

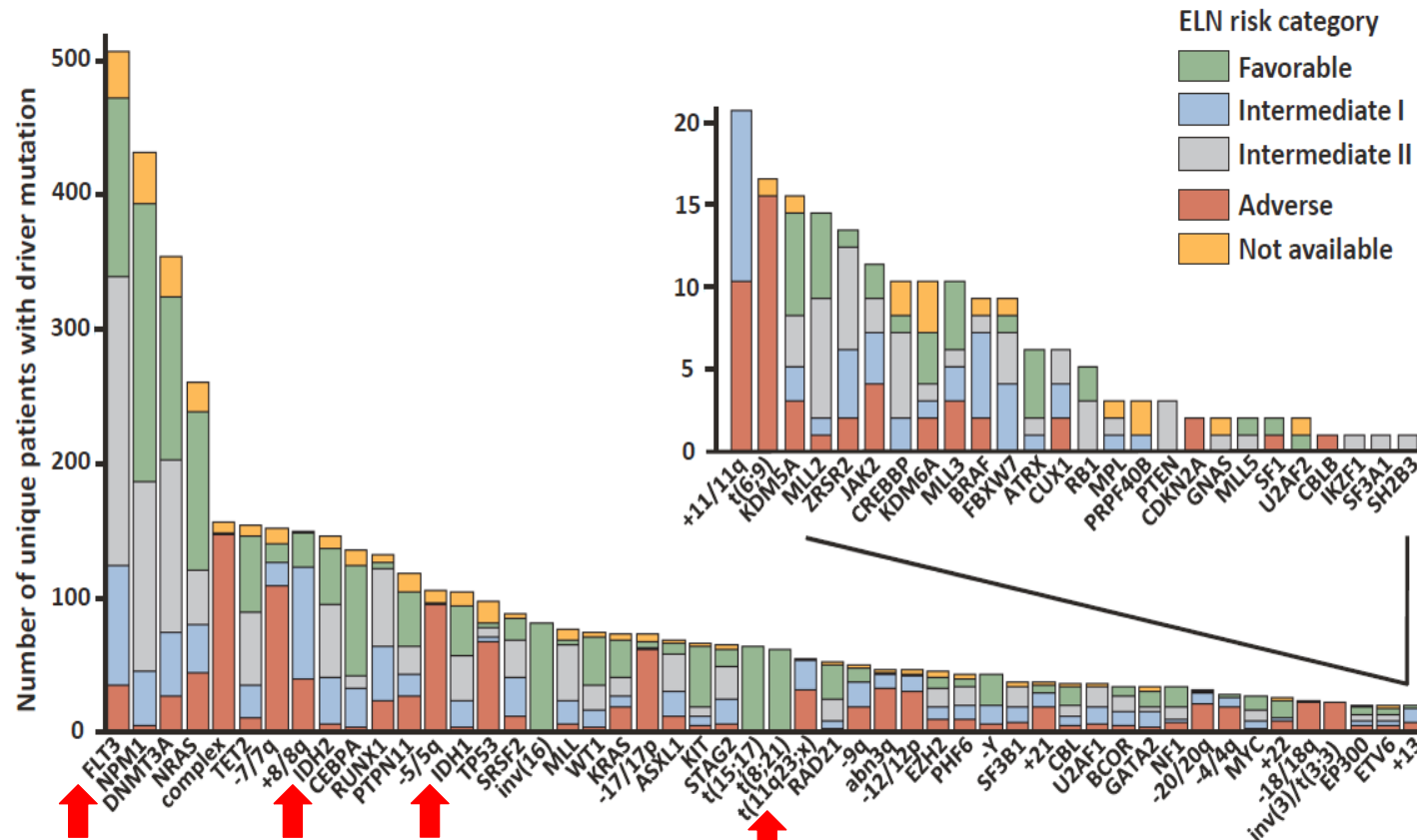
AML in 2026: Targeted Therapies in AML

Courtney DiNardo, MD

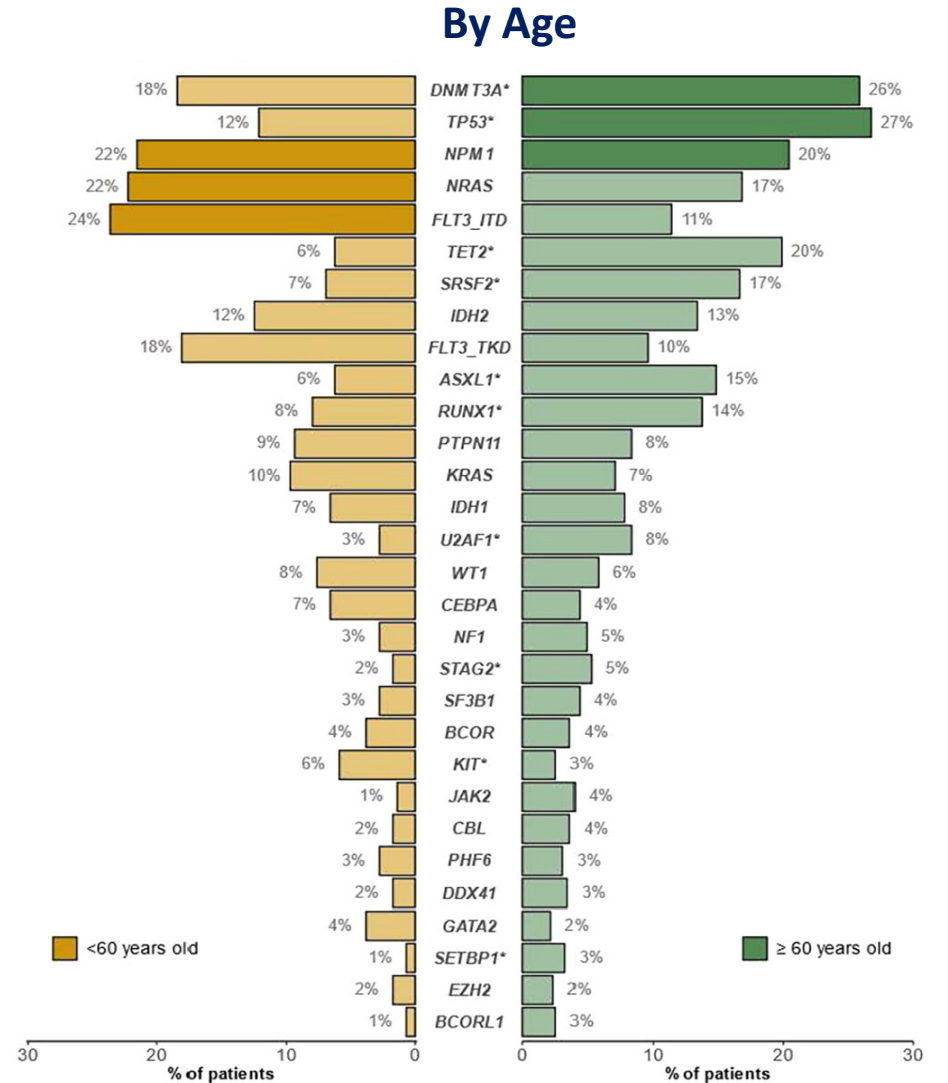
Department of Leukemia
UT MD Anderson Cancer Center



Cytogenetic and Mutational Landscape of AML



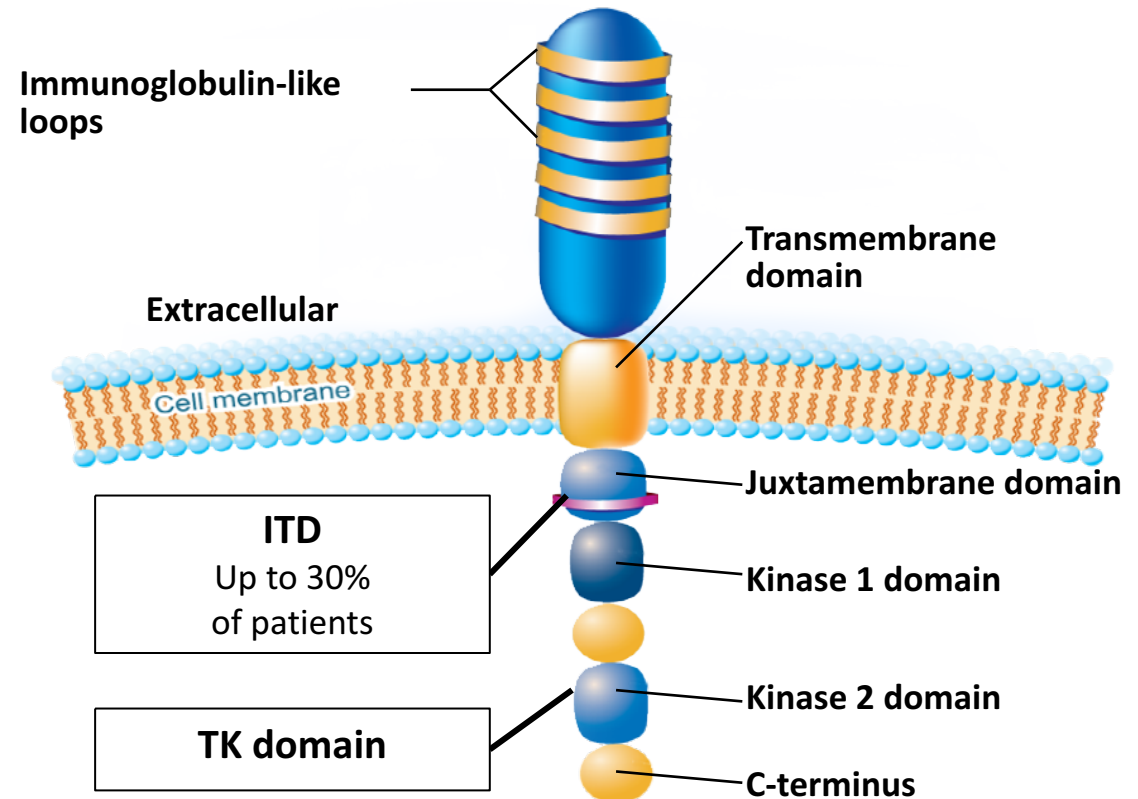
- Targeted resequencing of 111 myeloid cancer genes (combined with cytogenetic profiles) in 1540 AML
- 5236 driver mutations (i.e., fusion genes, copy number alterations, gene mutations) involving 77 loci
- 6 genes mutated in >10% pts; 13 genes 5–10% pts; 24 genes 2–5% pts; 37 genes <2% pts



*indicates mutations with significantly different incidence by age group

Characteristics of FLT3 Mutations in AML

- ***FLT3-ITD*** in ~25% and ***FLT3-TKD*** in ~10% AML
- More frequent in younger pts, *de novo* AML and diploid cytogenetics
- Leads to constitutive activation of FLT-3 receptor
- ***FLT3-ITD*** independent predictor of poor prognosis; often associated with more proliferative disease



Activated proliferation and pro-survival pathways

Quick Review of FLT3 Inhibitors

Midostaurin
(Type 1 – TKD and ITD)

- Approved in **Newly Dx** Fit AML in combo w/ chemotx
- GI effects/nausea/diarrhea, transaminitis, rash

Quizartinib
(Type 2 – FLT3-ITD only)

- Approved in **Newly Dx** Fit AML in combo with chemotx
- QTC prolongation, potential ventricular arrhythmias, myelosuppression, transaminitis

Gilteritinib
(Type 1 – TKD and ITD)

- Approved in **R/R AML** as monotherapy
- QTc prolongation, myelosuppression, and transaminitis

Important Differences of FLT3 inhibitors

| | | First generation | Second generation |
|---------|---------------------------------------|---|---|
| | | Lack specificity for FLT3 | More specific and potent |
| Type I | Pure ATP-competitive* | Sunitinib Lestaurtinib Midostaurin | Gilteritinib Crenolanib |
| | Active on <u>ITD+</u> and <u>TKD+</u> | | |
| Type II | Maintain the inactive conformation† | Sorafenib Tandutinib | Quizartinib Ponatinib Pacritinib Ibrutinib |
| | Active on <u>ITD+</u> only | | |

*blue and green compounds are clinically used in the US for FLT3-mutated AML

*Bind to the ATP-binding site when the receptor is in the active conformation.

†Interact with a hydrophobic region immediately adjacent to the ATP binding site that is only accessible when the receptor is in the inactive conformation; prevent receptor activation. As most TKD (D835) mutations favor the active conformation, Type II inhibitors are usually ineffective on TKD-positive cells.

2nd GEN:
 More potent and selective:
 FLT3, KIT, CSF1R,
 PDGFRA/B



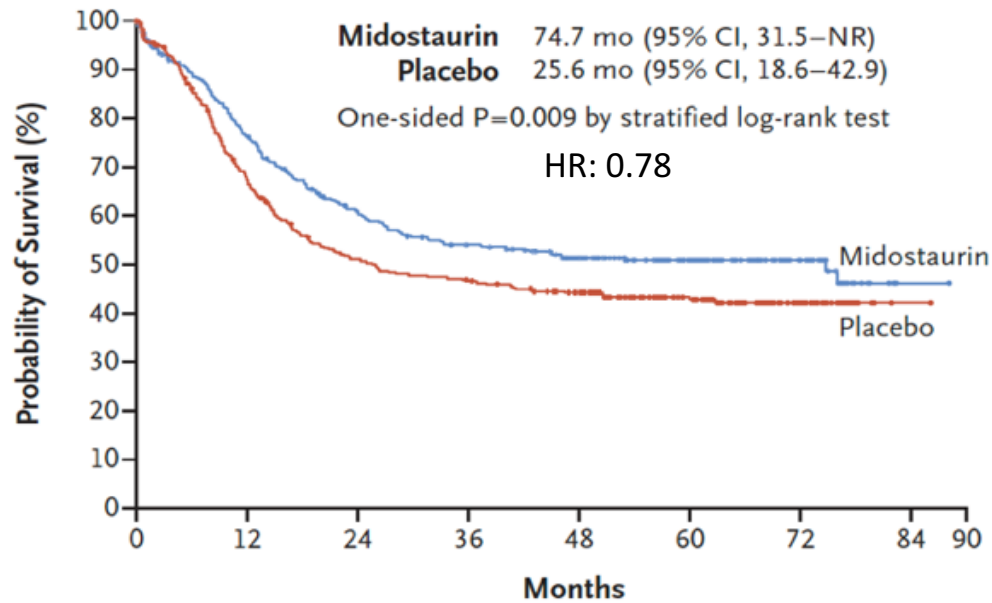
Midostaurin



Quizartinib

Approved Regimens for Newly Dx FLT3-Mutated AML

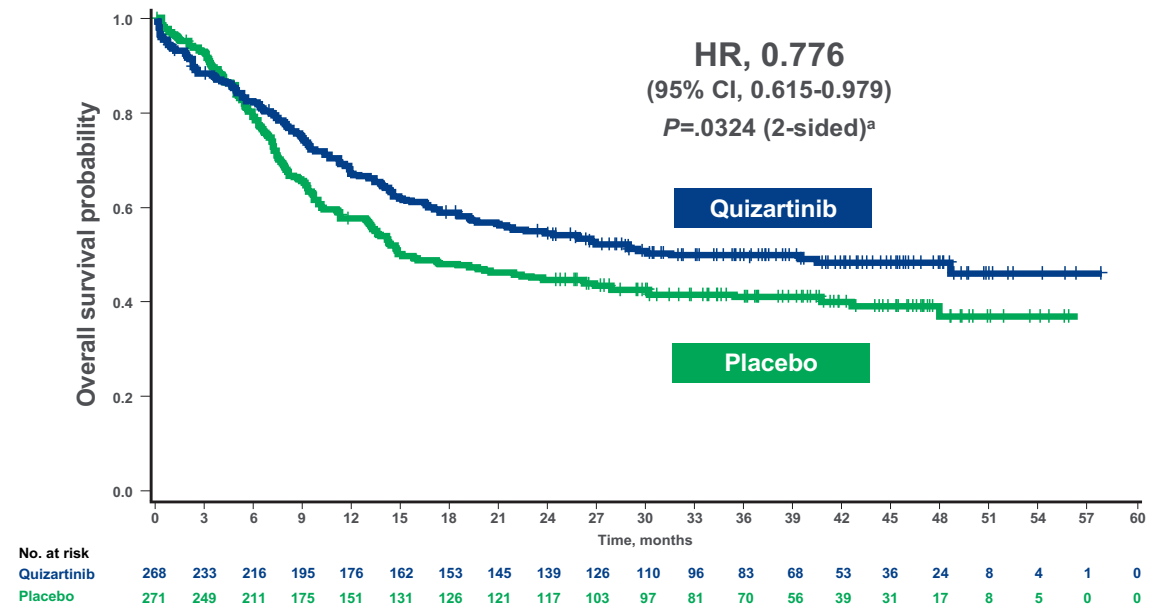
| | CR |
|-------------|-----|
| Midostaurin | 68% |
| Placebo | 61% |



FLT3-ITD and FLT3-TKD mutations, age < 60 yrs

- 60-day mortality: not reported

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



FLT3-ITD only, and age < 75 yrs

- 60-day mortality: quizartinib 7.5%, placebo 4.9% (mostly infections)

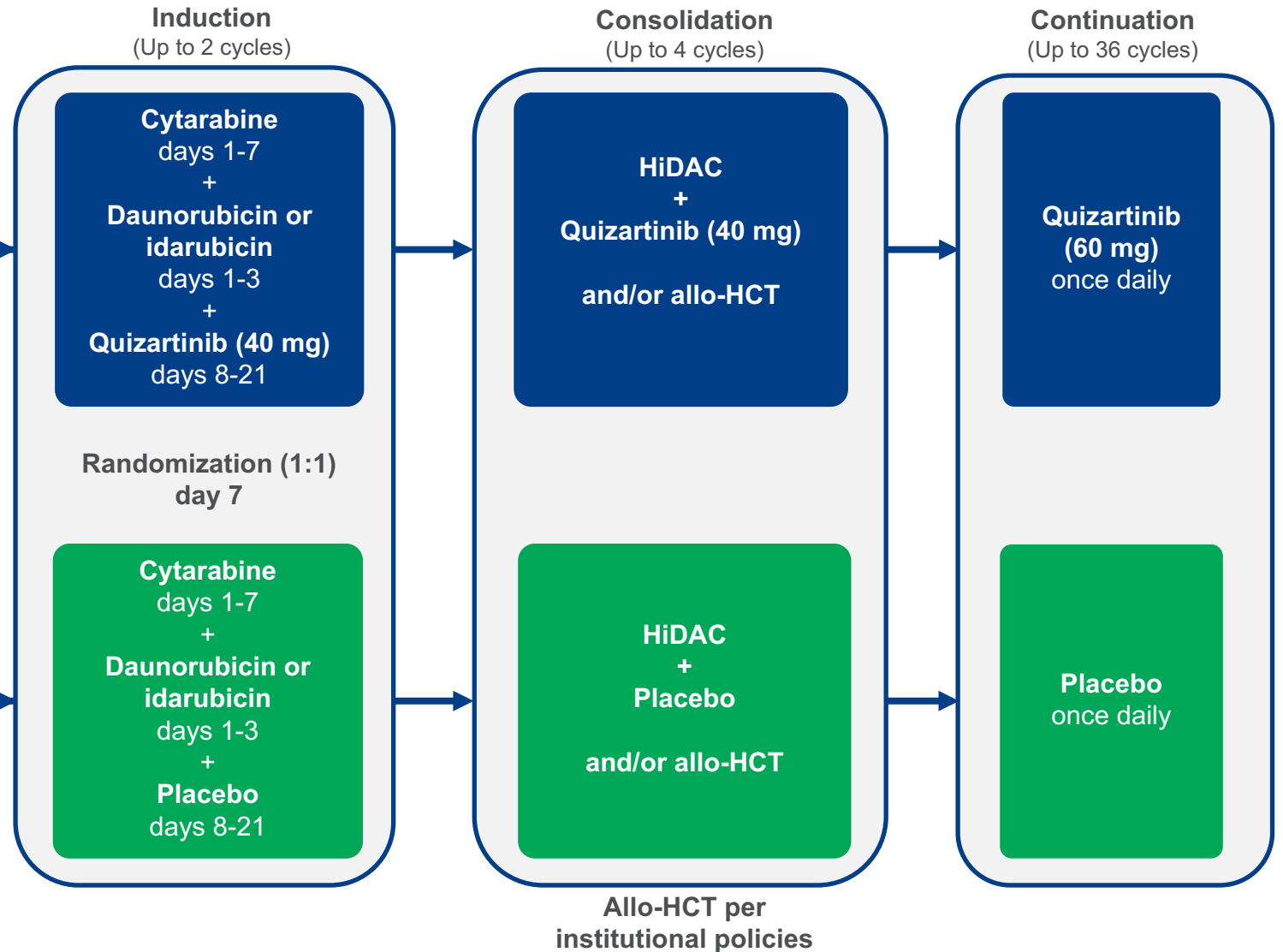
QuANTUM-First Phase 3 Trial: Quizartinib Plus Standard Induction Chemotherapy Followed by Single-Agent Quizartinib

Enrollment dates: September 2016 to August 2019
**trial designed and started before midostaurin approval, so randomization is to placebo*

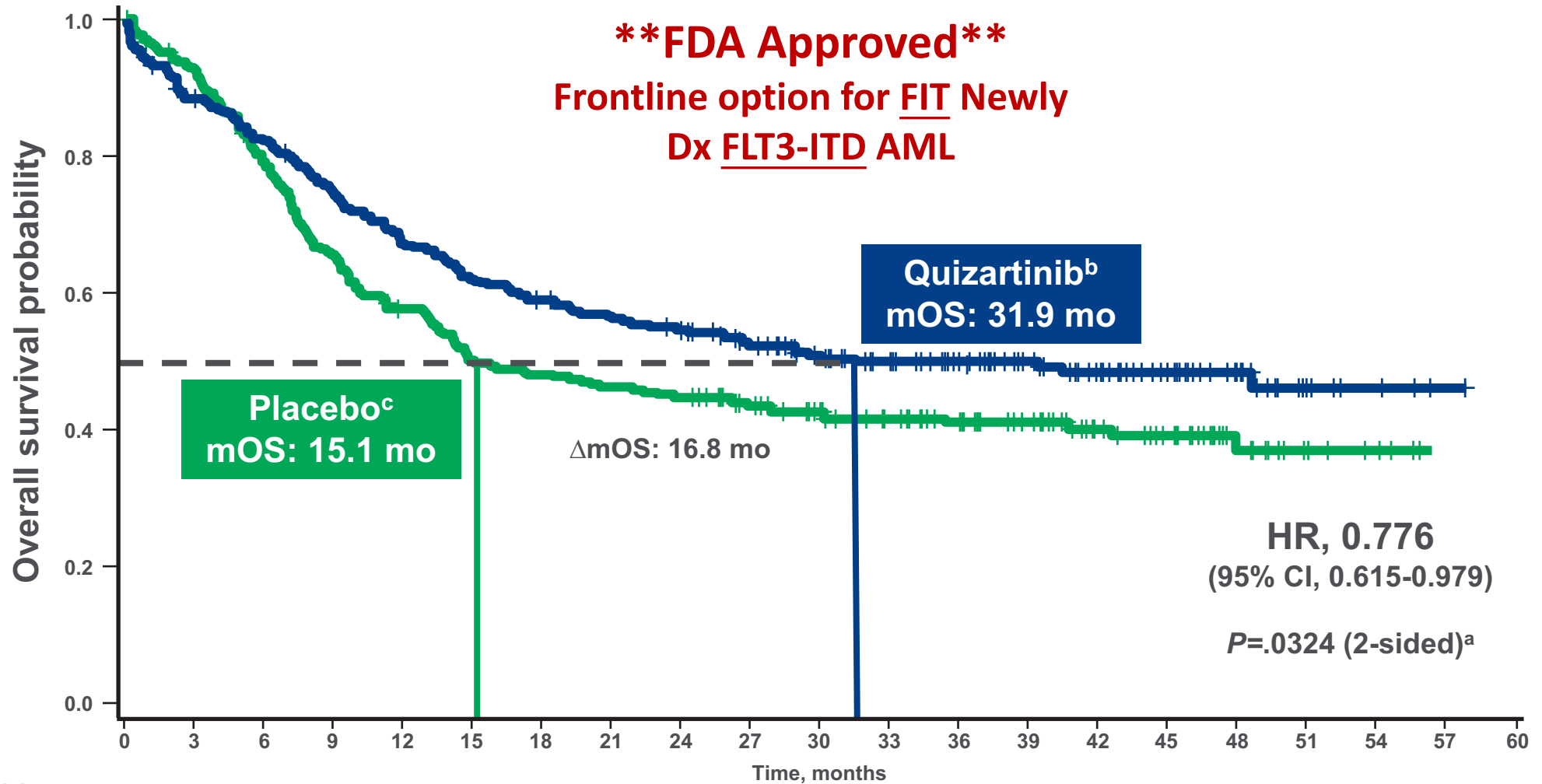
- Newly diagnosed **FLT3-ITD+** AML
- 18-75 years of age
- $\geq 3\%$ FLT3-ITD allelic frequency

Selected endpoints

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



Primary Endpoint: Overall Survival



No. at risk

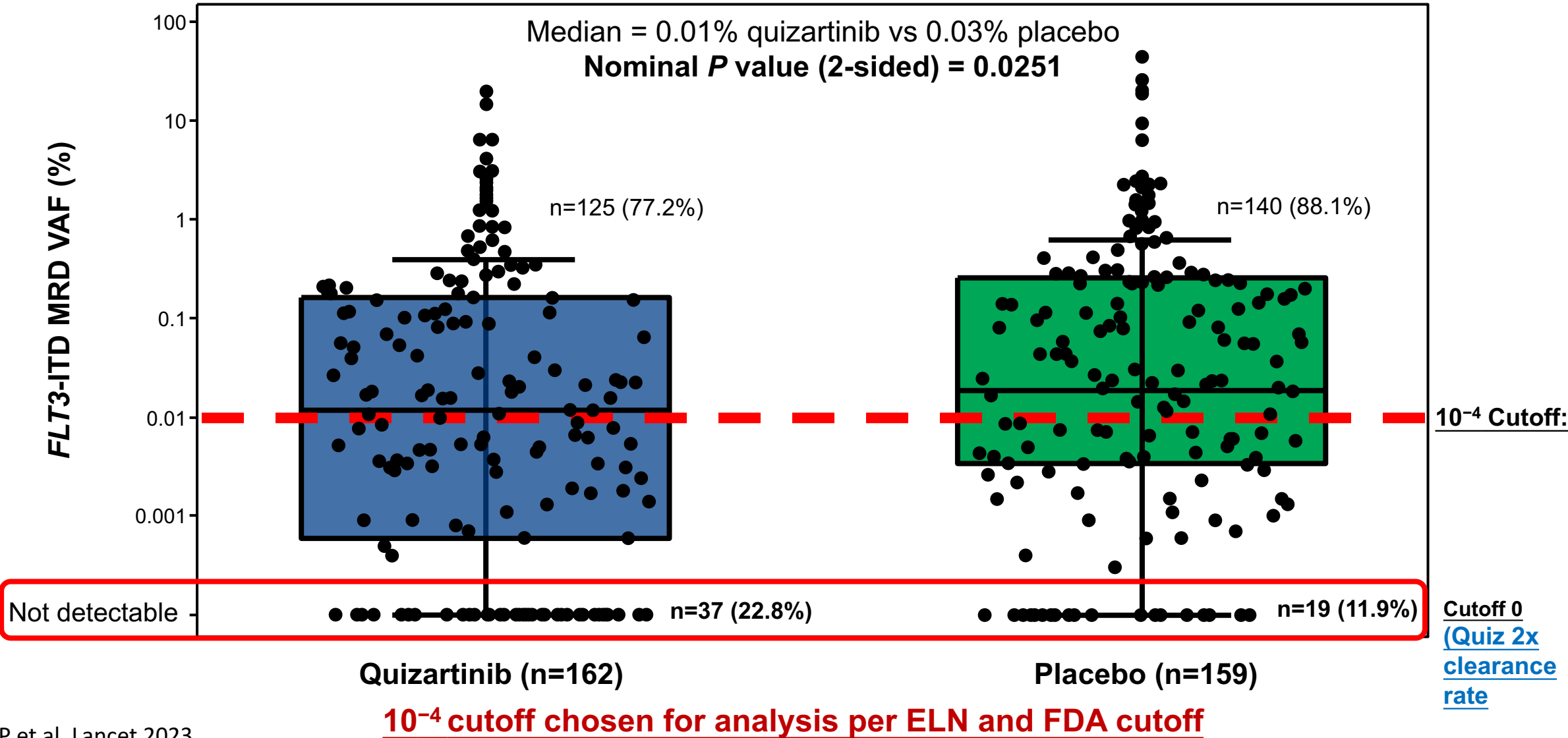
| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 | 57 | 60 |
|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|----|
| Quizartinib | 268 | 233 | 216 | 195 | 176 | 162 | 153 | 145 | 139 | 126 | 110 | 96 | 83 | 68 | 53 | 36 | 24 | 8 | 4 | 1 | 0 |
| Placebo | 271 | 249 | 211 | 175 | 151 | 131 | 126 | 121 | 117 | 103 | 97 | 81 | 70 | 56 | 39 | 31 | 17 | 8 | 5 | 0 | 0 |

HR, hazard ratio; mOS, median overall survival.

^a P value was calculated using a stratified log-rank test. ^b Median follow-up time for quizartinib arm, 39.2 months. ^c Median follow-up time for placebo arm, 39.2 months.

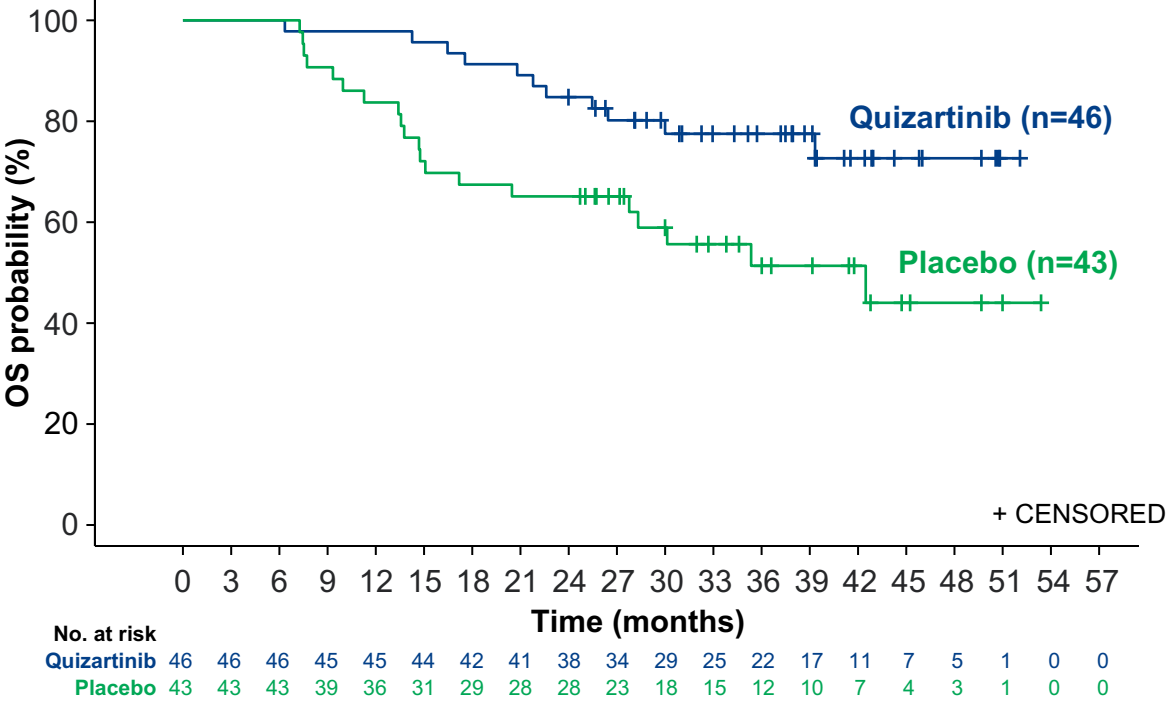
Quizartinib Treatment Is Associated with Lower *FLT3*-ITD MRD Detection, Among CRc Patients by the End of Induction

Post hoc analysis.



Impact of QUIZ maintenance in patients without SCT in CR1

OS in Patients Who Received Continuation Therapy Without Allo-HCT

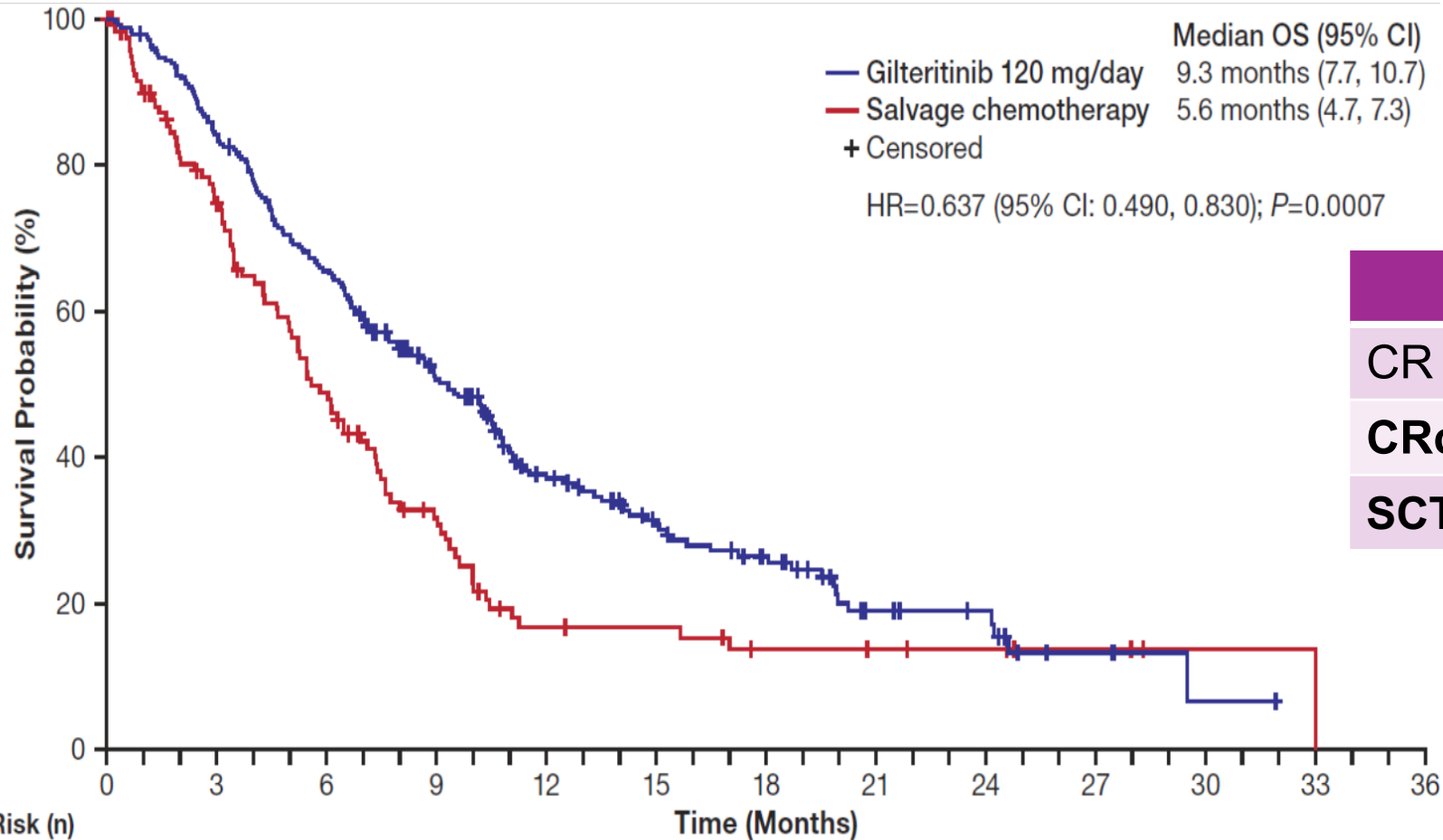


- Similar number of patients without allo-SCT in both groups were able to reach continuation phase (about 60-70% of non-SCT pts)

Allo-HCT, allogeneic hematopoietic cell transplantation; CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival.

R/R FLT3-m AML: ADMIRAL Phase 3 RCT (n=371)

Gilteritinib monotherapy vs SOC salvage (MEC, FLAG-IDA, azacitidine, LDAC)

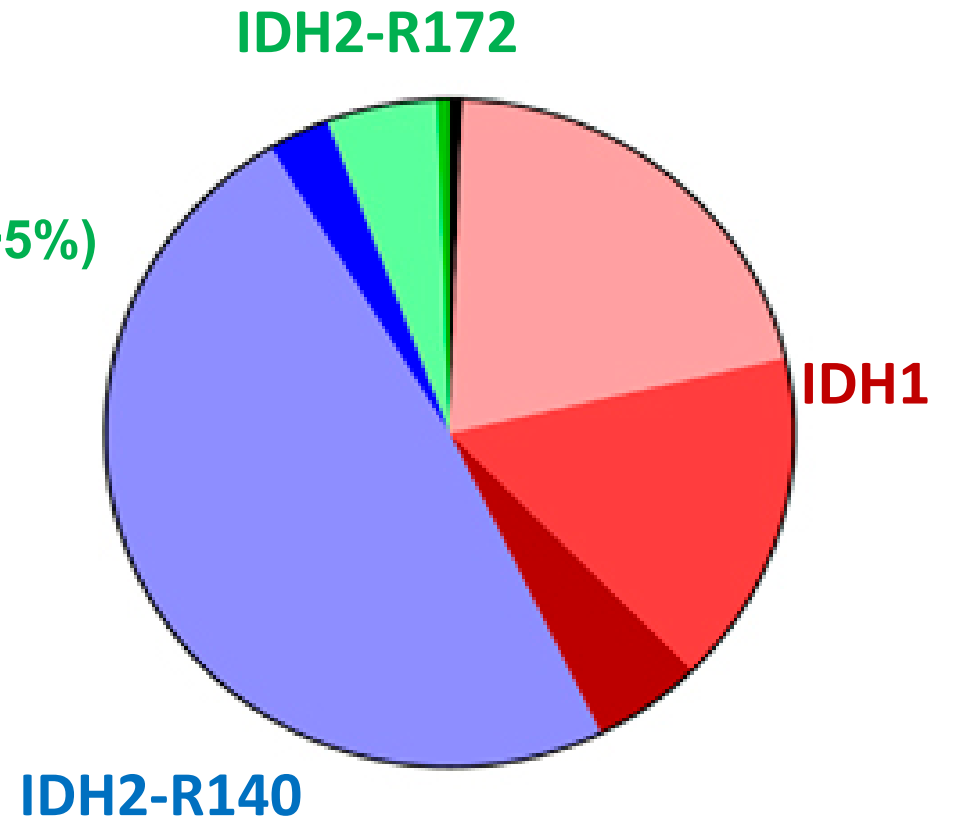


| | GILT | Chemotx |
|-----|------|---------|
| CR | 21% | 11% |
| CRc | 54% | 22% |
| SCT | 26% | 15% |

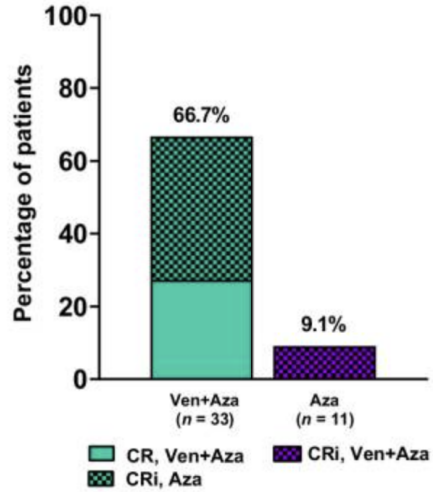
| Patients at Risk (n) | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 |
|-------------------------|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|
| Gilteritinib 120 mg/day | 247 | 206 | 157 | 106 | 64 | 44 | 31 | 14 | 11 | 4 | 1 | 0 | 0 |
| Salvage chemotherapy | 124 | 84 | 52 | 29 | 13 | 12 | 8 | 7 | 5 | 3 | 1 | 0 | 0 |

Characteristics of IDH mutations in AML

- **IDH mutations occur in ~ 20% of AML**
 - Most (~85%) occur in *de novo*, diploid or +8 AML
 - IDH1 in ~8-10% AML, IDH2 in ~ 12-15% AML
 - ↑ prevalence with ↑ patient age (~ 25% of older “unfit” AML)
 - Often sustained platelet count
- **Hot-Spot mutations in enzyme active site**
 - **IDH1-R132 (~40%)**, **IDH2-R140 (~55%)** or **IDH2-R172 (~5%)**
- **Can be acquired at progression**
 - ~10-15% of AML from MDS
 - ~20-25% of AML from MPN

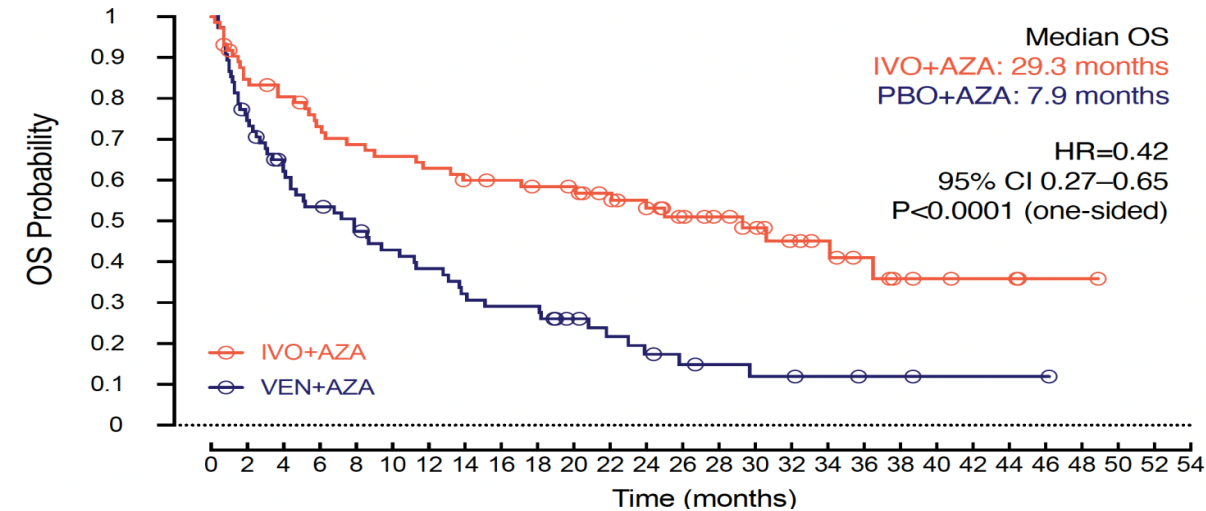
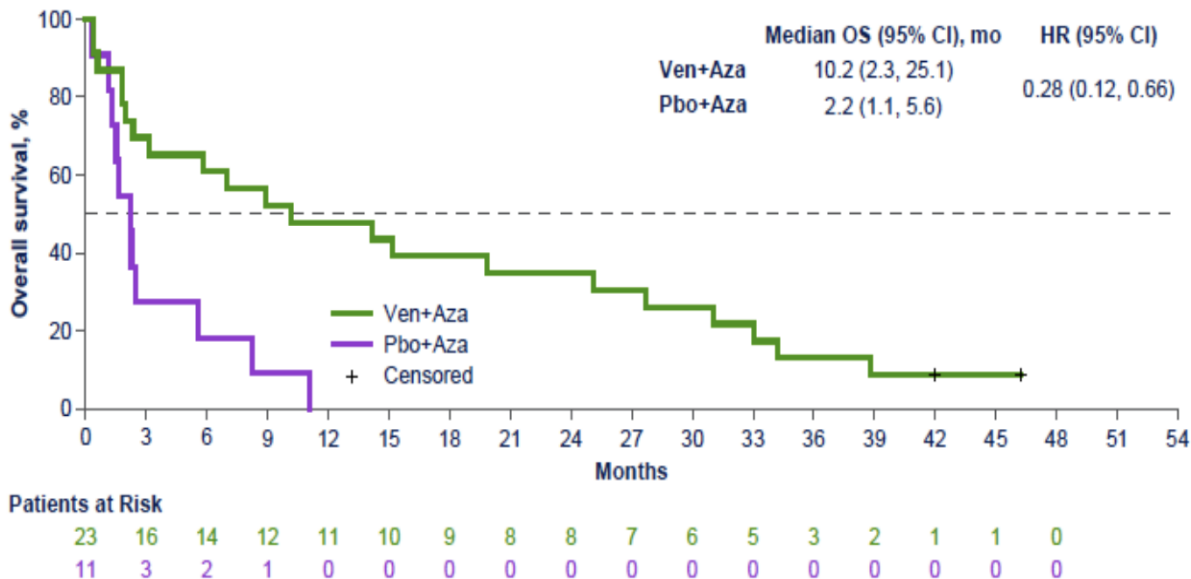
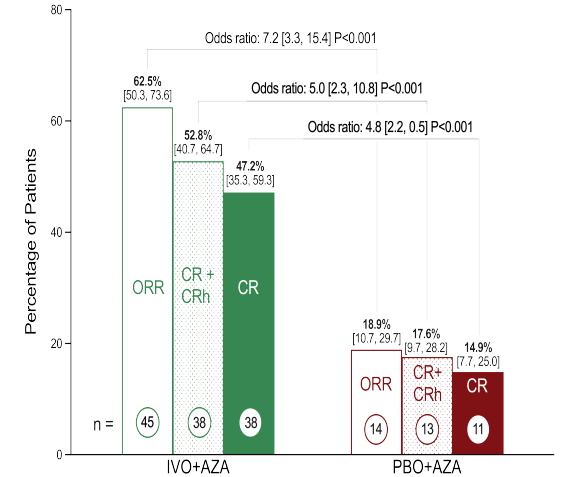


Long-term follow up of *IDH1*^{MUT} AML with HMA-based doublet therapy



VIALE-A¹
 AZA ± VEN
 ↓
Median OS: 10.2 months
CRc: 66.7%

AGILE²
 AZA ± IVO
 ↓
Median OS: 29.3 months
CRc: 52.8%

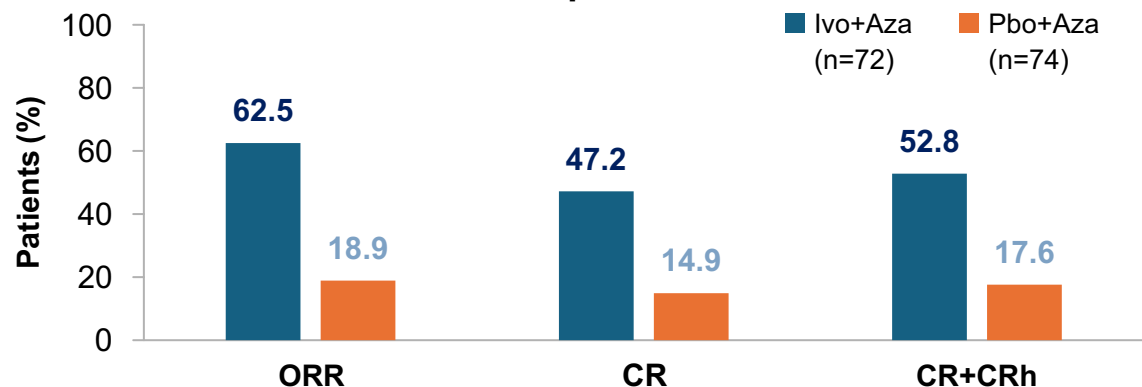


¹Pollyea et al., Clin Cancer Research 2022; Pratz et al., AJH 2024
²Montesinos et al., NEJM 2022; Dohner et al., EHA 2023

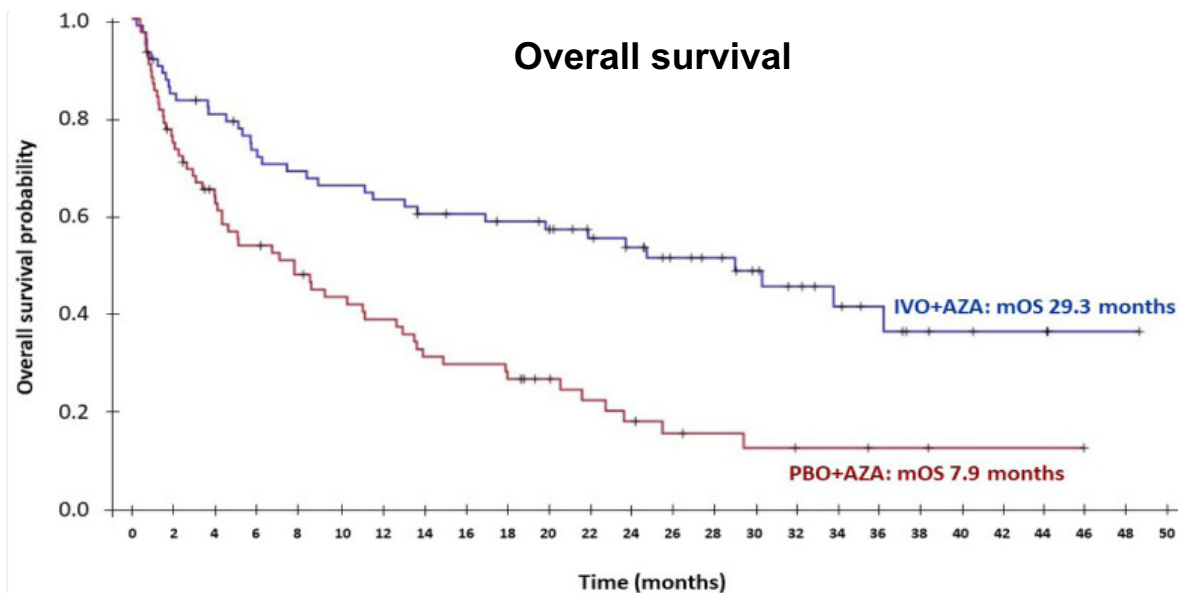
AGILE: Ivosidenib+Aza vs Pbo+Aza in ND *IDH1*^{mut} AML

Randomized, Ph3 trial in patients with untreated AML and an *IDH1* mutation (N=146)

Response



Overall survival



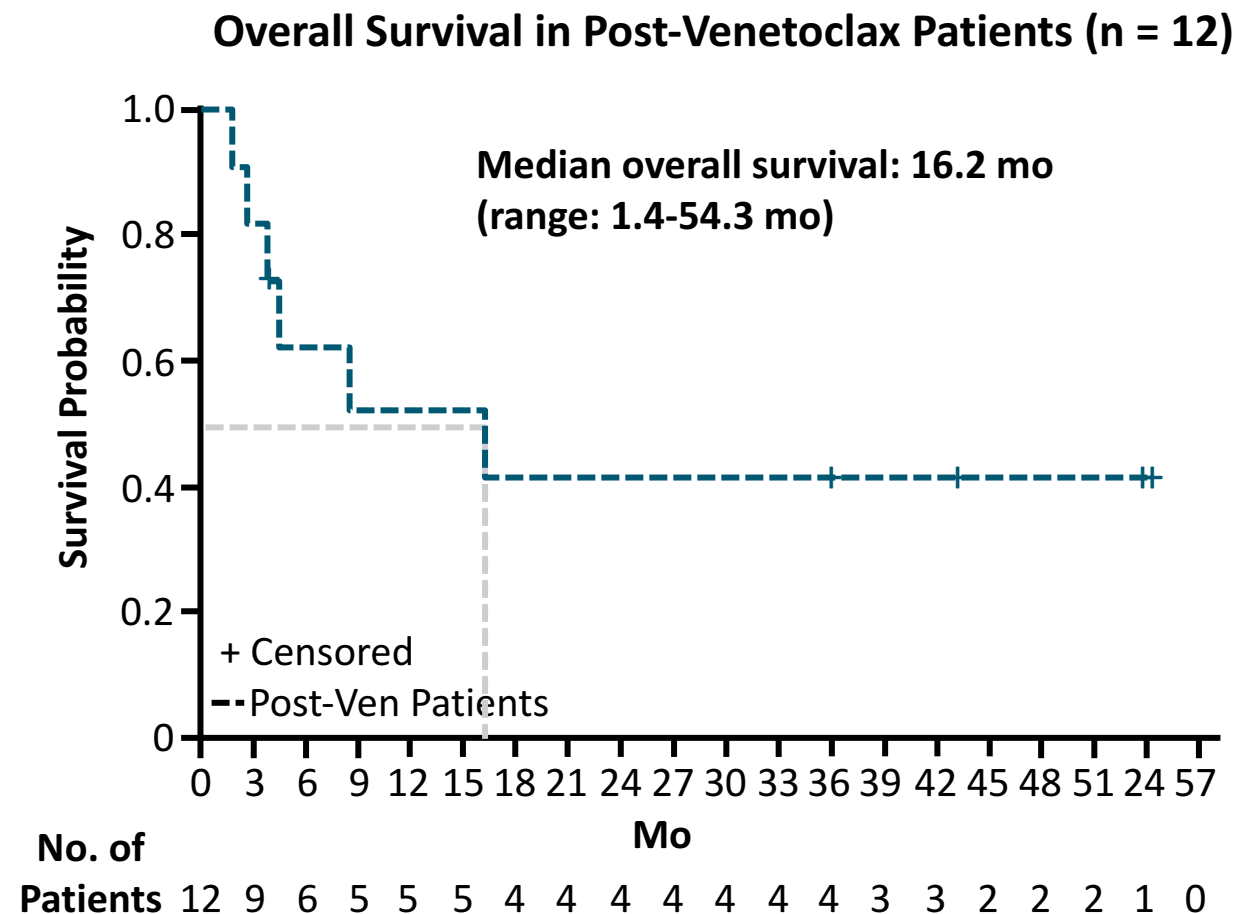
| Grade ≥3 AEs in ≥20% of patients in either arm, n (%) | Ivo+Aza (n=71) | Pbo+Aza (n=73) |
|---|----------------|----------------|
| Hematologic AEs | | |
| Anemia | 18 (25) | 19 (26) |
| Febrile neutropenia | 20 (28) | 25 (34) |
| Neutropenia | 19 (27) | 12 (16) |
| Thrombocytopenia | 17 (24) | 15 (21) |
| Non-hematologic AEs | | |
| Pneumonia | 16 (23) | 21 (29) |
| Infections | 15 (21) | 22 (30) |

| Other safety events, n (%) | Ivo+Aza (n=71) | Pbo+Aza (n=73) |
|--|----------------|----------------|
| Differentiation syndrome (any grade) | 10 (14) | 6 (8) |
| Grade ≥3 | 3 (4) | 3 (4) |
| QT interval prolonged on ECG (any grade) | 14 (20) | 5 (7) |
| Grade ≥3 | 7 (10) | 2 (3) |
| Discontinuation as a result of AEs | 19 (27) | 19 (26) |

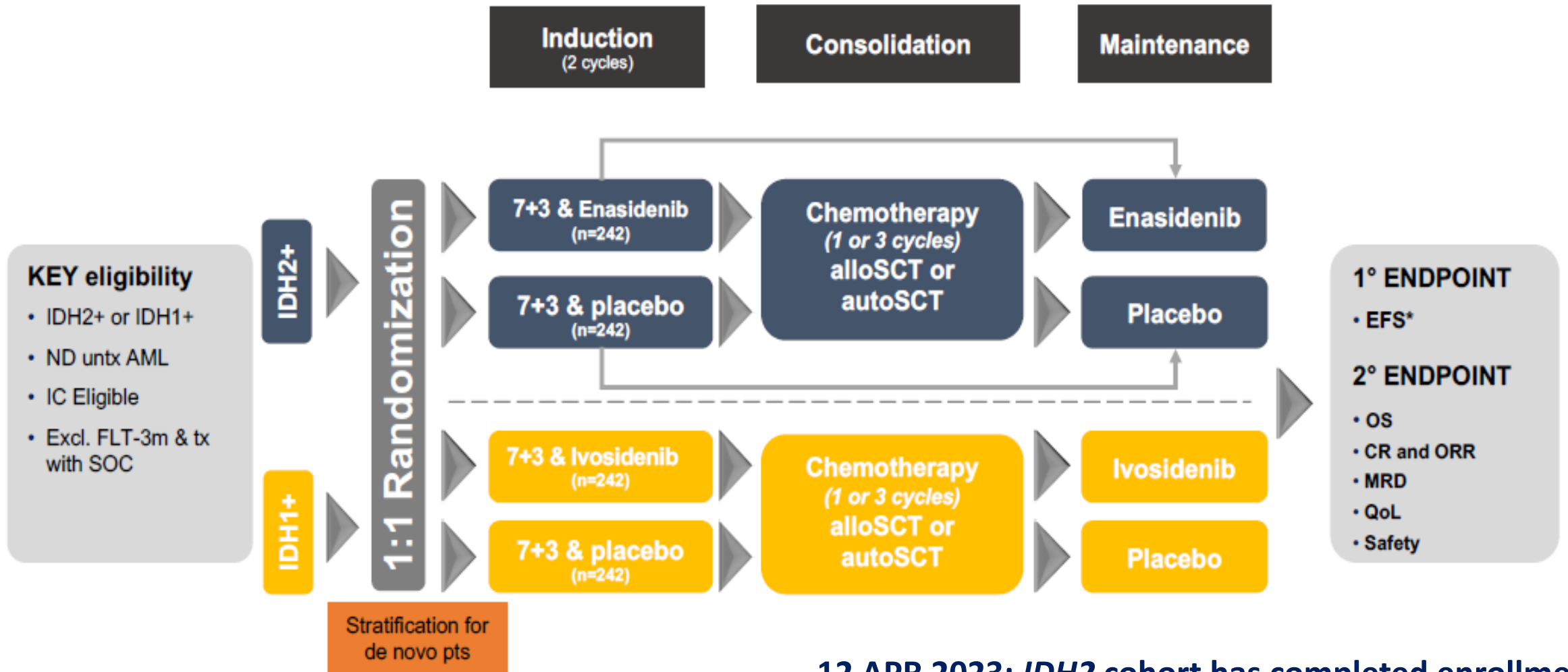
• Aza, azacitidine; ECG, electrocardiography; Ivo, ivosidenib; mut, mutated; ND, newly diagnosed.

Post-Venetoclax Olutasidenib Outcomes

- In 12 pts R/R to venetoclax (median duration of previous venetoclax therapy of 6.7 mo), olutasidenib yielded:
 - **CR/CRh: 33%**
 - **Median time to CR/CRh: 2.4 mo (1-2.8)**
 - **Median duration of CR/CRh: not reached (range: 4.8-50.6 mo)**
- **ORR: 50%; CR: 25%; CRh: 8%; CRi: 17%**
 - Median time to ORR: 1.7 mo
 - Median duration of ORR: NR (1.2-52.5 mo)



Randomized Phase II HOVON 150 / AMLSG 29-18 Trial

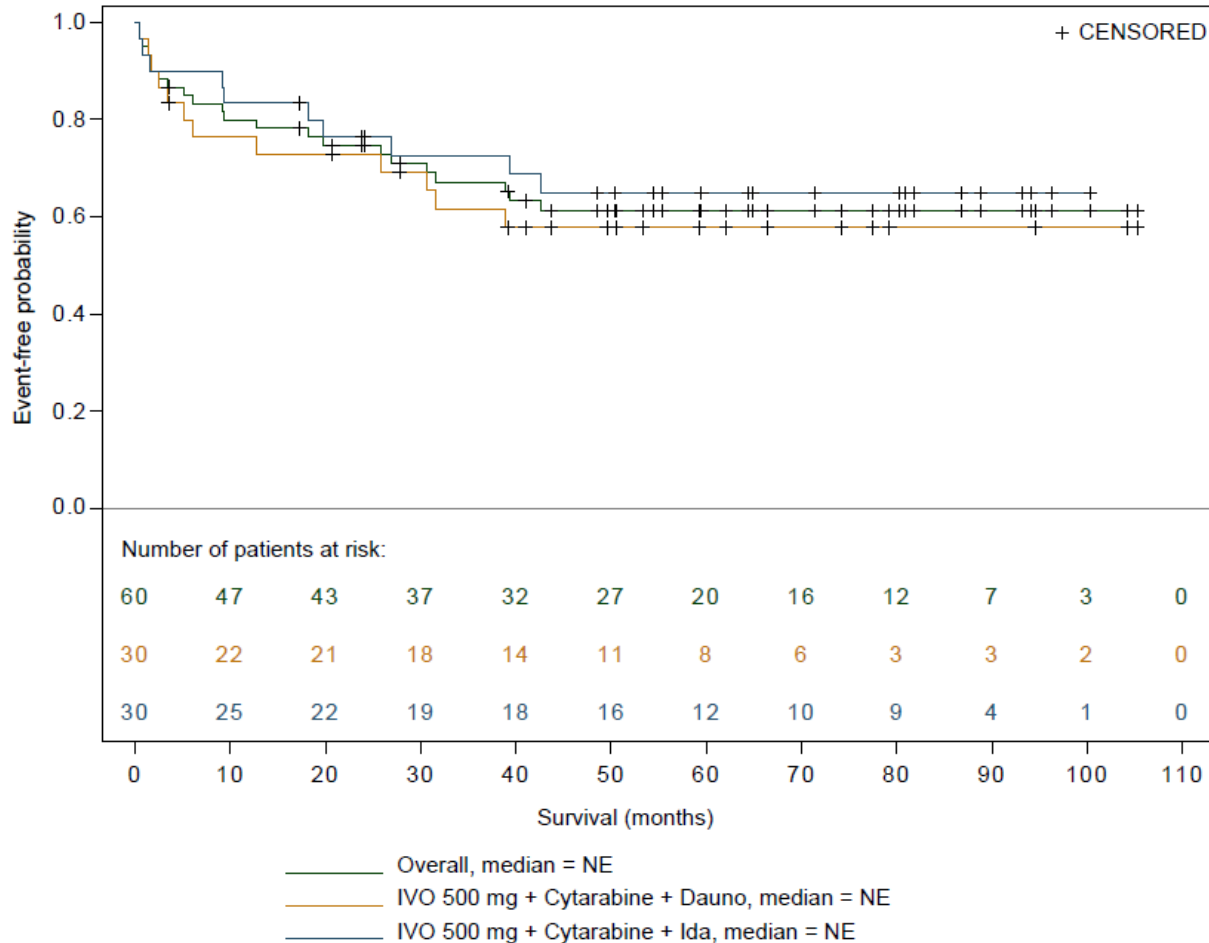


12 APR 2023: IDH2 cohort has completed enrollment
17 SEPT 2024: IDH1 cohort has completed enrollment

- Study design provided courtesy of HOVON and AMLSG chairs.

7+3+IVO: 3-year overall survival was 67%

Overall survival^b: IVO cohorts



Data cutoff: 16 January 2025

| | IVO 500 mg + Cytarabine + Dauno (n=30) | IVO 500 mg + Cytarabine + Ida (n=30) | Total (N=60) |
|--|---|---|----------------|
| OS probability, ^a % | | | |
| 12 months | 76 | 83 | 80 |
| 24 months | 73 | 76 | 75 |
| 36 months | 62 | 73 | 67 |
| 48 months | 58 | 65 | 61 |
| 60 months | 58 | 65 | 61 |
| OS duration, mo, median (95% CI) | NE (25.8–NE) | NE (39.4–NE) | NE (39.4–NE) |
| Sensitivity analysis, median (95% CI) | 30.6 (6.1–NE) | NE (39.4–NE) | 42.6 (25.8–NE) |
| 12-month EFS, % | 41 | 58 | 49 |

- **29 pts (48%) underwent HSCT**; 13 (22%) after induction, 14 (23%) after consolidation, 2 (3%) during maintenance
- **19 pts (32%) received IVO maintenance** (median time maintenance 19.4 mo, and 10 pts still on study survival f/u)

^aCalculated using Kaplan-Meier estimate of survival function.

^bOS sensitivity analyses censored patients at their time of HSCT, or the last dose date + 28 days if the HSCT date is not available.

AE Profiles and Clinical Expectations of IDH Inhibitors as monotherapy in R/R AML

CR = 20%
CRc = 26%
mOS= 9mo
(~20mo if CR)

CR = 25%
CRc = 33%
mOS= 9mo
(~20mo if CR)

CR = 32%
CRc = 35%
mOS= 12mo
(NR if CR, 18mo OS 78%)

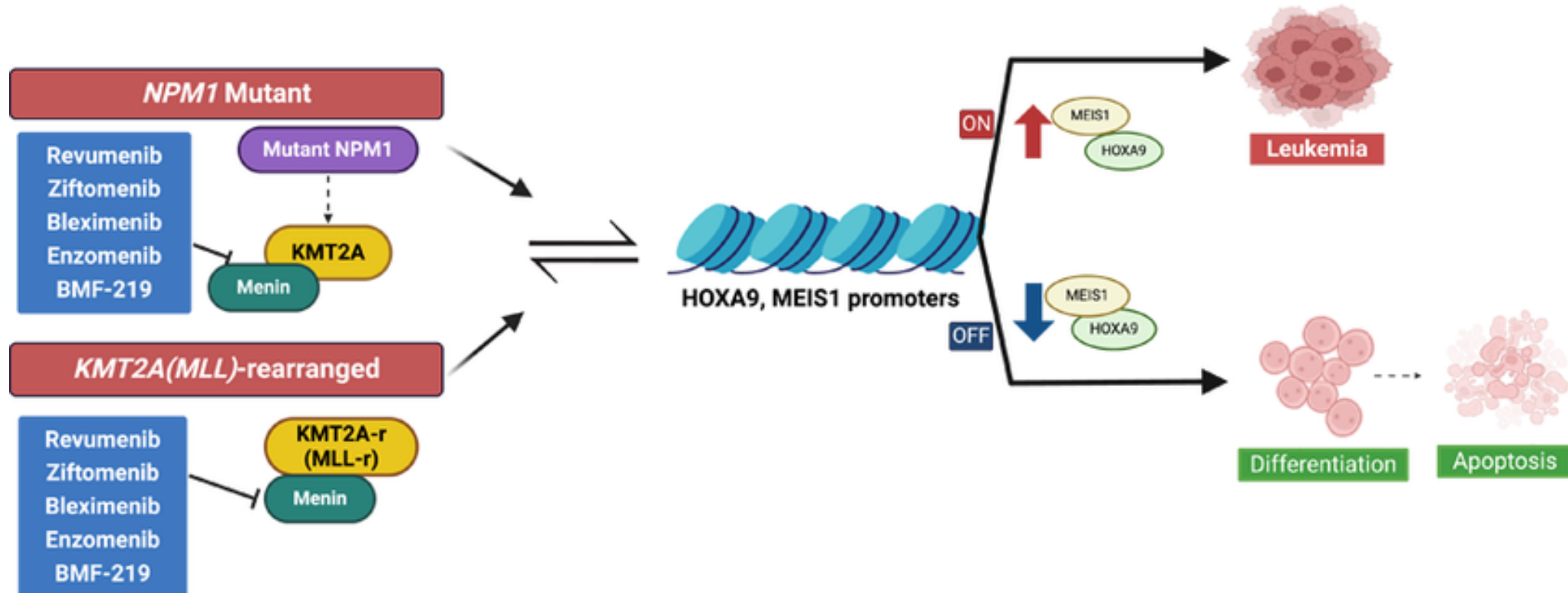
| Treatment-Related TEAEs, Grade 3/4, n (%) | Enasidenib (IDH2i) 100 mg/d (n = 153)^[1] | Ivosidenib (IDH1i) 500 mg/d (n = 179)^[2] | Olutasidenib (IDH1i) 150 mg BID (n = 153)^[3] |
|---|--|--|--|
| Hyperbilirubinemia | 13 (8) | NR | 2 (1) |
| Prolonged QT interval | --- | 14 (8) | 1 (<1) |
| IDH differentiation syndrome | 11 (7) | 7 (4) | 12 (7) |
| Anemia | 10 (7) | 4 (2) | 7 (5) |
| Thrombocytopenia | 8 (5) | 3 (2) | 6 (4) |
| Tumor lysis syndrome | 5 (3) | --- | 3 (2) |
| Decreased appetite | 3 (2) | --- | --- |
| Leukocytosis | 2 (1) | 3 (2) | 7 (5) |
| Hepatic AESI (transaminitis) | --- | ---- | 23 (15) |

NR, not reported; TEAEs, treatment-emergent adverse events.

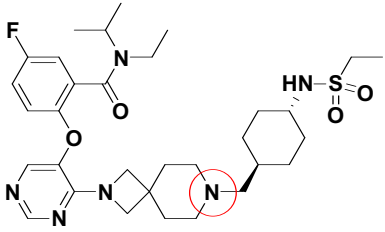
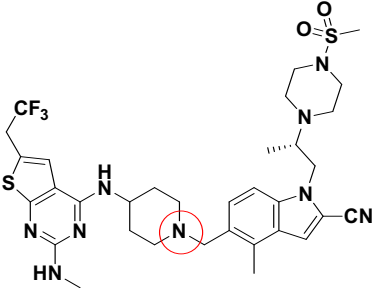
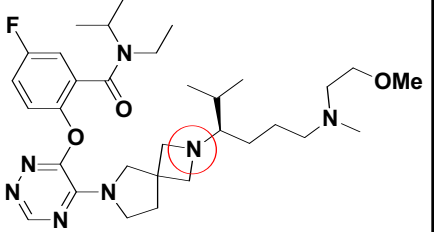
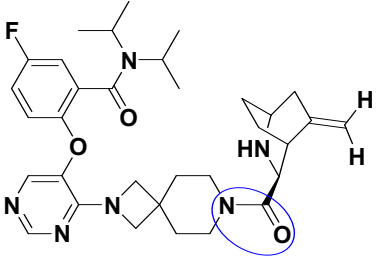
1. Stein EM, et al. Blood. 2017;130:722-731; 2. DiNardo CD, et al. N Engl J Med. 2018;378:2386-2398; 3. De Botton S, et al. Blood Adv. 2023;7:3117-3127.

What about the addition of a menin inhibitor?

- *KMT2Ar*, *NPM1mut*, *NUP98r* acute leukemias (and likely others) have dysregulated transcription of leukemic genes (e.g. *MEIS1*, *HOXA9*)
- Menin inhibitors selectively disrupt the menin-KMT2A interaction : new class of small molecule targeted therapies that lead to leukemic cell differentiation and cell death



Menin inhibitors have different chemical structure and physiochemical properties

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

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

- Each menin inhibitor has a different chemical structure and different physiochemical properties such as polar surface area, lipophilicity, and basicity that may impact safety and efficacy^{1,2}
- Lower lipophilicity and basicity associated with more rapid clearance and less accumulation

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

*Numeric values derived from ChemDraw based on NIH CID

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

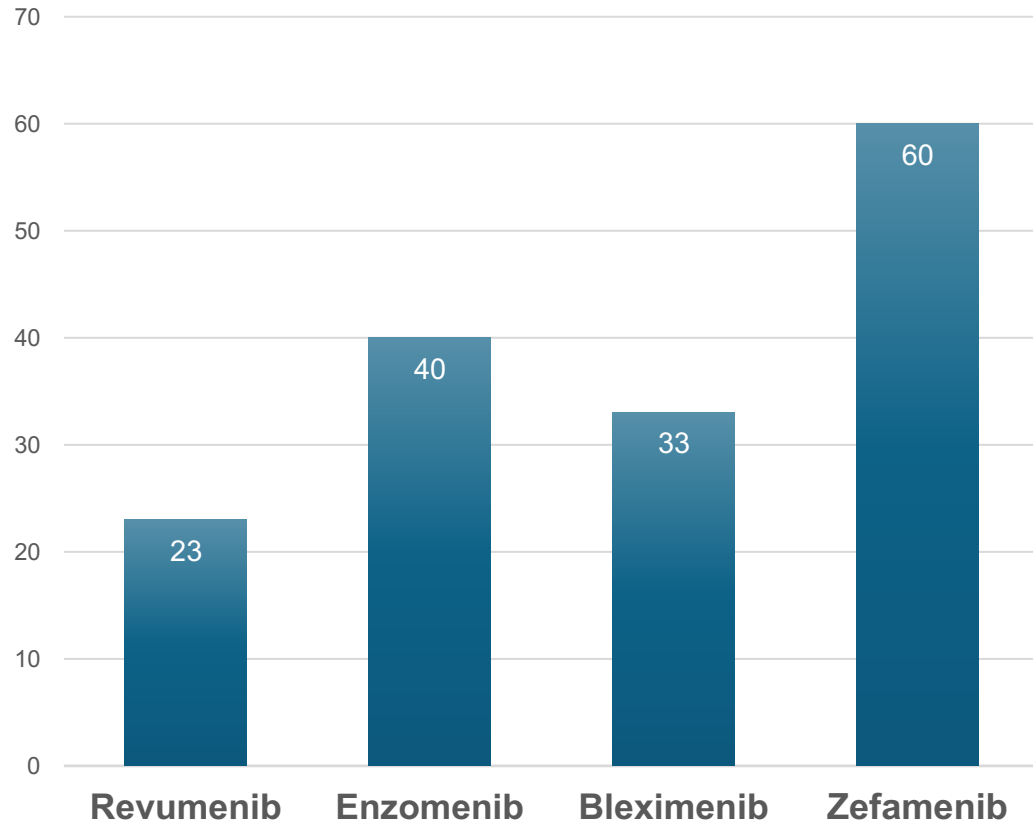
Incidence & Severity of AEs Across Menin Monotherapy Clinical Trials

| | Revumenib (n = 95) | Ziftomenib (n = 112) | Bleximenib (n = 146) | Enzomenib (n = 84) |
|--------------------------------|-----------------------|-------------------------|---------------------------|-----------------------|
| Trial | Phase II | Phase Ib/II | Phase I | Phase I/II |
| DLT (Y/N) | Phase I: QTc PR | Yes | Yes | No |
| DLT | Phase I: QTc PR | Grade 3 pneumonia | Grade 5 DS | NA |
| DS (all) | 27 (28.4%) | 26 (23.0%) | 14% (all doses) | 15 (12.9%) |
| DS (grade ≥3) | 14 (14.7%) | 15 (13.0%) | 6%-9% (90-150 BID) | 9 (7.8%) |
| Febrile neutropenia (grade ≥3) | 14 (14.7%) | 18 (22.0%) | 27 (18%) | 20 (23.8%) |
| Neutropenia (grade ≥3) | NR | 6 (5.0%) | 37 (25%) | 14 (16.7%) |
| Thrombocytopenia (grade ≥3) | NR | 6 (7.0%) | 46 (31%) | 18 (21.0%) |
| QTc PR (any) | 28 (29.5%) | 3 (2.7%) | 0 (0%) | 3 (2.6%)* |
| QTc PR (grade ≥3) | 15 (15.8%) | 2 (1.8%) | 0 (0%) | 3 (2.6%)* |

*Deemed not related to enzomenib use.

KMT2Ar R/R AML: Activity of Menin Inhibitors

CR/CR rate: 23-60%



Duration of Response: 6-12.5 mo

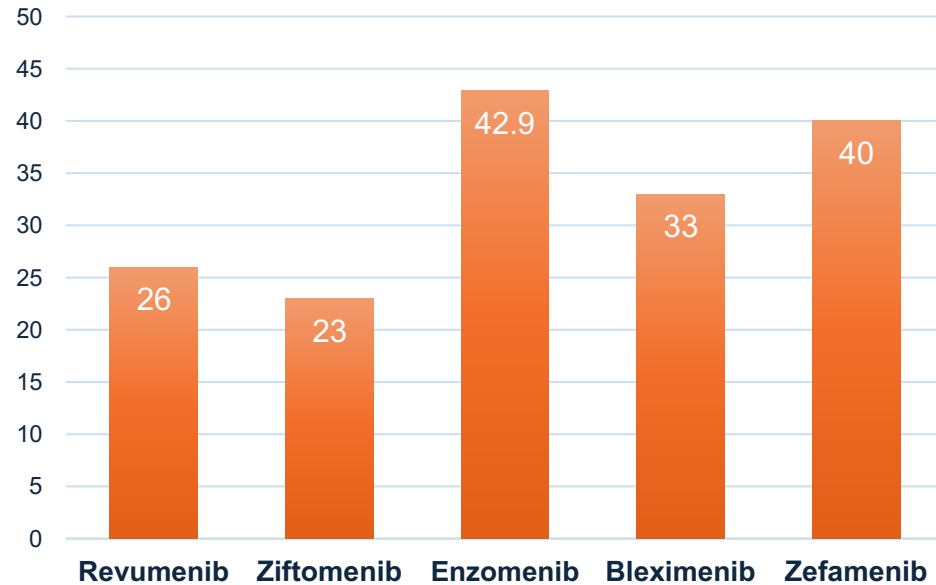
| Menin Inhibitor | Duration of CR/CRh | Median Overall Survival |
|--------------------------|--------------------|-------------------------|
| Revumenib 160-270 BID | 6.4 mos | 8.0 mos |
| Enzomenib 300 mg BID | 12.5 mos | 11.8 mos |
| Bleximenib 100 mg BID | 6.0 mos | Not reported |
| Zefamenib | Not reported | Not reported |

Issa G et al JCO 2024; Watts J et al ASH 2025; Searle E Et al ASH 2024; Wu D et al. ASH 2024. Abstract 2879

NPM1 R/R AML: Activity of Menin Inhibitors

CR/CR rate: 23-43%

Duration of Response: 4-8.5 mos

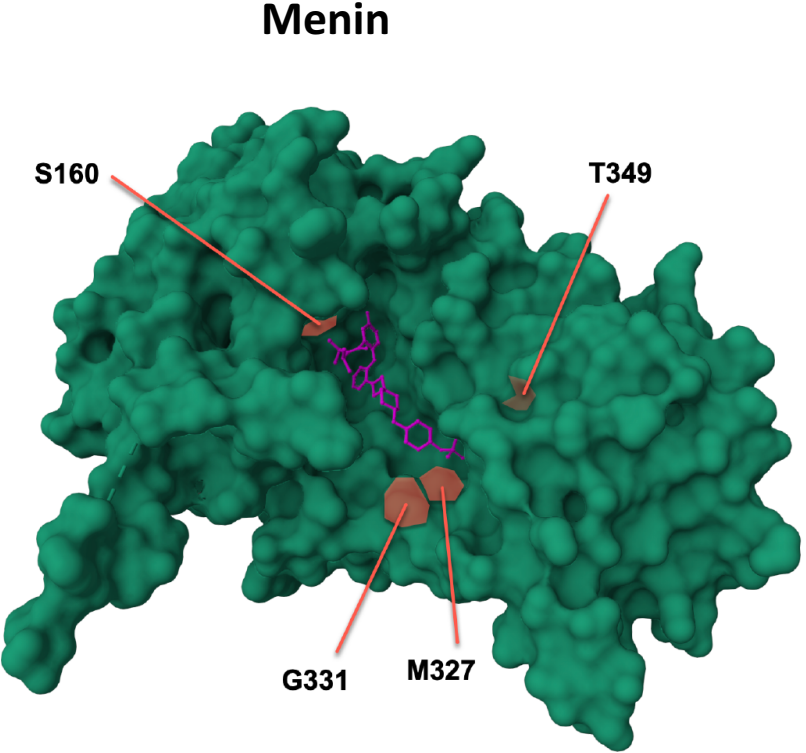
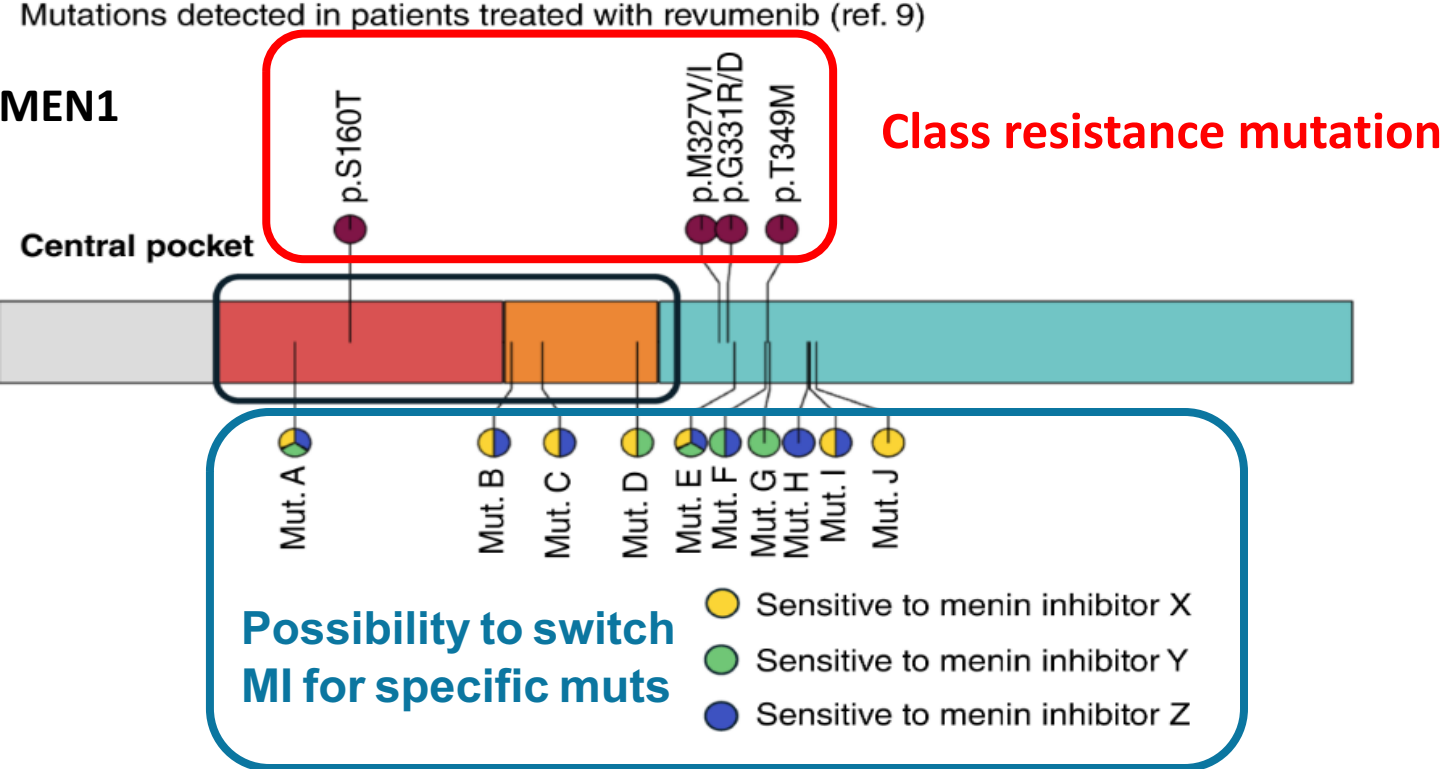


| Menin Inhibitor | Duration of CR/CRh | Median OS |
|------------------------------|--------------------|--------------|
| Revumenib 160-270 mg BID | 4.4 mos | 4.0 mos |
| Ziftomenib 600 mg qd | 4.6 mos | 6.6 mos |
| Enzomenib 300 mg BID | 5.7 mos | 8.5 mos |
| Bleximenib 200-300 mg BID | 6.0 mos | Not reported |
| Zefamenib | Not reported | Not reported |

Arellano M et al Blood 2025; Wang E et al JCO 2025; Watts J et al ASH 2025; Searle E et al ASH 2024; Wu D et al. ASH 2024. Abstract 2879

MEN1 Mutations in the Menin Binding Site: Drug Specific?

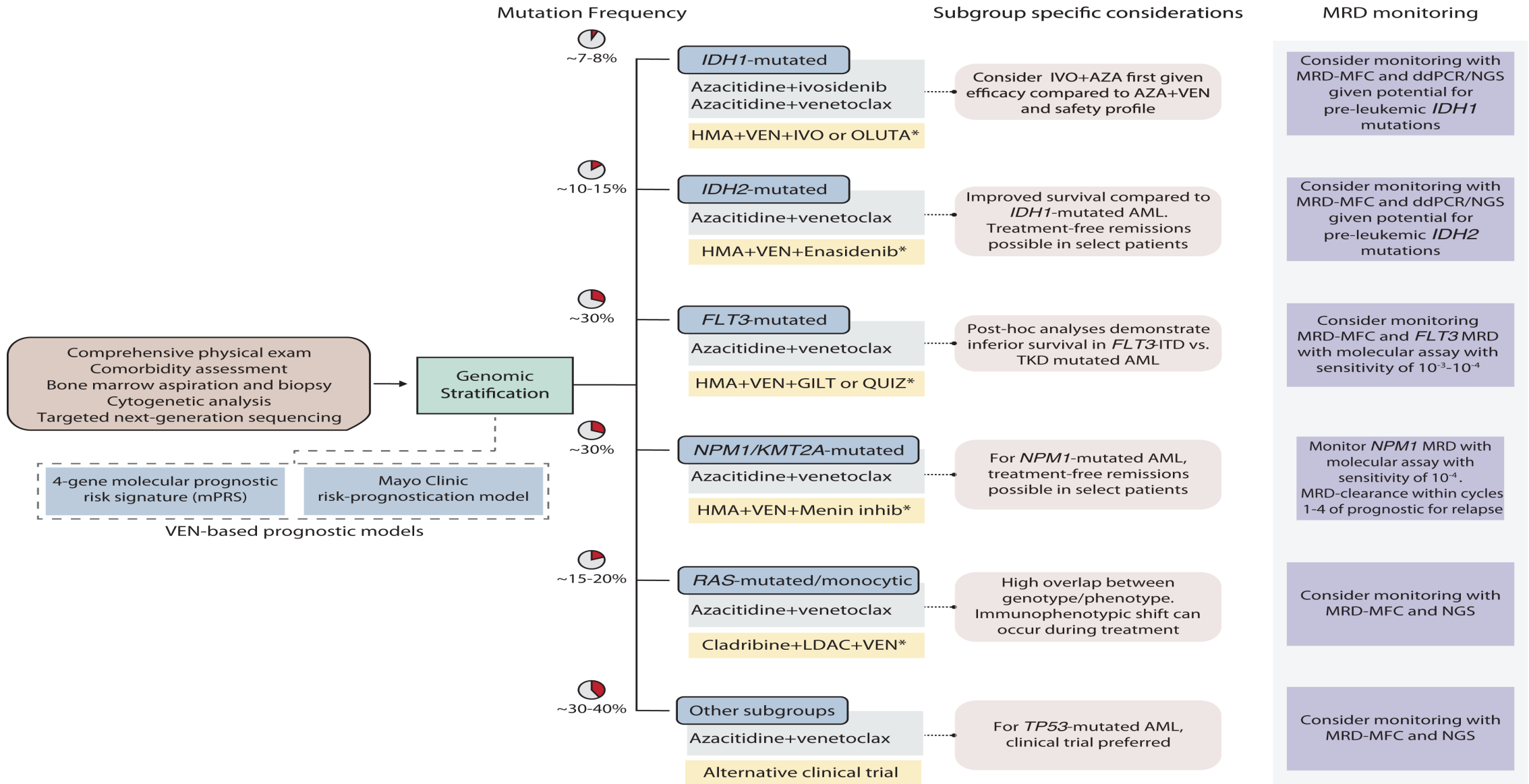
Correlate with short duration of remission with Menin Inhibitors as monotherapy



Work by **Wallace Bourgeois, MD (Armstrong Lab), ASH 2024**
Predicted resistance mutations by binding of each menin inhibitor

Issa GC et al, Blood Cancer Disc 2025

Mutation Informed Treatment Decisions



HMA + VEN + IDHi for newly dx AML

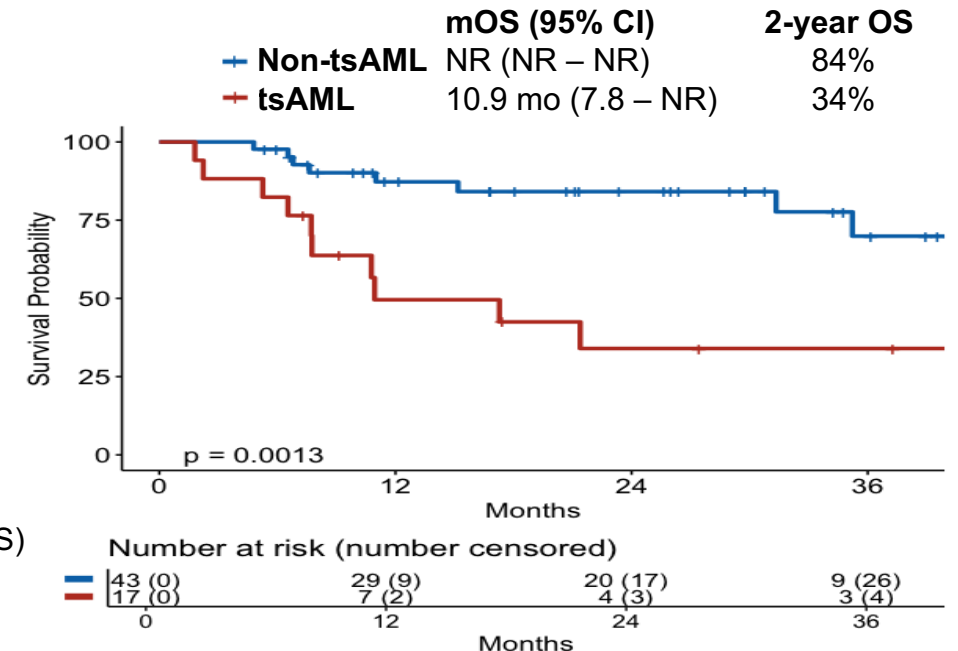
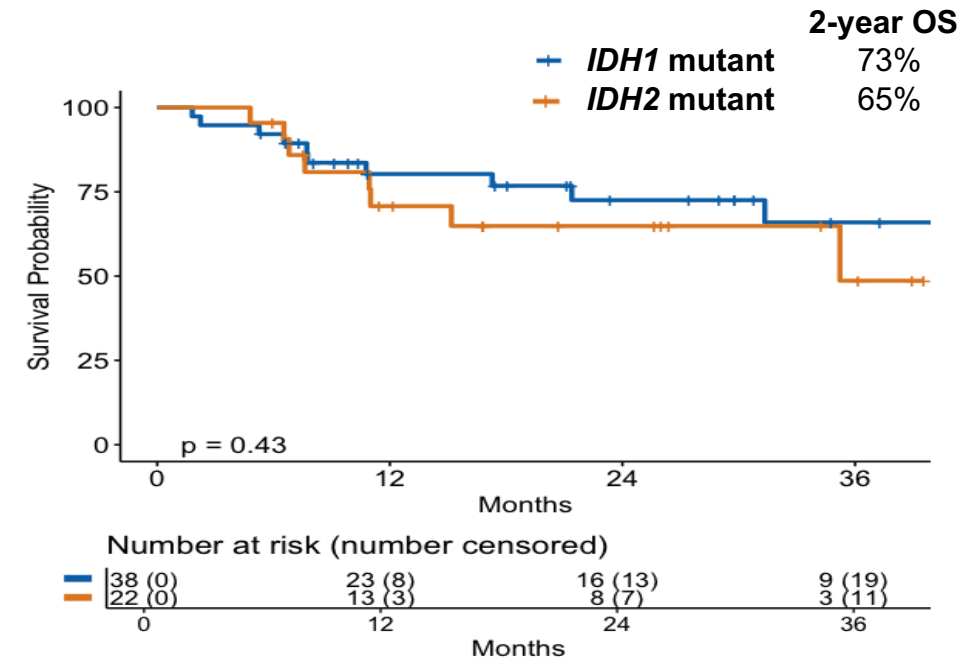
- Pooled analysis of **60 patients** with newly dx IDH1/2-*mutated* AML initiated on triplet regimens of:
 - AZA + VEN + IVO
 - Oral DAC + VEN + IDHi (enasidenib or ivosidenib)
- * Both studies include **14 days of VEN per cycle only**
 - 19 of 60 patients have undergone SCT
 - Median number of cycles completed is 5
 - **>50% of responding patients still on active treatment**
 - Median follow up 27 months

| | All Patients (n=60) | Excluding tsAML (n=43) |
|----------------------|---------------------|------------------------|
| CRc (CR + CRi + CRh) | 92% | 98% |
| 2-year OS | 69% | 84% |
| 2-year EFS | 67% | 79% |

30-day mortality: 0/50 (0%)

60-day mortality: 1/50 (2%)

tsAML = treated secondary AML (i.e. s/p HMA or other therapy for MDS)
[Excluded in AGILE and VIALE-A]



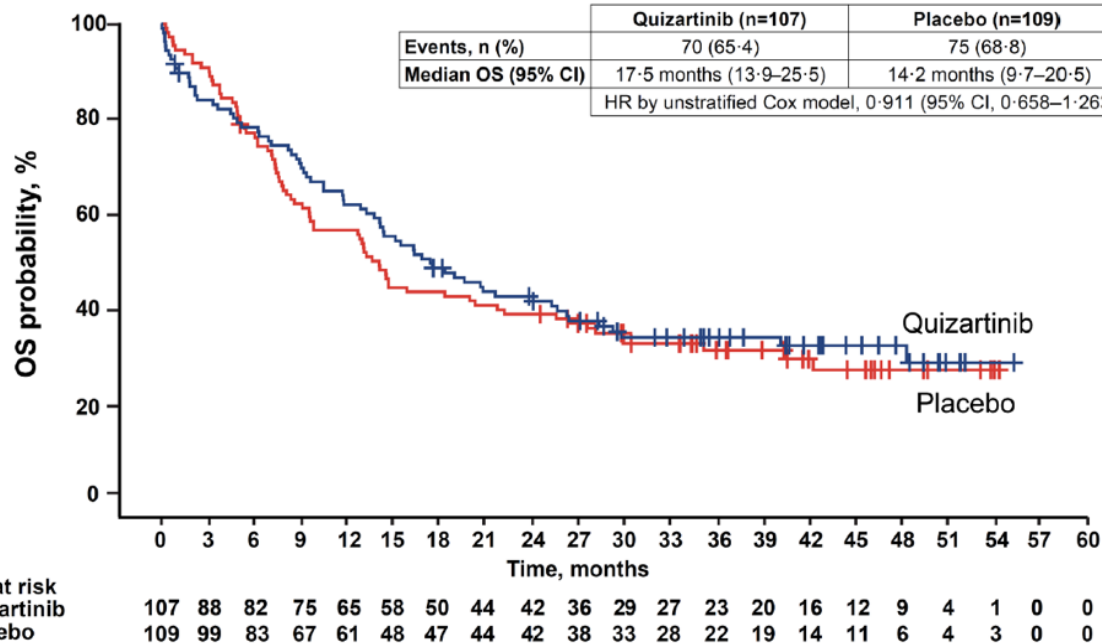
Ongoing “maintenance” triplet cycles once in remission

| Dose Attenuation in Subsequent Cycles | | | | |
|---------------------------------------|-------------------------|------------------|------------------|-----------------------------|
| | Venetoclax ¹ | HMA | | Cycle Duration ¹ |
| | | DEC-C | AZA | |
| Cycle 2 | 12 (7 – 14) | 5 (5 – 7) | 7 (7 – 7) | 35 (31 – 40) |
| Cycle 3 | 7 (7 – 14) | 4 (3 – 5) | 7 (7 – 7) | 36 (32 – 42) |
| Cycles 4-5 | 7 (7 – 7) | 4 (3 – 5) | 7 (5 – 7) | 35 (31 – 40) |
| Cycles 6-12 | 7 (5 – 7) | 3 (3 – 5) | 5 (5 – 7) | 35 (29 – 39) |
| ¹ Days, median (IQR) | | | | |

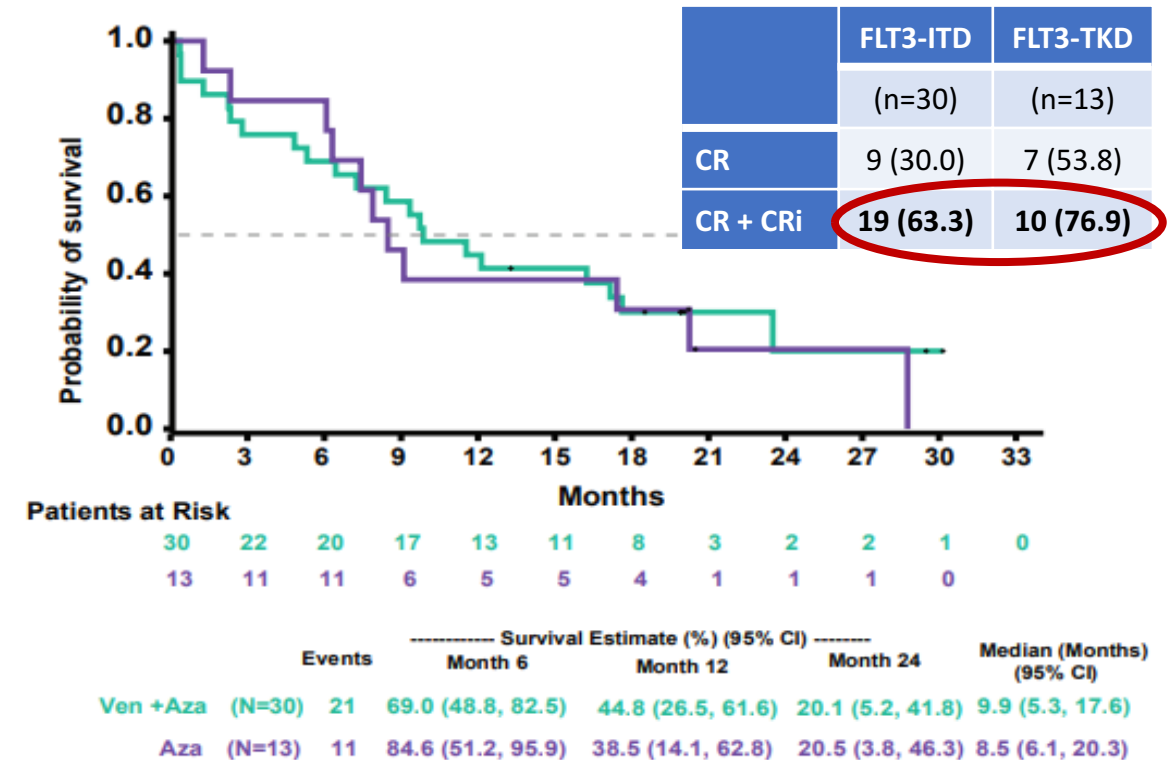
What is the optimal therapy for older FLT3-ITD mutated pts?

| | N | CR/CRi | mOS |
|---|-----------|------------|--------------|
| 7+3+QUIZ (≥ 60 yrs) | 107 | ~70% | 17.5 mo |
| AZA + VEN (VIALE-A) | 30 | 63% | 9.9 mo |
| HMA + VEN + FLT3i (GILT or QUIZ) | 59 | 93% | 28 mo |

QUANTUM-FIRST (7+3+QUIZ) for FLT3-ITD ≥ 60 yrs



VIALE-A (AZA +VEN) for FLT3-ITD

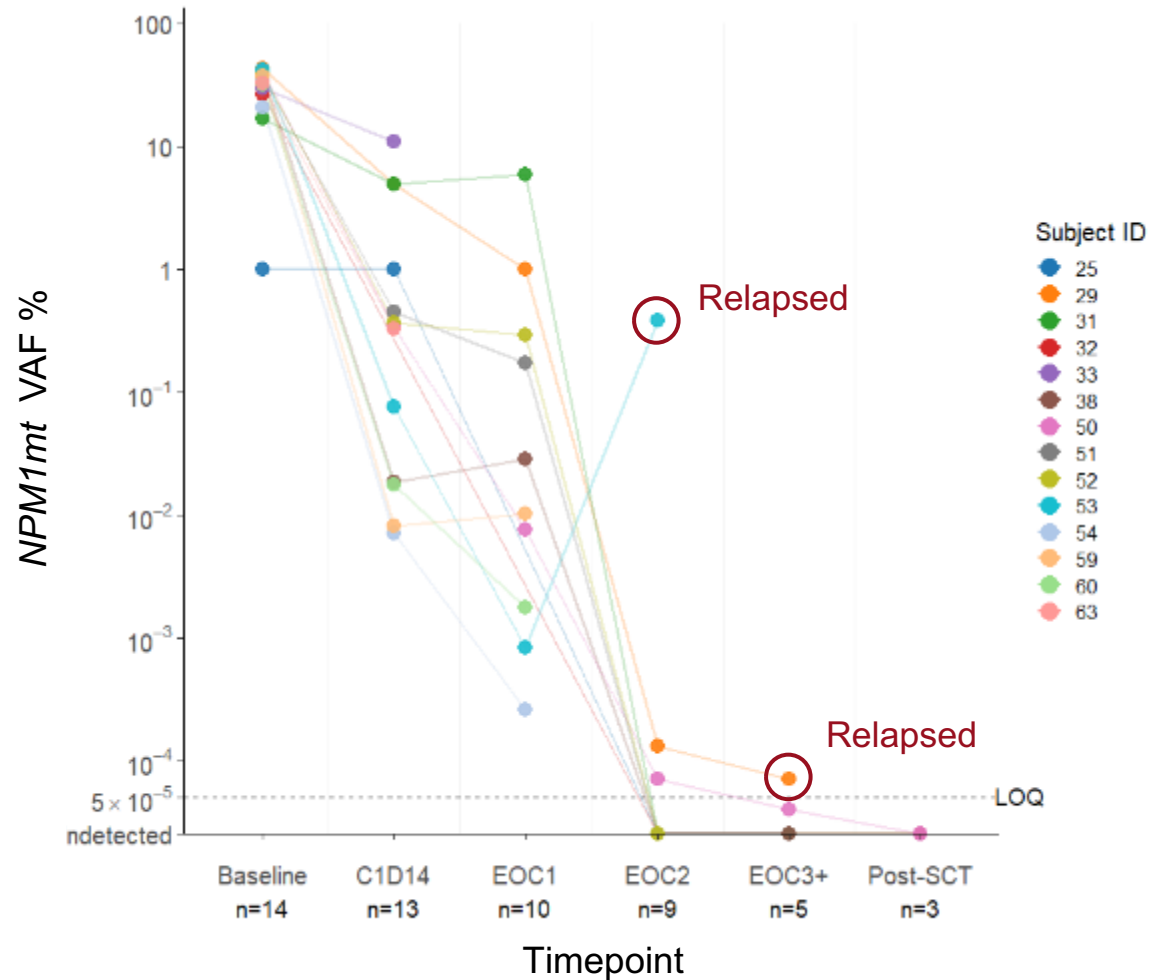
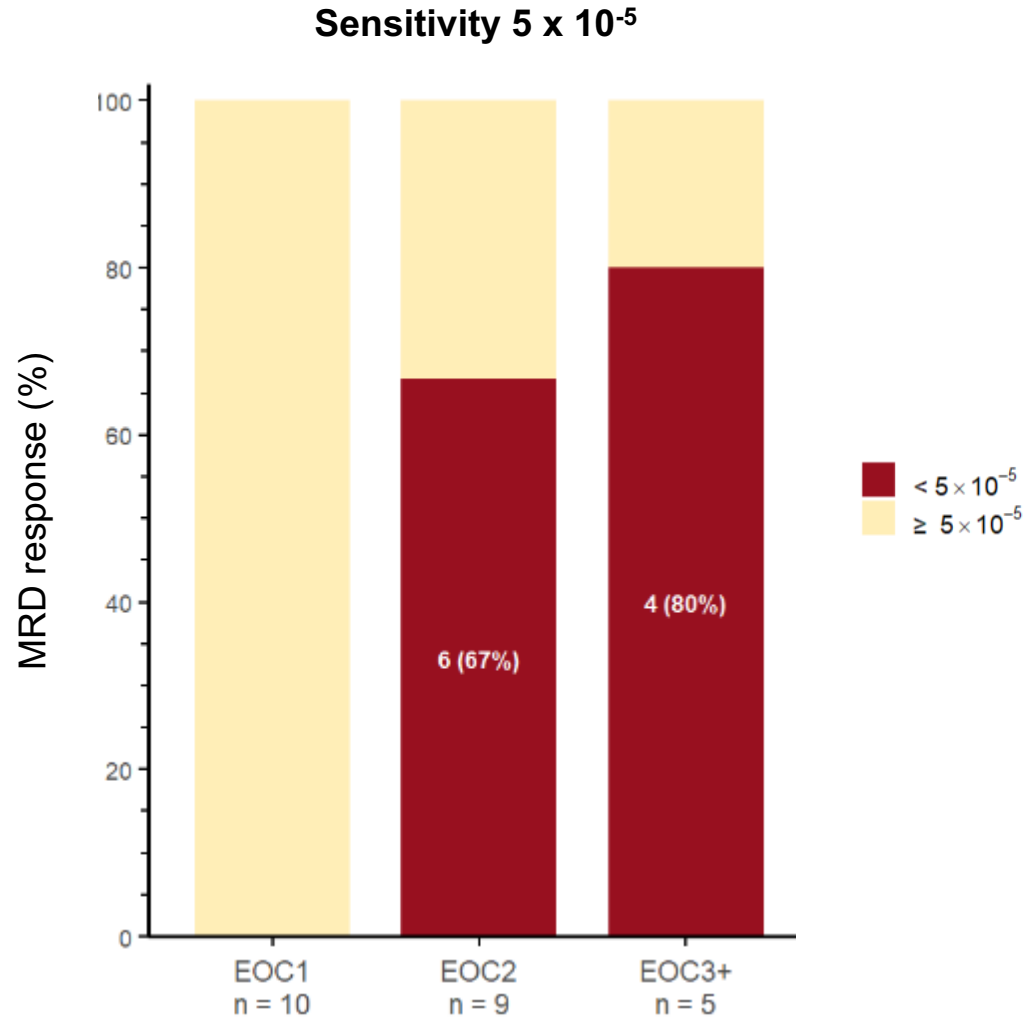


Menin inhibitor Triplets for ND KMT2Ar/NPM1m AML

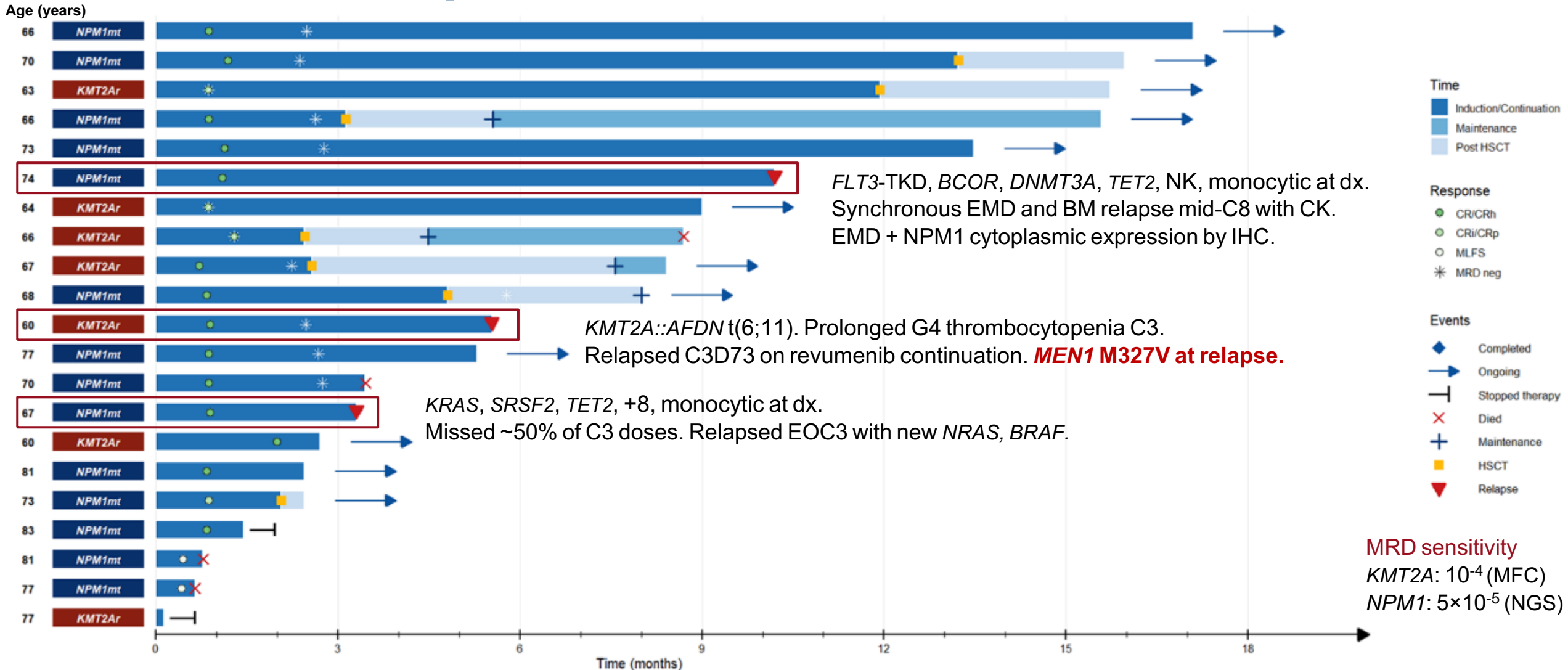
| | AZA/VEN + Revumenib (D1-28) | | ASTX727/VEN + Revumenib (D1-28) | | AZA/VEN + Ziftomenib (D8) | AZA/VEN + Bleximenib (D4) | |
|----------------------------|---|----------------------|--|----------------------|--|--|----------------------|
| Trial | Beat AML¹ | | SAVE² | | KOMET-007³ | ALE1002⁴ | |
| Population | Newly Dx AML ≥60 years NPM1m, KMT2Ar | | Newly Dx AML or MPAL >18 years unfit NPM1m, KMT2Ar, NUP98r | | Newly Dx AML >18 years unfit NPM1m | Newly Dx AML >18 years unfit NPM1m, KMT2Ar | |
| Therapeutic Dose(s) | 220 mg BID; 270 mg BID Dose-adjusted with azoles | | 220 mg BID; 270 mg BID Dose-adjusted for azoles | | 600 mg daily | 100 mg BID | |
| Subtype | KMT2Ar n=9 | NPM1m n=34 | KMT2Ar n=7 | NPM1m n=14 | NPM1m n=34 | KMT2Ar n=4 | NPM1m n=16 |
| ORR | 100% | 85% | 86% | 86% | 89% | 75% | 94% |
| CR/CRh | 78% | 68% | 86% | 79% | 78% | 75% | 75% |
| CR | 78% | 65% | 86% | 71% | 73% | NR | NR |
| DS (any) | 19% | | 19% | | 3% | NR | |

- High response rates with frontline combinations w/ Aza/Ven
- Myelosuppressive and cytopenias common-> infectious complications
 - Venetoclax dose is critical
- Survival data still maturing-> *KMT2Ar* AML and Intermediate-risk *NPM1m* have excellent outcomes

Molecular *NPM1mt* MRD in bone marrow by NGS



Patterns of relapse: SAVE in ND AML



Conclusions

- AML therapeutic options continue to improve, with increasingly individualized and effective treatments
- Awareness of genomics (cytogenetics and mutational data) are essential to determine optimal treatment
- Targeted therapies for patients with FLT3, IDH1/2, NPM1, KMT2Ar available
- Menin inhibitors have emerged as a new effective class of agents

