

Year in Review: Acute Myeloid Leukemia

A Multitumor CME/MOC-Accredited Live Webinar

Wednesday, April 17, 2024

5:00 PM – 6:00 PM ET

Faculty

Naval Daver, MD

Courtney D DiNardo, MD, MSCE

Moderator

Neil Love, MD

Faculty



Naval Daver, MD

Director, Leukemia Research Alliance Program
Professor
Department of Leukemia
The University of Texas
MD Anderson Cancer Center
Houston, Texas



MODERATOR

Neil Love, MD

Research To Practice
Miami, Florida



Courtney D DiNardo, MD, MSCE

Professor, Department of Leukemia
Division of Cancer Medicine
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Commercial Support

This activity is supported by educational grants from AbbVie Inc, Astellas, Daiichi Sankyo Inc, Syndax Pharmaceuticals, and Taiho Oncology Inc.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI Biopharma, a Sobi company, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Grail Inc, GSK, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Legend Biotech, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Mural Oncology Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, R-Pharm US, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Sumitomo Dainippon Pharma Oncology Inc, Syndax Pharmaceuticals, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc, and Zymeworks Inc.

Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

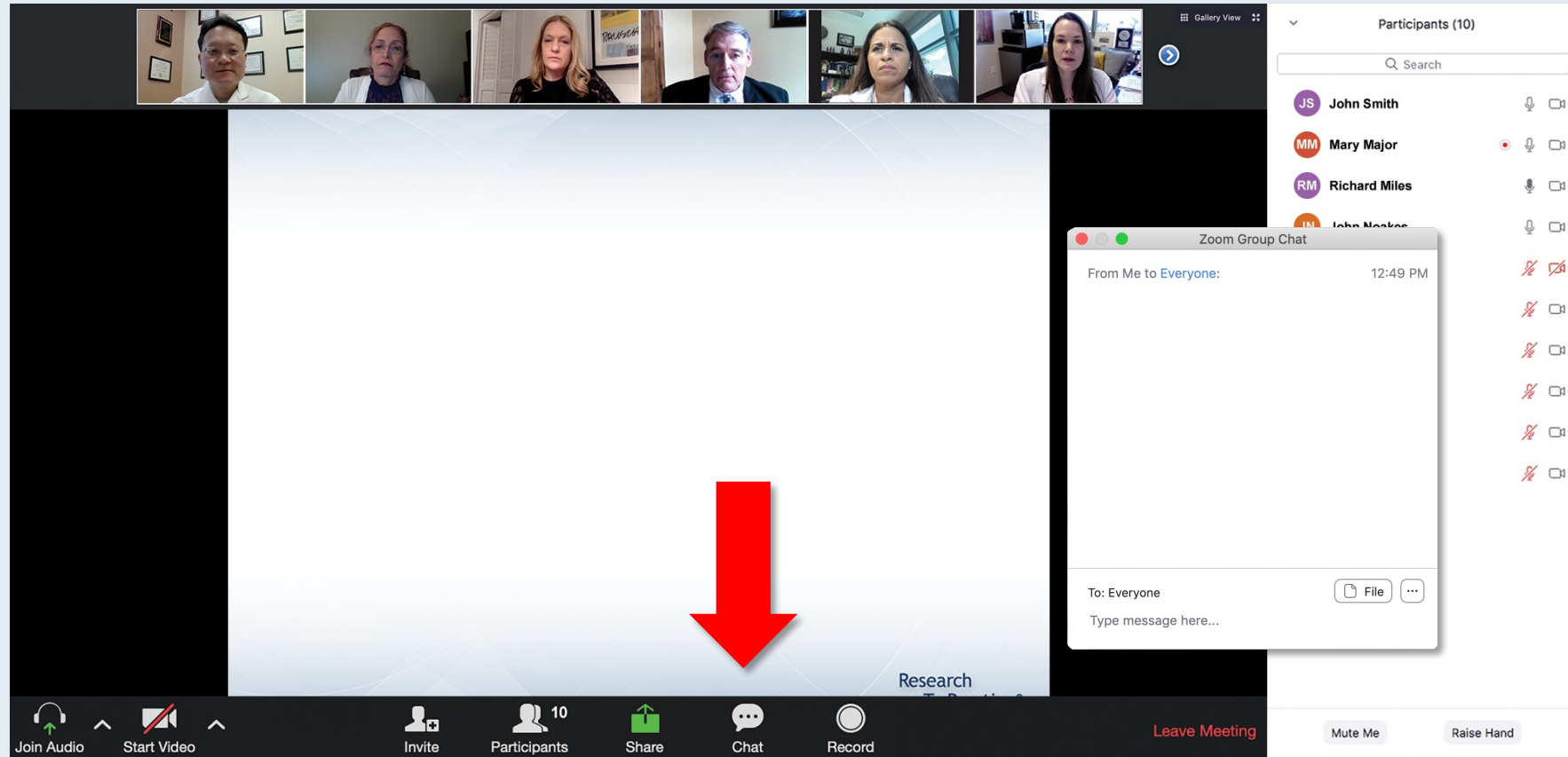
Dr Daver — Disclosures

Consulting Agreements	AbbVie Inc, Agios Pharmaceuticals Inc, Amgen Inc, Arog Pharmaceuticals Inc, Astellas, Bristol Myers Squibb, Celgene Corporation, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, ImmunoGen Inc, Jazz Pharmaceuticals Inc, Kite, A Gilead Company, Menarini Group, Novartis, Pfizer Inc, Servier Pharmaceuticals LLC, Shattuck Labs, Stemline Therapeutics Inc, Syndax Pharmaceuticals, Trillium Therapeutics Inc
Contracted Research	AbbVie Inc, Amgen Inc, Astellas, Bristol Myers Squibb, Daiichi Sankyo Inc, Fate Therapeutics, Genentech, a member of the Roche Group, Gilead Sciences Inc, GlycoMimetics Inc, Hanmi Pharmaceutical, ImmunoGen Inc, Kite, A Gilead Company, NovImmune SA, Pfizer Inc, Servier Pharmaceuticals LLC, Trillium Therapeutics Inc, Trovogene

Dr DiNardo — Disclosures

Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, GSK, Jazz Pharmaceuticals Inc, Rigel Pharmaceuticals Inc, Schrödinger, Servier Pharmaceuticals LLC
Contracted Research	AbbVie Inc, Bristol Myers Squibb, Foghorn Therapeutics, Immune-Onc Therapeutics Inc, Rigel Pharmaceuticals Inc, Schrödinger, Servier Pharmaceuticals LLC
Data and Safety Monitoring Board/ Committee	Genmab US Inc

We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys

The screenshot shows a Zoom meeting with a gallery view of participants at the top. The main content area displays a slide titled "Meet The Prof..." with the subtitle "Optimizing the Selection and Management of Therapy for Patients with Gastrointestinal Cancer". The date and time are "Wednesday, August 25, 5:00 PM – 6:00 PM". The speaker is identified as "Faculty Wells A Messersmith, MD" and the moderator as "Moderator Neil Love, MD". A "Quick Survey" overlay is active, listing several treatment options with radio buttons for selection: Carfilzomib +/- dexamethasone, Pomalidomide +/- dexamethasone, Carfilzomib + pomalidomide +/- dexamethasone, Elotuzumab + lenalidomide +/- dexamethasone, Elotuzumab + pomalidomide +/- dexamethasone, Daratumumab + lenalidomide +/- dexamethasone, Daratumumab + pomalidomide +/- dexamethasone, Daratumumab + bortezomib +/- dexamethasone, and Isazomib + Rd. A "Submit" button is at the bottom of the survey. On the right, a "Participants (10)" list shows names and icons for mute and video. The bottom toolbar includes "Join Audio", "Start Video", "Invite", "Participants", "Share", "Chat", "Record", "Leave Meeting", "Mute Me", and "Raise Hand".

The screenshot shows a Zoom meeting with a gallery view of participants at the top. The main content area displays a slide titled "Regulatory and reimbursement issues aside, which would you recommend for a 65-year-old patient with clear cell renal cell carcinoma (ccRCC) who has a follow-up 3 years later is found to have asymptomatic metastases (PS 0)?" Below the title is a numbered list of eight options: 1. Nivolumab/ipilimumab, 2. Avelumab/axitinib, 3. Pembrolizumab/axitinib, 4. Pembrolizumab/lenvatinib, 5. Nivolumab/cabozantinib, 6. Tyrosine kinase inhibitor (TKI) monotherapy, 7. Anti-PD-1/PD-L1 monotherapy, and 8. Other. A "Quick Poll" overlay is active, showing the same list of options with radio buttons for selection and a "Submit" button at the bottom. On the right, a "Participants (10)" list shows names and icons for mute and video. The bottom toolbar includes "Join Audio", "Start Video", "Invite", "Participants", "Share", "Chat", "Record", "Leave Meeting", "Mute Me", and "Raise Hand".

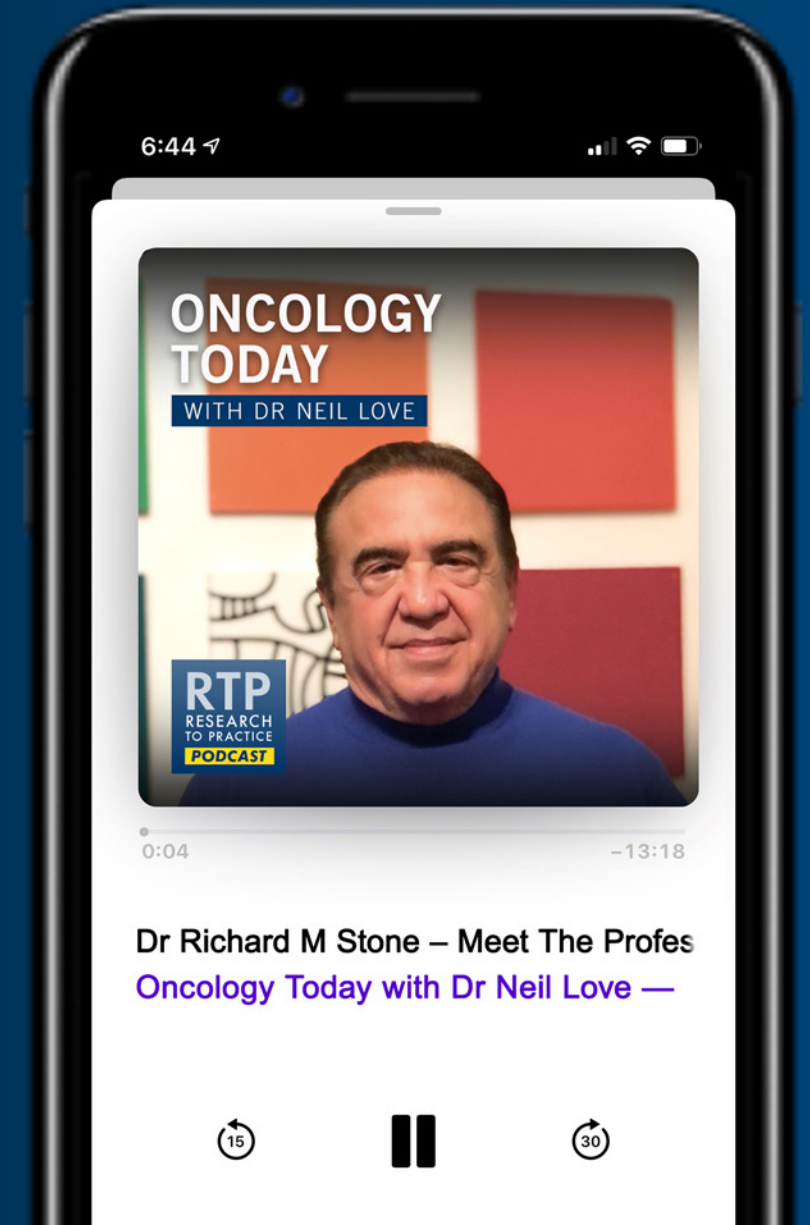
ONCOLOGY TODAY

WITH DR NEIL LOVE

Meet The Professor: Optimizing the Management of Acute Myeloid Leukemia and Myelodysplastic Syndromes — Part 3 of a 3-Part Series



DR RICHARD M STONE
DANA-FARBER CANCER INSTITUTE



What I Tell My Patients: Integrating New Research Information into Current Clinical Care

A Complimentary NCPD Hybrid Symposium Series Held During the 49th Annual ONS Congress April 24-27

Hormone Receptor-Positive Breast Cancer

Wednesday, April 24, 2024

6:00 PM – 8:00 PM ET

Faculty

Harold J Burstein, MD, PhD

Kelly Fischer, MSN, FNP-BC

Komal Jhaveri, MD, FACP

Melissa Rikal, FNP-BC, AOCNP

Antibody-Drug Conjugates

Thursday, April 25, 2024

12:15 PM – 1:45 PM ET

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Jamie Carroll, APRN, MSN, CNP

Kelly EH Goodwin, MSN, RN, ANP-BC

Erika Hamilton, MD

Hope S Rugo, MD

Endometrial Cancer

Thursday, April 25, 2024

6:00 AM – 7:30 AM ET

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Chronic Lymphocytic Leukemia and Bispecific Antibodies in Lymphoma

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Head and Neck Cancer

Friday, April 26, 2024

6:00 AM – 7:30 AM ET

Faculty

Meetal Dharia, NP-C, AOCNP

Robert L Ferris, MD, PhD

Robert Haddad, MD

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Ovarian Cancer

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Sara M Tinsley-Vance, PhD, APRN, AOCN

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LIVE WEBINAR

Prostate Cancer

Wednesday, May 1, 2024

7:00 PM – 8:00 PM ET

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Gastroesophageal and Colorectal Cancers

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Second Opinion: Urologic Oncology Investigators Discuss How They Apply Clinical Research in the Care of Patients with Prostate Cancer

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Friday, May 3, 2024

8:00 AM – 10:00 AM CT (9:00 AM – 11:00 AM ET)

Faculty

Rahul Aggarwal, MD

Adam S Kibel, MD

Additional faculty to be announced

Moderator

Elisabeth I Heath, MD

Second Opinion: Urologic Oncology Investigators Discuss How They Apply Clinical Research in the Care of Patients with Urothelial Bladder Cancer

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**Monday, May 6, 2024
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Faculty to be announced

Moderator

Neil Love, MD

Year in Review:

Targeted Therapy for Non-Small Cell Lung Cancer

A Multitumor CME/MOC-Accredited Live Webinar

Wednesday, May 8, 2024

5:00 PM – 6:00 PM ET

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Justin F Gainor, MD

Karen Reckamp, MD, MS

Moderator

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Agenda

INTRODUCTION

MODULE 1: Available and Emerging Nontargeted Therapies for Acute Myeloid Leukemia (AML) — Dr Daver

MODULE 2: Current and Emerging Role of Biomarker-Directed Therapeutic Approaches for Patients with AML — Dr DiNardo

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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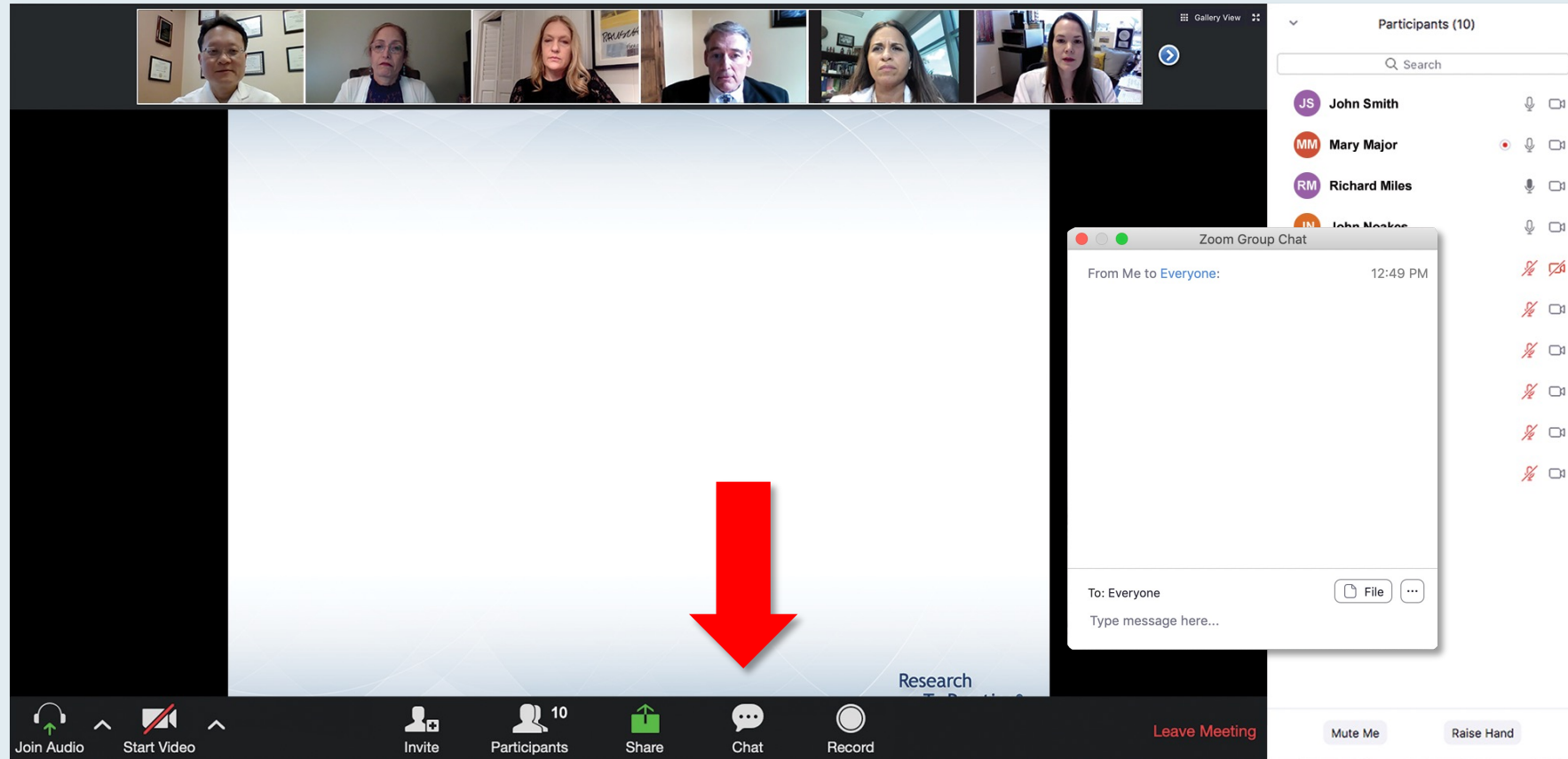
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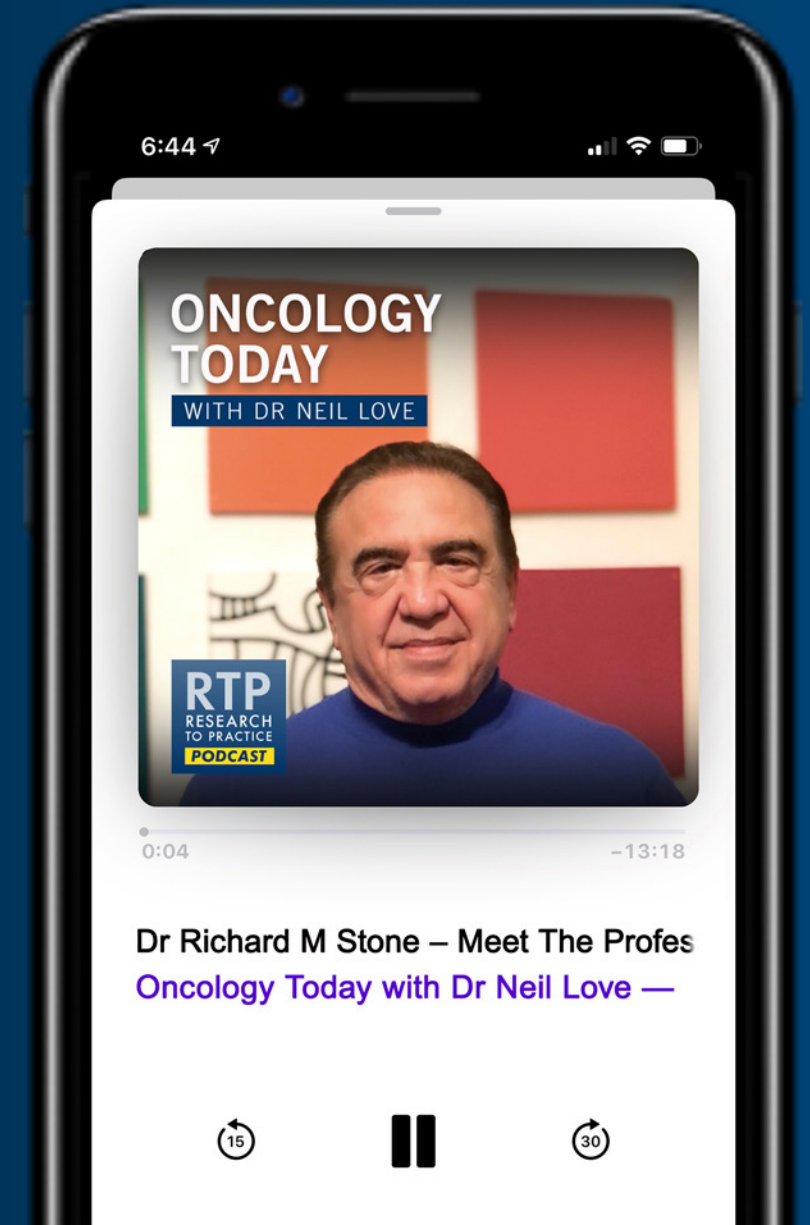
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This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.



RTP: Year in Review

Available and Emerging Nontargeted Therapies for AML

Naval Daver, MD
Director, Leukemia Research Alliance Program,
Professor
Department of Leukemia
MD Anderson Cancer Center

RTP: Current and Emerging Role of
Biomarker-Directed Therapeutic
Approaches for Patients with AML

Courtney DiNardo

Key Data Sets

Naval Daver, MD

- Pratz KW et al. **Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated** acute myeloid leukemia. *Am J Hematol* 2024;99(4):615-24.
- Garciaz S et al. Acute myeloid leukemia patients who **stopped venetoclax** or/and **azacytidine** for other reasons than progression have a prolonged treatment free remission and overall survival. A **Filo study**. ASH 2023;Abstract 161.
- Kadia T et al. A phase 2 study of the **fully oral combination of ASTX727 (decitabine/cedazuridine)** plus **venetoclax** for **older and/or unfit** patients with acute myeloid leukemia. ASH 2023;Abstract 833.
- Ruhnke L et al. **Venetoclax** plus **high-dose cytarabine** and **mitoxantrone (HAM-ven)** as **salvage** treatment for **relapsed/refractory** AML: Updated results of the phase-I/II **SAL relax** trial. ASH 2023;Abstract 160.
- Suo X et al. **Venetoclax** combined with **daunorubicin and cytarabine (2 + 6)** in acute myeloid leukemia: Updated results of a phase II trial. ASH 2023;Abstract 969.

Key Data Sets

Naval Daver, MD (continued)

- Wei AH et al. Long-term survival with **oral azacitidine** for patients with acute myeloid leukemia in first remission after chemotherapy: Updated results from the randomized, placebo-controlled, **phase 3 QUAZAR AML-001** trial. *Am J Hematol* 2023 April;98(4):E84-7.
- Guolo F et al. **Optimal duration** of **CPX-351** treatment and best timing for consolidation with allogeneic stem cell transplantation: Evidence from a large real-world Italian study. ASH 2023;Abstract 731.
- Yang Li et al. **Selinexor** in combination with **venetoclax** and **azacitidine** for **newly diagnosed (ND) unfit** acute myeloid leukemia (AML): A multicenter, open-label prospective study. ASH 2023;Abstract 55.
- Garcia-Manero G et al. **Eprenetapopt** combined with **venetoclax** and **azacitidine** in **TP53-mutated** acute myeloid leukaemia: A phase 1, dose-finding and expansion study. *Lancet Haematol* 2023;10(4):e272-83.

Key Data Sets

Naval Daver, MD (continued)

- Pabst T et al. **Cusatuzumab plus azacitidine in newly diagnosed acute myeloid leukaemia ineligible for intensive chemotherapy (CULMINATE)**: Part one of a randomised, phase 2, dose optimisation study. *Lancet Haematol* 2023;10(11):e902-12.
- Daver NG et al. **Pivekimab sunirine (IMGN632), a novel CD123-targeting antibody-drug conjugate, in relapsed or refractory acute myeloid leukaemia: A phase 1/2 study.** *Lancet Oncol* 2024;25(3):388-99.
- Stein AS et al. A first-in-human study of **CD123 NK cell engager SAR443579 in relapsed or refractory acute myeloid leukemia, B-cell acute lymphoblastic leukemia, or high-risk myelodysplasia.** ASCO 2023;Abstract 7005.

Key Data Sets

Courtney D DiNardo, MD, MSCE

- Erba HP et al. **Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First):** A randomised, double-blind, placebo-controlled, **phase 3** trial. *Lancet* 2023;401(10388):1571-83.
- Perl A et al. **Quantum-first trial: FMS-like tyrosine kinase 3-internal tandem duplication (FLT3-ITD)-specific measurable residual disease (MRD) clearance** assessed through induction (IND) and consolidation (CONS) is associated with improved overall survival (OS) in **newly diagnosed** (nd) FLT3-ITD+ AML patients (pts). ASH 2023;Abstract 832.
- Montesinos P et al. Preliminary results of **QUIWI**: A double blinded, randomized clinical trial comparing standard **chemotherapy plus quizartinib** versus **placebo** in adult patients with **newly diagnosed FLT3-ITD wild-type** AML. EHA 2023;Abstract S130.
- Pratz KW et al. **Gilteritinib in combination with induction and consolidation chemotherapy** and as **maintenance** therapy: A phase IB study in patients with **newly diagnosed** AML. *J Clin Oncol* 2023;41(26):4236-46.

Key Data Sets

Courtney D DiNardo, MD, MSCE (continued)

- Perl AE et al. Outcomes in patients with **FLT3-mutated relapsed/refractory** acute myelogenous leukemia who underwent transplantation in the **phase 3 ADMIRAL** trial of **gilteritinib** versus **salvage chemotherapy**. *Transplant Cell Ther* 2023;29(4):265.e1-10.
- Levis MJ et al. **BMT-CTN 1506 (MORPHO)**: A randomized trial of the **FLT3 inhibitor gilteritinib** as **post-transplant maintenance** for FLT3-ITD AML. EHA 2023;Abstract LB2711.
- Atluri H et al. Phase Ib/2 study of **oral decitabine/cedazuridine (ASTX727)** and **venetoclax** in **combination** with the targeted mutant **IDH1 inhibitor ivosidenib** or the targeted mutant **IDH2 inhibitor enasidenib**: 2023 Update. ASH 2023;Abstract 968.
- de Botton S et al. **Olutasidenib (FT-2102)** induces durable complete remissions in patients with **relapsed or refractory IDH1-mutated** AML. *Blood Adv* 2023;7(13):3117-27.

Key Data Sets

Courtney D DiNardo, MD, MSCE (continued)

- Aldoss I et al. **Revumenib** monotherapy in patients with **relapsed/refractory KMT2Ar** acute leukemias: Efficacy and safety results from the **augment-101** phase 1/2 study. ASH 2023;Abstract LBA-5.
- Issa GC et al. Early results of the phase I/II study investigating the **all-oral combination** of the **menin inhibitor revumenib (SNDX-5613)** with **decitabine/cedazuridine (ASTX727)** and **venetoclax** in acute myeloid leukemia (**SAVE**). ASH 2023;Abstract 58.
- Fathi A et al. Activity, tolerability, and resistance profile of the **menin inhibitor ziftomenib** in adults with **R/R NPM1-mutated** AML. EHA 2023;Abstract LB2713.
- Jabbour E et al. A first-in-human phase 1 study of the **menin-KMT2A (MLL1) inhibitor JNJ-75276617** in adult patients with **relapsed/refractory** acute leukemia harboring **KMT2A or NPM1 alterations**. ASH 2023;Abstract 57.

Agenda

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MODULE 1: Available and Emerging Nontargeted Therapies for Acute Myeloid Leukemia (AML) — Dr Daver

MODULE 2: Current and Emerging Role of Biomarker-Directed Therapeutic Approaches for Patients with AML — Dr DiNardo

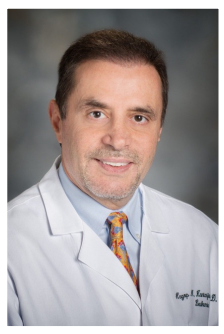
Agenda

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Department of Leukemia, MD Anderson Department Leadership



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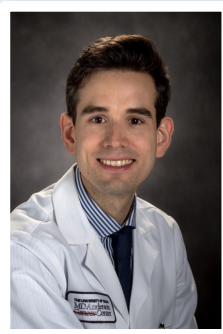
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**Tapan
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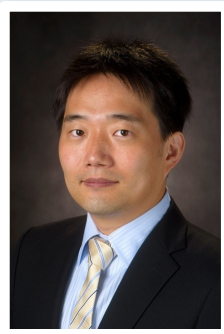
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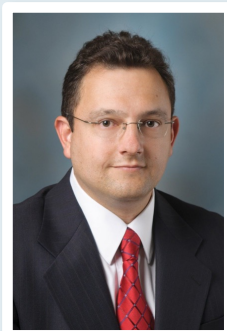


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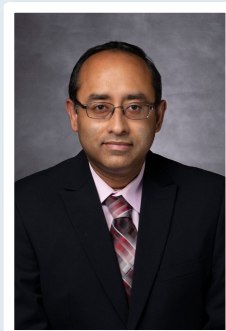
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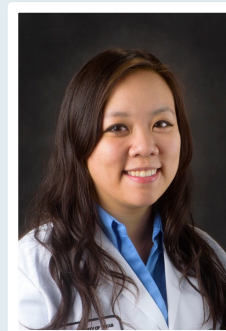
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Valero, MD**



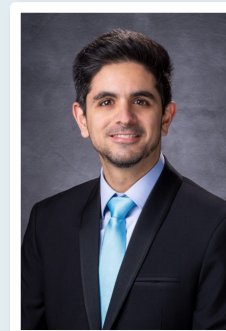
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Bose, MD**



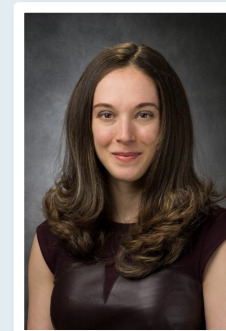
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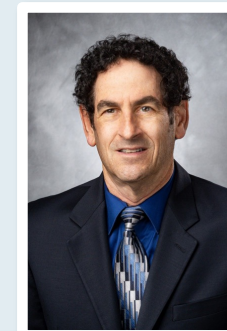
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Chien, MD**



**Fadi
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**Danielle
Hammond, MD**



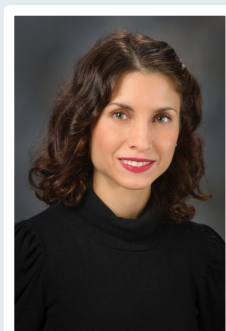
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Kornblau, MD**



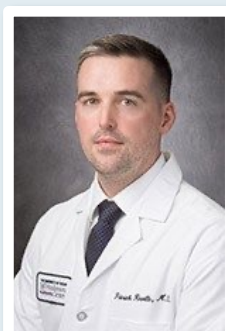
**Abhishek
Maiti, MD**



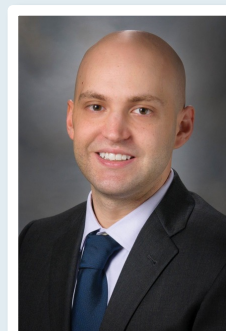
**Lucia
Masarova, MD**



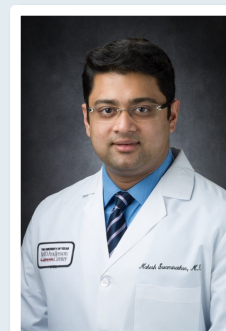
**Maro
Ohanian, DO**



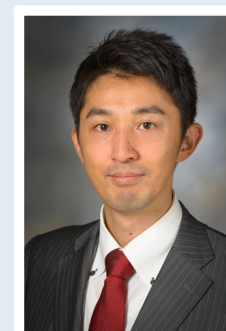
**Patrick K
Reville,
MD, MPH**



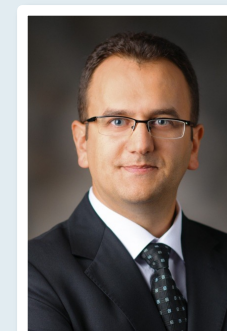
**Nicholas
James
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**Mahesh
Swaminathan,
MB, BS**



**Koichi
Takahashi,
MD, PhD**



**Musa
Yilmaz, MD**

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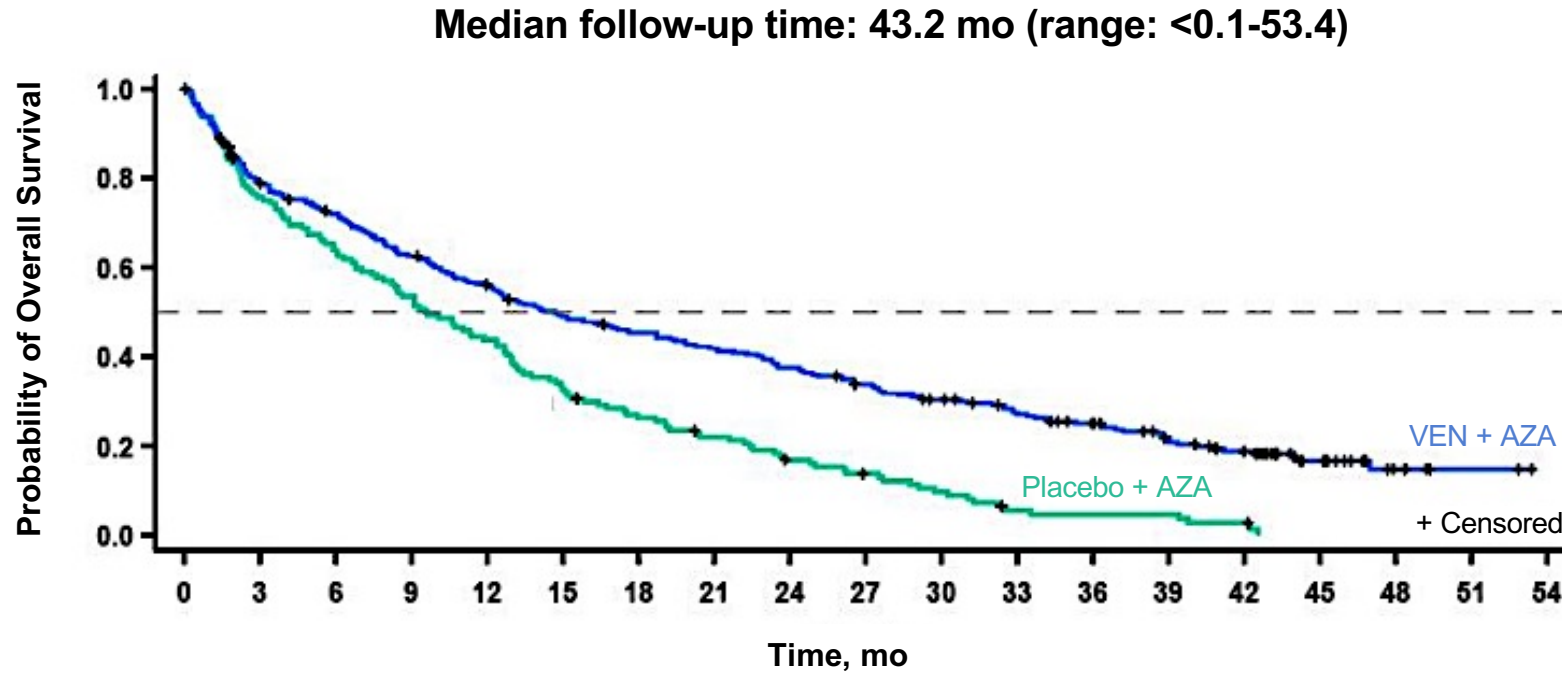
In general, do you provide direct care for your patients with AML?

1. No
2. Yes, but only older patients not eligible for intensive chemotherapy
3. Yes, both older and younger patients

Novel Venetoclax-Based Approaches

- Pratz KW et al. **Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated** acute myeloid leukemia. *Am J Hematol* 2024;99(4):615-24.
- Garciaz S et al. Acute myeloid leukemia patients who **stopped venetoclax** or/and **azacytidine** for other reasons than progression have a prolonged treatment free remission and overall survival. A **Filo study**. ASH 2023;Abstract 161.
- Kadia T et al. A phase 2 study of the **fully oral combination of ASTX727 (decitabine/cedazuridine)** plus **venetoclax** for **older and/or unfit** patients with acute myeloid leukemia. ASH 2023;Abstract 833.
- Ruhnke L et al. **Venetoclax plus high-dose cytarabine and mitoxantrone (HAM-ven) as salvage treatment for relapsed/refractory AML: Updated results of the phase-I/II SAL relax trial**. ASH 2023;Abstract 160.
- Suo X et al. **Venetoclax combined with daunorubicin and cytarabine (2 + 6) in acute myeloid leukemia: Updated results of a phase II trial**. ASH 2023;Abstract 969.

Long term OS with AZA+VEN needs further improvement (3 year follow-up)



	Events/Patients n (%)	OS median, mo (95% CI)
VEN + AZA	222/286 (77.6)	14.7 (12.1-18.7)
Placebo + AZA	138/145 (95.2)	9.6 (7.4-12.7)

HR = 0.58 (95% CI, 0.465-0.723)
***P* < .001**

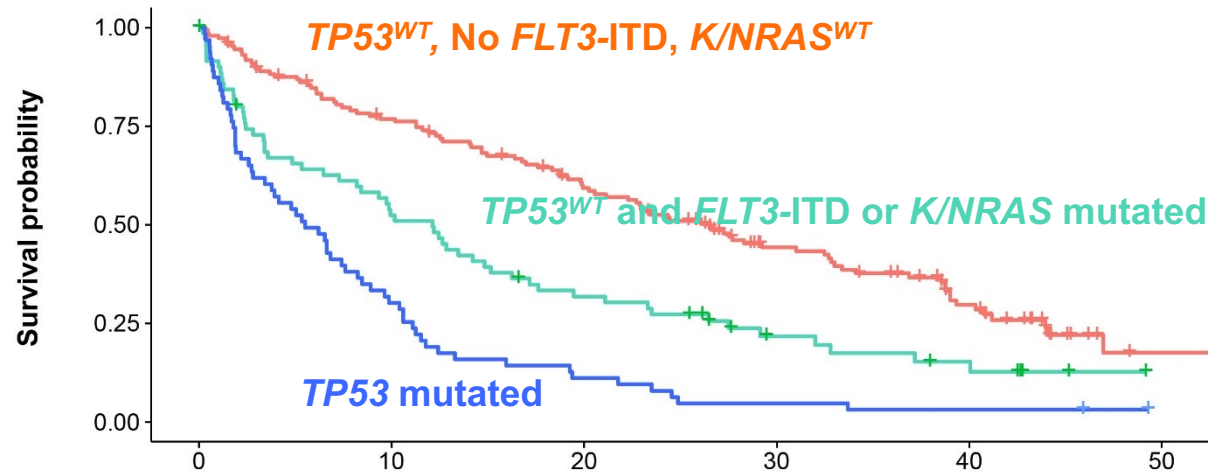
HR reduction from 0.66 (95% CI, 0.52-0.85) at 75% OS analysis

No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
VEN + AZA	286	220	199	173	153	133	122	113	101	89	78	67	57	45	34	18	6	2	0
Placebo + AZA	145	109	92	77	63	47	37	30	22	17	12	6	5	5	3	0	0	0	0

What are the most urgent populations in need of improvement?

Patients receiving Ven+Aza distinguishable into 3 subgroups by OS benefit

- First a higher benefit group was identified, with a median OS > 24 months
- Subsequently a lower benefit group was determined, with a median OS < 6 months
- Patients fitting neither criteria were categorized as the intermediate benefit group, with a median OS of 12 months

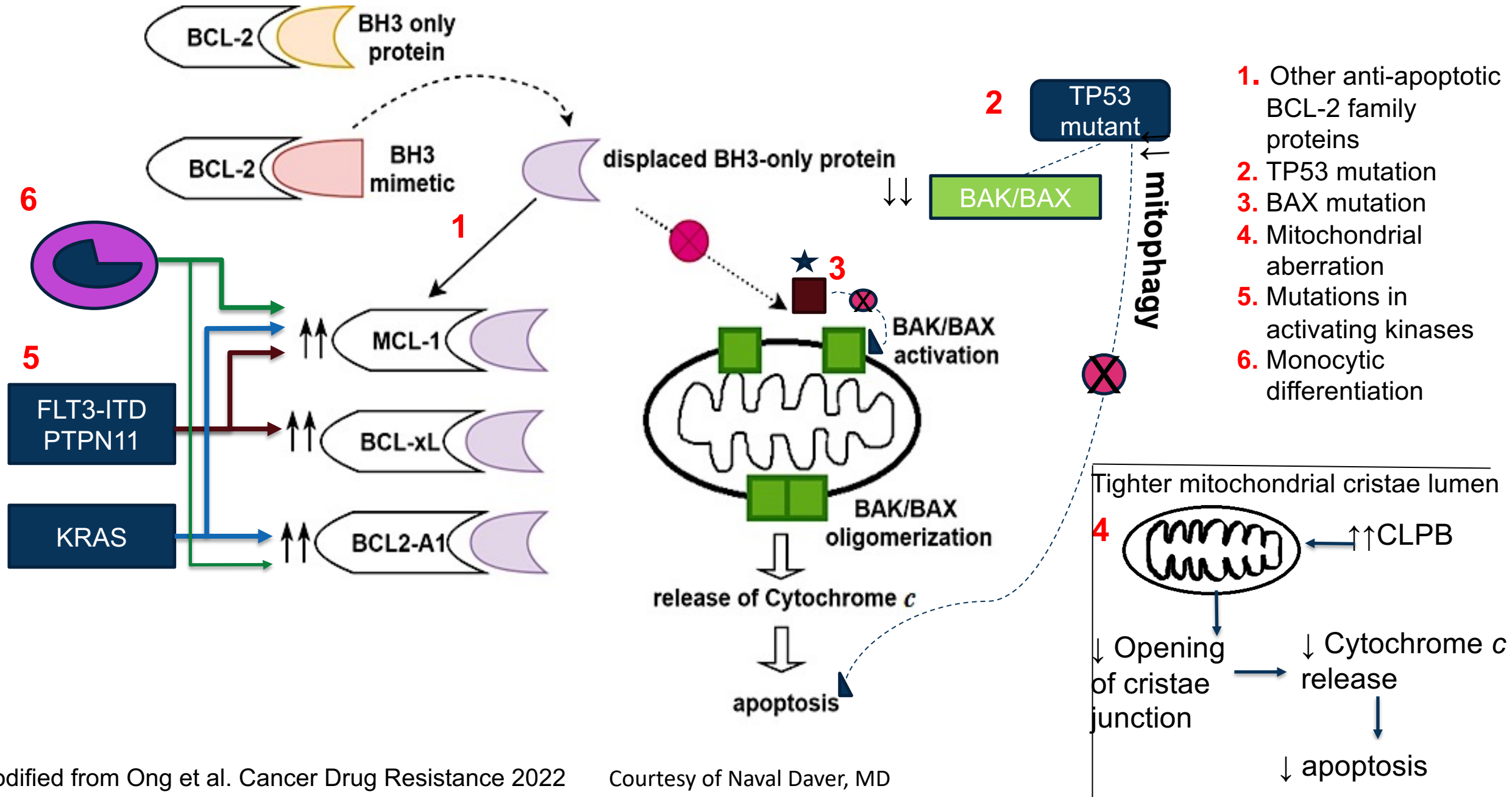


Ven + Aza (N = 279)	n	Events	Median OS, months (95% CI)
Higher Benefit	145	96	26.51 (20.24, 32.69)
Intermediate Benefit	71	57	12.12 (7.26 – 15.15)
Lower Benefit	63	61	5.52 (2.79 – 7.59)

- **Majority of patients in the Ven+Aza arm are in the higher benefit group: 52% (145/279)**
- The remainder of the patients are distributed equally between the intermediate and lower benefit groups: 25.4% (71/279) and 22.6% (63/279), respectively

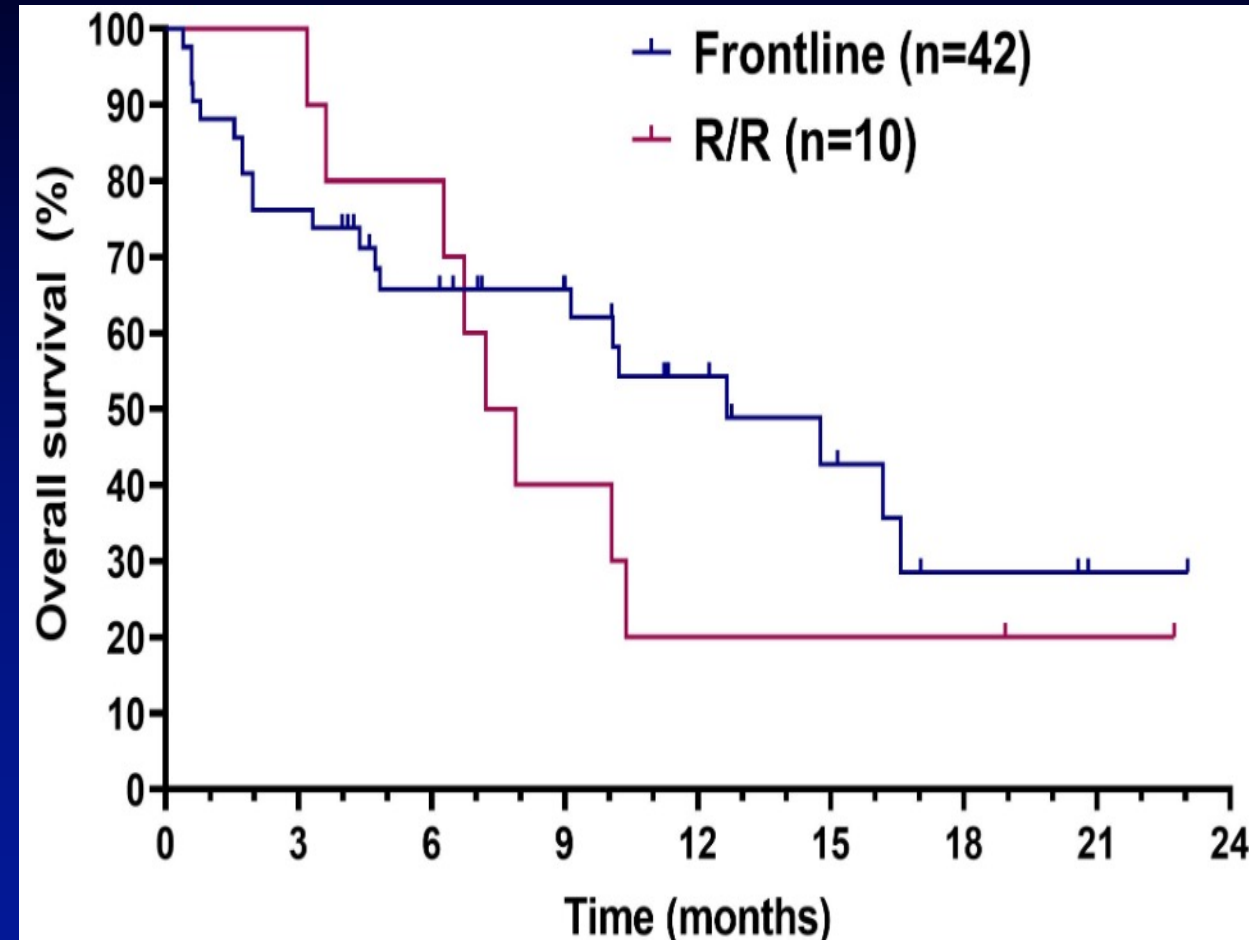
Benefit Group	Patients at Risk					
Higher Benefit	145	107	79	47	25	2
Interm. Benefit	71	36	21	10	6	0
Lower Benefit	63	19	7	3	2	0

Venetoclax Resistance: Road to “Triplets”



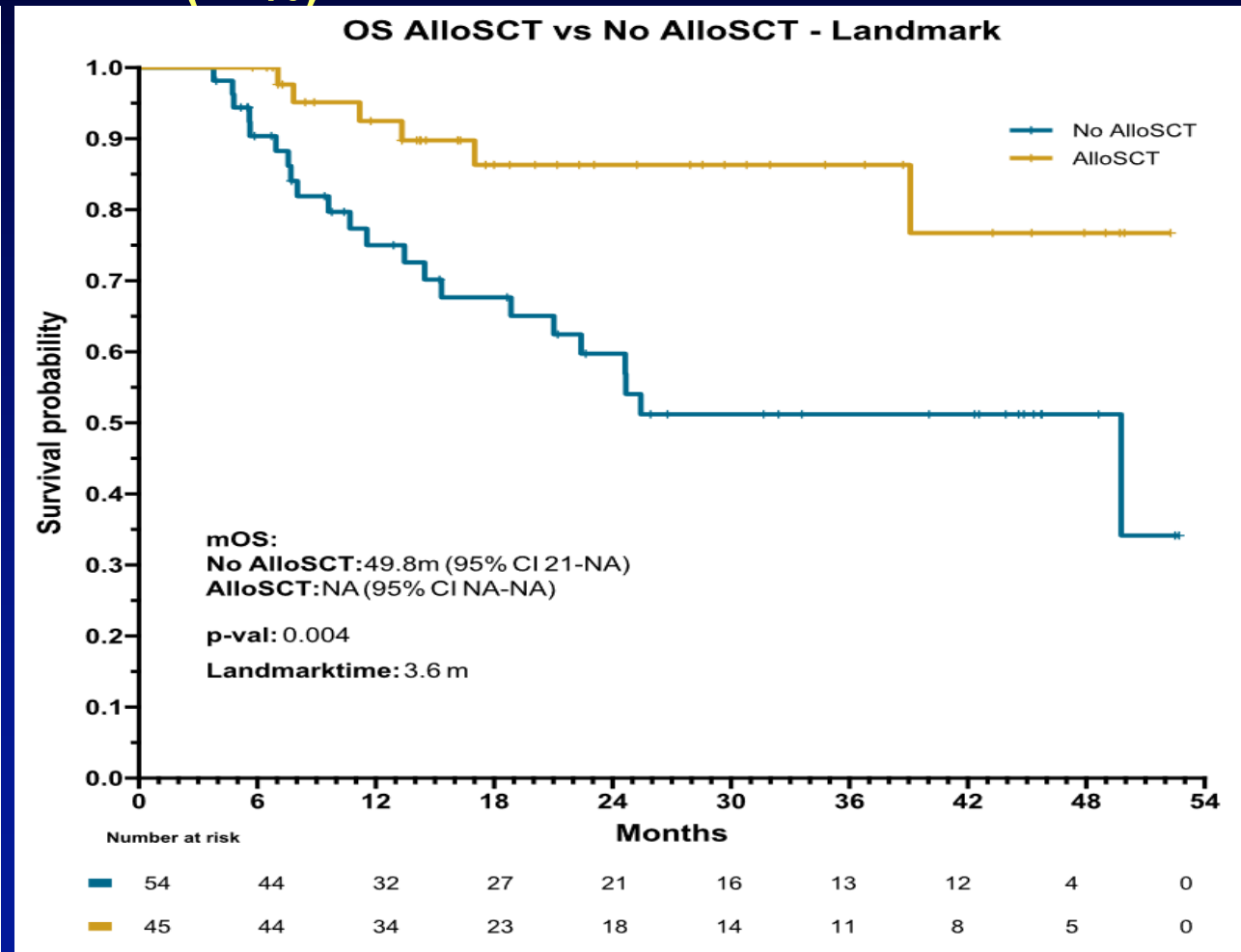
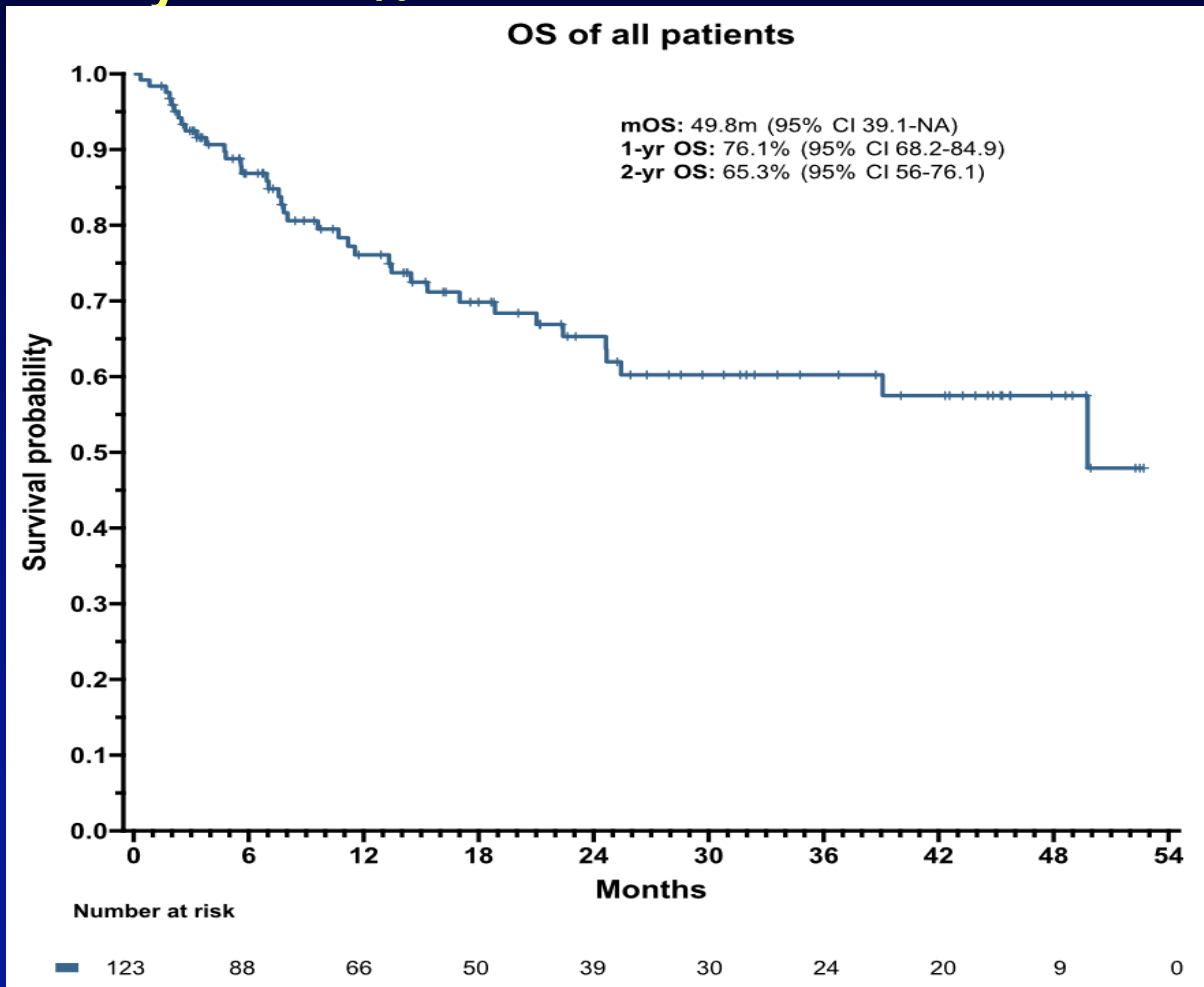
Oral DAC + Venetoclax in Older /Unfit AML

- 52 pts: 42 frontline (median age 79 yrs [50-92]); 10 R-R. 17/42 Rx secondary AML
- Oral DAC 35mg/Dx5, VEN 40mg/Dx21-28
- ORR 28/42=67%: CR 36%, CRi 26%. MLFS 5%. FCM-MRD 7/22=32%
- Median OS 12.7 mos
- R-R ORR 5/10=50%. Median OS 7.6 mos



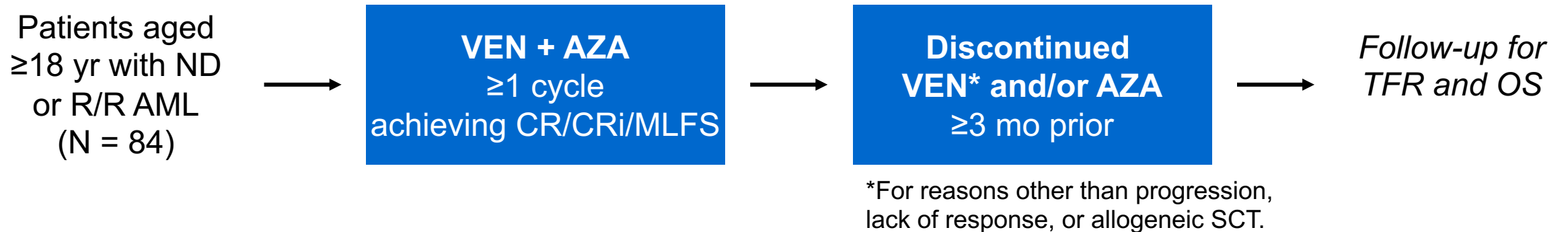
Triple-Nucleoside Regimen (CDA- LDaraC-AZA) + Venetoclax in Newly Dx older AML

- 123 pts; median age 68 yrs (57-84)
- CDA-LD araC VEN x 2 alternating with AZA VEN x2. Total 2 years
- CR 92/123 = 75%. CR+CRi 105/123 = 92%. MRD-negative 81%. Early (4-wk) death 3/123 (2%)
- **2-yr OS 65%. Median OS 50 mos. Allo SCT = 51/123 (41%)**



STOP-VEN: Study Design

- Retrospective study of patients treated at French FILO centers and US Moffit Cancer Center between Nov. 2018 and July 2023



- Primary Endpoints:** OS, TFR (from last day of VEN)
- Secondary Endpoints:** Multivariate analysis of OS and TFR by Cox regression based on disease and mutation status

STOP-VEN: Investigator Conclusions

- In this retrospective analysis, discontinuation of VEN + AZA treatment in responding patients with ND or R/R AML was associated with sustained responses and survival
 - Median TFR: 60 mo and 10 mo, respectively
 - Median OS: 44 mo and 19 mo, respectively
- MRD negativity was associated with sustained remission
 - Median OS in ND AML: NR
 - Median OS in R/R AML: 31 mo
- Investigators concluded that it is feasible to discontinue VEN + AZA in patients with ND AML in remission and will explore this strategy in a prospective clinical trial

Improving Cytotoxic therapy, non-FLT3, non-CBF approaches with the Addition of Venetoclax to frontline IC

Induction:

- Cladribine **5 mg/m²** IV daily for 5 days on D1-5
- Idarubicin **10 mg/m²** IV daily for 3 days on D1-3
- Cytarabine **1500 mg/m²** (1000 mg/m² for patients ≥ 60) IV daily for 5 days on D1-5

Consolidation:

- Cladribine **5 mg/m²** IV daily for 3 days on D1-3
- Idarubicin **8 mg/m²** IV daily for 2 days on D1-2
- Cytarabine **1000 mg/m²** (750 mg/m² for patients ≥ 60) IV daily for 3 days on D1-3

Venetoclax dosing:

- 400 mg daily (modifications made for CYP3A4i)
- Given on days 2-8 of each cycle

Cytoreduce to WBC < 20,000 prior to venetoclax

TLS monitoring per institutional standard

Antimicrobial Prophylaxis in all patients: antibacterial, antiviral, antifungal

Course	Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	
CLIA+VEN Induction (28-day cycles)	Venetoclax 400 mg		█							
	Cladribine (5 mg/m ²)	█								
	Cytarabine (1500 mg/m ²)	█								
	Idarubicin (10 mg/m ²)	█								
CLIA+VEN Consolidation (28-day cycles)	Venetoclax 400 mg		█							
	Cladribine (5 mg/m ²)	█								
	Cytarabine (1000 mg/m ²)	█								
	Idarubicin (8 mg/m ²)	█								

Emerging Nontargeted Therapies for AML

- Wei AH et al. Long-term survival with **oral azacitidine** for patients with acute myeloid leukemia in first remission after chemotherapy: Updated results from the randomized, placebo-controlled, **phase 3 QUAZAR AML-001** trial. *Am J Hematol* 2023 April;98(4):E84-7.
- Guolo F et al. **Optimal duration** of **CPX-351** treatment and best timing for consolidation with allogeneic stem cell transplantation: Evidence from a large real-world Italian study. ASH 2023;Abstract 731.
- Yang Li et al. **Selinexor** in combination with **venetoclax** and **azacitidine** for **newly diagnosed (ND) unfit** acute myeloid leukemia (AML): A multicenter, open-label prospective study. ASH 2023;Abstract 55.
- Garcia-Manero G et al. **Eprenetapopt** combined with **venetoclax** and **azacitidine** in **TP53-mutated** acute myeloid leukaemia: A phase 1, dose-finding and expansion study. *Lancet Haematol* 2023;10(4):e272-83.

Emerging Nontargeted Therapies for AML (Continued)

- Pabst T et al. **Cusatuzumab** plus **azacitidine** in **newly diagnosed** acute myeloid leukaemia **ineligible for intensive chemotherapy (CULMINATE)**: Part one of a randomised, phase 2, dose optimisation study. *Lancet Haematol* 2023;10(11):e902-12.
- Daver NG et al. **Pivekimab sunirine (IMGN632)**, a **novel CD123-targeting antibody-drug conjugate**, in **relapsed or refractory** acute myeloid leukaemia: A phase 1/2 study. *Lancet Oncol* 2024;25(3):388-99.
- Stein AS et al. A first-in-human study of **CD123 NK cell engager SAR443579** in **relapsed or refractory** acute myeloid leukemia, B-cell acute lymphoblastic leukemia, or high-risk myelodysplasia. ASCO 2023;Abstract 7005.

Pivekimab (IMGN632) With AZA+VEN in Newly Diagnosed AML

- PVEK with AZA + VEN (14-21 days) in newly diagnosed CD123+ AML (NCT04086264)
- Peripheral Edema All grades (44%), Grade 3/4 (4%)
- IRRs: 16% (all Grade 1/2)
- No capillary leak syndrome, CRS, or VOD events
- Study discontinuation: 2/50 (1 generalized edema, 1 prolonged myelosuppression)
- 30-day mortality: 0; 60-day mortality 2/50 (4%) (1 PNA, 1 disease progression)
- EOC1 r: ANC>500 34 days, PLT>50 22 days
- Post-remission cycles : ANC>500 28 days, PLT>50 22 days
- Among 29 responders with evaluable central MRD ($\leq 0.02\%$): MRDneg 22/29 (76%)

Responses (N=50)			
	CR rate	CCR rate	CCR _{mrds} rate
Overall Population (N=50)	54% (27/50)	68% (34/50)	76% (22/29)
Strictly meet unfit FDA criteria (n=23)	61% (14/23)	78% (18/23)	79% (11/14)

Molecular Stratification in Subsets	PVEK Triplet	
Higher benefit (<i>TP53</i> ^{wt} , no <i>FLT3</i> -ITD, <i>K/NRAS</i> ^{wt})	CCR CR MRD-	94% (17/18) 89% (16/18) 73% (11/15)
Intermediate benefit (<i>TP53</i> ^{wt} and <i>FLT3</i> -ITD or <i>K/NRAS</i> ^{mut})	CCR CR MRD-	71% (5/7) 71% (5/7) 100% (5/5)
Lower benefit (<i>TP53</i> ^{mut})	CCR CR MRD-	50% (7/14) 21% (3/14) 50% (3/6)

First-in-Human Study of the CD123 NK Cell Engager SAR443579 in Relapsed or Refractory Acute Myeloid Leukemia, B-Cell Acute Lymphoblastic Leukemia or High Risk-Myelodysplasia: Updated Safety, Efficacy, Pharmacokinetics and Pharmacodynamics

Ashish Bajel,¹ Sylvain Garciaz,² Pinkal Desai,³ Gerwin A. Huls,⁴ Abhishek Maiti,⁵ Mojca Jongen-Laurencic,⁶ Nicolas Boissel,⁷ Stephane De Botton,⁸ David C. deLeeuw,⁹ Shaun A. Fleming,¹⁰ C. Michel Zwaan,¹¹ Martha L. Arellano,¹² David Avigan,¹³ Jennifer N. Saultz,¹⁴ Ioannis Mantzaris,¹⁵ Kyle Jensen,¹⁶ Timothy Wagenaar,¹⁶ Gu Mi,¹⁶ Samira Ziti-Ljajic,¹⁷ Dobrin Draganov,¹⁶ Giovanni Abbadessa,¹⁶ Anthony Selwyn Stein,¹⁸

¹Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Australia; ²Institut Paoli-Calmettes, Aix-Marseille University, Marseille, France; ³Weill Cornell Medicine, New York, NY; ⁴University Medical Center Groningen, Groningen, Netherlands; ⁵MD Anderson Cancer Center, Houston, TX; ⁶Erasmus University Medical Center, Rotterdam, Netherlands; ⁷Hôpital Saint-Louis, Paris, France; ⁸Institut Gustave Roussy, Paris, France; ⁹Amsterdam University Medical Center, Amsterdam, Netherlands; ¹⁰The Alfred Hospital, Melbourne, Australia; ¹¹Prinses Máxima Center for Pediatric Oncology Research, Utrecht, Netherlands; ¹²Emory University, Atlanta, GA; ¹³Beth Israel Deaconess Medical Center, Boston, MA; ¹⁴Oregon Health & Science University, Portland, OR; ¹⁵Montefiore Medical Center, Bronx, NY; ¹⁶Sanofi, Cambridge, MA; ¹⁷Sanofi, Chilly-Mazarin, France; ¹⁸City of Hope National Medical Center, Duarte, CA

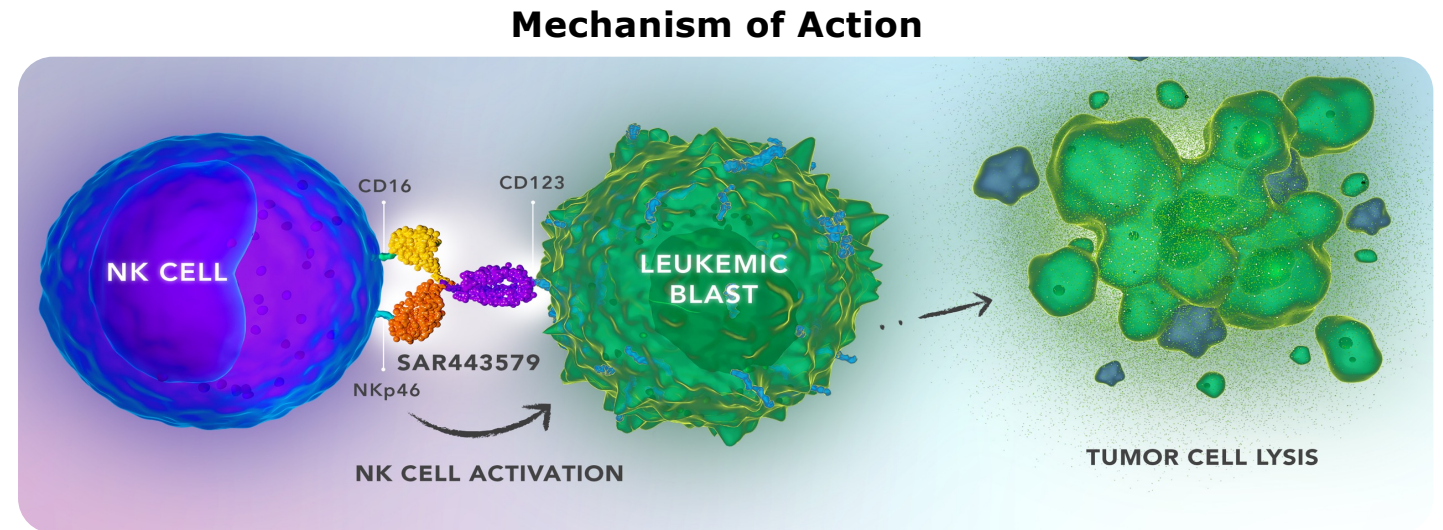
Poster presented at the 65th Annual Meeting of the American Society of Hematology (ASH), San Diego, CA.

December 9–12, 2023 #3474

Courtesy of Naval Daver, MD

Background

- CD123 is widely expressed in hematological malignancies¹⁻⁴
- T cell engagers targeting CD123 have displayed some preliminary clinical efficacy; however, they have been associated with safety concerns including cytokine release syndrome and neurotoxicity⁵
- SAR443579 (SAR'579) is a trifunctional anti-CD123 NKp46xCD16 NKCE targeting the CD123 antigen and co-engaging NKp46 and CD16a on NK cells triggering tumor cell death
- TCD17197 (NCT05086315) is an ongoing first-in-human phase 1/2 open-label, multicenter trial evaluating SAR'579 in patients with R/R AML, B-ALL, or HR-MDS
- In early clinical results, SAR'579 was well tolerated up to 3000 µg/kg QW with no dose-limiting toxicities and clinical remissions were identified at a maximal target dose of 1000 µg/kg/infusion⁶
- Here we present updated results from TCD17197 on SAR'579 doses ranging from 10 µg/kg through 6000 µg/kg at a data cutoff of October 23, 2023



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FLT3 Inhibition for AML

- Erba HP et al. **Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First):** A randomised, double-blind, placebo-controlled, **phase 3** trial. *Lancet* 2023;401(10388):1571-83.
- Perl A et al. **Quantum-first trial:** FMS-like tyrosine kinase 3-internal tandem duplication (**FLT3-ITD**)–**specific measurable residual disease (MRD)** clearance assessed through induction (IND) and consolidation (CONS) is associated with improved overall survival (OS) in **newly diagnosed** (nd) FLT3-ITD+ AML patients (pts). ASH 2023;Abstract 832.
- Montesinos P et al. Preliminary results of **QUIWI:** A double blinded, randomized clinical trial comparing standard **chemotherapy plus quizartinib** versus **placebo** in adult patients with **newly diagnosed FLT3-ITD wild-type** AML. EHA 2023;Abstract S130.
- Pratz KW et al. **Gilteritinib** in combination **with induction and consolidation chemotherapy** and as **maintenance** therapy: A phase IB study in patients with **newly diagnosed** AML. *J Clin Oncol* 2023;41(26):4236-46.

FLT3 Inhibition for AML (Continued)

- Perl AE et al. Outcomes in patients with **FLT3-mutated relapsed/refractory** acute myelogenous leukemia who underwent transplantation in the **phase 3 ADMIRAL** trial of **gilteritinib** versus **salvage chemotherapy**. *Transplant Cell Ther* 2023;29(4):265.e1-10.
- Levis MJ et al. **BMT-CTN 1506 (MORPHO)**: A randomized trial of the **FLT3 inhibitor gilteritinib** as **post-transplant maintenance** for FLT3-ITD AML. EHA 2023;Abstract LB2711.

Newly Dx IC-eligible FLT3-ITD Mutated: QuANTUM-First Updates

Background: The addition of QUIZ to IC induction, Consolidation and Maintenance Improves OS

QuANTUM-First Trial Protocol (NCT02668653)¹

Enrollment dates: Sep 2016 to Aug 2019
Data cutoff: Aug 13, 2021; Sep 30, 2022 (MRD data)

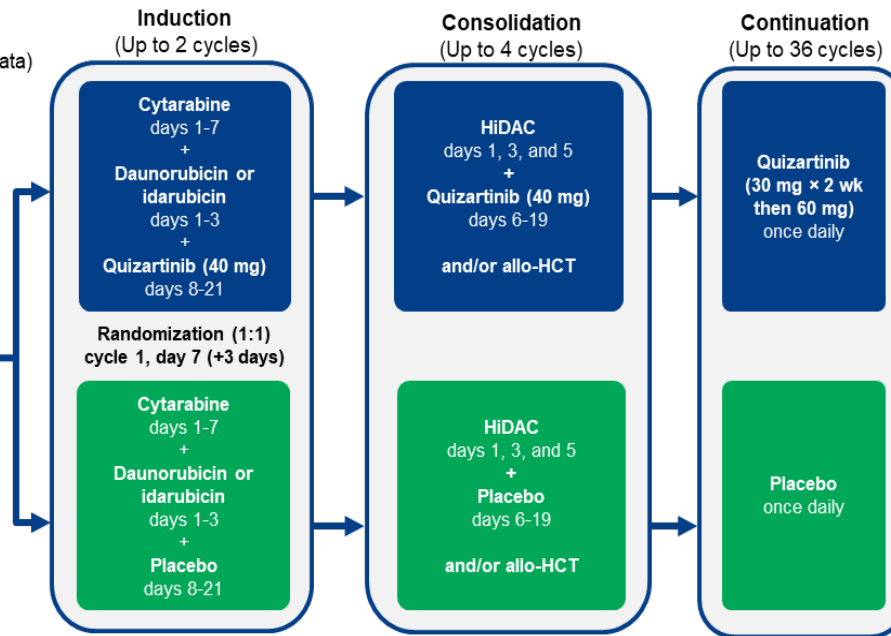
Stratification factors

- Region: NA, EU, and Asia/other regions
- Patient age: <60 years, ≥60 years
- WBC^a: <40×10⁹/L, ≥40×10⁹/L

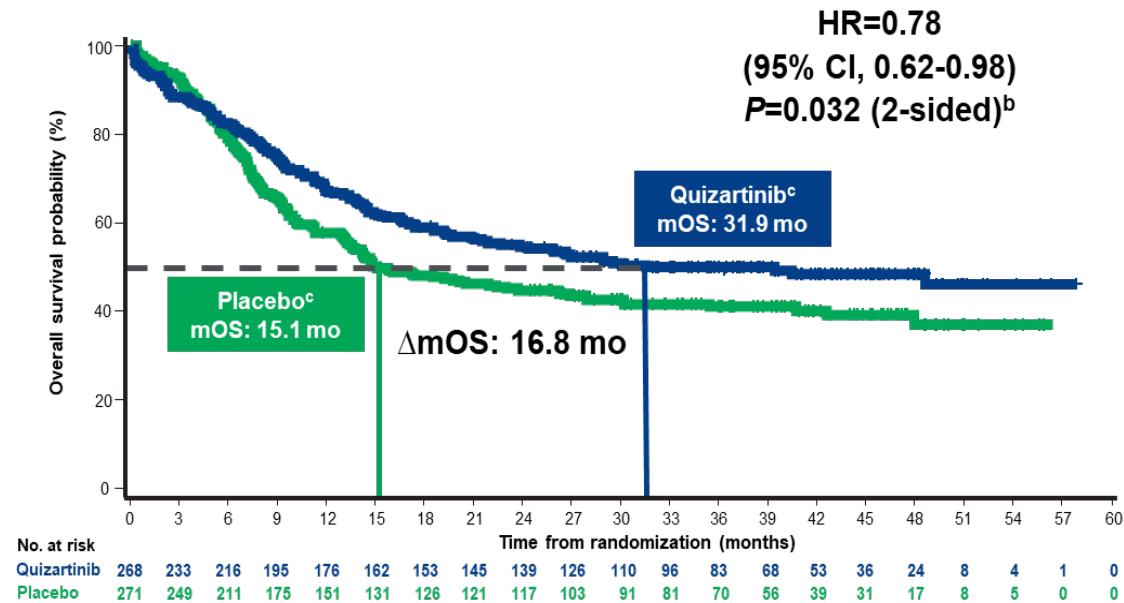
- Newly diagnosed *FLT3*-ITD+ AML
- 18-75 years of age
- ≥3% *FLT3*-ITD allele frequency
- Patients begin 7+3 chemotherapy during screening

Key endpoints^a

- Primary endpoint: OS
- Secondary endpoints: EFS, CR, CRc, CR/CRc with MRD– end of induction, safety
- Exploratory endpoints: RFS, DoCR



Primary Endpoint: Overall Survival¹



Rates of CR/CRi per IRC After 1-2 Courses of Induction

	CR (%)	CR/CRi (%)
Quizartinib	54.9	71.6
Placebo	55.4	64.9

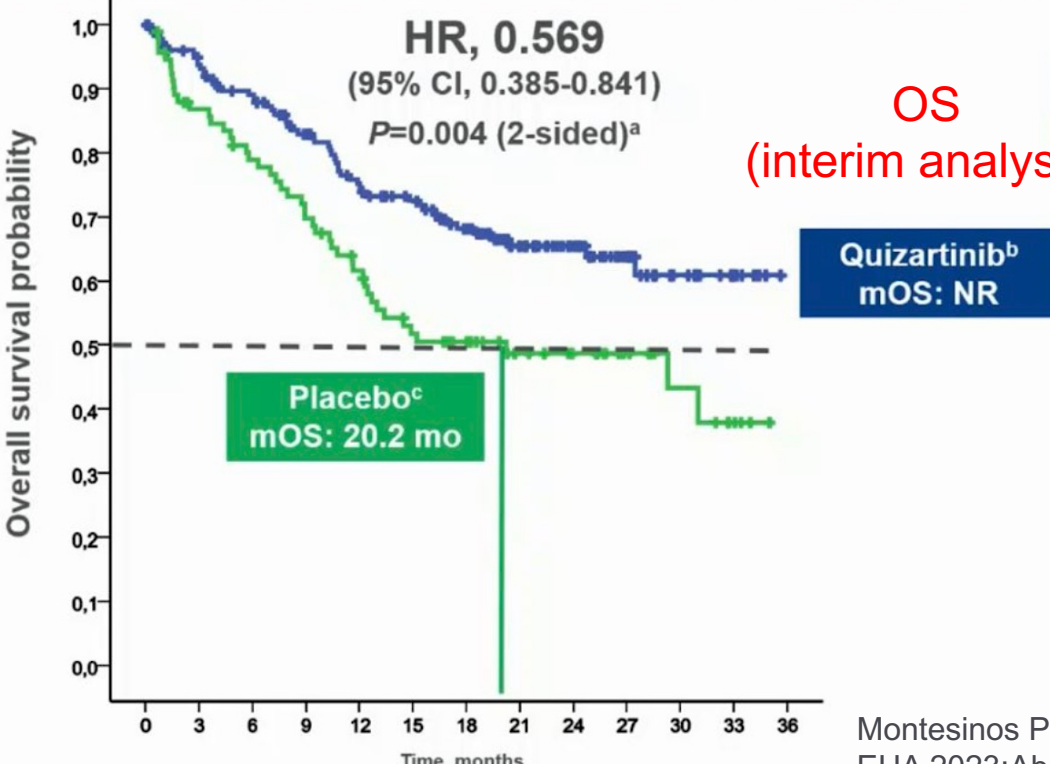
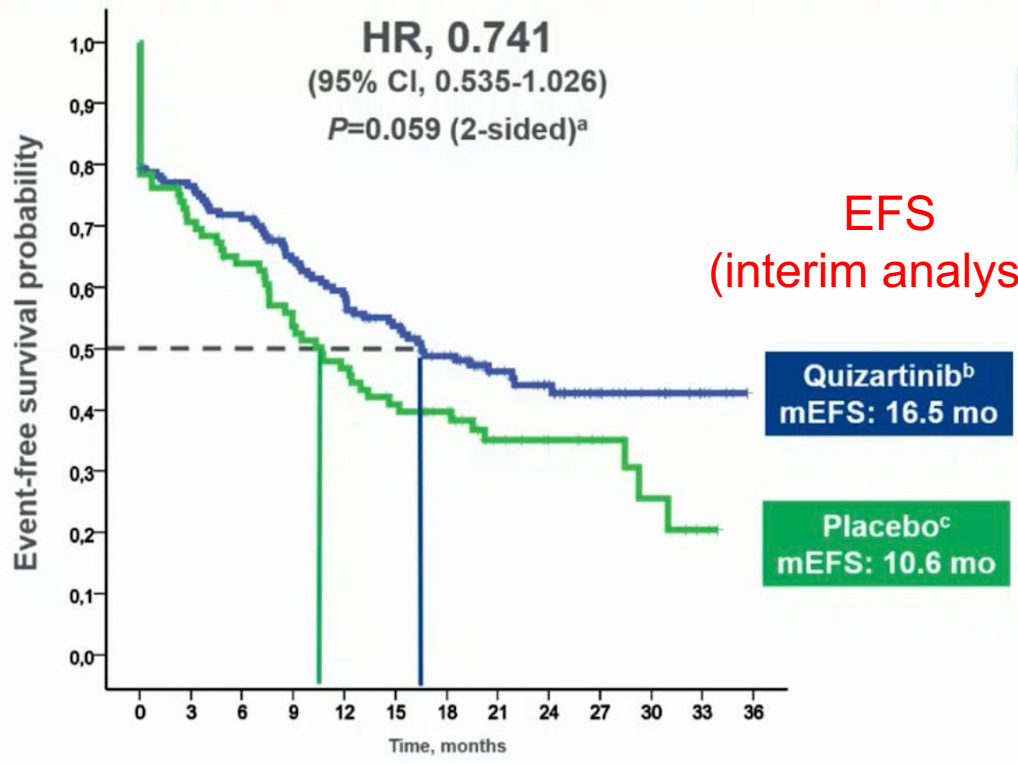
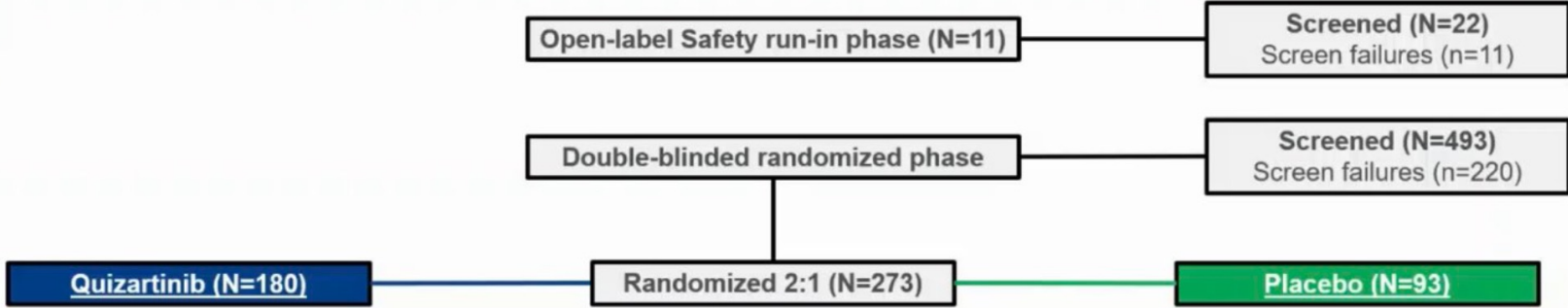
QuANTUM-First: Conclusions

There is a clear prognostic utility of FLT3-ITD specific MRD measurements in management of patients with FLT3-ITD AML

Elimination of detectable FLT3-ITD MRD is associated with longer OS (in patients both w/wo QUIZ)

QUIZ is associated with deeper responses and more frequent MRD clearance

QUIWI: A Double-Blinded, Randomized Phase 2 Study Comparing Standard Chemotherapy Plus Quizartinib Versus Placebo Newly Diagnosed FLT3-ITD Wildtype AML



Courtesy of Courtney D DiNardo, MD, MSCE

Montesinos P et al. EHA 2023; Abstract S130.

QUIZ for patients with FLT3-“like” gene expression signature

Mosquera Orgueira A, ASH #974

Background: A FLT3-like transcriptomic signature is present in 28-53% of FLT3-ITD neg patients¹

The QUIWI Trial compared QUIZ vs PBO + standard chemo in FLT3-ITD wild-type AML (n=284)

***2-yr OS was 63.5% (QUIZ) vs 47% (PBO)**

***49.7% of QUIWI cases had “FLT3-LIKE” expression**

The FLT3-like signature¹

Differential Expression: 649 distinct genes were significantly differentially expressed in FLT3 mutants vs. WT samples.

FLT3 Clustering: FLT3-ITD mutants consistently clustered together in multiple datasets. 28-53% of all FLT3-ITD negative patients were FLT3-like.

Mutation Landscape: *NPM1* and *DNMT3A* mutations were highly enriched in FLT3-like AMLs.

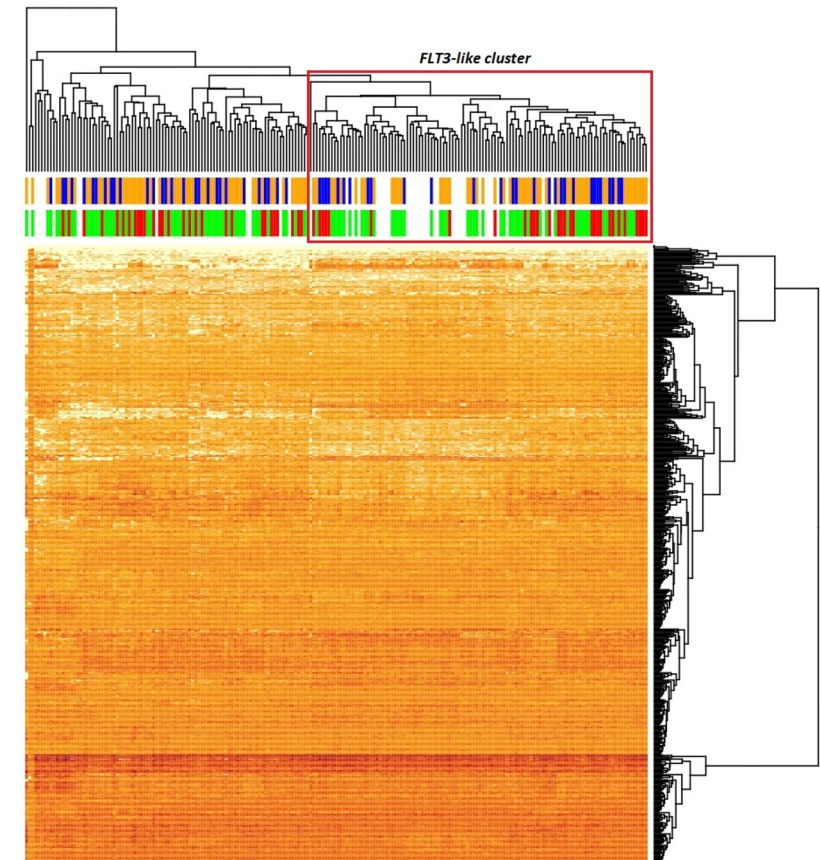
Implications: Findings suggest that FLT3-like AMLs have unique gene expression profiles.

Overview of the Non-FLT3-Like Transcriptomic Cluster

FLT3-Like Patients: 50% of FLT3-ITD negative patients (N=81)

ELN-17 Classification:

- Low Risk: 18.2%
- Intermediate Risk: 39.5%
- High Risk: 42.0%

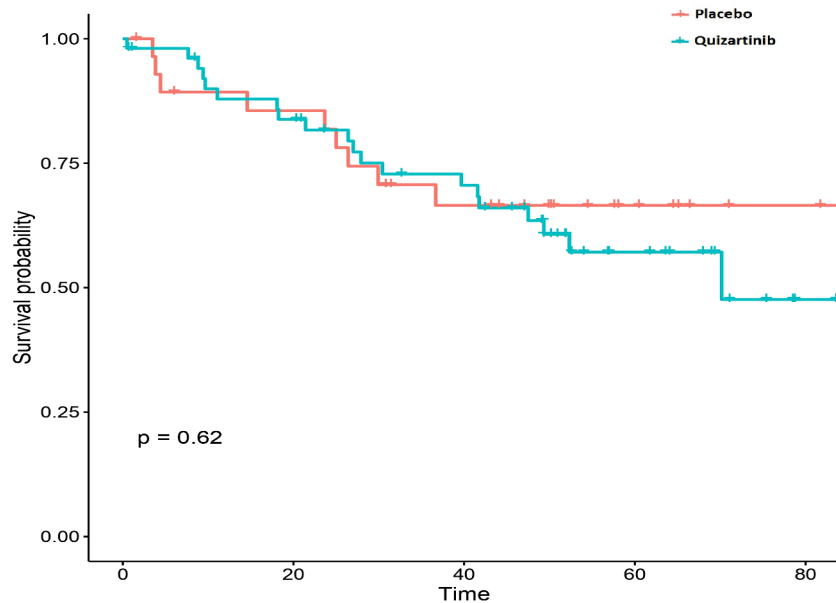


¹Mosquera et al, Plos One 2021

QUIZ for patients with FLT3-"like" gene expression signature

QUIWI trial of QUIZ in wild-type FLT3 patients (PETHEMA group)

NON-FLT3-LIKE AML (n=81)



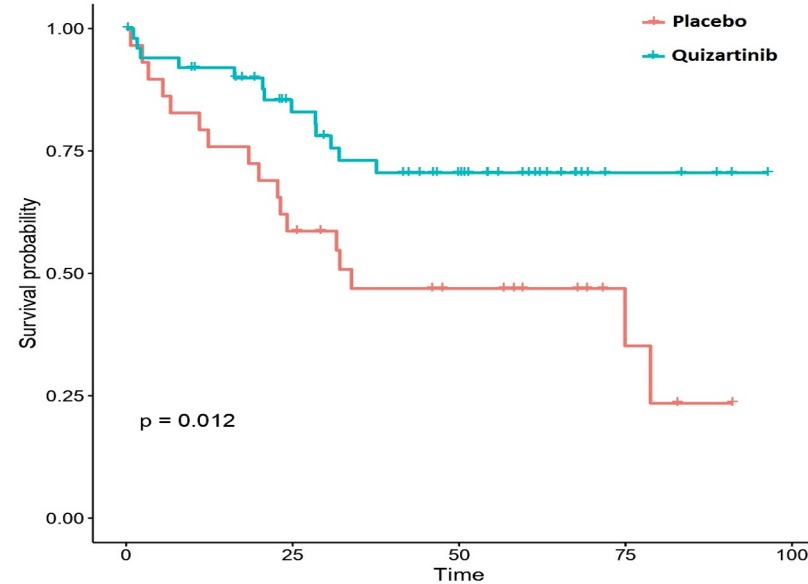
Characteristics of Non-FLT3-Like Cluster

50.33% of FLT3-ITD negative patients (N=81)

ELN-17 Classification:

- Low Risk: 18.2%
- Intermediate Risk: 39.5%
- High Risk: 42.0%

FLT3-LIKE AML (n=80)



Characteristics of FLT3-Like Patients

49.67% of FLT3-ITD negative patients (N=80)

ELN-17 Classification:

- Low Risk: 30.4%
- Intermediate Risk: 40.5%
- High Risk: 29.1%

NPM1^{mut} & *DNMT3A*^{mut} enrichment

FLT3-like AMLs: 42.5% *NPM1*^{mut}, 38.7%
DNMT3A^{mut}, 23.7% double mutants

Non-FLT3-like AMLs: 6.2% *NPM1*^{mut}, 14.8%
DNMT3A^{mut}, 2.5% double mutants

**FLT3-Like with *NPM1* or
DNMT3A mut
26% were FLT3-TKD**

Mosquera A, ASH #974

Courtesy of Courtney D DiNardo, MD, MSCE

QUIWI results of QUIZ for FLT3-ITD wild-type AML

- The QUIWI trial provides initial evidence of efficacy of quizartinib with standard chemotherapy for FLT3-WT patients with “FLT3-like” disease based on expression patterns
- Expression patterns are hard to obtain in real time in the clinical setting, but this contributes to the growing body of evidence suggesting a more personalized and targeted approach for AML therapy is possible

FLT3-like “Gene Expression” Predicts Outcome on Quizartinib (QIWI)

- FLT3-like gene expression signature that clustered a proportion of FLT3 WT with FLT3 mutated
- 206 pts—112 (54%) cluster enriched in FLT3-mutant cases (71%).
- 80 cases (50%) of FLT3 WT were “FLT3-like”
- FLT3-like pts benefited from addition of QUIZ

HR/p Value	Not FLT3-like QUIZ vs NO	FLT3-like QUIZ vs NO
EFS	1.07/.8	0.45/.009
RFS	0.88/.76	0.37/.01
OS	1.22/.62	0.41/.01

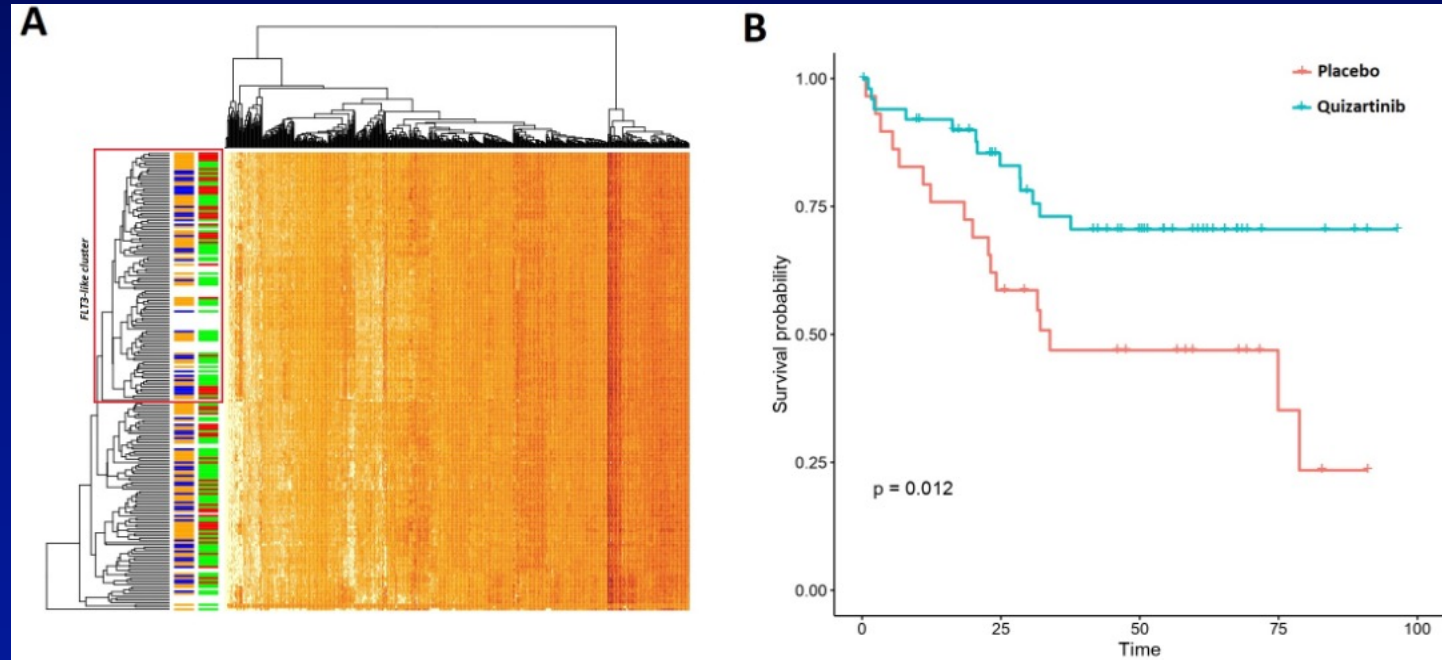


Figure 1. A) Heatmap representing the 595-signature in the 206 patients available for analysis. The top dendrogram represents the hierarchical clustering of genes in the signature. The left side dendrogram represents the hierarchical clustering of samples according to the gene expression signature. Two colored row bars are represented. The left one represents the treatment arm in the clinical trial: quizartinib (orange), placebo (blue) and screening failure due to FLT3-mutation (white). The right one represents the status of patients at last follow-up: alive (green), death (red) and screening failure due to FLT3 mutation (white). The FLT3-like cluster is highlighted in the red box, as it is characterized by an enrichment in FLT3 mutant AML cases (71.1% of all FLT3-mutated cases). B) Kaplan-Meier plot representing the overall survival of patients in the FLT3-like cluster, indicating a superiority of quizartinib over placebo in this group.

MORPHO Study Design: GILT post HSCT maintenance

- PCR-NGS MRD Assay (MRD6)
- *First 2cc aspirate sent for MRD*
- **46% + 4.5% = 50.5% FLT3-ITD MRD+**

AML with a FLT3-ITD mutation
Morphologic first remission with only 1 or 2 inductions

46% detectable:
21.1% $\geq 10^{-4}$ (MRD4)
15.4% $\geq 10^{-5}$ (MRD5)
9.6% $\geq 10^{-6}$ (MRD6)

Registration

Marrow aspirate sample for MRD analysis

Allogeneic transplant within 1 year of CR1
Any conditioning, donor, or GVHD prophylaxis allowed

Day +30 to +90 after transplant:
Engraftment (ANC ≥ 500 , platelets $\geq 20K$, transfusion independent)
Able to take oral medication
No active grades II-IV acute GVHD requiring > 0.5 mg/kg prednisone daily

19.9% detectable \geq MRD6
Including 4.5% who were undetectable pre-HCT

Sample for MRD analysis

Randomization

Gilteritinib
120 mg po daily

Placebo

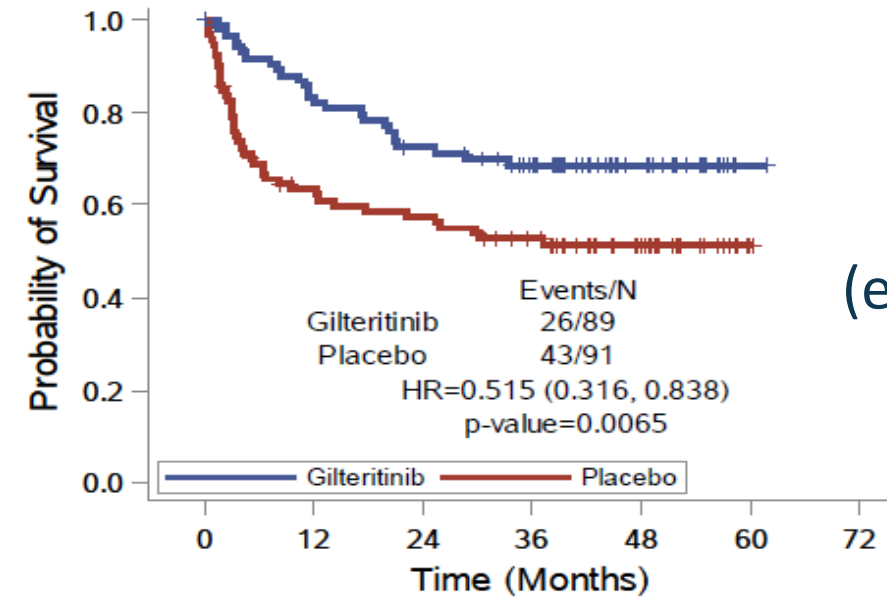
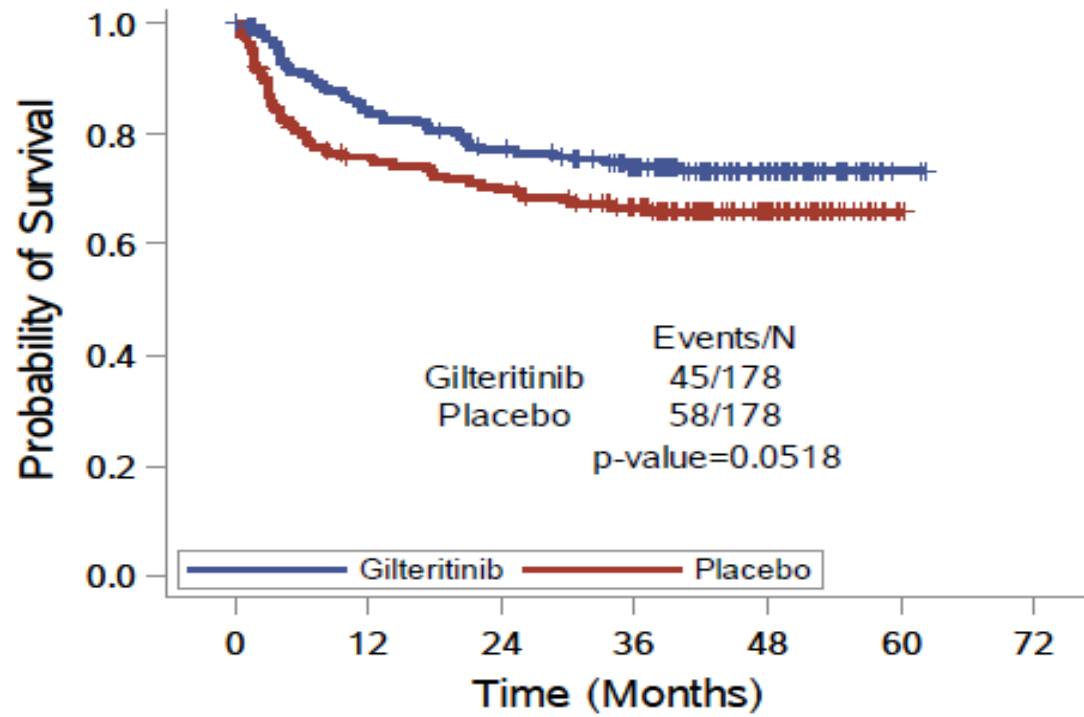
24 months maintenance treatment

Stratification:
Conditioning regimen intensity (myeloablative vs. reduced intensity)
Time from transplant to randomization (30-60 days vs. 61-90 days)
Measurable residual disease $\geq 10^{-4}$ (presence vs absence from registration sample)

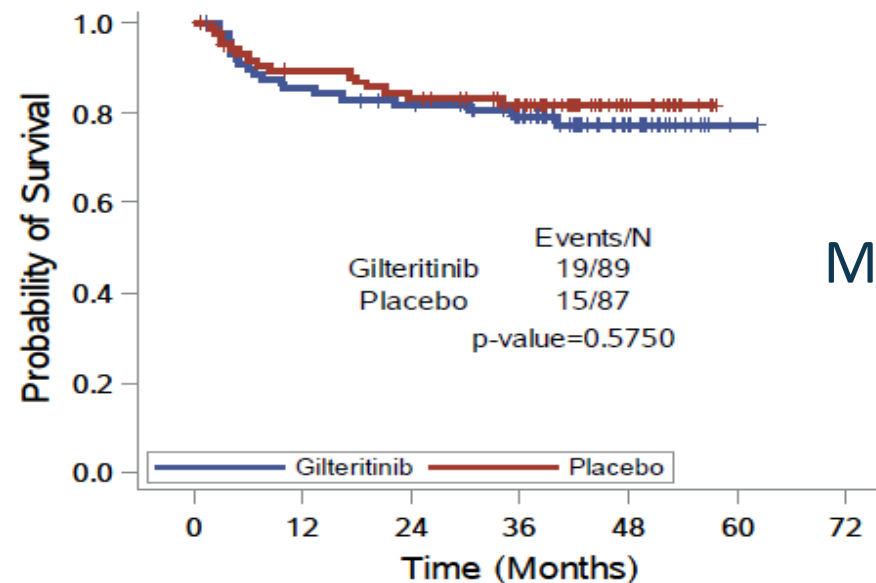
24 months maintenance treatment

Post-Hoc MRD Analysis of MORPHO Study: FLT3i post SCT improves RFS in MRD+ patients

Primary objective:
Relapse-free survival (RFS)
HR = 0.679 (0.459-1.005)
P = 0.0518



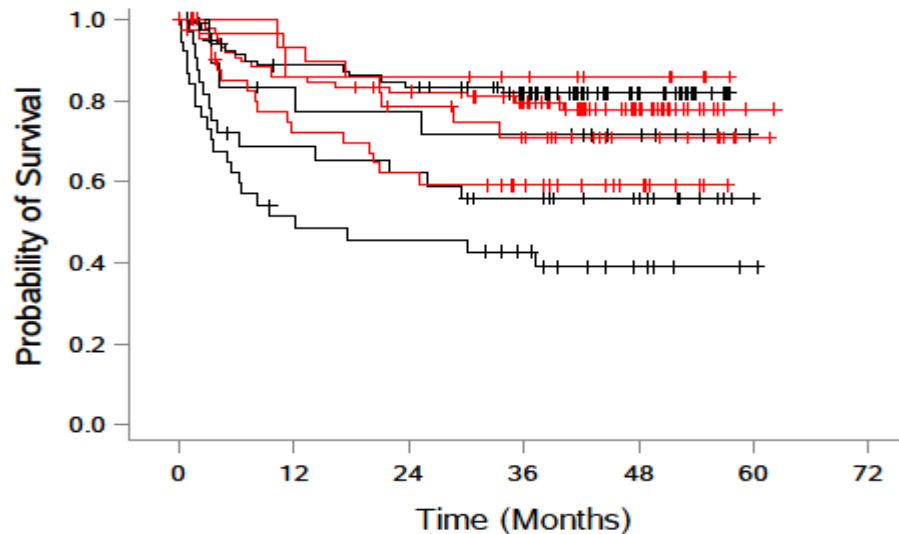
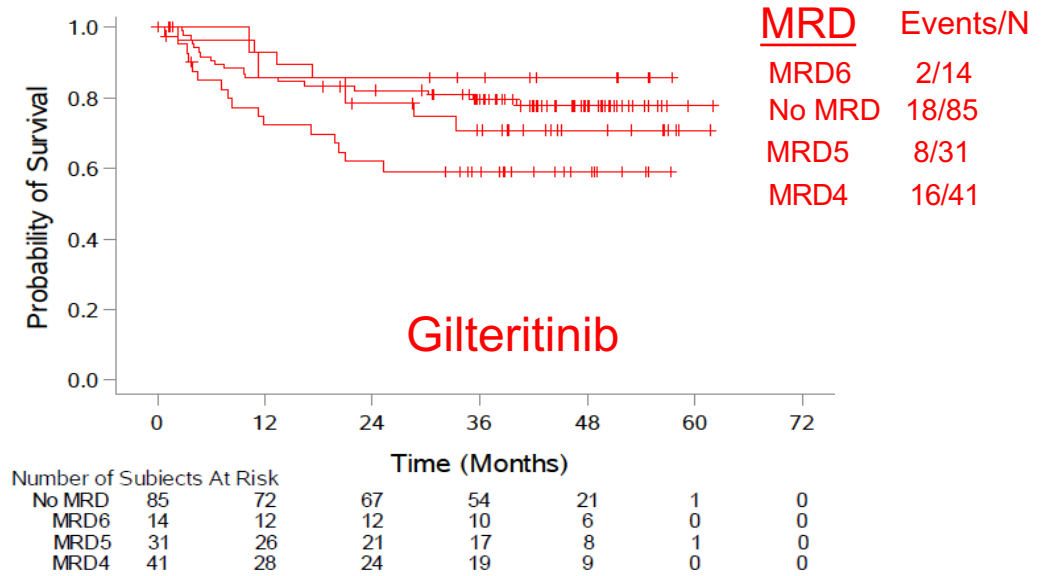
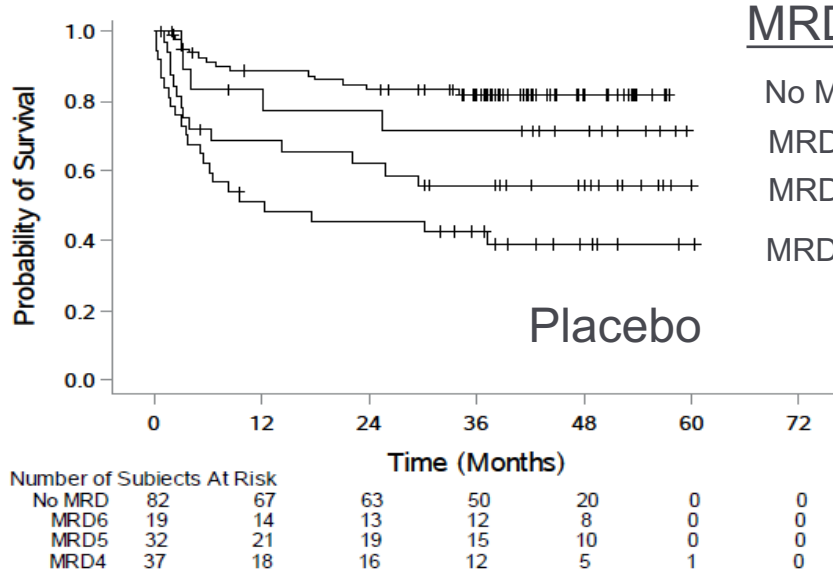
RFS: MRD
positive
(either pre or
post SCT)



RFS:
MRD negative

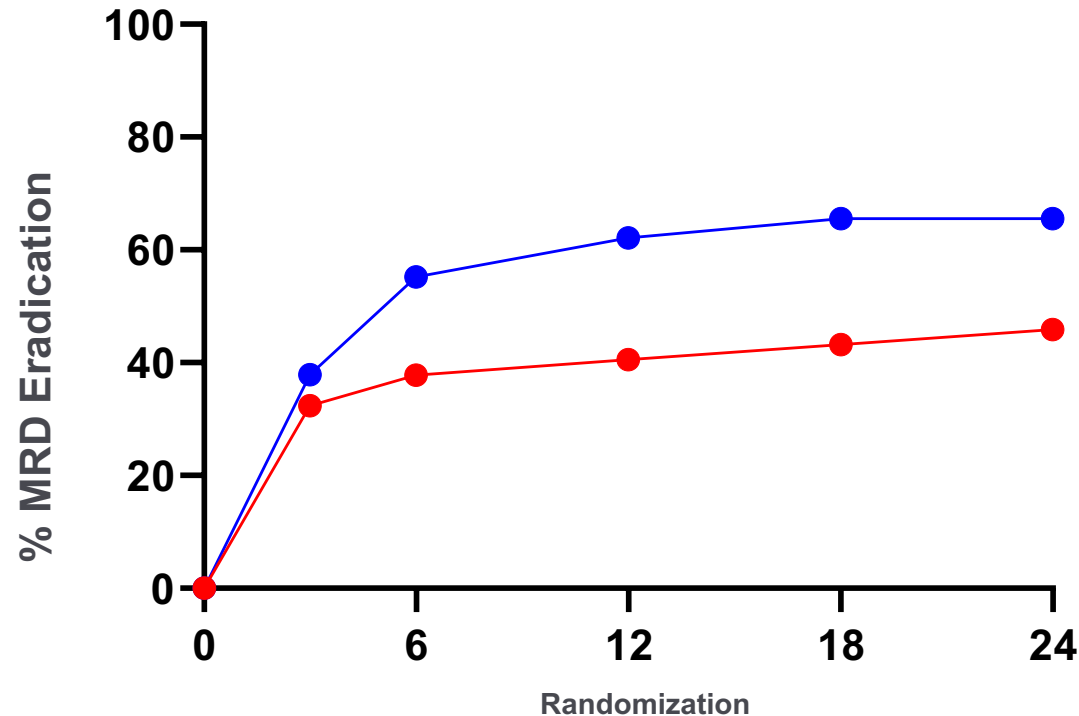
Levis M ASH #973

FLT3 MRD at any level impacts RFS, and is improved with GILT



$10^{-6} \leq \text{MRD6} < 10^{-5}$
 $10^{-5} \leq \text{MRD5} < 10^{-4}$
 $10^{-4} \leq \text{MRD4}$

FLT3-ITD MRD eradication post-SCT is improved with GILT



- FLT3-ITD clones post-SCT are more often eradicated with GILT compared to placebo
 - MRD was eradicated in 69% of pts on GILT vs 44% with placebo
- Relapse or eradication predominantly occurs during the first 6 months post-SCT
- Any level of FLT3-ITD MRD impacts RFS (the higher the MRD the worse the RFS)

GILT as post-HSCT maintenance

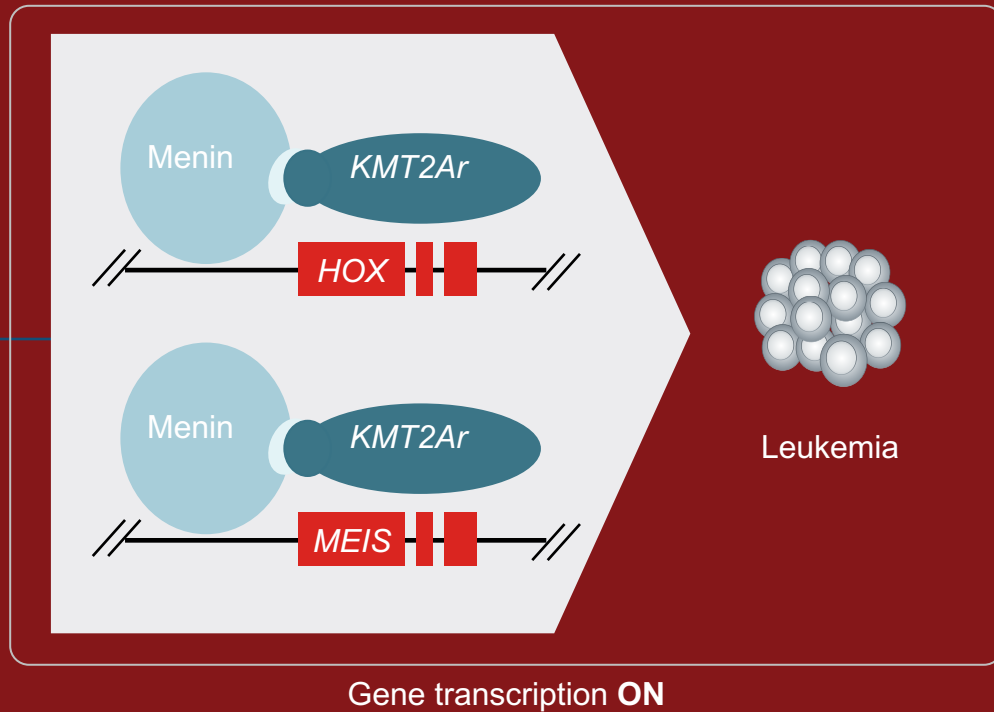
- Identification of FLT3 MTD **at any level** peri-transplant impacts RFS, and is improved with gilteritinib post-HSCT maintenance (the higher the MRD level, the worse the RFS)
- FLT3-ITD MRD eradication post-SCT is improved with GILT
- **Relapse or eradication predominantly occurs during the first 6 months post-SCT**

Menin Inhibition for NPM1-Mutated and KMT2Ar Acute Leukemias

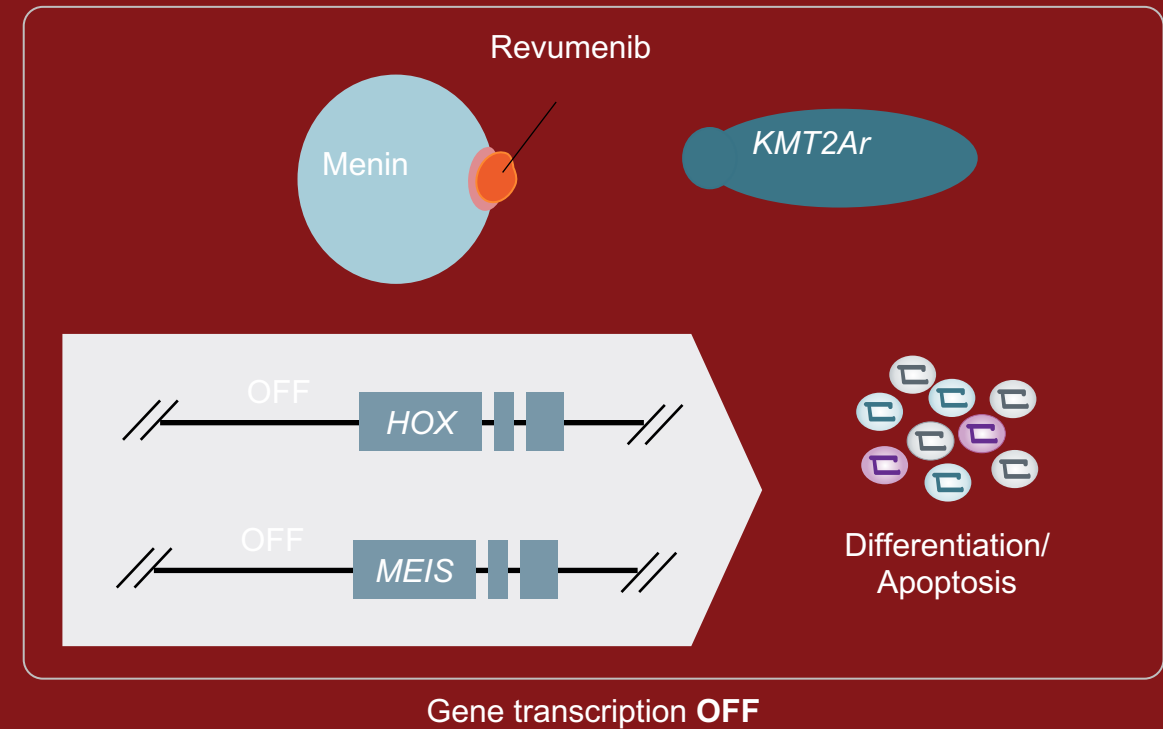
- Aldoss I et al. **Revumenib** monotherapy in patients with **relapsed/refractory KMT2Ar** acute leukemias: Efficacy and safety results from the **augment-101** phase 1/2 study. ASH 2023;Abstract LBA-5.
- Issa GC et al. Early results of the phase I/II study investigating the **all-oral combination** of the **menin inhibitor revumenib (SNDX-5613)** with **decitabine/cedazuridine (ASTX727)** and **venetoclax** in acute myeloid leukemia (**SAVE**). ASH 2023;Abstract 58.
- Fathi A et al. Activity, tolerability, and resistance profile of the **menin inhibitor ziftomenib** in adults with **R/R NPM1-mutated** AML. EHA 2023;Abstract LB2713.
- Jabbour E et al. A first-in-human phase 1 study of the **menin-KMT2A (MLL1) inhibitor JNJ-75276617** in adult patients with **relapsed/refractory** acute leukemia harboring **KMT2A or NPM1 alterations**. ASH 2023;Abstract 57.

Menin Inhibitors for R/R AML

KMT2Ar acute leukemia



Menin inhibition



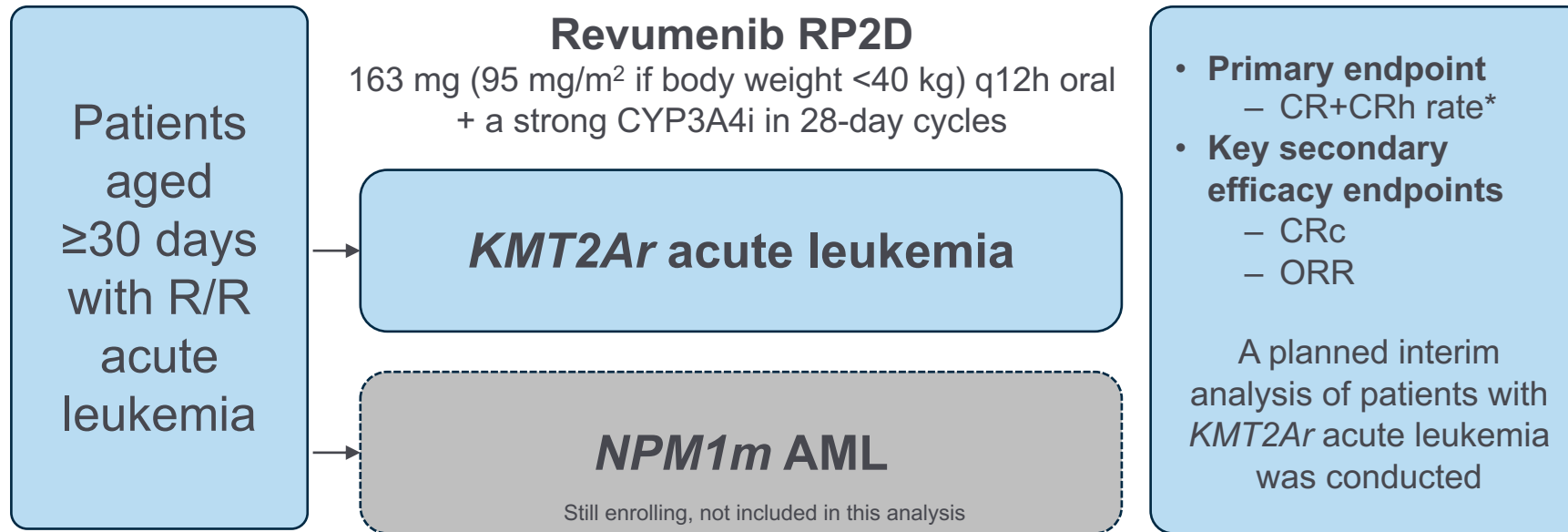
Overview of Menin Inhibitors in Development for AML

Agent (Former Name) Route of Administration	NCT Identifier (Trial Name)	Study Phase (n)	Phase 1/ 2 Expansion Cohorts for R/R Disease	Current Status
Revumenib (SNDX-5613) ^[1] PO BID	NCT04065399 (AUGMENT-101)	Phase 1 (n = 186)	<ul style="list-style-type: none"> ALL or MPAL with <i>KMT2Ar</i> AML with <i>KMT2Ar</i> AML with <i>NPM1mut</i> 	In expansion (10 sites) FDA breakthrough
Ziftomenib (KO-539) ^[2] PO QD	NCT04067336 (KOMET-001)	Phase 1/2 (n = 199)	<ul style="list-style-type: none"> AML with <i>KMT2Ar</i> AML with <i>NPM1mut</i> 	Recruiting (25 sites)
BMF-219 ^[3] PO	NCT05153330	Phase 1 (n = 177)	<ul style="list-style-type: none"> AML/ALL/MPAL, DLBCL, and MM/PCD 	Recruiting (6 sites)
D1594b ^[4] PO BID	NCT04752163	Phase 1/2 (n = 20)	<ul style="list-style-type: none"> AML/ALL with <i>KMT2Ar</i> AML with <i>NPM1mut</i> 	Active (1 site)
DSP-5336 ^[5] PO QD	NCT04988555	Phase 1/2 (n = 70)	<ul style="list-style-type: none"> R/R AML, R/R ALL Phase 2: <i>NPM1mut/KMT2Ar</i> 	Recruiting (6 sites)
JNJ-75276617 ^[6] PO QD	NCT04811560	Phase 1 (n = 110)	<ul style="list-style-type: none"> AML/ALL with <i>KMT2Ar</i> AML with <i>NPM1mut</i> 	Recruiting (27 sites)

1. Issa GC, et al. Blood. 2022;140: Abstract 63; 2. Erba HP, et al. Blood. 2022;140: Abstract 64; 3. Clinicaltrials.gov. Accessed August 31, 2023.

<https://clinicaltrials.gov/ct2/show/NCT05153330>; 4. Clinicaltrials.gov. Accessed August 31, 2023. <https://clinicaltrials.gov/ct2/show/NCT04752163>; 5. Daver N, et al. Blood. 2022;140: Poster 1460; 6. Kwon MC, et al. Blood. 2022;140: Poster 2637.

AUGMENT-101: Revumenib Monotherapy for R/R KMT2Ar



*CR+CRh rate >10% in adult evaluable population considered lower efficacy bound

Parameter	Efficacy population (n=57)	Safety population (n=94) ^a
Median age, y (range)	34.0 (1.3–75)	37.0 (1.3–75)
Age <18 y, n (%)	13 (23)	23 (25)
Age ≥18 y, n (%)	44 (77)	71 (76)
Sex, n (%)		
Female	33 (58)	56 (60)

AUGMENT-101: Revumenib Monotherapy for R/R *KMT2Ar*

Revumenib is effective and safe in pediatric and adult patients with R/R *KMT2Ar* acute leukemia

Durable MRD-negative remissions were observed in responders

High rates of transplants among responders

Discontinuations and dose reductions due to adverse events were low

Study was stopped early after meeting the primary efficacy endpoint at the predefined interim analysis. A New Drug Application for *KMT2Ar* leukemia has been initiated under the FDA Real-Time Oncology Review program based on these data

The independent NPM1m cohort continues to enroll at all sites

SAVE: SNDX + ASTX727 + VEnetoclax triplet

Early results **of all-oral SAVE** [revumenib (SNDX-5613), oral decitabine (ASTX727) and VEnetoclax] → acceptable safety and high efficacy in **children and adults** with R/R AML susceptible to menin inhibition

High rates of response in heavily pretreated population

- **ORR 100%** (9/9), **CR/CRh 44%** (4/9), **MRD-neg 67%** (6/9)
- 5/9 patients to alloHSCT, 2 resumed revumenib maintenance with ongoing remission > 11 months

No severe differentiation syndrome or ≥Grade 3 QT prolongation

Myelosuppression, confounded by expected risk with HMA + Ven in R/R AML

- Future mitigation measures to include intermittent revumenib dosing, without compromising efficacy given clearance of leukemia by day 14

This study continues to accrue patients

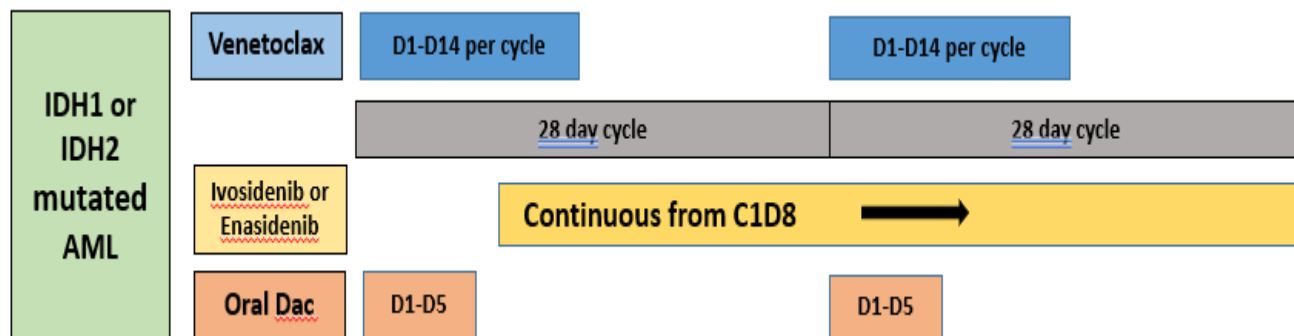
Generalized Conclusions

- AML therapeutic options continue to improve with increasingly individualized treatments
- Monitoring MRD is essential for ongoing risk assessment, and we now have studies showing that acting on MRD can improve patient outcome
- Menin inhibitors are a new effective class of therapy in AML, with initial studies evaluating patients with R/R *NPM1* and *KMT2A-rearranged* leukemias

IDH Inhibitors in AML

- Atluri H et al. Phase Ib/2 study of **oral decitabine/cedazuridine (ASTX727)** and **venetoclax** in **combination** with the targeted mutant **IDH1 inhibitor ivosidenib** or the targeted mutant **IDH2 inhibitor enasidenib**: 2023 Update. ASH 2023;Abstract 968.
- de Botton S et al. **Olutasidenib (FT-2102)** induces durable complete remissions in patients with **relapsed or refractory IDH1-mutated AML**. *Blood Adv* 2023;7(13):3117-27.

Update of HMA+VEN+IDHi for IDHm AML



Selected RP2D Combination Doses	
Arm A: ASTX727 (D1-5) + VEN 600 mg (D1-14) + Ivosidenib 500 mg daily (D8 onwards)	
Arm B: ASTX727 (D1-5) + VEN 400 mg (D1-14) + Enasidenib 100 mg daily (D8 onwards)	

Prior Treatments (R/R Only)		
	IDH1 (n=11)	IDH2 (n=19)
Prior HMA + VEN	6 (55)	13 (68)
No Prior VEN	3 (27)	6 (32)
Prior IDHi	4 (36)	3 (16)
HMA/VEN/IDHi naïve	1 (9)	4 (21)

Baseline Characteristics					
Variable	All (n=57)	Newly Diagnosed (n=27)		Relapsed Refractory (n=30)	
		IDH1 (n=11)	IDH2 (n=16)	IDH1 (n=11)	IDH2 (n=19)
Age (years)	72 (41-86)	74 (70-80)	71 (62-83)	73 (41-86)	70 (56-84)
Male	35 (61)	4 (36)	12 (75)	8 (72)	11 (58)
ECOG	1 (1-2)	2 (1-2)	2 (1-2)	1 (1-2)	1 (1-2)
ELN Risk (2022)					
ELN Favorable	7 (12)	3 (27)	2 (13)	1 (9)	1 (5)
ELN Intermediate	2 (4)	-	1 (6)	-	2 (10)
ELN Adverse	47 (82)	8 (72)	13 (81)	10 (91)	16 (85)
Cytogenetic Risk					
Intermediate Risk	37 (65)	8 (73)	14 (88)	4 (36)	11 (58)
Adverse Risk	20 (35)	3 (27)	2 (12)	7 (64)	8 (42)
Co-Occurring Mutations					
NPM1	9 (16)	3 (27)	3 (19)	2 (18)	1 (5)
KRAS/NRAS	6 (14)	1 (9)	3 (19)	1 (9)	1 (5)
FLT3	1 (2)	-	-	1 (9)	-
TP53	12 (21)	-	2 (12)	6 (55)	4 (21)

Conclusions

Safety profile and tolerability of triplet combination of ASTX727 + VEN + IDHi in both ND and R/R AML appears reassuring and may prove to be the optimal method of incorporating all effective therapies (HMA+VEN vs HMA+IVO vs HMA+VEN+IVO)

Triplet outcomes to date:

CRc rates of 96.2% (ND-AML) and 56.6% (RR-AML)

Median OS NR (ND-AML); mOS 17.7 and 10.4 months for *IDH1* and *IDH2* RR-AML

Phase 1/2 Study of Novel IDH1 Inhibitor Olutasidenib

Multiple Cohorts of Monotherapy and Combination With Aza^[1]

Monotherapy

Olutasidenib 150 mg BID

Cohort 1: R/R AML (N = 153)

Cohort 2: MRD-positive AML in CR/CRi

Cohort 3: R/R AML/MDS treated with prior IDH1 inhibitors; standard treatments contraindicated

Cohort 7: ND AML; standard treatments contraindicated

Combination Therapy

Olutasidenib 150 mg BID + Aza

Cohort 4: R/R AML/MDS with no prior HMA or IDH1 inhibitor

Cohort 5: R/R AML/MDS with progression on HMA

Cohort 6: R/R AML most recently treated with IDH1 inhibitor monotherapy

Cohort 8: ND AML eligible for frontline Aza

Primary endpoint

CR + CRh

Key secondary endpoints

- ORR
- DoR
- transfusion independence
- OS
- Safety

Results of Cohort 1 led to FDA approval of olutasidenib in December 2022 for *IDH1*-mutated R/R AML^[2]

Olutasidenib and Ivosidenib Data in R/R AML

***NOTE:** This is a summary of data from independent trials, not a head-to-head comparison within a single study.

PARAMETERS	OLUTASIDENIB ¹	IVOSIDENIB ^{2,3}
Composite complete remission (CR + CRh)	35%	33%
Median duration of CR/CRh (95% CI)	25.9 months (13.5, NR)	8.2 months (5.6, 12)
Complete remission rate (CR)	32%	25%
Median duration of CR	28.1 months	10.1 months
Overall response rate (CR + CRh + CRi + PR + MLFS)	48%	42%
Median duration of overall response	11.7 months	6.5 months

Courtesy of Courtney D DiNardo, MD, MSCE

What I Tell My Patients: Integrating New Research Information into Current Clinical Care

A Complimentary NCPD Hybrid Symposium Series Held During the 49th Annual ONS Congress April 24-27

Hormone Receptor-Positive Breast Cancer

Wednesday, April 24, 2024

6:00 PM – 8:00 PM ET

Faculty

Harold J Burstein, MD, PhD

Kelly Fischer, MSN, FNP-BC

Komal Jhaveri, MD, FACP

Melissa Rikal, FNP-BC, AOCNP

Antibody-Drug Conjugates

Thursday, April 25, 2024

12:15 PM – 1:45 PM ET

Faculty

Jamie Carroll, APRN, MSN, CNP

Kelly EH Goodwin, MSN, RN, ANP-BC

Erika Hamilton, MD

Hope S Rugo, MD

Endometrial Cancer

Thursday, April 25, 2024

6:00 AM – 7:30 AM ET

Faculty

Jennifer Filipi, MSN, NP

Kathryn M Lyle, MSN, WHNP-BC, AGNP-C

David M O'Malley, MD

Shannon N Westin, MD, MPH, FASCO, FACOG

Chronic Lymphocytic Leukemia and Bispecific Antibodies in Lymphoma

Thursday, April 25, 2024

6:00 PM – 8:00 PM ET

Faculty

John N Allan, MD

Brad S Kahl, MD

Robin Klebig, MSN, APRN, CNP, AOCNP

Mollie Moran, APRN-CNP, AOCNP

What I Tell My Patients: Integrating New Research Information into Current Clinical Care

A Complimentary NCPD Hybrid Symposium Series Held During the 49th Annual ONS Congress April 24-27

Head and Neck Cancer

Friday, April 26, 2024

6:00 AM – 7:30 AM ET

Faculty

Meetal Dharia, NP-C, AOCNP

Robert L Ferris, MD, PhD

Robert Haddad, MD

Lynsey P Teulings, APRN

Ovarian Cancer

Friday, April 26, 2024

6:00 PM – 7:30 PM ET

Faculty

Courtney Arn, CNP

Floor J Backes, MD

Kathleen N Moore, MD, MS

Jaclyn Shaver, MS, APRN, CNP, WHNP

Non-Small Cell Lung Cancer with an EGFR Mutation

Friday, April 26, 2024

12:15 PM – 1:45 PM ET

Faculty

Marianne J Davies, DNP, ACNP, AOCNP, FAAN

Alexander I Spira, MD, PhD

Jillian Thompson, MSN, ANP-BC, AOCNP

Helena Yu, MD

Hepatobiliary Cancers

Saturday, April 27, 2024

6:00 AM – 7:30 AM ET

Faculty

Blanca Ledezma, MSN, NP, AOCNP

Stacey Stein, MD

Amanda K Wagner, APRN-CNP, AOCNP

Mark Yarchoan, MD

What I Tell My Patients: Integrating New Research Information into Current Clinical Care

A Complimentary NCPD Hybrid Symposium Series Held During the 49th Annual ONS Congress April 24-27

Myelofibrosis

Saturday, April 27, 2024

12:15 PM – 1:45 PM ET

Faculty

Ilene Galinsky, NP

Andrew T Kuykendall, MD

Sara M Tinsley-Vance, PhD, APRN, AOCN

Abdulraheem Yacoub, MD

LIVE WEBINAR

Prostate Cancer

Wednesday, May 1, 2024

7:00 PM – 8:00 PM ET

Faculty

Andrew J Armstrong, MD, ScM

Brenda Martone, MSN, NP-BC, AOCNP

Gastroesophageal and Colorectal Cancers

Saturday, April 27, 2024

6:00 PM – 8:00 PM ET

Faculty

Deanna A Griffie, MSN, AGNP-C

Caroline Kuhlman, MSN, APRN-BC

Manish A Shah, MD

John Strickler, MD

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.