What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Acute Myeloid Leukemia

A CME Friday Satellite Symposium Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024
3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)

Faculty

Alexander Perl, MD
Richard M Stone, MD
Eunice S Wang, MD
Andrew H Wei, MBBS, PhD

Moderator

Eytan M Stein, MD

RTP RESEARCH TO PRACTICE

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Moderator

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Dr Perl — Disclosures
Faculty

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Contracted Research	Astellas, Daiichi Sankyo Inc, Syndax Pharmaceuticals
Data and Safety Monitoring Board/Committee	Foghorn Therapeutics
Nonrelevant Financial Relationships	Beat AML LLC, Leukemia & Lymphoma Society

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Dr Stone — Disclosures
Faculty

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Dr Wang — Disclosures
Faculty

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Data and Safety Monitoring Boards/Committees	AbbVie Inc, Gilead Sciences Inc
Speakers Bureaus	Astellas, Daiichi Sankyo Inc, DAVA Oncology, Pfizer Inc
Nonrelevant Financial Relationship	UpToDate (section editor)

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Prof Wei — Disclosures
Faculty

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Consulting Agreements	AbbVie Inc, Aculeus Therapeutics, Novartis, Servier Pharmaceuticals LLC, Shoreline Biosciences
Contracted Research	AbbVie Inc, Amgen Inc, Astex Pharmaceuticals, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Janssen Biotech Inc, Novartis, Servier Pharmaceuticals LLC, Syndax Pharmaceuticals
Data and Safety Monitoring Board/Committee	HOVON
Speakers Bureaus	AbbVie Inc, Astellas, Bristol Myers Squibb, Novartis, Servier Pharmaceuticals LLC
Nonrelevant Financial Relationship	Prof Wei is an employee of the Walter and Eliza Hall Institute (WEHI). WEHI receives milestone and royalty payments related to the development of venetoclax. Current and past employees of WEHI may be eligible for financial benefits related to these payments. Prof Wei receives such a financial benefit

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Dr Stein — Disclosures
Moderator

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Contracted Research	Astellas, Bristol Myers Squibb, Genentech, a member of the Roche Group, Syndax Pharmaceuticals

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Rounds with the Investigators: Compelling Teaching Cases Focused on the Management of Breast Cancer

A 3-Part CME Hybrid Satellite Symposium Series in Partnership with the 2024 San Antonio Breast Cancer Symposium®

HER2-Low and HER2-Ultralow Breast Cancer

Tuesday, December 10, 2024

7:15 PM – 8:45 PM CT

New Developments in Endocrine Treatment for Breast Cancer

Wednesday, December 11, 2024

7:15 PM – 9:15 PM CT

Management of Metastatic Breast Cancer

Thursday, December 12, 2024

7:00 PM – 9:00 PM CT

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Save The Date

Fourth 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, February 28 to March 2, 2025

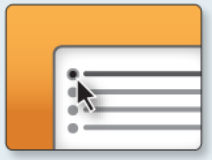
Fontainebleau Hotel, Miami Beach, Florida

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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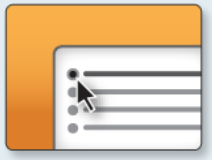
Clinicians Attending via Zoom

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



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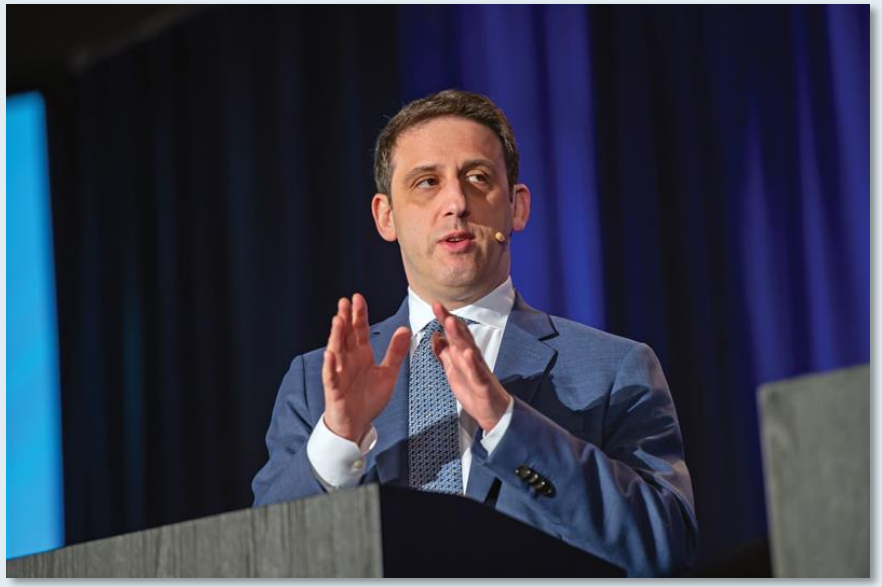
About the Enduring Program



- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint 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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Survey of General Medical Oncologists: November 22nd – December 5th

Results available on iPads and Zoom chat room

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Agenda

Module 1: Treatment for Older Patients with Acute Myeloid Leukemia (AML) — Prof Wei

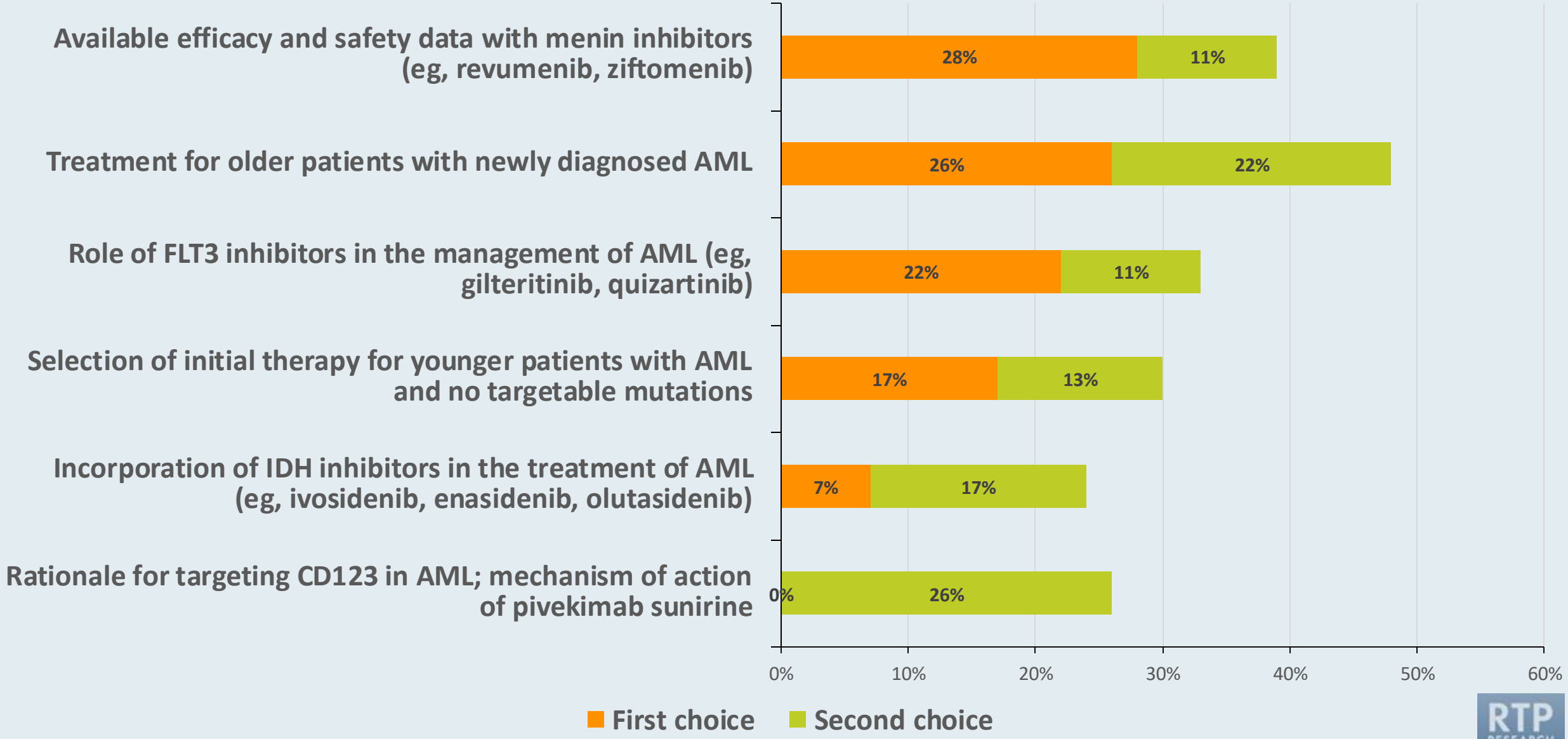
Module 2: Selection of Initial Therapy for Younger Patients with AML without a Targetable Mutation, Including Those with Secondary AML — Dr Stone

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

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

Module 5: Potential Role of Menin Inhibitors and Other Novel Agents in the Treatment of AML — Dr Wang

Topics of Interest for Future CME Programs



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Treatment for Older Patients with Acute Myeloid Leukemia

Andrew Wei
Peter MacCallum Cancer Centre
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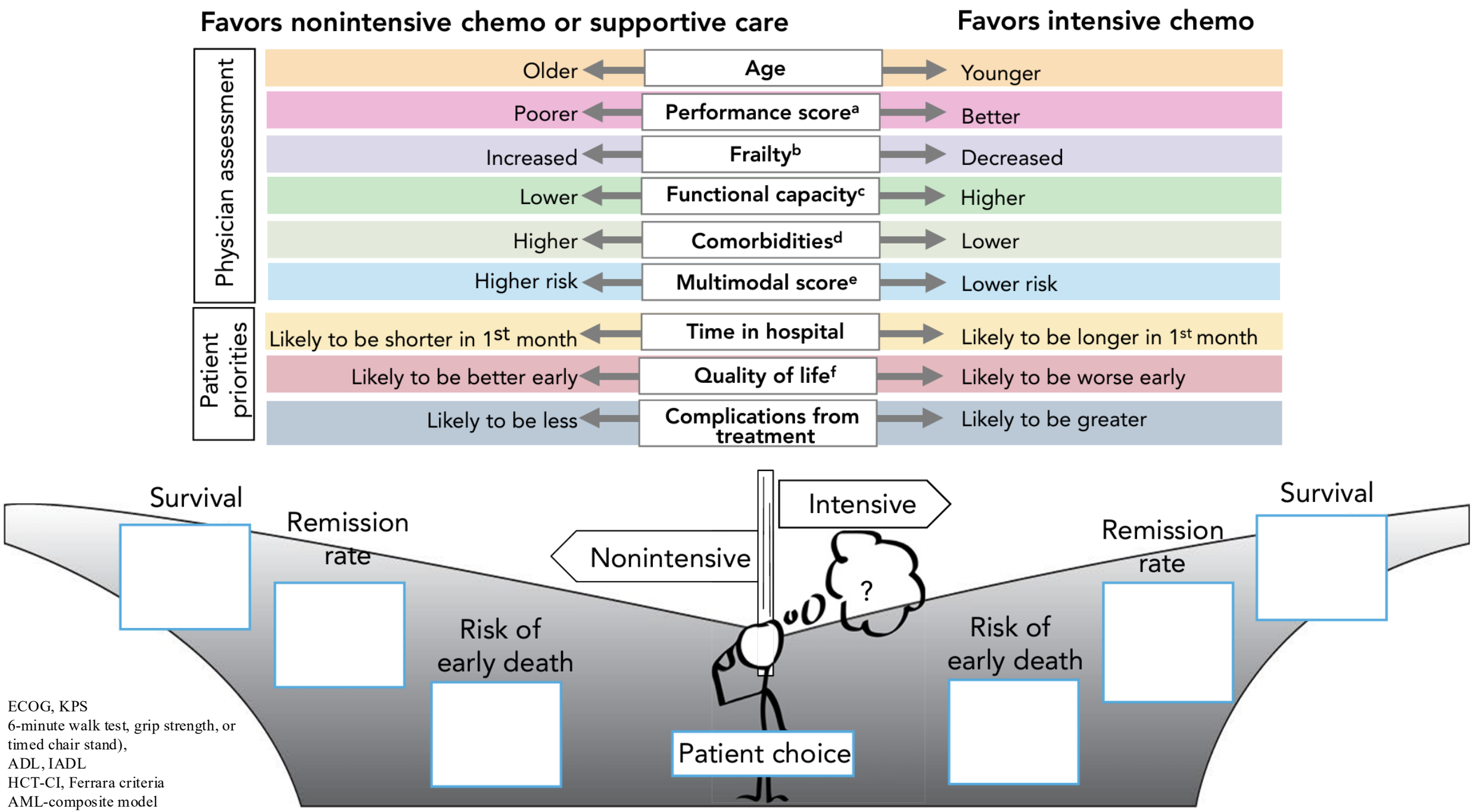
The Royal Melbourne Hospital



a. ECOG, KPS
b. 6-minute walk test, grip strength, or timed chair stand),
c. ADL, IADL
d. HCT-CI, Ferrara criteria
e. AML-composite model
f. FACT-G

Wei, Blood 2021

AML treatment landscape 2024

Fit for intensive chemo

Unfit for intensive chemo

Rapid molecular screening and clinical trials consideration

***FLT3*^{MUT}**	***FLT3*-ITD**	**AML pCT Prior MDS, CMML AML MR (CG)**	**Non-adverse AML**	**IDH1 mut**	**Non-IDH1 mut**		**TP53 mut**
7+3 Mido	*7+3 Quiz*	*CPX-351*	*7+3 GO*	*AZA IVO*	*AZA VEN*	*LDAC VEN*	*HMA +/- VEN*
59% CR (Stone 2017)	*72% CRc (Erba 2023)*	*48% CRc (Lancet 2018)*	*81% CRc (Castaigne, 2012)*	*53% CRc (Montesinos 2022)*	*66% CRc (Di Nardo 2020)*	*54% CRc (Wei 2020)*	*(Pollyea 2022) (Geissler 2024)*

Risk stratification: ELN 2022 (Döhner 2022)

Suitable for HCT	Not suitable for HCT
HCT in CR1	Oral AZA *(Wei 2020)*

Risk stratification: ELN 2024-LI (Döhner 2024)

Suitable for HCT	Not suitable for HCT
HCT	Continue therapy

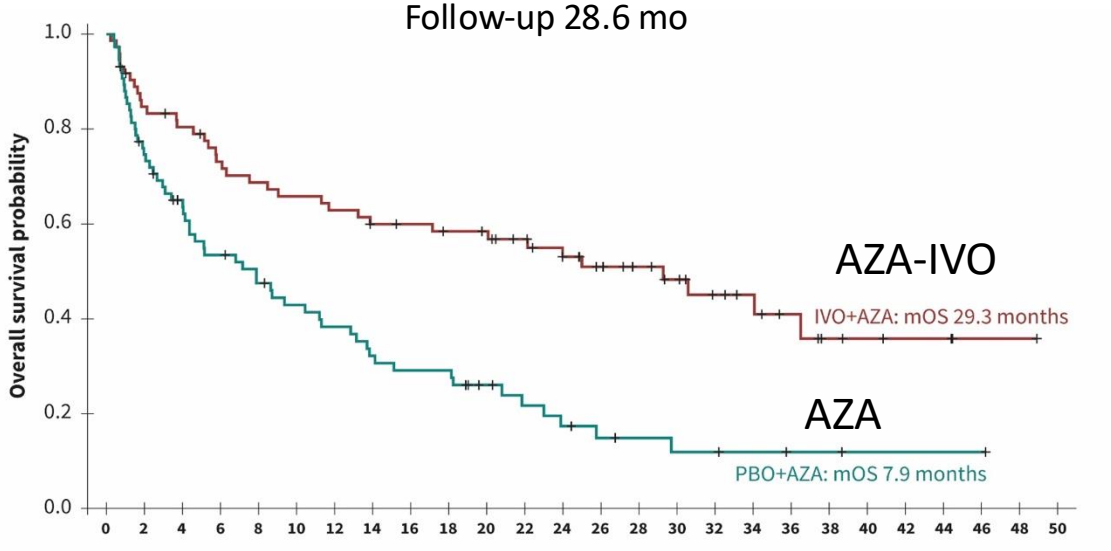
MRD monitoring

MRD directed intervention

Less intensive options for *IDH1* mutant AML

Outcome	AZA-IVO (n=72)	AZA (n=74)
CR	**47%**	15%
CR/CRh	53%	18%
Median OS	**29.3 mo**	7.0 mo
Time to CR	2.1 mo	3.7 mo
Feb neut	27.8%	33.8%

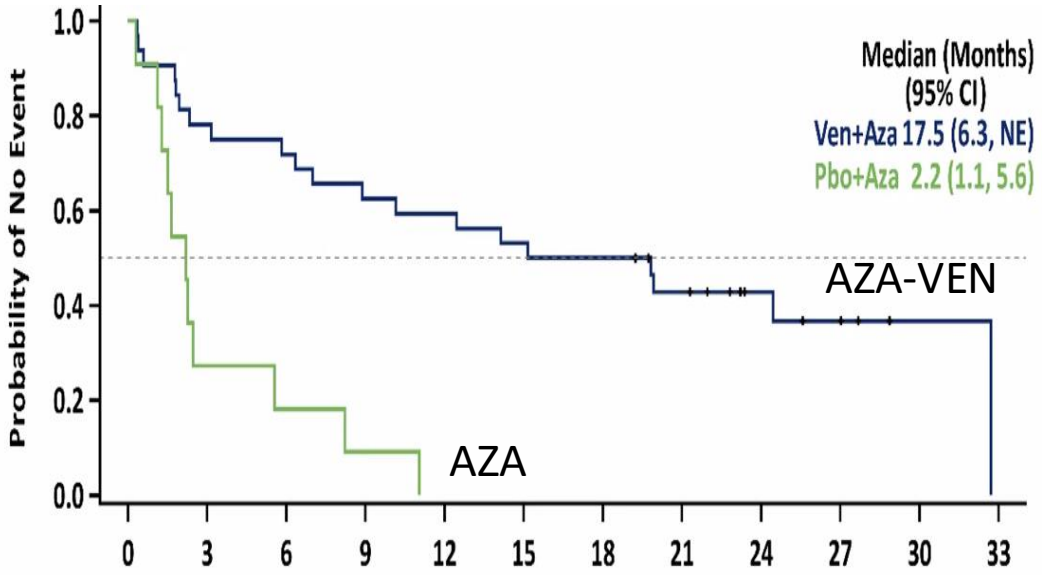
Follow-up 28.6 mo



Months

De Botton, ASCO 2023

Outcome	AZA-VEN (n=32)	AZA (n=11)
CR	28%	0
CR/CRh	59%	9.1%
Median OS	17.5 mo	2.2 mo
Time to CR	**1.2 mo**	3.4 mo
Feb neut	29.6%	14.3%



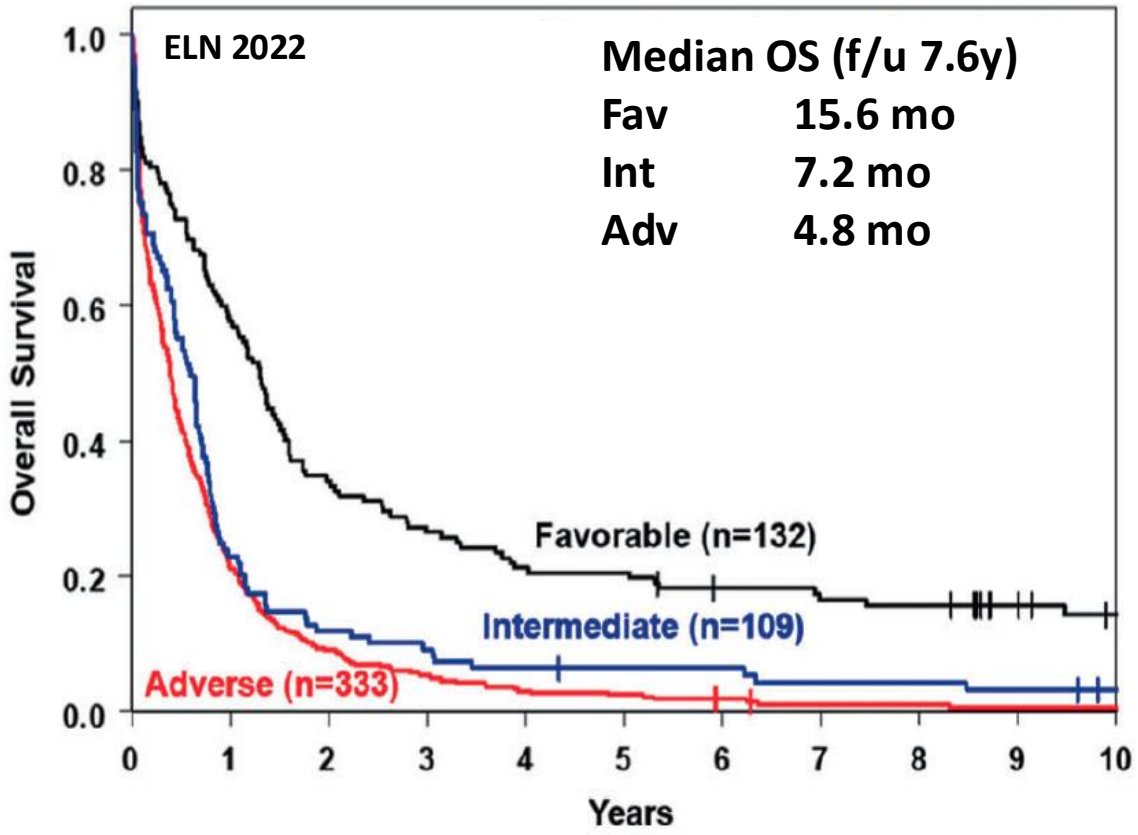
Months

Pollyea, et al, Clin Cancer Res. 2022

New risk models for less intensive therapy in elderly AML

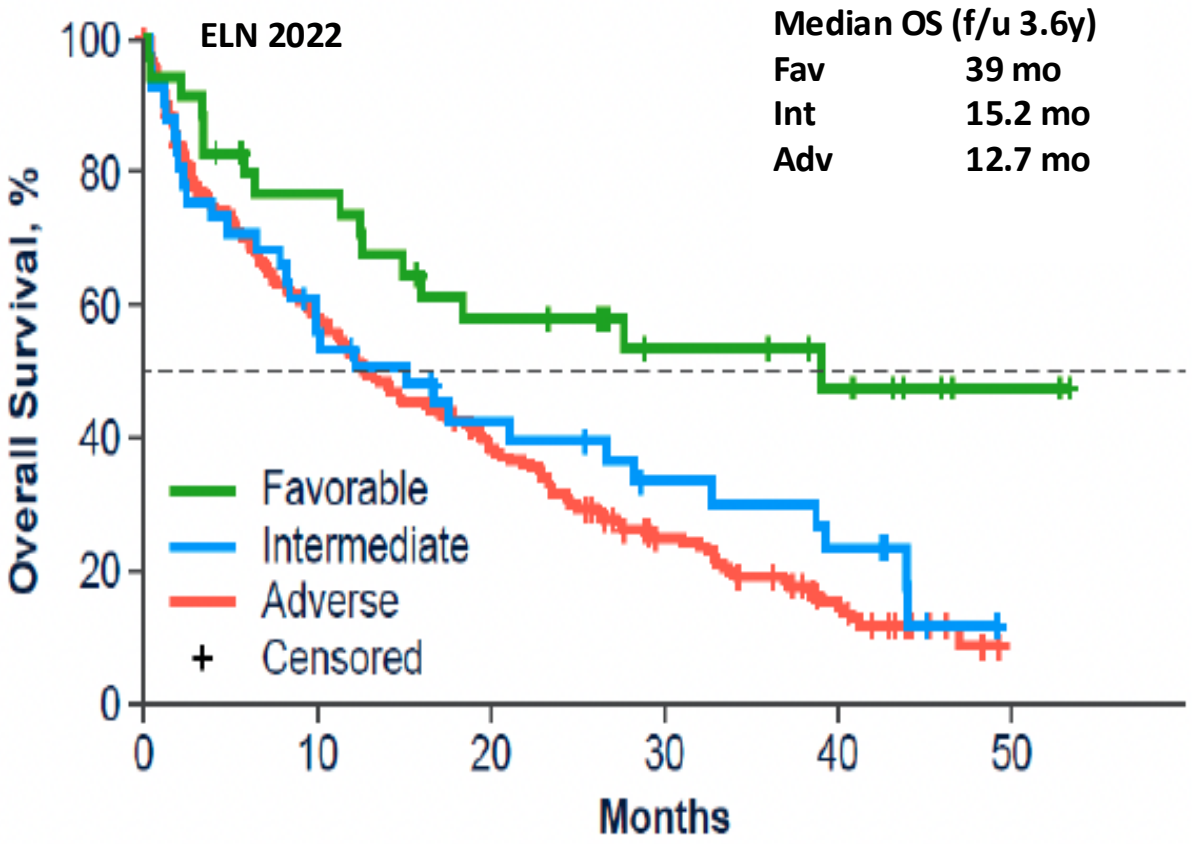
7+3

>60 years



Mrózek, Leukemia, 2023

Non-Intensive



Döhner, Blood (2024)

New risk models for less intensive therapy in elderly AML

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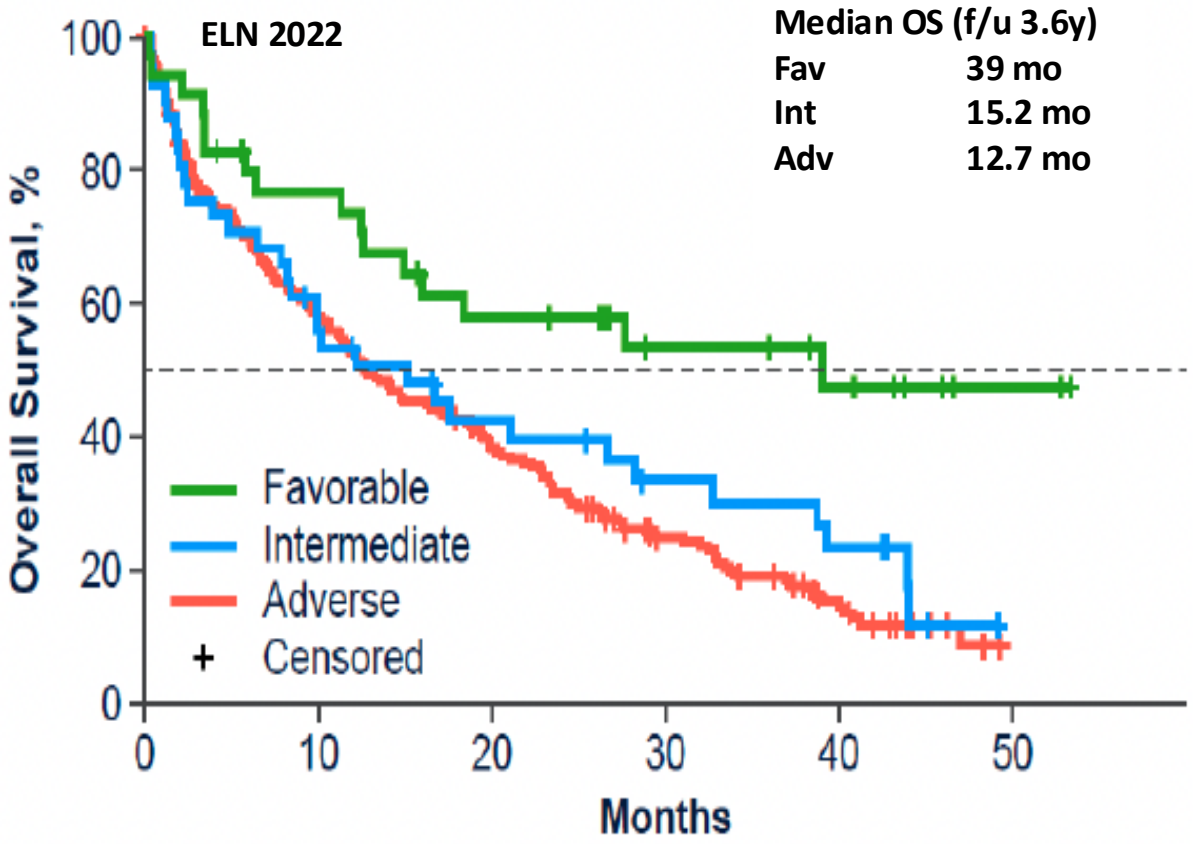
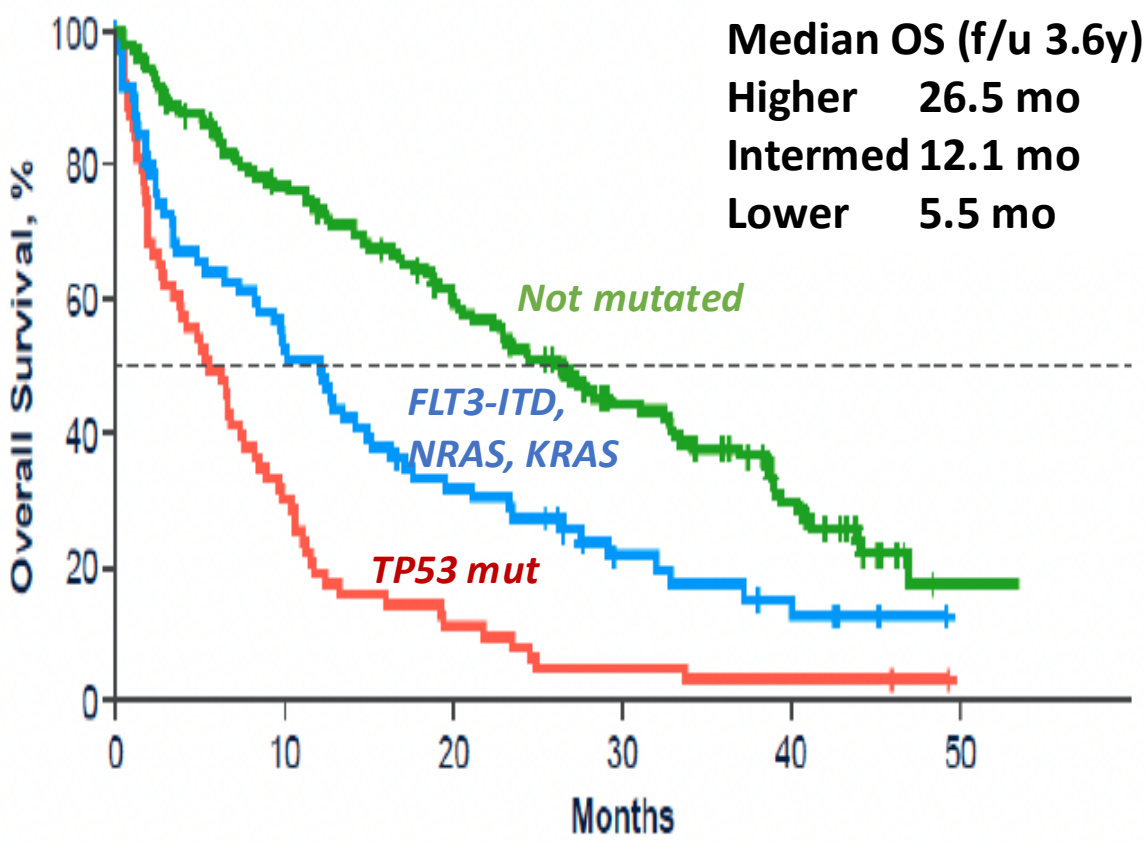


AZA-VEN risk stratification



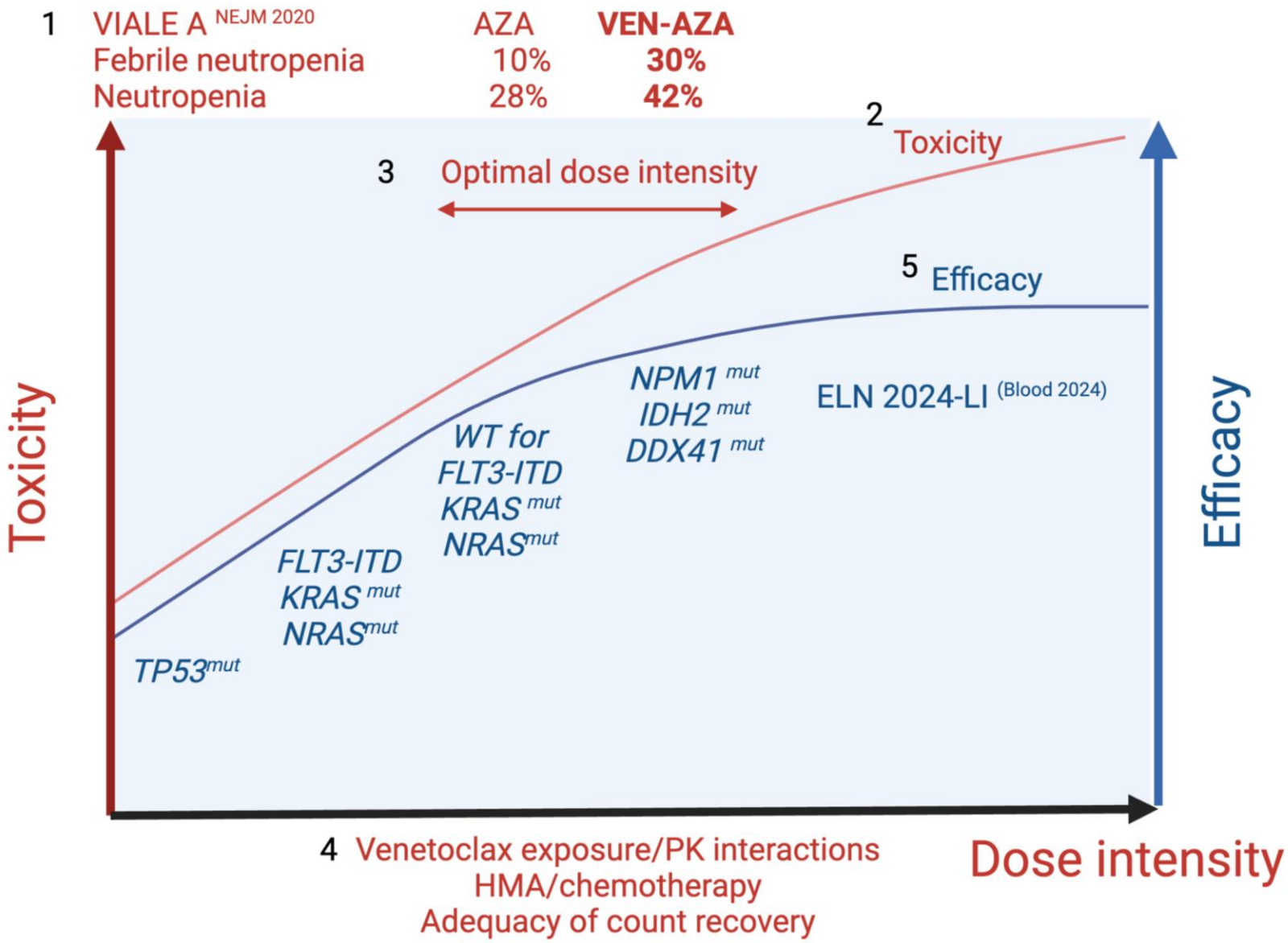
Döhner, Blood (2024)

ELN 2024- Less intensive risk classification

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

Döhner, Blood (2024)

Minimizing risk in elderly AML



Practice points

Preserve HSC integrity

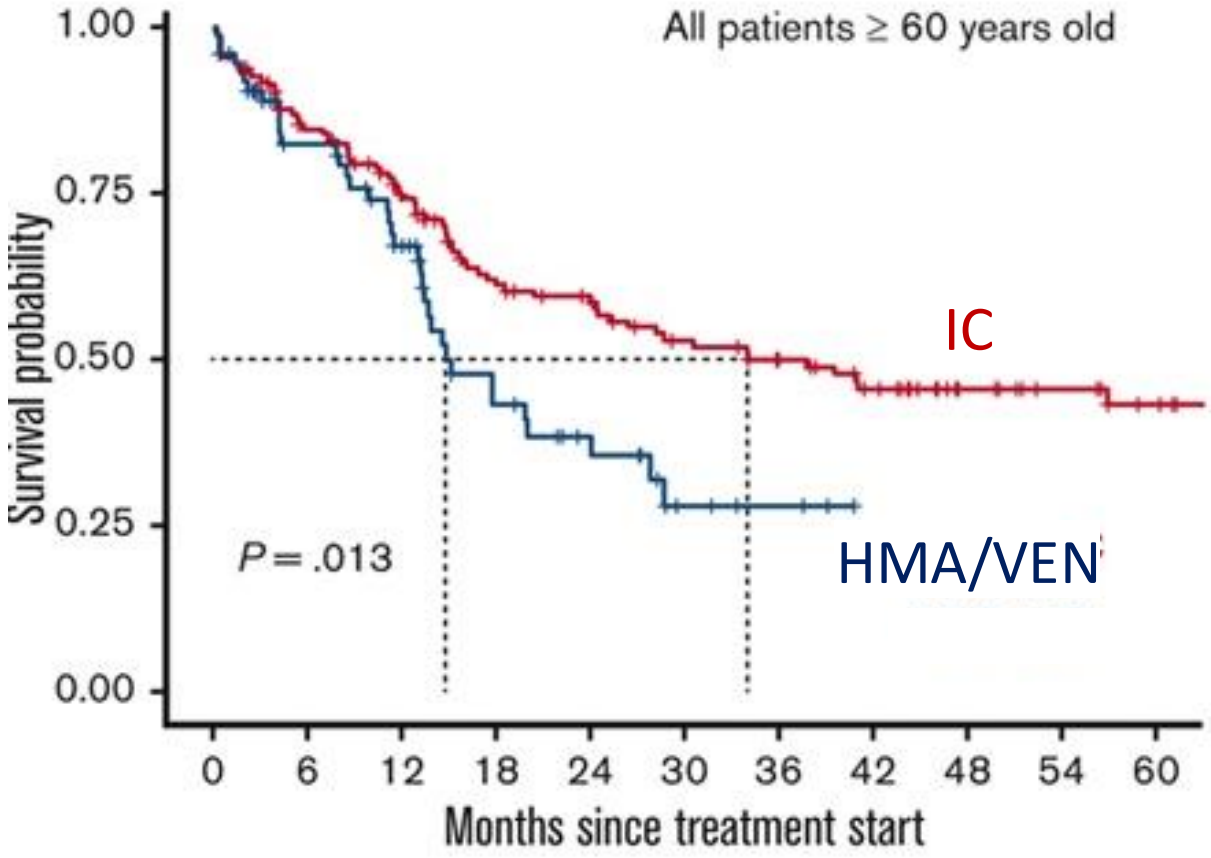
- Avoid XS venetoclax
- Allow CR recovery
- Reduce VEN duration
- Reduce AZA dose

Avoid TRM

- Admit until blasts cleared
- Esp favorable molecular risk
- Interrupt VEN once blasts cleared
- Antimicrobial risk plan
- Consider HMA only if likely benefit of VEN low

IC vs HMA-VEN AML ≥60 yo with NPM1 mut

	Intensive N=147	VEN-AZA N=74
Age	65.9 (60-79)	74.9 (63-89)
60-75	137 (93%)	41 (55%)
>75	10 (6.8%)	33 (45%)
Prior MDS/MPN	8 (5.4%)	13 (18%)
FLT3-ITD	58 (39%)	22 (30%)
Proceeded to SCT	55 [37%]	14 [19%]



Bewersdorf et al, Blood Advances 2024

A Retrospective Analysis of Intensive Chemotherapy versus Venetoclax/Hypomethylating Agents for Patients Aged 60-75 with Favorable-Risk, NPM1-Mutated AML

Zale A et al. ASH 2024;Abstract 450.

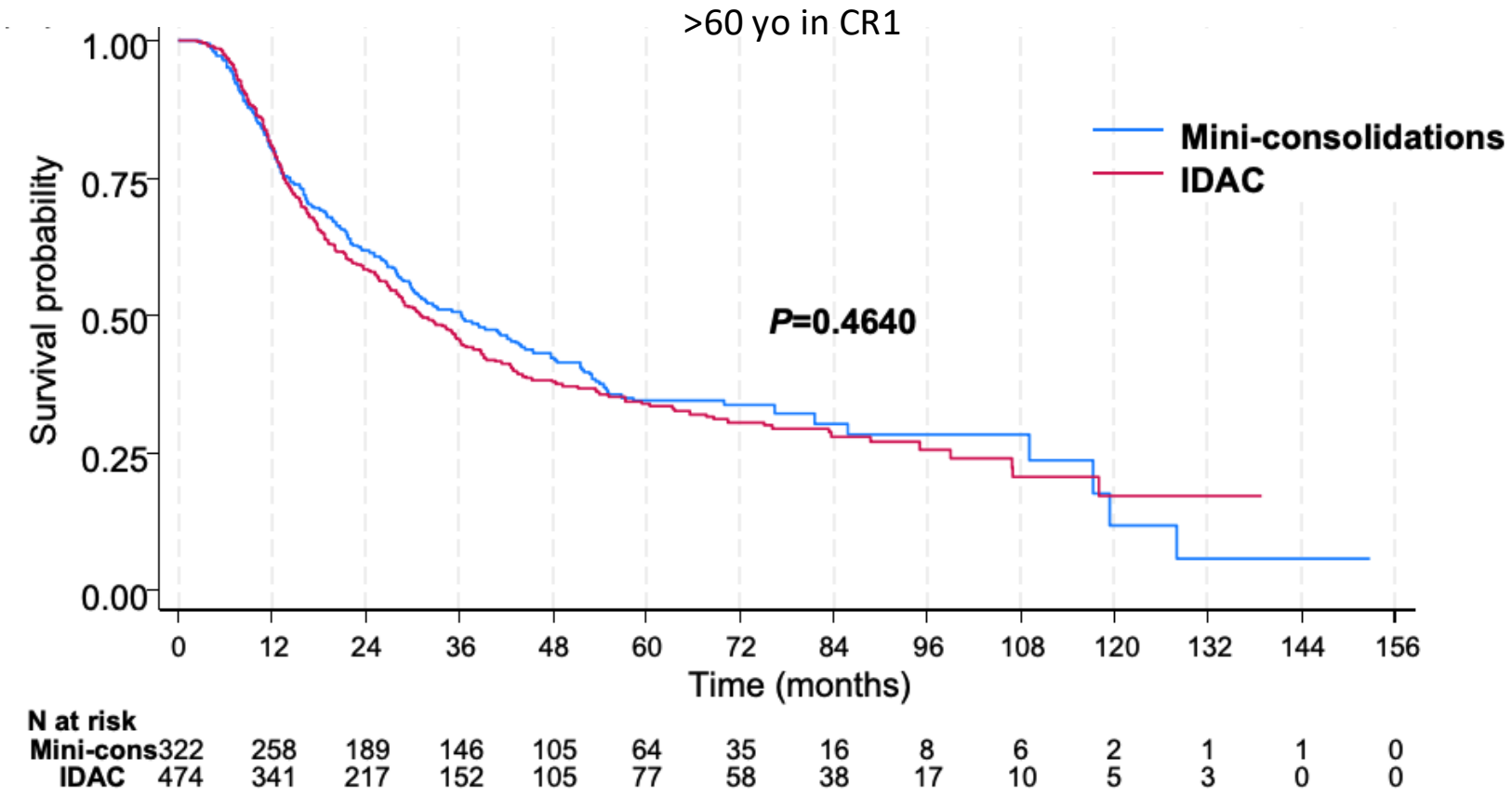
ORAL ABSTRACTS | SUNDAY, DECEMBER 8 | 10:45 AM PT

55 pts with ELN 2022 favorable NPM1m 60-75 yrs

	Intensive chemo (n=36)	VEN-AZA (n=19)
Median age	66.1	69.6
Allo CR1	69%	37%
Median OS	6.2y	4.9y

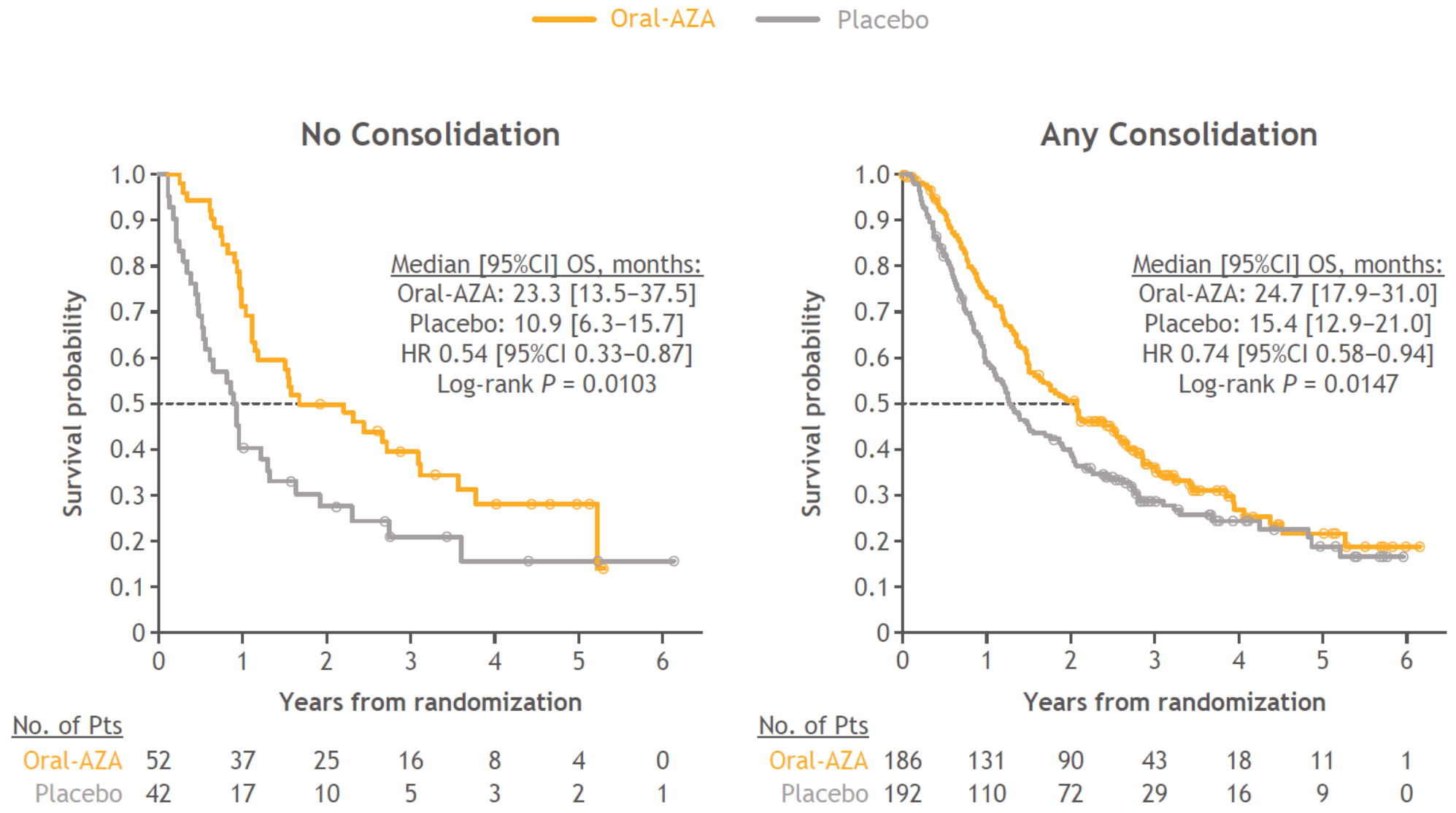
How important is intensive consolidation in elderly AML?

- IDAC (n=474); median cycles 2
- IDA 8 mg/m² D1, cytarabine 50 mg/m² BD D1–5 (n=322); median cycles 4



Recher, Am J Haem 2024

How important is intensive consolidation in elderly AML?

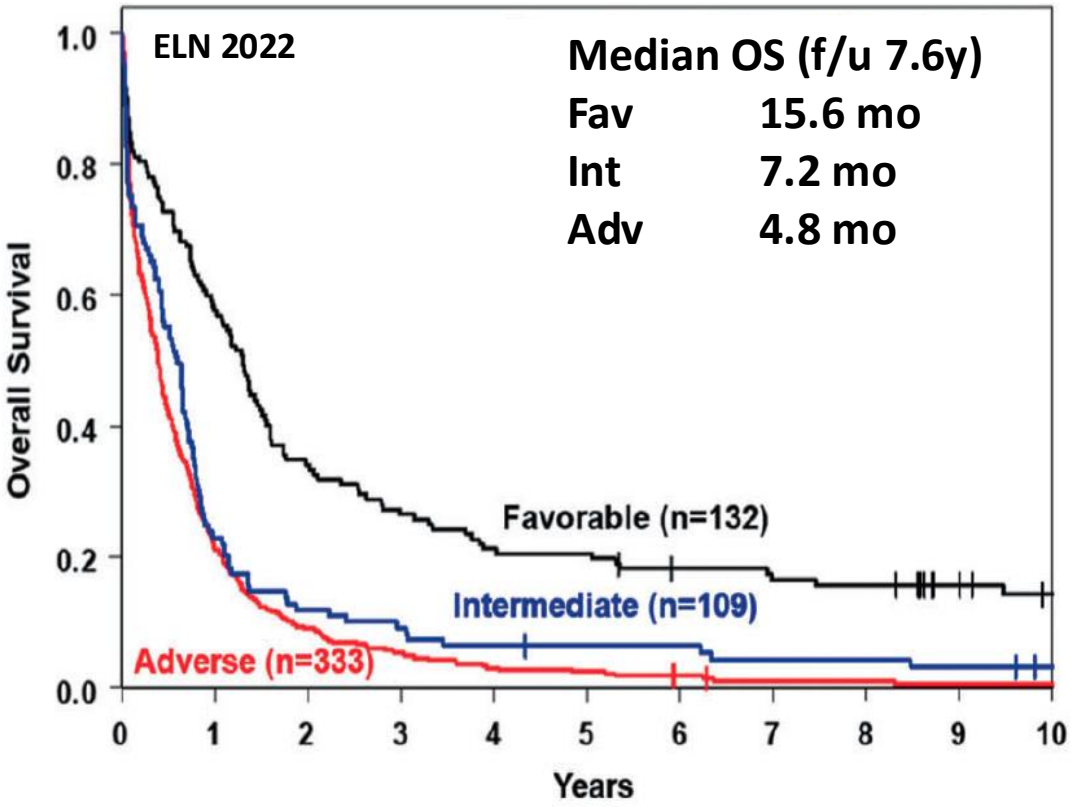


Wei et al, Hematologica 2023

Can VEN enhance intensive chemotherapy outcomes in elderly AML?

7+3

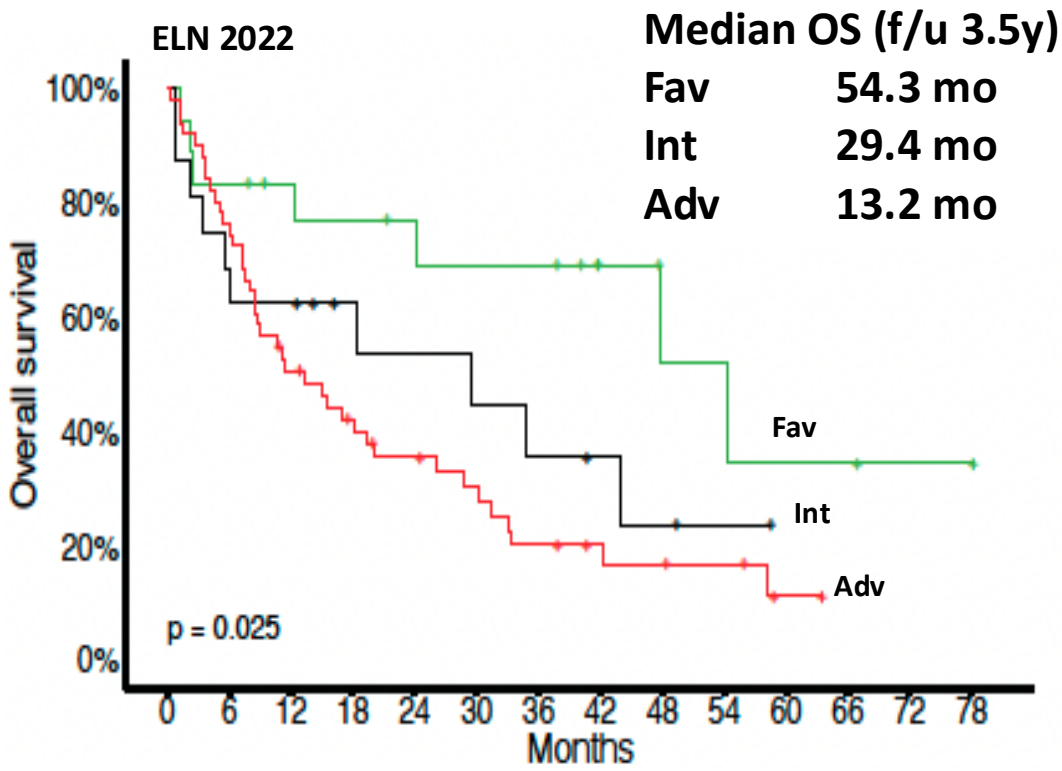
>60 years



Mrózek, Leukemia, 2023

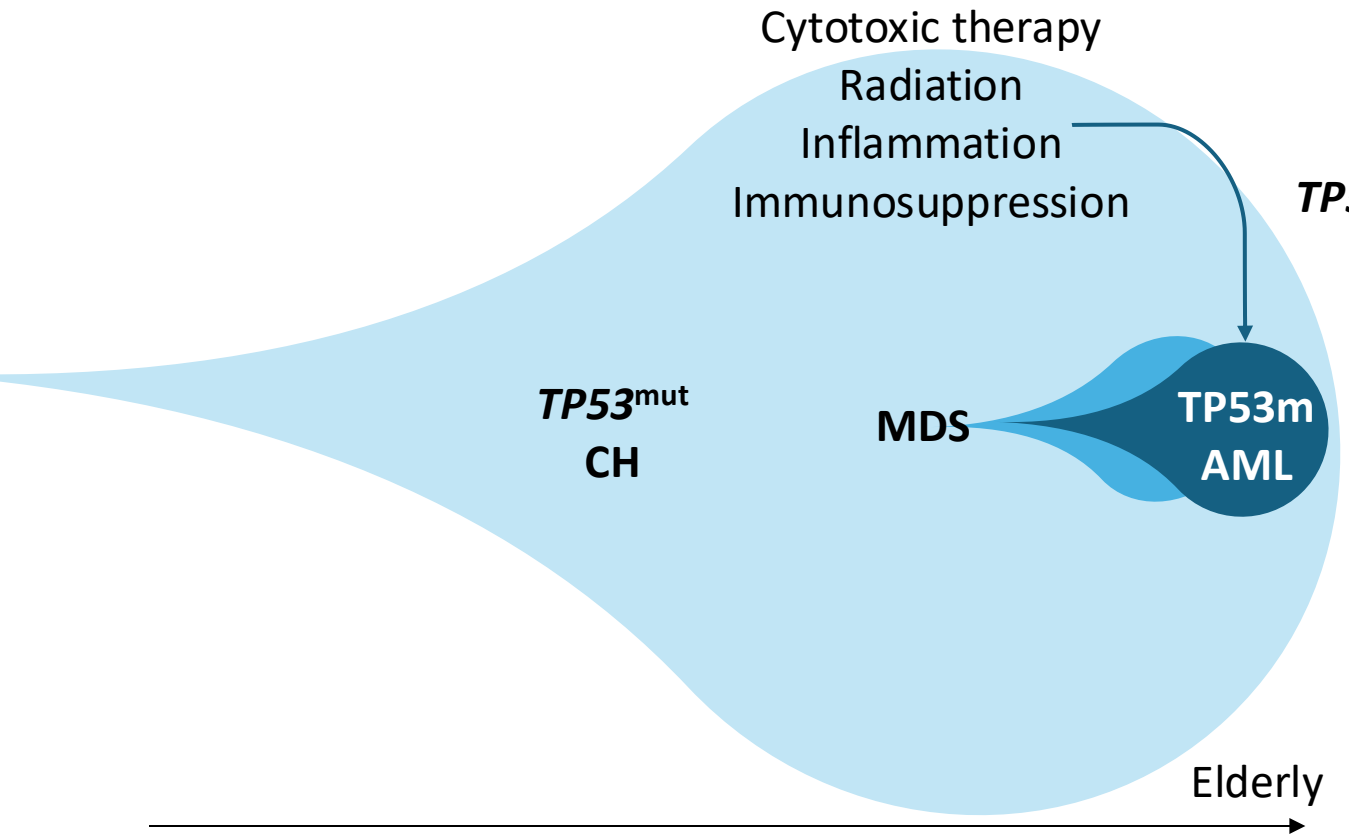
5+2+Venetoclax [CAVEAT] n=81

Median age 71 (63-80)



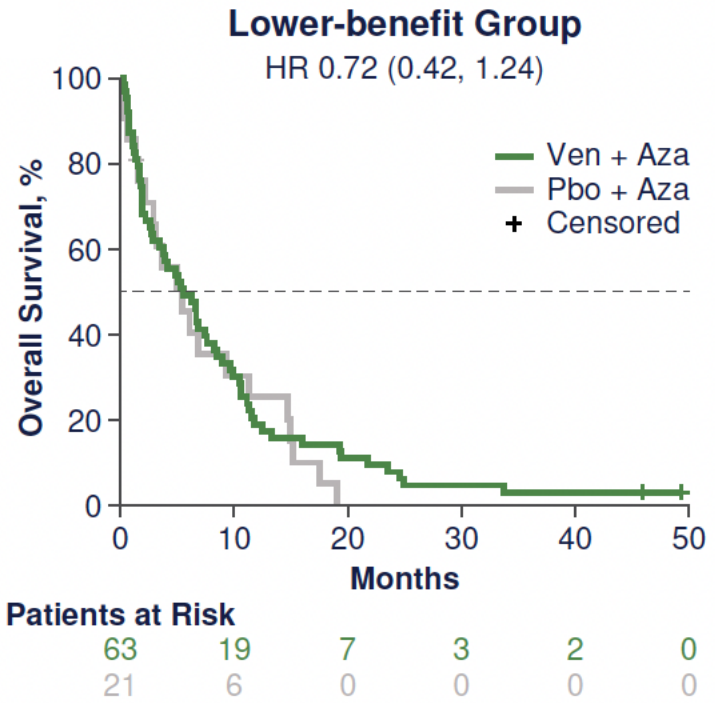
Chua et al, submitted

TP53 mutant myeloid disease: high unmet need



Age	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
TP53 mut AML	0	0	0	5%	5%	6%	**16%**	**19%**
TP53 mut MDS	0	0	0	0	0	6%	**8%**	**7%**

Stengel et al. Leukemia 2017



TP53 mutated

Lower	n	Events	Median OS, months (95% CI)
Ven + Aza	63	61	5.5 (2.8, 7.6)
Pbo + Aza	21	20	5.4 (2.1, 11.3)

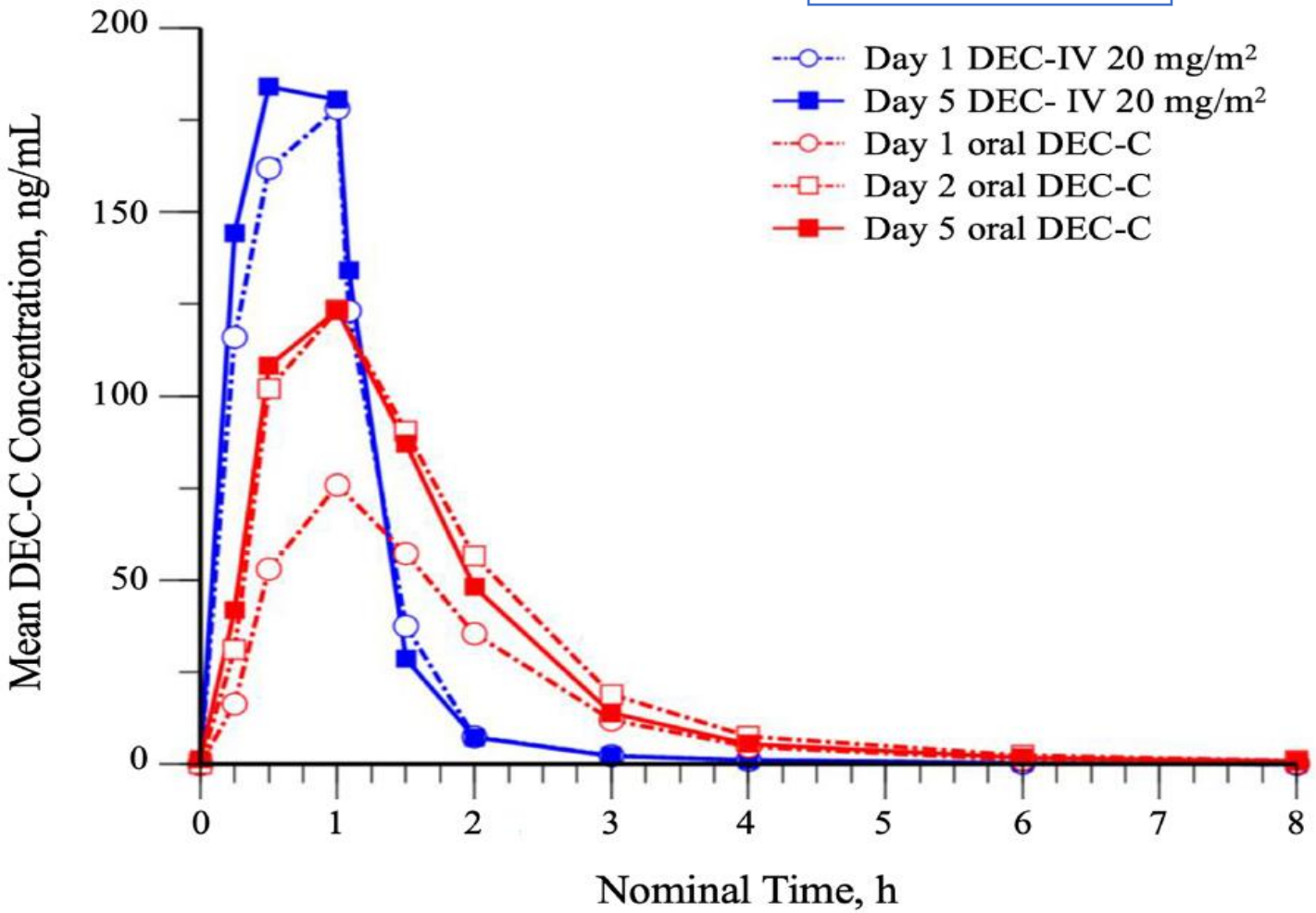
Döhner, Blood (2024)

Phase III study Decitabine-Cedazuridine in AML

Median age: 78
Median follow-up: 23.6 mo

DEC-C → IV DEC
IV DEC → DEC-C

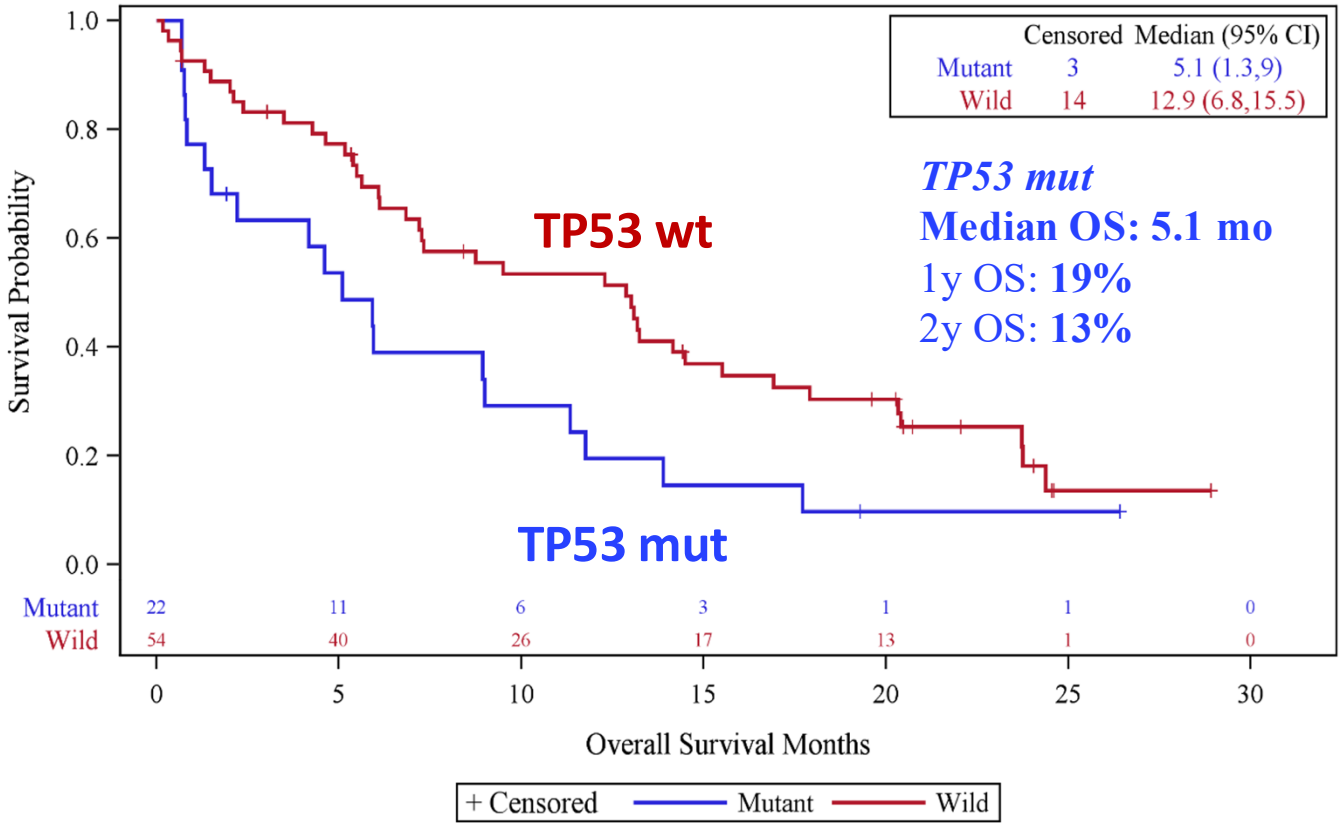
C3+ DEC-C



Giessler et al, BJH 2024

Decitabine-Cedazuridine in AML

Response	Oral DEC-C (n=80)
CR	23.8%
CR/CRh	26.3%
CR/CRi/PR	35%
Median time to CR	3 months
Median duration CR/CRh	9 months
RBC/Plt Tx independent	38%/24%



Giessler et al, BJH 2024

All oral AML therapy

Newly diagnosed AML	Regimen	N	Outcome	OS	Ref
Non-targeted	DEC-C VEN	60	ORR 67% (CR 40%)	mOS 10.2m	ASH 2024 #2896 (Bazinet)
IDH1/2	DEC-C VEN IDHi	38	ORR 92%	2-year OS 82%	ASH 2024 #2883 (Marvin-Peek)
Relapsed/refractory AML	**Regimen**	**N**	**Outcome**	**OS**	**Ref**
FLT3	DEC-C VEN GILTERITINIB	15	CRc 26% MLFS	mOS 6 m	ASH 2023 #2910 (Briski)
NPM1 mut KMT2A::r	DEC-C VEN SNDX-4613	26	CRc 58%		ASH 2024 #216 (Issa)

Concluding statements

- Therapy for elderly AML has been transformed
- New considerations
  - Consideration of targeted therapy
  - Increasing role of molecular risk stratification
  - Emerging novel combinations, less toxicity, MRD guided therapy

Questions from General Medical Oncologists/Hematologists

- How long after starting venetoclax with an HMA do you typically check bone marrow?
- Which initial treatment would you recommend for a 78-year-old patient with AML with a PS of 1?
- The dose/schedule of venetoclax needs modification almost all the time. How low can we go without losing response?
- Can you comment on dosing strategies for venetoclax? Can you comment on when to add targeted agents?
- Do you give antifungal prophylaxis with venetoclax/HMA?

Questions from General Medical Oncologists/Hematologists

- **Patient achieved complete response with first cycle of Aza + Ven and has been on treatment for last 3 years (currently on Aza every 6 weeks and venetoclax 1 week on and 1 week off). Is there any role for discontinuation of treatment or changing to single-agent oral HMA or venetoclax by itself? (He also has IDH1 mutation if we need a second-line option in future.)**
- **What strategies can allow the patients to be on Aza/Ven for the longest periods without risk of recurrent infections?**

Questions from General Medical Oncologists/Hematologists

- 76 yo man with AML and no targetable mutations, on Aza/Ven in CR with severe cytopenias. This patient has been on treatment for 1.5 years. Still in CR; however, ANC 0.6, anemia and thrombocytopenia for several months. Holding treatment for count recovery. Can treatment be discontinued? What about MRD testing?

Agenda

Module 1: Treatment for Older Patients with Acute Myeloid Leukemia (AML) — Prof Wei

Module 2: Selection of Initial Therapy for Younger Patients with AML without a Targetable Mutation, Including Those with Secondary AML — Dr Stone

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

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

Module 5: Potential Role of Menin Inhibitors and Other Novel Agents in the Treatment of AML — Dr Wang

RTP RESEARCH TO PRACTICE

Selection of Initial Therapy for Younger Patients with AML without a Targetable Mutation, including those with secondary AML

Richard M. Stone, MD

Director, Translational Research, Adult Leukemia Program, Medical Oncology

Chief of Staff, Dana-Farber Cancer Institute

Professor of Medicine, Harvard Medical School

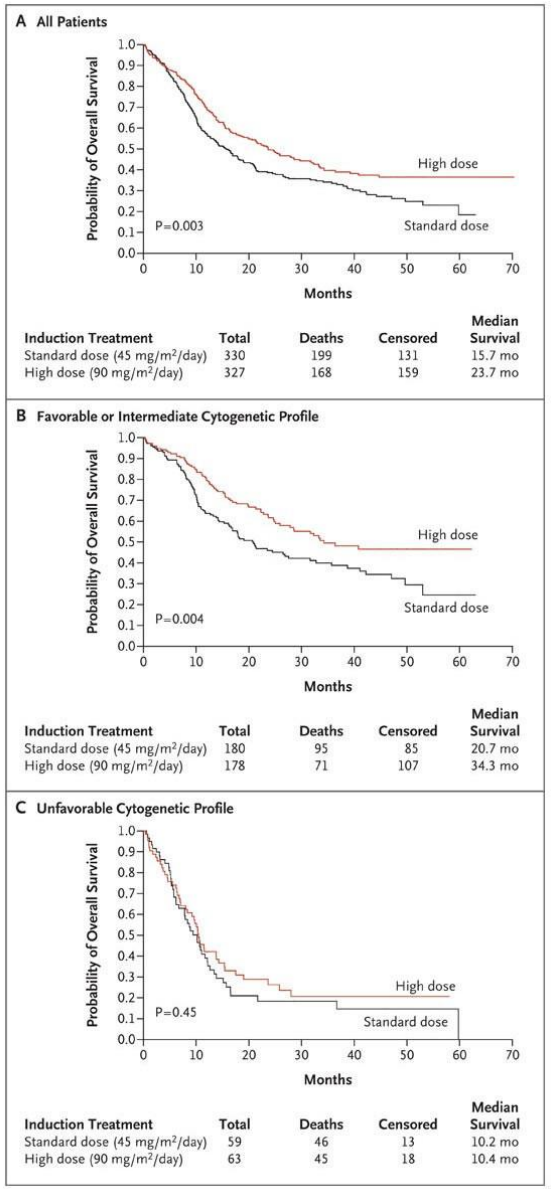
December 6, 2024

Dana-Farber Cancer Institute

Questions-1

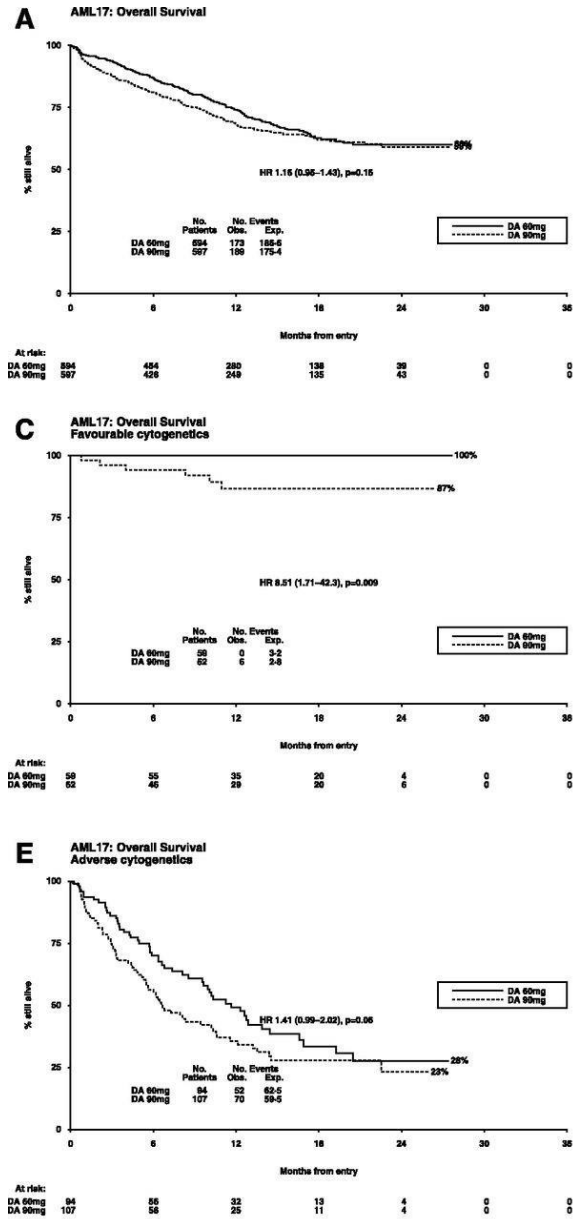
- What is “without a targetable mutation”?
  - Now Without: *FLT3*- ITD, *FLT3*-TKD
  - Soon Also: *NPM1;* maybe *IDH1/2*, *KIT*
- Is 3 (dauno or ida) +7 (ara-C) the standard intensive chemo ?
  - Optimal dauno dose
  - ? Add nucleoside analog
  - ? Add gemtuzumab
  - ? Add venetoclax

90 mg/m² better than 45 mg/m² dauno



Fernandez HF, et al. *NEJM.* 2009;361:1249-1259

90 mg/m² no better than 60 mg/m² dauno



Burnett AK, et al. *Blood.* 2015; 125: 3878–3885

Rollig C, *J Clin Oncol* 2024: 90 not better than 60 and double induction not needed in good responders.

Nucleoside analogs+ 3+7

CLAG: cladribine/Cytarabine/G-CSF

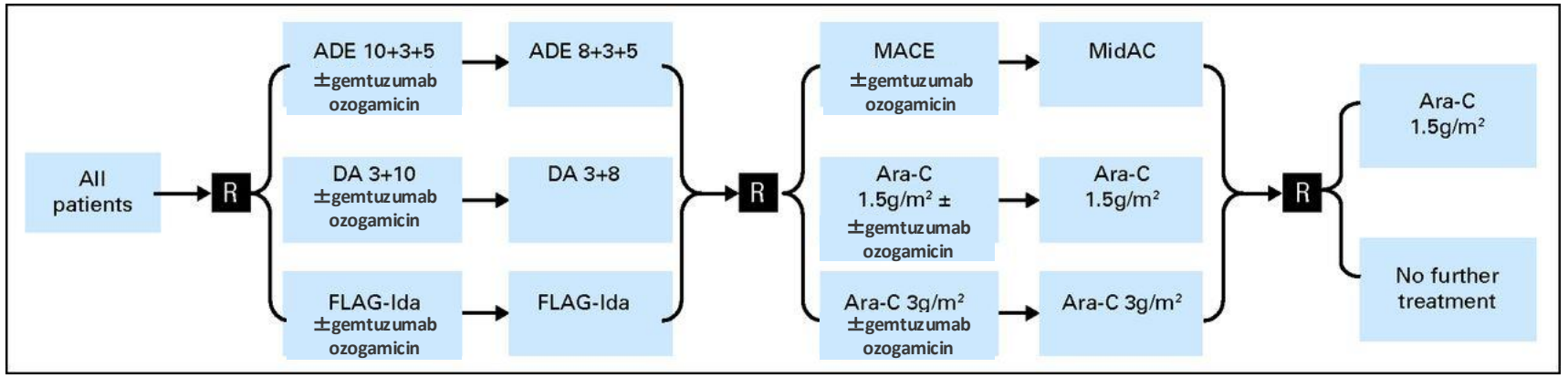
GCLAM: G-CSG/cladribine/cytarabine/mitoxantrone

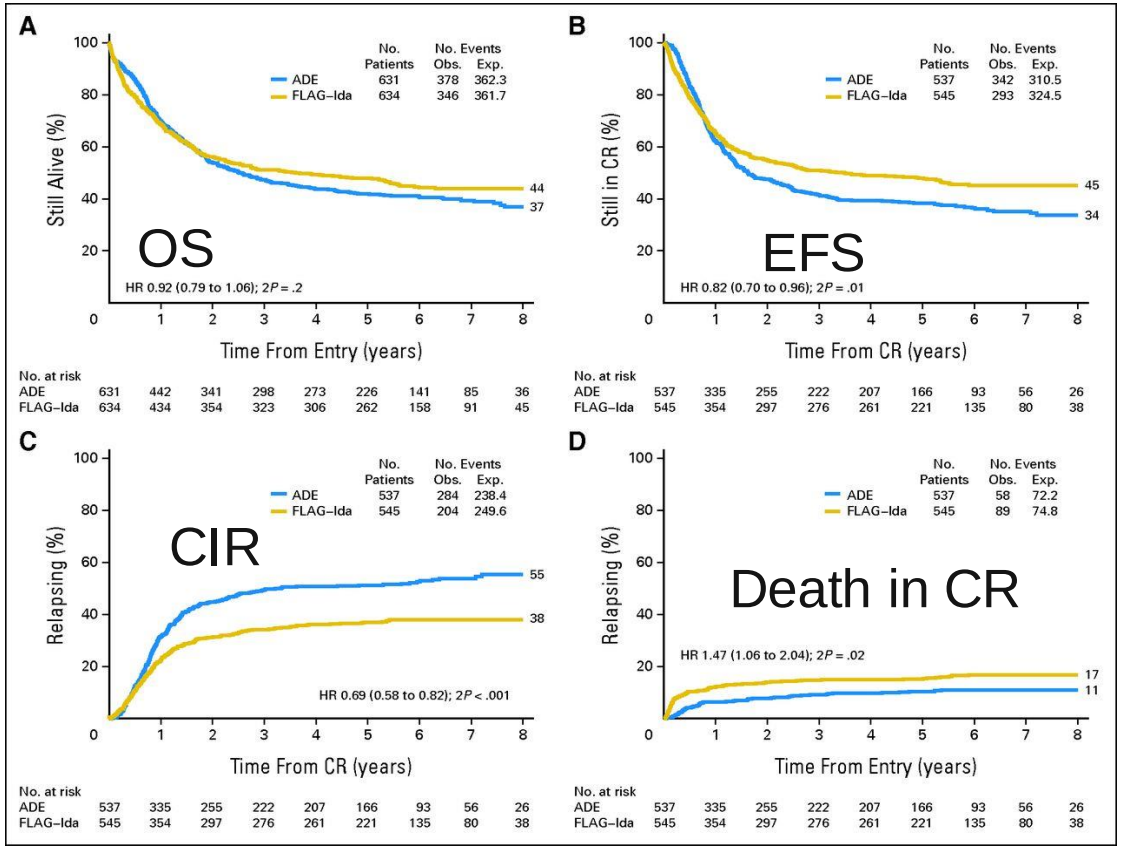
FLAG-IDA: fludarabine/cytarabine/G-CSF/idarubicin

Cladribine/dauno/cytarabine

Polish randomized study suggests better CR rate and LFS w 3 drug c/w 2 (Holwiecki J, et al leukemia 2004; 18; 989-97)

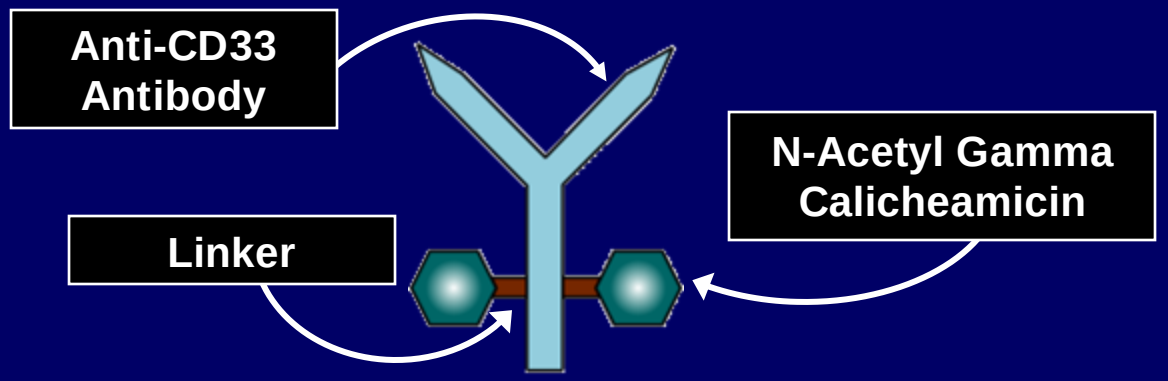
Nucleoside analogs+ 3+7: MRC AML15





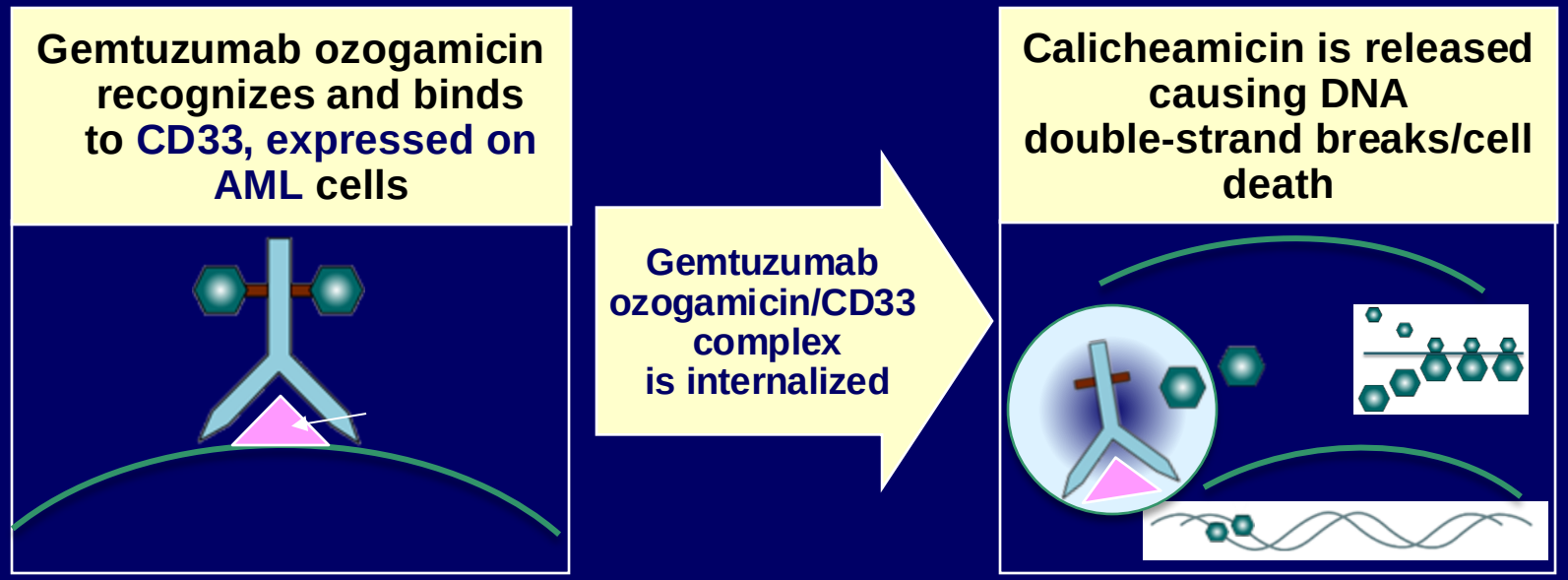
Burnett AK, et al. J Clin Oncol. **2013**

Gemtuzumab ozogamicin

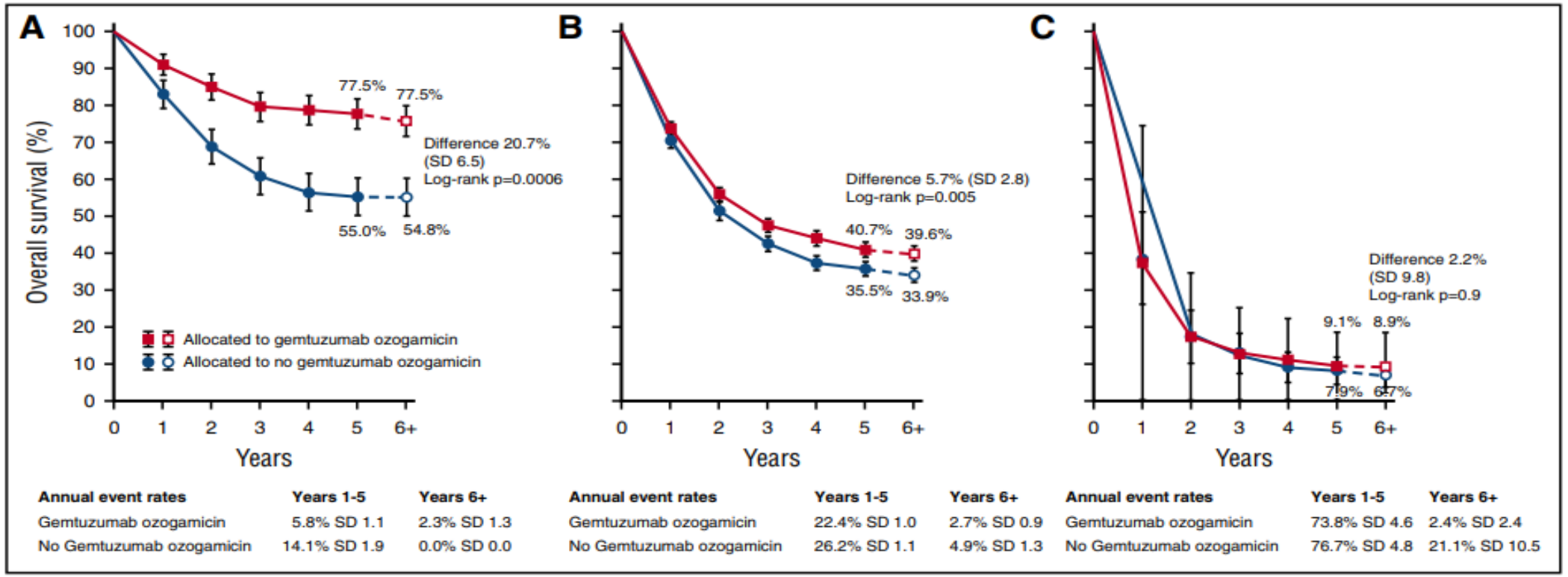


CD33 expressed on blasts in 90% of pts

Mechanism of Action



A meta-analysis of 5 studies (2 French, 2 UK, 1 US; 3.5k pts) suggested that addition of GO to Chemo most useful in CBF (inv 16 and t(8;21)) AML



Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	5.8% SD 1.1	2.3% SD 1.3
No Gemtuzumab ozogamicin	14.1% SD 1.9	0.0% SD 0.0

Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	22.4% SD 1.0	2.7% SD 0.9
No Gemtuzumab ozogamicin	26.2% SD 1.1	4.9% SD 1.3

Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	73.8% SD 4.6	2.4% SD 2.4
No Gemtuzumab ozogamicin	76.7% SD 4.8	21.1% SD 10.5

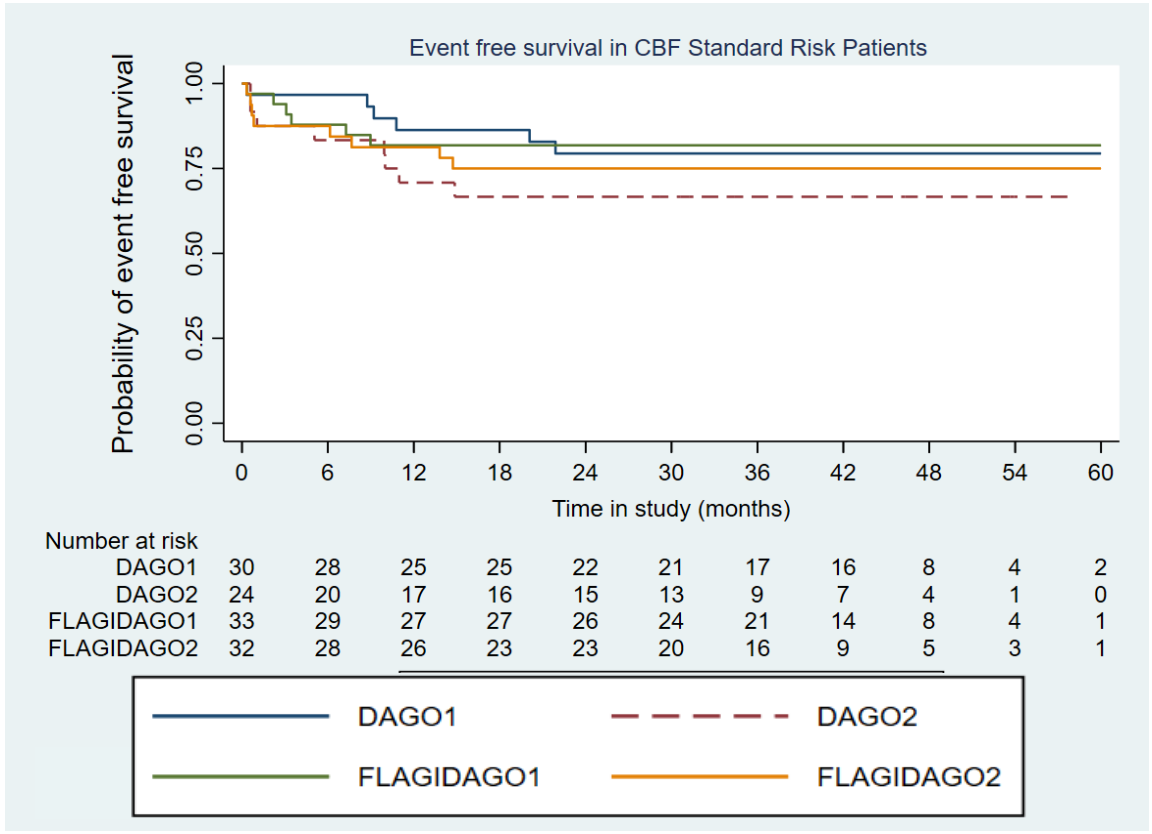
Fav CG

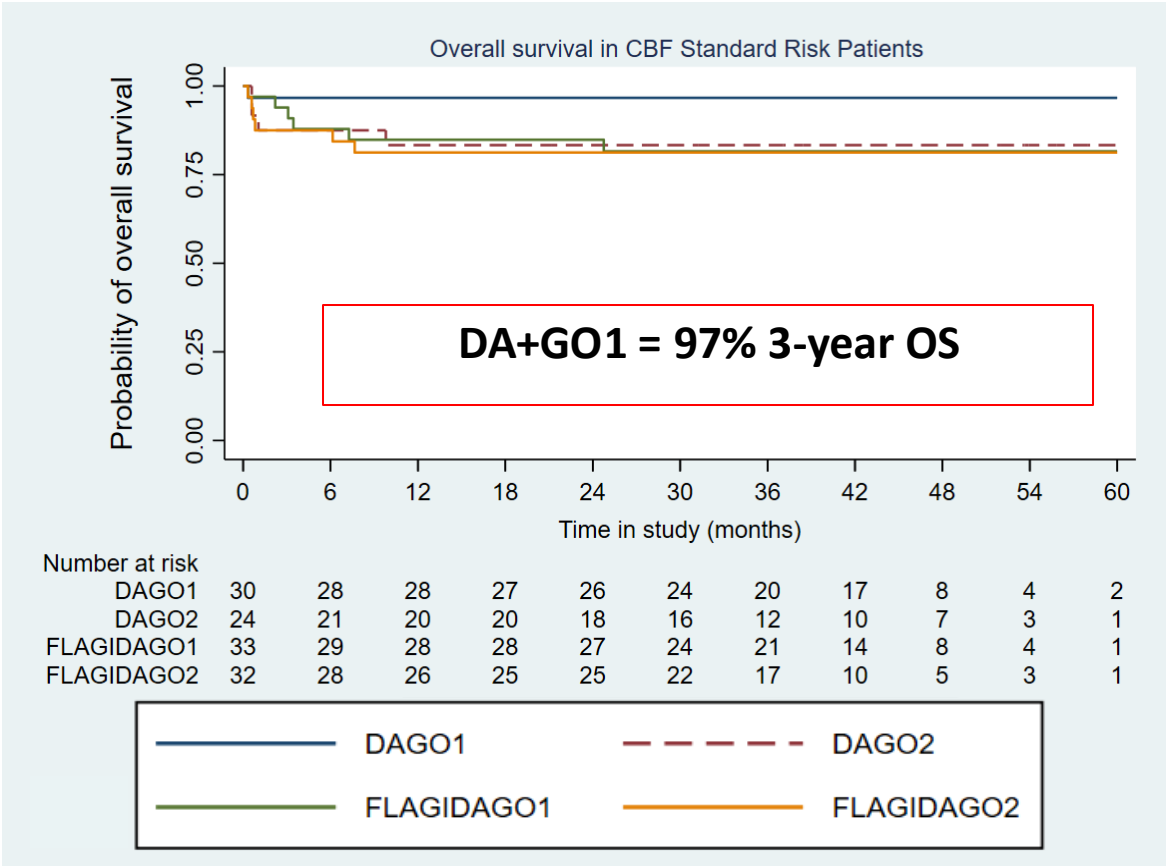
Int CG

Adv CG

Hills RK, et al. *Lancet Oncol* 2014; 15: 686-96.

UK NCRI AML 19: Event Free and Overall Survival in CBF AML





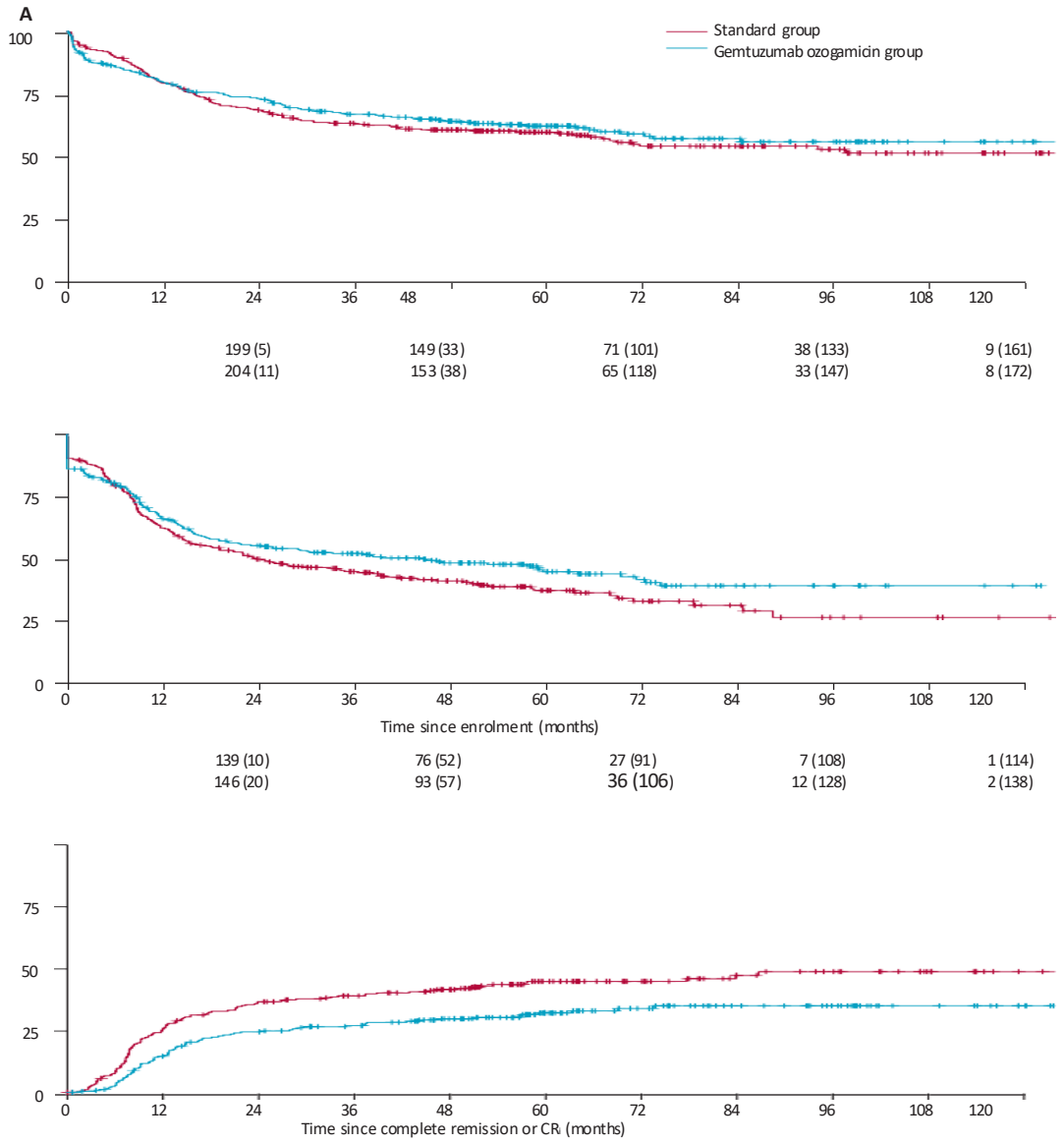
Russell NH, et al. *J Clin Oncol.* 2024; 42(10):1158

Intensive chemotherapy with or without gemtuzumab ozogamicin in patients with *NPM1*-mutated acute myeloid leukaemia (AMLSG 09–09): a randomised, open-label, multicentre, phase 3 trial

OS

EFS

CIR



Ida/Ara-C/ Etoposide/ ATRA without GO (red) or with GO (blue)

Dohner H et al, *Lancet Hematol* 2024;10:e495–509.

Venetoclax plus intensive chemo

- **FLAG-IDA-VEN; fludarabine/cytarabine/G-CSF/idarubicin VEN**

- **VEN+3+7**
  - Wang H, et al, *Lancet Haematol* 2022
  - n=33, CR 91%, MRD NEG CR: 97%, 12% sepsis
  - Mantzaris I, et al. Abstract #57, Sat AM (Saturday, December 7, 2024: 10:00 AM)
  - Stone R, et al. Abstract #4261, Monday Poster Session (Monday, December 9, 2024, 6:00 PM-8:00 PM)

- **Ven+2+5 in older pts (Chua CC, et al, *JCO* 2020)**

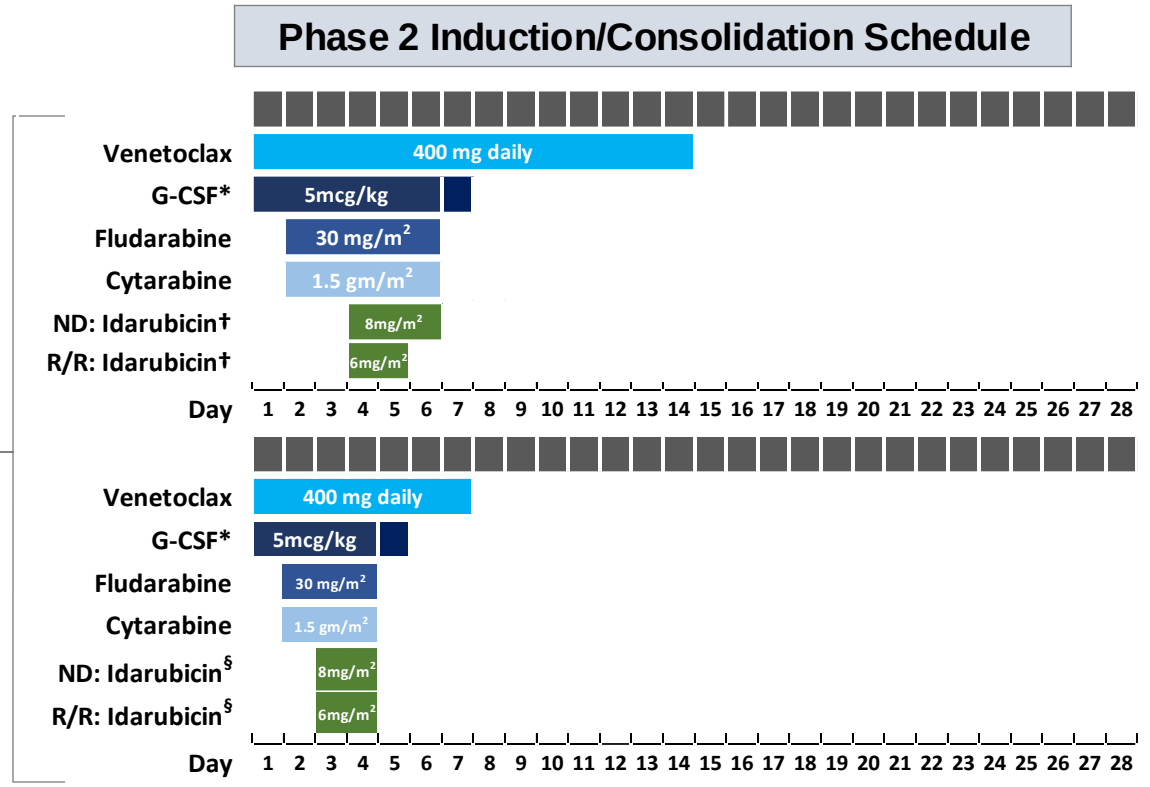
- **VEN+ cladribine/idarubicin/cytarabine (Kadai TM, et al, *Lancet Haematol* 2021)**
  - n=50 CR+CRi 47 patients (94%); 37 of 45 (82%) had undetectable measurable residual disease (MRD). One ind death

FLAG-IDA-VEN: Study Cohorts and Treatment Schedule, DiNardo et al, Am J Hematol, 2022. ?Alternative to '3=7"

Phase 1b	Phase 2A	Phase 2B
R/R-AML	ND-AML	R/R-AML
N=16	N=29	N=23

Induction	Consolidation
Venetoclax 400 mg D1-14	Venetoclax 400 D1-7
G-CSF D1-6	G-CSF D1-4
Pegfilgrastim or biosimilar D7	Pegfilgrastim or biosimilar D5
Fludarabine 30 mg/m^2 D2-6	Fludarabine 30 mg/m^2 D2-4
Cytarabine 1.5 gm/m^2 D2-6	Cytarabine 1.5 gm/m^2 D2-4
ND: Idarubicin 8 mg/m^2 D4-6	ND: Idarubicin 8 mg/m^2 D3-4
R/R: Idarubicin 6 mg/m^2 D4-5	R/R: Idarubicin 6 mg/m^2 D3-4

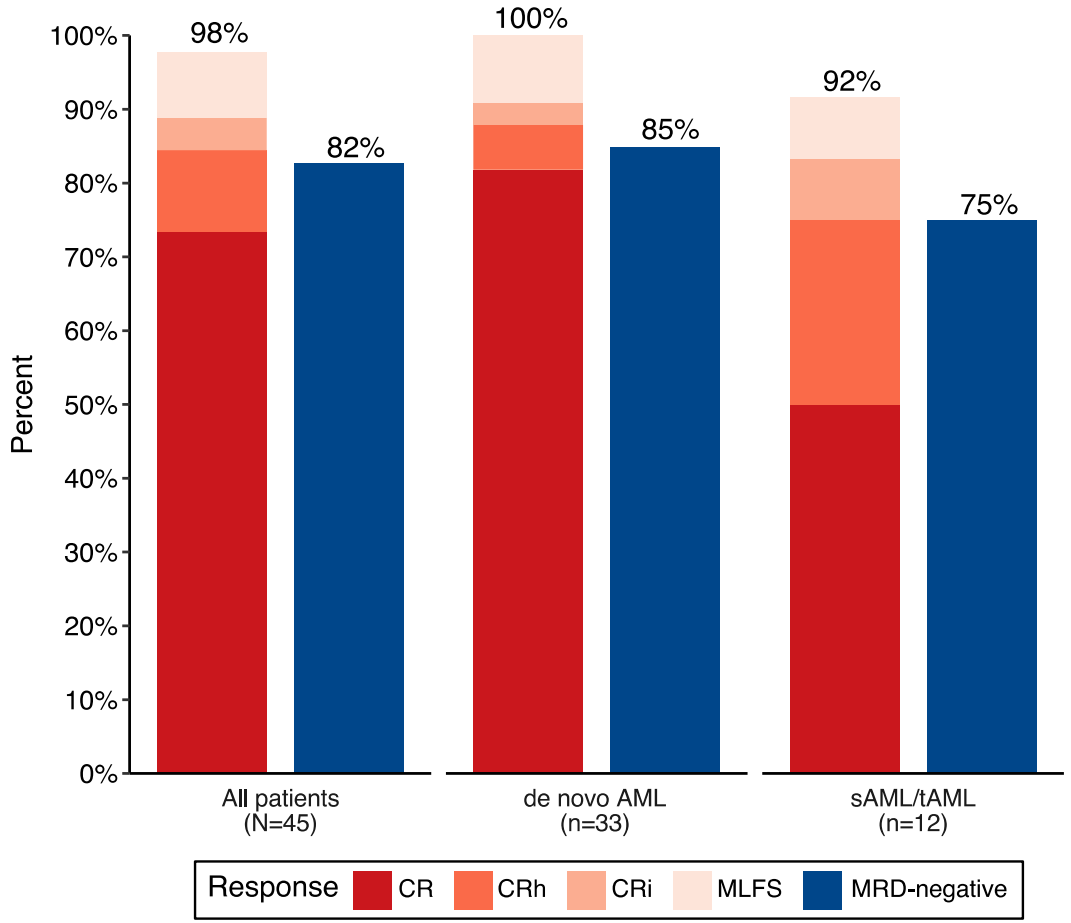
Phase 1b		Phase 2
Cytarabine 2 gm/m^2	RP2D*	**Cytarabine 1.5 gm/m^2**
Venetoclax D1-21		**Venetoclax D1-14**

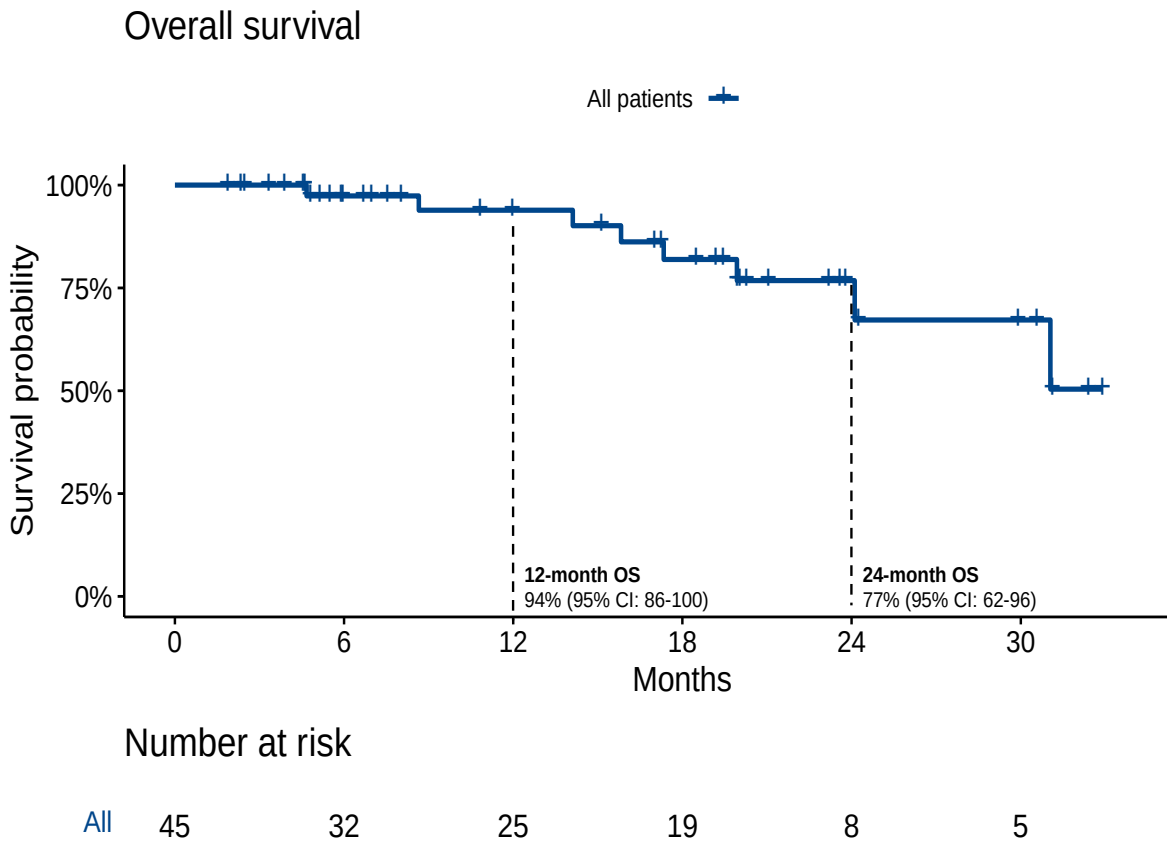


*G-CSF: 5 mcg/kg the day prior to and days of IV chemotherapy followed by 1 dose of pegfilgrastim or biosimilar each 28 D cycle
† Induction: ND-AML: Idarubicin 8 mg/m^2 days 4-6, R/R-AML Idarubicin 6 mg/m^2 days 4 and 5
§ Consolidation: Idarubicin permitted on days 3 and 4 in 2 post-remission cycles (ie. C2 or C3 and C5 or C6) at physician discretion

* 5/6 initially enrolled P1b patients developed bacteremia/sepsis with P1b dosing

FLAG-IDA + Venetoclax : Frontline





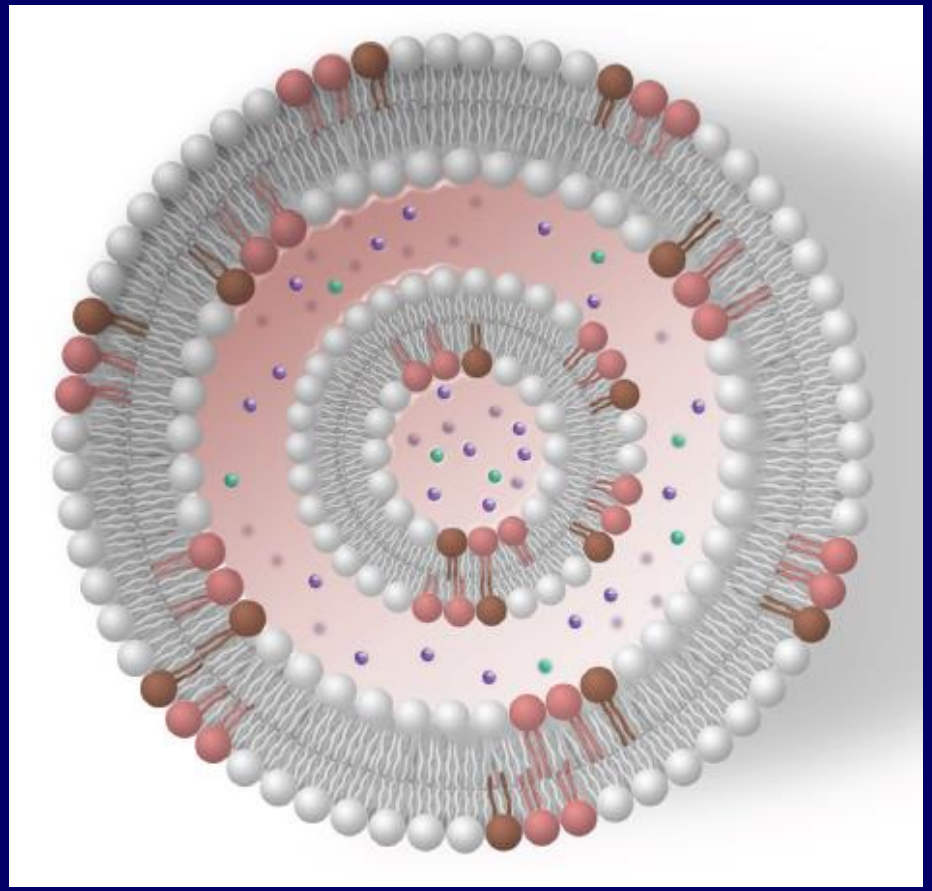
DiNardo et al, Am J Hematol, 2022

Questions-2

- What is secondary AML?
  - Clinical Definition
    - After prior MDS or after prior cytotoxic chemo
  - CPX-351 definition (CPX-351 [liposomal dauno/ara-C])
    - Clinical definition plus AML- w MDS-related cytogenetics
      - ? Prior HMA an issue
  - A useful definition: Adverse risk ELN 2022

CPX-351

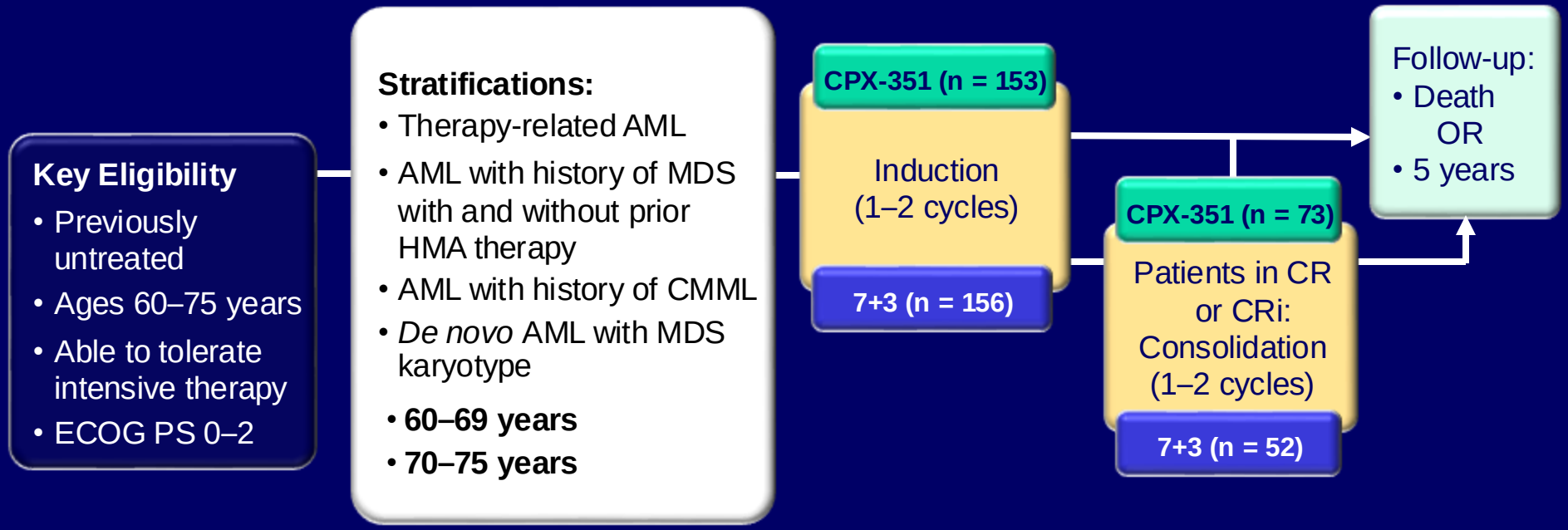
- CPX-351 is a liposomal co-formulation of cytarabine and daunorubicin designed to achieve synergistic antileukemia activity
  - 5:1 molar ratio of cytarabine:daunorubicin provides synergistic leukemia cell killing *in vitro*[1]
  - In patients, CPX-351 preserved delivery of the 5:1 drug ratio for over 24 hours, with drug exposure maintained for 7 days[2]
  - Selective uptake of liposomes by bone marrow leukemia cells in xenograft models[3]



. Tardi P et al. *Leuk Res.* 2009;33(1):129–139.
2. Feldman EJ et al. *J Clin Oncol.* 2011;29(8):979–985;
3. Lim WS et al. *Leuk Res.* 2010;34(9):1245–1223.

CPX-351 Phase III Study Design

- Randomized, open-label, parallel-arm, standard therapy–controlled
  - 1:1 randomization, enrolled from December 2012 to November 2014
  - Patients with CR or CRi could be considered for allogeneic HCT, based on institutional criteria



AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CR, complete response; CRi, CR with incomplete platelet or neutrophil recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HMA, hypomethylating agents; MDS, myelodysplastic syndrome.

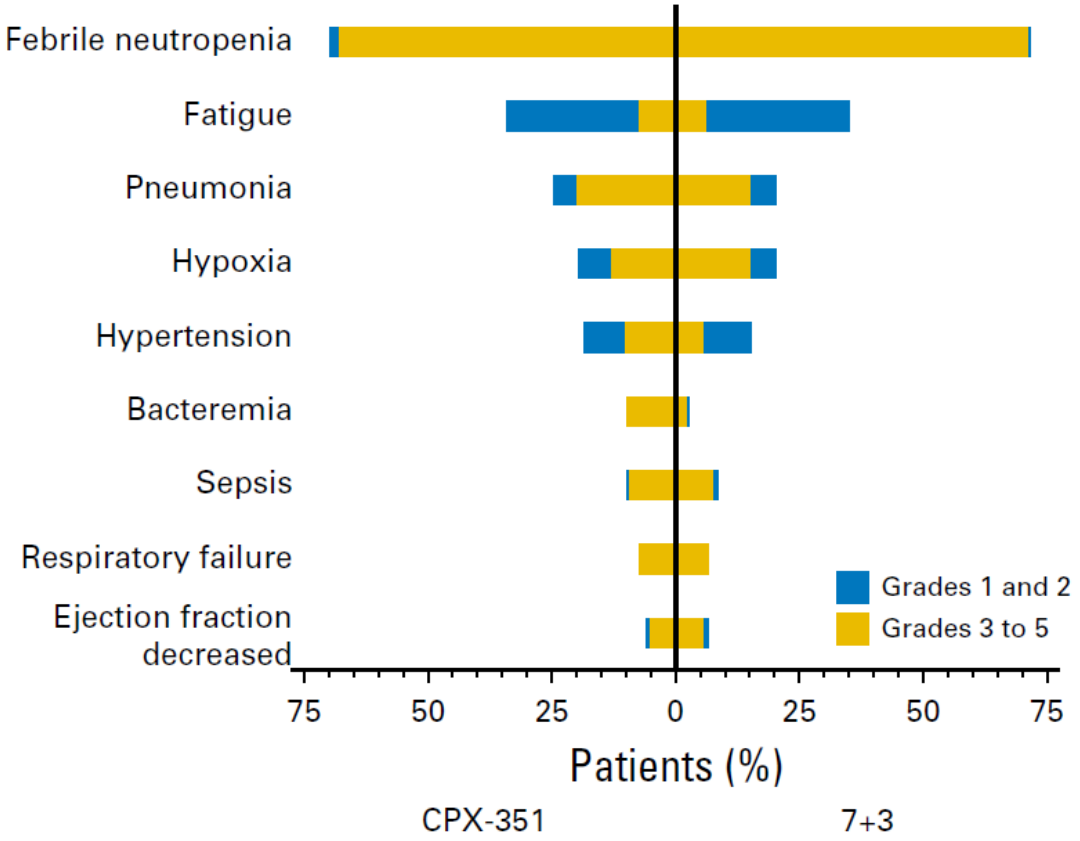
1. World Health Organization. *WHO Classification of Tumours of Haematopoitic and Lymphoid Tissues*. Swerdlow S et al (ed). Lyon, IRAC Press, 2008.

Delayed Recovery of ANC and Platelet Count with CPX-351 Compared with 7+3 in Older, sAML

	ANC ≥500/mcL		Platelets ≥50,000/mcL	
	CPX-351	7+3	CPX-351	7+3
Patients receiving 1 induction	n = 58	n = 34	n = 58	n = 34
Median, days	35	29	36.5	29
Patients receiving 2 inductions	n = 15	n = 18	n = 15	n = 18
Median, days	35	28	35	24

Lancet JE, et al. *J Clin Oncol.* 2018; 36: 2684-92

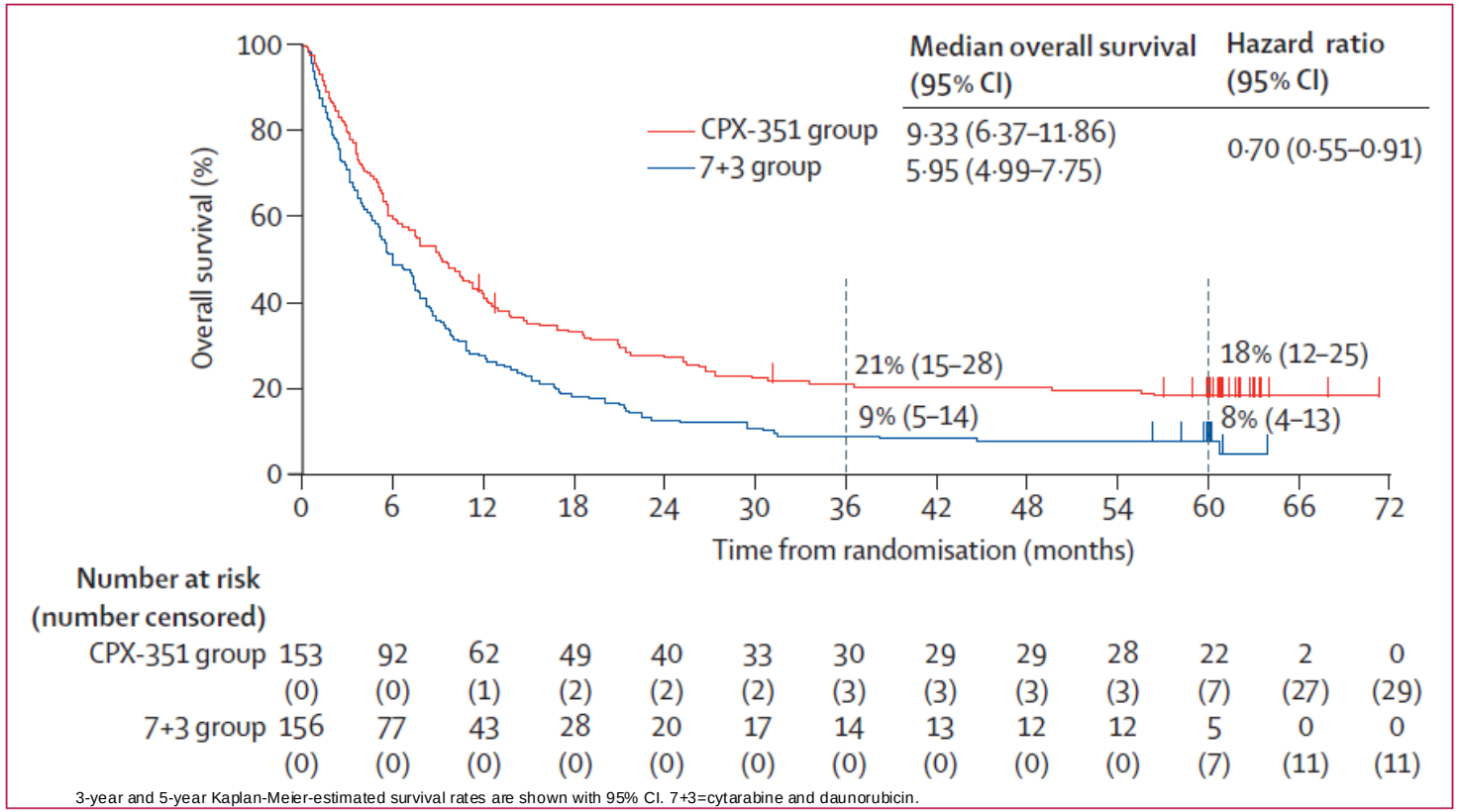
Phase 3 Study of CPX-351 Versus 7+3 in Older Patients With Newly Diagnosed sAML: Adverse Events



- AEs generally similar between arms
- Higher rate of all grades of hemorrhage, as well as fatal CNS hemorrhage (2.0% vs 0.7%) with CPX-351

Lancet JE, et al. *J Clin Oncol.* 2018; 36: 2684-92

Overall survival CPX 351 v 3+7 in sec AML, age 60-75: 5-year results[1]

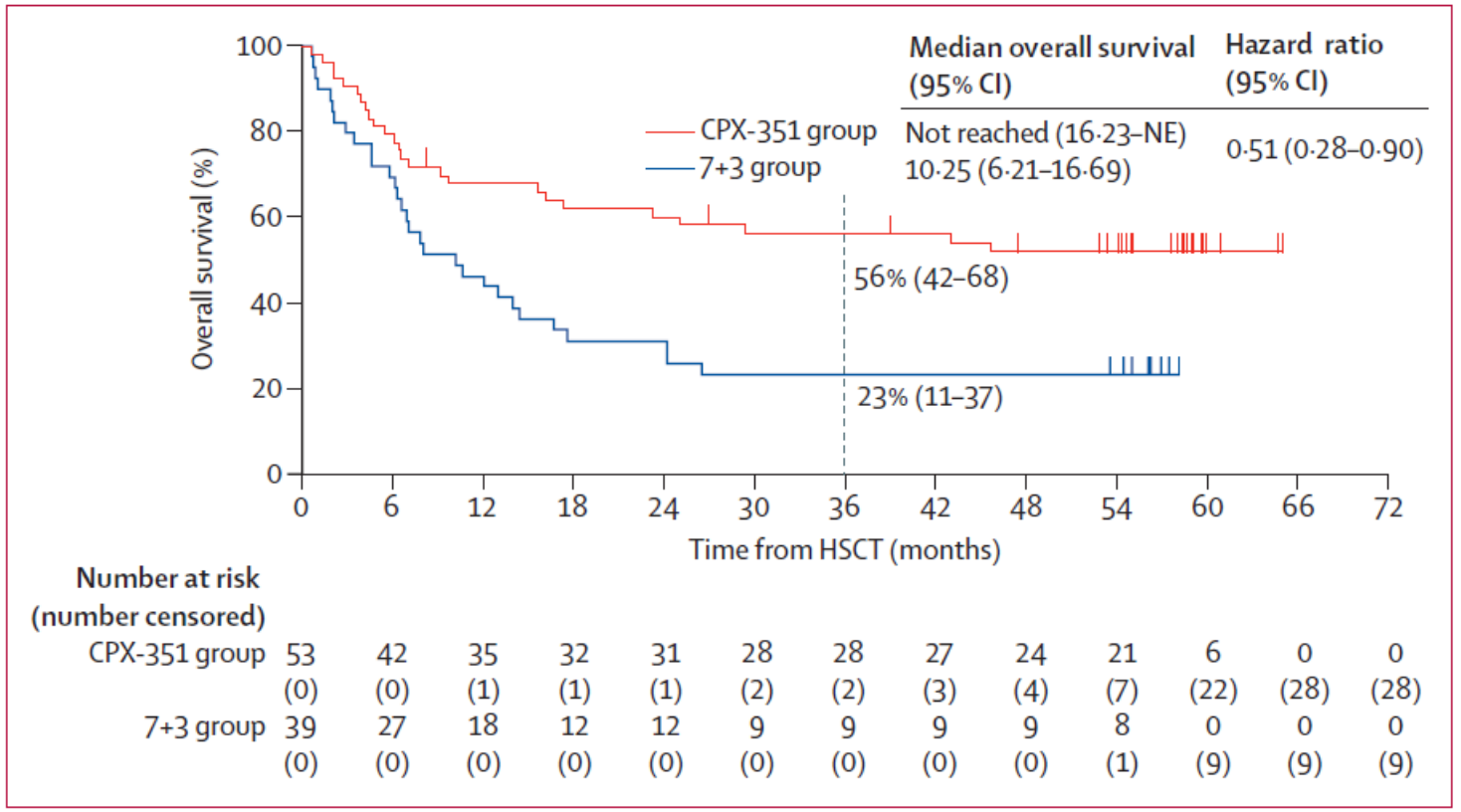


3-year and 5-year Kaplan-Meier-estimated survival rates are shown with 95% CI. 7+3=cytarabine and daunorubicin.

	CPX-351 (n = 153)	7+3 (n = 156)	Odds ratio	*P* value
CR+CRi	47.7%	33.3%	1.77 (1.11, 2.81)	0.016
HSCT rate	34.0%	25.0%	1.54 (0.92, 2.56)	0.098
Deaths ≤30 days*	5.9%	10.3%		
Deaths ≤60 days*	13.7%	21.2%		

1. Lancet JE, et al. *Lancet Hematol* 2021;8:e481–91. **2.** Lancet JE, et al. *J Clin Oncol* 2018;36(26):2684-2692.

Overall survival from date of HSCT: 5-year results[1]

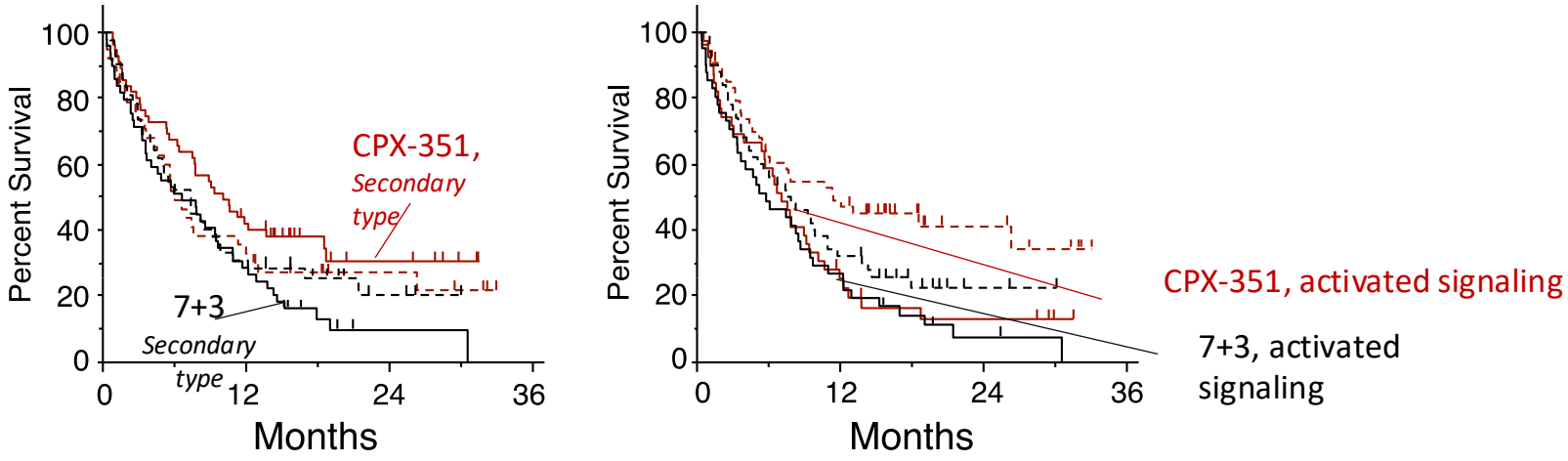


3-year Kaplan-Meier-estimated survival rates are shown with 95% CI. 5-year estimates were not available as the follow-up time from the date of HSCT is less than 5 years. 7+3=cytarabine and daunorubicin. HSCT=haematopoietic stem-cell transplantation. NE=not estimable.

1. Lancet JE, et al. *Lancet Hematol* 2021;8:e481–91. **2.** Lancet JE, et al. *J Clin Oncol* 2018;36(26):2684-2692.

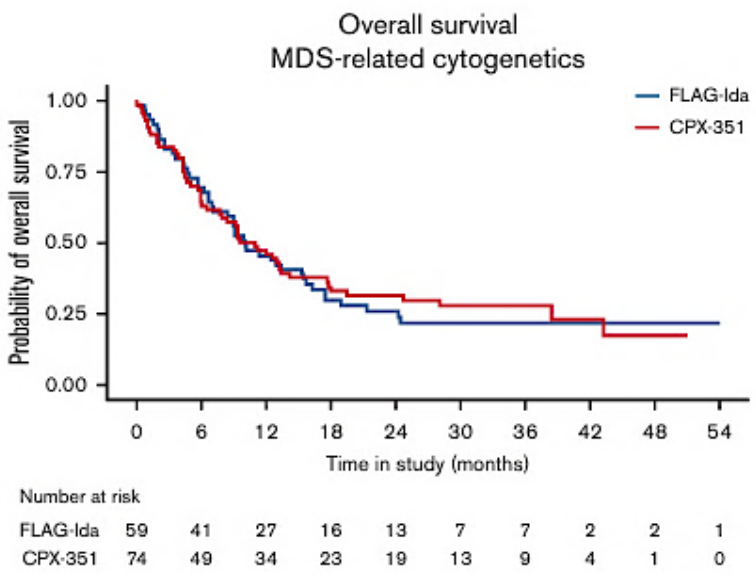
Overall Survival in Pivotal Phase 3 Study of CPX-351 by Secondary-type and Activated Signaling Mutations

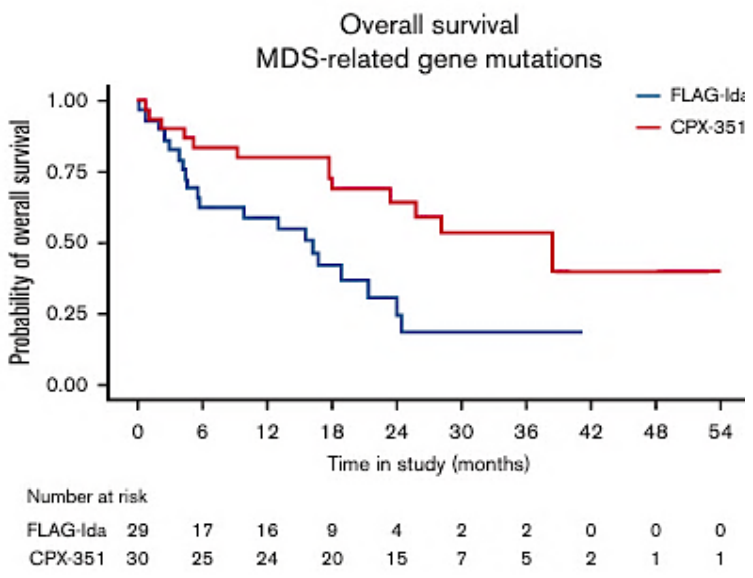
		Secondary-Type *SRSF2, U2AF1, SF3B1, ZRSR2, ASXL1, BCOR, EZH2, STAG2*		*Activated Signaling* *FLT3, NRAS, KRAS, PTPN11, NF1, CBL, RIT1*	
		Median Survival	(95% CI)	Median Survival	(95% CI)
CPX-351	mutated	10.1	(6.4-18.5)	7.0	(3.8-9.3)
	unmutated	6.0	(4.3-12.0)	11.3	(5.6-NR)
7+3	mutated	6.6	(3.6-9.5)	5.7	(3.2-8.6)
	unmutated	7.3	(4.3-9.8)	7.6	(4.3-10.9)

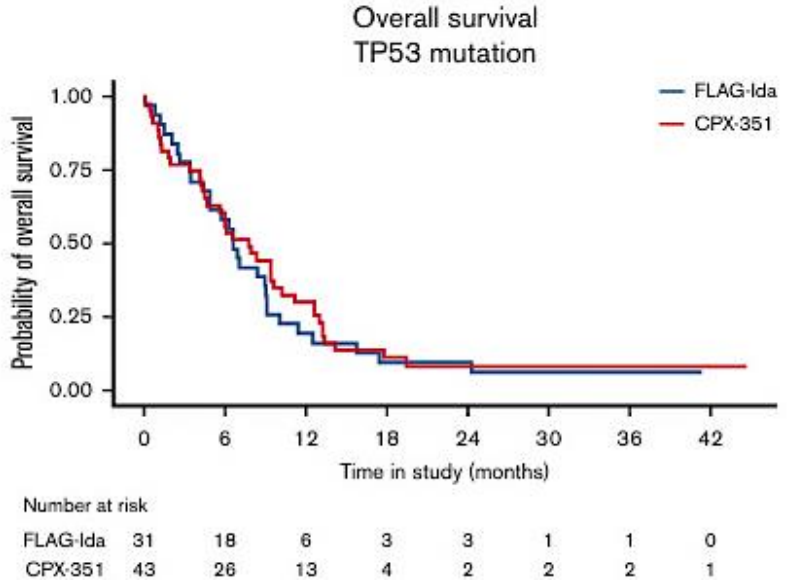


Lindsley RC et al. ASH 2019; please see updated and more complete results:
Shimony S Abstract #60, Sat AM (Saturday, December 7, 2024: 10:45 AM)

A randomized comparison of CPX-351 and FLAG-Ida in adverse karyotype AML and high-risk MDS: UK NCRI AML19 trial

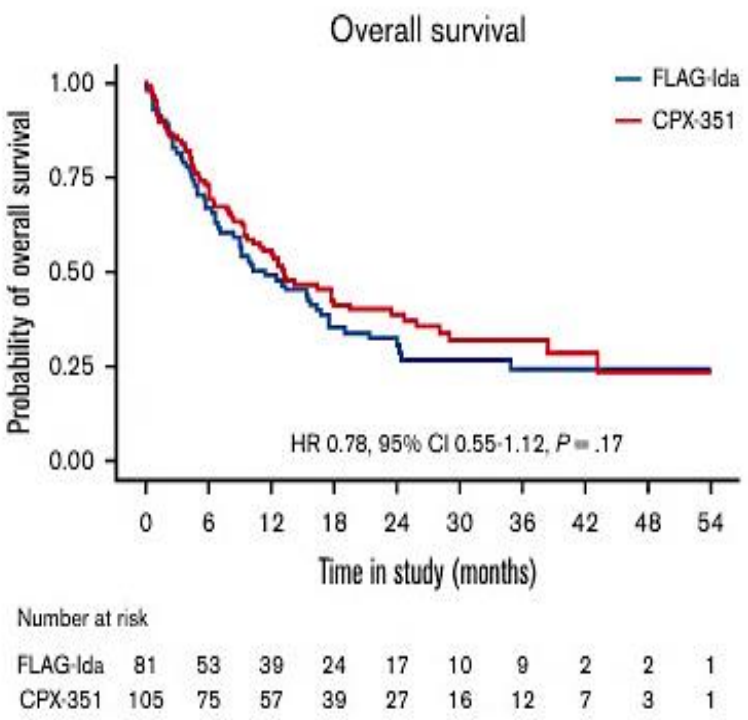


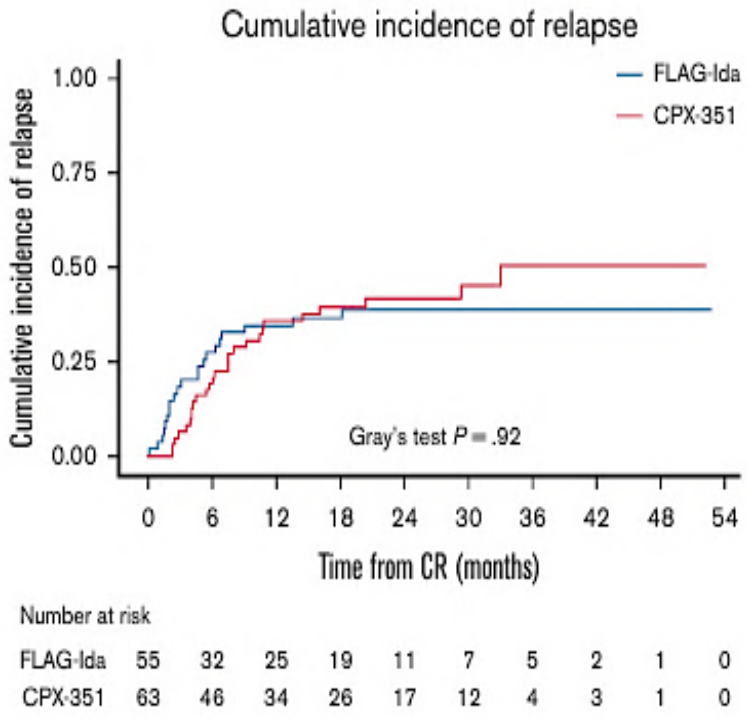


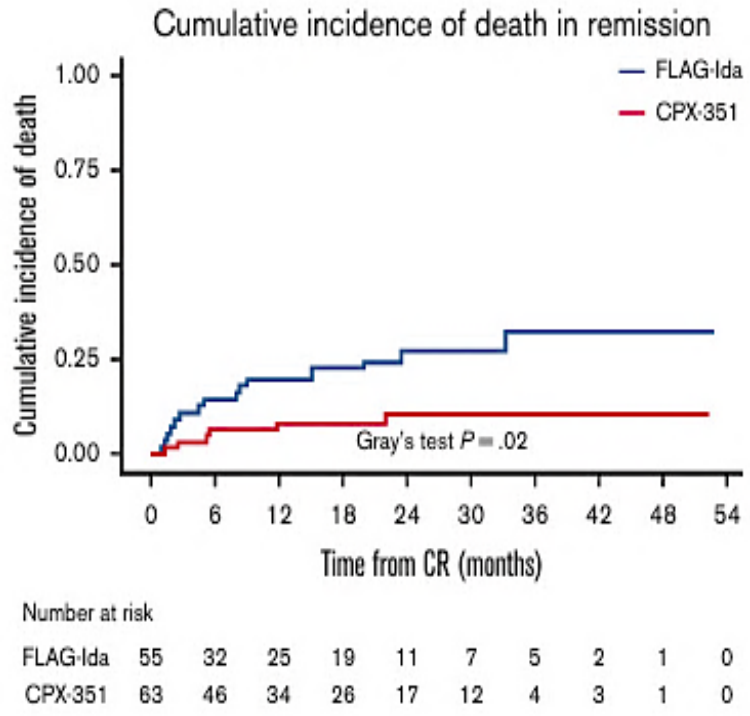


Othman J, et al. *Blood Adv.* 2023; 7(16): 4539-49

A randomized comparison of CPX-351 and FLAG-Ida in adverse karyotype AML and high-risk MDS: UK NCRI AML19 trial

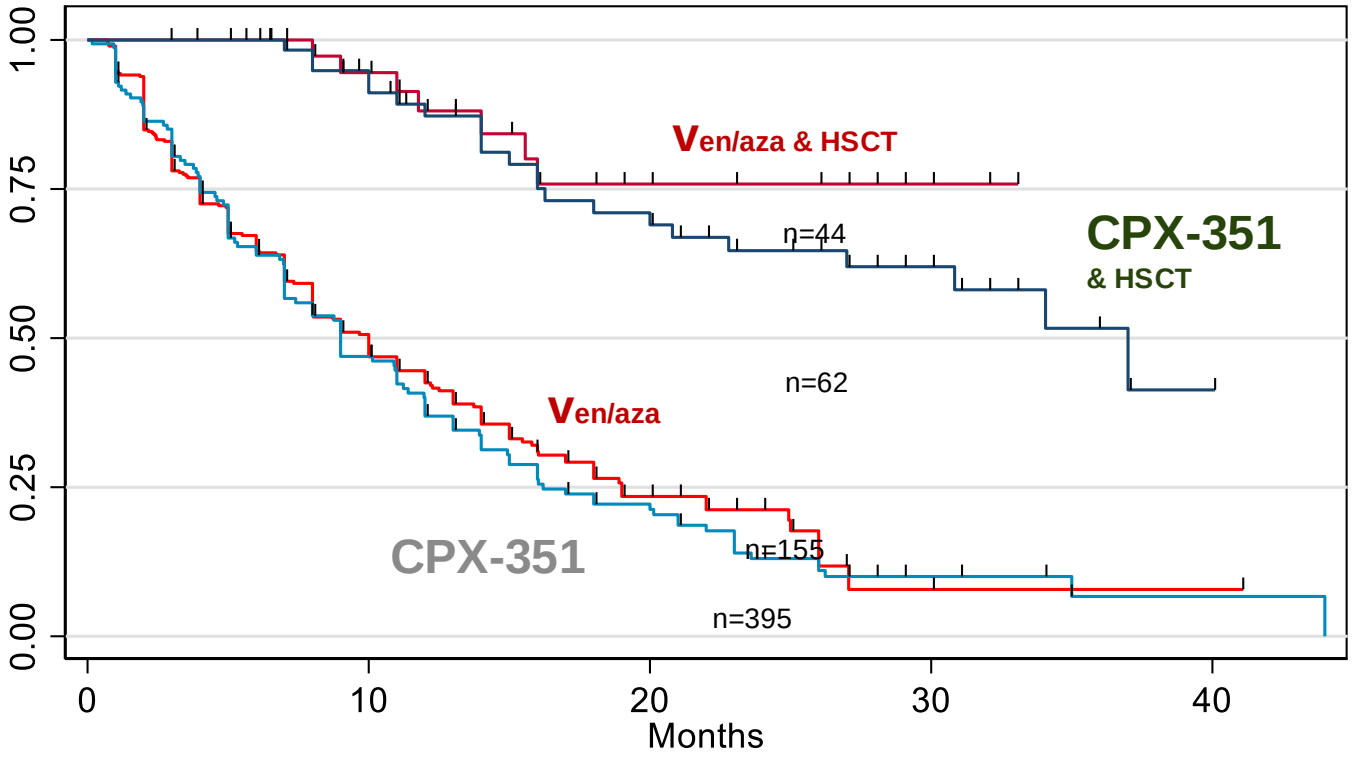






Othman J, et al. *Blood Adv.* 2023; 7(16): 4539-49

Transplant is Critical for Survival Regardless of Initial Treatment; AZA/Ven v CPX retrospective



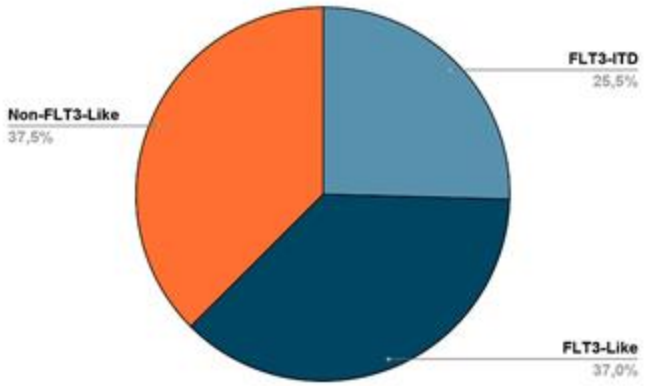
	Venetoclax / Azacitidine	CPX-351
Number (%)	44 (10%)	61 (28%)
Median Time to Transplant (range)	186 days (87 - 578)	171 days (34 - 903)
Median OS w/ HSCT	NR	37 mos
Median OS w/o HSCT	10 mos	9 mos

Matthews, A , et al , Blood Adv 2022; 6: 3997-4005

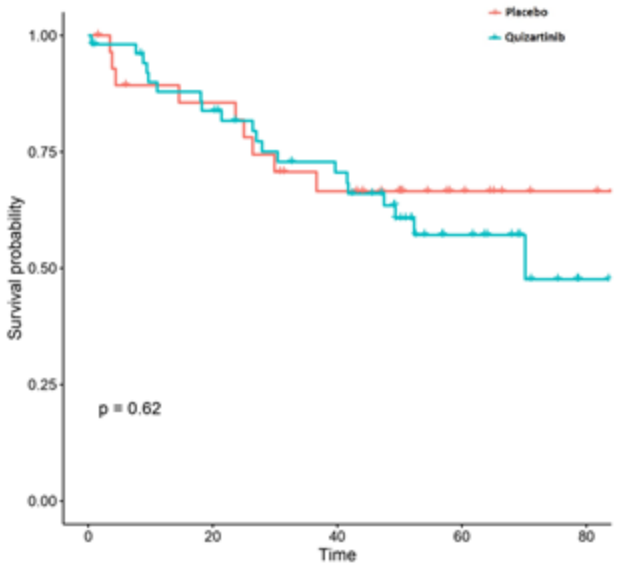
3 (ida) +7 +/- Quizartinib in newly diagnosed AML ages 18-70 **without** *FLT3*-ITD

The QUIWI trial: maybe a new approach if confirmed

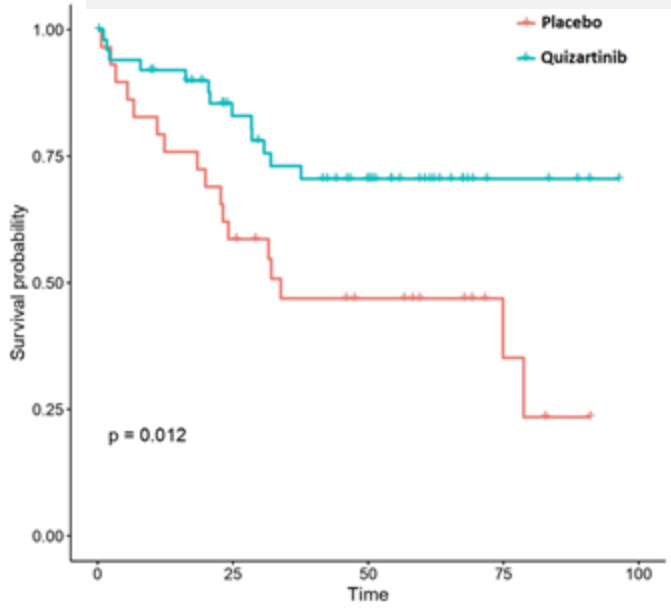
OS Benefit of adding quizartinib based on “FLT3-Like” Signature



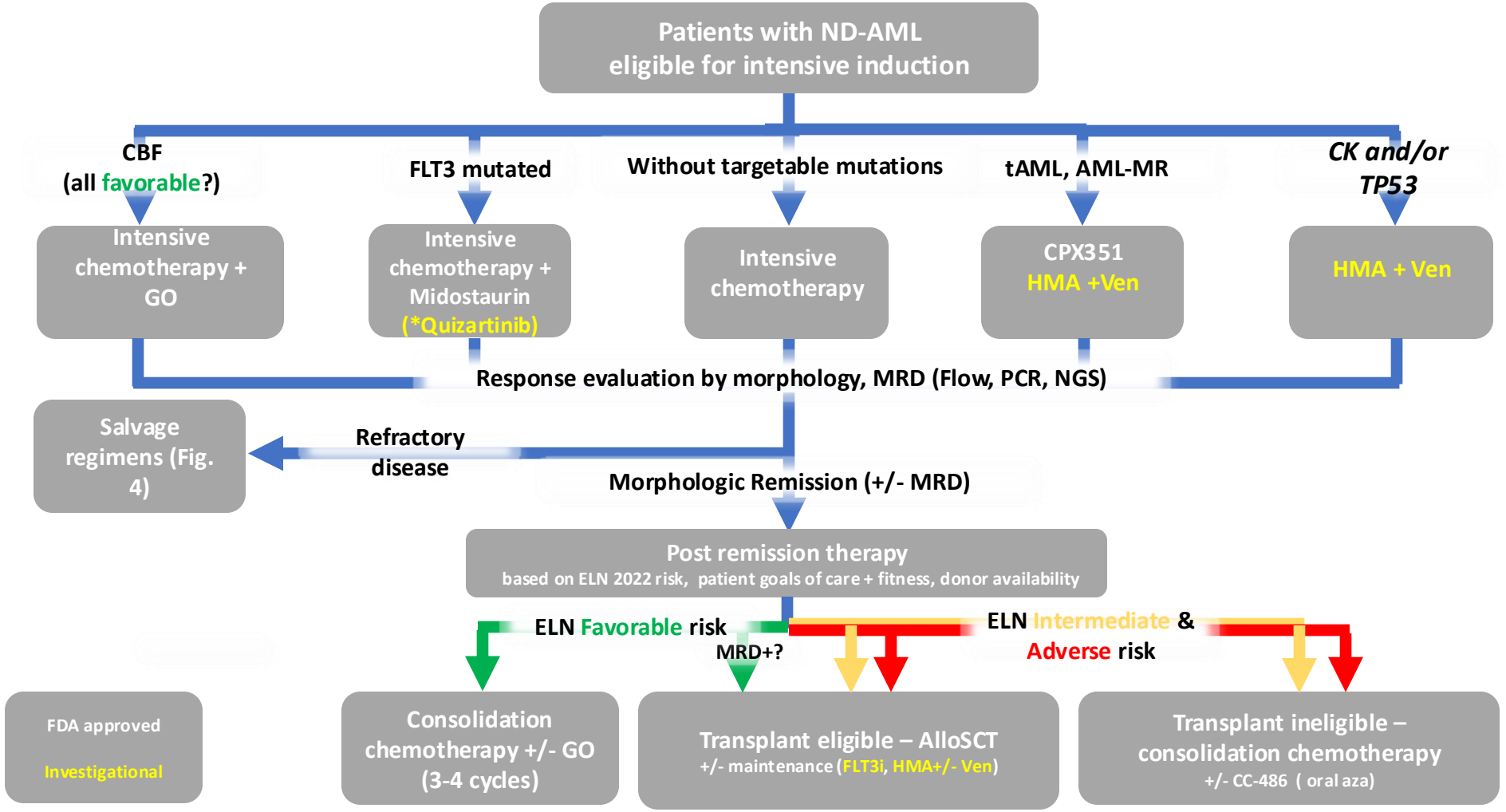
Non FLT3-Like



FLT3-Like

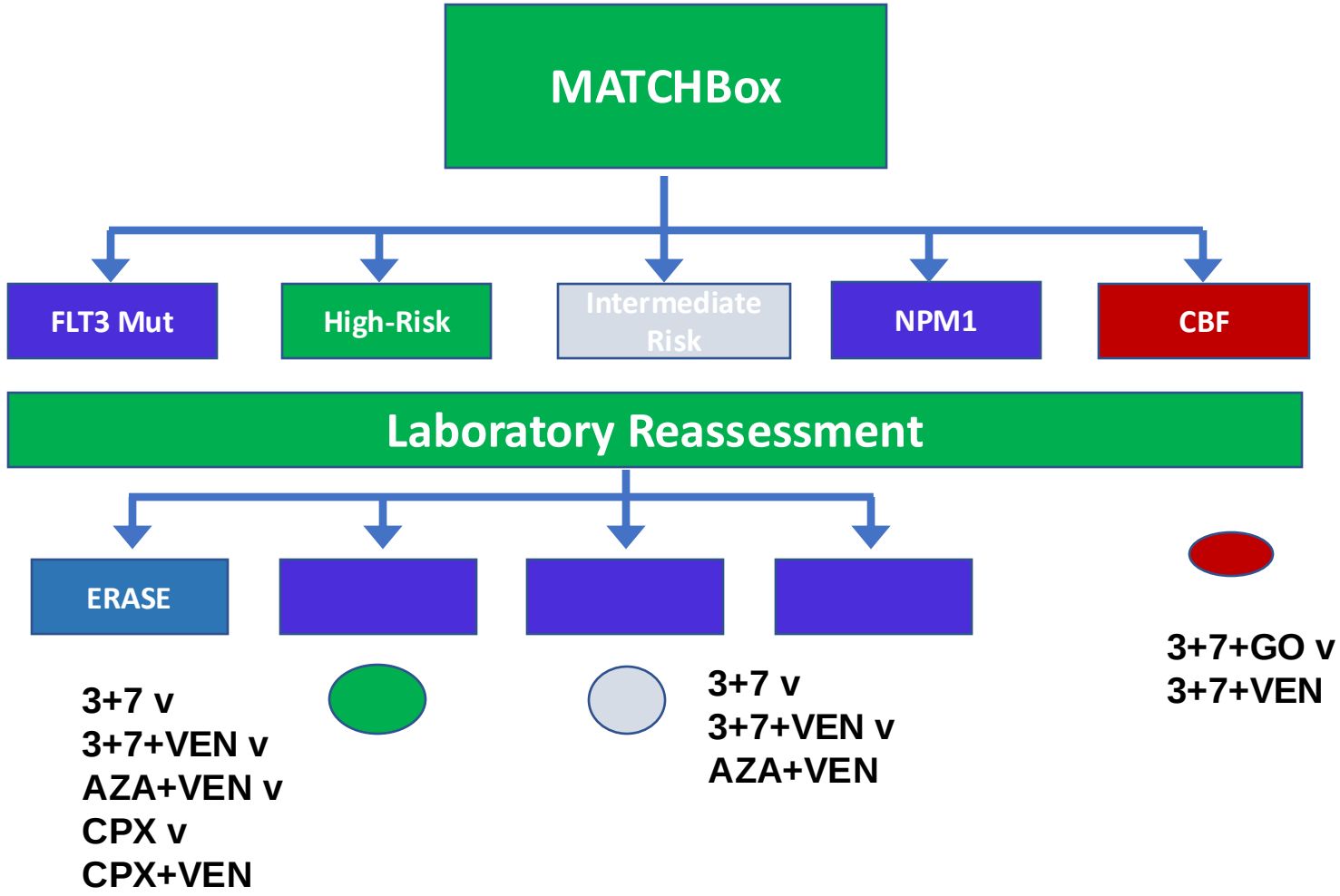


Mosquera, A et al, ASH 2023; and see Montesinos P, et al, abstract #1512 (Saturday, December 7, 2024, 5:30 PM-7:30 PM)



Shimony S, Stahl M, Stone R, Am J Hematol, 2023

First Generation Studies in the Younger MyeloMatch Basket



Questions from General Medical Oncologists/Hematologists

- **Which initial treatment would you most likely recommend for a 65-year-old man with AML with a PS of 1 and pancytopenia, 35% marrow myeloblasts, a complex karyotype and a TP53 mutation?**
- **A 65-year-old patient with a h/o MDS treated with Luspatercept, now with AML with 35% marrow blasts, trisomy 8 and TP53, ASXL1 and U2AF1 mutations (VAFs 45, 20 and 45, respectively). Which therapy would you recommend?**
- **Can we give azacitidine and venetoclax induction for young and fit patients?**

Questions from General Medical Oncologists/Hematologists

- How do you choose between 7+3 vs other regimens such as FLAG-Ida or FLAG-Ida + venetoclax in younger patients?
- Is FLAG-Ida + venetoclax an option for patients who relapse after 7+3?

Agenda

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

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

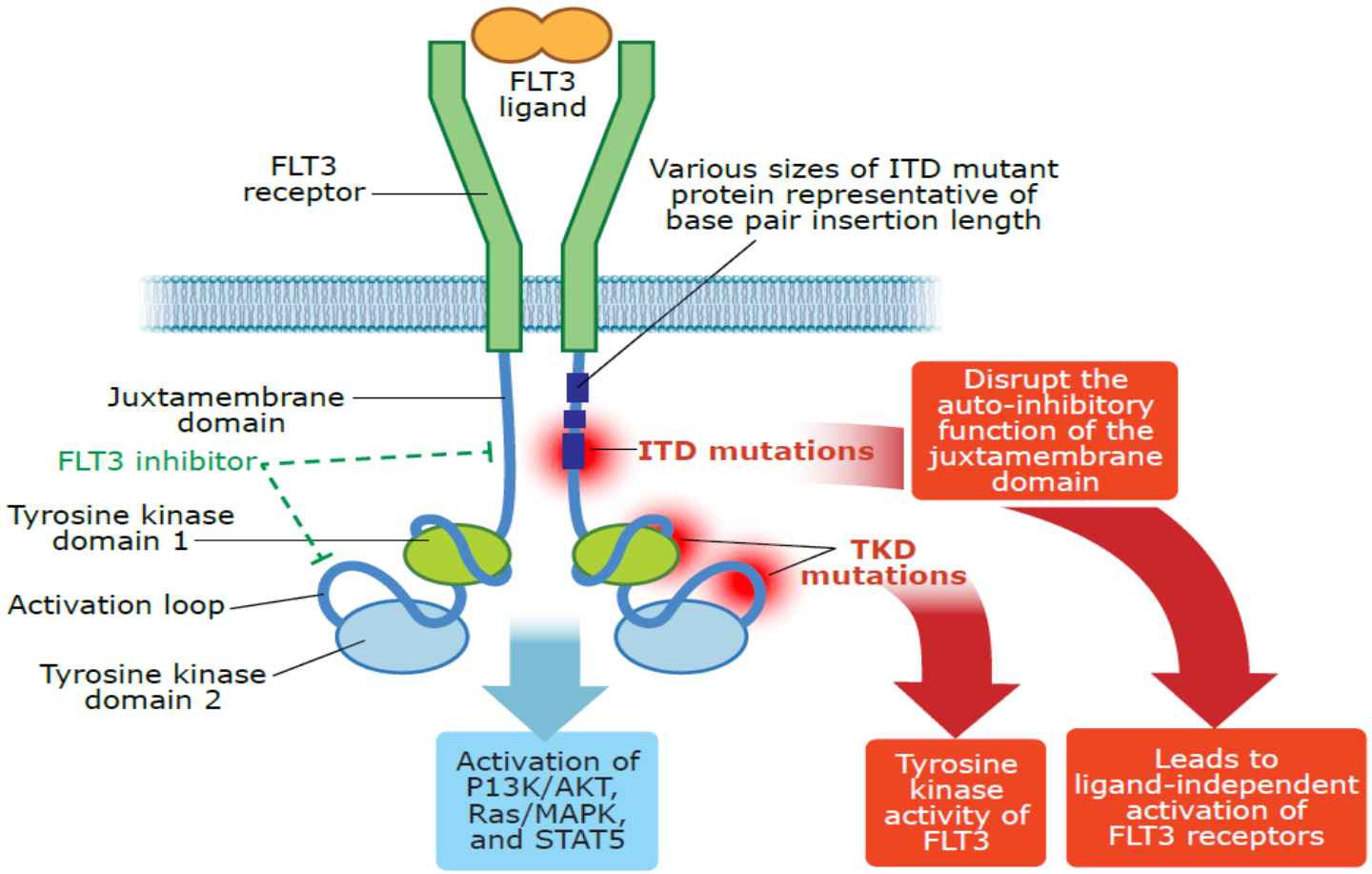
Module 5: Potential Role of Menin Inhibitors and Other Novel Agents in the Treatment of AML — Dr Wang

Penn Medicine
Abramson Cancer Center
Leukemia Program

Role of FLT3 Inhibitors in AML Management

Alexander E. Perl, MD
Associate Professor of Medicine
Perelman School of Medicine at the University of Pennsylvania

Mutated FLT3: the target



Incidence

- FLT3-ITD 20-25%
- FLT3-TKD 5-10%

Clinical features

- Leukocytosis
- High marrow blast percent
- Proliferative disease

Genetic associations

- Diploid karyotype
- NPM1 mutation
- t(6;9)
- t(15;17)

Frequently sub-clonal

- gained at relapse/progression
- Sometimes lost at relapse/progression

ITD= internal tandem duplication, first described in 1996
TKD= tyrosine kinase domain, first described in 2001

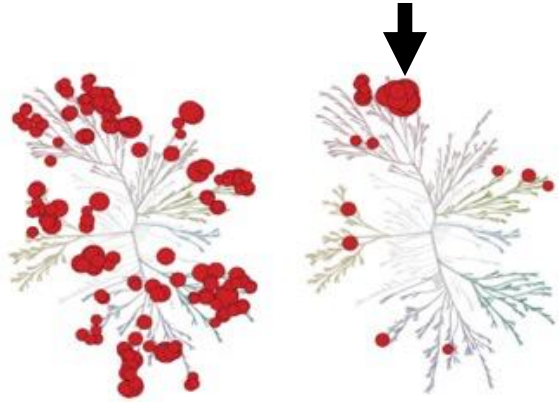
figure courtesy of Ashkan Emadi

ASH 2024: subclinical FLT3-ITD+ incidence and outcomes
Olson P, et al. #847 Monday 2:45PM Oral presentation

How exactly do FLT3 inhibitors work?

		IC_{50} (medium)	IC_{50} (plasma)	Single agent clinical activity	Kinase inhibition
1st generation	Lestaurtinib	2 nM	700 nM	-	**Type 1**
	Midostaurin	6 nM	~1000 nM	-	**Type 1**
	Sorafenib	3 nM	~265 nM	+/-	**Type 2**
2nd generation	Quizartinib	1 nM	18 nM	+	**Type 2**
	Crenolanib	2 nM	48 nM	+	**Type 1**
	Gilteritinib	3 nM	43 nM	+	**Type 1**

Class 3 RTK's:
FLT3, KIT, CSF1R,
PDGFRA/B

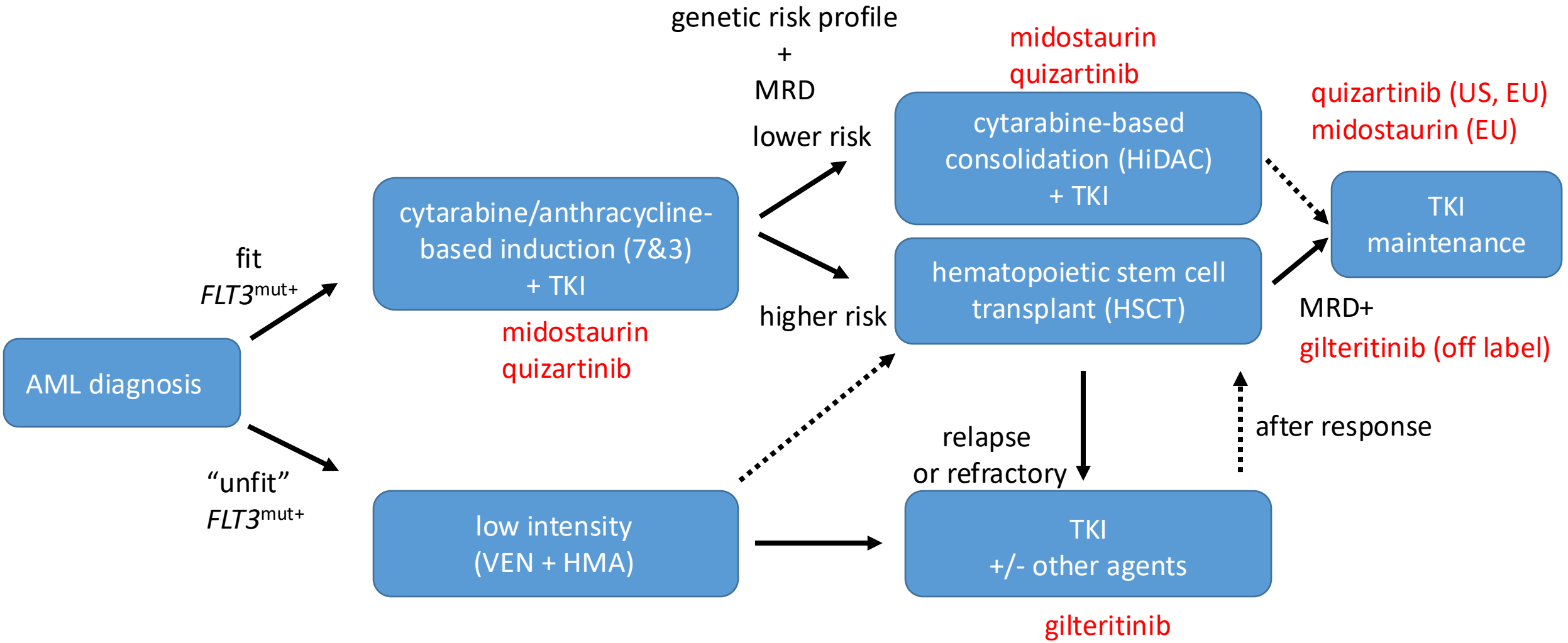


Midostaurin **Quizartinib**

- Direct antileukemic cytotoxicity (single agent)
  - apoptosis and differentiation
  - requires potent, sustained FLT3 kinase inhibition
- potentiation of cytotoxic chemotherapy (combination therapy)
  - this can be quantified by MRD
  - requirement for potent, sustained FLT3 kinase inhibition less clear
  - may arise from blocking of FLT3 ligand stimulation (*FLT3*-WT or *FLT3*$^{mut+}$)
- Immunomodulatory effects
  - NK, dendritic cells
  - IL-15 mediated potentiation of GVL post-HSCT

Pratz KW, et al. Blood 2010;115(7):1425-32
Zarrinkar PP, et al. Blood. 2009 Oct 1;114(14):2984-92
Galanis A, et al. Blood 2014 Jan 2;123(1):94-100
Levis M, Perl AE. Blood Adv. 2020 Mar 24;4(6):1178-1191
Smith CC, et al. Nature. 2012 Apr 15;485(7397):260-3
Tarver TC, et al. Blood Adv. 2020 Feb 11;4(3):514-524
Sexauer A, et al. Blood. 2012 Nov 15;120(20):4205-14
Whartenby K, et al. PNAS. 2005 Nov 15;102(46):16741-6
Mathew NR, et al. Nat Med. 2018 Mar;24(3):282-291.

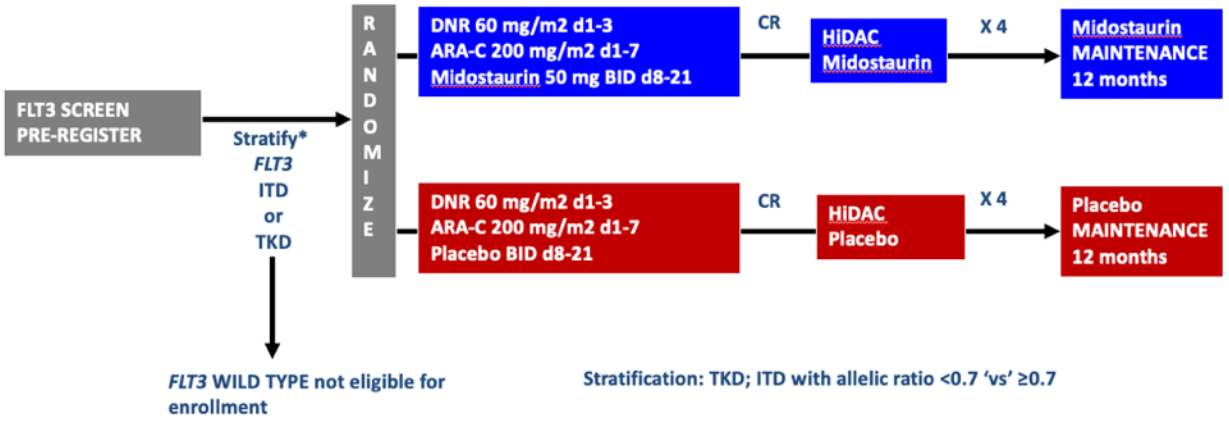
The current AML treatment approach for *FLT3*$^{mut+}$ AML



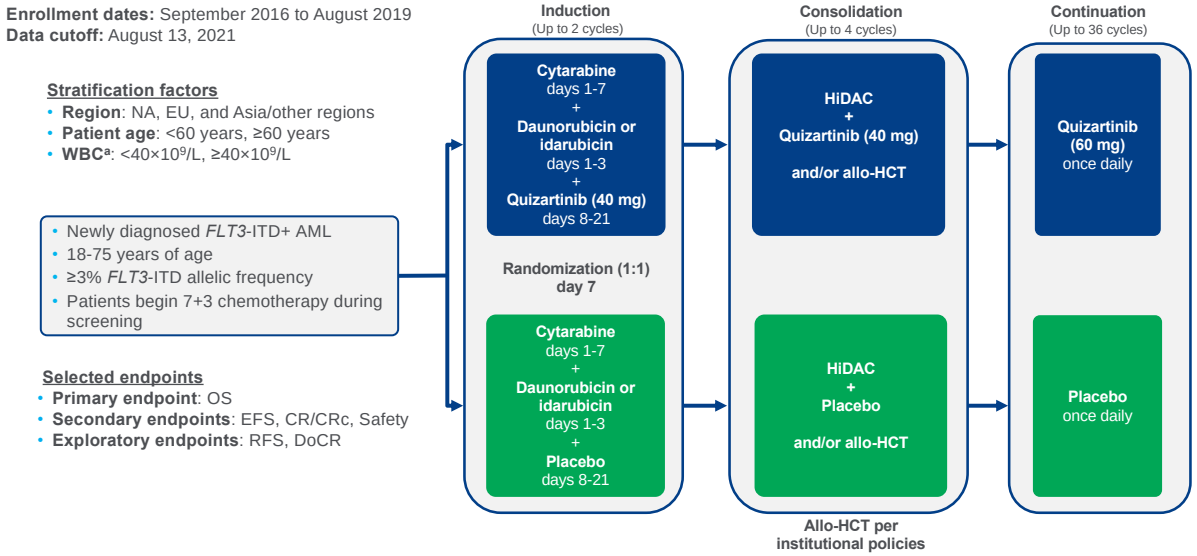
Is there one FLT3 inhibitor to rule them all?

Comparing RATIFY and QuANTUM-First: design/eligibility

RATIFY/C10603



QuANTUM-First



Primary endpoint: OS

- 3277 patients were screened, 717 were randomized (555 with FLT3-ITD)
- FLT3-ITD and TKD mutations (cutoff >0.05 allelic ratio for either)
- Median age 48 years (range 18-60.9)
- Median follow-up 59 months
- HSCT was an off-protocol therapy
- maintenance given post-consolidation only
- MRD not collected

Primary endpoint: OS

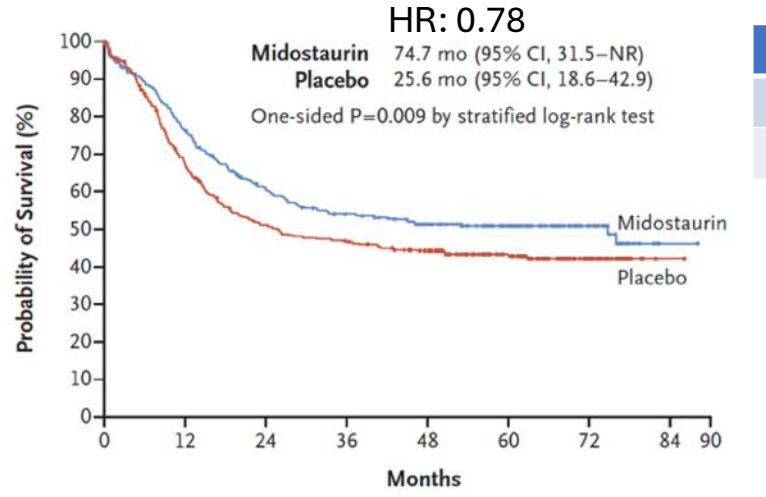
- 3468 patients were screened, and 539 with FLT3-ITD were randomized
- FLT3-ITD only (cutoff of 3% VAF)
- Median age 56 (range 20-75)
- Median follow-up 39 months
- HSCT allowed on study
- maintenance given both post-HSCT and post-consolidation
- prospective monitoring of MRD

ASH 2024: Ten-year follow up from RATIFY
(Stone RM, et al. #218: Saturday 2:15 PM oral presentation)

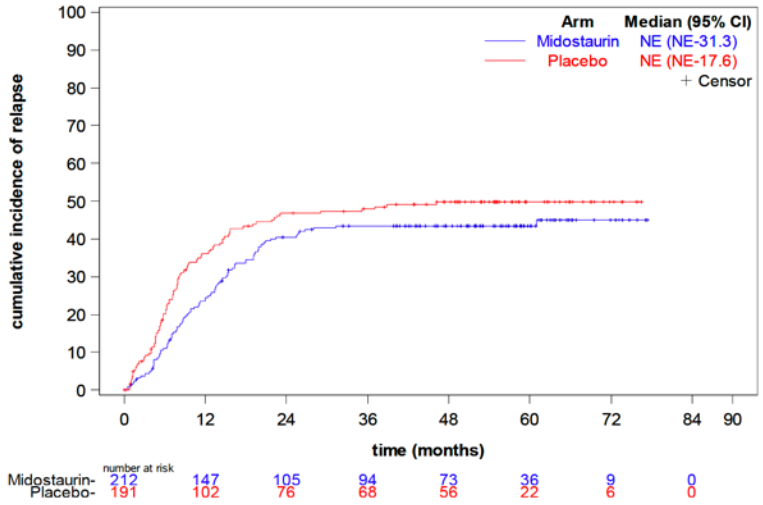
Stone RM, et al. *N Engl J Med.* 2017 Aug 3;377(5):454-464
Erba HP, et al. *Lancet*. 2023 May 13;401(10388):1571-1583

Response, relapse, and survival

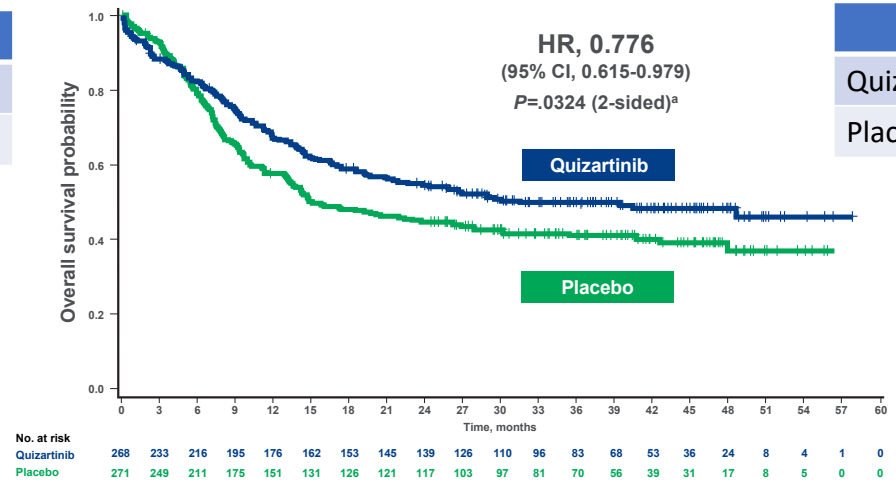
RATIFY (midostaurin)



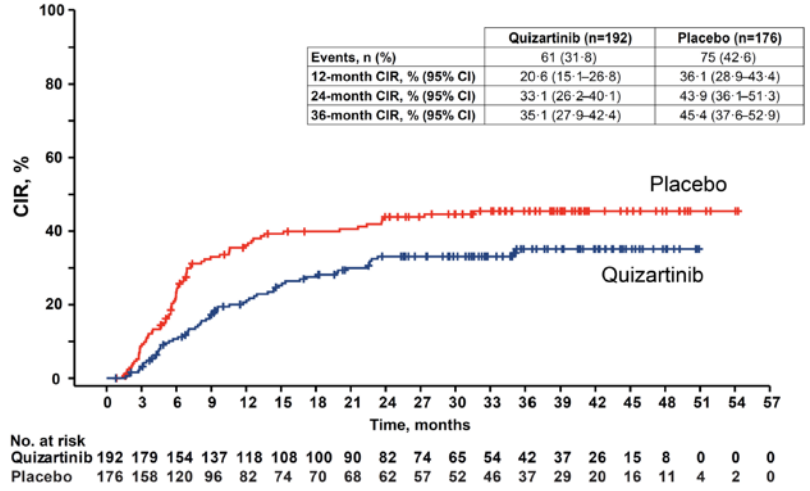
	CR
Midostaurin	68%
Placebo	61%



QuANTUM-First (quizartinib)



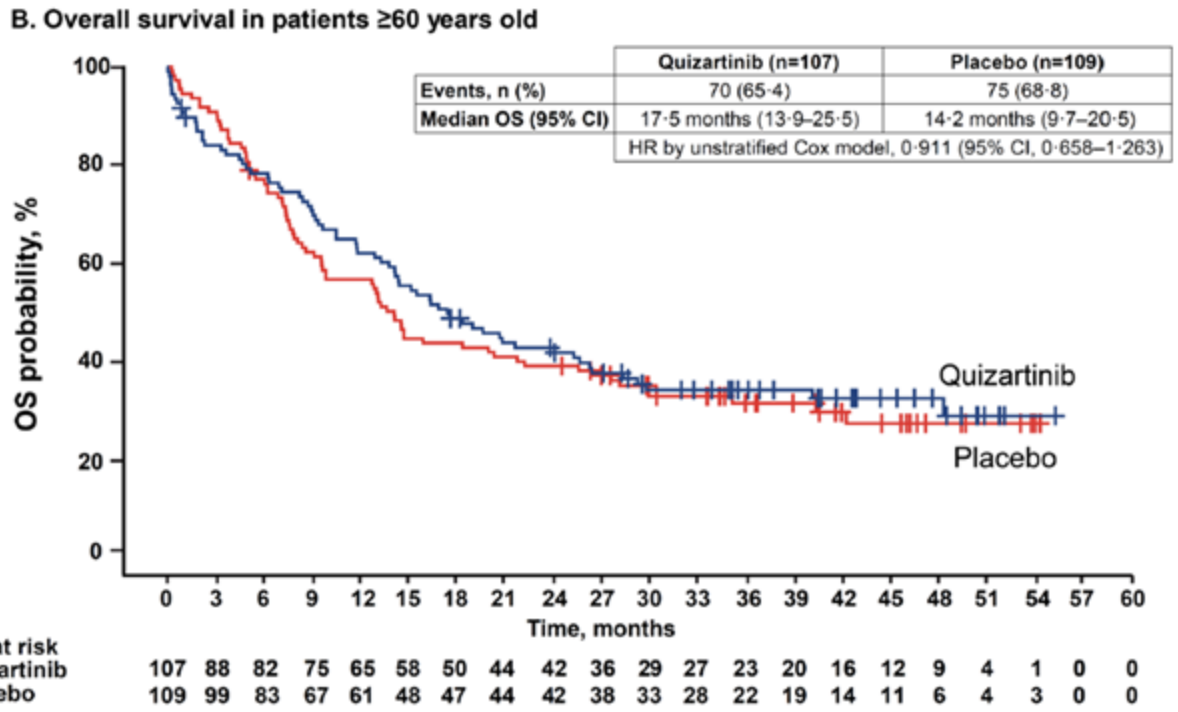
	CR	CR/CRi
Quizartinib	54.9%	71.6
Placebo	55.4%	64.9



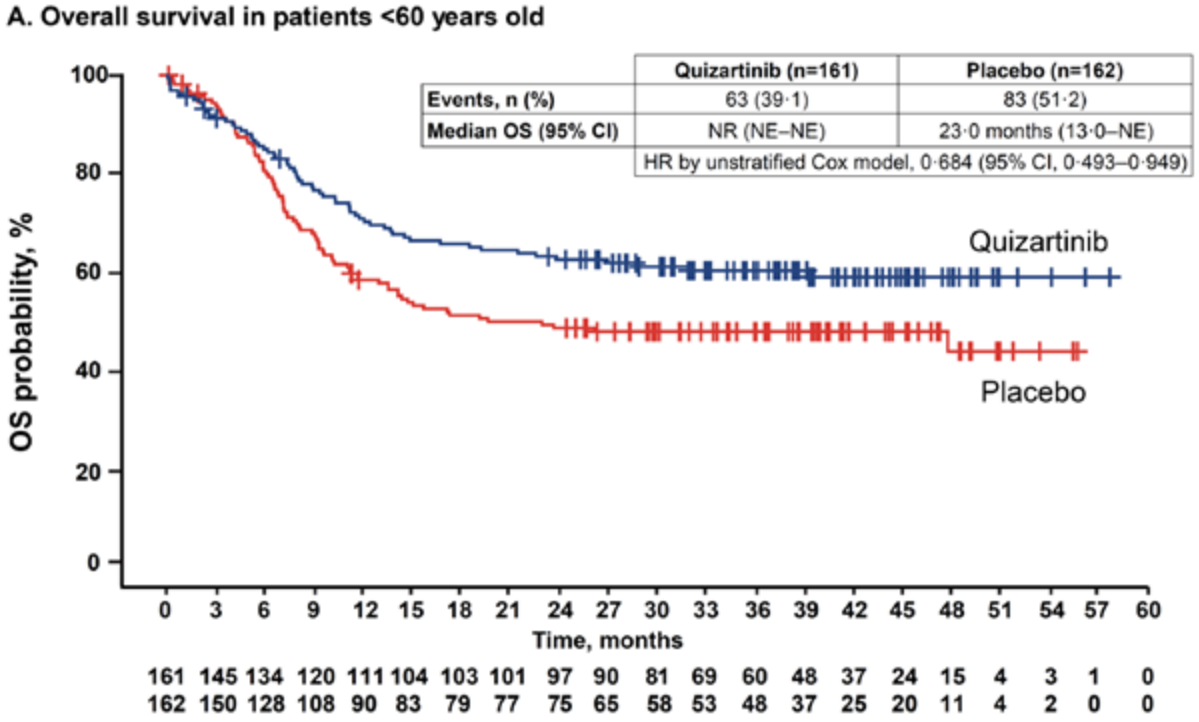
Stone RM, et al. *N Engl J Med.* 2017 Aug 3;377(5):454-464
Erba HP, et al. *Lancet*. 2023 May 13;401(10388):1571-1583

Younger patients particularly benefit from quizartinib

RATIFY



QuANTUM-First



QuANTUM-First 60-day mortality: quizartinib 7.5%, placebo 4.9% (mostly infections)
ANC recovery was 7 days longer in quiz arm; platelets 2 days longer in quiz arm

ASH 2024: QuANTUM-First analysis of outcomes by co-mutations
Levis MJ, et al. #848 Monday 3PM oral presentation

Stone RM, et al. *N Engl J Med.* 2017 Aug 3;377(5):454-464
Erba HP, et al. *Lancet*. 2023 May 13;401(10388):1571-1583

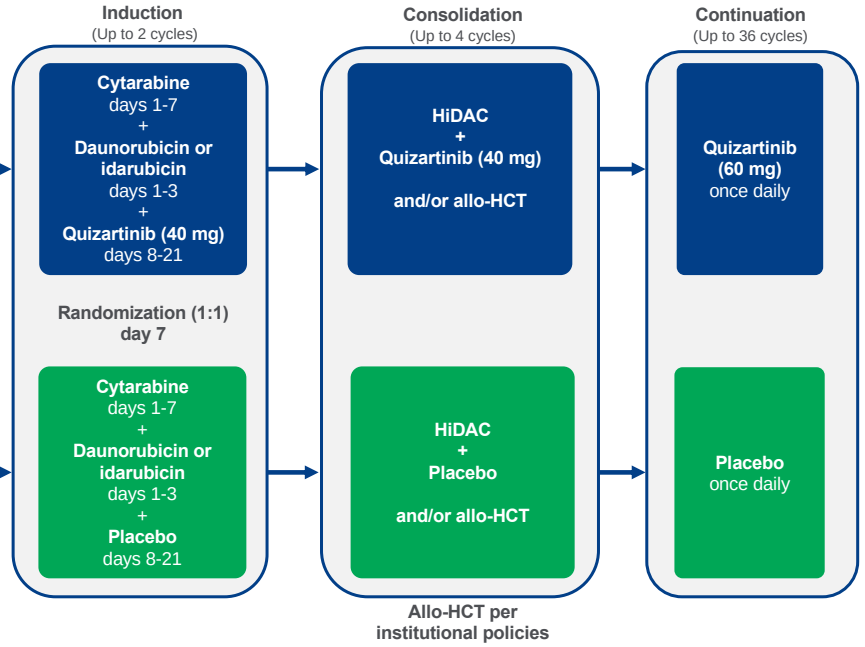
QuANTUM-First: Achievement of CRc with MRD Negativity (<10^{-4} Cutoff) by the End of Induction Correlated with Longer OS Regardless of Treatment Arm

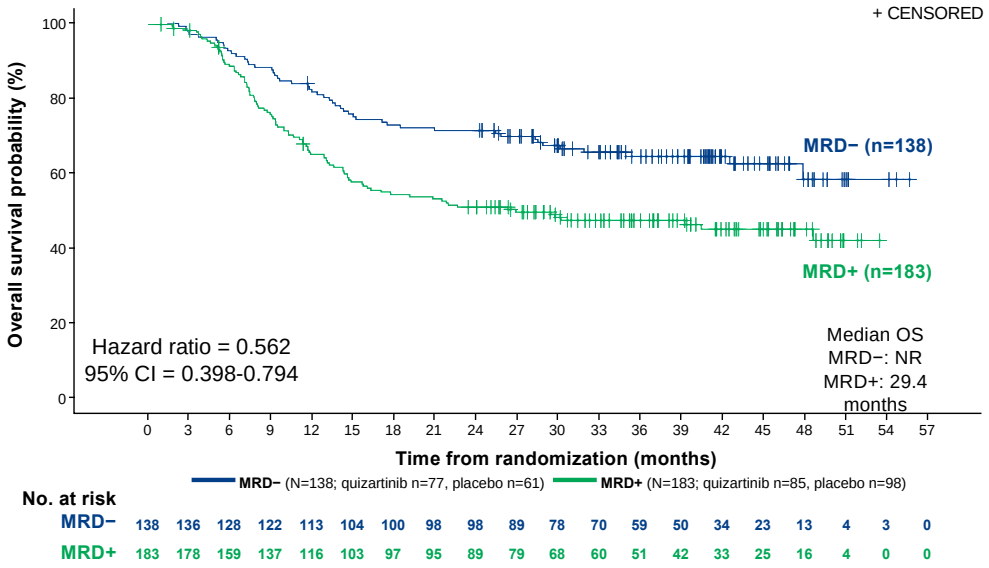
Enrollment dates: September 2016 to August 2019
Data cutoff: August 13, 2021

Stratification factors
- **Region**: NA, EU, and Asia/other regions
- **Patient age**: <60 years, ≥60 years
- **WBC**[a]: <40×10^9/L, ≥40×10^9/L

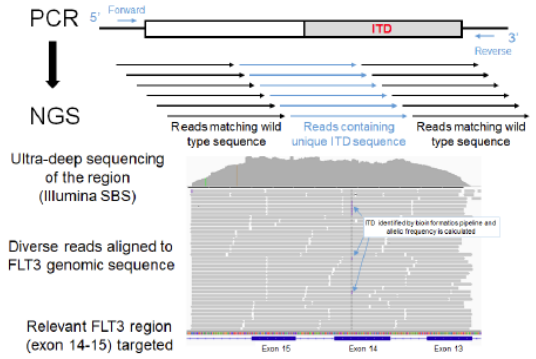
- Newly diagnosed *FLT3*-ITD+ AML
- 18-75 years of age
- ≥3% *FLT3*-ITD allelic frequency
- Patients begin 7+3 chemotherapy during screening

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





MRD assay for FLT3-ITD:WT burden

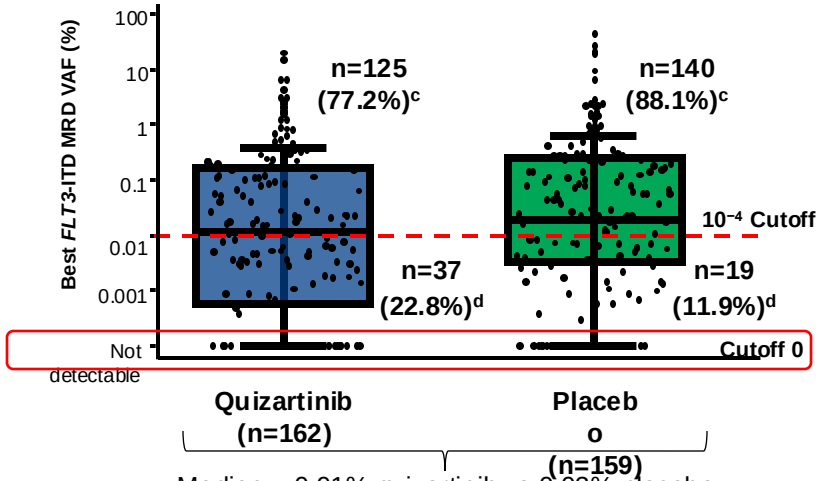


quantitative to 1 x 10^{-4}
limit of ITD detection: 2 x 10^{-6}

Levis MJ, et al. *Blood*. 2020 Jan 2;135(1):75-78
Erba HP, et al. *Lancet*. 2023 May 13;401(10388):1571-1583

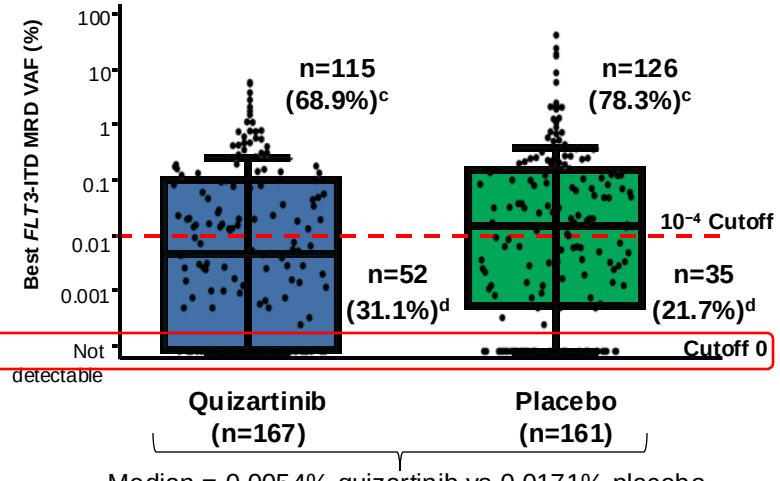
Across the Treatment Course, Quizartinib Leads to Deeper Responses and More Frequently Eliminates Detectable MRD Than Placebo

CRc After Induction
(1 or 2 cycles)



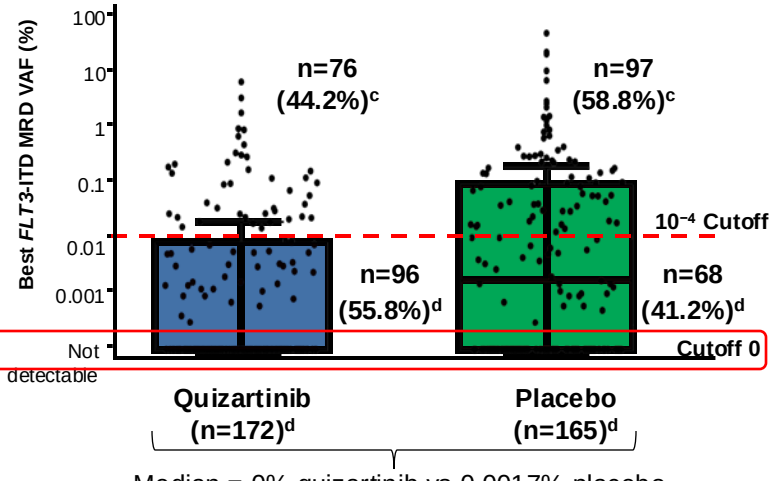
Median = 0.01% quizartinib vs 0.03% placebo
Nominal *P* value (2-sided) = 0.0251

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

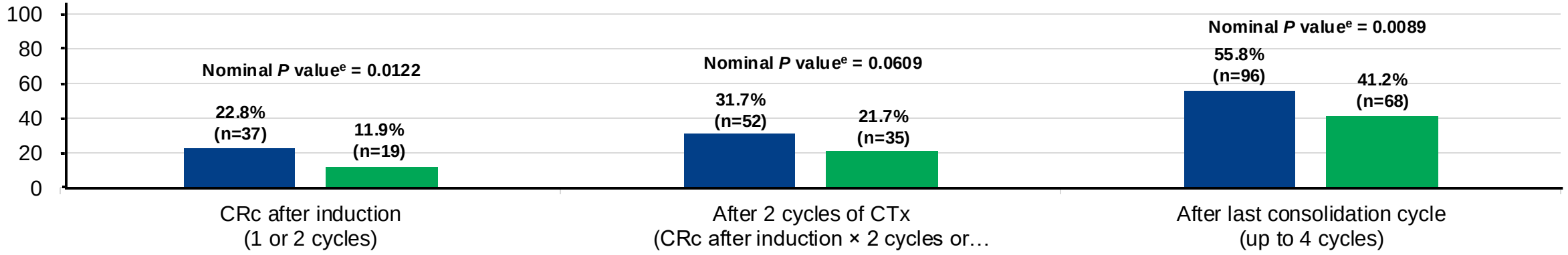


Median = 0.0054% quizartinib vs 0.0171% placebo
Nominal *P* value (2-sided) = 0.0540

After Last Consolidation Cycle[b]
(up to 4 cycles)



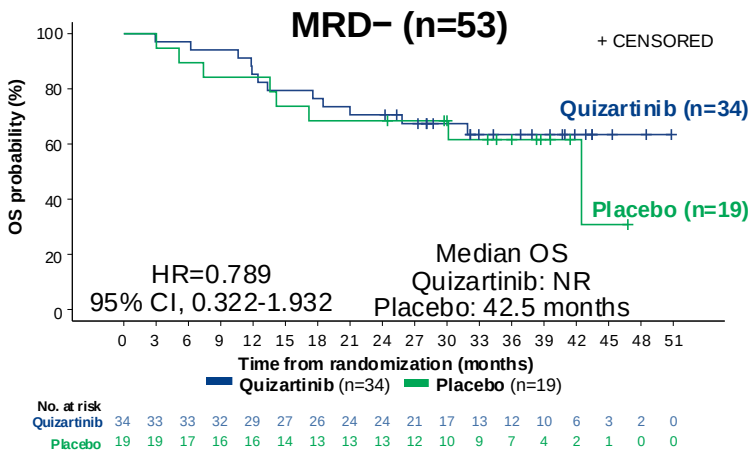
Median = 0% quizartinib vs 0.0017% placebo
Nominal *P* value (2-sided) = 0.0006

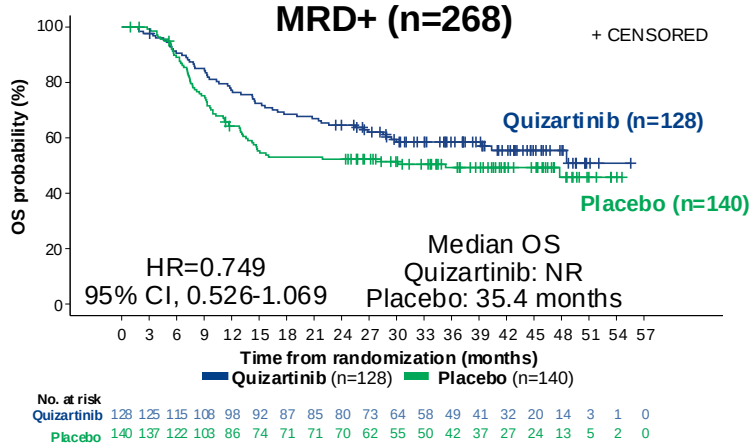


Perl AE, et al. ASH 2023 Abstract #832

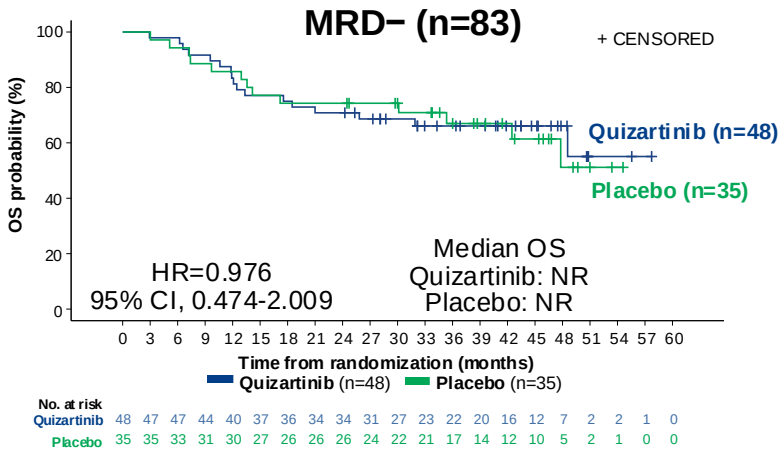
FLT3-ITD MRD Reduction Predicts Survival Across Therapy Time Points (Cutoff 0)

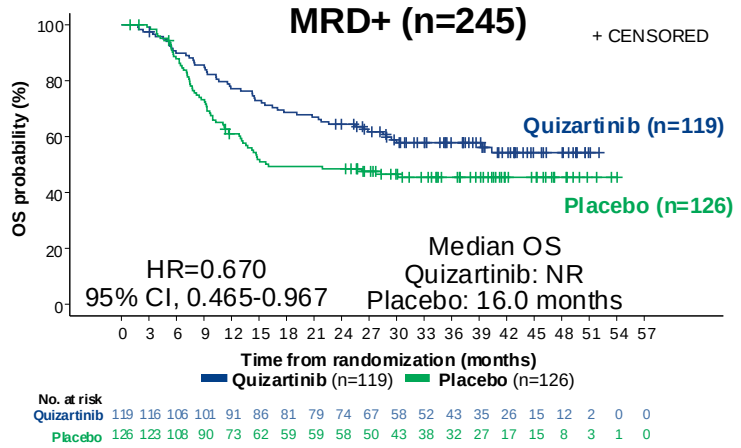
CRc After Induction
(1 or 2 cycles)



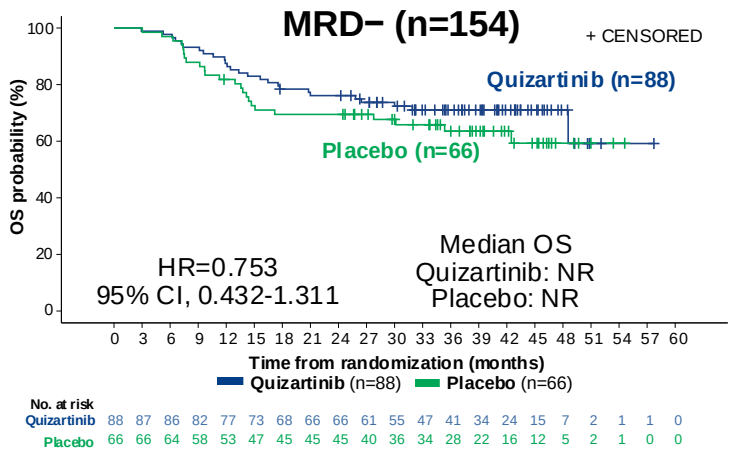


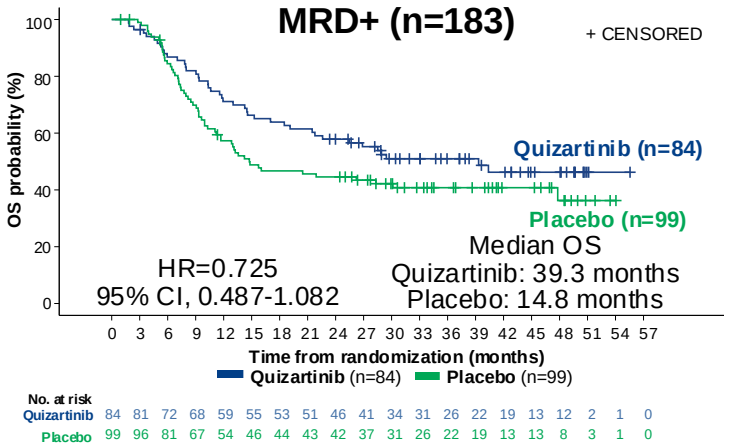
After 2 Cycles of CTx[a]
(CRc after induction × 2 cycles or
CRc after induction #1 + consolidation #1)





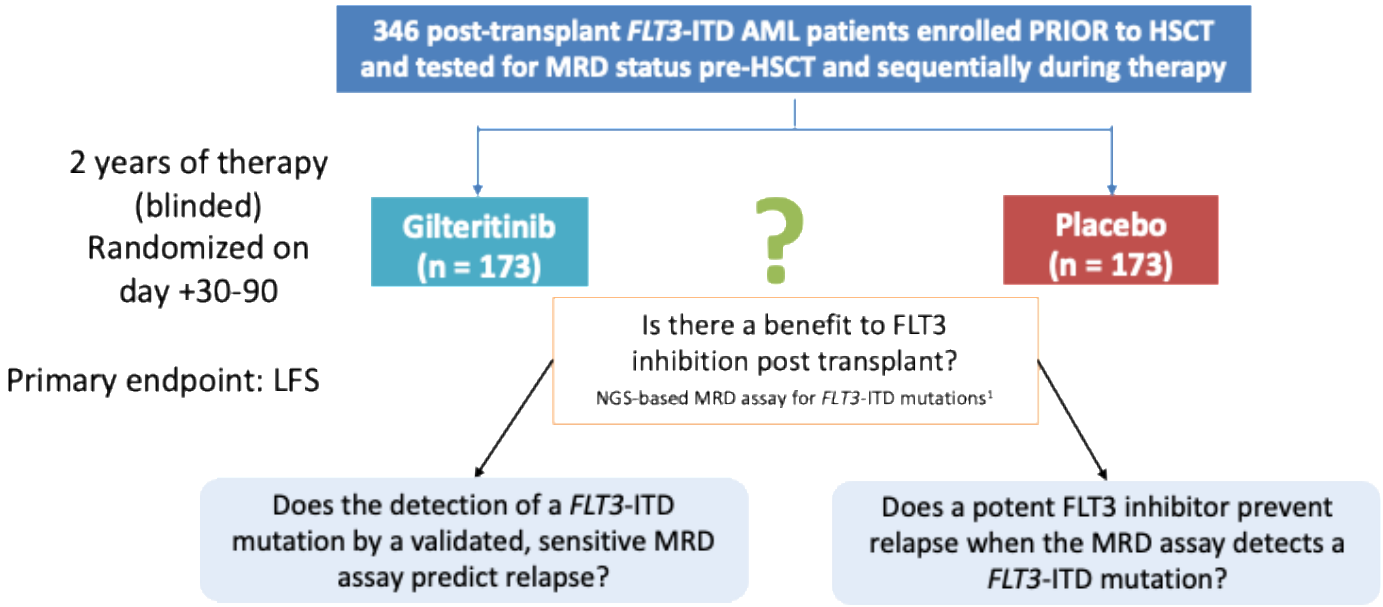
After Last Consolidation Cycle[b]
(up to 4 cycles)

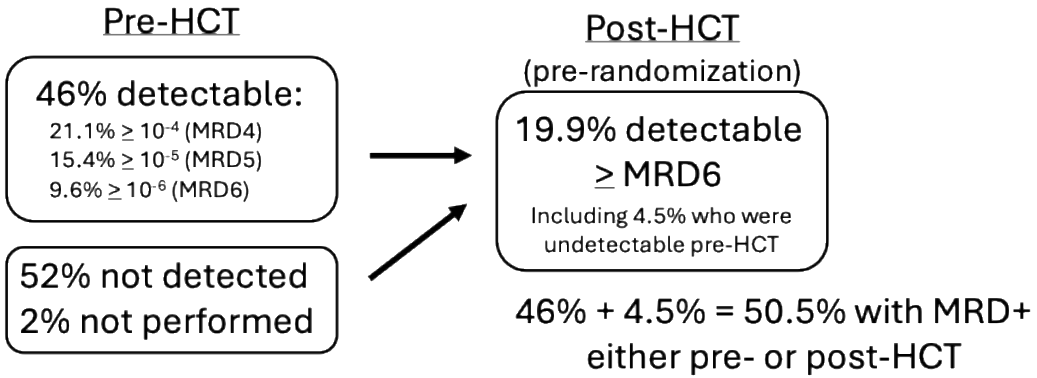




Perl AE, et al. ASH 2023 Abstract #832

BMT-CTN 1506/MORPHO study





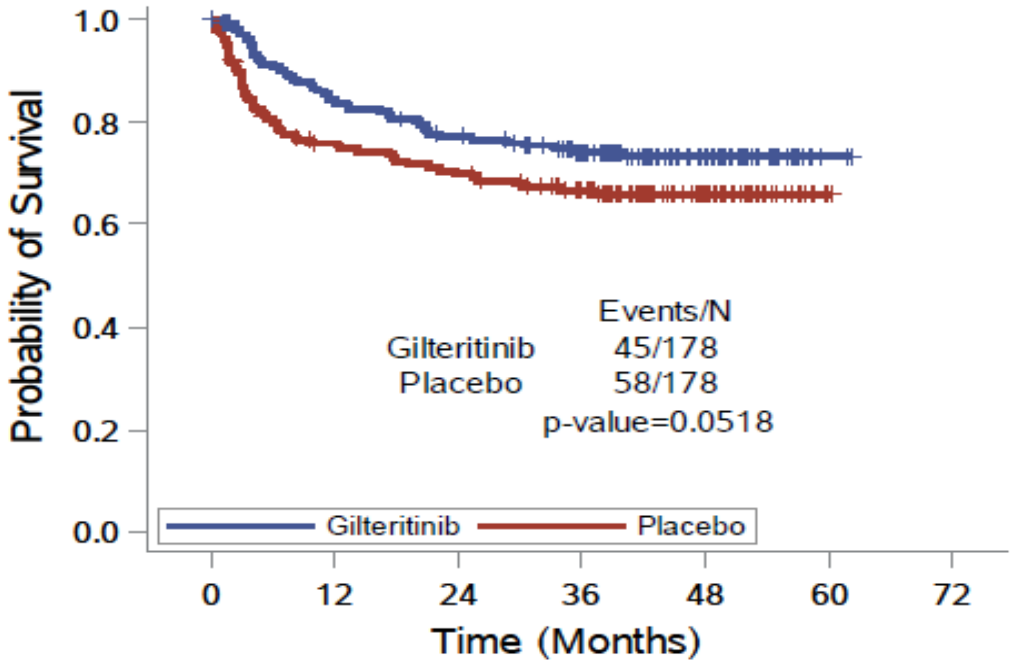
PCR-NGS assay
- Two-step assay:
- PCR of juxtamembrane region, amplicons analyzed by NGS
- Detects FLT3-ITD mutation with sensitivity of ~1 x 10^{-6}

MRD analyzed in 350/356 (98.3%) pre-HCT and 347/356 (97.5%) in post-HCT.
- First 2 cc aspirate collected for MRD

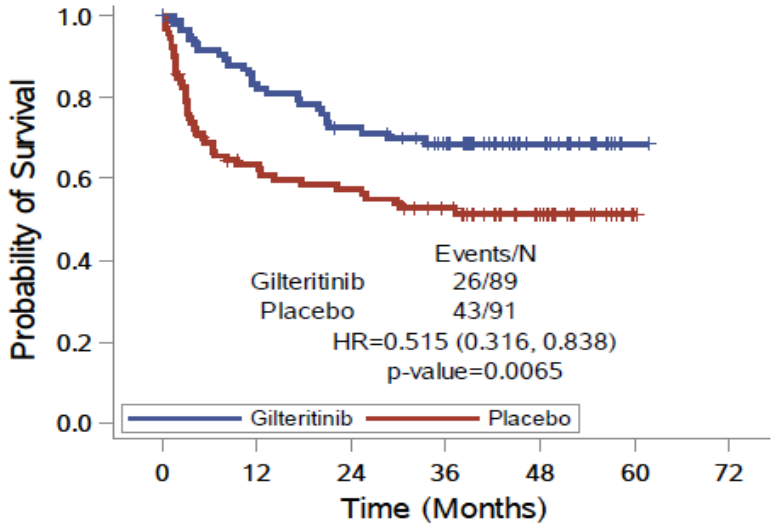
Levis MJ, et al. *J Clin Oncol.* 2024 May 20;42(15):1766-1775

BMT-CTN 1506/MORPHO: primary endpoint

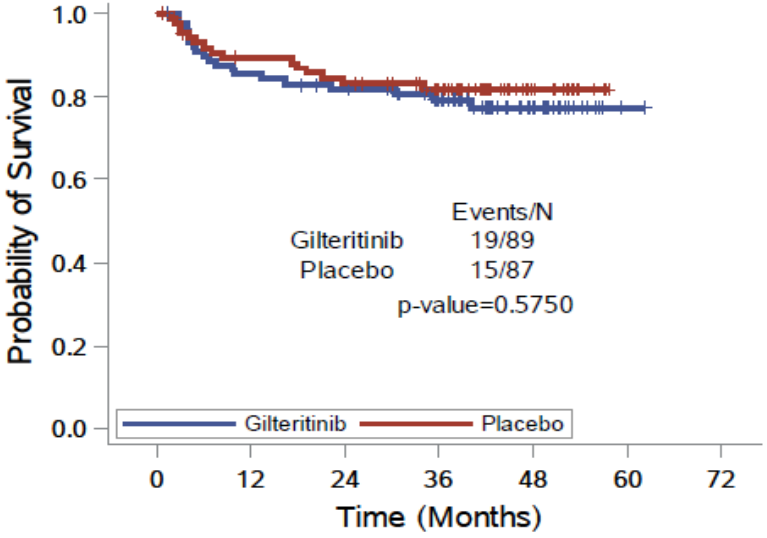
Primary objective:
Relapse-free survival (RFS)
HR = 0.679 (0.459-1.005)
P = 0.0518



RFS
MRD positive

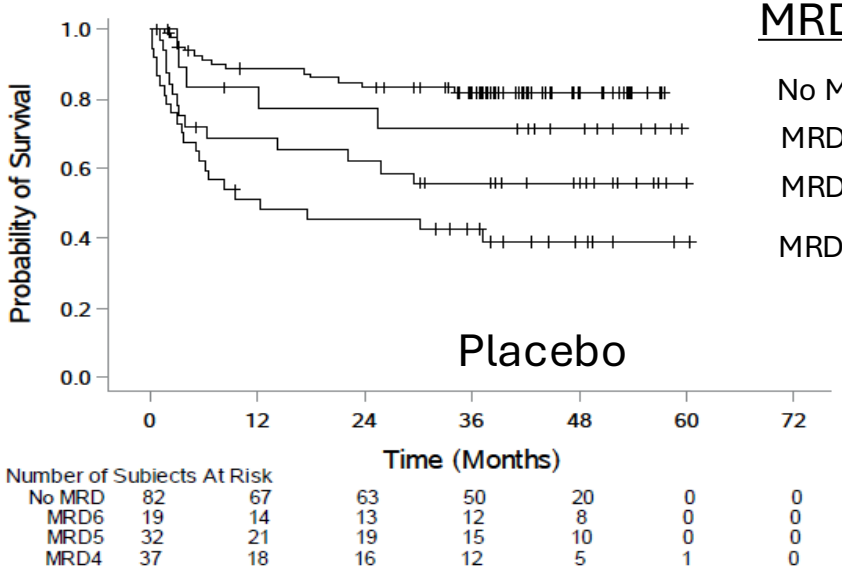


RFS
MRD negative



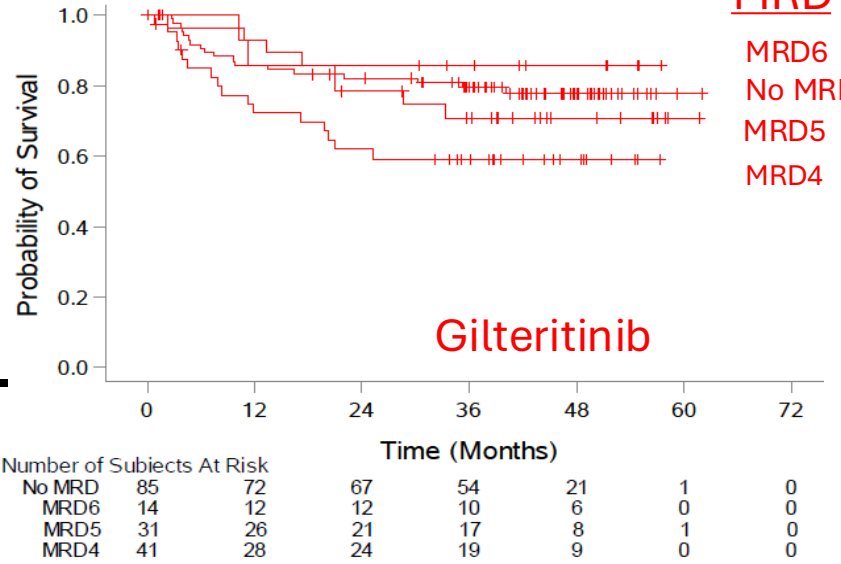
Levis MJ, et al. *J Clin Oncol.* 2024 May 20;42(15):1766-1775

All levels of detectable MRD impact RFS



Placebo

MRD	Events/N
No MRD	14/82
MRD6	5/19
MRD5	14/32
MRD4	22/37



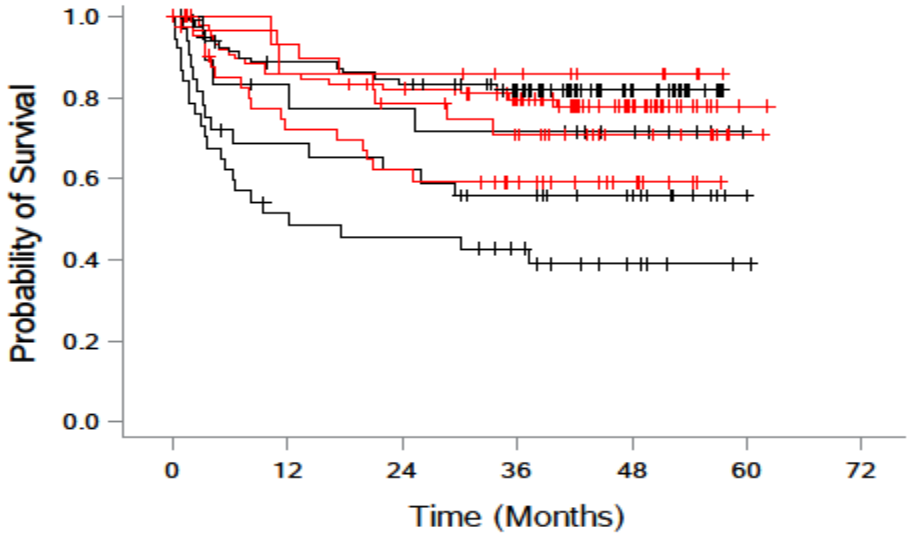
Gilteritinib

MRD	Events/N
MRD6	2/14
No MRD	18/85
MRD5	8/31
MRD4	16/41

$10^{-6} \leq$ MRD6 $< 10^{-5}$

$10^{-5} \leq$ MRD5 $< 10^{-4}$

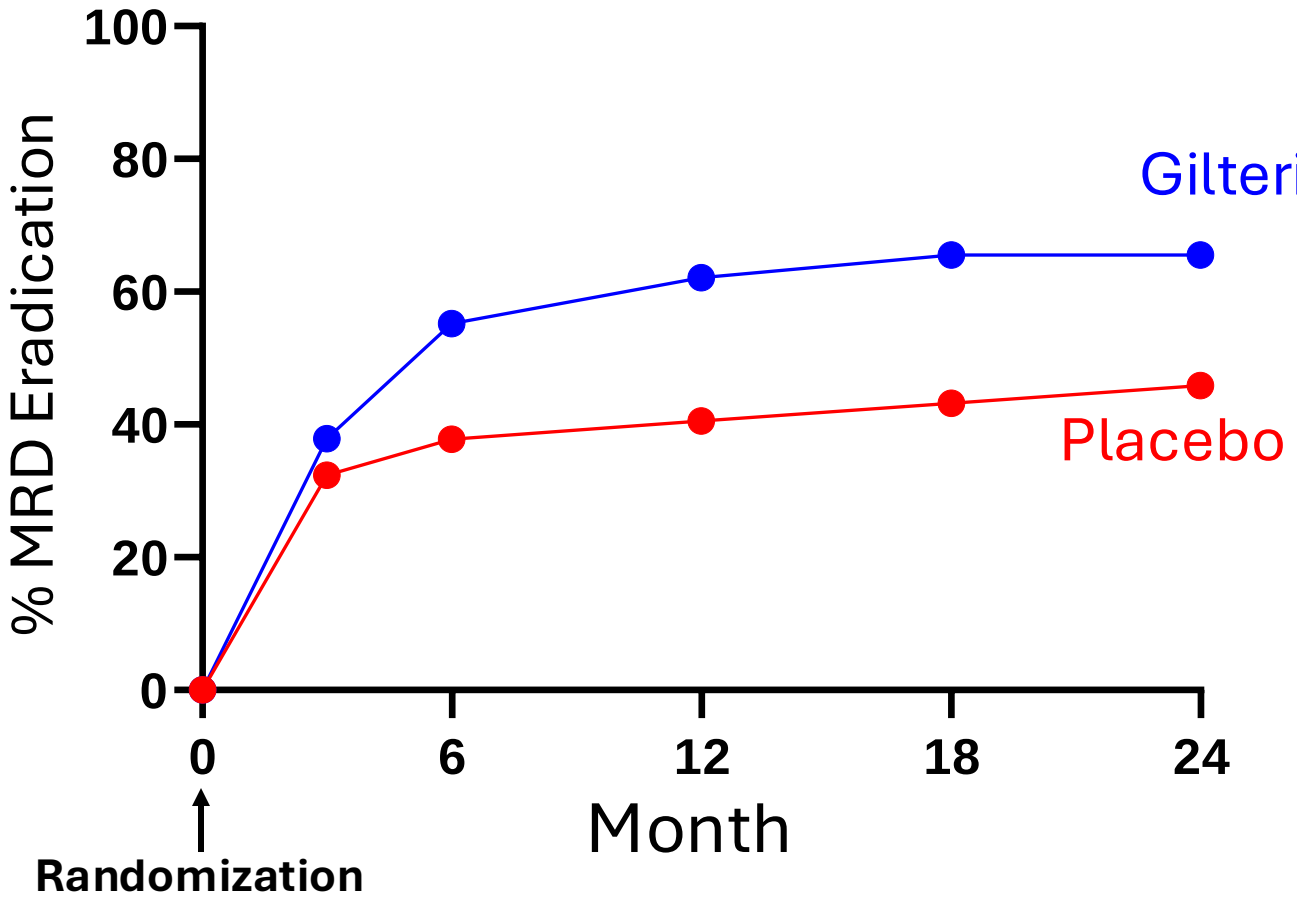
$10^{-4} \leq$ MRD4



At each level of MRD: RFS with gilteritinib > RFS with placebo

Levis MJ, et al. ASH 2023, #973

Time course of post-HCT MRD eradication according to treatment arm



<u>Definition of MRD eradication:</u>

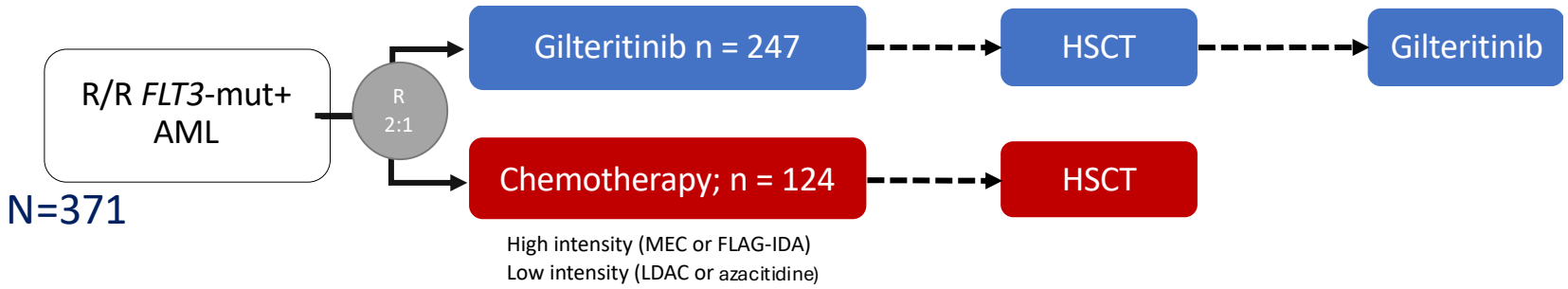
1. FLT3-ITD clone becomes undetectable
2. FLT3-ITD clone does not recur
3. Participant does not relapse

Levis MJ, et al. ASH 2023, #973

Gilteritinib: phase 3 ADMIRAL study in R/R *FLT3*$^{mut+}$ AML

Key Eligibility Criteria:

- Refractory to initial induction or untreated first relapse after prior CRc
  - Prior frontline midostaurin or sorafenib allowed
- Central laboratory-confirmed *FLT3*-ITD or *FLT3*-TKD (D835/I836) by PCR
- ECOG performance status ≤2
- Normal liver, renal function
- QTcF ≤450 msec by central ECG reading



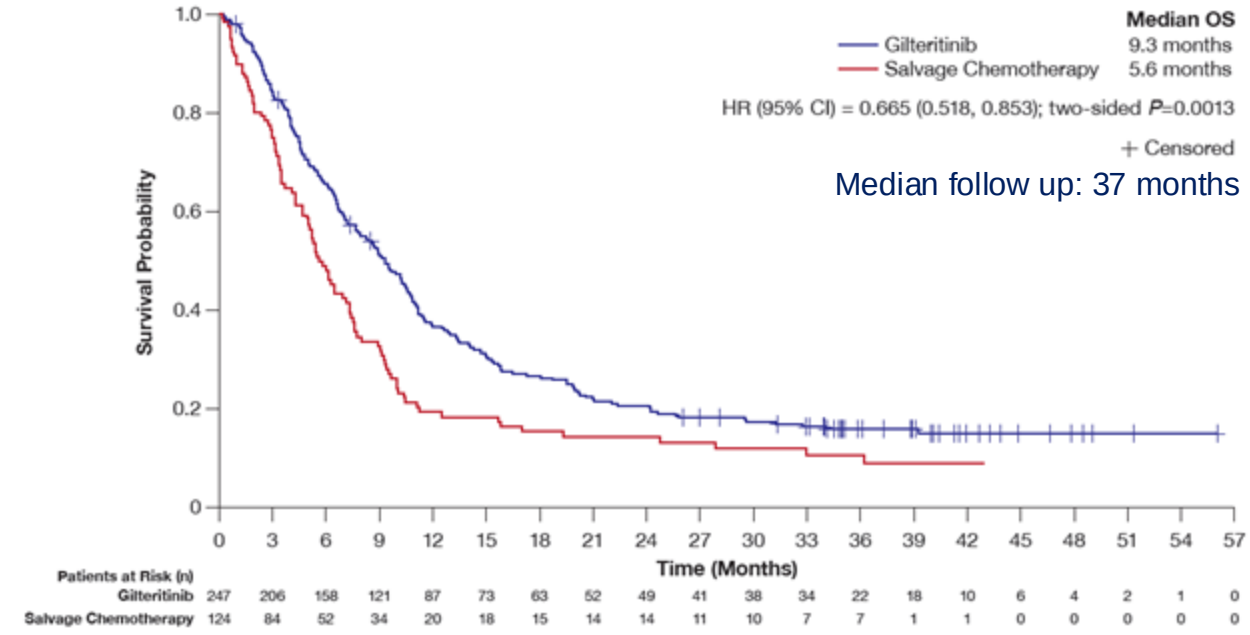
N=371

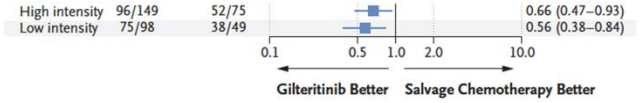
High intensity (MEC or FLAG-IDA)
Low intensity (LDAC or azacitidine)

CR/CRh

34%

15.3%



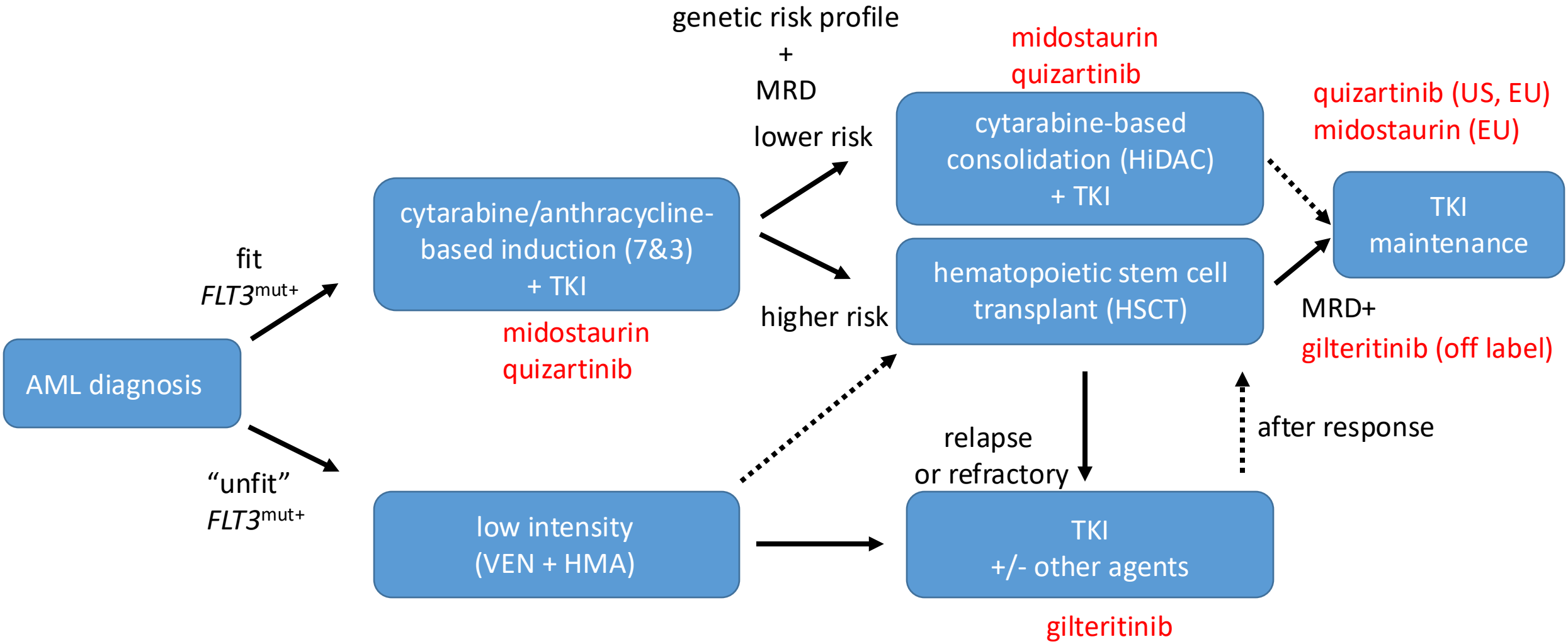


Gilteritinib Side effects:

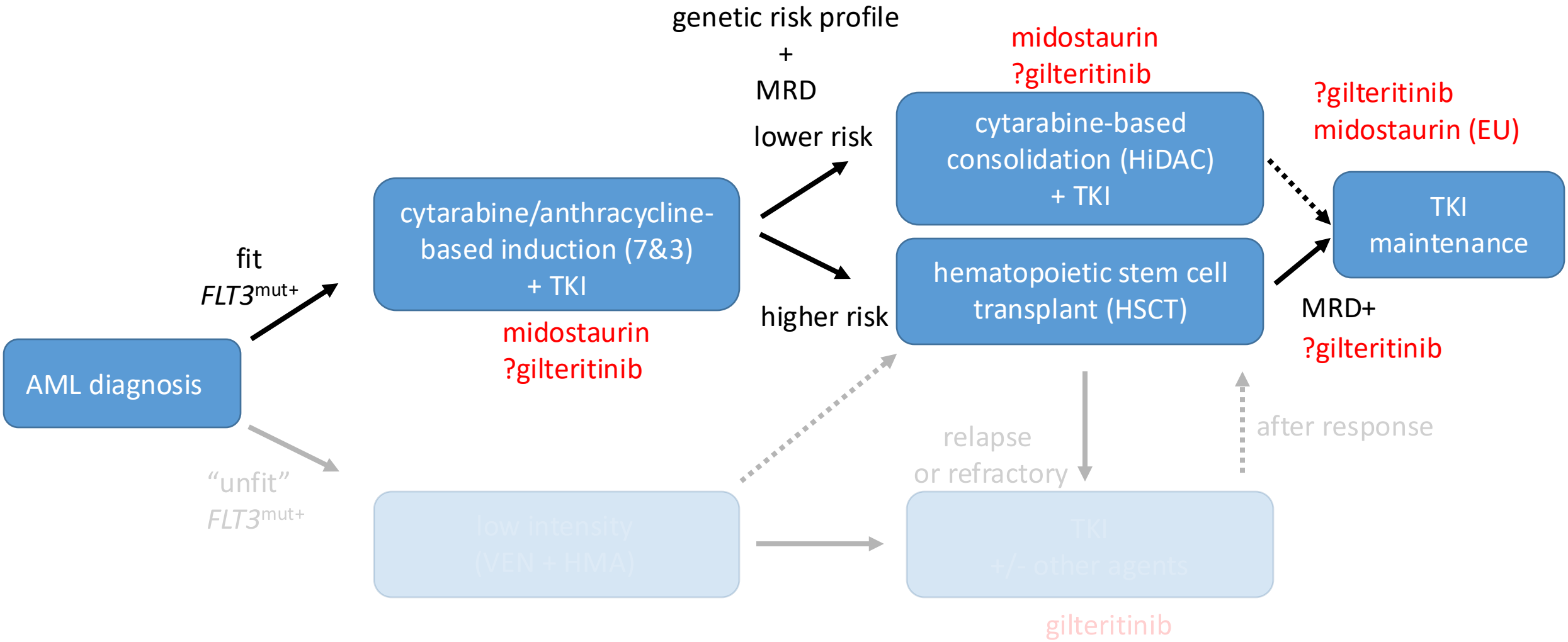
- Cytopenias
- Abnormal LFTs
- GI irritation
- Elevated CPK
- Monitor QT
- Potential for differentiation syndrome
- Rare but serious: pancreatitis, PRES, cardiomyopathy, bowel injury

Perl AE, et al. N Engl J Med. 2019 Oct 31;381(18):1728-1740
Perl AE, et al. *Blood* 2022. Jun 9;139(23):3366-3375

The current AML treatment approach for *FLT3*$^{mut+}$ AML

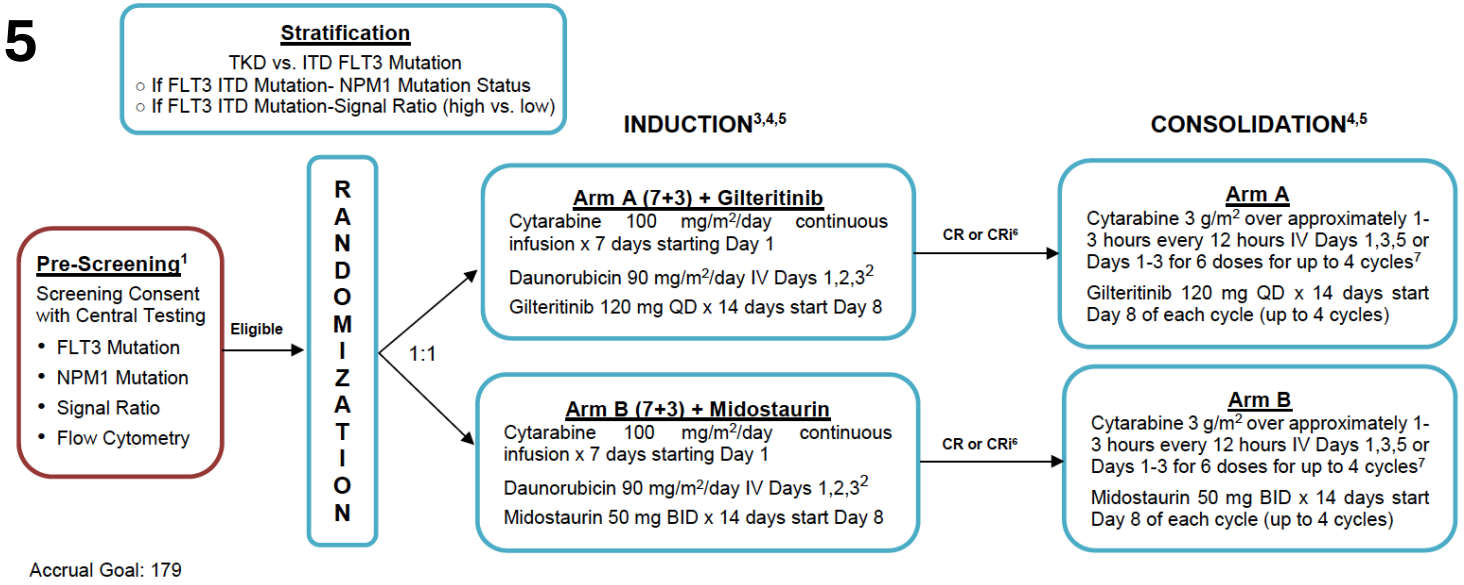


The current AML treatment approach for *FLT3*$^{mut+}$ AML



Randomized studies of gilt vs. mido + IC

PrECOG 0905

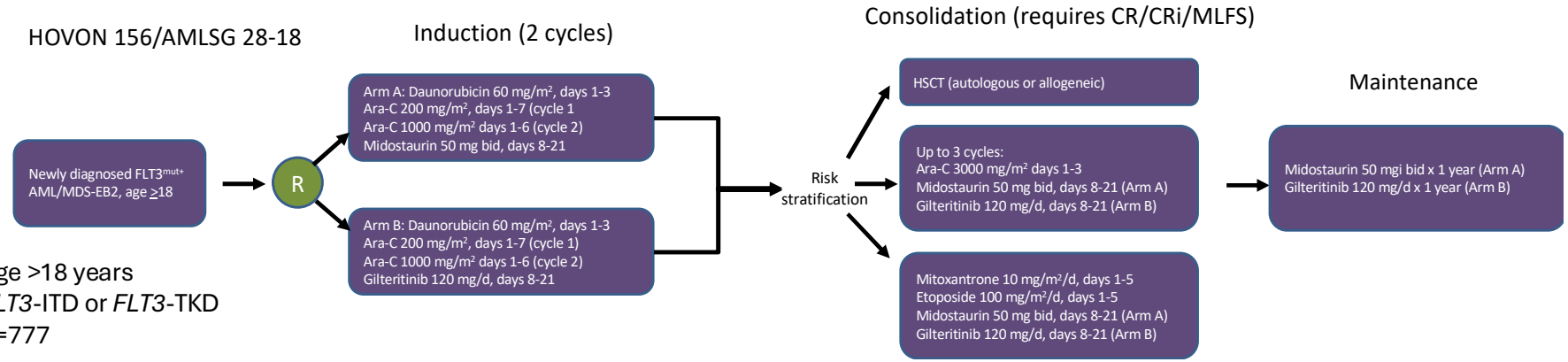


ASH 2024 oral presentation:
Luger SM, et al. #221 Sat 3 PM

NCT03836209

Primary endpoint: *FLT3*mut(-) CRc rate for each arm (PCR-NGS for *FLT3*-ITD, PCR for *FLT3*-TKD)

PASHA

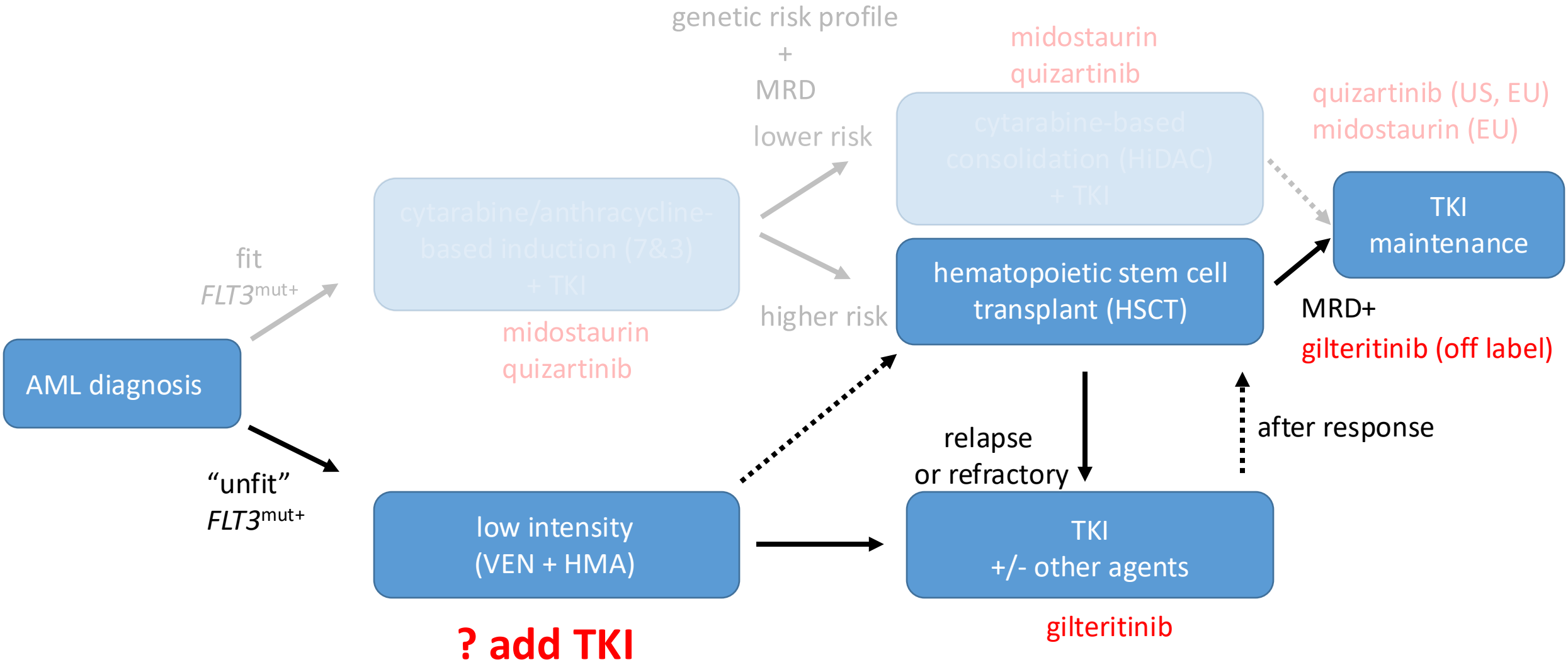


NCT04027309

Primary endpoint: EFS (MRD is a secondary endpoint)

crenolanib phase 3 had similar design—trial suspended enrollment in past year

The current AML treatment approach for *FLT3*$^{mut+}$ AML



VEN + AZA + gilteritinib for unfit/older ND *FLT3*$^{mut+}$ AML

Cycle 1: Azacitidine 75 mg/m2/d days 1-7
Venetoclax 400 mg/d (after 3d ramp up) d3-14
Gilteritinib 80 mg daily d1-14 (check d14 marrow)

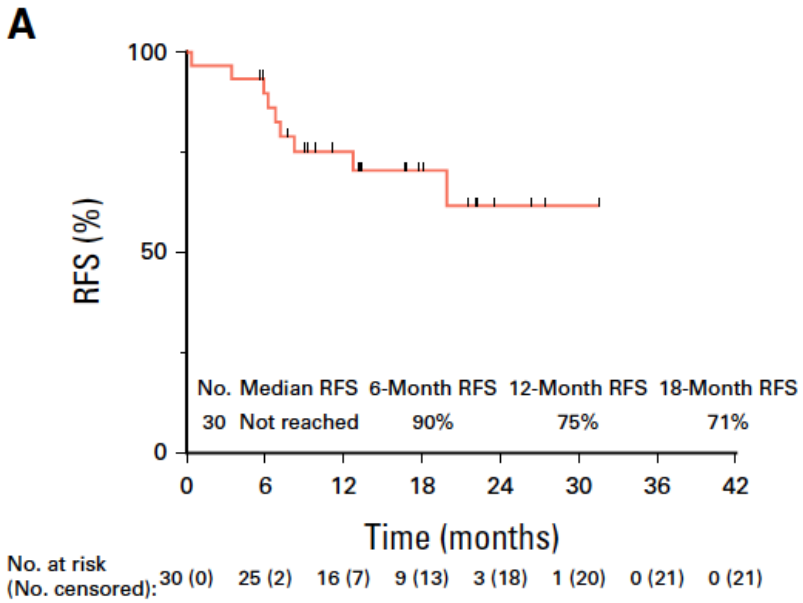
Cycle 2 and later: further reduction
aza to day 1-5 and ven to day 1-7
gilt 80 mg day 1-28 (ie continuously)

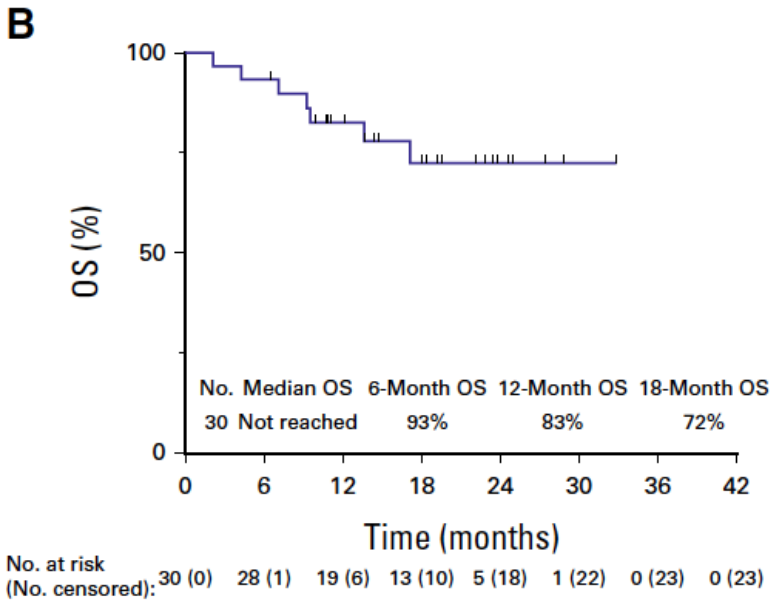
93% (28/30) of newly diagnosed patients had either <5% blasts or marrow hypoplasia at C1D14

ND: Median time to ANC> 500= 37 days
ND: Median time to Plts >50K= 25 days

Response, n/N (%)	Frontline	R/R
mCRc (CR/CRi/MLFS)	30 (100%)	15 (68%)
CR	27 (90%)	4 (18%)
CRi	2 (6%)	2 (9)
MLFS	1 (4%)	9 (41%)
PR	0	1 (5%)*
No response	0	6 (27%)
Early death	0	0
*extramedullary-only disease		

13/20 (65%) *FLT3*-ITD <5 x 10^{-5} by 4 cycles

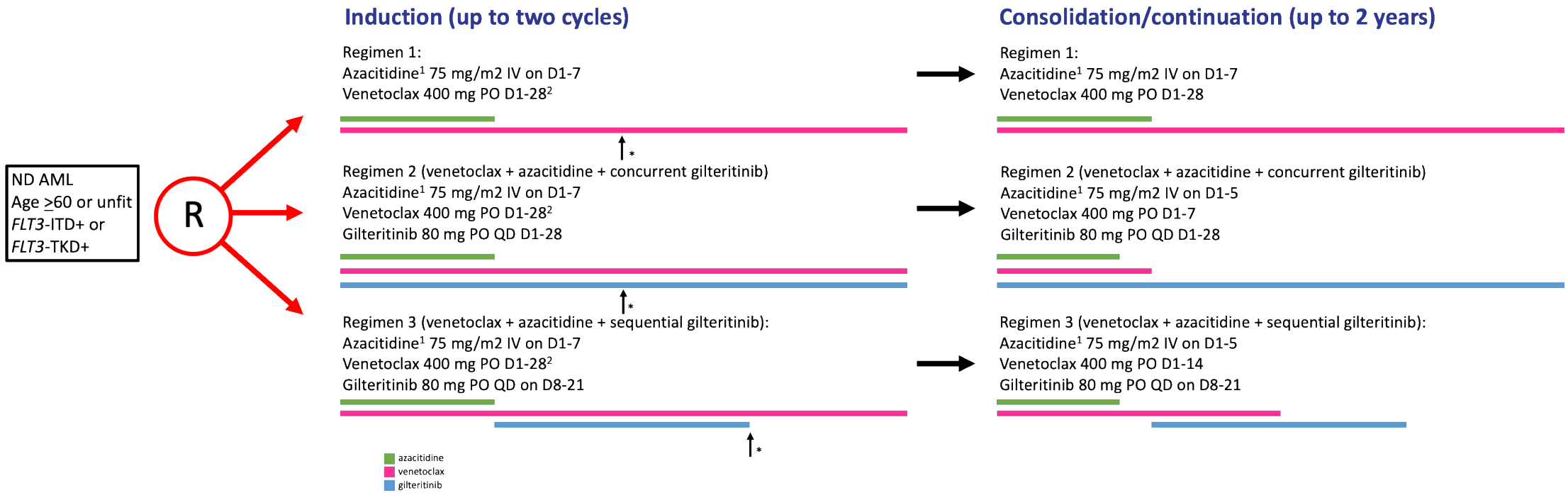




ASH 2024: Long-term follow up oral presentation
Short NJ, et al. Abstract #220: Saturday 2:45PM

Short NJ, et al. J Clin Oncol. 2024 May 1;42(13):1499-1508

MyeloMATCH MM1OA-EA02 study



*chemotherapy is withheld during induction until count recovery if no evidence of leukemia is seen at the time of a mid-cycle marrow biopsy (vertical arrow)
consolidation begins after count recovery to ANC>500 and platelets >50K
marrow biopsies for flow MRD are done after cycles 2 and 4 to measure the primary endpoint

ND= newly diagnosed; AML= acute myeloid leukemia; FLT3= FMS-like tyrosine kinase 3; ITD= internal tandem duplication; TKD= tyrosine kinase domain (D835 or I836del); MRD= measurable residual disease

NCT06317649

ASH 2024:
MM1OA-EA02 (Altman JK, et al. #2907.1 Sunday 6-8PM (trial in progress poster)
Intervene study--ven/LDAC + mido vs. placebo (Chua CC, et al. #217: Saturday 2PM oral presentation)

What else is new for FLT3 inhibitors?

New FLT3 inhibitors
- tuspetinib (FLT3, SYK, KIT, JAK1/2, RSK2 inhibitor)
- emavusertib (IRAK4/FLT3)
- BMF-500 (covalent)
- FF-10101 (covalent)
- PHI-101 (highly potent)

- Novel combinations
  - menin inhibitors + FLT3 inhibitors
- New populations that may benefit from FLT3 inhibition
  - ?FLT3-ITD(-)

ASH 2024:
Phase 2 trial emavusertib preliminary results (Winer ES, et al. #737: Monday 11:30 AM)
Tuspetinib + venetoclax in R/R AML (Daver NG, et al. #4255 Monday 6-8PM Posters)
PHI-101 phase 1 (Shin D-Y, et al. #1495, Saturday 5:30—7:30 PM Posters)
Randomized IC + quizartinib vs. PBO for FLT3-ITD(-) AML (Montesinos P, et al. #1512: Sat 5:30-7:30 PM Posters)

Levis MJ, et al. Blood Adv. 2024 May 28;8(10):2527-2535

Questions from General Medical Oncologists/Hematologists

- **Which initial treatment would you recommend for an 80-year-old patient with AML and a FLT3-TKD mutation who is ineligible for intensive chemotherapy?**
- **68 yo woman, FLT3-TKD, received 7+3 plus gilteritinib with CR. What is the role of targeted treatment as maintenance post-transplant? Do you continue the FLT3 inhibitor?**
- **Which initial treatment would you recommend for a 60-year-old patient with AML and a FLT3-ITD mutation who is eligible for intensive chemotherapy? Which FLT3 agent is best used in initial therapy: midostaurin, quizartinib or gilteritinib?**

Questions from General Medical Oncologists/Hematologists

- What is your global view of the QT prolongation associated with quizartinib?
- In the absence of disease progression or unacceptable toxicity, what is the recommended minimum time to allow for a clinical response with gilteritinib?
- 65 yo patient with AML with a FLT3 mutation receives 7 + 3 induction and midostaurin, attains remission and receives 3 cycles of consolidation. Four months later, he has disease progression with a FLT3-ITD mutation (allelic burden 0.4). What would you recommend?

Questions from General Medical Oncologists/Hematologists

- Is midostaurin still acceptable, or should all patients get a next-generation FLT3 inhibitor?
- Any role for combination therapies in front-line or salvage line in patients with FLT3-mutant AML who are not candidates for intensive therapy?
- Did you start incorporating quizartinib in the front line? What are the most common AEs compared to midostaurin?

Agenda

Module 1: Treatment for Older Patients with Acute Myeloid Leukemia (AML) — Prof Wei

Module 2: Selection of Initial Therapy for Younger Patients with AML without a Targetable Mutation, Including Those with Secondary AML — Dr Stone

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

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

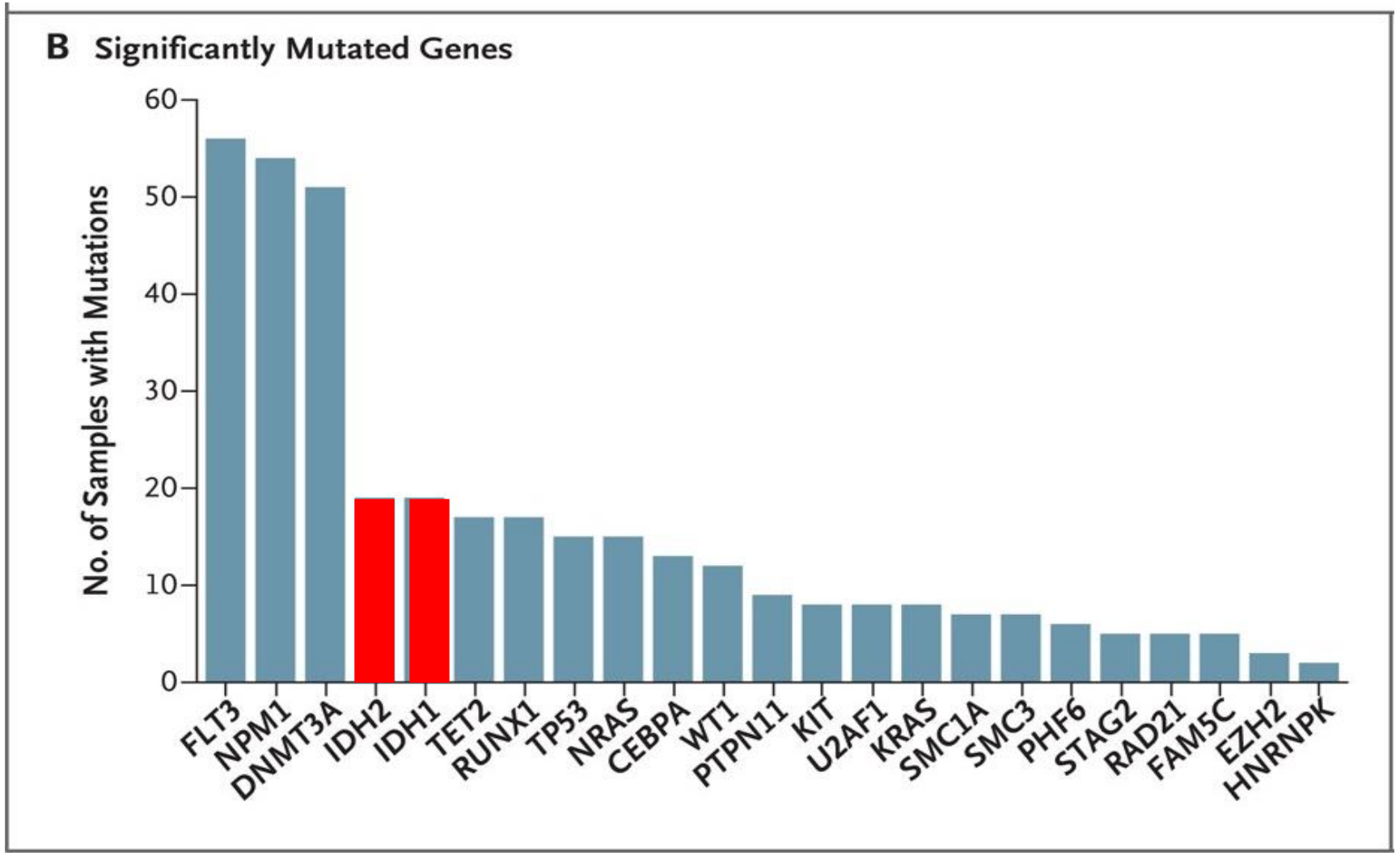
Module 5: Potential Role of Menin Inhibitors and Other Novel Agents in the Treatment of AML — Dr Wang

Incorporation of IDH Inhibitors into the Care of Patients with AML

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

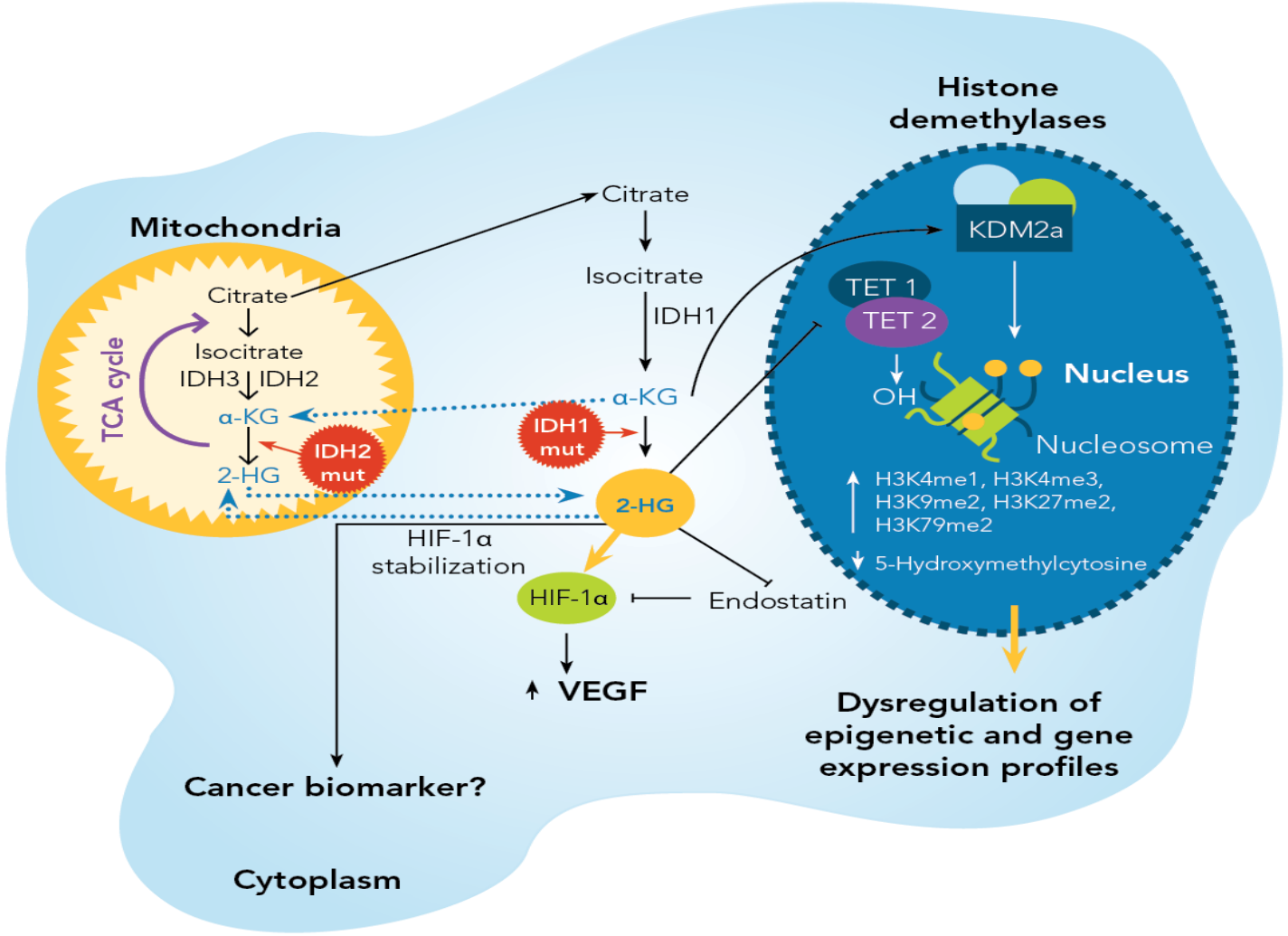
Memorial Sloan Kettering
Cancer Center

The Burden of IDH Mutations in AML



The Cancer Genome Atlas Research Network. N Engl J Med 2013;368:2059-2074

IDH1 and IDH2 Mutated Acute Myeloid Leukemia Background



Prensner and Chinnaiyan Nature, 2011

IDH1/2 Mutated AML – Relapsed and Refractory Disease

	Ivosidenib (IDH1)	Olutasidenib (IDH1)
Basis of Approval	Single arm phase 2	Single arm phase 2
CR/CRh	32.8%	35%
Duration of Response (median)	8.2 months	25.9 months

"Of note, olutasidenib is the second *IDH1* inhibitor to be approved for the treatment of patients with R/R *IDH1*-mutated AML; ivosidenib was approved for this indication in 2018. The overall efficacy results seemed similar, although no firm conclusions can be made on cross-trial comparisons. DOR should not be compared across studies because of differences in both measured and unmeasured confounders, as well as differences in the median duration of follow-up."

de Botton S et al. Blood Adv. 2023 Feb 3;7(13):3117–3127.
Norsworthy KJ et. al. Clinical Cancer Research, 2019.
Woods A, et. al., Clinical Cancer Research, 2024.

Safety Comparison – Ivosidenib and Olutasidenib

Ivosidenib

Table 3. Treatment-emergent ARs in the safety population[a]

Preferred term[b]	Any grade	Grade ≥3
Fatigue	69 (39%)	6 (3%)
Leukocytosis	68 (38%)	15 (8%)
Arthralgia	64 (36%)	8 (4%)
Diarrhea	60 (34%)	4 (2%)
Dyspnea	59 (33%)	16 (9%)
Edema	57 (32%)	2 (1%)
Nausea	56 (31%)	1 (1%)
Mucositis	51 (28%)	6 (3%)
Electrocardiogram QT prolonged	46 (26%)	18 (10%)
Rash	46 (26%)	4 (2%)
Pyrexia	41 (23%)	2 (1%)
Cough	40 (22%)	1 (<1%)
Constipation	35 (20%)	1 (1%)
Differentiation syndrome	34 (19%)	23 (13%)
Decreased appetite	33 (18%)	3 (2%)
Myalgia	33 (18%)	1 (1%)
Vomiting	32 (18%)	2 (1%)
Abdominal pain	29 (16%)	2 (1%)
Headache	28 (16%)	0
Pleural effusion	23 (13%)	5 (3%)
Chest pain	29 (16%)	5 (3%)
Hypotension	22 (12%)	7 (4%)
Neuropathy	21 (12%)	2 (1%)

Olutasidenib

Table 3. Treatment-emergent ARs in the safety population.

Preferred term	Any grade	Grade ≥3
Nausea	57 (38)	0
Fatigue/malaise	55 (36)	2 (1)
Arthralgia[a]	43 (28)	4 (3)
Constipation	39 (26)	0
Leukocytosis	38 (25)	14 (9)
Dyspnea[a]	37 (24)	4 (3)
Rash[a]	36 (24)	2 (1)
Pyrexia	36 (24)	1 (1)
Mucositis	35 (23)	5 (3)
Diarrhea	31 (20)	2 (1)
Transaminitis[a]	31 (20)	18 (12)
Abdominal pain	28 (18)	1 (1)
Edema[a]	27 (18)	4 (3)
Cough[a]	26 (17)	1 (1)
DS	25 (16)	13 (8)
Vomiting	25 (16)	1 (1)
Headache	19 (13)	0
Hypertension[a]	16 (10)	7 (5)

Norsworthy et. al., Clinical Cancer Research, 2019
Woods A, et. al., Clinical Cancer Research, 2024

IDH Inhibitor Enasidenib in Relapsed/Refractory AML

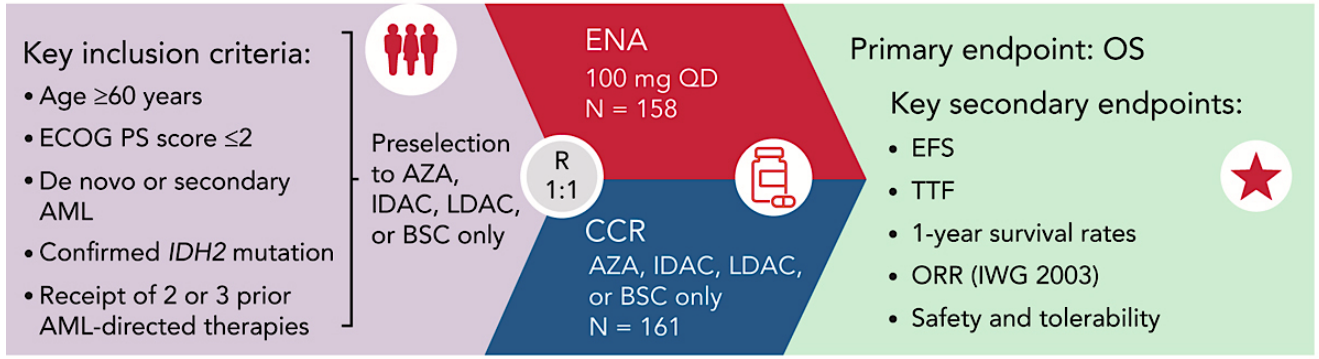
	Ivosidenib (IDH1)	Olutasidenib (IDH1)	Enasidenib (IDH2)
Basis of Approval	Single arm phase 2	Single arm phase 2	Single arm phase 2
CR/CRh	32.8%	35%	23%
Duration of Response (median)	8.2 months	25.9 months	8.2 months

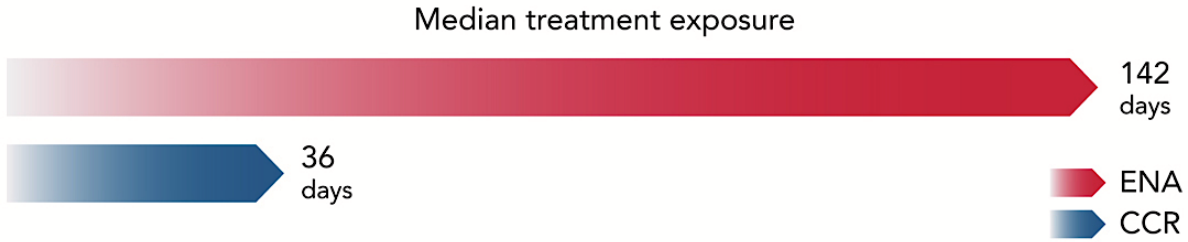
de Botton S et al. Blood Adv. 2023 Feb 3;7(13):3117–3127.
Norsworthy KJ et. al. Clinical Cancer Research, 2019.
Stein EM et al. Blood (2017) 130 (6): 722–731.
Woods A, et. al., Clinical Cancer Research, 2024.

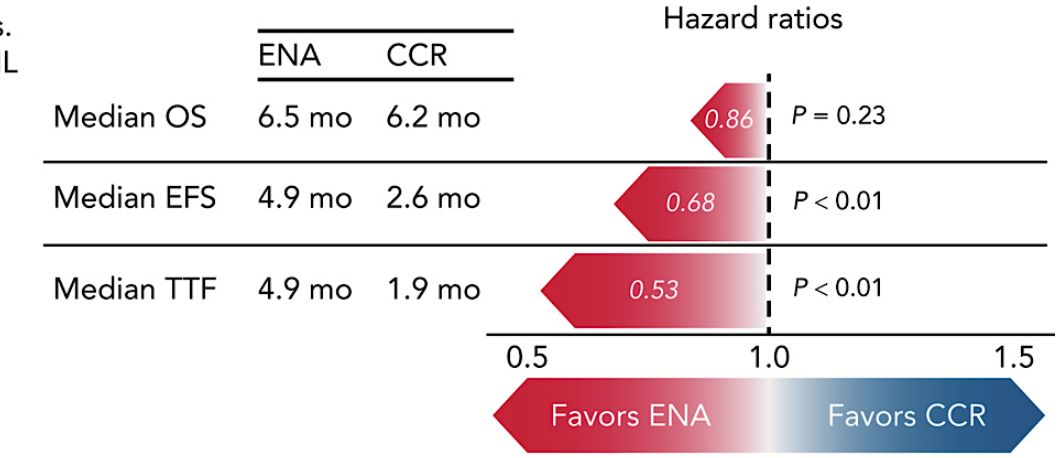
Enasidenib Use in IDH2 Mutated AML– Relapsed and Refractory Disease

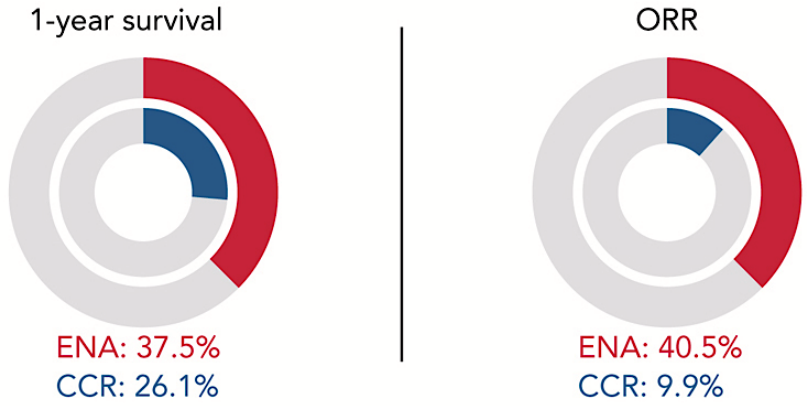
IDHentify: a randomized, open-label, phase 3 trial to evaluate the efficacy and safety of enasidenib vs. conventional care regimens in older patients with late-stage, heavily pretreated mutant-*IDH2* R/R AML

IDHentify: study design and key endpoints





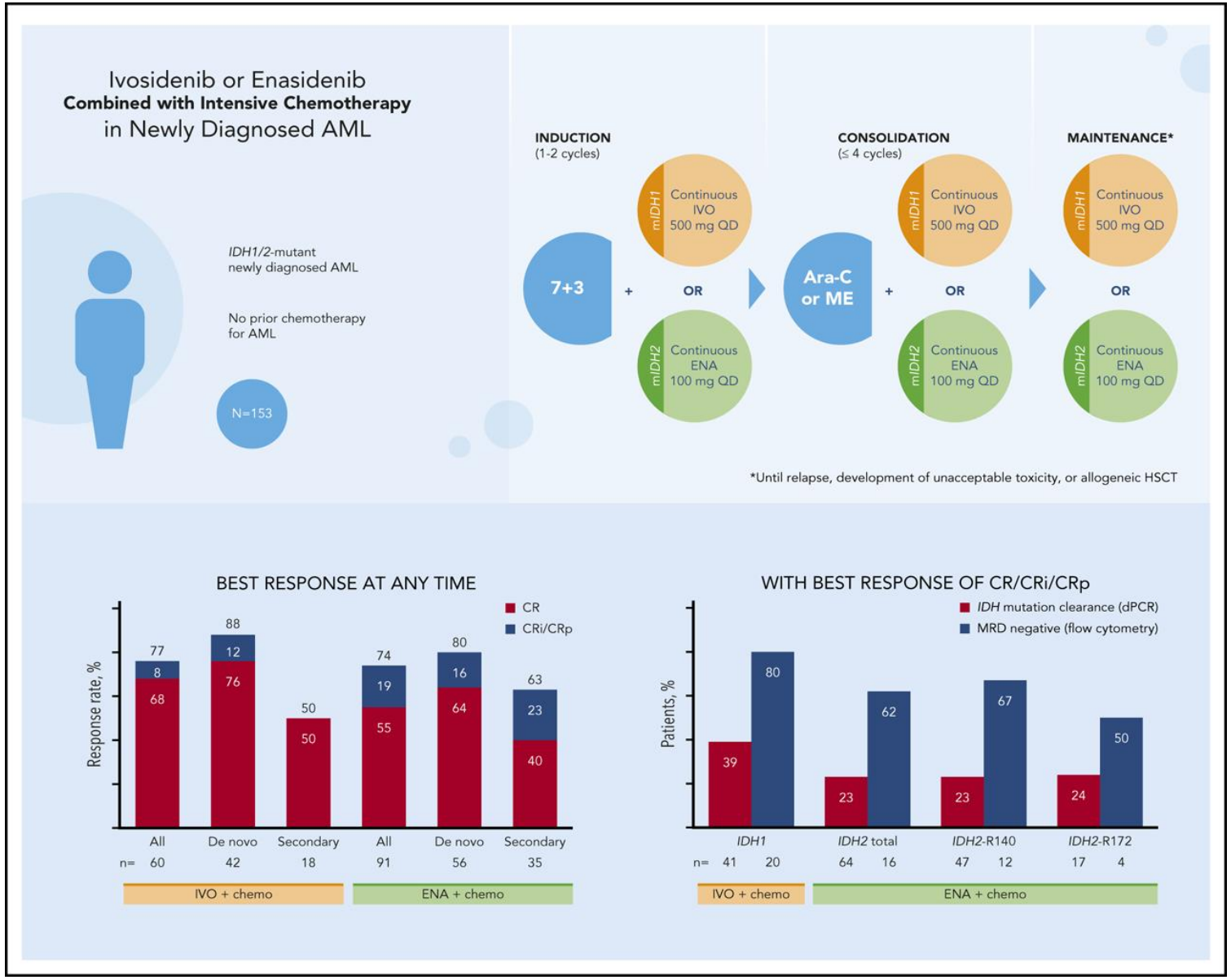




AML, acute myeloid leukemia; AZA, azacitidine; BSC, best supportive care; CCR, conventional care regimens; ECOG PS, Eastern Cooperative Oncology Group performance status; ENA, enasidenib; EFS, event-free survival; IDAC, intermediate-dose cytarabine; IDH2, isocitrate dehydrogenase-2; IWG, International Working Group; LDAC, low-dose cytarabine; mo, months; ORR, overall response rate; OS, overall survival; R, randomization; R/R, relapsed/refractory; TTF, time to treatment failure.

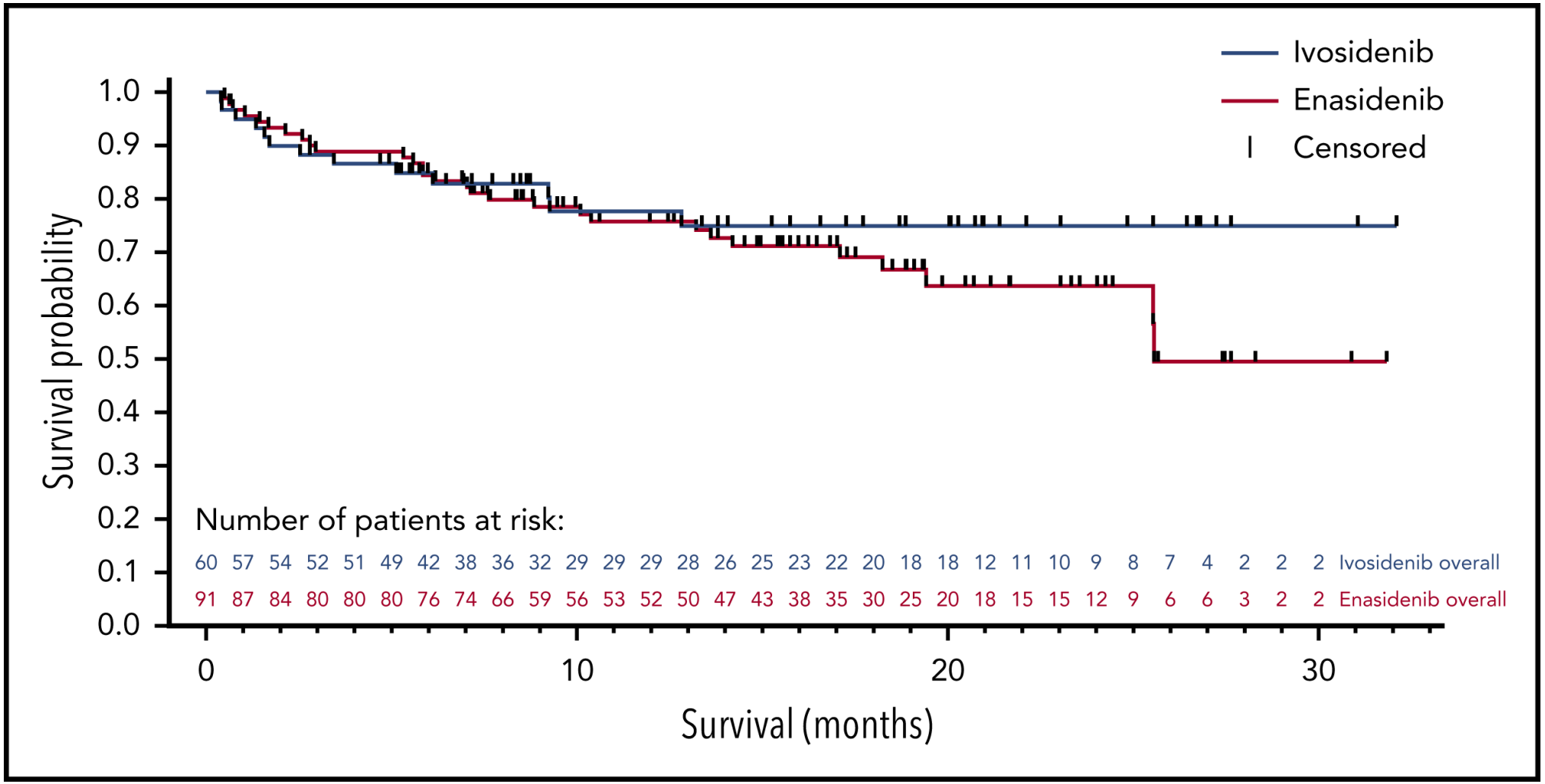
de Botton S et al. Blood (2023) 141 (2): 156–167.

IDH Inhibitors with Chemotherapy for Newly Diagnosed AML



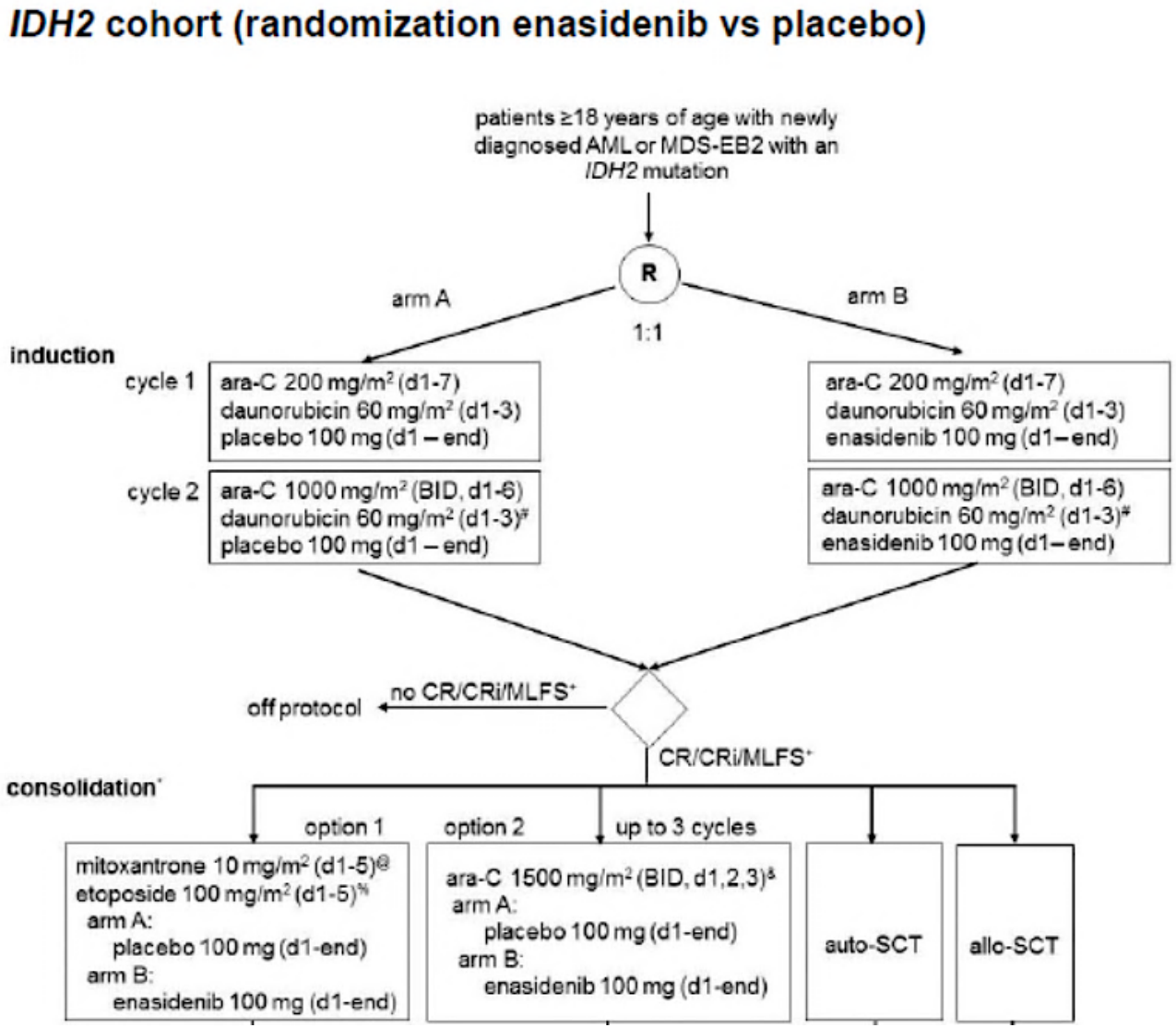
Stein EM, Dinardo CD et. al. Blood 2021

Enasidenib/Ivosidenib with Chemotherapy



Stein EM, Dinardo CD et. al. Blood 2021

IDH Inhibitors with Chemotherapy – Randomized Phase 3



https://hovon.nl/en/trials/ho150

IDH Inhibitors with Chemotherapy for Newly Diagnosed AML

HOVON HO150 AML

Closed

GO TO ECRF

Main info

Identifier:	HOVON 150 AML / AMLSG 29-18
Sponsor:	HOVON
Working group party:	Leukemia
Age:	>= 18
Stage:	1st Line
Echelon:	Level C-HIC&C-SCT

Included patients: 974 (of 971)

Active sites: 191 (of 219)

1 sites are pending

Title:

A phase 3, multicenter, double-blind, randomized, placebo-controlled study of ivosidenib or enasidenib in combination with induction therapy and consolidation therapy followed by maintenance therapy in patients with newly diagnosed acute myeloid leukemia or myelodysplastic syndrome with excess blasts-2, with an IDH1 or IDH2 mutation, respectively, eligible for intensive chemotherapy.

https://hovon.nl/en/trials/ho150

Ivosidenib – Newly Diagnosed AML

Table 1. Baseline characteristics of patients with newly diagnosed AML

Characteristic	Ivosidenib 500 mg, N = 34
Age, median (range), y	76.5 (64-87)
Age category, n (%), y	
60 to <75	15 (44)
≥75	19 (56)
Women/men, n	15/19
ECOG PS at baseline, n (%)	
0	8 (24)
1	20 (59)
2	5 (15)
3	1 (3)

Table 1. Baseline characteristics of patients with newly diagnosed AML

Characteristic	Ivosidenib 500 mg, N = 34
Nature of AML, n (%)	
De novo	8 (24)
Secondary	
History of MDS	18 (53)
History of MPD	4 (12)
Treatment-related	3 (9)
Other	1 (3)
Prior hypomethylating agent, n (%)	16 (47)
Cytogenetic risk status by investigator, n (%)	
Intermediate	24 (71)
Poor	9 (26)
Unknown	1 (3)

Roboz GJ et al. Blood (2020) 135 (7): 463–471.

Ivosidenib Monotherapy in Newly Diagnosed AML

Response category	Ivosidenib 500 mg, n = 33*
CR + CRh rate, n (%) [95% CI]	14 (42.4) [25.5-60.8]
Time to CR/CRh, median (range), mo	2.8 (1.9-12.9)
Duration of CR/CRh, median [95% CI], mo	NE [4.6 to NE]
CR rate, n (%) [95% CI]	10 (30.3) [15.6-48.7]
Time to CR, median (range), mo	2.8 (1.9-4.6)
Duration of CR, median [95% CI], mo	NE [4.2 to NE]
CRh rate, n (%) [95% CI]	4 (12.1) [3.4-28.2]
Time to CRh, median (range), mo	3.7 (1.9-12.9)
Duration of CRh, median [95% CI], mo	6.5 [2.8 to NE]
ORR by IWG, n (%) [95% CI]†	18 (54.5) [36.4-71.9]
Time to first response, median (range), mo	1.9 (0.9-3.6)
Duration of response, median [95% CI], mo	NE [4.6 to NE]
Best response by IWG, n (%)	
CR	10 (30.3)
CRi or CRp	6 (18.2)
PR	1 (3.0)
MLFS	1 (3.0)
SD	10 (30.3)
PD	3 (9.1)
Not assessed	2 (6.1)

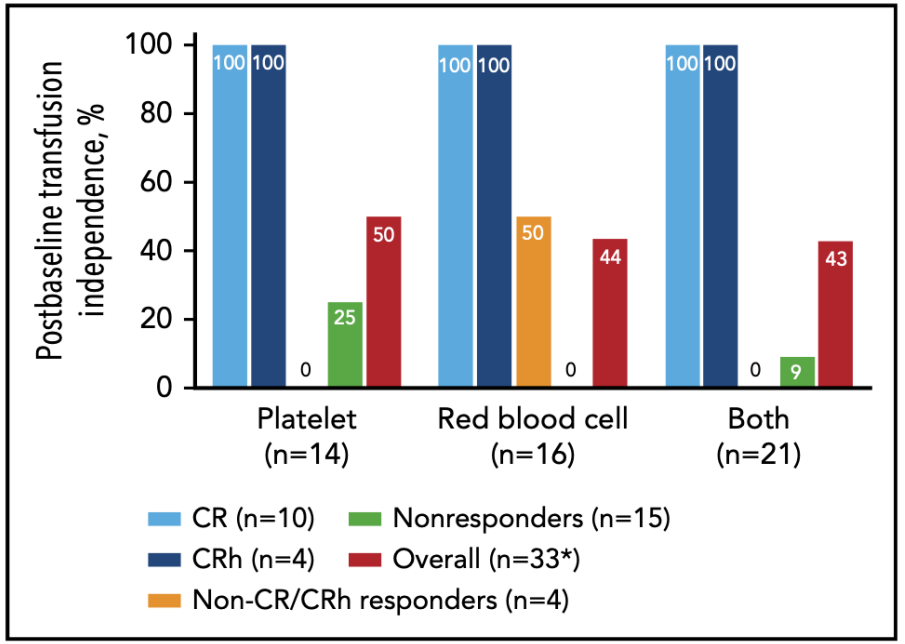


Figure 3. Transfusion independence in patients who were transfusion dependent at baseline. Non-CR/CRh responders include patients with CR with incomplete hematologic recovery/incomplete platelet recovery and morphologic leukemia-free state not meeting the criteria for CRh, and patients with PR. Nonresponders include patients with stable disease and progressive disease. *One patient enrolled in dose-escalation phase was positive for the *IDH1*-D54N mutation by local testing and was not positive for the *IDH1*-R132 mutation by the companion diagnostic test; this patient was therefore excluded from the efficacy analyses.

Roboz GJ et al. Blood (2020) 135 (7): 463–471.

Risk Adapted Use of Enasidenib for Newly Diagnosed AML

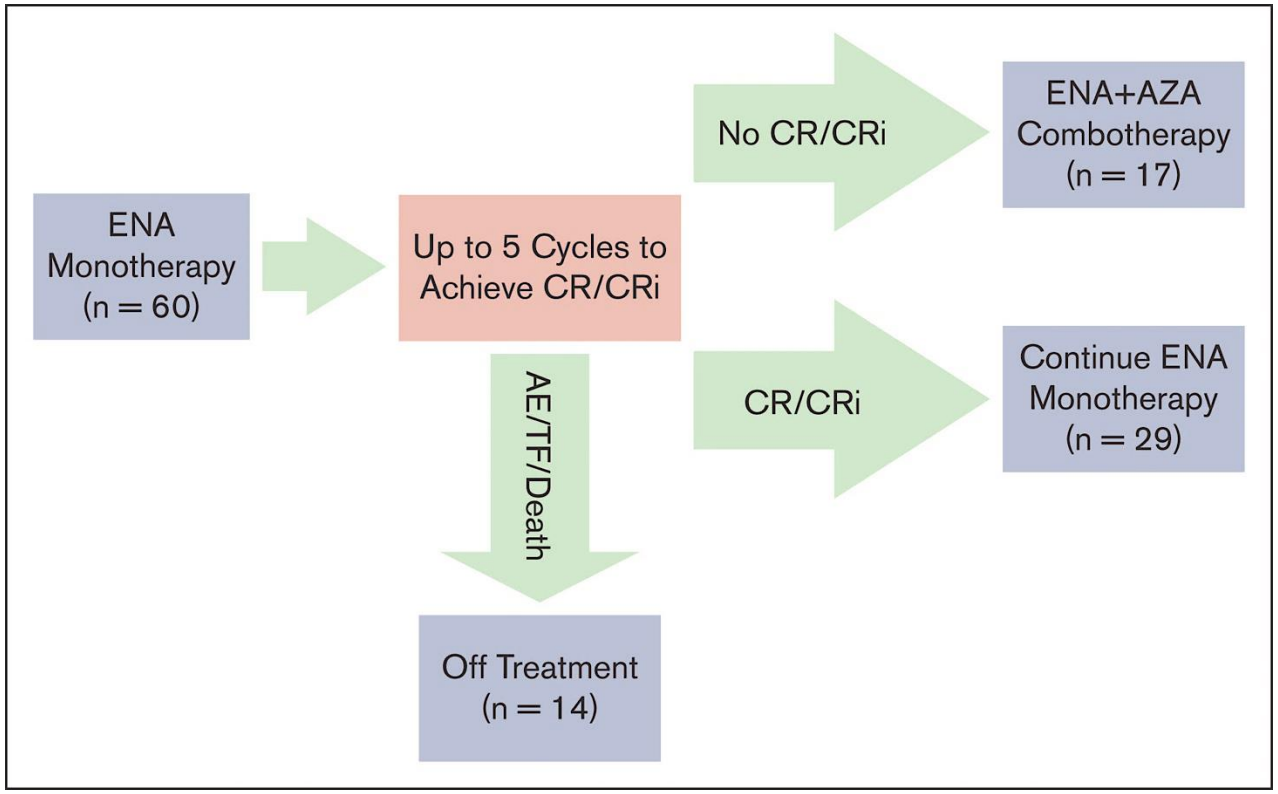
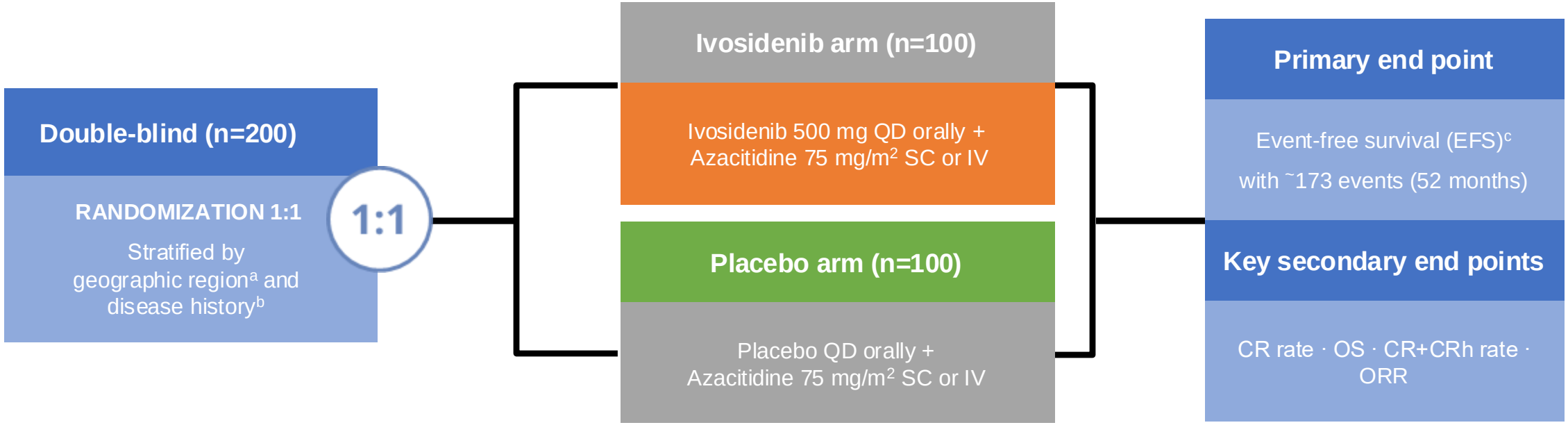


Table 2. Treatment outcomes

Treatment outcomes	Phase 2 and Exp (n = 60)	Phase 1b (n = 17)
Best response, n (%)		
CR	22 (37)	4 (24)
CRh	5 (8)*	2 (12)
CRi	2 (3)	1 (6)
MLFS	1 (2)	1 (6)
Partial remission	2 (3)	1 (6)
Stable disease	21 (35)	3 (18)
Progressive disease	2 (3)	0 (0)
Treatment failure	1 (2)	0 (0)
Not evaluated	4 (7)†	5 (29)‡
cCR rate [CR/CRi], n (%, 95% CI)	29 (48, adjusted: 30.3-60.5)§	7 (41, 18-67)
Median time to best response [CR/CRi]	(n = 29)	(n = 7)
Months (range)	3 (0.9-11)	3.7 (0.7-6.8)
Overall response rate [CR/CRi/MLFS], n (%, 95% CI)	30 (50, 37-63)	8 (47, 23-72)

Cai S, et. al. Blood Adv. 2024 Jan 23;8(2):429-440.

IDH1 Inhibitor Ivosidenib with Azacitidine



Dohner H et. al, ASH 2021

Ivo-aza Responses

Table 2. Hematologic Response, Response Duration, and Time to Response (Intention-to-Treat Population).*

Response Category	Ivosidenib + Azacitidine (N = 72)	Placebo + Azacitidine (N = 74)
Best response — no. (%)		
Complete remission	34 (47)	11 (15)
Complete remission with incomplete hematologic or platelet recovery	5 (7)	1 (1)
Partial remission	4 (6)	2 (3)
Morphologic leukemia-free state	2 (3)	0
Stable disease	7 (10)	27 (36)
Progressive disease	2 (3)	4 (5)
Could not be evaluated	1 (1)	2 (3)
Not assessed	17 (24)	27 (36)
Complete remission		
Percentage of patients (95% CI)	47 (35–59)	15 (8–25)
Odds ratio vs. placebo (95% CI); P value	4.8 (2.2–10.5); two-sided P<0.001	
Median duration of complete remission (95% CI) — mo	NE (13.0–NE)	11.2 (3.2–NE)
Median time to complete remission (range) — mo	4.3 (1.7–9.2)	3.8 (1.9–8.5)

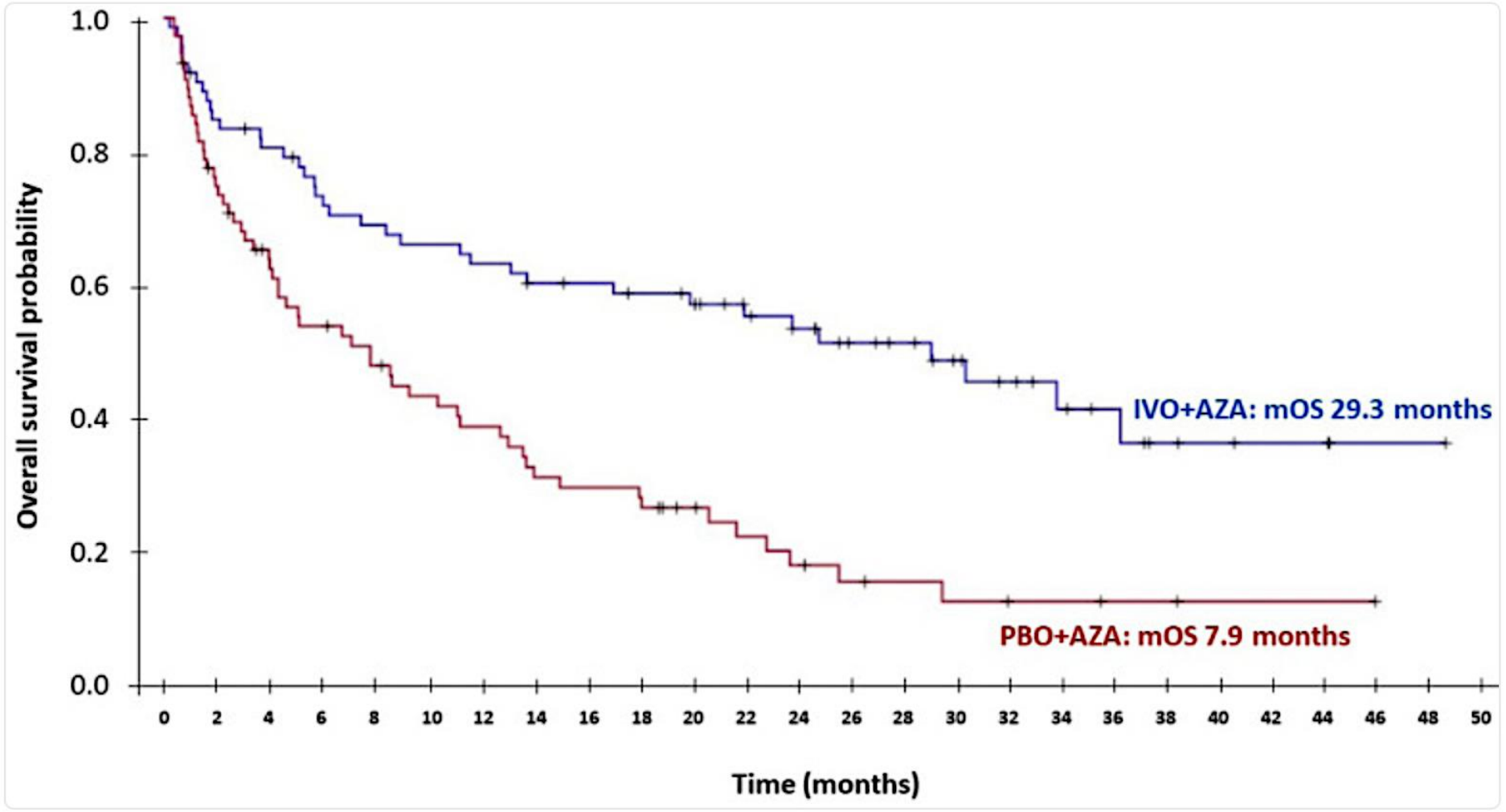
Table 2. Hematologic Response, Response Duration, and Time to Response (Intention-to-Treat Population).*

Response Category	Ivosidenib + Azacitidine (N = 72)	Placebo + Azacitidine (N = 74)
Complete remission or complete remission with partial hematologic recovery		
No. of patients	38	13
Percentage of patients (95% CI)	53 (41–65)	18 (10–28)
Odds ratio vs. placebo (95% CI); P value	5.0 (2.3–10.8); two-sided P<0.001	
Median duration of complete remission or complete remission with partial hematologic recovery (95% CI) — mo	NE (13.0–NE)	9.2 (5.8–NE)
Median time to complete remission or complete remission with partial hematologic recovery (range) — mo	4.0 (1.7–8.6)	3.9 (1.9–7.2)
Objective response		
No. of patients	45	14
Percentage of patients (95% CI)	63 (50–74)	19 (11–30)
Odds ratio vs. placebo (95% CI); P value	7.2 (3.3–15.4); two-sided P<0.001	
Median duration of response (95% CI) — mo	22.1 (13.0–NE)	9.2 (6.6–14.1)
Median time to first response (range) — mo	2.1 (1.7–7.5)	3.7 (1.9–9.4)

* Response was determined according to modified International Working Group criteria. "Not assessed" refers to patients without postbaseline disease assessments. Two-sided P values were calculated from a Cochran–Mantel–Haenszel test stratified according to the randomization stratification factors (disease status and geographic region). Percentages may not total 100 because of rounding. NE denotes could not be estimated.

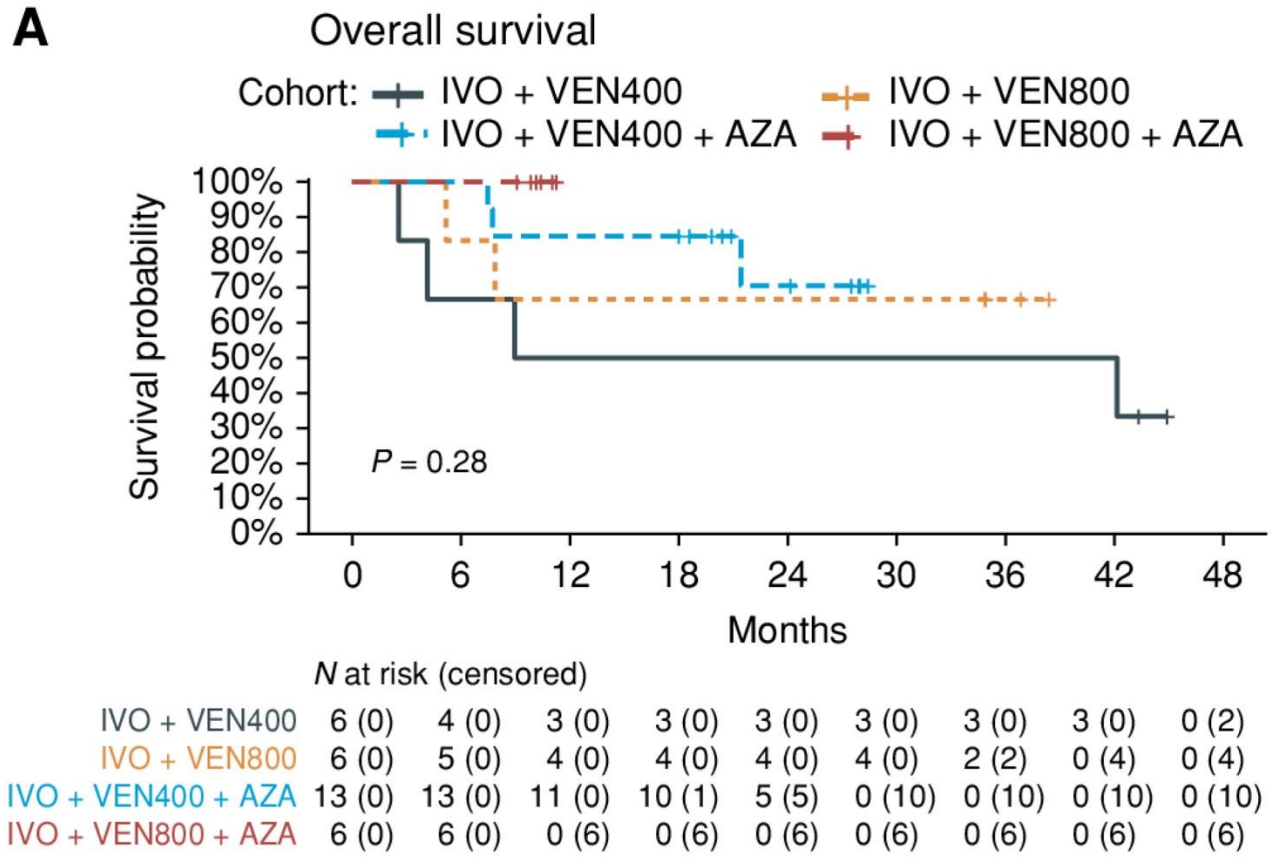
Montesinos P et al. N Engl J Med 2022;386:1519-1531

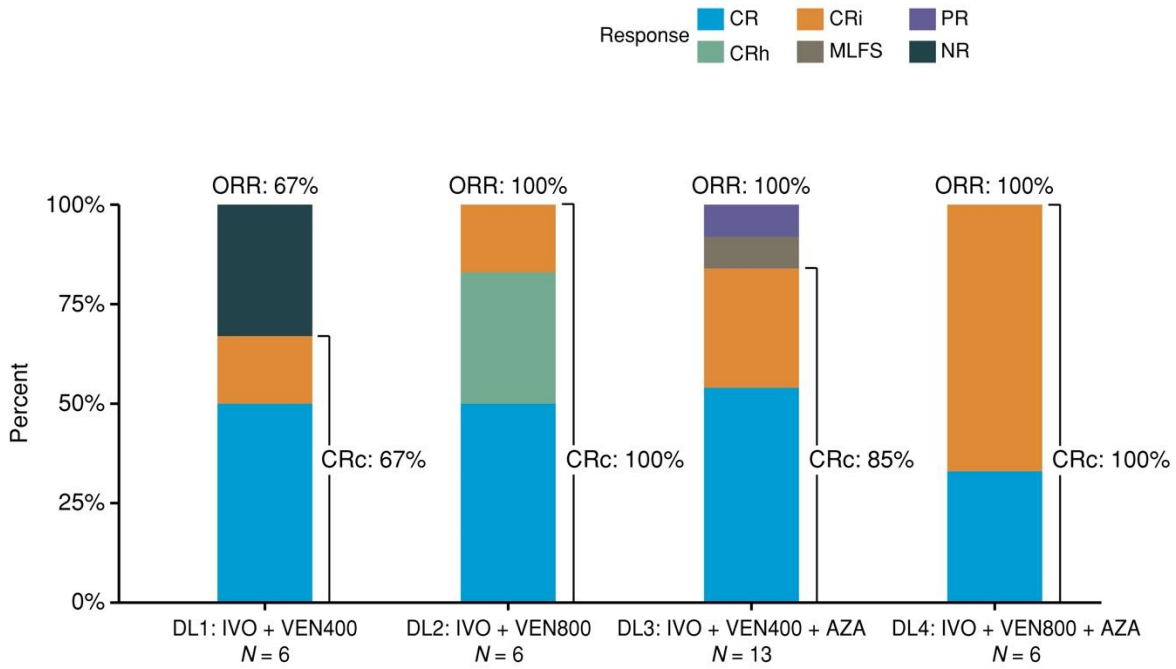
IDH1 Inhibitors for Newly Diagnosed AML



Dohner H, et. al. Hemasphere 2023

Triplet Combination – Aza, Ivo, Ven





Lachowiez C et, al Blood Cancer Discovery 2023

Conclusions

- IDH inhibitors, are firmly established as beneficial treatment options for patients with IDH1 or IDH2 mutant relapsed and refractory AML.
  - Randomized phase 3 study with Enasidenib versus Conventional Care Options had significant imbalances in the treatment arms that confound the results.
  - The choice to use ivosidenib or olutasidenib in patients with relapsed/refractory IDH1 mutant AML should be driven by side effect profile for the patient in front of you.

- The combination of Ivosidenib or Enasidenib with induction chemotherapy is safe. Efficacy being investigated in HOVON placebo-controlled phase 3 study (results 2027-2028?)

- Ivo/Aza for newly diagnosed IDH1 mutant AML should be a standard of care for newly diagnosed IDH1 mutant patients unfit for intensive chemotherapy

- Benefit of triplets (aza/ven/ivo) versus doublets (aza/ven or aza/ivo) is VERY expensive. More isn't necessarily better (or cheaper!)

Questions from General Medical Oncologists/Hematologists

- What would you recommend as the next line of treatment for an older patient with AML with an IDH1 mutation who has disease progression after venetoclax/azacitidine?
- If an older patient has an IDH1 mutation, how do you choose between giving Aza/Ven and Aza/ivosidenib?
- 80 yo woman, IDH1 and FLT3-ITD-mutated AML. For patients with R/R AML that harbors FLT3 and IDH1 mutations who have not received targeted therapy in the front line, how do you choose which agent to use first — IDH1 inhibitor or FLT3 inhibitor?

Agenda

Module 1: Treatment for Older Patients with Acute Myeloid Leukemia (AML) — Prof Wei

Module 2: Selection of Initial Therapy for Younger Patients with AML without a Targetable Mutation, Including Those with Secondary AML — Dr Stone

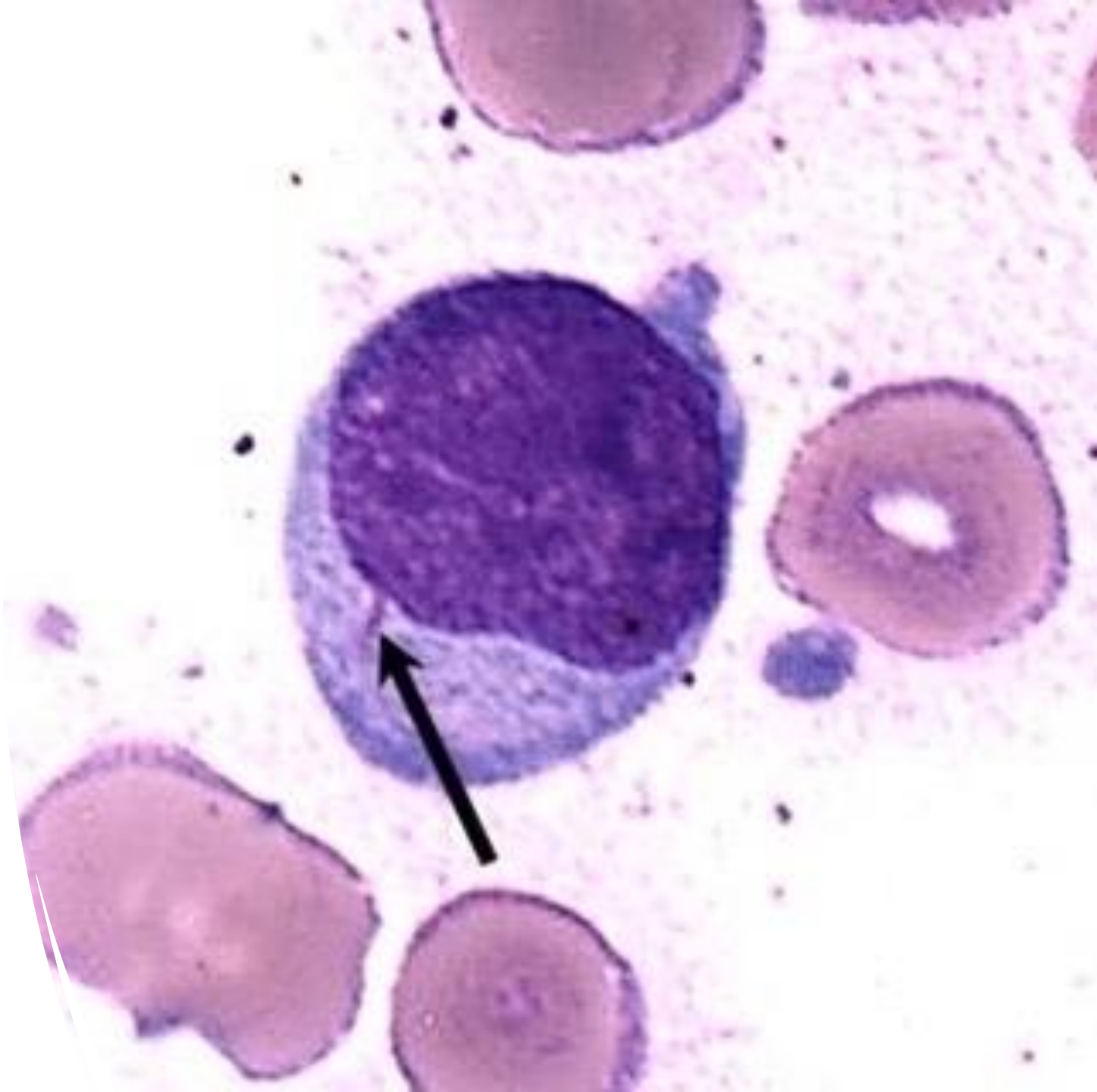
Module 3: Role of FLT3 Inhibitors in AML Management — Dr Perl

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

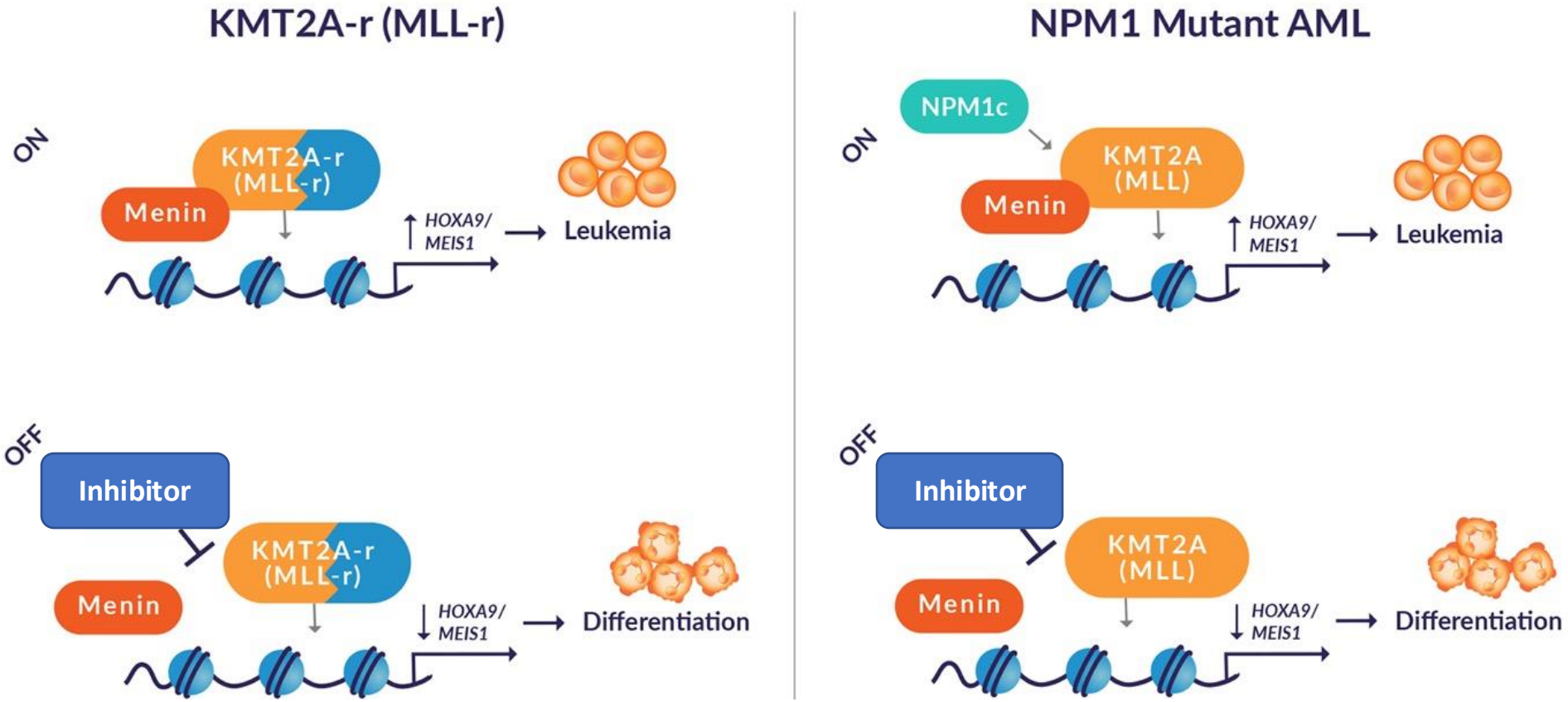
Module 5: Potential Role of Menin Inhibitors and Other Novel Agents in the Treatment of AML — Dr Wang

Potential Role of Menin Inhibitors and Other Novel Agents in Treatment of AML

Eunice S. Wang MD
Leukemia Service
Roswell Park Comprehensive Cancer Center, Buffalo, NY



Menin Inhibition: Targeted therapy for AML



Targeting the menin-KMT2A(MLL) interaction to reverse epigenetic dysregulation in MLL-rearranged AML

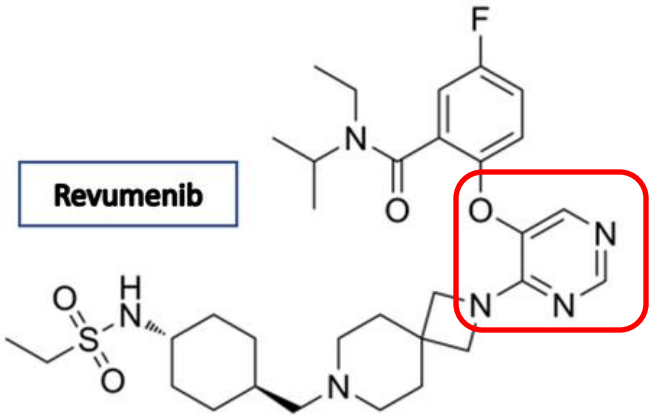
A central role for menin-KMT2A(MLL) interaction in epigenetic dysregulation in NPM1-mutant AML

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

Menin Inhibitors in Clinical Development (Nov 2024)

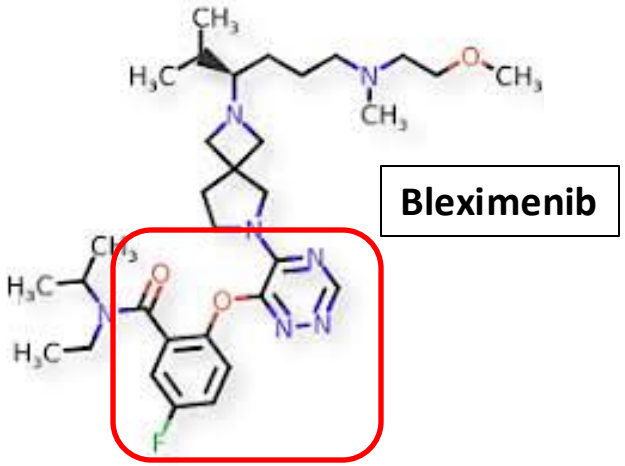
Trial name (NCT)	Agent (route)	Phase 1/ 2 expansion cohorts For relapsed/refractory disease	Phase /# pts	Current status
AUGMENT-101 (NCT04065399)	**Revumenib** (SNDX-5613) PO BID	(a) ALL or MPAL with *KMT2Ar* (b) AML with *KMT2Ar; (c) NPM1*	Phase 1 /2 (n=186)	**Ph2 NPM1^{mut} pending FDA approval Nov 15, 2024**
KOMET-001 (NCT04067336)	**Ziftomenib** (KO-539) PO QD	(a) AML with KMT2Ar (b) AML with NPM1c	Phase 1 /2 (n=199)	**Registrational trial (44 sites) FDA breakthrough NDA in 2025**
NCT04811560	**Bleximenib** (JNJ-75276617) PO QD	(a) AML/ALL with *KMT2Ar* (b) AML with *NPM1c*	Phase 1 (n=110)	**Phase 1 (EHA 2024) Recruiting in combination with chemo**
NCT04988555	**Enzomenib** (DSP-5336) PO QD	RR-AML/RR-ALL Ph2:*NPM1/KMT2Ar*	Phase 1/2 (n=70)	**Phase 1 (EHA 2024) Recruiting**
COVALENT-101 (NCT05153330)	BMF-219 PO	(a) AML/ ALL (KMT2Ar, *NPM1*) (b)DLBCL; (c) MM; (d) CLL/SLL	Phase 1 (n=177)	Multiple cohorts Actively enrolling

Menin Inhibitors: Orally bioavailable inhibitors of the protein-protein interaction between menin and KMT2A

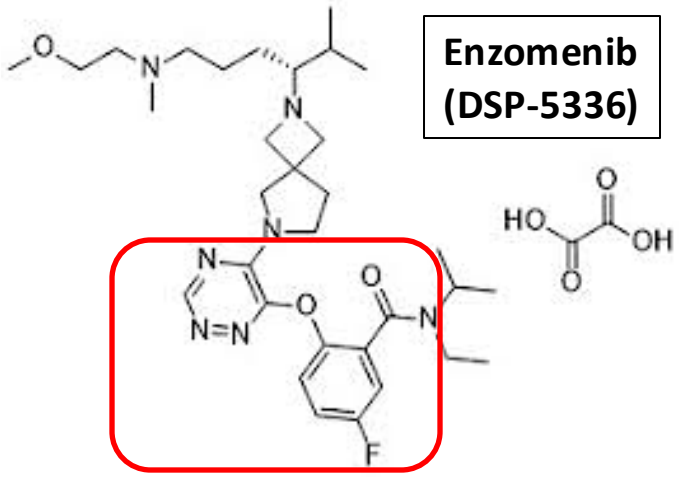


Revumenib

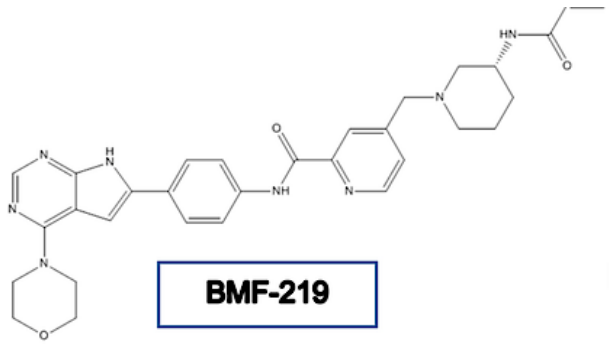
pyrimidine



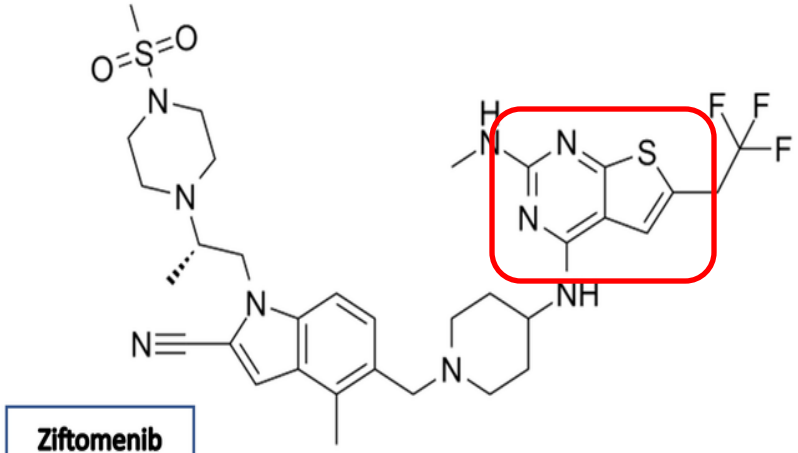
Bleximenib



Enzomenib
(DSP-5336)



BMF-219

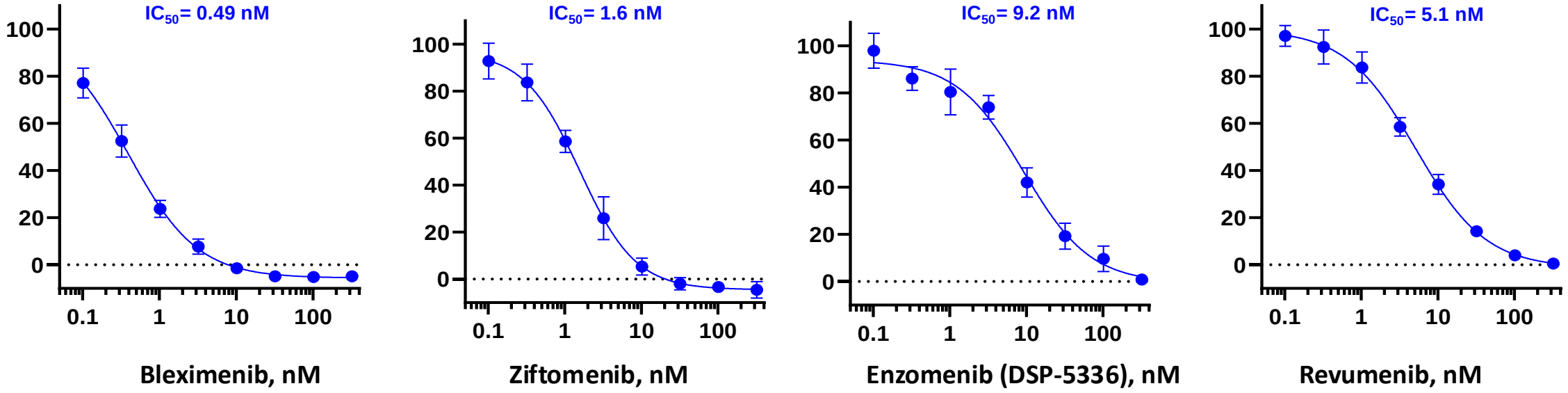


Ziftomenib

thienopyrimidine

Multiple agents potently inhibit protein-protein binding of Menin to KMT2A complex

Bleximenib	Ziftomenib	Enzomenib (DSP-5336)	Revumenib



- All compounds inhibit the protein-protein binding of menin to KMT2A complex
- Similar 50% inhibitory in vitro concentrations (0.49 to 9.2 nM)

Perner F, et. al. AACR, 2023

Revumenib: First approved menin inhibitor (Nov 15, 2024)

SNDX-5613 (analogue of VTP50469) inhibits MLL-menin interaction and exhibits potent inhibition in KMT2Ar AML models.

Menin interactions with KMT2A (MLL1) fusion proteins are involved in driving acute leukemias with a *KMT2A* gene rearrangement (*KMT2Ar*, also known as mixed-lineage leukemia). The menin-KMT2A interaction is now a therapeutic target – and you can take action with revumenib.

First menin inhibitor

A first-in-class, oral, selective inhibitor that disrupts the menin-KMT2A (MLL1) interaction

Inclusive population

Approved for use in both adult and pediatric patients (1 year and older)

Only targeted therapy

First and only targeted therapy for any lineage of R/R acute leukemia with a *KMT2A* translocation (AML, ALL, and MPAL)

Krivtsov AV et al Cancer Cell 36: 660, 2019; Uckelmann HJ et al Science 367: 586, 2020.

Phase 2: Revumenib in R/R *KMT2Ar* Acute Leukemias
Patient characteristics (n=94)

Parameter	Efficacy Population (n = 57)[a]	Safety Population (N = 94)[b]
Age, years, median (range)	34.0 (1.3-75.0)	37.0 (1.3-75.0)
<18, No. (%)	13 (22.8)	23 (24.5)
≥18 to <65, No. (%)	37 (64.9)	58 (61.7)
≥65, No. (%)	7 (12.3)	13 (13.8)
Primary refractory, No. (%)	14 (24.6)	18 (19.1)
Relapse refractory, No. (%)	32 (56.1)	54 (57.4)
Acute leukemia type, No. (%)		
AML	49 (86.0)	78 (83.0)
ALL	7 (12.3)	14 (14.9)
Acute leukemia of ambiguous lineage	1 (1.8)	2 (2.1)
Prior lines of therapy, No., median (range)	2 (1-11)	2 (1-11)
1, No. (%)	17 (29.8)	25 (26.6)
2, No. (%)	14 (24.6)	28 (29.8)
≥3, No. (%)	26 (45.6)	41 (43.6)
Prior venetoclax, No. (%)	41 (71.9)	61 (64.9)
Prior HSCT, No. (%)	26 (45.6)	47 (50.0)

Issa G et al JCO (Aug 2024 online)

Phase 2: Revumenib in R/R *KMT2Ar* AML/ALL (n=94)

Any grade TEAEs that occurred in ≥25% patients

All terms, n (%)	Safety population (n=94)[a]
Nausea	42 (45)
Febrile neutropenia	36 (38)
Diarrhea	33 (35)
Vomiting	29 (31)
Differentiation syndrome	26 (28)
Hypokalemia	26 (28)
Epistaxis	25 (27)
QTc prolongation	24 (26)

Grade ≥3 TEAEs that occurred in ≥10% patients

All terms, n (%)	Safety population (n=94)[a]
Febrile neutropenia	35 (37)
Decreased neutrophil count	15 (16)
Decreased white blood cell count	15 (16)
Decreased platelet count	14 (15)
Anemia	17 (18)
Differentiation syndrome	15 (16)
QTc prolongation	13 (14)
Sepsis	11 (12)
Hypokalemia	10 (11)

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

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

Note: 50% dose reduction in presence of azoles

Issa G et al JCO (Aug 2024 online)

Phase 2: Revumenib in *KMT2Ar* R/R Acute Leukemias (n=57)

Parameter	Efficacy population (n=57)
ORR, n (%)	**36 (63)**
CR+CRh rate, n (%)	13 (23)
95% CI	12.7–35.8
P value, 1-sided	0.0036
CRc	25 (44)
95% CI	30.7–57.6
Negative MRD status[a]	
CR+CRh	7/10 (70)
CRc	15/22 (68)

Parameter	Efficacy population (n=57)
Best response, n (%)	
CR	10 (18)
CRh	3 (5)
CRi	1 (1.8)
CRp	11 (19)
MLFS	10 (18)
PR	1 (1.8)
PD	4 (7)
No response	14 (25)
Other[b]	3 (5)

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

Issa G et al JCO (Aug 2024 online)

Phase 2 Revumenib in *KMT2Ar* AML/ALL: Responders (n=13)

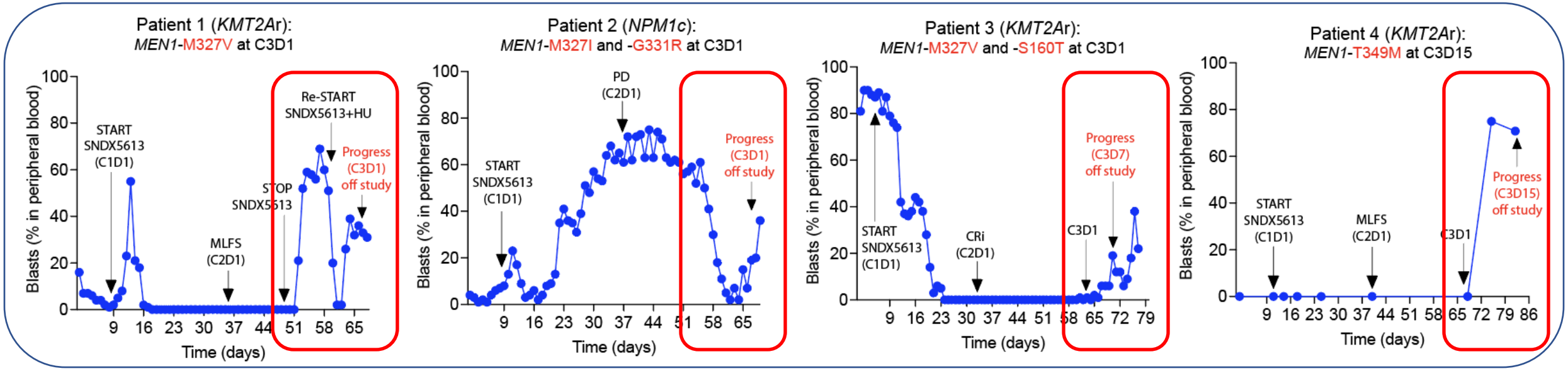
Parameter	Patients achieving CR+CRh (n=13)
Median duration of CR+CRh, months (95% CI)	6.4 (3.4–NR)
Proceeded to HSCT, n (%)	14/36 (39)
Proceeded to HSCT in CR or CRh	6/14 (43)
Proceeded to HSCT in MLFS or CRp	8/14 (57)
Restarted revumenib post HSCT, n (%)	7/14 (50)*

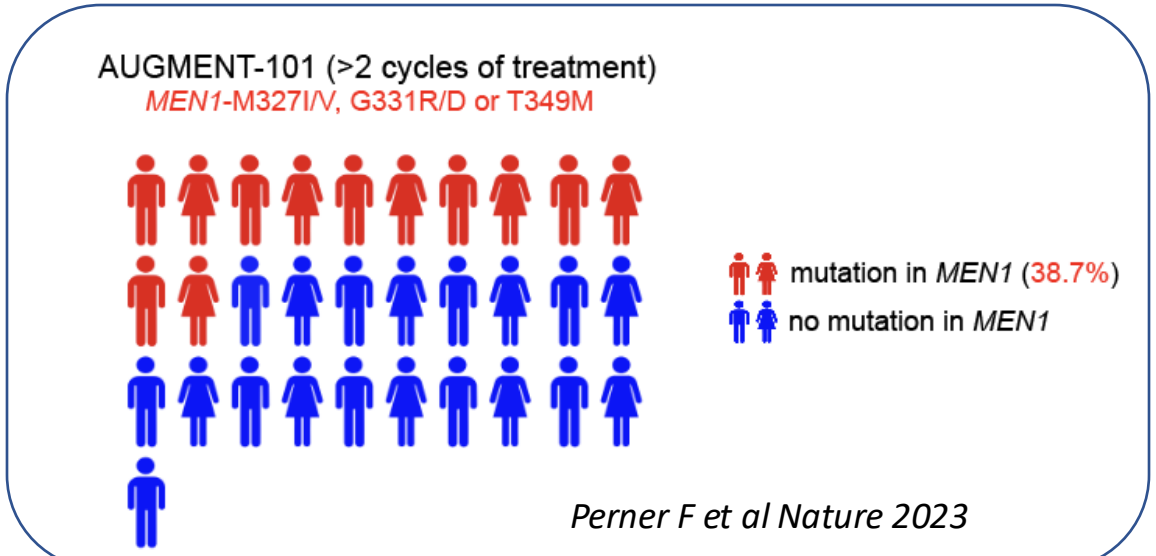
Data cutoff: July 24, 2023
*3 additional patients remained eligible to initiate revumenib after HSCT at the time of data cutoff.

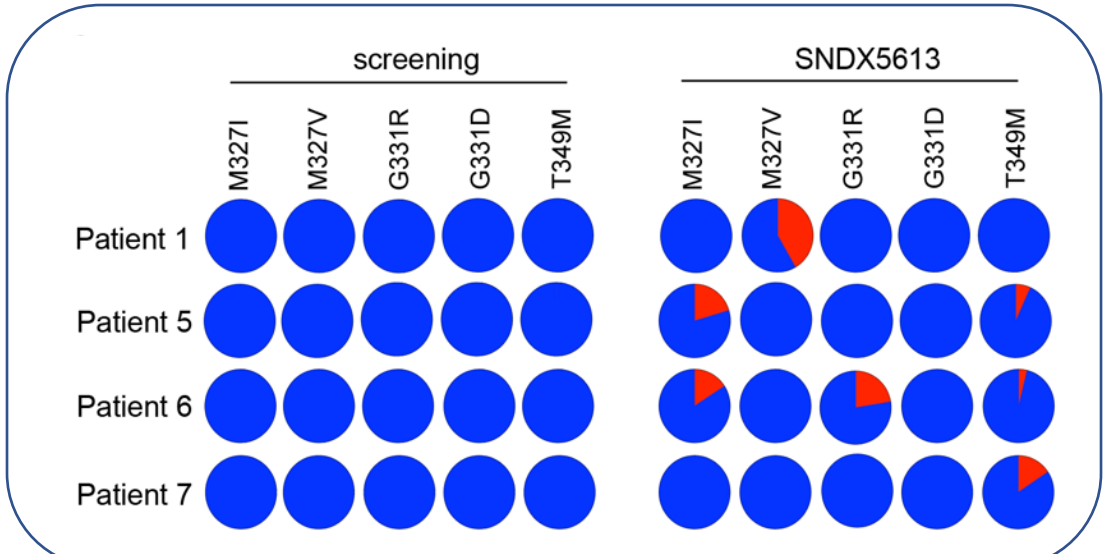
Median overall survival (n=57) = 8.0 months (95% CI 4.1-10.9)

Issa G et al JCO (Aug 2024 online)

Somatic Mutations in Menin in patients on Revumenib

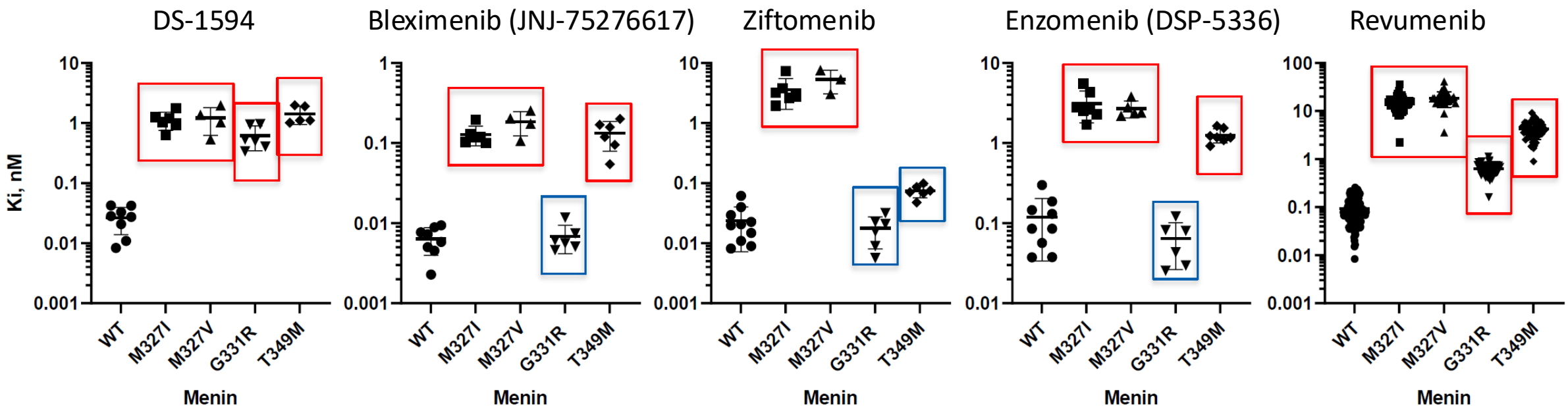






Acquired Resistance Mutations Differentially Affect Clinical Inhibitors

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23



- Binding affinities of all compounds reduced by I/V mutations at M327
  - Range from 20x (Bleximenib [JNJ-75276617]) to 200x (Ziftomenib)
- T349M reduces binding for most inhibitors
- G331R change has variable effects across inhibitors

Perner et al AACR 2023

Ziftomenib 600 mg qd in *NPM1*^{mut} R/R AML (n=20)

≥20% Treatment-Emergent Adverse Events, n (%)	*NPM1*-m, n=20
Patients with TEAEs (All Grades)	**19 (95)**
Diarrhea	9 (45)
Hypokalemia	6 (30)
Nausea	6 (30)
Anemia	6 (30)
Back pain	6 (30)
Epistaxis	5 (25)
Patients with TEAEs (≥Grade 3)	**17 (85)**
Anemia	17 (85)
Thrombocytopenia	5 (25)
Febrile neutropenia	4 (20)

Adverse events are listed by preferred term. TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

12-April-2023 Data Cut

≥20% Treatment-Related Adverse Events, n (%)	*NPM1*-m, n=20
Patients with TRAEs (All Grades)	**12 (60)**
Nausea	4 (20)
Differentiation Syndrome	4 (20)
Patients with TRAEs (≥Grade 3)	**6 (30)**

Phase 1b: NPM1 mut R/R AML on ziftomenib 600 mg

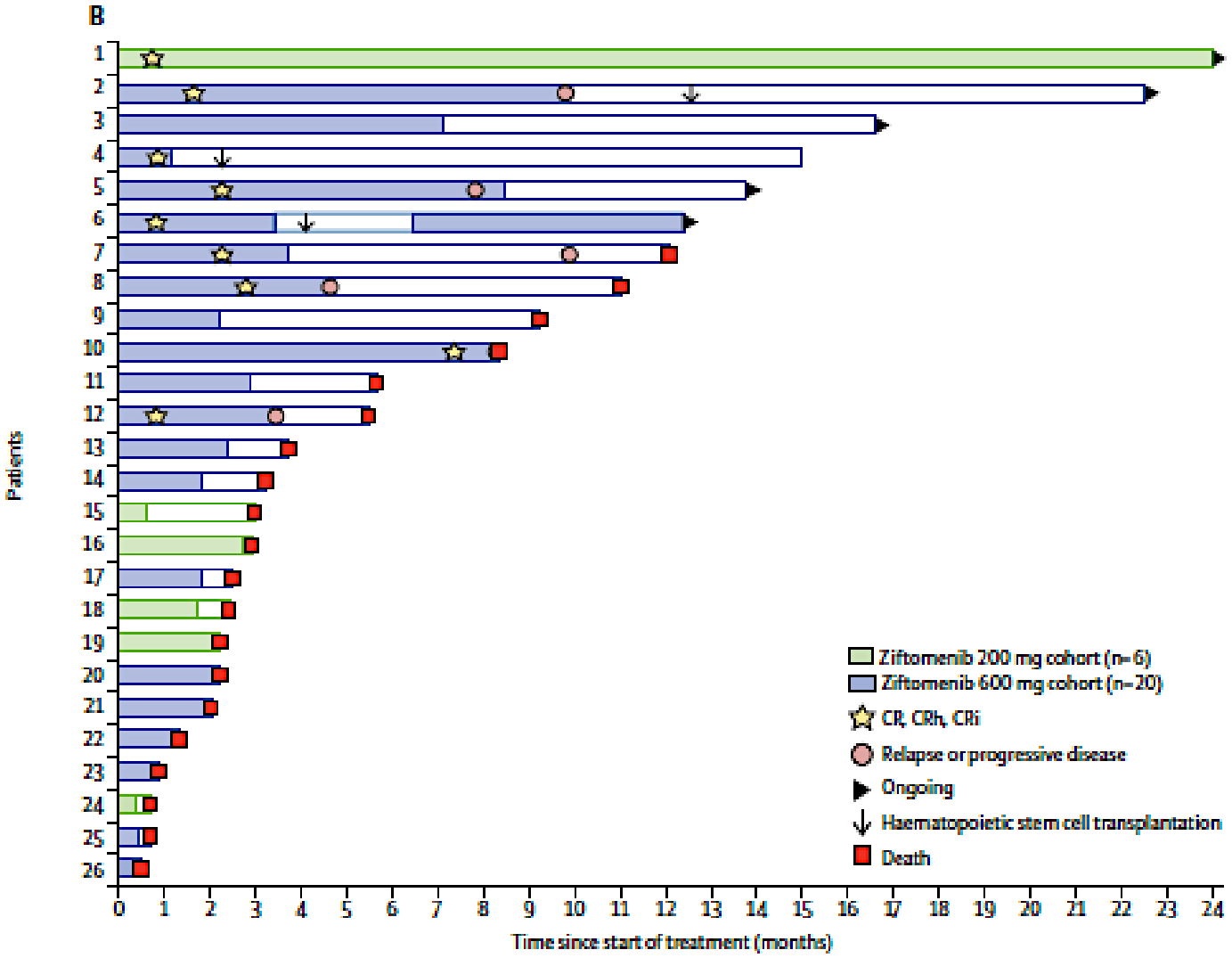
- **No reports of drug-induced QTc prolongation**
- **One grade 3 DS that was manageable; all other DS were grade ≤2**
- **Ziftomenib pharmacokinetics are NOT affected by CYP3A4 Inhibitors, therefore no dose reduction is needed in presence of azole anti-fungal drugs.**

Wang E, Issa G et al Lancet Oncology Oct 2024

Ziftomenib 600 mg qd in *NPM1*^{mut} R/R AML (n=20)

Response	600 mg, n=20
CR	**7 (35)**
CRc rate (CR+CRh+CRi)	**8 (40)**
Overall response rate (CR+CRh+CRi+MLFS)	**9 (45)**
CR	7 (35)
CRh	0
CRi	1 (5)
MLFS	1 (5)

Median time to first response: 51 days



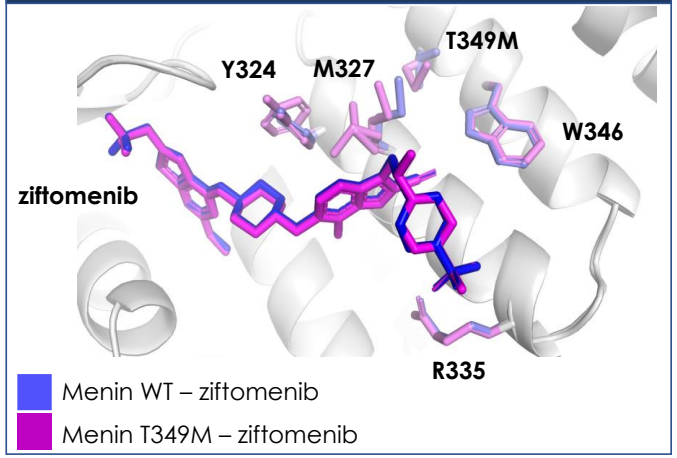
Wang E, Issa G et al Lancet Oncol 2024

Ziftomenib and Known Menin Gatekeeper Mutations

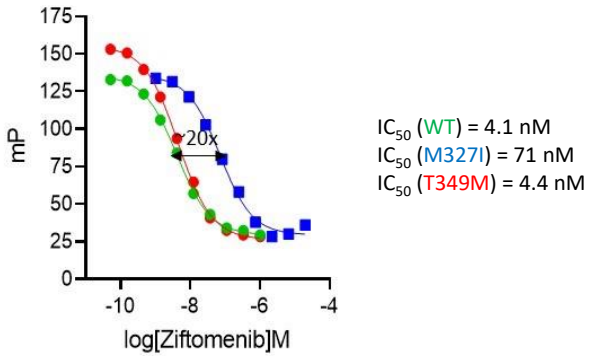
In vitro assays

- No major conformational changes observed in Menin^{T349M} vs. wild-type (WT) protein
- Ziftomenib retains activity against 2 of 3 known *MEN1* mutant loci

Crystal structure of ziftomenib binding to menin



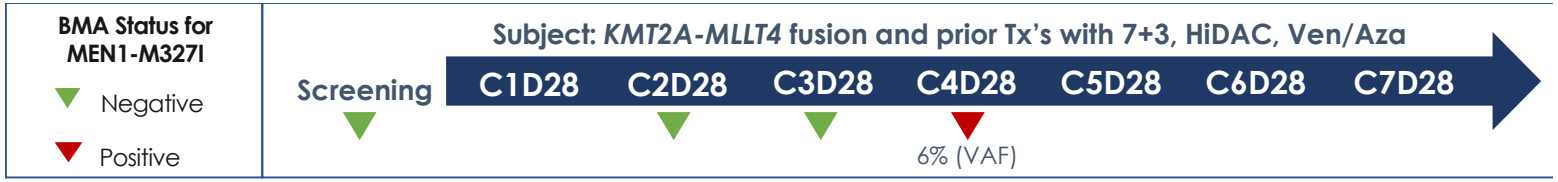
Inhibitory activity of ziftomenib



Patients treated with ziftomenib

- MEN1 mutant RNA was not detected in 13 of 13 other subjects who received ≥2 cycles of ziftomenib and had measurable disease (SD or PD), suggesting that progression in these subjects is not due to MEN1 mutations.

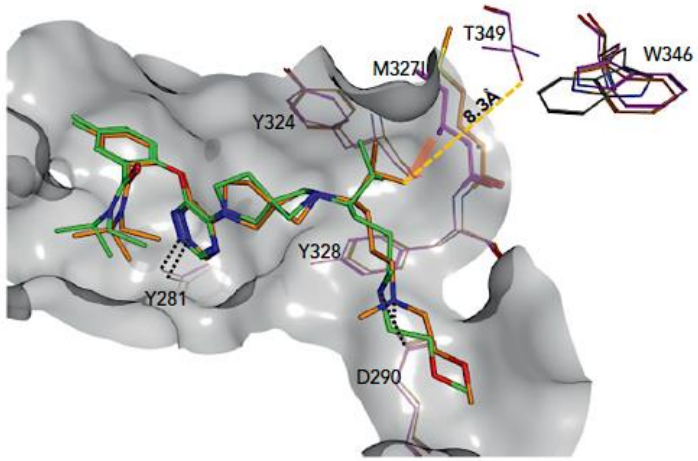
- Using NGS, 1 of 29 subjects (3.4%) developed a resistance mutation (MEN1-M327I) as well as a new RAS mutation on ziftomenib therapy.

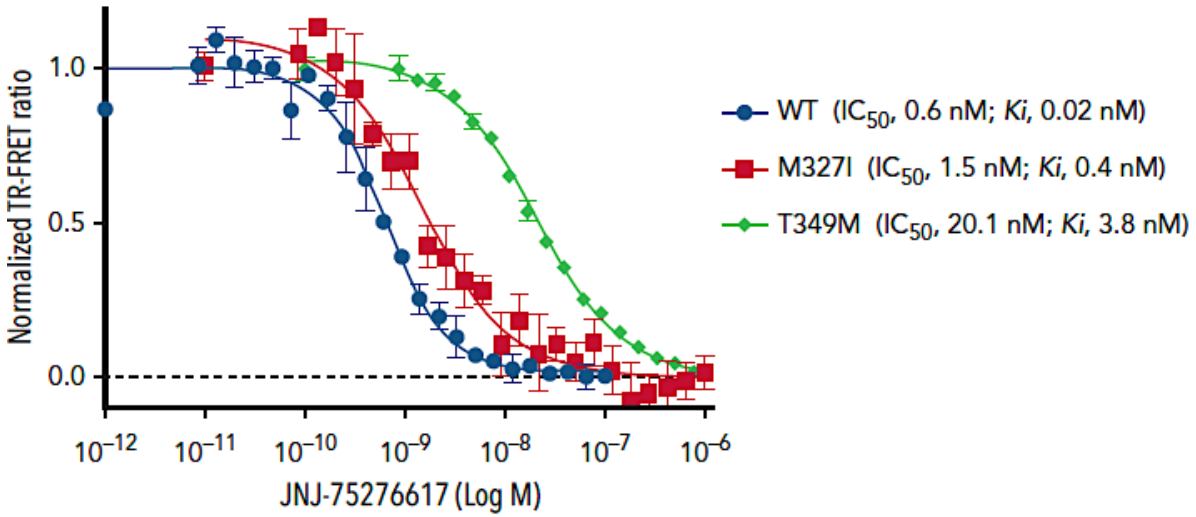


[1]Pemer et al. Abstract #3457 presented at *AACR* April 14-19, 2023, Orlando, FL.

Wang E, Issa G et al Lancet Oncology 2024

Bleximenib (JNJ-75276617) in *NPM1*^{mut} & *KMT2Ar* R/R AML





Kwon M et al Blood 144 (11): 1206, 2024

TRAEs Observed in ≥5% of Pts (N=86)	All Grades	Grade ≥3
Total, n (%)	**45 (52)**	**26 (30)**
Differentiation syndrome (DS)	10 (12)	4 (5)
Neutropenia	10 (12)	9 (11)
Nausea	7 (8)	0 (0)
Thrombocytopenia	7 (8)	5 (6)
Anemia	6 (7)	4 (5)
Fatigue	5 (6)	0 (0)
Arthralgia	4 (5)	0 (0)

Symptoms of differentiation syndrome are not included in this summary; AEs were graded according to CTCAE v5.0

Efficacy subset	45-130 mg BID Cohorts (N=33, acute leukemia)	
ORR (≥PR), n (%)	**15 (46)**	
Ongoing responders	8 (53)	
Best response, n (%)		
CR/CRh/CRi	**9 (27)**	
CR/CRh	7 (21)	
CR	6 (18)	
MLFS/PR	**6 (18)**	
Median time to first response, mos	1.8 (0.9-3.3)	
Median duration of response, mos	6.5 (1.0-NE)	
	KMT2A (N=19)	**NPM1 (N=14)**
ORR, n (%)	8 (42)	7 (50)

Responses were investigator-assessed per modified ELN 2017 recommendations (AML) or ESMO 2016 with NCCN 2020 modifications (ALL)

Jabbour E et al ASH 2023

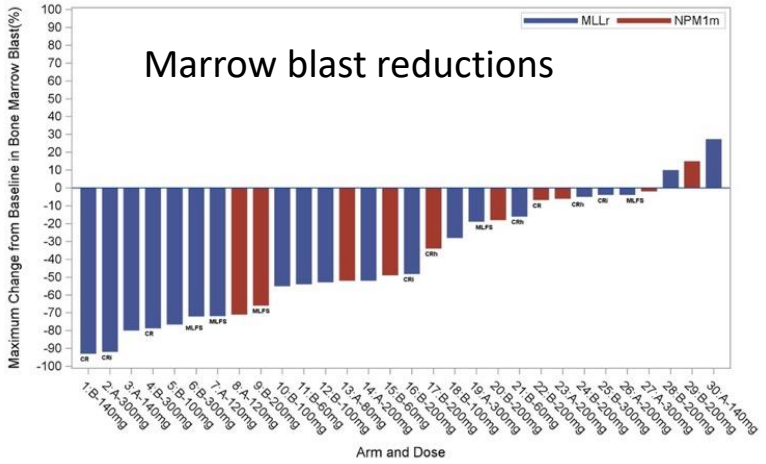
Enzomenib (DSP-5336) in *NPM1^{mut}* and *KMT2Ar* R/R AML

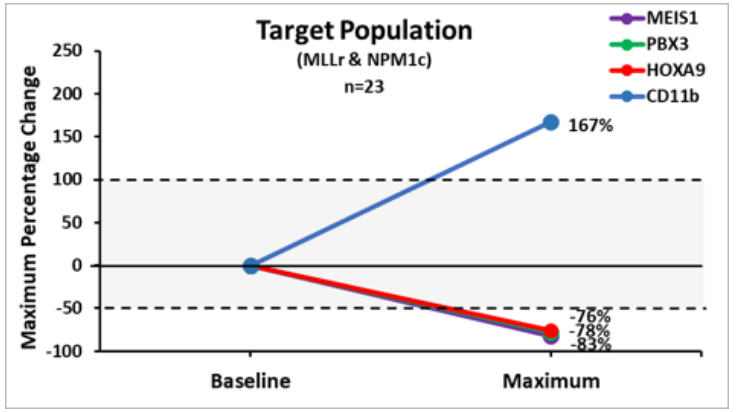
No dose limiting toxicities to date

Preferred Term	Any Grade	Grade 3+
Vomiting	10 (17.5%)	1 (1.8%)
Nausea	7 (12.3%)	1 (1.8%)

- No DLTs were reported
- No treatment-related deaths
- No DSP-5336 discontinuations due to drug-related adverse events
- Differentiation syndrome (DS) reported in 3 patients (5.7%)
  - These patients did not have hematologic differentiation
  - No mortality or permanent discontinuations of DSP-5336 due to DS
  - No DS prophylaxis used when starting DSP-5336

Responses by ELN 2017 in AML patients w/KMT2Ar or NPM1m at doses ≥ 140 mg BID*	**KMT2Ar** ≥ 140 mg BID *n = 12*	**NPM1m** ≥ 140 BID mg *n = 9*	**KMT2Ar + NPM1m** ≥ 140 mg BID *n = 21*
Objective Response Rate	8 (67%)	4 (44%)	12 (57%)
Composite CR	5 (42%)	3 (33%)	7 (33%)
CR + CRh	2 (17%)	3 (33%)	5 (24%)





Daver N et al EHA abstract 2024

Clinical Efficacy of Menin Inhibitor Monotherapy

Agent (# pts)	Revumenib (n=57)	Ziftomenib (n=20)	Bleximenib (n=33)	Enzomenib (n=21)
Phase Trial	**Phase 2**	**Phase 1b**	**Phase 1**	**Phase 1**
Drug dose	163 mg bid with CYP450 inhibitor	600 mg qd	45-130 mg bid	≥ 140 mg bid
KMT2Ar	94 (100%)	NA	19 (58%)	12 (57%)
***NPM1*^{mut}**	NA	20 (100%)	14 (42%)	9 (43%)
CR	10 (18%)	7 (35%)	6 (18%)	0 (0%)
CR/CRh	13 (23%)	7 (35%)	7 (21%)	5 (24%)
CRc (CR/CRh/CRi)	14 (25%)	8 (40%)	9 (27%)	7 (33%)
ORR (CRc+PR + MLFS)	36 (63%)	9 (45%)	15 (46%)	12 (57%)

1. Issa G et al JCO (Aug 2024); 2. Wang E et al Lancet Oncol (Oct 2024); 3. Jabbour E et al ASH 2023; 4. Daver N et al EHA abstract 2024

Adverse Events of Menin Inhibitor Monotherapy

Agent (# pts)	Revumenib (n=94)	Ziftomenib (n=83)	Bleximenib (n=86)	Enzomenib (n=57)
Trial	Phase 2	Phase 1/1b	Phase 1	Phase 1
DLT (Y/N)	Ph1: QTc PR	Yes	Yes	No
DLT	Ph1: QTc PR	Gr3 pneumonia Gr4/5 DS	Gr5 DS	NA
DS (all)	26 (28%)	12 (15%)	10 (12%)	3 (5.7%)
DS (≥Gr3)	15 (16%)	10 (12%)	4 (5%)	0 (0%)*
Febr Np (≥Gr3)	36 (38%)	18 (22%)	20 (23%)	12 (21%)
Neutrop (≥Gr3)	27 (28.7%)	7 (8%)	9 (11%)	6 (10.5%)
Thromb (≥Gr3)	20 (21%)	6 (7%)	5 (6%)	8 (14%)
QTc PR (any)	24 (25%)	0 (0%)	1 (1%)	7 (12%)
QTc PR (≥Gr3)	13 (14%)	0 (0%)	1 (1%)	1 (1.8%)

1. Issa G et al JCO (online Aug 2024); 2. Wang E et al (in press); 3. Jabbour E et al ASH 2023;
*4. Daver N et al EHA 2024; *=No DS mitigation used*

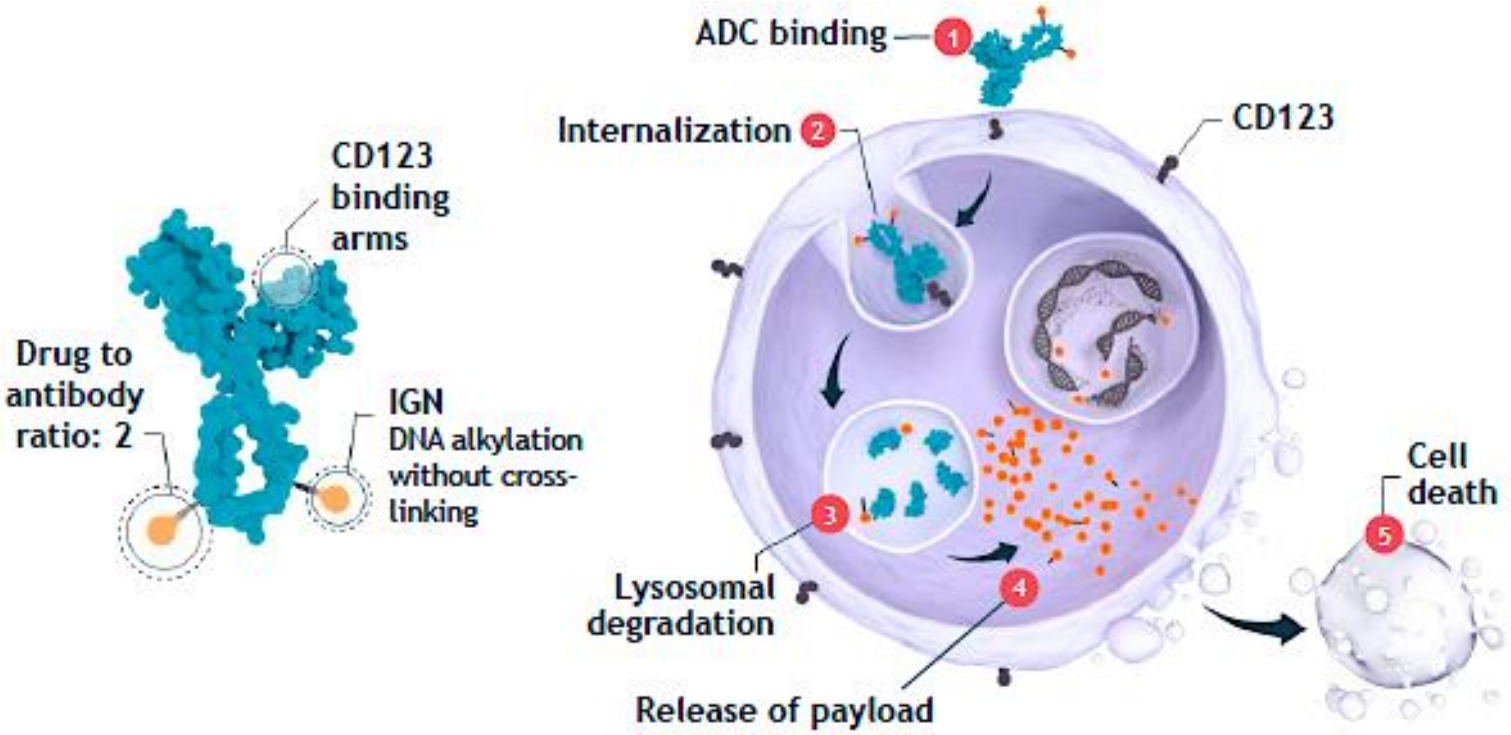
Menin Inhibitor + Ven/Aza Triplet Therapy

Agent (# pts)	Bleximenib + Ven/Aza	SAVE (Revumenib + Ven/Aza)	Beat AML Rev + Ven/Aza
Trial	**Phase 1**	**Phase 1**	**Phase 1**
Disease	**R/R AML**	**R/R AML**	**ND AML older adults**
Number Pts	N=34	N =9	N=24
Start Menin Inhib	C1 D4	C1 D1	C1 D1
Differentiation Synd	2 (Gr3, Gr5)	2 (22%) all Gr1-2	4 (15%)/ 1 Gr3
QTc prolongation	0 (0%)	3 (33%) all Gr 1-2	12 (46%)/3 Gr3+ (12%)
CR	4 (12%)	3 (33%)	18 (69%)
CR/CRh	8 (24%)	4 (44%)	20 (77%)
CRc (CR/CRh/CRi)	14 (41%)	9 (100%)	23 (96%)
ORR (CRc+PR +MLFS)	27 (80%)	9 (100%)	24 (100%)

1. *Issa G et al ASH 2023; 2. Wei A et al EHA 2024; 3. Zeidner J et al EHA 2024*

Targeting CD123: Pivekimab sunirine (IMGN632)

- First-in-class antibody drug conjugate (ADC)
- Comprises a high-affinity CD123 antibody, cleavable linker, and unique indolinobenzodiazepine pseudodimer (IGN) payload which causes single strand breaks and less toxicity to normal marrow progenitors than other payloads.



Daver et al ASH abstract 2023

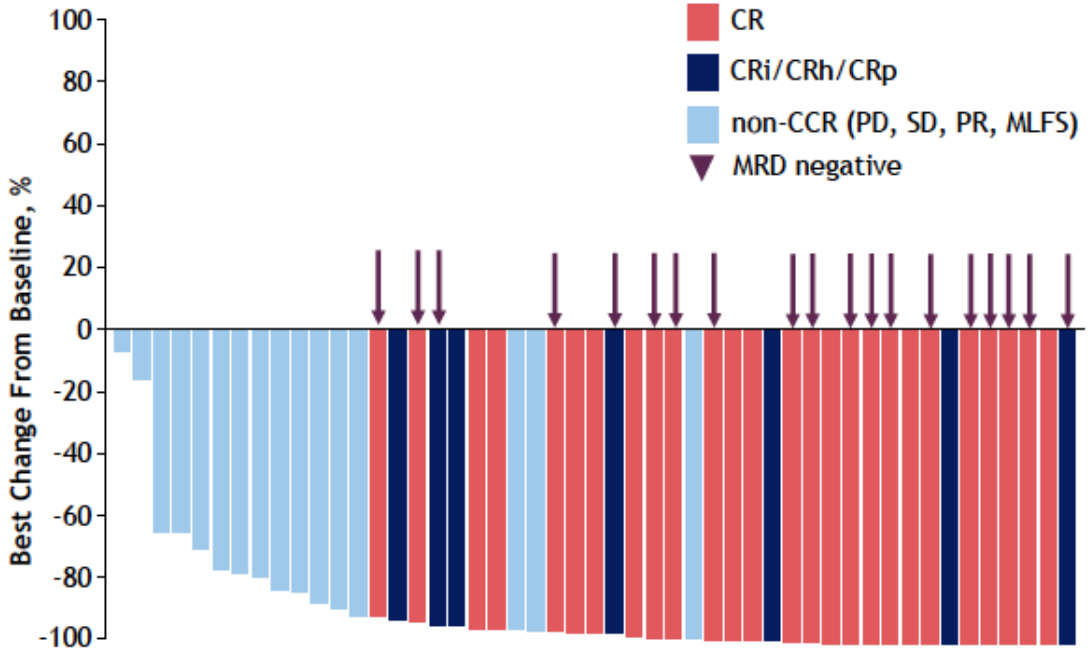
Pivekimab sunirine + AZA/VEN Triplet in CD123+ R/R AML

	CR rate	CCR rate[b]	CCR_{mrd-}[c]
Overall Population (N=50)	54% (27/50)	68% (34/50)	76% (22/29)
Meets unfit FDA criteria[d] (n=23)	61% (14/23)	78% (18/23)	79% (11/14)

Non-hematologic AEs: Infusion reactions (16%), edema
No prolonged count recovery (ANC 34d, platelets 22d)
No VOD/SOS complications

22 of 29 CCRs were MRD-negative (76%)
Time to MRD-negativity= 1.87 months

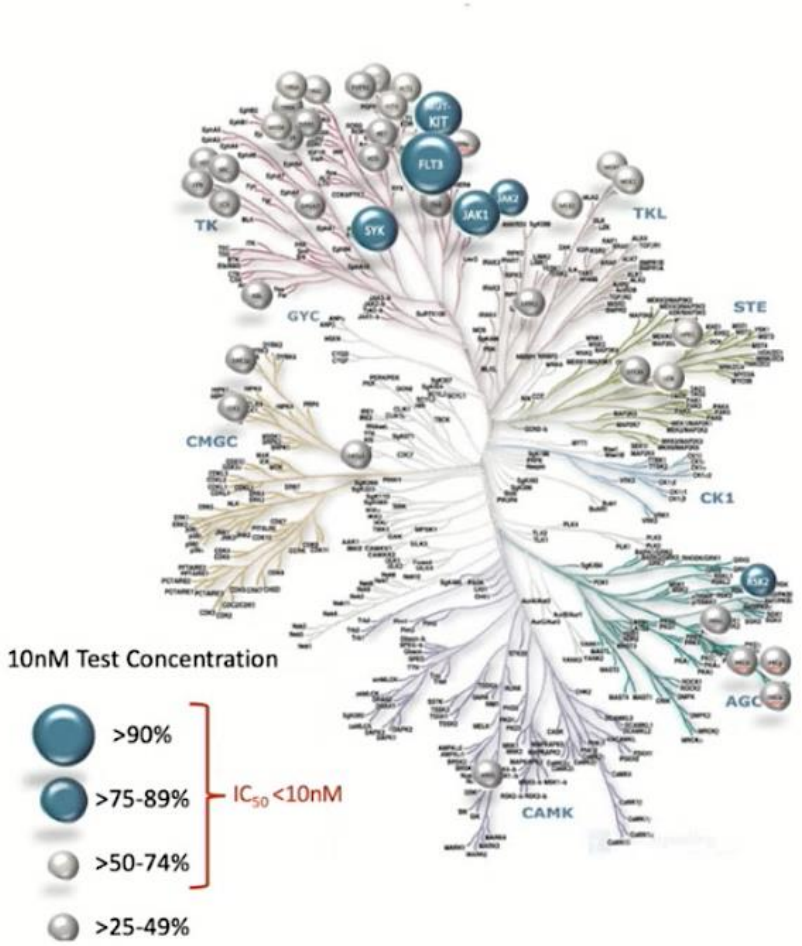
Broad anti-leukemic activity with CR rates 54-61%
Activity seen in poor risk AML subtypes (TP53+, CK)



- In the overall population the CCR_{mrd-} rate was 76% (22/29)
- Of MRD-negative patients, all except one, had undetectable disease below lower limit of detection (0.02%)

Daver N et al ASH abstract 2023

Tuspetinib: Oral inhibitor of FLT3, SYK, KIT, JAK



Assay Methodology	Kinase	Mutation Status	Activity
Binding Affinity (K_D, nM)	FLT3	WT	0.58
		ITD	0.37
		D835Y	0.29
		D835H	0.4
		ITD/D835V	0.48
		ITD/F691L	1.3
Inhibition of Kinase Enzyme Activity (IC_{50}, nM)	FLT3	WT	1.1
		ITD	1.8
		D835Y	1.0
	SYK	WT	2.9
	JAK	JAK-1	2.8
		JAK-2	6.3
		JAK-2 (V617F)	9.9
	c-KIT	WT	> 500
		D816H	3.6
		D816V	3.5
	RSK	RSK-2	9.7
	TAK1-TAB1	TAK1-TAB1	7.0

<u>Phase 1</u>
<u>Monotherapy in R/R AML</u>

RP2D: 80 mg daily
TEAE: Diarrhea 11%

13% CRc in all patients
(29% in ven-naïve)
36% CRC in ven-naïve at the RP2D dose level

Daver N et al ASH 2023

Tuspetinib/Ven in Ven-naïve and prior Ven R/R AML (n=49)

Key Findings

- TUS/VEN is active across broad populations of R/R AML
- TUS/VEN is active in FLT3^{WT}, representing ~70% of AML patients
- TUS/VEN has activity in difficult-to-treat Prior-VEN AML population

Composite Complete Remission (CRc) in Evaluable Patients[1]

FLT3 Status	ALL	VEN-Naïve	VEN-Prior	FLT3i-Prior
ALL	25% (9/36)	43% (3/7)	21% (6/29)	
FLT3^{WT}	20% (5/25)	33% (2/6)	16% (3/19)	
FLT3^{MUT}	36% (4/11)	100% (1/1)	30% (3/10)	44% (4/9)

[1]Data cut Oct 23, 2023

Patient Status

49 : Patients dosed with TUS/VEN

36 : Evaluable patients who completed C1 or discontinued prior to C1

13 : Too early to assess (in C1 and still on study)

Daver N et al ASH 2023

Summary: Menin Inhibitors and other novel agents

- Menin inhibitors: Newest targeted therapy for AML/ALL
  - Clear clinical activity in *NPM1*^{mut} and *KMT2Ar* leukemias, other diseases?
  - However… short duration of responses, improved activity in Rx-naive pts, and emergence of menin resistance
  - Combination regimens in the upfront setting are underway….

- Pivekimab sunirine: Anti-CD123 antibody drug conjugate
- Tuspetinib: Multi-kinase inhibitor (FLT3, SYK, KIT, JAK)
- Immunotherapy: Anti-CD47, bispecifics, CAR-T, adaptive cell therapy

Questions from General Medical Oncologists/Hematologists

- Please comment on CD123-targeting drugs — how different is pivekimab from tagraxofusp?
- Why are menin inhibitors active in patients with KMT2A rearrangements and NPM1 mutations? Would these agents be worth a try in patients without these alterations?
- Please comment on how you are using menin inhibitors, and from your experience, what are the associated safety issues, if any?
- When do we expect to see menin inhibitors used in the community?

Questions from General Medical Oncologists/Hematologists

- **Can the faculty comment on CAR T-cell therapy in AML? Have preliminary results been presented? How is CAR T being further evaluated?**
- **What other novel agents/approaches are under investigation in AML? Do you believe any of these will eventually reach our clinics?**

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