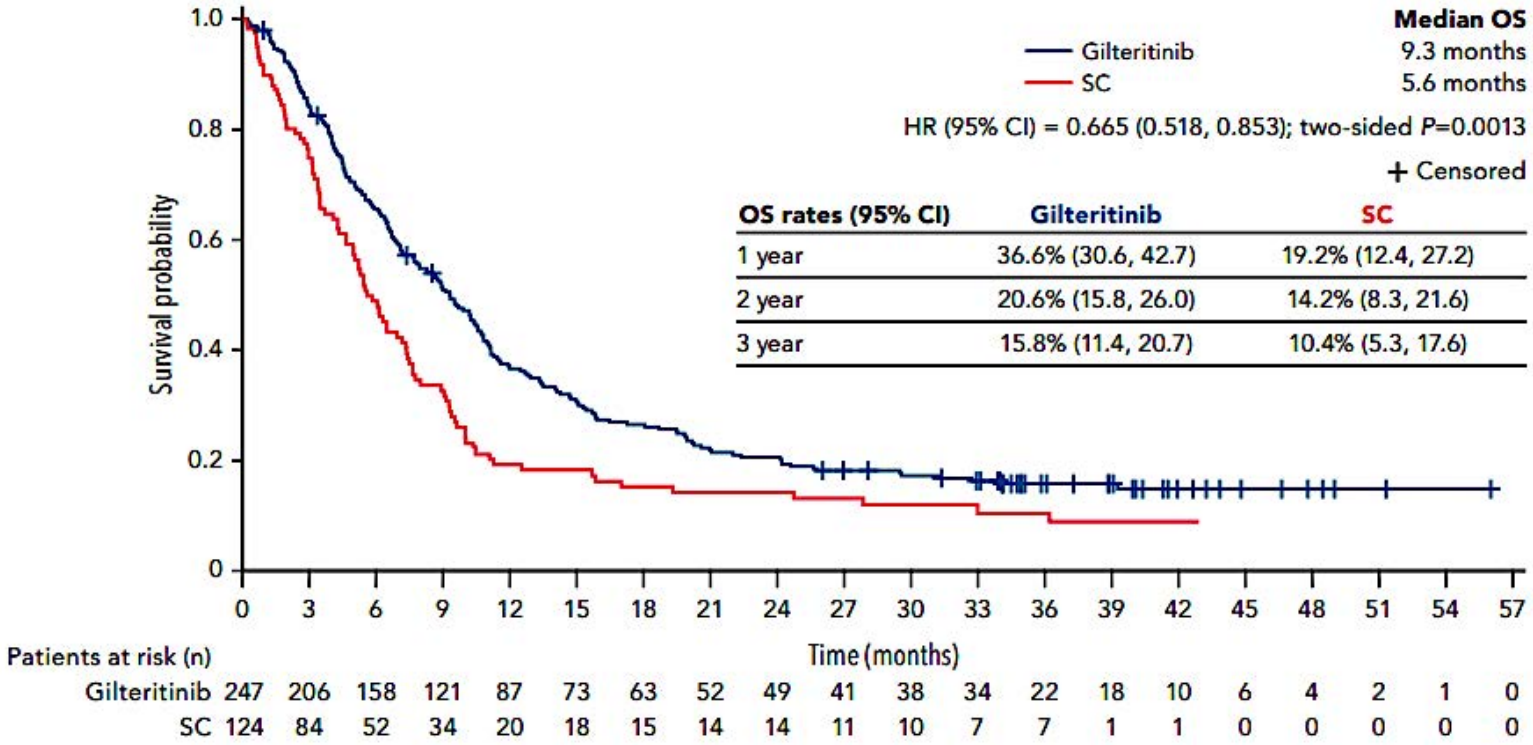
Grade 3 or higher Adverse Event, n(%)	Gilteritinib (N=178)	Placebo (N=177)
Neutrophil count decreased	44 (24.7%)	14 (7.9%)
Platelet count decreased*	27 (15.2%)	10 (5.6%)
Anemia	11 (6.2%)	3 (1.7%)
Alanine aminotransferase (ALT) increased	6 (3.4%)	4 (2.2%)
Creatine phosphokinase increased	12 (6.7%)	0 (0%)

* Includes unique cases of platelet count decrease and thrombocytopenia

BMT CTN
Blood & Marrow Transplant Clinical Trials Network

Levis MJ, et al. *J Clin Oncol.* 2024;42:1766-1775

Follow-up of Patients with Rel/Ref *FLT3*m AML Treated with Gilteritinib in the Phase III Admiral Trial



- 26 gilteritinib treated patients alive for > 2 years without relapse
- 18 underwent allo HSCT; 16 restarted gilteritinib post allo HSCT

Perl AE, et al. *Blood* 2022;139:3366-3375.

Investigator Survey Results

Regulatory and reimbursement issues aside, which initial treatment would you generally recommend for a 60-year-old patient with AML and a FLT3 mutation who was eligible for intensive chemotherapy?

	FLT3-ITD	FLT3-TKD
 Dr Erba	7 + 3 + quizartinib	7 + 3 + midostaurin
 Dr Fathi	7 + 3 + quizartinib	7 + 3 + midostaurin
 Dr Lin	7 + 3 + quizartinib	7 + 3 + midostaurin
 Dr Perl	7 + 3 + quizartinib	7 + 3 + midostaurin
 Dr Stein	7 + 3 + midostaurin	7 + 3 + midostaurin
 Dr Cortes	7 + 3 + quizartinib	7 + 3 + gilteritinib
 Dr DiNardo	HMA + venetoclax + gilteritinib or quizartinib	HMA + venetoclax + gilteritinib
 Dr Wang	7 + 3 + quizartinib	7 + 3 + midostaurin

Regulatory and reimbursement issues aside, which initial treatment would you generally recommend for an 80-year-old patient with AML and a FLT3 mutation who was not eligible for intensive chemotherapy?

	FLT3-ITD	FLT3-TKD
 Dr Erba	Azacitidine + venetoclax	Azacitidine + venetoclax
 Dr Fathi	Decitabine + venetoclax OR HMA + venetoclax + gilteritinib	Decitabine + venetoclax
 Dr Lin	Azacitidine + venetoclax	Azacitidine + venetoclax
 Dr Perl	Azacitidine + venetoclax +/- gilteritinib	Azacitidine + venetoclax
 Dr Stein	Azacitidine + venetoclax	Azacitidine + venetoclax
 Dr Cortes	Azacitidine + venetoclax + quizartinib	Azacitidine + venetoclax + gilteritinib
 Dr DiNardo	Azacitidine (5 days) + venetoclax + gilteritinib (80 mg)	Azacitidine (5 days) + venetoclax + gilteritinib (80 mg)
 Dr Wang	Azacitidine + venetoclax + gilteritinib	Azacitidine + venetoclax + gilteritinib

Based on available evidence, do you believe FLT3 inhibitors are likely to be used for patients without FLT3 mutations in the near future?

 Dr Erba	Yes
 Dr Fathi	Too early to tell
 Dr Lin	Yes
 Dr Perl	Yes
 Dr Stein	No
 Dr Cortes	Yes
 Dr DiNardo	No
 Dr Wang	No

RTP
RESEARCH
TO PRACTICE

A patient with AML and a FLT3-ITD mutation receives 7+3 chemotherapy and a FLT3 inhibitor, and an MRD assay ordered after the completion of induction therapy is negative. Would you proceed to ASCT? What would be your most likely approach to maintenance therapy?

	Transplant	Maintenance
 Dr Erba	Yes	No maintenance therapy
 Dr Fathi	Yes	No maintenance if MRD-negative, FLT3 inhibitor if MRD-positive
 Dr Lin	Yes	No maintenance if MRD-negative, FLT3 inhibitor if MRD-positive
 Dr Perl	Yes	Gilteritinib for 2 years if peri-HSCT MRD-positive, otherwise no maintenance
 Dr Stein	Yes	No maintenance therapy
 Dr Cortes	Yes	No maintenance therapy
 Dr DiNardo	Yes	FLT3 inhibitor maintenance for 2-3 years
 Dr Wang	Yes	No maintenance therapy

HSCT = hematopoietic stem cell transplant

Regulatory and reimbursement issues aside, which treatment would you generally recommend next for a 60-year-old patient with AML and a FLT3-ITD mutation who experienced disease progression after 7 + 3 + quizartinib followed by ASCT?

 Dr Erba	Gilteritinib
 Dr Fathi	HMA + venetoclax or HMA + venetoclax + gilteritinib
 Dr Lin	Azacitidine + venetoclax + gilteritinib
 Dr Perl	Gilteritinib-based therapy
 Dr Stein	Gilteritinib
 Dr Cortes	Azacitidine + venetoclax + gilteritinib
 Dr DiNardo	HMA + venetoclax + gilteritinib
 Dr Wang	Azacitidine + venetoclax + gilteritinib

Regulatory and reimbursement issues aside, which treatment would you generally recommend next for an 80-year-old patient with AML and a FLT3-ITD mutation who experienced disease progression on azacitidine/venetoclax?

 Dr Erba	Gilteritinib
 Dr Fathi	Gilteritinib or HMA + gilteritinib
 Dr Lin	Gilteritinib
 Dr Perl	Gilteritinib
 Dr Stein	Gilteritinib
 Dr Cortes	Gilteritinib
 Dr DiNardo	Gilteritinib or HMA + gilteritinib
 Dr Wang	Gilteritinib

Agenda

Module 1: Up-Front Therapy for Older Patients with Acute Myeloid Leukemia (AML) — Dr Lin

Module 2: Selection of Therapy for Younger Patients with AML without a Targetable Mutation; Promising Investigational Strategies — Dr Perl

Module 3: Role of FLT3 Inhibitors in AML Management — Dr Erba

Module 4: Incorporation of IDH Inhibitors into the Care of Patients with AML — Dr Fathi

Module 5: Current and Future Role of Menin Inhibitors in the Treatment of AML — Dr Stein

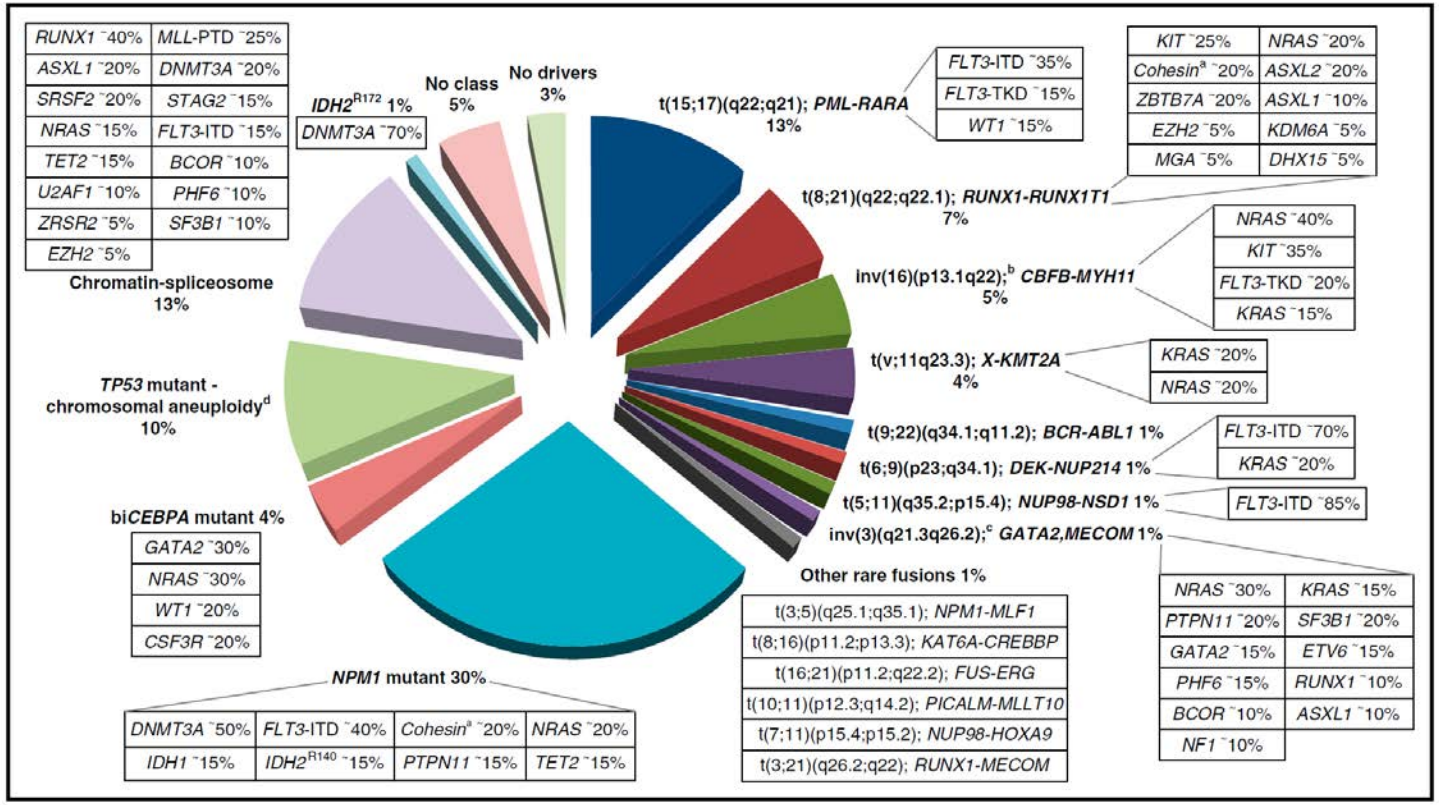
Incorporation of IDH Inhibitors into the Care of Patients with AML

Amir Fathi, MD

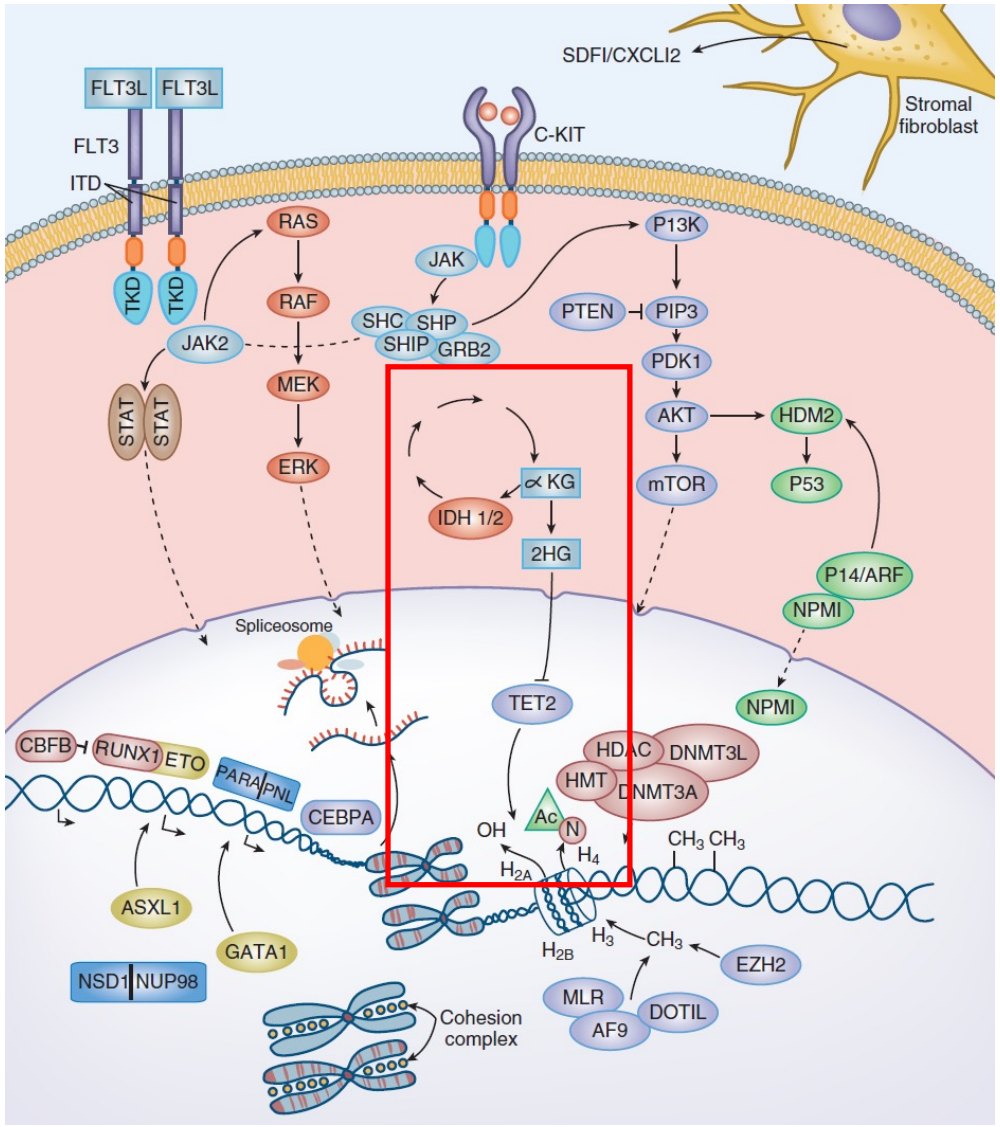
Director, Leukemia Program

MGH Brigham Cancer Institute

AML gets more complex!

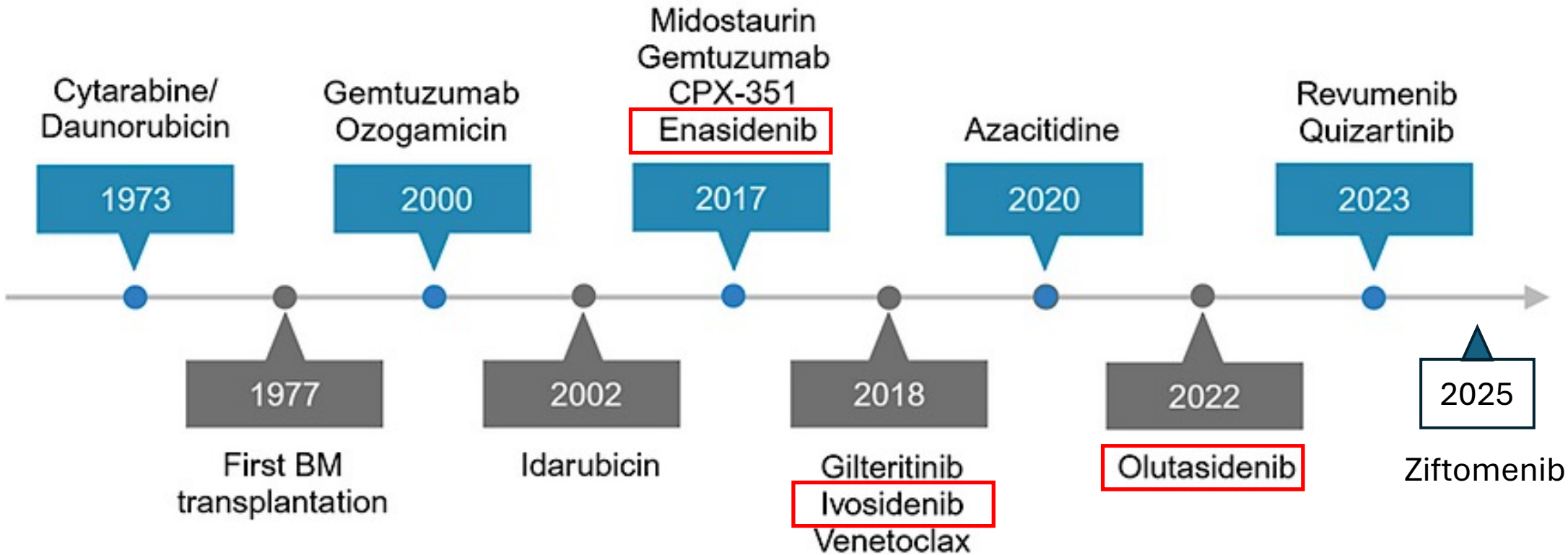


Dohner H. et al. (Blood. 2017;129(4):424-447)



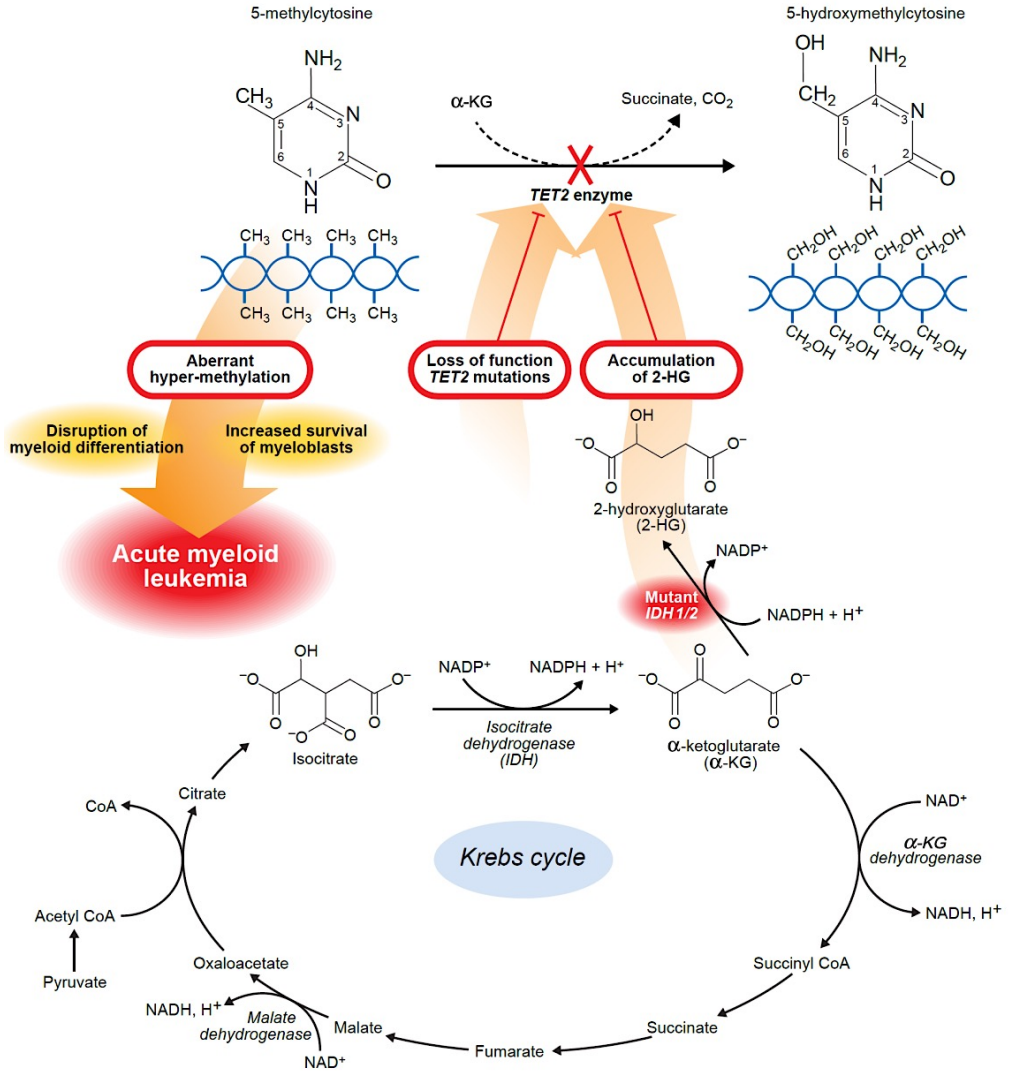
Brunner AM & Graubert TA

Timeline of the FDA Approved AML Therapies



Adapted from Zhang Z et al. Biomarker Research, 2024.

IDH1/2-mutant AML



- Mardis et al, NEJM 2009: First description of *IDH1* mutations in ~8% of patients with AML, associated with normal cytogenetic status (cn-AML).
- Subsequent studies found a larger subset, ~15%, of patients with mutations in the *IDH2* gene.
- IDH proteins, essential to the Krebs Cycle, catalyze decarboxylation of isocitrate to α-ketoglutarate (α-KG) in cytoplasm (IDH1) and mitochondria (IDH2).
- Mutant IDH enzymes catalyze an NADPH-dependent reduction of α-KG to 2-hydroxyglutarate (2-HG).
- This leads to accumulation of 2-HG onco-metabolite in IDH-mutant tumors.

-Ward et al. Cancer cell, 2010
-Gross et al. J Exp Med 207:339-44, 2010.
-Dang et al. Nature 462:739-44, 2009.

Enasidenib in R/R *IDH2*+ AML: Phase I/II Study

- Single-arm, first-in-human, dose-escalation and -expansion study

Phase I Dose Escalation

Enasidenib
Cumulative daily doses of 50-650 mg
Continuous 28-day cycles
(n = 113)

Adult patients with AML (R/R or untreated, aged ≥60 yr, and not candidates for SoC tx) or MDS (R/R or high risk by IPSS-R, not candidates for SoC tx)

- Phase II endpoints
  - Efficacy: ORR, OS, EFS
  - Exploratory: PK/PD

4-Arm Phase I Dose Expansion

Enasidenib
100 mg QD
Continuous 28-day cycles
(n = 126)

- Patients with R/R AML aged ≥60 yr, or any age if relapsed post-BMT
- Patients with R/R AML aged <60 yr, no prior BMT
- Untreated AML aged ≥60 yr, ineligible for SoC tx
- Any other *IDH2*-positive advanced hematologic malignancy ineligible for other arms

Total patients with R/R AML receiving enasidenib 100 mg/day: n = 214 of 345

Phase II

Enasidenib
100 mg QD
Continuous 28-day cycles
(n = 106)

Adult patients with R/R AML

- Relapse after allogeneic SCT
- Second or later relapse
- Refractory to initial induction/reinduction
- Relapse within 1 yr of initial tx, excluding patients with favorable-risk cytogenetics

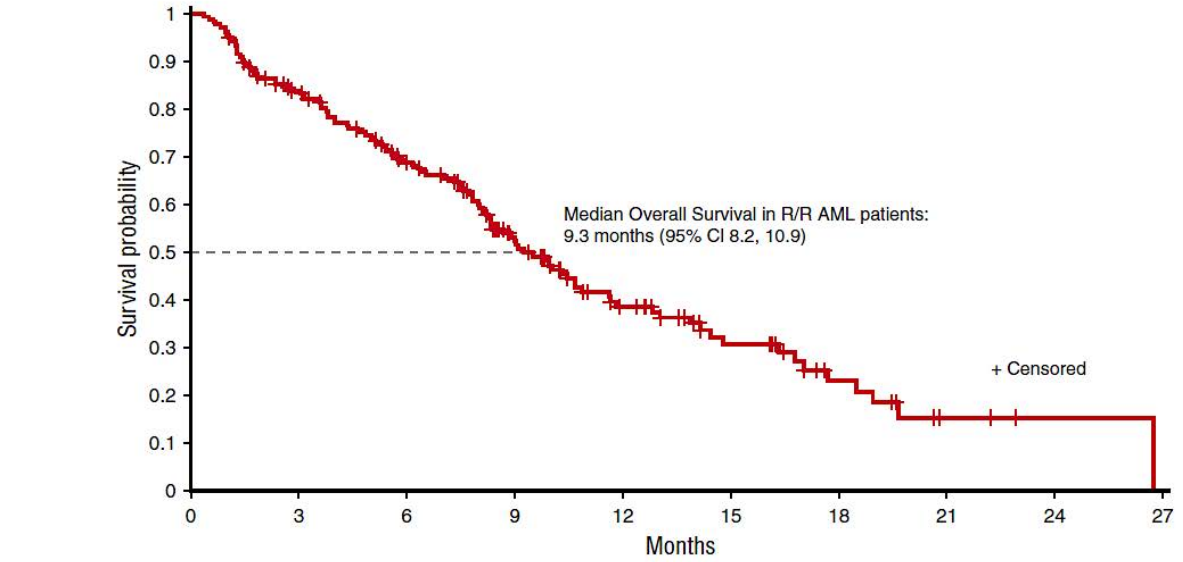
Stein. Blood. 2019;133:676. Stein. Blood. 2017;130:722.
NCT01915498.

Enasidenib - Responses in R/R AML

	Relapsed or refractory AML									
	Enasidenib 100 mg per day (n = 109)					All doses (N = 176)				
Response	No.	%	95% CI	Median	Range	No.	%	95% CI	Median	Range
ORR*†	42	38.5	29.4-48.3			71	40.3	33.0-48.0		
Best response										
CR	22	20.2	13.1-28.9			34	19.3	13.8-25.9		
CR with incomplete hematologic recovery/CR with incomplete platelet recovery	7	6.4				12	6.8			
Partial remission	3	2.8				11	6.3			
Morphologic leukemia-free state	10	9.2				14	8.0			
Stable disease‡	58	53.2				85	48.3			
Progressive disease§	5	4.6				9	5.1			
Not evaluable	2	1.8				3	1. 7			
Time to first response, mo				1.9	0.5-9.4				1.9	0.5-9.4
Duration of response, mo			3.8-9.7	5.6				3.9-7.4	5.8	
Time to CR, mo				3.7	0.7-11.2				3.8	0.5-11.2
Duration of response in patients who attained CR, mo ‖			5.3-NR	8.8				6.4-NR	8.8	

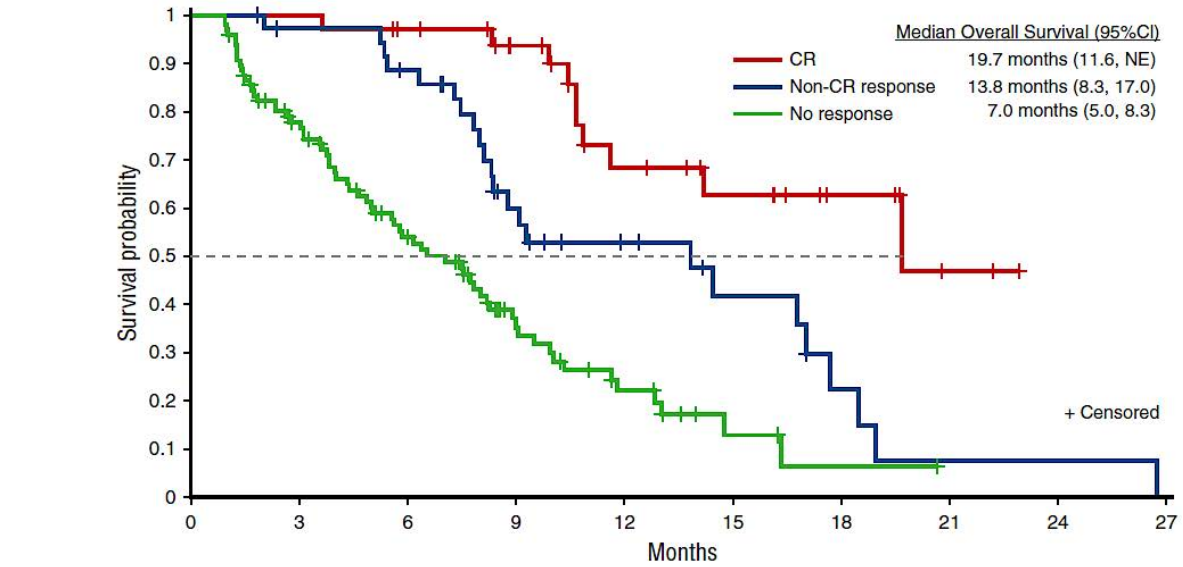
Stein et al. Blood 2017.

Enasidenib – Survival in R/R AML



Patients at risk:

	176	138	105	63	37	21	10	3	1	0



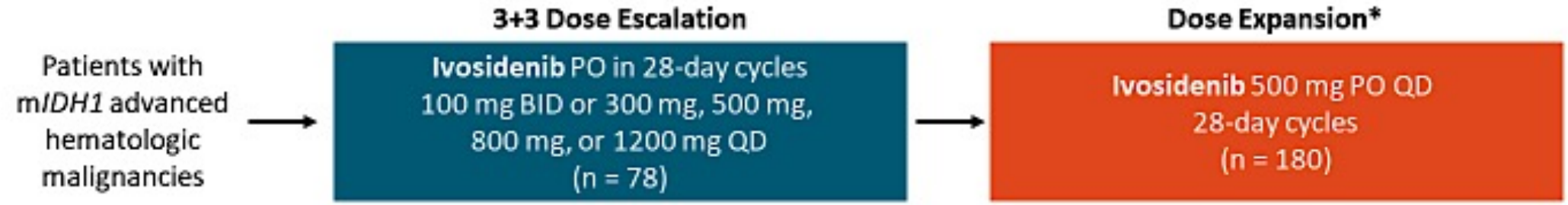
Patients at risk:

CR	34	34	31	25	15	11	6	2	0	
Non-CR response	37	34	30	17	11	7	3	1	1	0
No response	97	68	43	20	10	3	1	0		

Stein et al. Blood 2017.

Ivosidenib in *IDH1*-Mutated AML: Study Design

- Multicenter, single-arm, open-label phase I trial



*Cohorts included: R/R AML in second relapse, relapse after SCT, refractory to induction or reinduction, or relapse ≤1 yr (n = 126); untreated AML ineligible for SoC (n = 25); non-AML m*IDH1* R/R advanced hematologic malignancy (n = 11); R/R AML not eligible for other R/R AML arm (n = 18).

- Primary endpoints: safety and tolerability, MTD, RP2D, clinical activity (CR + CRh rate) in patients with untreated *IDH1*-mutated AML who received ivosidenib 500 mg
- Secondary endpoints: DLT, PK/PD, clinical activity in advanced hematologic malignancies
- Exploratory endpoints: determination of comutations and m*IDH1* VAF

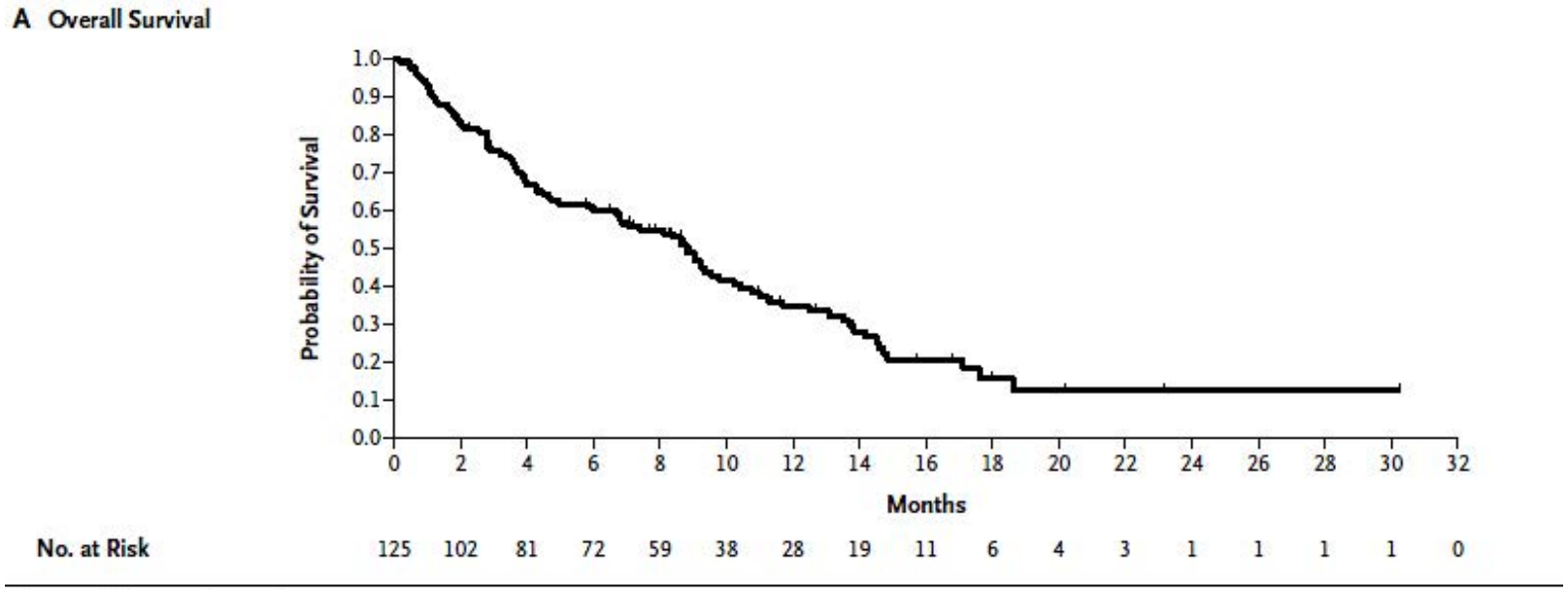
DiNardo. NEJM. 2018;378:2386. Roboz. Blood. 2020;135:463.

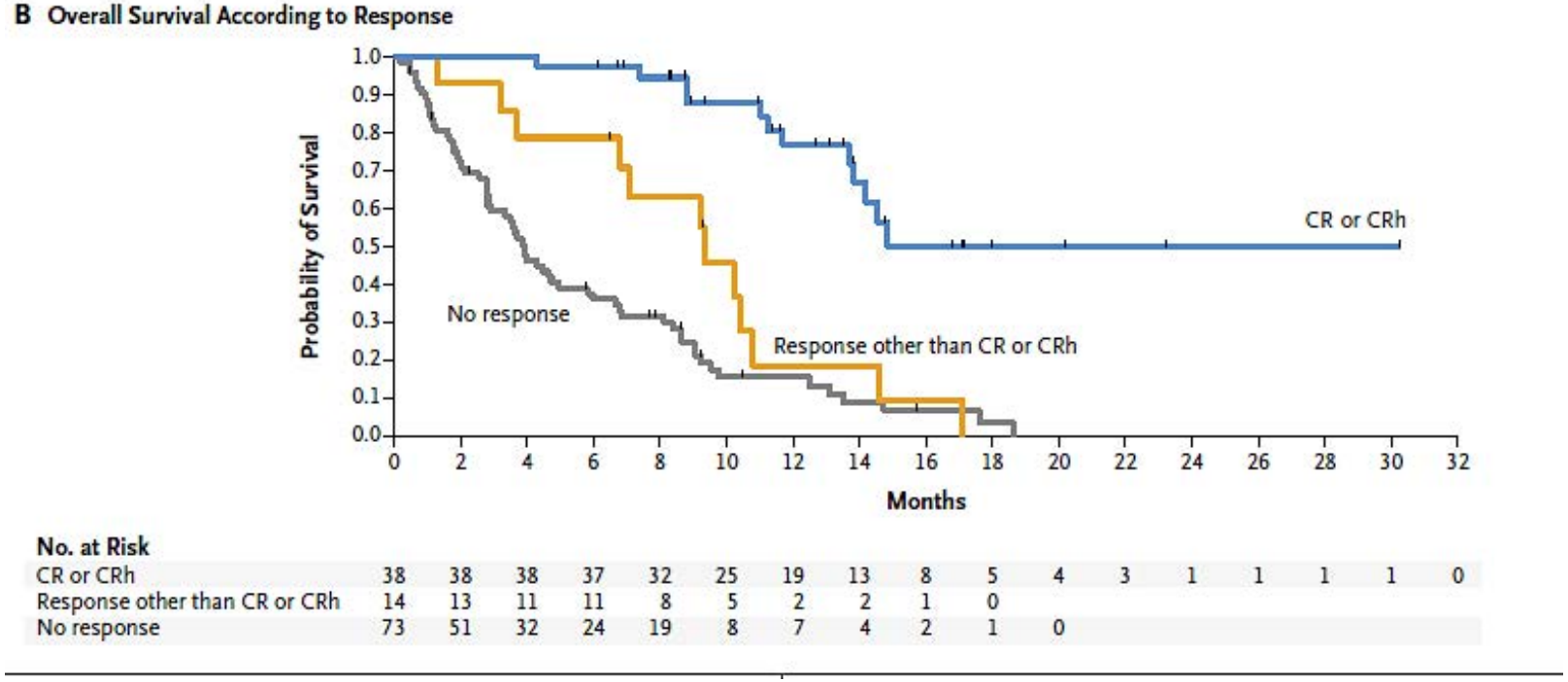
Ivosidenib – Responses in R/R AML

Response	Primary Efficacy Population (N=125)	Relapsed or Refractory AML (N=179)
Best response — no. (%)		
CR	27 (21.6)	39 (21.8)
CRi or CRp	16 (12.8)	21 (11.7)
Partial remission	0	0
MLFS or bone marrow CR¶	9 (7.2)	10 (5.6)
Stable disease	44 (35.2)	69 (38.5)
Progressive disease	13 (10.4)	15 (8.4)
Could not be evaluated	0	0
Not assessed	16 (12.8)	25 (14.0)

DiNardo et al. New Engl J Med, 2018.

Ivosidenib – Survival in R/R AML

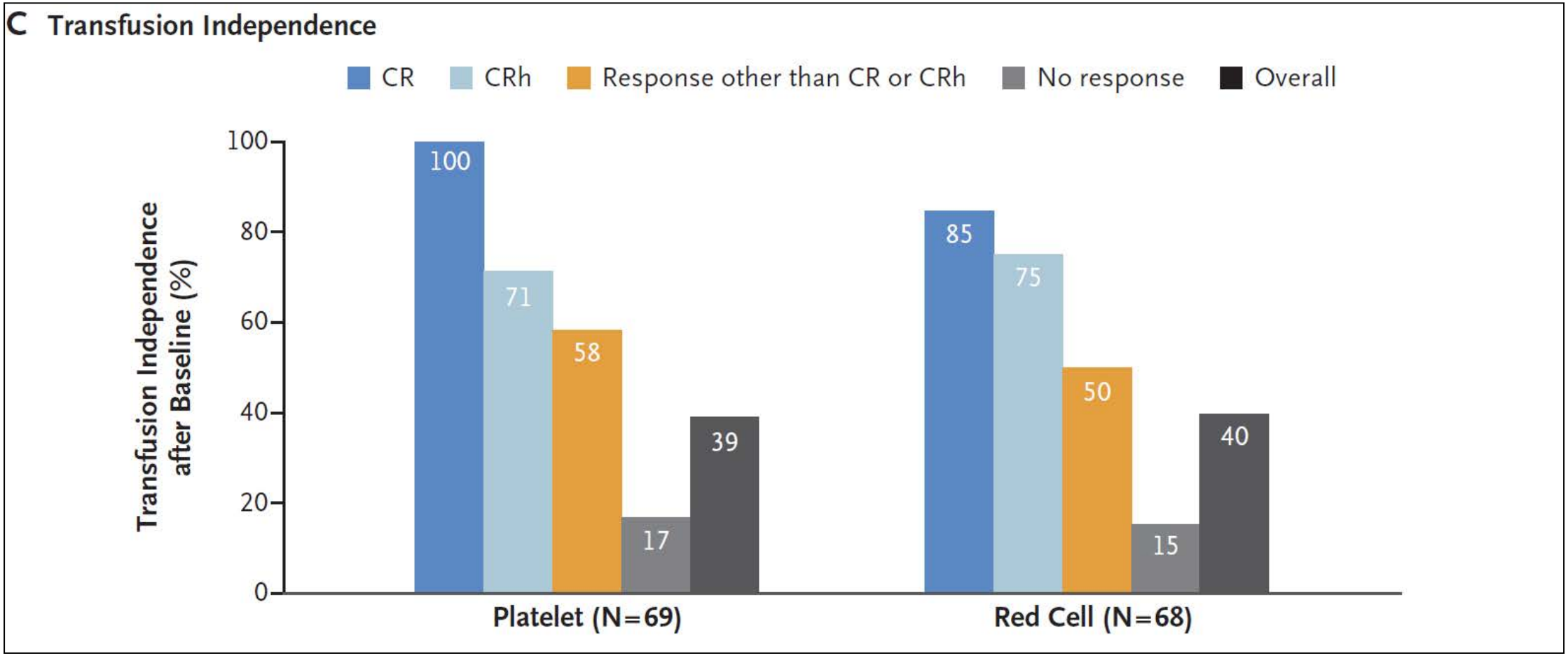




DiNardo et al. New Engl J Med, 2018.

Ivosidenib in R/R AML: Transfusion Independence

Transfusion independence was observed across all response categories at 500 mg among those dependent at baseline



DiNardo et al. New Engl J Med, 2018.

IDH-Differentiation Syndrome

Table 1. Frequency of Signs and Symptoms Consistent With IDH-DS[a]

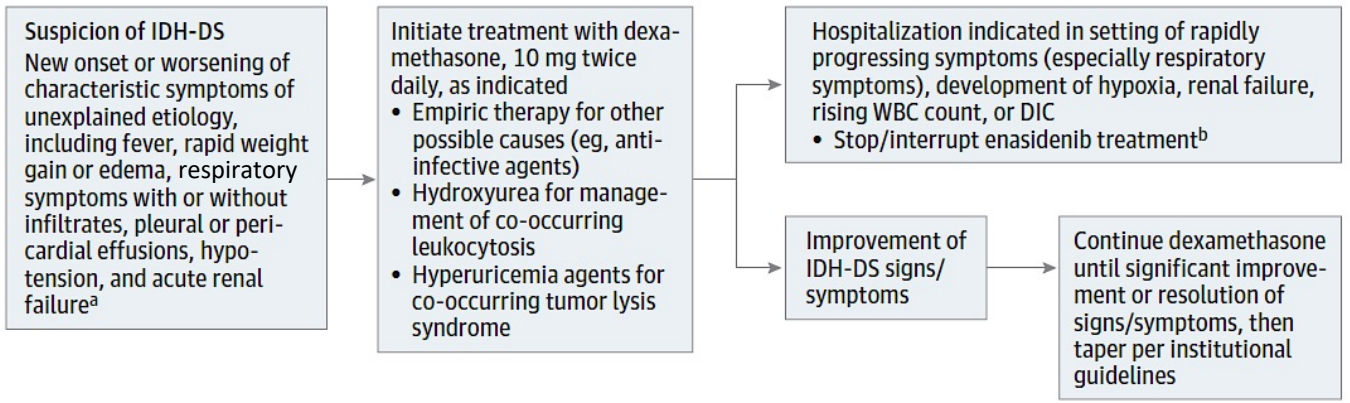
Sign or Symptom	Patients With IDH-DS, No. (%) (n = 33)[b]
Dyspnea	28 (85)
Unexplained fever (body temperature of 38.0°C for 2 d)	26 (79)
Pulmonary infiltrates	24 (73)
Hypoxia	19 (58)
Acute kidney injury (CTCAE grade ≥2)	14 (42)
Pleural effusion	
Bone pain or arthralgia	
Lymphadenopathy	
Rash	
Disseminated intravascular coagulopathy	
Edema or weight gain of >5 kg from screening	
Pericardial effusion	

Abbreviations: CTCAE, Common Terminology Criteria fo
IDH-DS, isocitrate dehydrogenase differentiation syndro

[a] Signs and symptoms included in this table are based or
differentiation syndrome review committee review of

[b] Patients may have had multiple symptoms.

Figure. Differentiation Syndrome Review Committee Amended Protocol for Isocitrate Dehydrogenase Differentiation Syndrome (IDH-DS) Diagnosis and Management



DIC indicates disseminated intravascular coagulation; WBC, white blood cells.

[a] Typical onset is between 7 to 10 days and 5 months from start of enasidenib treatment or reinitiation of enasidenib after prolonged treatment interruption.

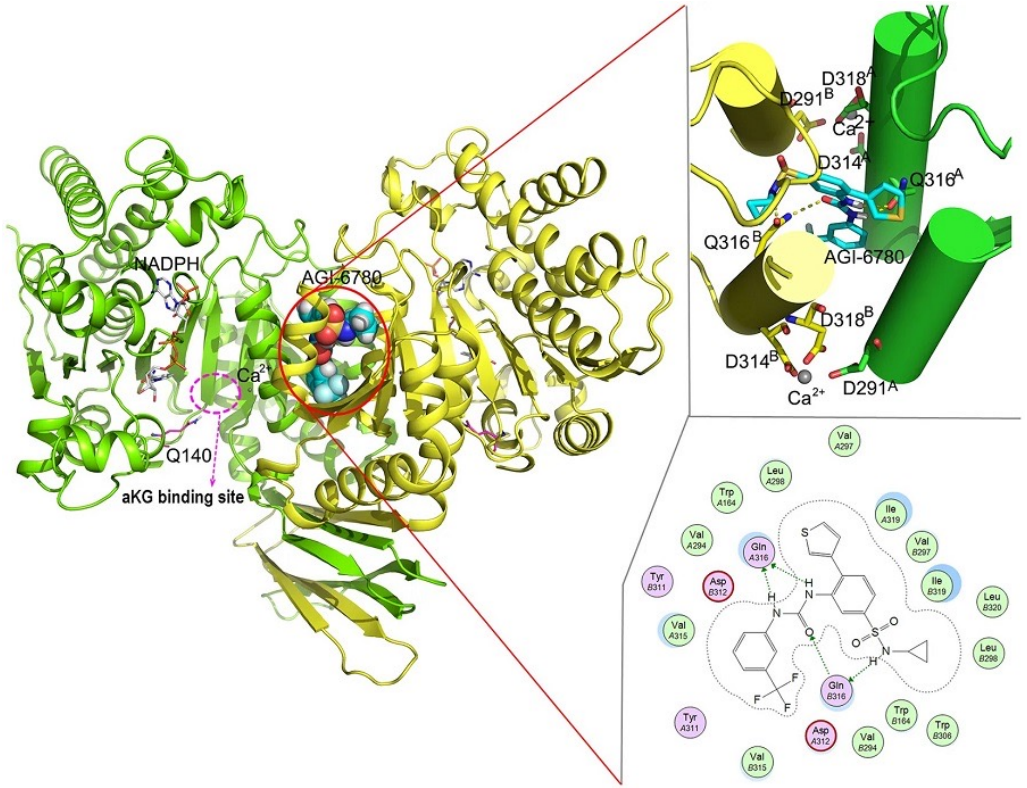
[b] Owing to the long half-life of enasidenib, treatment may not immediately reverse symptoms of IDH-DS.

Fathi AT et al. *JAMA Oncol*. 2018;4:1106-10.

Acquired Resistance to IDH Inhibitors (enasidenib)

- *IDH2*-mutated pts treated with enasidenib, with initial response, developed therapeutic resistance and a recurrent increase in circulating 2-HG.

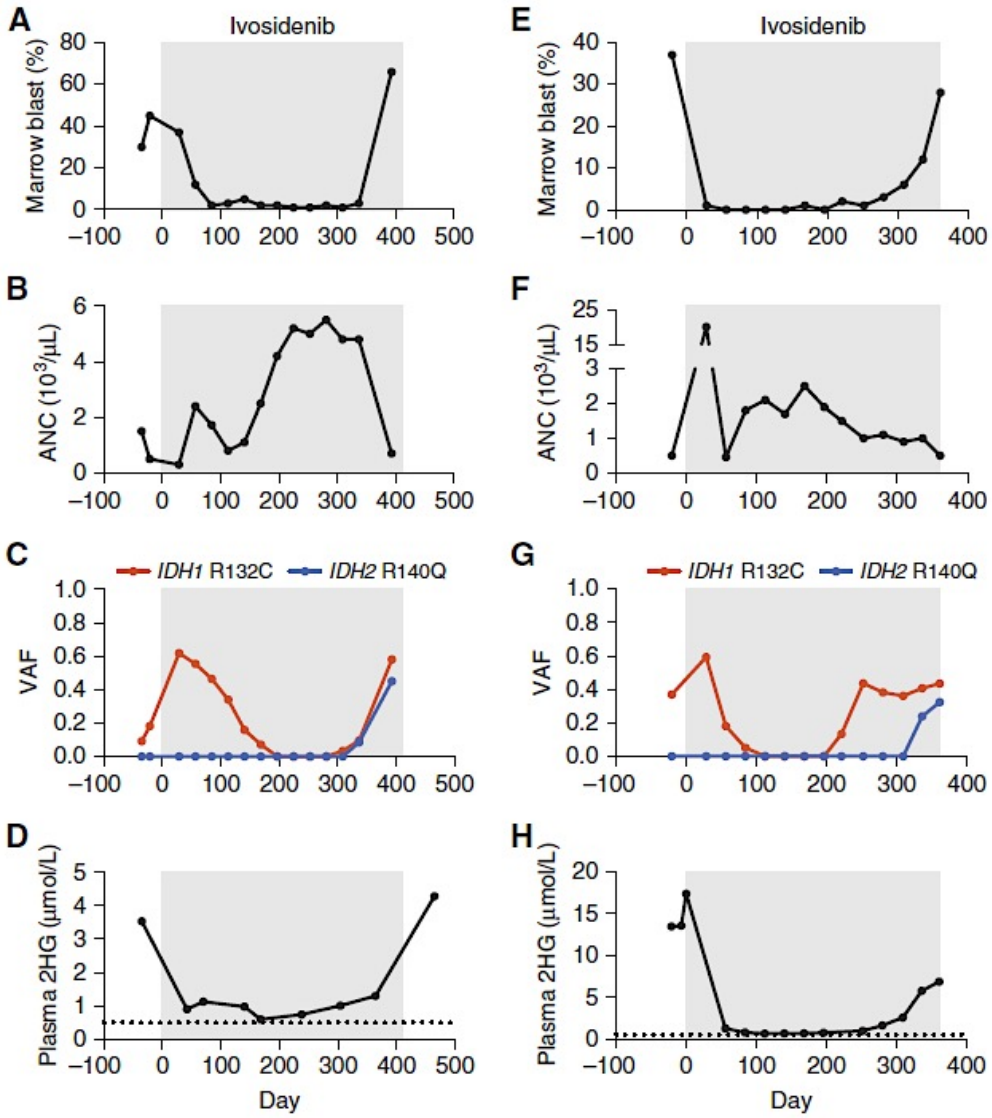
- Resistance was associated with the emergence of second-site IDH2 mutations in trans, occurring in the IDH2 allele without the neomorphic R140Q mutation.



Intlekofer, et al. Nature 2018
Kim A. Blood 2019
Chen J et al. Sci Rep. 2017

Acquired Resistance to IDH Inhibitors

- Four other cases of therapeutic resistance mediated by mutant *IDH* "isoform switching", from IDH1 to IDH2 or vice versa.
- This isoform switch appeared to restore 2HG production by the tumor, and clinical progression on therapy.

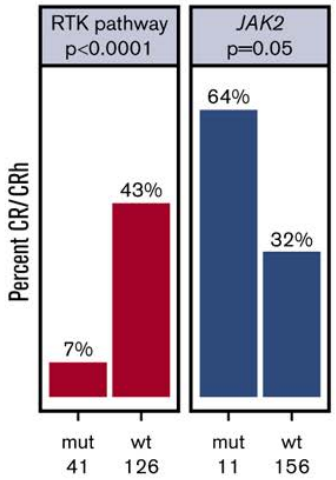


Harding, et al. Cancer Discov 2018

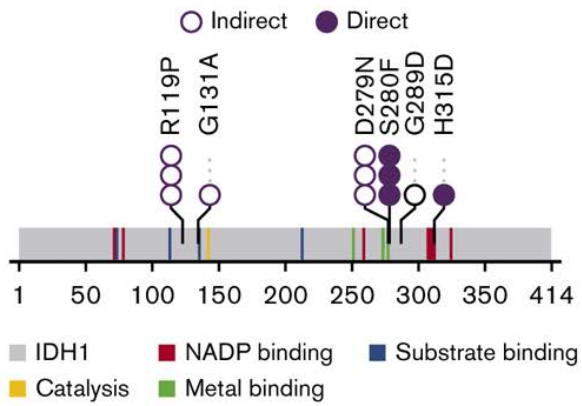
Acquired Resistance to Ivosidenib

Molecular mechanisms mediating relapse following ivosidenib monotherapy in *IDH1*-mutant relapsed or refractory AML

Baseline mutations associated with response (*JAK2*) or primary resistance (RTK pathway) to ivosidenib

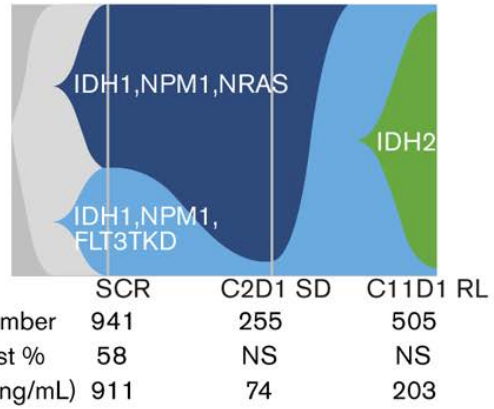


Second-site *IDH1* mutations emerging during ivosidenib treatment



Pathway, n (%)	Patients with emerging mutations at relapse/PD	
	All (n = 74)	Best response of CR or CRh (n = 26)
RTK pathway	20 (27)	9 (35)
IDH-related	17 (23)	9 (35)
IDH1 second-site	10 (14)	5 (19)
IDH2	9 (12)	6 (23)
Differentiation	13 (18)	8 (31)
Chromatin	8 (11)	7 (27)
Epigenetics	6 (8)	2 (8)

***IDH2* mutation acquired in *IDH1*-mutant clone with elevation of 2-HG at relapse (single-cell DNA-seq, individual patient)**



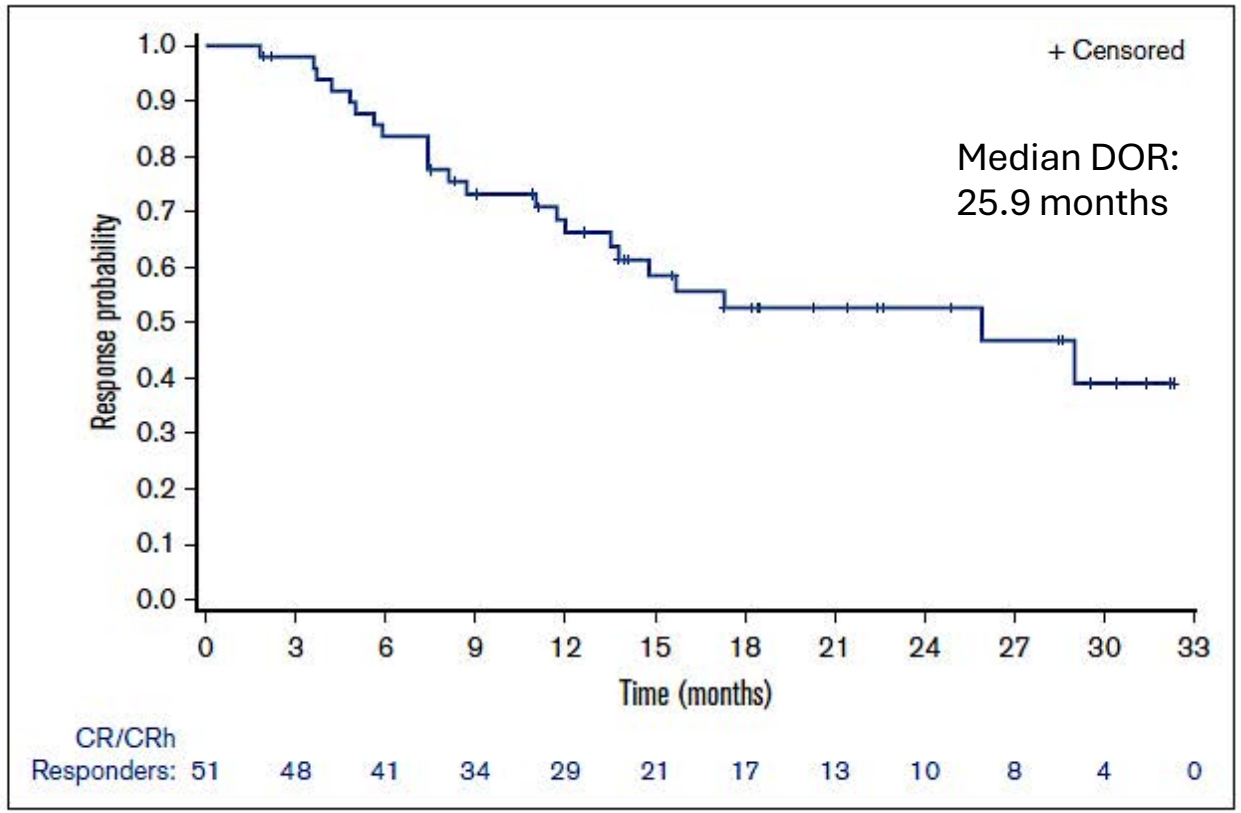
Choe S et al. Blood Adv 2020

Olutasidenib

Olutasidenib (FT-2102) induces durable complete remissions in patients with relapsed or refractory *IDH1*-mutated AML

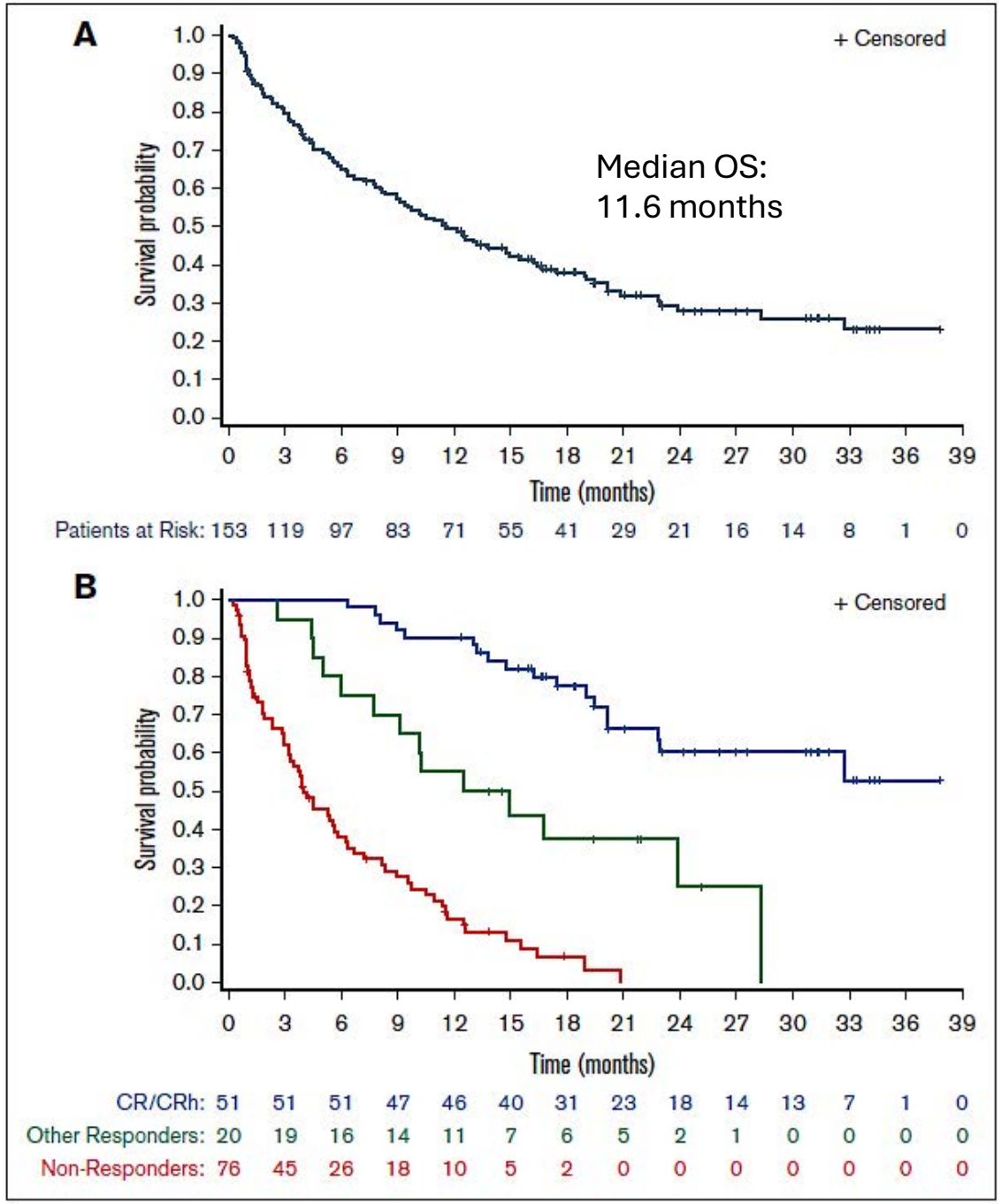
Stéphane de Botton,[1] Pierre Fenaux,[2] Karen Yee,[3] Christian Récher,[4] Andrew H. Wei,[5] Pau Montesinos,[6] David C. Taussig,[7] Arnaud Pigneux,[8] Thorsten Braun,[9] Antonio Curti,[10] Carolyn Grove,[11] Brian A. Jonas,[12] Asim Khwaja,[13] Ollivier Legrand,[14] Pierre Peterlin,[15] Montserrat Arnan,[16] William Blum,[17] Daniela Cilloni,[18] Devendra K. Hiwase,[19] Joseph G. Jurcic,[20] Jürgen Krauter,[21] Xavier Thomas,[22] Justin M. Watts,[23] Jay Yang,[24] Olga Polyanskaya,[25] Julie Brevard,[25] Jennifer Sweeney,[25] Emma Barrett,[25] and Jorge Cortes[26]

Response rates	Efficacy-evaluable population (n = 147)
CR* or CRh	
n (%) [95% CI]	51 (35) [27.0-43.0]
Median time to CR/CRh, mo (range)	1.9 (0.9-5.6)
CR*	
n (%) [95% CI]	47 (32) [24.5-40.2]
Median time to CR, months (range)	2.8 (0.9-7.4)
Overall response	
N (%) [95% CI]	71 (48) [40.0-56.7]
Median time to first overall response, mo (range)	1.9 (0.9-10.2)
Best overall response, n (%)	
CR*	47 (32)
CRh	4 (3)
CRi	15 (10)
PR	3 (2)
MLFS	2 (1)
SD†	42 (29)
Progressive disease	10 (7)
Not evaluable/not done	6 (4) / 18 (12)



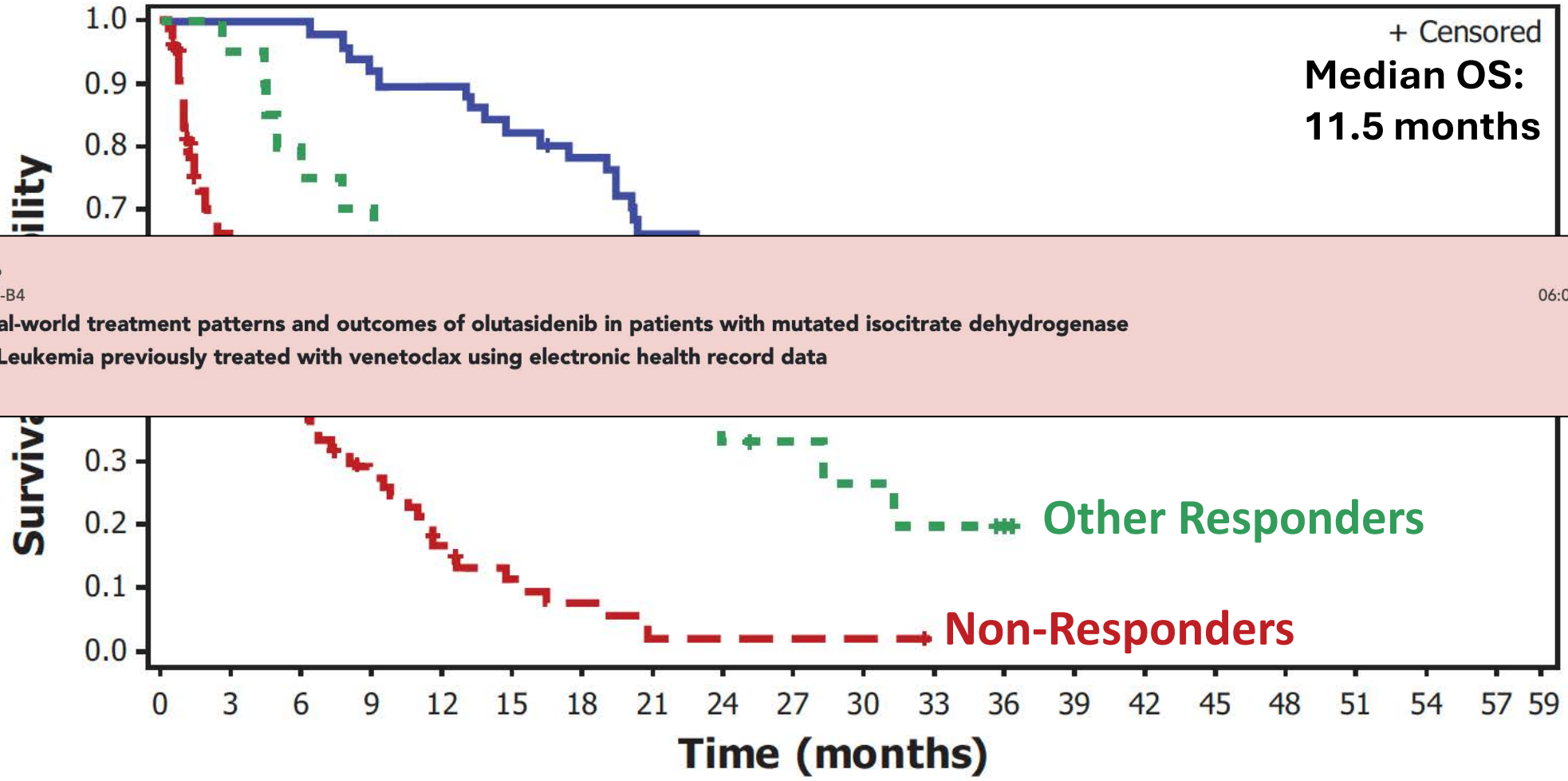
De Botton, et al. Blood Adv, 2023.

Olutasidenib – Survival in R/R AML



De Botton, et al. Blood Adv, 2023.

Olutasidenib: Final 5-Year Results from the Pivotal Cohort — OS by Responder Status



PRESENTATION ID 4616
OCCC - West Halls B3-B4
Sunday, December 7
06:00 PM - 08:00 PM EST

Assessment of real-world treatment patterns and outcomes of olutasidenib in patients with mutated isocitrate dehydrogenase 1 Acute Myeloid Leukemia previously treated with venetoclax using electronic health record data

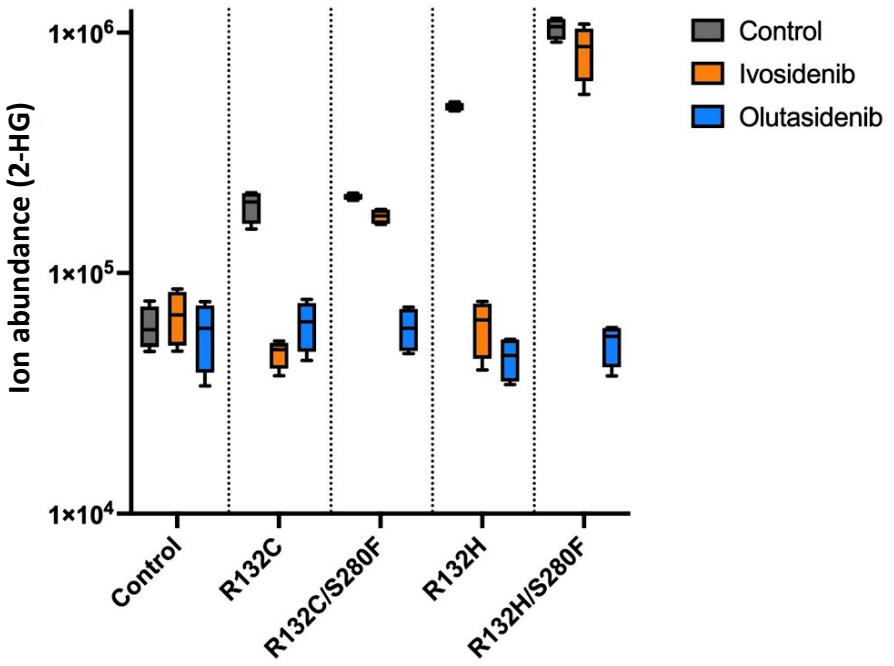
Jorge Cortes, MD

Cortes J et al. *J Hematol Oncol* 2025 November 14;18:102.

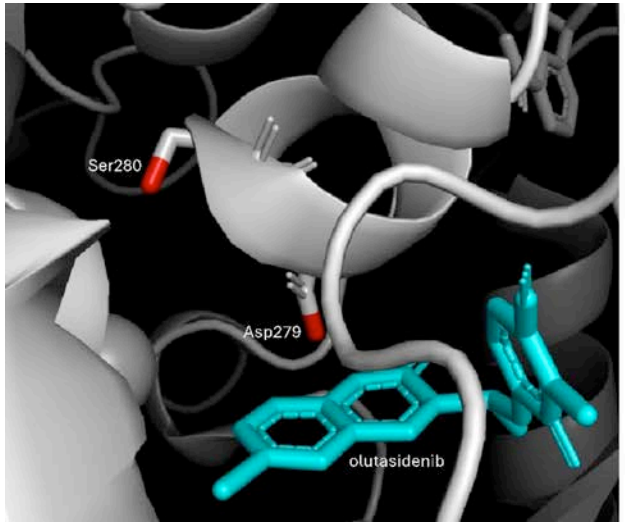
Olutasidenib versus Ivosidenib

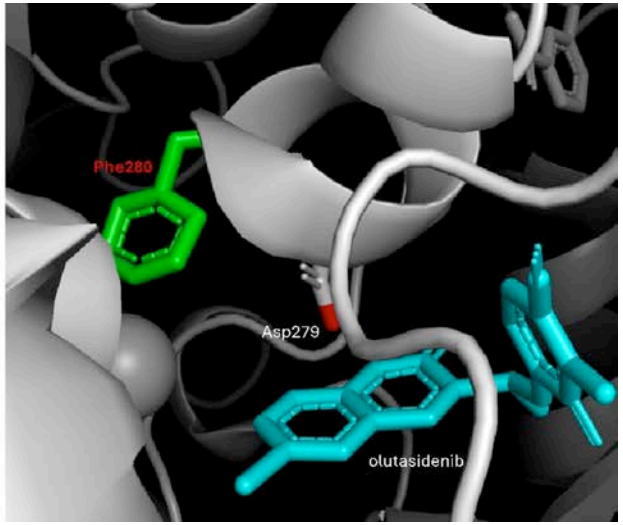
Table 1 Clinical efficacy in R/R AML patients receiving monotherapy in the primary efficacy populations

	Olutasidenib $N=147$[a]	Ivosidenib $N=125$[b]
CR/CRh	35%	30%
CR	32%	22%
CRh	3%	8%
Duration of CR/CRh in months, median (95% CI)	25.9 (13.5, NR)	8.2 (5.5, 12)



- Watts et al postulate that ivosidenib may bind the allosteric pocket longer in a more constant state, causing interaction with wildtype IDH1.
- The smaller olutasidenib molecule has weaker binding affinity to wild-type IDH1, making it perhaps a more selective inhibitor of mutant IDH1.





Watts, et al. Curr Treat Options Oncol, 2024.

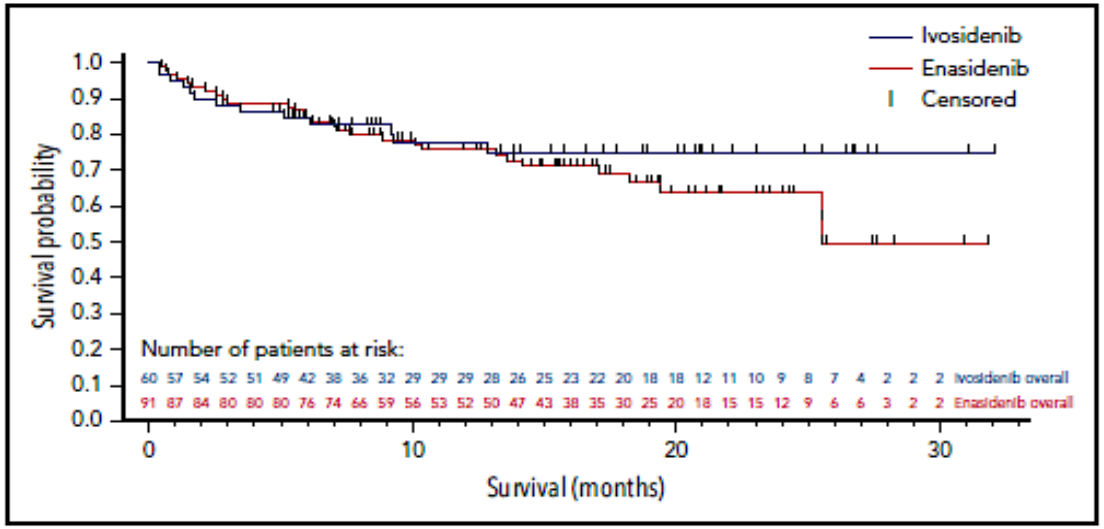
IDHi Combinations – With 7+3

Ivosidenib or enasidenib combined with intensive chemotherapy in patients with newly diagnosed AML: a phase 1 study

Eytan M. Stein,[1,*] Courtney D. DiNardo,[2,*] Amir T. Fathi,[3] Alice S. Mims,[4] Keith W. Pratz,[5] Michael R. Savona,[6] Anthony S. Stein,[7] Richard M. Stone,[8] Eric S. Winer,[8] Christopher S. Seet,[9] Hartmut Döhner,[10] Daniel A. Pollyea,[11] James K. McCloskey,[12] Olatoyosi Odenike,[13] Bob Löwenberg,[14] Gert J. Ossenkoppele,[15] Prapti A. Patel,[16] Mikhail Roshal,[17] Mark G. Frattini,[18] Frederik Lersch,[19] Aleksandra Franovic,[20] Salah Nabhan,[21] Bin Fan,[21] Sung Choe,[21] Hongfang Wang,[21] Bin Wu,[21] Lei Hua,[21] Caroline Almon,[21] Michael Cooper,[21] Hagop M. Kantarjian,[2,†] and Martin S. Tallman[1,†]

Response category	Ivosidenib 500 mg + chemotherapy, n (%)			Enasidenib 100 mg + chemotherapy, n (%)		
	All, N = 60	De novo AML, n = 42	Secondary AML, n = 18	All, N = 91*	De novo AML, n = 56	Secondary AML, n = 35
CR/CRi/CRp	46 (77)	37 (88)	9 (50)	67 (74)	45 (80)	22 (63)
CR	41 (68)	32 (76)	9 (50)	50 (55)	36 (64)	14 (40)
CRi/CRp	5 (8)	5 (12)	—	17 (19)	9 (16)	8 (23)
MLFS	4 (7)	3 (7)	1 (6)	10 (11)	5 (9)	5 (14)
PR	2 (3)	—	2 (11)	2 (2)	1 (2)	1 (3)
Treatment failure†	8 (13)	2 (5)	6 (33)	12 (13)	5 (9)	7 (20)

- The 30- and 60-day mortality was 5% and 10% in the ivosidenib, and 5% and 9% in the enasidenib cohorts.

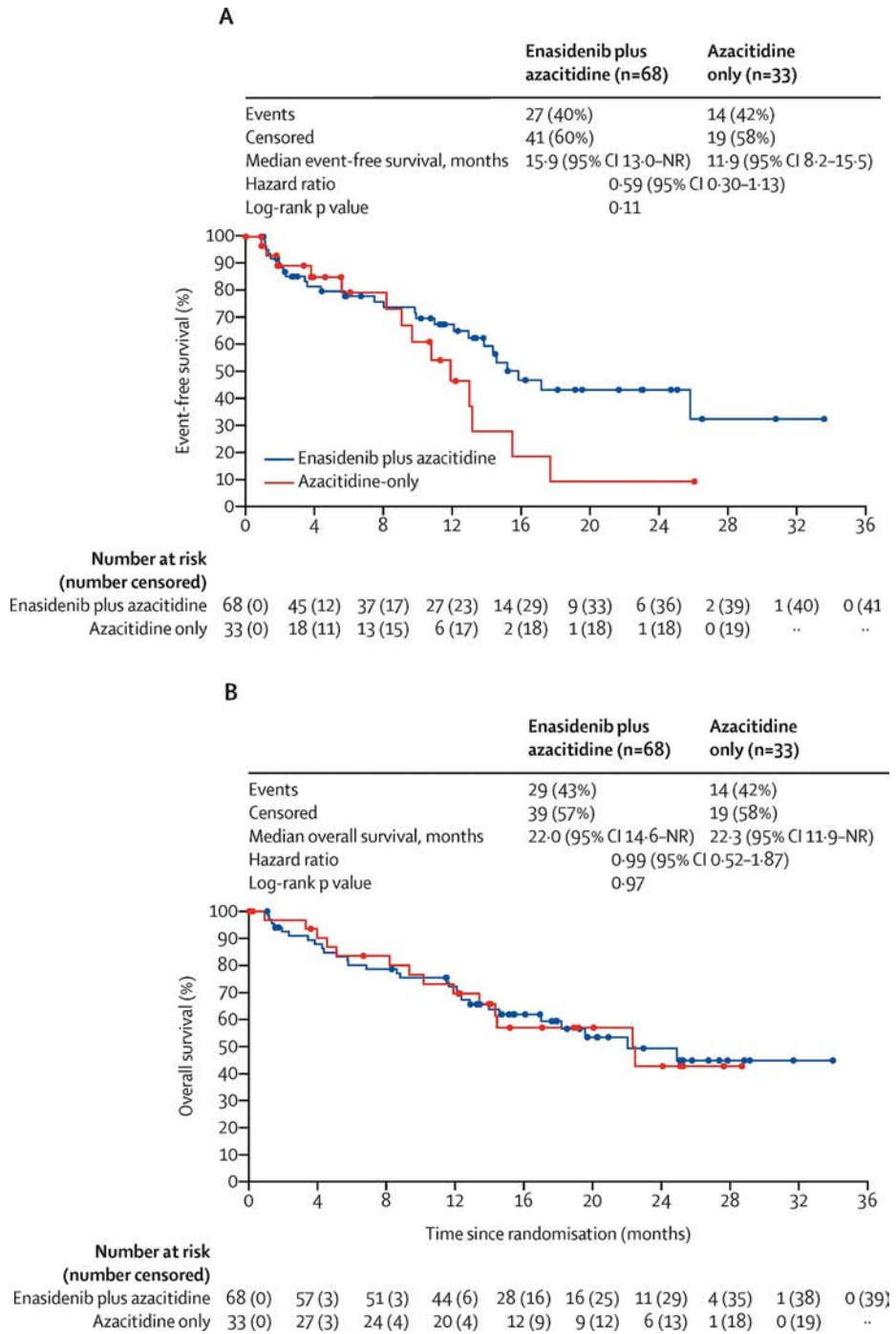


Stein EM, et al. Blood, 2021.

Enasidenib + HMA

	Enasidenib plus azacitidine (n=68)	Azacitidine only (n=33)	p value
Overall response*	50 (74%; 95% CI 61–84)	12 (36%; 95% CI 20–55)	0·0003
Complete remission	37 (54%; 95% CI 42–67)	4 (12%; 95% CI 3–28)	<0·0001
Complete remission or complete remission with partial haematological recovery	39 (57%)	6 (18%)	0·0002
Complete remission with incomplete blood count or platelet recovery	6 (9%)	6 (18%)	..
Partial remission	4 (6%)	2 (6%)	..
Morphological leukaemia-free state	3 (4%)	0	..
Stable disease	13 (19%)	16 (48%)	..
Disease progression	1 (1%)	1 (3%)	..
Not evaluable or missing data	4 (6%)	4 (12%)	..
Time to first response, months	1·9 (1·1–3·9)	3·6 (1·9–4·4)	..
Time to complete remission, months	5·4 (3·8–7·6)	4·4 (3·8–5·6)	..
Duration of response, months	24·1 (95% CI 10·0–NR)	9·9 (95% CI 5·5–13·6)	..
Duration of complete remission, months	NR (95% CI 7·7–NR)	12·7 (95% CI 11·7–NR)	..

Data are n (%; 95% CI), n (%), median (IQR), or median (95% CI). Data cutoff Aug 20, 2019. NR=not reached. *Overall response defined as proportion of patients with complete remission, complete remission with incomplete blood count or platelet recovery, partial remission, or morphological leukaemia-free state.



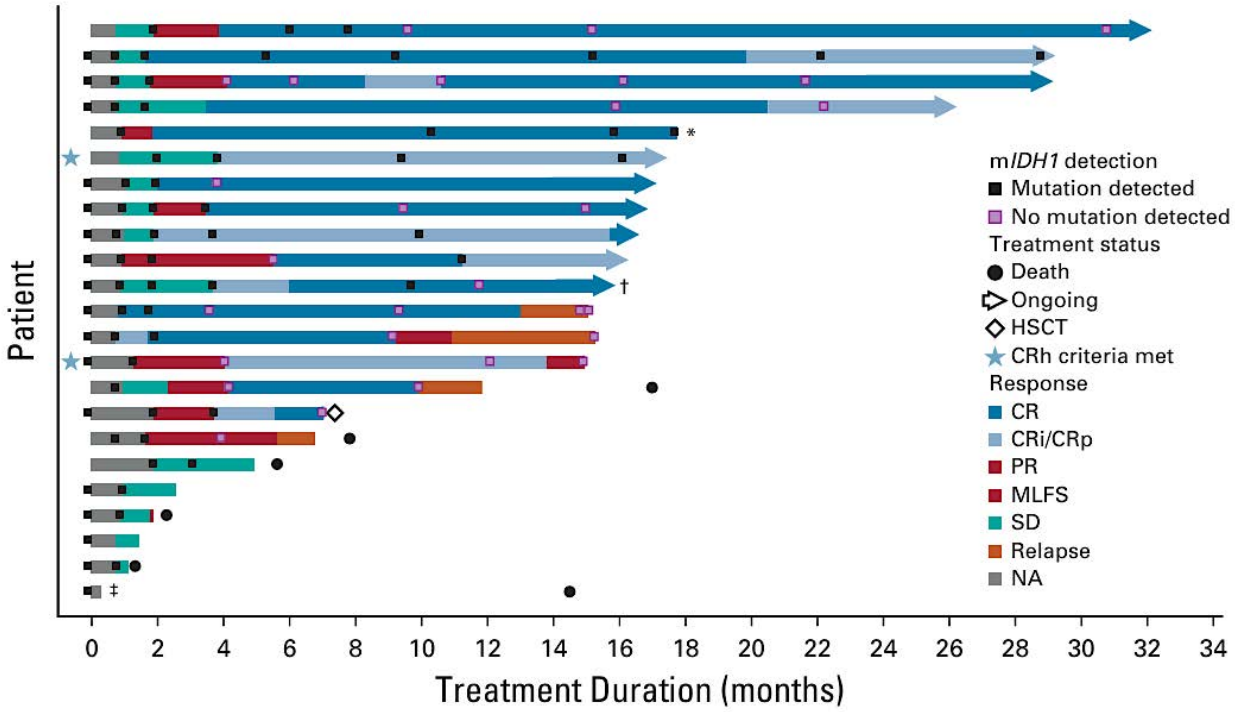
DiNardo CD, et al. Lancet Oncol, 2021.
DiNardo CD, et al. Blood, 2019

Ivosidenib + HMA

Mutant Isocitrate Dehydrogenase 1 Inhibitor Ivosidenib in Combination With Azacitidine for Newly Diagnosed Acute Myeloid Leukemia

Courtney D. DiNardo, MD[1]; Anthony S. Stein, MD[2]; Eytan M. Stein, MD[3]; Amir T. Fathi, MD[4]; Olga Frankfurt, MD[5]; Andre C. Schuh, MD[6]; Hartmut Döhner, MD[7]; Giovanni Martinelli, MD[8]; Prapti A. Patel, MD[9]; Emmanuel Raffoux, MD[10]; Peter Tan, MBBS[11]; Amer M. Zeidan, MBBS[12]; Stéphane de Botton, MD, PhD[13]; Hagop M. Kantarjian, MD[1]; Richard M. Stone, MD[14]; Mark G. Frattini, MD, PhD[15]; Frederik Lersch, RN[16]; Jing Gong, PhD[15]; Diego A. Gianolio, PhD[17]; Vickie Zhang, PhD[17]; Aleksandra Franovic, PhD[18]; Bin Fan, PhD[17]; Meredith Goldwasser, ScD[17]; Scott Daigle, MS[17]; Sung Choe, PhD[17]; Bin Wu, PhD[17]; Thomas Winkler, MD[17]; and Paresh Vyas, MD, PhD[19]

Response Category	Response
CR + CRh,[a] No. (%) [95% CI]	16 (69.6) [47.1 to 86.8]
Median time to CR/CRh, months (range)	2.8 (0.8-11.5)
Median duration of CR/CRh, months [95% CI]	NE [12.2 to NE]
CR, No. (%) [95% CI]	14 (60.9) [38.5 to 80.3]
Median time to CR, months (range)	3.7 (0.8-15.7)
Median duration of CR, months [95% CI]	NE [9.3 to NE]
CRh,[a] No. (%)	2 (8.7)
ORR,[b] No. (%) [95% CI]	18 (78.3) [56.3 to 92.5]
Median time to response, months (range)	1.8 (0.7-3.8)
Median duration of response, months [95% CI]	NE [10.3 to NE]
Best response,[c] No. (%)	
CR	14 (60.9)
CRi/CRp	2 (8.7)
MLFS	2 (8.7)
SD	4 (17.4)
NA	1 (4.3)



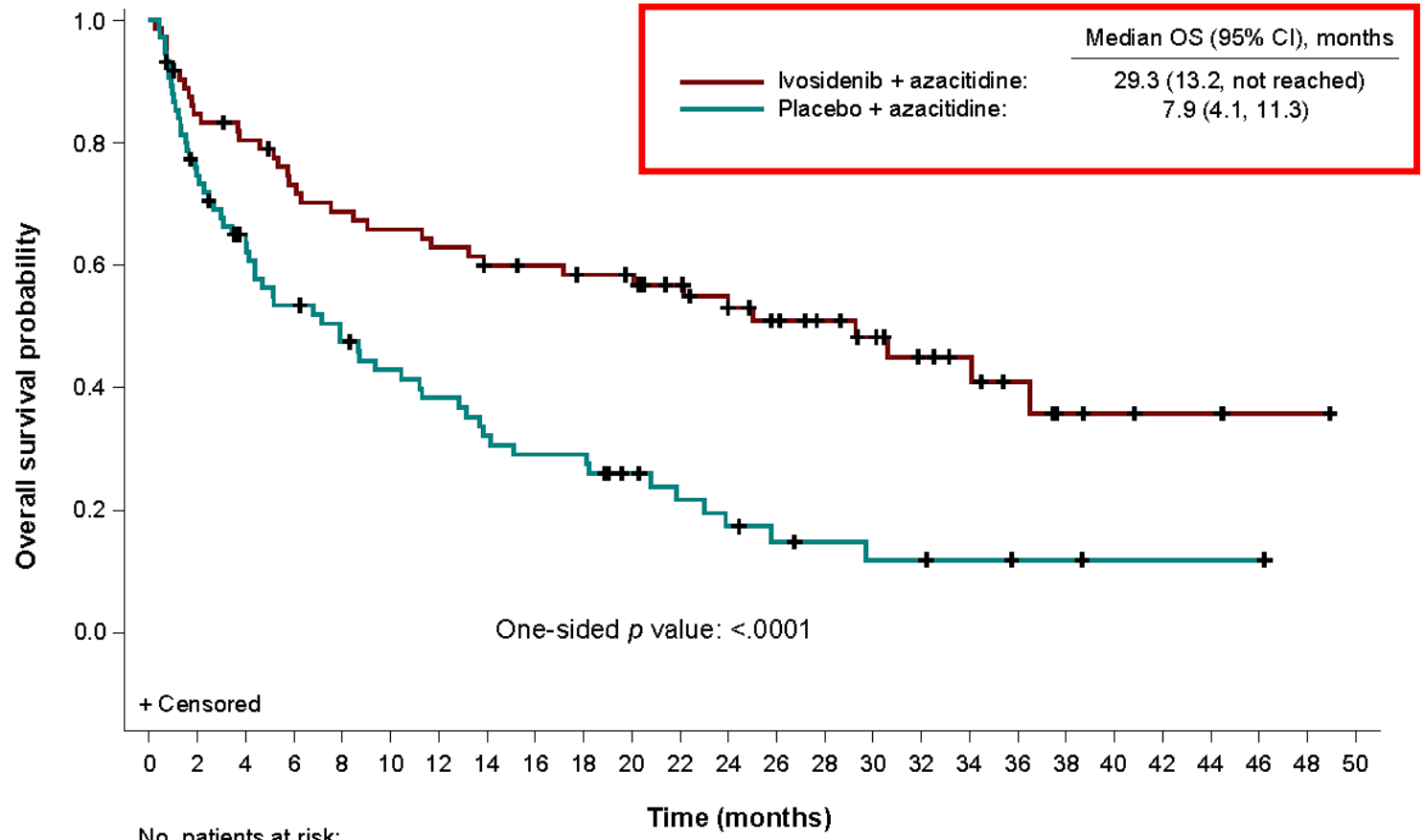
DiNardo CD, et al. J Clin Oncol, 2021.

IDHi – AGILE PH3 Clinical Trial in Older patients

ORIGINAL ARTICLE

Ivosidenib and Azacitidine in *IDH1*-Mutated Acute Myeloid Leukemia

Pau Montesinos, M.D., Ph.D., Christian Recher, M.D., Ph.D., Susana Vives, M.D., Ewa Zarzycka, M.D., Jianxiang Wang, M.D., Giambattista Bertani, M.D., Michael Heuser, M.D., Rodrigo T. Calado, M.D., Ph.D., Andre C. Schuh, M.D., Su-Peng Yeh, M.D., Scott R. Daigle, M.S., Jianan Hui, Ph.D., Shuchi S. Pandya, M.D., Diego A. Gianolio, Ph.D., Stephane de Botton, M.D., Ph.D., and Hartmut Döhner, M.D.

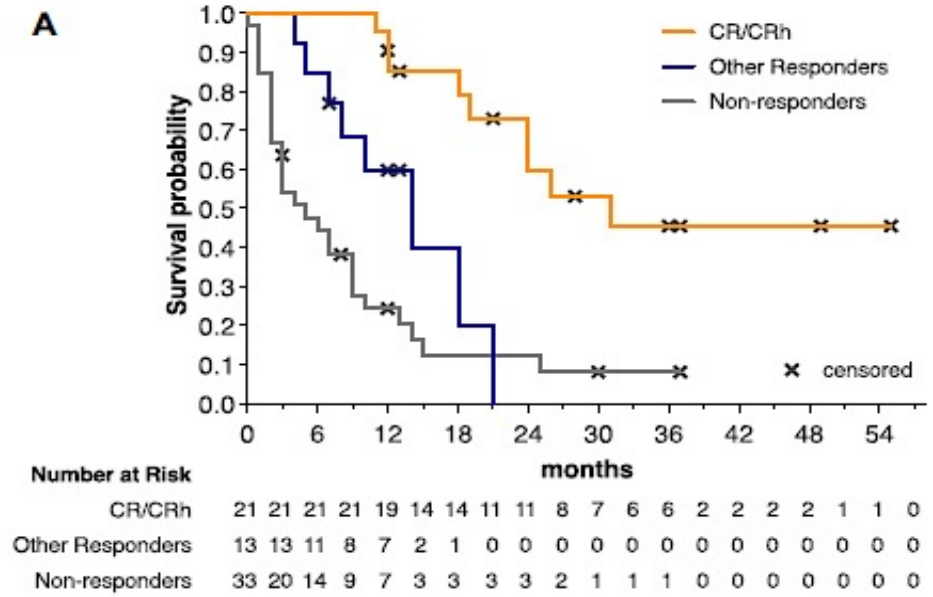


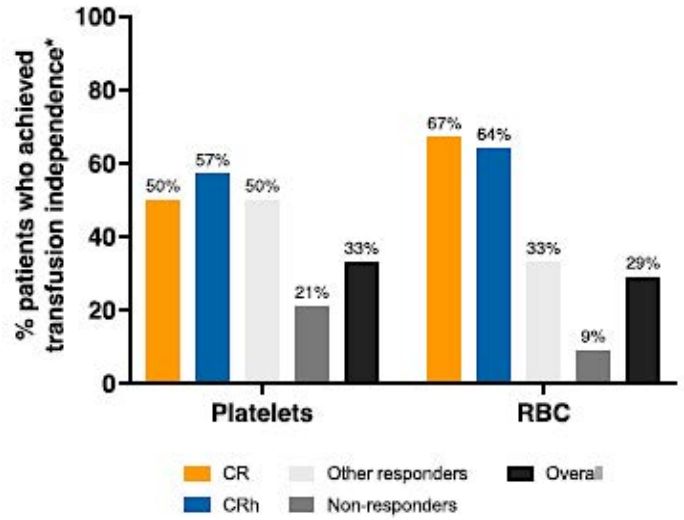
Montesinos P, et al. N Eng L Med, 2022.
Montesinos P, et al. Blood Adv, 2025.

Olutasidenib in combination with azacitidine induces durable complete remissions in patients with relapsed or refractory m*IDH1* acute myeloid leukemia: a multicohort open-label phase 1/2 trial

Table 2 Response rates to olutasidenib and azacitidine combination treatment

Response rates	R/R AML (N = 67)	R/R AML excluding prior olutasidenib (N = 51)
CR rate		
Response rate, n (%) [95% CI]	18 (27%) [95% CI 16.8 - 39.1]	16 (31%) [95% CI 19.1 - 45.9]
Time to CR, median months (range)	2.95 (1-7.6)	3.3 (1-7.6)
Duration of CR, median months [95% CI]	20.3 [95% CI 3.7 - NR][a]	20.3 (95% CI 5.6 - NR)[c]
CR/CRh rate		
Response rate, n (%) [95% CI]	21 (31%) [95% CI 20.6 - 43.8]	19 (37%) [95% CI 24.1 - 51.9]
Time to CR/CRh, median months (range)	3 (1-9.5)	3.6 (1-9.5)
Duration of CR/CRh, median months [95% CI]	14.7 [95% CI 4.6 - NR][a]	14.7 [95% CI 4.6 - NR][c]





Cortes J, et al. J Hematol Oncol. 2025 Jan 16;18:7.

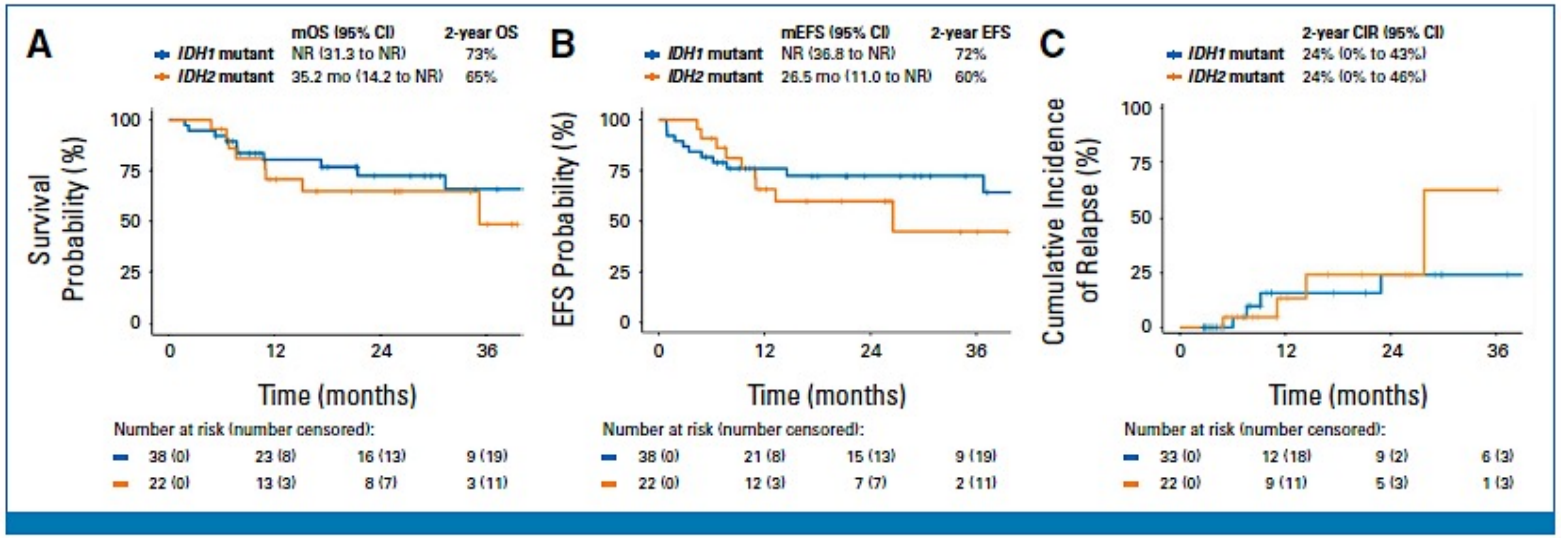
IDHi - Triplet

Outcomes of Frontline Triplet Regimens With a Hypomethylating Agent, Venetoclax, and Isocitrate Dehydrogenase Inhibitor for Intensive Chemotherapy–Ineligible Patients With Isocitrate Dehydrogenase–Mutated AML

Courtney D. DiNardo, MD, MSCE[1]; Jennifer Marvin-Peek, MD[1]; Sanam Loghavi, MD[2]; Koichi Takahashi, MD, PhD[1]; Ghayas C. Issa, MD[1]; Wei-Ying Jen, BM BCh, FRCPath[1]; Naval G. Daver, MD[1]; Patrick K. Reville, MD, MPH[1]; Nicholas J. Short, MD[1]; Koji Sasaki, MD, PhD[1]; Jillian K. Mullin, RN, MN[1]; Corey A. Bradley, BS[1]; Gautam Borthakur, MD[1]; Abhishek Maiti, MD[1]; Yesid Alvarado, MD[1]; Naveen Pemmaraju, MD[1]; Hussein A. Abbas, MD, PhD[1]; Danielle E. Hammond, MD[1]; Fadi Haddad, MD[1]; Guillermo Montalban Bravo, MD[1]; Kelly S. Chien, MD[1]; Musa Yilmaz, MD[1]; Steven M. Kornblau, MD[1]; Elias Jabbour, MD[1]; Farhad Ravandi, MD[1]; Tapan Kadia, MD[1]; Guillermo Garcia-Manero, MD[1]; Marina Y. Konopleva, MD, PhD[3]; and Hagop M. Kantarjian, MD[1]

TABLE 2. Clinical Outcomes of the Frontline Cohort

Outcome Measure	All (N = 60)	Non-tsAML (n = 43)	tsAML (n = 17)	IDH1^{mut} (n = 37)	IDH2^{mut} (n = 23)
2-year OS	69 (57 to 83)	84 (73 to 97)	34 (16 to 71)	72 (57 to 90)	67 (49 to 91)
2-year EFS	67 (56 to 81)	79 (66 to 93)	34 (21 to 73)	72 (58 to 88)	62 (44 to 87)
2-year CIR[a]	24 (6 to 39)	20 (0 to 36)	38 (0 to 65)	26 (0 to 46)	22 (0 to 43)
30-day mortality	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
60-day mortality	1 (2)	0 (0)	1 (6)	0 (0)	1 (4)
CRc[b]	55 (92)	42 (98)	13 (71)	32 (86)	23 (100)
ORR	57 (95)	43 (100)	14 (82)	34 (92)	23 (100)
MRD negativity[c]	45 (87)	35 (88)	10 (83)	25 (81)	20 (95)



DiNardo CD, et al. J Clin Oncol, 2025.

IDHi - Triplet

TABLE 3. Nonhematologic Adverse Events

Event[a]	All Grades, No. (%)	Grade ≥3, No. (%)
All	46 (77)	26 (43)
Infectious	25 (42)	22 (37)
All (noninfectious)	36 (60)	12 (20)
Hyperbilirubinemia	16 (27)	3 (5)
Diarrhea	12 (20)	1 (2)
Transaminitis	9 (15)	1 (2)
Acute kidney injury	8 (13)	0 (0)
Constipation	8 (13)	0 (0)
Nausea	8 (13)	0 (0)
Vomiting	5 (8)	1 (2)
Hypokalemia	4 (7)	0 (0)
Differentiation syndrome	3 (5)	2 (3)
Fatigue	3 (5)	0 (0)
Cough	2 (3)	0 (0)
Hyperphosphatemia	2 (3)	1 (2)
Hyperuricemia	2 (3)	0 (0)
QTc prolongation	2 (3)	1 (2)
Abdominal pain	1 (2)	1 (2)
Alopecia	1 (2)	0 (0)
Arthralgias	1 (2)	0 (0)
Hypomagnesemia	1 (2)	0 (0)
Hypocalcemia	1 (2)	0 (0)
Rash	1 (2)	0 (0)
Tumor lysis syndrome	1 (2)	1 (2)

Outcomes of Frontline Triplet Regimens With a Hypomethylating Agent, Venetoclax, and Isocitrate Dehydrogenase Inhibitor for Intensive Chemotherapy–Ineligible Patients With Isocitrate Dehydrogenase–Mutated AML

Courtney D. DiNardo, MD, MSCE[1]; Jennifer Marvin-Peek, MD[1]; Sanam Loghavi, MD[2]; Koichi Takahashi, MD, PhD[1]; Ghayas C. Issa, MD[1]; Wei-Ying Jen, BM BCh, FRCPath[1]; Naval G. Daver, MD[1]; Patrick K. Reville, MD, MPH[1]; Nicholas J. Short, MD[1]; Koji Sasaki, MD, PhD[1]; Jillian K. Mullin, RN, MN[1]; Corey A. Bradley, BS[1]; Gautam Borthakur, MD[1]; Abhishek Maiti, MD[1]; Yesid Alvarado, MD[1]; Naveen Pemmaraju, MD[1]; Hussein A. Abbas, MD, PhD[1]; Danielle E. Hammond, MD[1]; Fadi Haddad, MD[1]; Guillermo Montalban Bravo, MD[1]; Kelly S. Chien, MD[1]; Musa Yilmaz, MD[1]; Steven M. Kornblau, MD[1]; Elias Jabbour, MD[1]; Farhad Ravandi, MD[1]; Tapan Kadia, MD[1]; Guillermo Garcia-Manero, MD[1]; Marina Y. Konopleva, MD, PhD[3]; and Hagop M. Kantarjian, MD[1]

- The median ANC recovery (>500 cells/mL) by day 34 and platelet recovery (>50K/mL) by day 20.
- Once in remission, transfusions were infrequent.
- Early mortality was low, with 2% 60-day mortality and no 30-day mortality.

DiNardo CD, et al. J Clin Oncol, 2025.

How about Maintenance?

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

Multicenter Phase I Trial of Ivosidenib as Maintenance Treatment Following Allogeneic Hematopoietic Cell Transplantation for *IDH1*-Mutated Acute Myeloid Leukemia

Amir T. Fathi[1], Haesook T. Kim[2], Robert J. Soiffer[3], Mark J. Levis[4], Shuli Li[2], Annette S. Kim[5], Zachariah DeFilipp[1], Areej El-Jawahri[1], Steve L. McAfee[1], Andrew M. Brunner[1], Philip C. Amrein[1], Alice S. Mims[6], Laura W. Knight[1], Devon Kelley[1], AJ S. Bottoms[1], Lindsey H. Perry[1], Jonathan L. Wahl[3], Jennifer Brock[3], Elayne Breton[4], Dylan M. Marchione[7], Vincent T. Ho[3], and Yi-Bin Chen[1]

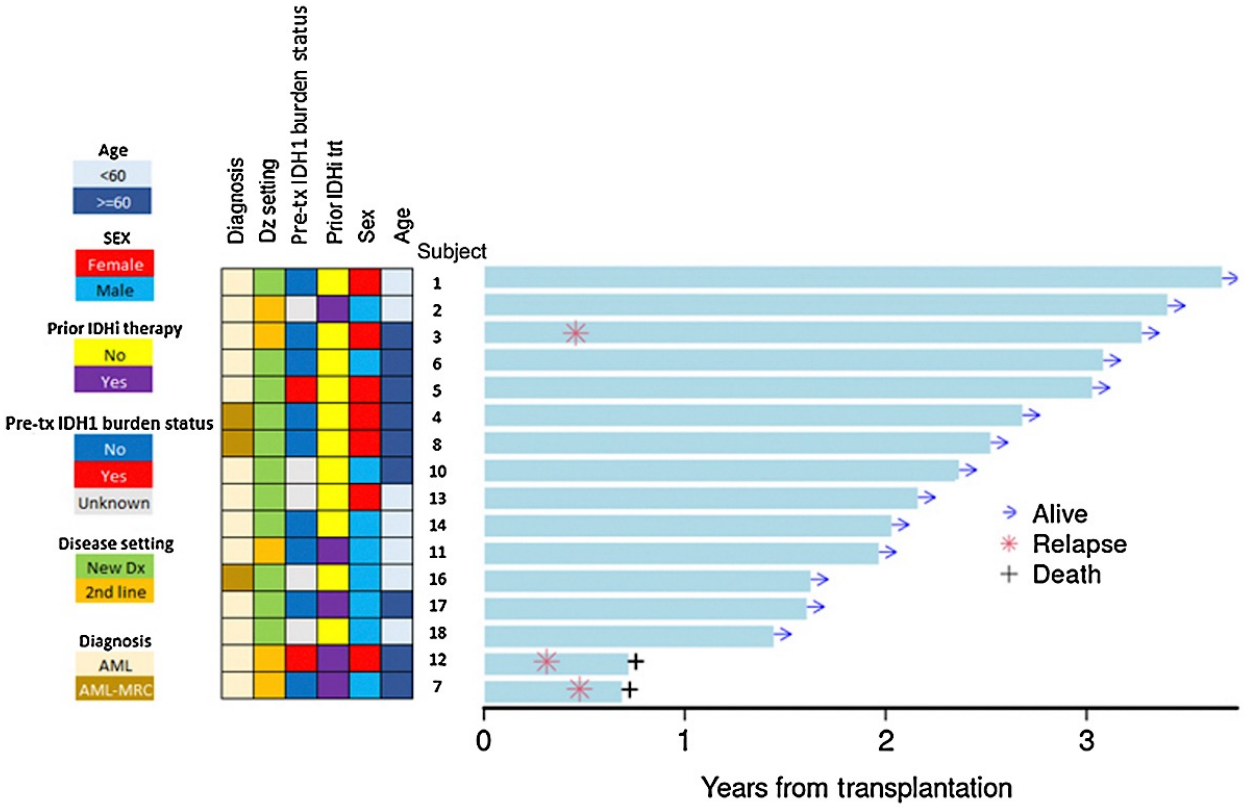
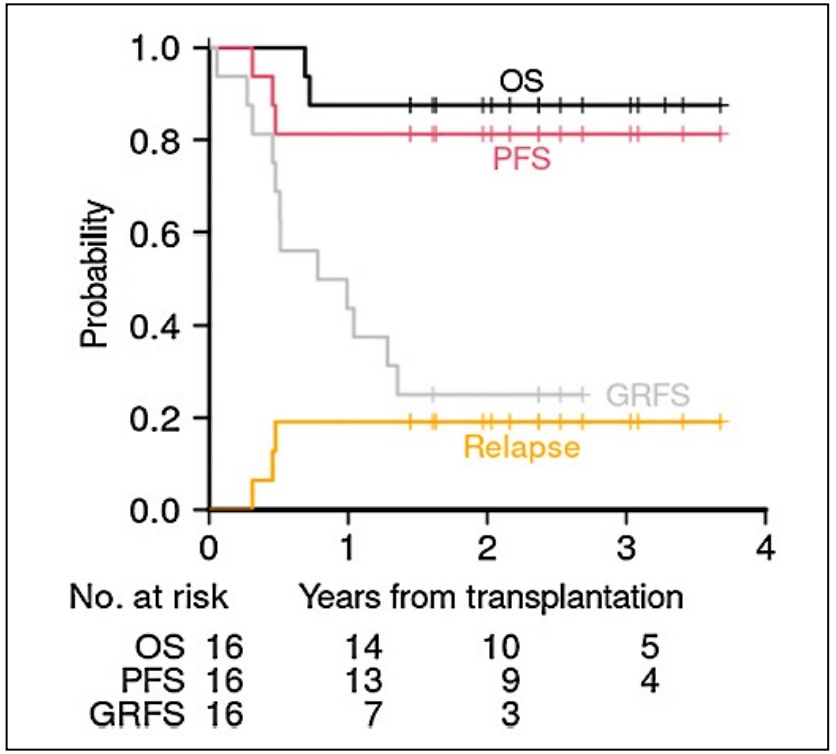


Table 3. Summary of survival and clinical outcomes.

	Estimate (95% CI)
2-year OS	88% (59–97)
2-year PFS	81% (52–94)
2-year GRFS	25% (8–47)
2-year CINRM	0% (NA)
2-year CIR	19% (4–41)
6 m cum inc of Gr II–IV aGVHD	6.3% (0.4–25)
6 m cum inc of Gr III–IV aGVHD	0% (NA)
2-yr cGVHD	63% (32–82)
2-yr mod/severe cGVHD	56% (28–77)

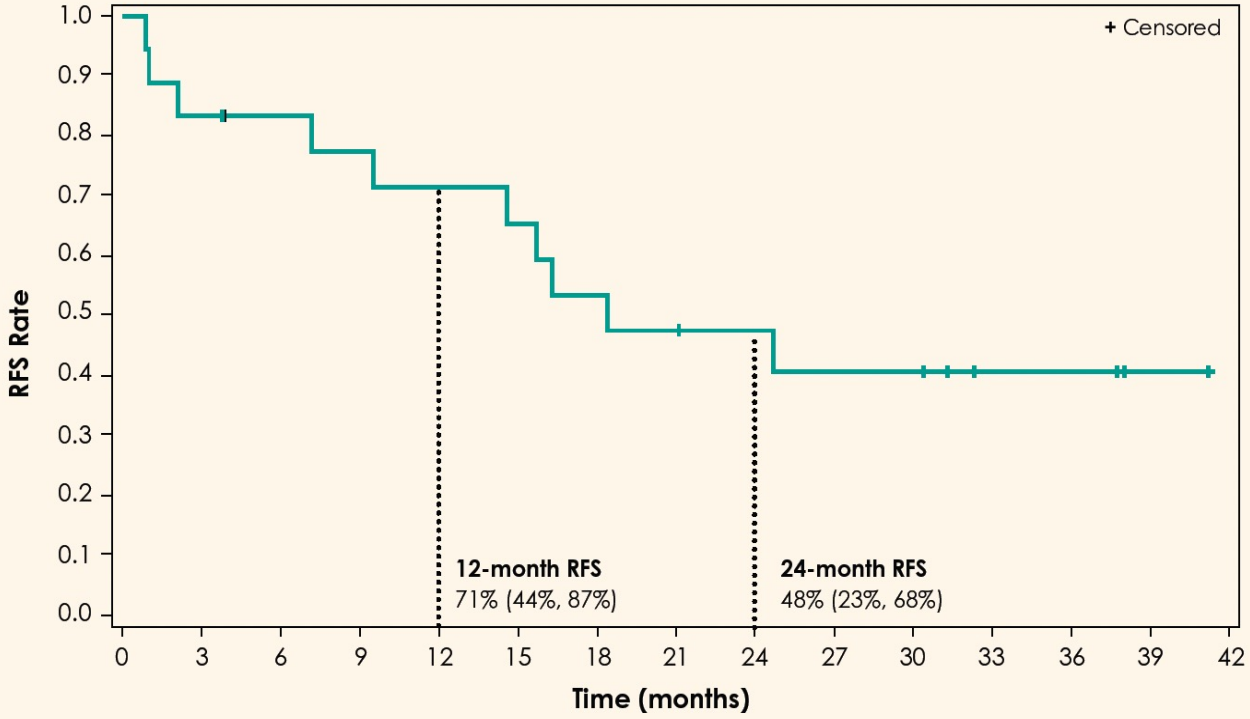
Note: NRM, relapse, acute GVHD, and chronic GVHD are the cumulative incidence estimates. CI, confidence interval.



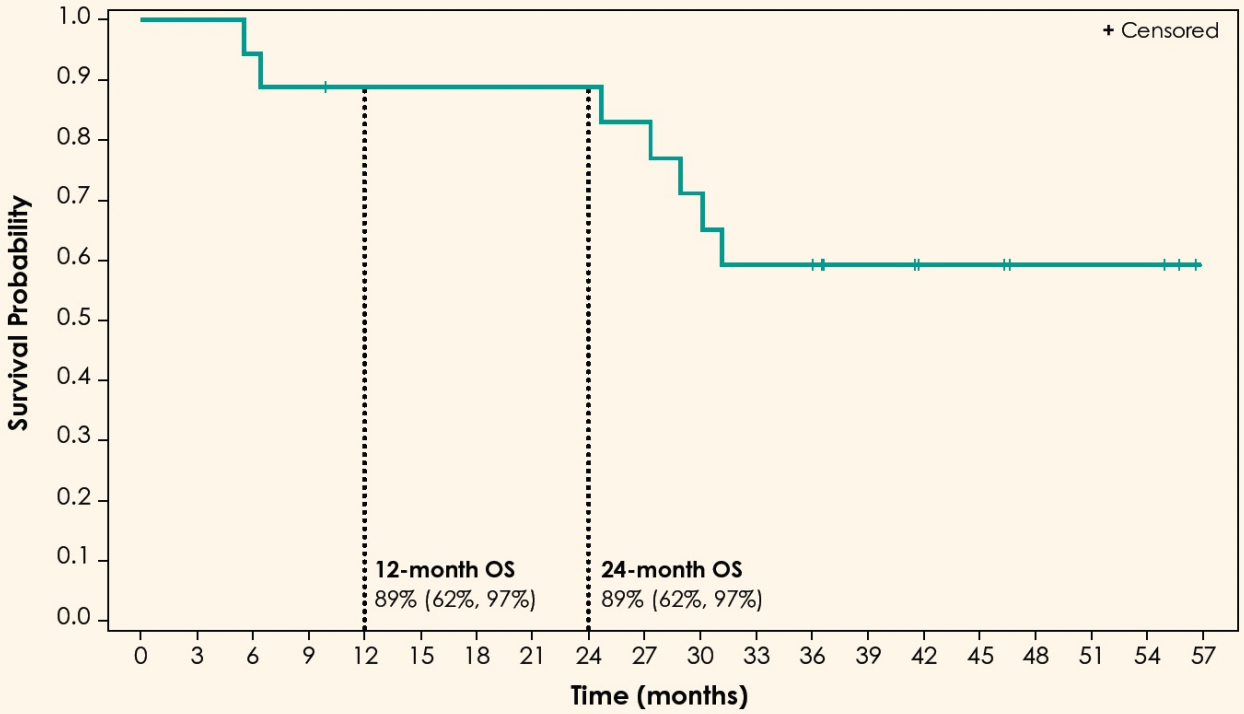
Fathi et al. Clin Cancer Res, 2023

Olutasidenib as Maintenance Therapy in IDH1-Mutated AML

RFS



OS



Wei AH et al. EHA 2025;Abstract PF530; Wei AH et al. SOHO 2025;Abstract AML-619.

Conclusions

- IDH inhibitors are now key members of AML therapeutics, both in the R/R and upfront settings.
- Ivosidenib is approved in combination with HMA for upfront AML.
- Enasidenib, ivosidenib, and olutasidenib are approved for R/R AML.
- Triplet therapies with IDH inhibitors are showing much promise in earlier phase trials, and they may soon compete with standard therapies.
- IDH inhibitors may also have a role in the maintenance setting. Trials are ongoing.

Investigator Survey Results

Regulatory and reimbursement issues aside, which initial treatment would you generally recommend for an 80-year-old patient with AML and an IDH mutation who was not eligible for intensive chemotherapy?

	IDH1	IDH2
 Dr Erba	Azacitidine + ivosidenib	Azacitidine + venetoclax
 Dr Fathi	HMA + ivosidenib	Decitabine + venetoclax ± enasidenib
 Dr Lin	Azacitidine + ivosidenib	Azacitidine + venetoclax
 Dr Perl	Azacitidine + ivosidenib	Azacitidine + venetoclax
 Dr Stein	HMA + ivosidenib	Azacitidine + venetoclax
 Dr Cortes	Azacitidine + ivosidenib	Azacitidine + venetoclax + enasidenib
 Dr DiNardo	HMA + venetoclax + ivosidenib	HMA + venetoclax + enasidenib
 Dr Wang	Azacitidine + ivosidenib	Oral decitabine (decitabine/cedazuridine) + venetoclax

Regulatory and reimbursement issues aside, which treatment would you generally recommend next for a 60-year-old patient with AML and an IDH1 mutation who experienced disease progression after 7 + 3 followed by ASCT?

 Dr Erba	Ivosidenib + azacitidine
 Dr Fathi	Ivosidenib or HMA + ivosidenib
 Dr Lin	Azacitidine + venetoclax
 Dr Perl	Azacitidine + venetoclax
 Dr Stein	Azacitidine + venetoclax
 Dr Cortes	Olutasidenib
 Dr DiNardo	HMA + venetoclax + IDHi (ivosidenib or olutasidenib)
 Dr Wang	Oral decitabine (decitabine/cedazuridine) + venetoclax + ivosidenib

IDHi = IDH inhibitor

Regulatory and reimbursement issues aside, which treatment would you generally recommend next for an 80-year-old patient with AML and an IDH1 mutation who experienced disease progression on azacitidine/venetoclax?

 Dr Erba	Olutasidenib
 Dr Fathi	HMA + ivosidenib
 Dr Lin	Olutasidenib
 Dr Perl	Ivosidenib
 Dr Stein	Ivosidenib
 Dr Cortes	Olutasidenib
 Dr DiNardo	Olutasidenib
 Dr Wang	Olutasidenib

RTP RESEARCH TO PRACTICE

In which situations, if any, would you use an IDH1 inhibitor for a patient with relapsed/refractory IDH1-mutant AML who had previously received an IDH1 inhibitor?

 Dr Erba	If there are no other options
 Dr Fathi	One can use olutasidenib, if ivosidenib was used previously
 Dr Lin	Change of IDH1 inhibitor or prolonged time off IDH1 inhibitor
 Dr Perl	Relapse while not on an IDH1 inhibitor; IDH1 mutation present at relapse; tolerability issues with prior IDH1 inhibitor
 Dr Stein	None
 Dr Cortes	Frail patient unable to receive intensive chemo or combinations
 Dr DiNardo	Reasonable to try ivo or oluta if the other has failed — but would give in a combination with an HMA + ven at the time of relapse to improve synergy and response
 Dr Wang	All situations as my understanding is that olutasidenib can work in patients treated with prior ivosidenib

RTP RESEARCH TO PRACTICE

Based on published research data and your own clinical experience, how would you indirectly compare the global efficacy and tolerability/toxicity of olutasidenib to that of ivosidenib for patients with relapsed/refractory AML and an IDH1 mutation?

	Efficacy	Tolerability/toxicity
 Dr Erba	Efficacy is about the same	Ivosidenib is more tolerable
 Dr Fathi	Efficacy is about the same	Ivosidenib is more tolerable
 Dr Lin	Olutasidenib is more efficacious	Tolerability is about the same
 Dr Perl	Efficacy is about the same	Tolerability is about the same
 Dr Stein	Efficacy is about the same	Tolerability is about the same
 Dr Cortes	Olutasidenib is more efficacious	Ivosidenib is more tolerable
 Dr DiNardo	Efficacy is about the same	Tolerability is about the same
 Dr Wang	Olutasidenib is more efficacious	Tolerability is about the same

Based on published research data and your own clinical experience, how would you indirectly compare the risk of differentiation syndrome with olutasidenib to that with ivosidenib for patients with relapsed/refractory AML and an IDH1 mutation?

 Dr Erba	The risk is about the same
 Dr Fathi	The risk is about the same
 Dr Lin	The risk is greater with ivosidenib
 Dr Perl	The risk is about the same
 Dr Stein	The risk is about the same
 Dr Cortes	The risk is about the same
 Dr DiNardo	The risk is about the same
 Dr Wang	The risk is about the same

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Up-Front Therapy for Older Patients with Acute Myeloid Leukemia (AML) — Dr Lin

Module 2: Selection of Therapy for Younger Patients with AML without a Targetable Mutation; Promising Investigational Strategies — Dr Perl

Module 3: Role of FLT3 Inhibitors in AML Management — Dr Erba

Module 4: Incorporation of IDH Inhibitors into the Care of Patients with AML — Dr Fathi

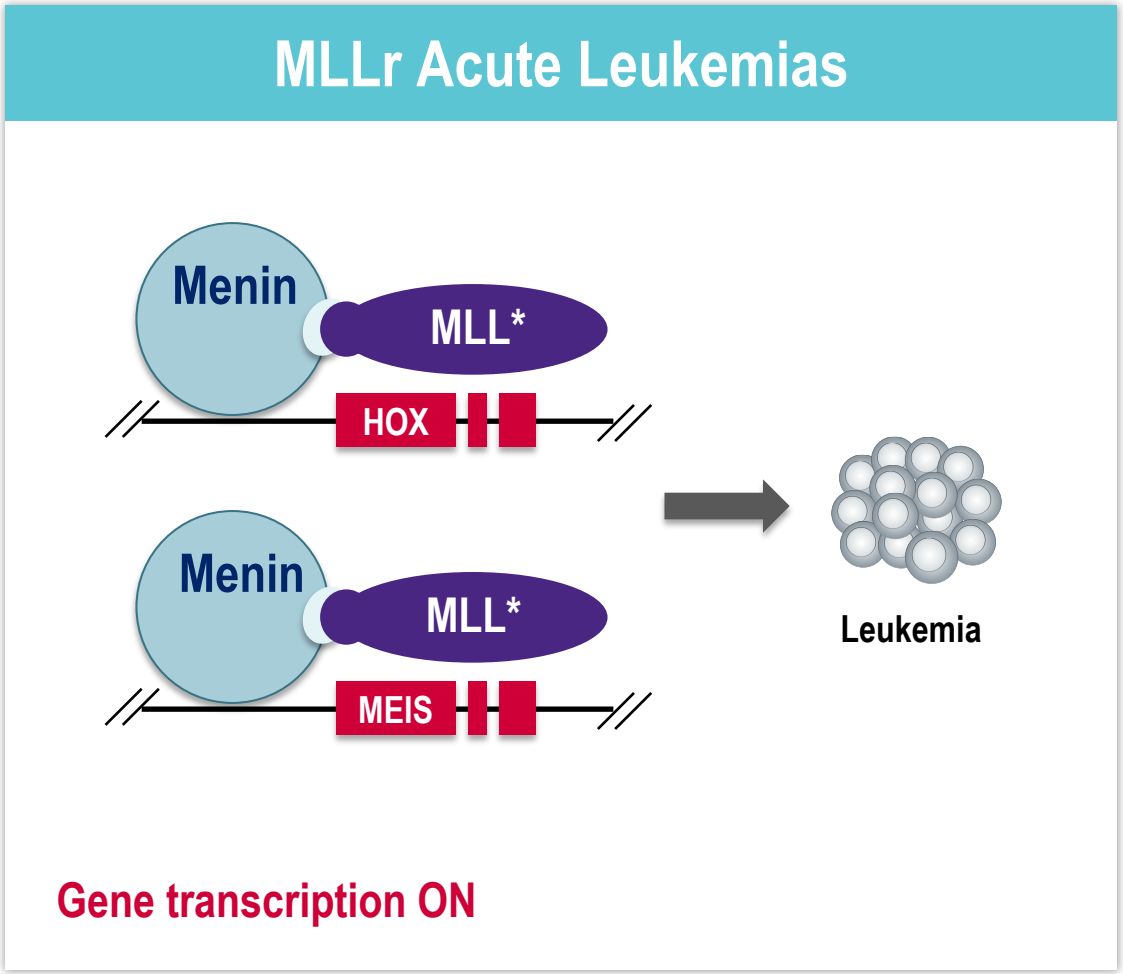
Module 5: Current and Future Role of Menin Inhibitors in the Treatment of AML — Dr Stein

Menin Inhibitors in Acute Myeloid Leukemia

Eytan M. Stein
Chief, Leukemia Service
Director, Program for Drug Development in Leukemia
Memorial Sloan Kettering Cancer Center
New York, New York

Memorial Sloan Kettering
Cancer Center

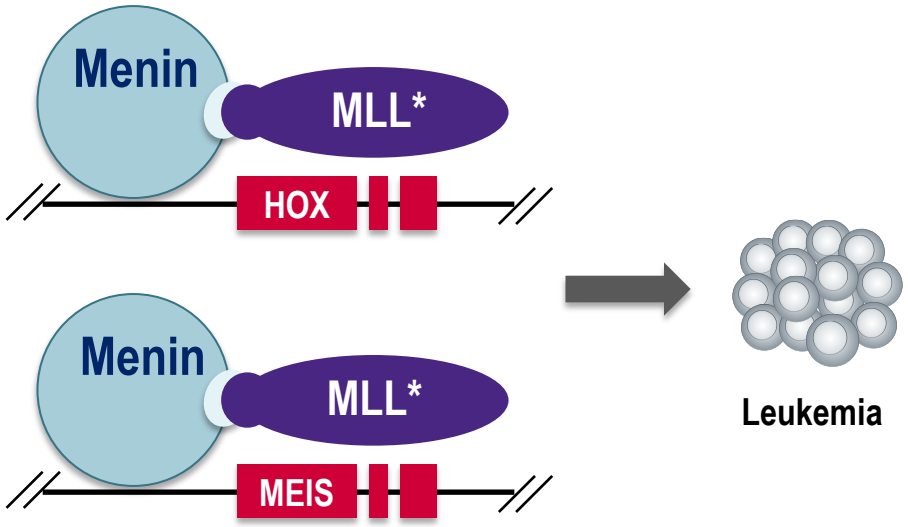
Pathogenesis of KMT2A-rearranged and NPM1-mutant Acute Leukemias



MLL* = MLLr or MLL1 wildtype; Adopted from: Uckelmann HJ, et al. Presented at ASH Annual Meeting, 2018

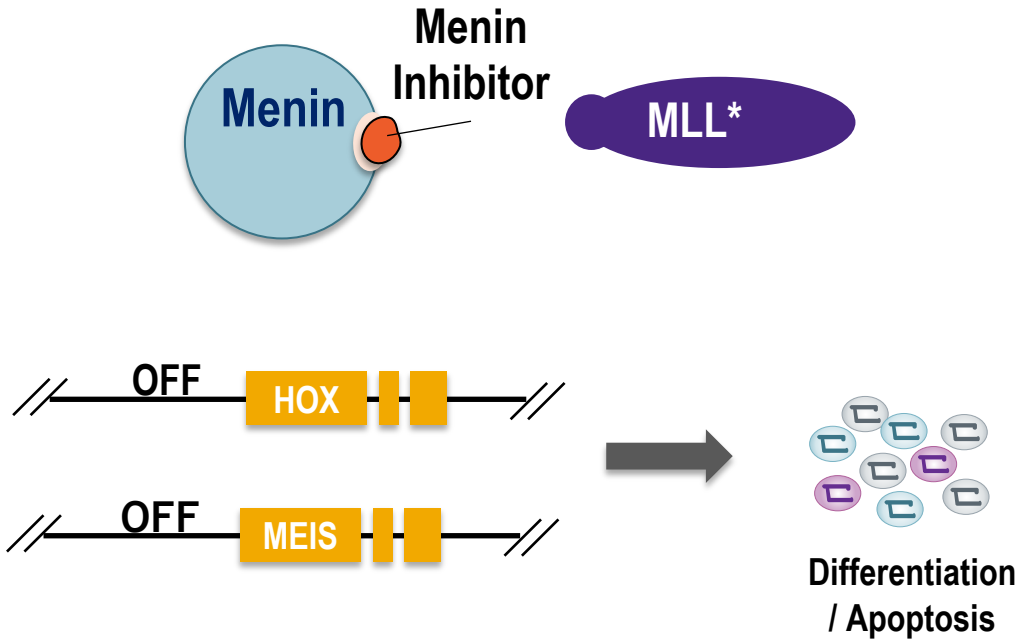
Menin inhibitors turn off leukemic transcriptional programs by binding to menin and displacing MLL complexes

MLLr Acute Leukemias



Gene transcription ON

Menin Inhibitor



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MLL* = MLLr or MLL1 wildtype; Adopted from: Uckelmann HJ, et al. Presented at ASH Annual Meeting, 2018

Menin Inhibitors – Structures

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
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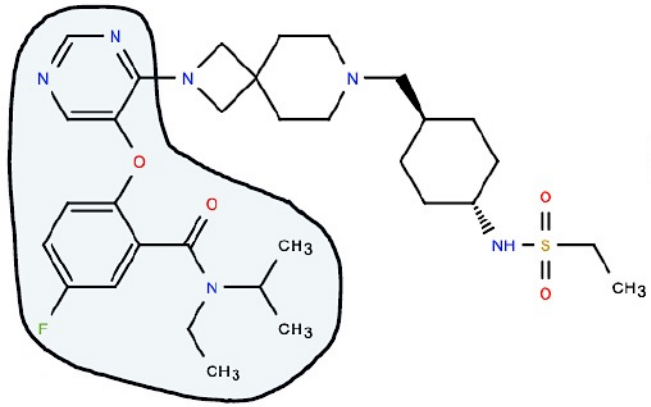
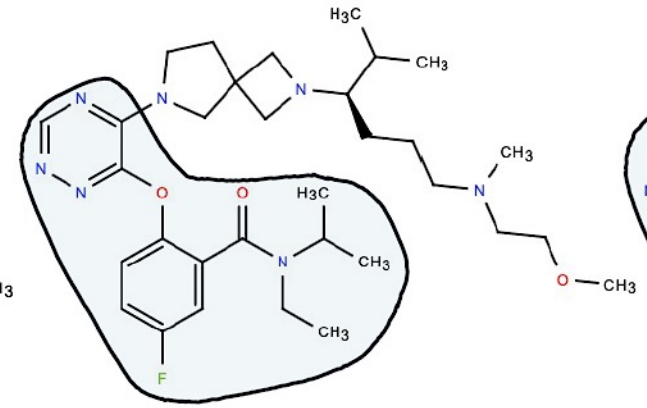
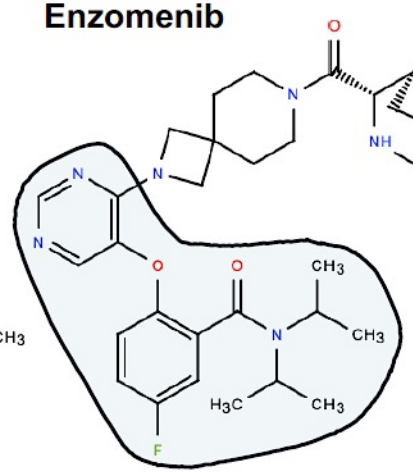
Revumenib



Bleximenib



Enzomenib



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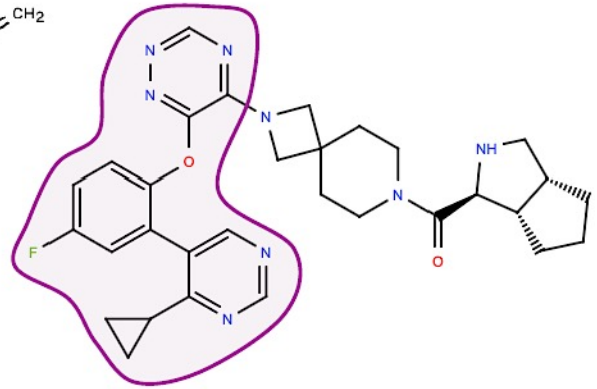
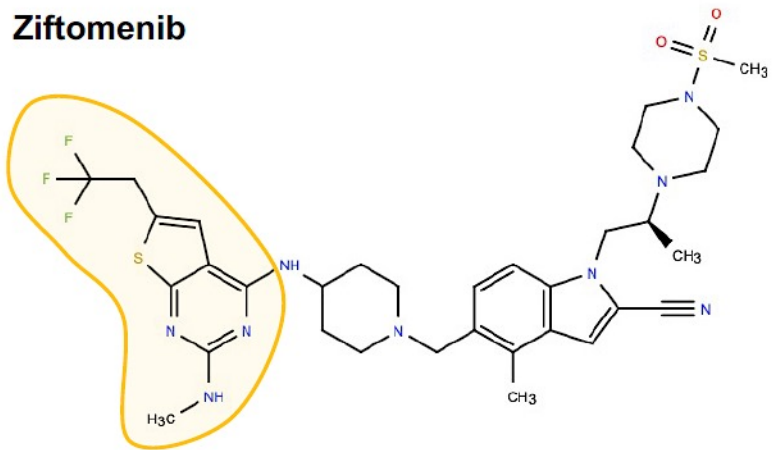
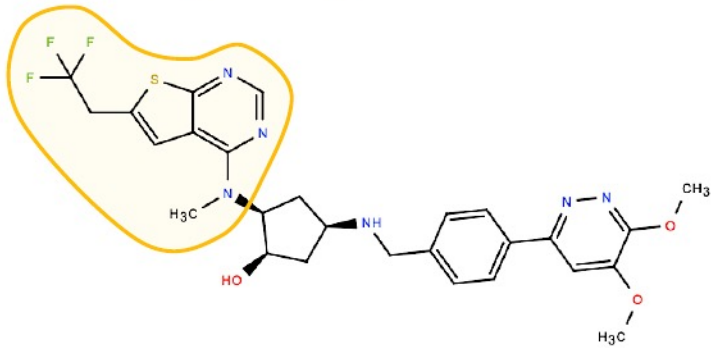


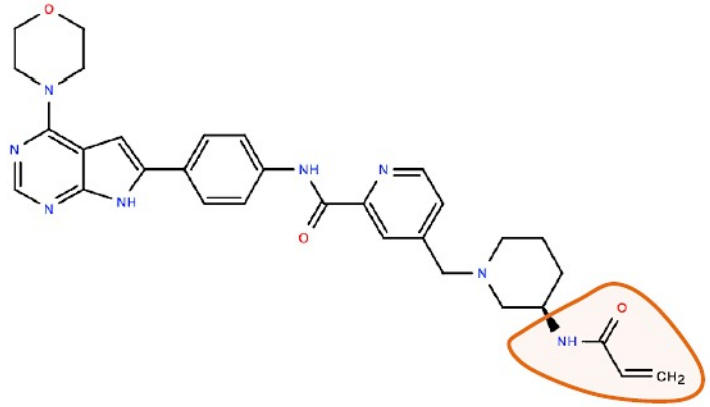
Ziftomenib



Emilumenib (DS-1594)



Icovamenib



Courtesy of Ghayas Issa, MD

Issa G et al. *Blood Cancer Discov* 2025;6(6):547-560.

AUGMENT-101: Phase 2 Trial of Revumenib in KMT2Ar or NPM1m R/R AML

Key Inclusion Criteria
- Aged ≥30 days
- R/R AML, ALL, or MPAL with *KMT2Ar* or *NPM1m*
- Patients with primary refractory or relapsed refractory disease allowed

Key Exclusion Criteria
- Active CNS disease

Revumenib RP2D
163 mg (95 mg/m^2 if <40 kg) q12h orally + strong CYP3A4i in 28-day cycles[a]

***KMT2Ar* Acute Leukemia**

***NPM1m* AML**
(not included in this analysis)

Primary Endpoints
- CR+CRh rate[b]
- Safety and tolerability

Key Secondary Endpoints
- CRc (CR+CRh+CRi+CRp) rate
- ORR (CRc+MLFS+PR)
- DOR
- Time to response

[a]Treatment 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.
[b]CR+CRh rate >10% in evaluable population considered lower efficacy bound.

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CNS, central nervous system 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; DOR, duration of response; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; MLFS, morphological leukemia-free state; *NPM1m*, nucleophosmin 1–mutated; ORR, overall response rate; PR, partial remission; q12h, every 12 hours; RP2D, recommended phase 2 dose; R/R, relapsed/refractory.

AUGMENT-101: Revumenib KMT2A R/R Acute Leukemia – Demographics

Demographic and Disease Characteristics	Revumenib N = 104
Unknown	10 (10)
Ethnicity, n (%)	
Hispanic or Latino	23 (22)
Not Hispanic or Latino	76 (73)
Unknown	5 (5)
Disease Characteristics	
Leukemia morphological type, n (%)	
Acute myeloid leukemia (AML)	86 (83)
Acute lymphoblastic leukemia (ALL)	16 (15)
Mixed phenotype acute leukemia (MPAL)	2 (2)
Translocations[1], n (%)	
t(9;11)	23 (22)
t(11;19)	20 (19)
t(6;11)	10 (10)
t(10;11)	10 (10)
t(4;11)	7 (7)
t(1;11)	3 (3)
t(11;17)	2 (2)
t(11;22)	2 (2)
t(11;16)	1(1)
KMT2A fusion partner unknown	26 (25)
Disease status, n (%)	
Primary refractory	22 (21)
Untreated relapse	21 (20)
Refractory relapse	61 (59)
Prior treatment	
Number of prior regimens, median (range)	2 (1, 11)
Prior stem cell transplantation, n (%)	46 (44)
Number of prior relapses, n (%)	
0	22 (21)
1	55 (53)
2	20 (19)
≥3	7 (7)
t(11;22)	2 (2)
t(11;16)	1(1)
KMT2A fusion partner unknown	26 (25)
Disease status, n (%)	
Primary refractory	22 (21)
Untreated relapse	21 (20)
Refractory relapse	61 (59)
Prior treatment	
Number of prior regimens, median (range)	2 (1, 11)
Prior stem cell transplantation, n (%)	46 (44)
Number of prior relapses, n (%)	
0	22 (21)
1	55 (53)
2	20 (19)
≥3	7 (7)

1 One patient did not have a translocation type reported

Revumenib USPI

AUGMENT-101: Revumenib KMT2Ar AML

Table 11. Efficacy Results in Patients with Relapsed or Refractory Acute Leukemia with KMT2A translocation (Study SNDX-5613-0700)

Endpoint	Revumenib
CR[1]+CRh[2] n (%) 95% CI Median DOCR+CRh[3] (months) 95% CI	22 (21.2) (13.8, 30.3)[6] 6.4[6] (2.7, NE)
CR n (%) 95% CI Median DOCR[4] (months) 95% CI	13 (12.5) (6.8, 20.4)[6] 4.3[6] (1.0, NE)
CRh n (%) 95% CI Median DOCRh[5] (months) 95% CI	9 (8.7) (4.0, 15.8)[6] 6.4[6] (1.9, NE)

AUGMENT-101: Revumenib NPM1 Mutant R/R AML

Table 13. Efficacy Results in Patients with Relapsed or Refractory Acute Myeloid Leukemia with an *NPM1* mutation (Study SNDX-5613-0700)

Endpoint	Revumenib N = 65
CR[1]+CRh[2] n (%) 95% CI Median DOCR+CRh[3] (months) 95% CI	15 (23.1) (13.5, 35.2)[6] 4.5[6] (1.2, 8.1)
CR n (%) 95% CI Median DOCR[4] (months) 95% CI	12 (18.5) (9.9, 30)[6] 3.7[6] (1.0, 8.1)
CRh n (%) 95% CI Observed DOCRh[5] (months)	3 (4.6) (1.0, 12.9)[6] 1.8, 2.0, 4.5

ASH 2025: Revumenib

Monday, December 8
04:30 PM - 06:00 PM EST
PRESENTATION ID 1001 (Oral)
OCCC - Chapin Theater (W320)
Revumenib for patients with relapsed or refractory (R/R) KMT2Ar acute leukemia: Outcomes by leukemia type in the phase 2 AUGMENT-101 study
Ibrahim Aldoss, MD

Abstract conclusions: Revumenib monotherapy provides clinically meaningful and durable responses, including high rates of MRD negativity, in heavily pretreated pts with R/R KMT2Ar AL regardless of leukemia type: AML, ALL, or MPAL. The safety profile of revumenib is consistent with prior reports and is generally similar across acute leukemia subtypes.

FDA approves ziftomenib for relapsed or refractory AML with an NPM1 mutation

“On November 13, 2025, the Food and Drug Administration approved ziftomenib, a menin inhibitor, for adults with relapsed or refractory acute myeloid leukemia (AML) with a susceptible nucleophosmin 1 (*NPM1*) mutation who have no satisfactory alternative treatment options.

Efficacy was evaluated in KO-MEN-001 (NCT04067336), an open-label, single arm, multicenter trial in 112 adults with relapsed or refractory AML with an *NPM1* mutation identified using next-generation sequencing or polymerase chain reaction. Patients with *NPM1* mutations, including Type A, B, and D mutations and other *NPM1* mutations likely to result in cytoplasmic localization of the NPM1 protein, were enrolled.”

“The prescribing information includes warnings and precautions for differentiation syndrome, QTc interval prolongation, and embryo-fetal toxicity.

The recommended ziftomenib dose is 600 mg taken orally once daily until disease progression or unacceptable toxicity.”

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ziftomenib-relapsed-or-refractory-acute-myeloid-leukemia-npm1-mutation

KO-MEN-001: Ziftomenib R/R NPM1 Mutant AML – Demographics

Demographics and Disease Characteristics	Ziftomenib (600 mg once daily) N=112
<65 years	42 (38)
≥65 years	70 (63)
Sex, n (%)	
Male	49 (44)
Female	63 (56)
Race, n (%)	
White	88 (79)
Black or African American	2 (2)
Asian	4 (4)
Other	2 (2)
Unknown	16 (14)
Ethnicity, n (%)	
Hispanic or Latino	3 (3)
Not Hispanic or Latino	87 (78)
Unknown	22 (20)
Disease Characteristics	
Type of AML, n (%)	
De novo AML	95 (85)
Secondary AML	17 (15)
Disease status, n (%)	
Primary Refractory	7 (6)
Refractory Relapse	37 (33)
Untreated Relapse	68 (61)
Median number of prior lines of therapy (range)	2 (1, 7)
Prior stem cell transplantation, n (%)	26 (23)

Ziftomenib USPI

KO-MEN-001: Ziftomenib R/R NPM1 Mutant AML – Response

Table 7 Efficacy Results in Patients with Relapsed or Refractory AML

Endpoint	Ziftomenib (600 mg once daily) N=112
CR[a]+CRh[b], n (%)	24 (21.4)
95% CI	(14.2, 30.2)
Median DOCR+CRh[c] (months)	5.0
95% CI	(1.9, 8.1)
CR[a], n (%)	19 (17.0)
95% CI	(10.5, 25.2)
Median DOCR[d] (months)	5.0
95% CI	(2.8, 8.1)
CRh[b], n (%)	5 (4.5)
95% CI	(1.5, 10.1)
Observed DOCRh[e] (months)	0.0^{+}, 1.5^{+}, 1.5, 1.6, 11.4

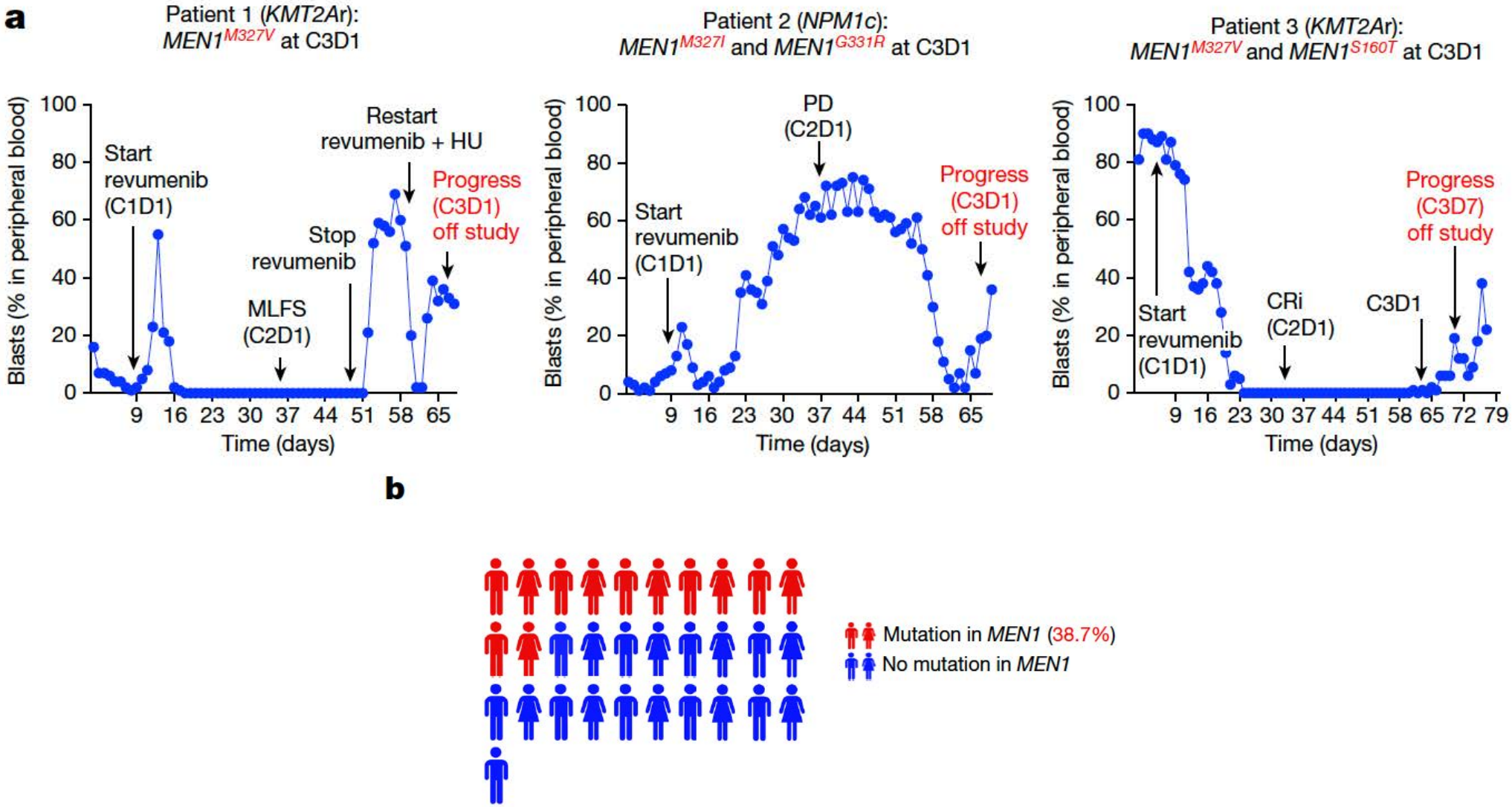
Single Agent Menin Inhibitors for Relapsed and Refractory Acute Leukemia

Name	Patient Population	Response Rates for KMT2Ar	Response Rates for NPM1	Duration of CR/CRh (median)	Toxicity
Revumenib*	KMT2A NPM1 NUP98r	ORR – 63% CR/CRh – 21.2% - MRD neg 70%	ORR 48% CR/CRh (26%) -	KMT2A - 6.4 months NPM1 4.5 months	QT prolongation DS
Ziftomenib	NPM1	ORR – 33% CR/CRh – 15%	ORR - 33% CR/CRh 22% MRD neg – 56%**	NPM1 5.0 months	DS Pruritus (23%)
Bleximenib	KMT2A NPM1	CR/CRh – 33.3%	CR/CRh -33.3%	6 months	DS
Enzomenib	KMT2A NPM1	ORR – 65.2 CR/CRh – 30.4%	ORR – 58.8% CR/CRh - 47.1%	NPM1 - 7.0 months	DS (10.7%)
BN104	KMT2A NPM1	CR/CRh – 60.9%	CR/CRh – 40%	N/A	N/A
AZD3632	KMT2A NPM1 Other HOX upregulated leukemias	N/A	N/A	N/A	N/A

*Approved
** NGS assay with level of detection of 0.34%

Issa et al, JCO 2025, Ziftomenib USPI, Revumenib USPI, Searle E, et al, ASH 2024, Zeidner, EHA 2024

Why do Patients Relapse – MEN1 Resistance Mutations



Perner F, Stein EM, et. al. *Nature* 2023

Menin Inhibitors in Combination with Other Agents

	N	ORR *n* (%)	CR/CRh *n* (%)	Source
R/R AML				
SAVE (SNDX-5613 + ASTX727 + Ven[a]; NCT05360160)	33	27 (82%)	16 (48%)	Issa et al., 2024 (53)
AUGMENT-102: FA + revumenib (NCT05326516)[a]	27	14 (52%)	6 (22%)	Shukla et al., 2024 (54)
Aza + ven + bleximenib (NCT05453903)[b]	56	47 (84%)	15 (28%)	Wei et al., 2025 (56)
Aza + ven + ziftomenib (NCT05735184)[b]	39	22 (56%)	12 (31%)	Fathi et al., 2024 (50)
Newly diagnosed AML				
7 + 3 + ziftomenib (NCT05735184)	71	67 (94%)	58 (82%)	Erba et al., 2025 (55)
7 + 3 + bleximenib (NCT05453903)	21	20 (95%)	17 (81%)	Recher et al., 2024 (51)
Aza + ven + revumenib (NCT03013998)	43	38 (88%)	30 (70%)	Zeidner et al., 2025 (52)
Aza + ven + bleximenib (NCT05453903)	33	29 (83%)	19 (58%)	Wei et al., 2025 (56)

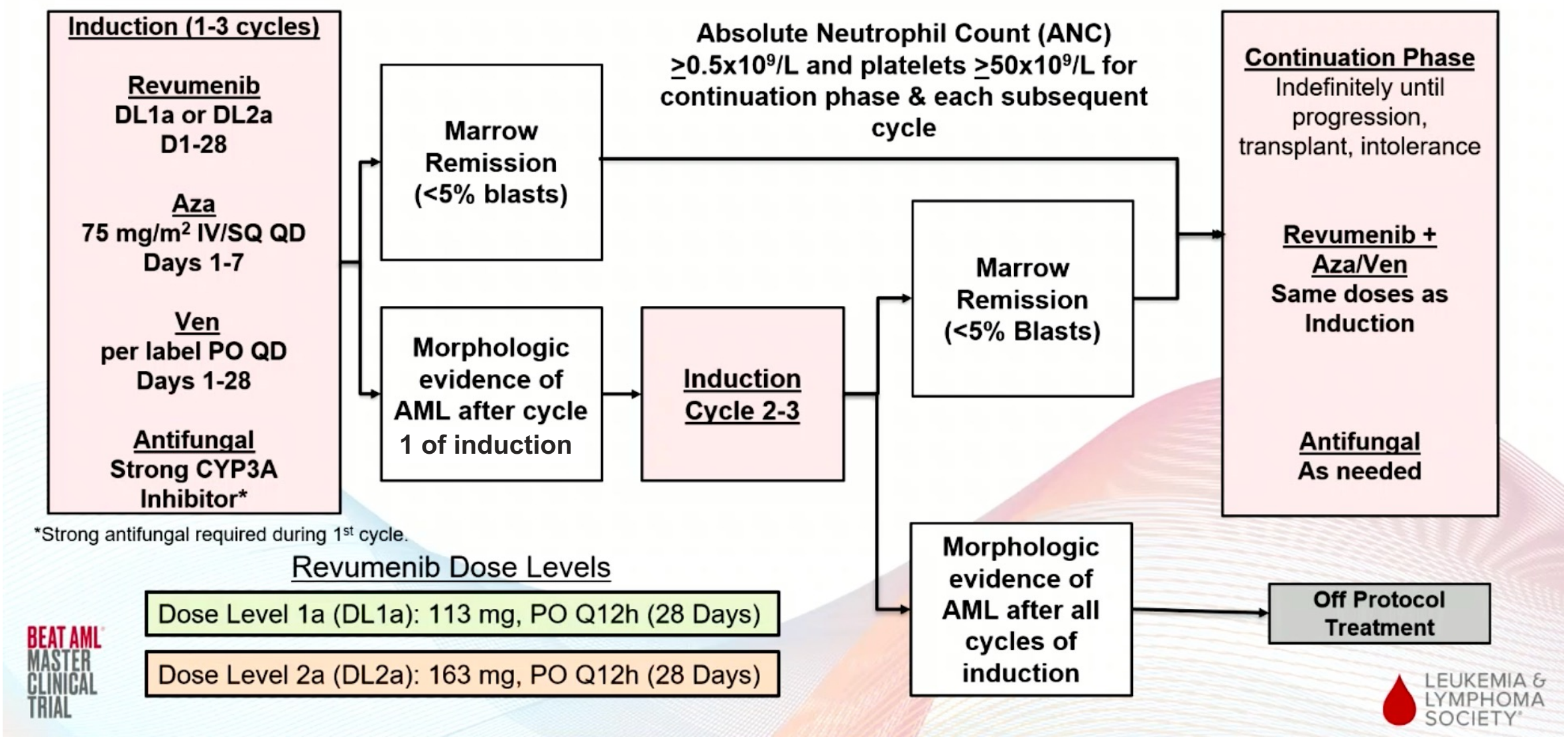
Abbreviations: 7 + 3, cytarabine and daunorubicin; Aza, azacitidine; CR/CRh, complete remission or complete remission with partial hematologic recovery; FA, fludarabine and cytarabine; ORR, overall response rate; SAVE, SNDX-5613 (revumenib) with ASTX727 (oral decitabine/cedazuridine) and venetoclax; Ven, venetoclax.

[a]Revumenib was previously known as SNDX-5613. ASTX727 is oral decitabine (decitabine/cedazuridine). Results of revumenib shown for all doses levels tested. FA + revumenib, CRh not reported but only CR.

[b]Results of ziftomenib shown for 600 mg only (the recommended phase II dose of monotherapy) and patients not previously exposed to menin inhibitors. Results of bleximenib shown at the 50 or 100 or 150 mg twice a day dosages (100 mg twice a day was chosen as the recommended phase II dosage); results of enzomenib shown for active dosages >140 mg twice a day.

Issa G et al. *Blood Cancer Discov* 2025;6(6):547-560.

AZA/VEN/REVUMENIB: STUDY DESIGN



Zeidner J, et. al, EHA 2025

Clinical Outcomes of Aza/Ven/Revumenib

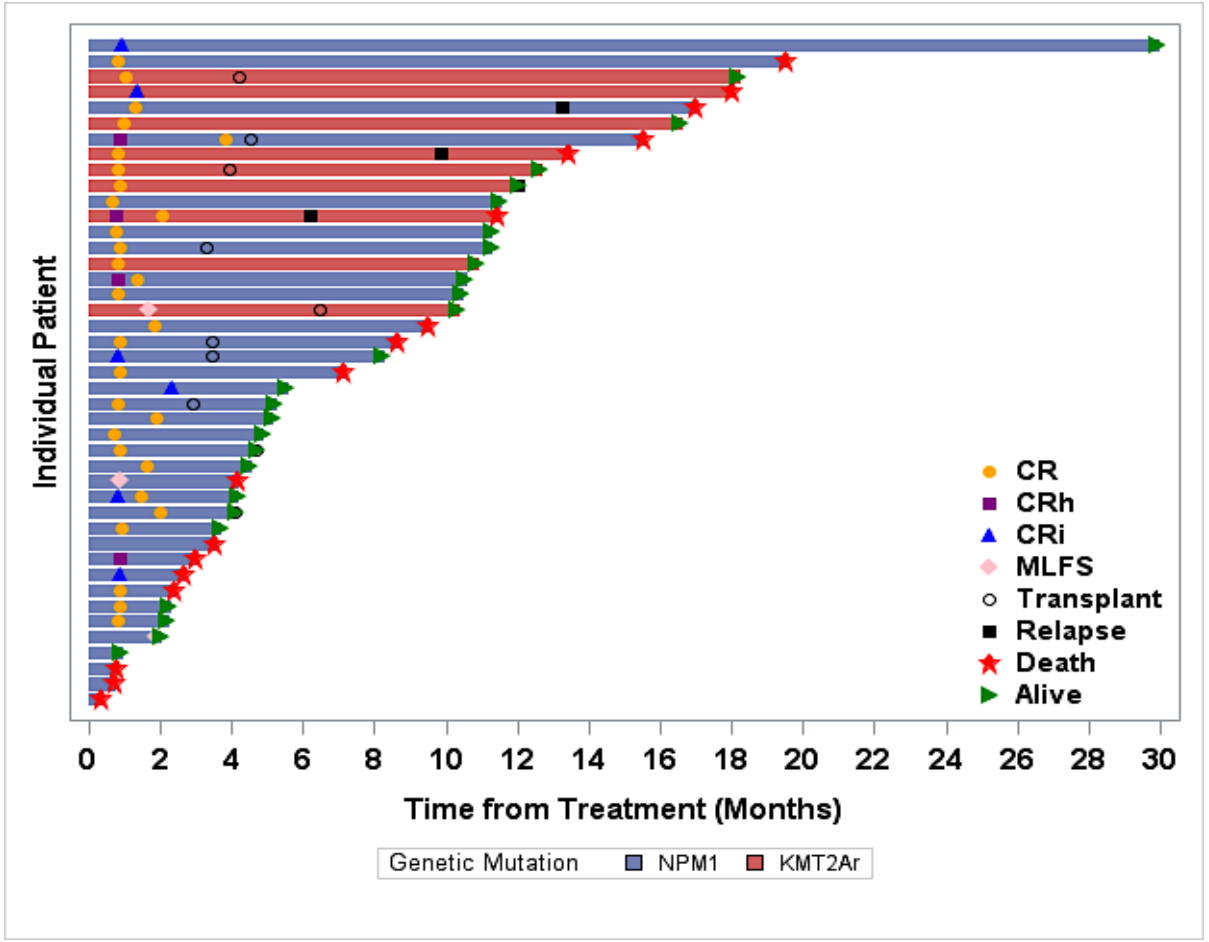
Clinical Outcomes	Dose Level 1	Dose Level 2	All		
	(n=21)	(n=22)	*KMT2Ar* (n=9)	*NPM1m* (n=34)	All (n=43)
Best Response, no. (%)					
CR	13 (61.9)	16 (72.7)	7 (77.8)	22 (64.7)	29 (67.4)
CRh	0 (0.0)	1 (4.5)	0 (0.0)	1 (2.9)	1 (2.3)
CRi	4 (19.0)	1 (4.5)	1 (11.1)	4 (11.8)	5 (11.6)
MLFS	2 (9.5)	1 (4.5)	1 (11.1)	2 (5.9)	3 (7.0)
Not Evaluable[1]	2 (9.5)	3 (13.6)	0 (0.0)	5 (14.7)	5 (11.6)
ORR (CR/CRh/CRi/MLFS)	19 (90.5%)	19 (86.4%)	9 (100%)	29 (85.3%)	38 (88.4%)
CRc (CR/CRh/CRi)	17 (81.0%)	18 (81.8%)	8 (88.9%)	27 (79.4%)	35 (81.4%)

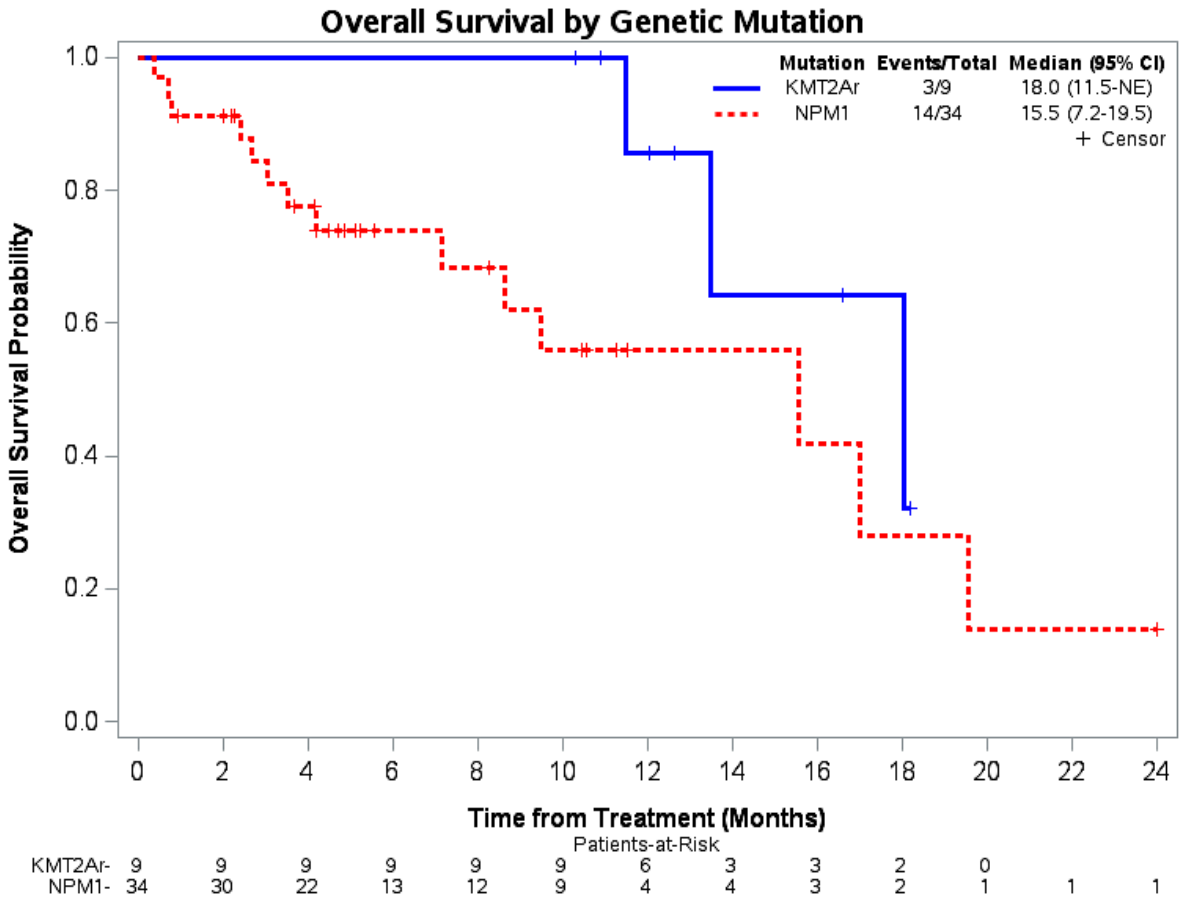
- **No patient had refractory disease after 1-2 cycles**
- **84% of evaluable patients achieved remission within 1st cycle of therapy**
- **100% of evaluable pts achieved flow MRD-negative remission (sensitivity 0.02%)**
  - **76% after cycle 1; 89% after cycle 2**
- **31% achieved *NPM1m* NGS-negative remission (sensitivity 0.005%)**

1 Not Evaluable = 5 pts had either early death (n=3) or withdrew from study (n=2) prior to end of cycle 1 BM Bx

Zeidner J, et. al, EHA 2025

Survival Outcomes of Aza/Ven/Revumenib





- 10 pts (23%) received an allogeneic stem cell transplant
- 4 pts relapsed (*KMT2Ar*: n=3; *NPM1m*: n=1)

- Median F/U = 6.9 months
- 1 year OS = 63% (*KMT2Ar*: 83% vs. *NPM1m*: 55%)

Zeidner J, et. al, EHA 2025

ASH 2025: Revumenib

Saturday, December 6
09:30 AM - 11:00 AM EST
PRESENTATION ID 47 (Oral)
OCCC - Valencia Room W415A
Phase II Study of the all-oral combination of revumenib (SNDX-5613) with decitabine/cedazuridine (ASTX727) and venetoclax (SAVE) in newly diagnosed AML
Wei-Ying Jen, BM BCh, FRCPath

Abstract conclusions: SAVE, an all-oral combination, shows promising activity in older adults with ND NPM1m or KMT2Ar AML who are ineligible for intensive chemotherapy. Ongoing enrollment and longer follow-up are required to establish the durability of response.

KOMET-007: Ziftomenib Plus 7+3 in NPM1m or KMT2A-r ND AML

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)

Erba H et al. EHA 2025;Abstract S136.

KOMET-007: Ziftomenib in Combination with Aza/Ven in NPM1m or KMT2A-r R/R AML

Table 3. Clinical Activity in Response-Evaluable[a] R/R Patients (N=49)

Response, n (%)	*NPM1*-m				*KMT2A*-r			
	200 mg n=7	400 mg n=6	600 mg n=9	Total n=22	200 mg n=11	400 mg n=9	600 mg n=6	Total n=27[b]
CRc	4 (57)	3 (50)	4 (44)	11 (50)	2 (18)	1 (11)	1 (17)	4 (15)
ORR	5 (71)	4 (67)	6 (67)	15 (68)	4 (36)	4 (44)	1 (17)	9 (33)
CR	1 (14)	2 (33)	2 (22)	5 (23)	2 (18)	0	1 (17)	3 (11)
CRh	2 (29)	1 (17)	0	3 (14)	0	1 (11)	0	1 (4)
CRi	1 (14)	0	2 (22)	3 (14)	0	0	0	0
MLFS	1 (14)	1 (17)	2 (22)	4 (18)	2 (18)	3 (33)	0	5 (19)
PR	0	0	0	0	0	0	0	0
NR	2 (29)	2 (33)	1 (11)	5 (23)	6 (54)	5 (56)	4 (67)	15 (56)
NE	0	0	2 (22)	2 (9)	1 (9)	0	1 (17)	3 (11)

Table 4. Clinical Activity in Menin Inhibitor-Naive R/R Patients (N=39)

Response, n (%)	Menin Inhibitor-Naive	
	NPM1-m n=19	*KMT2A*-r n=20
CRc	11 (58)	4 (20)
ORR	15 (79)	7 (35)
CR	5 (26)	3 (15)
CRh	3 (16)	1 (5)
CRi	3 (16)	0
MLFS	4 (21)	3 (15)
PR	0	0
NR	2 (11)	10 (50)
NE	2 (10)	3 (15)

Table 5. Clinical Activity By Prior Venetoclax (N=49)

Response, n (%)	NO Prior VEN		Prior VEN	
	NPM1-m n=8	*KMT2A*-r n=7	*NPM1*-m n=14	*KMT2A*-r n=20
CRc	6 (75)	1 (14)	5 (36)	3 (15)
ORR	**8 (100)**	**3 (43)**	**7 (50)**	**6 (30)**
CR	4 (50)	1 (14)	1 (7)	2 (10)
CRh	1 (13)	0	2 (14)	1 (5)
CRi	1 (13)	0	2 (14)	0
MLFS	2 (25)	2 (29)	2 (14)	3 (15)
PR	0	0	0	0
NR	0	4 (57)	5 (36)	11 (55)
NE	0	0	2 (14)	3 (15)

Fathi AT et al. ASH 2024;Abstract 2880.

ASH 2025: Ziftomenib

Monday, December 8
10:30 AM - 12:00 PM EST
PRESENTATION ID 766 (Oral)
OCCC - Chapin Theater (W320)
Ziftomenib in combination with venetoclax and azacitidine in newly diagnosed NPM1-m acute myeloid leukemia: Phase 1b results from KOMET-007
Gail Roboz

Abstract conclusions: In the ongoing KOMET-007 study, ziftomenib RP2D of 600 mg once daily combined with Ven/Aza was well tolerated and demonstrated robust clinical activity in patients with newly diagnosed NPM1-m AML, including 84% CRc after a median of 3.5 weeks and 54% CRc MRD-negativity after a median of 8.4 weeks. Low rates of ziftomenib-related cytopenia and no additional myelosuppression were observed with this combination. One case each of differentiation syndrome (grade 2) and investigator-assessed QTc (grade 3) were successfully resolved. Taken together, these data support the RP2D determination and advancement of this ziftomenib-based combination in the KOMET-017 (NCT07007312) randomized phase 3 study in patients with newly diagnosed NPM1-m AML.

ASH 2025: Ziftomenib

Monday, December 8
10:30 AM - 12:00 PM EST
PRESENTATION ID 764 (Oral)
OCCC - Chapin Theater (W320)
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
Amir Fathi, MD

Abstract conclusions: In the ongoing KOMET-007 study, ziftomenib RP2D of 600 mg QD + Ven/Aza was well tolerated with robust clinical activity in patients with R/R NPM1-m or KMT2A-r AML. No ziftomenib-related QTc prolongation was reported. One case of DS (NPM1-m, Gr 3) successfully resolved with protocol-specified mitigation. These data support further investigation of ziftomenib-based combinations in R/R NPM1-m and KMT2A-r AML.

Adverse Events with Menin Inhibitors

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

On target (menin) effects

Reported in clinical trials:

- Differentiation syndrome
- Myelosuppression

Off target effects

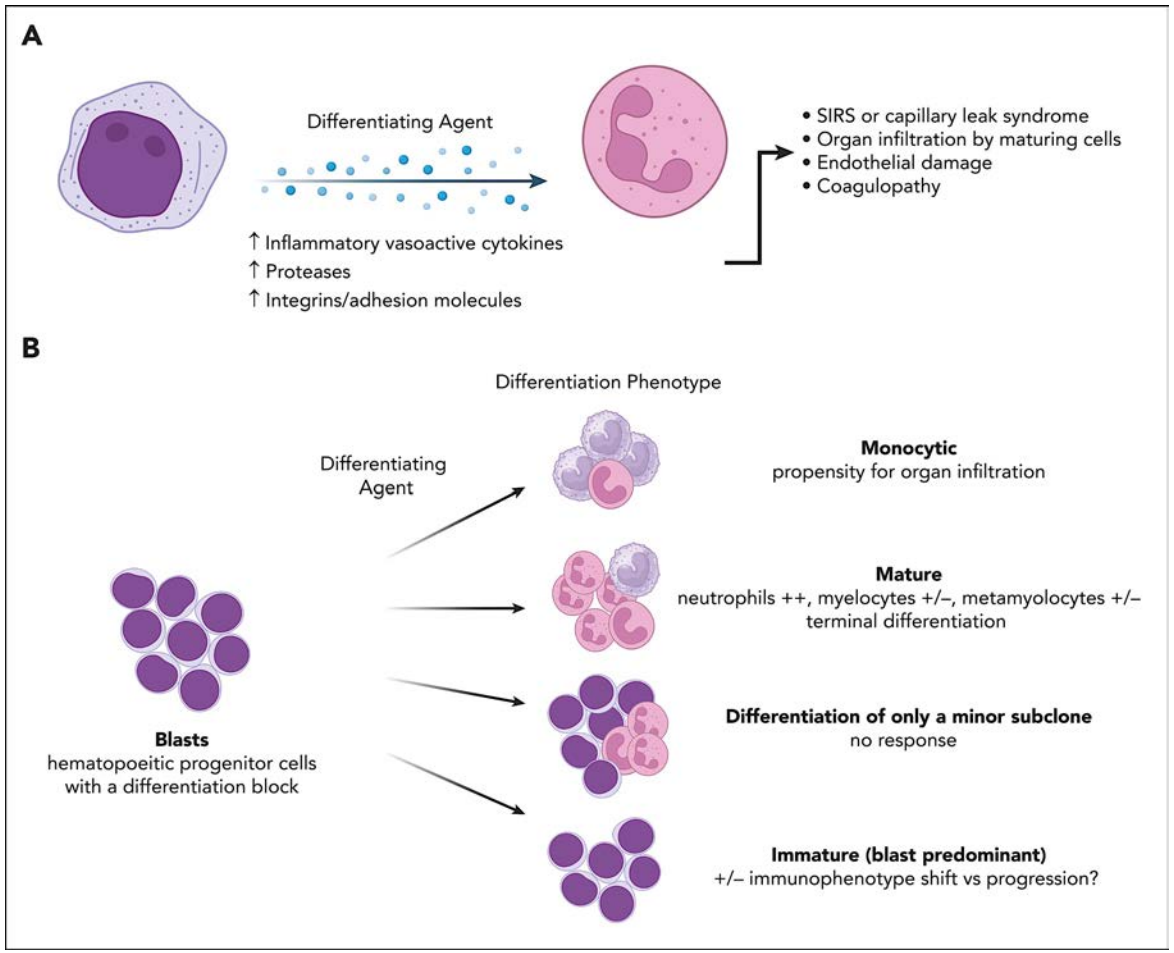
- QT prolongation (revumenib, 10% Gr 3)
- DDI (CYP3A inhibitors or substrates)
- Pruritus (ziftomenib, 13% Gr 1-2)

Potential AEs (preclinical/animal studies):

- MEN1 syndrome
- Bone growth
- Neurologic
- Cardiac
- Embryo-Fetal toxicity

Courtesy of Ghayas Issa, MD

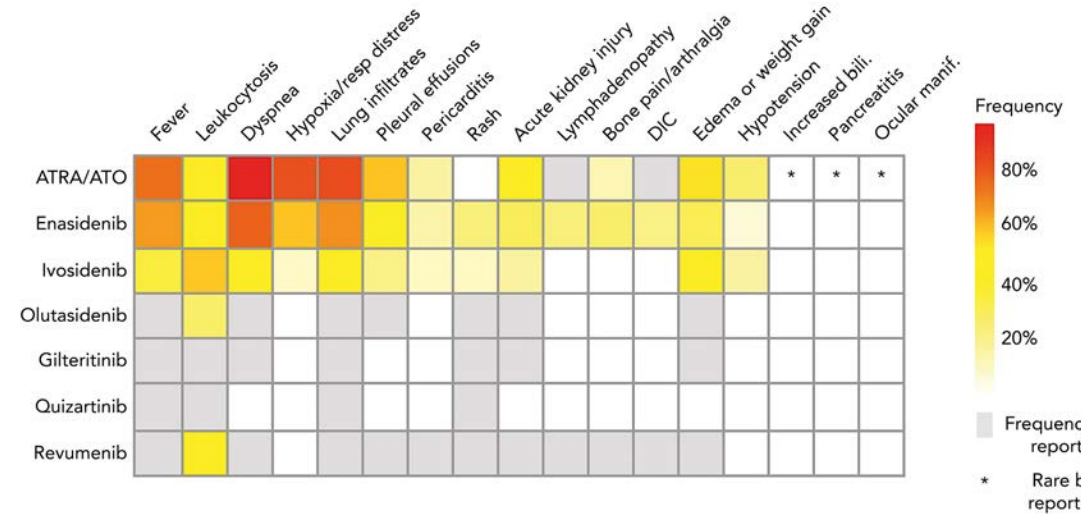
Phenotypes of Differentiation and Frequency of DS



A

DS Characteristics	ATRA/ATO	IDH-I			FLT3-I		Menin-I
		Ena	Ivo	Olu	Gilt	Quiz	Rev
Rate (%)	19-25%	12-19%	11-19%	14%	3%	5%	16-26%
Median time to onset (range), days	12 (0-46)	19 (1-86)	20 (1-78)	18 (1-561)	- (2-75)		18 (5-41)
Recurrence (%)	Rare	15%	12%				
Severe DS (%)	6-12%	7%	4%	7%	Rare		0-16%

B



Issa, Stein and Dinardo, Blood 2025

Treatment of DS

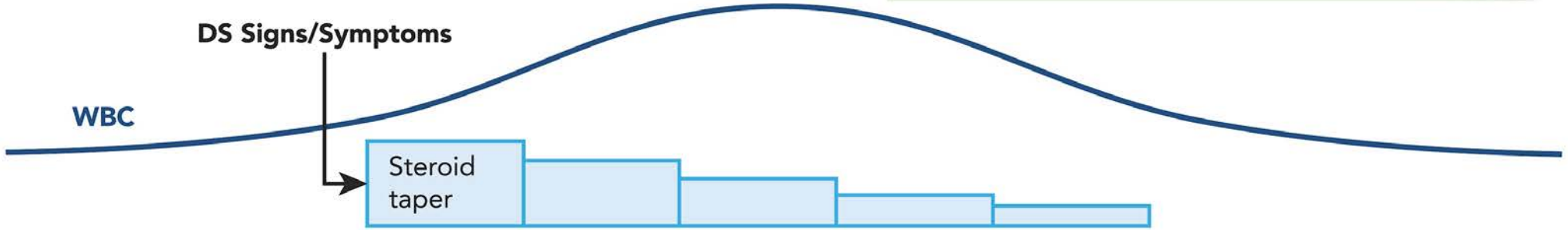
Inform patient and monitor diligently for signs/symptoms DS
High index of suspicion during cycle 1-2
High risk of severe DS if high burden or rapidly proliferative disease

Monitoring tests
CBC, electrolytes, creatinine, LDH, LFTs, PT, PTT, fibrinogen

If chest pain/dyspnea/hypoxia → chest imaging (lung infiltrates, pleuropericardial effusions) +/– EKG, TTE (pericarditis)

Supportive treatment
Hospitalization for most cases
Diuresis if edema/weight gain
Blood cultures, empiric antibiotics and rule out infection

Cytoreduction for leukocytosis (**hydroxyurea**, Ara-C, GO)
Monitor and manage TLS



Any sign/symptom of DS → **Dexamethasone** 10 mg PO twice daily for 3 days followed by tapering doses if improvement
Consider holding differentiating agent for severe cases

Cycle 1 | Cycle 2

Issa, Stein and Dinardo, Blood 2025

Atypical Menin-DS?

A provocative case of steroid-refractory inflammation

Baseline
- 40F w prior Burkitt lymphoma and therapy-related AML with t(11;19) *KMT2A:ELL* and *FLT3*-ITD s/p alloHCT experiences relapse and starts revumenib 163 mg Q12H (12 months after alloHCT)

D16
- She's admitted for fevers and hypoxia consistent with menin-DS, which responds to steroids and cytoreduction

D37
- She improves clinically and D37 BmBx shows MLFS (MRD indeterminate by flow)

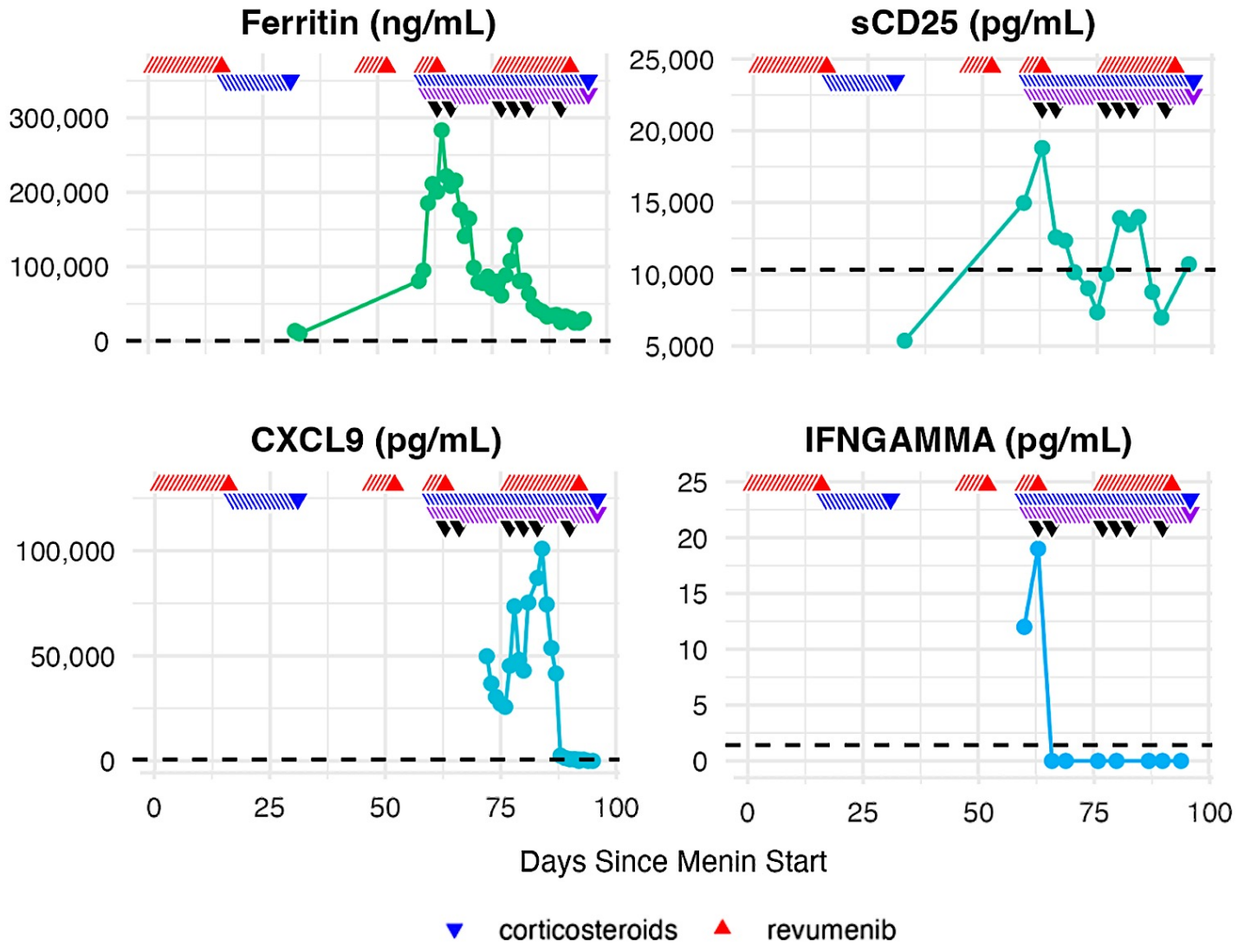
D40+
- Steroid-refractory fevers, hypoxemia, and hypotension with resumption of revumenib; marked elevated inflammatory markers (see next slide)

Courtesy Chin KK

Markedly elevated inflammatory markers with MENINi

D59 Labs

- **WBC** 0.1×10³/μL, **HgB** 8.6 g/dL, **PLT** 36×10³/μL
- **Ferritin** 80,867 ng/mL
- **sCD25** (sIL2) 3,482 U/mL
- **Serum CXCL9** 49,778 pg/mL (normal ≤669 pg/mL)
- **Serum IFNγ** 2,069 pg/mL (normal ≤1.4)



D64 BmBx

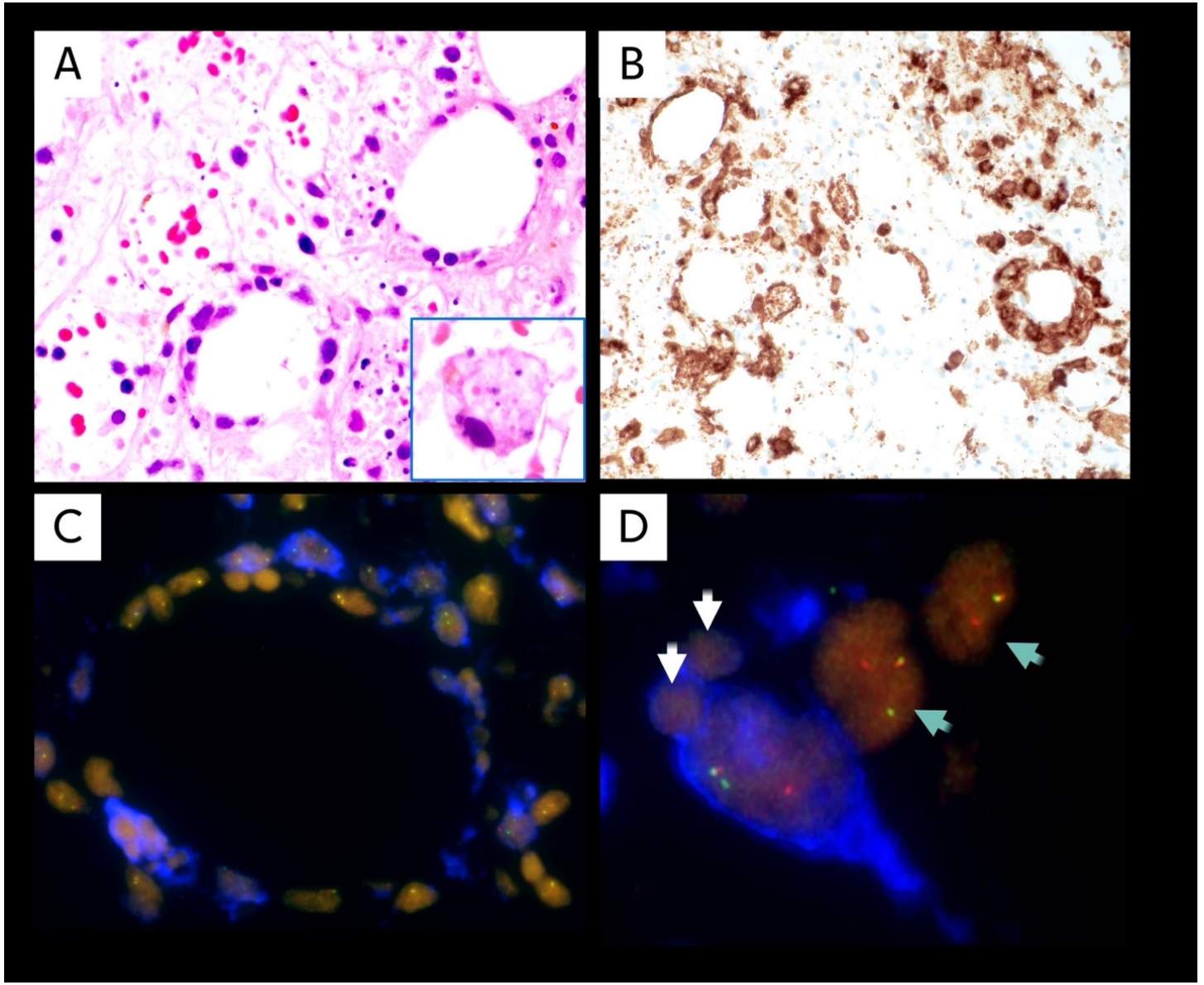
Evidence of hemophagocytosis in leukemia derived histiocytes

A. H&E section (x600) of bone marrow biopsy shows an increase in histiocytes including hemophagocytic histiocytes (inset).

B. Immunohistochemical staining for CD163 (brown, x400) highlights an increase in histiocytes on the bone marrow biopsy with strong membranous and cytoplasmic staining.

C. Combined immunophenotyping using CD163 (aqua), and FISH testing using *KMT2A* break-apart probes (5'MLL in green and 3' MLL in orange, Abbott Molecular, Des Plaines, IL). Most CD163 positive cells are positive for *KMT2A* translocation, i.e., t(11;19).

D. A CD163 positive cells show *KMT2A* split signal pattern, with evidence of hemophagocytic feature, i.e., two red blood cells (white arrows) in the cytoplasm. Two CD163 negative cells (green arrows) are also positive for *KMT2A* translocation



Concluding Thoughts

- Menin inhibitors, overall, have high rates of overall response, moderate rates of CR/CRh and modest duration of response.
  - BUT, all of the above is still generally better than what would be expected with other standard of care therapies for R/R disease.

  - Prognostic impact of MRD eradication for single agent menin inhibitors in R/R leukemia with currently available diagnostics is unclear.

  - Some resistance (up to 40% with revumenib?) mediated by MEN1 resistance mutations.
    - Contribution of MEN1 mutations to relapse with other menin inhibitors in clinical development largely unknown.

  - Outcomes after failure of menin inhibitors are poor. For patients who have not previously received ven, using a ven based strategy may be worthwhile.

Investigator Survey Results

Regulatory and reimbursement issues aside, which treatment would you generally recommend next for a 60-year-old patient with AML and a KMT2A rearrangement who experienced disease progression after 7 + 3 followed by ASCT?

 Dr Erba	Revumenib
 Dr Fathi	Revumenib
 Dr Lin	Azacitidine + venetoclax + revumenib
 Dr Perl	Azacitidine + venetoclax + revumenib
 Dr Stein	Revumenib
 Dr Cortes	Revumenib-based combination, possibly with azacitidine + venetoclax
 Dr DiNardo	HMA + venetoclax + menin inhibitor
 Dr Wang	Revumenib

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, which treatment would you generally recommend next for an 80-year-old patient with AML and a KMT2A rearrangement who experienced disease progression on azacitidine/venetoclax?

 Dr Erba	Revumenib
 Dr Fathi	Revumenib
 Dr Lin	Revumenib
 Dr Perl	Revumenib
 Dr Stein	Revumenib
 Dr Cortes	Revumenib
 Dr DiNardo	Revumenib
 Dr Wang	Revumenib

Regulatory and reimbursement issues aside, which treatment would you generally recommend next for a 60-year-old patient with AML and an NPM1 mutation who experienced disease progression after 7 + 3 followed by ASCT?

 Dr Erba	Ziftomenib
 Dr Fathi	HMA + venetoclax
 Dr Lin	Azacitidine + venetoclax + revumenib
 Dr Perl	Azacitidine + venetoclax + ziftomenib
 Dr Stein	Azacitidine + venetoclax
 Dr Cortes	Ziftomenib-based combination, possibly with azacitidine + venetoclax
 Dr DiNardo	HMA + venetoclax
 Dr Wang	Ziftomenib

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, which treatment would you generally recommend next for an 80-year-old patient with AML and an NPM1 mutation who experienced disease progression on azacitidine/venetoclax?

 Dr Erba	Ziftomenib
 Dr Fathi	Revumenib or ziftomenib
 Dr Lin	Revumenib or ziftomenib
 Dr Perl	Ziftomenib
 Dr Stein	Revumenib
 Dr Cortes	Ziftomenib
 Dr DiNardo	Ziftomenib
 Dr Wang	Ziftomenib

RTP RESEARCH TO PRACTICE

Based on published research data and your own clinical experience, how would you indirectly compare the global efficacy and tolerability/toxicity of the available and investigational menin inhibitors for relapsed/refractory AML with an NPM1 mutation?

	Efficacy	Tolerability/toxicity
 Dr Erba	Enzomenib is most efficacious	Enzomenib is the most tolerable
 Dr Fathi	Efficacy is about the same	Tolerability is about the same
 Dr Lin	Efficacy is about the same	Tolerability is about the same
 Dr Perl	Efficacy is about the same	Enzomenib is the most tolerable
 Dr Stein	Efficacy is about the same	Tolerability is about the same
 Dr Cortes	Efficacy is about the same	Tolerability is about the same
 Dr DiNardo	Efficacy is about the same	Tolerability is about the same
 Dr Wang	Efficacy is about the same	Enzomenib is the most tolerable

Based on published research data and your own clinical experience, how would you indirectly compare the risk of differentiation syndrome with the available and investigational menin inhibitors for relapsed/refractory AML?

 Dr Erba	The risk is about the same
 Dr Fathi	Risk appears to vary a bit across agents, but head-to-head data are lacking
 Dr Lin	The risk is about the same
 Dr Perl	The risk is greater with ziftomenib
 Dr Stein	The risk is about the same
 Dr Cortes	The risk is about the same
 Dr DiNardo	The risk is about the same
 Dr Wang	The risk is greater with bleximenib

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Have you observed HLH-like syndrome in a patient with AML who was receiving a menin inhibitor?

 Dr Erba	No
 Dr Fathi	Yes, a few times
 Dr Lin	No
 Dr Perl	No
 Dr Stein	Yes, 5 times
 Dr Cortes	No
 Dr DiNardo	Yes, 3 times
 Dr Wang	No

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Cases from the Community
Investigators Discuss Available Research Guiding the Selection of Therapy for Patients with Chronic Lymphocytic Leukemia

A CME-Accredited Friday Satellite Symposium Preceding the 67th ASH Annual Meeting

Friday, December 5, 2025
11:30 AM – 1:30 PM ET

Faculty

Matthew S Davids, MD, MMSc
Bita Fakhri, MD, MPH
Professor Constantine Tam, MBBS, MD
Jennifer Woyach, MD

Moderator

Neil Love, MD

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