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ABSTRACT #47

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

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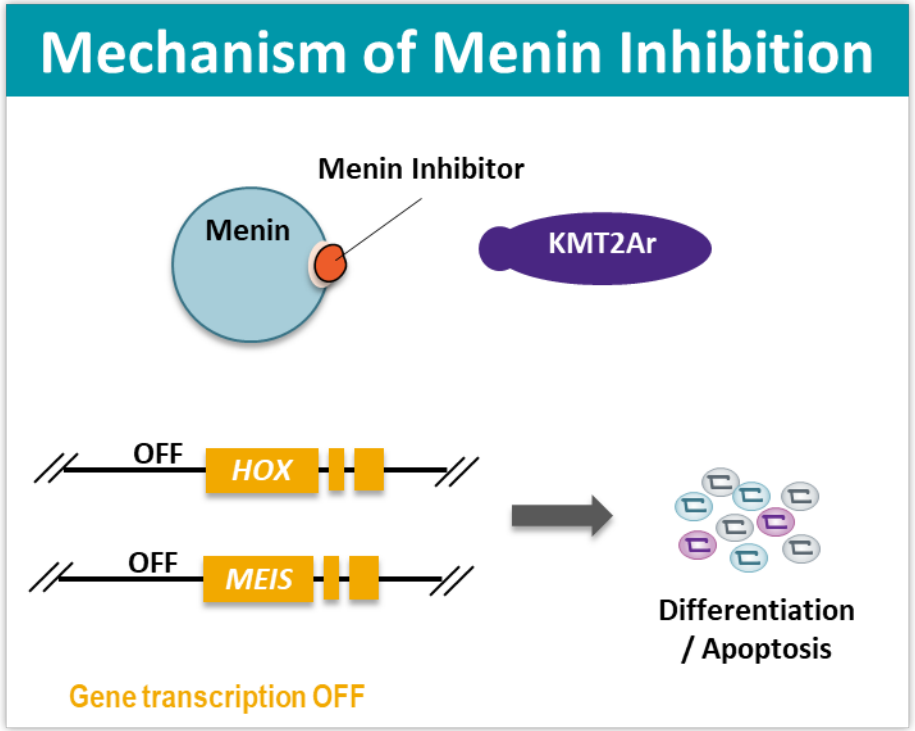
Introduction – menin inhibition

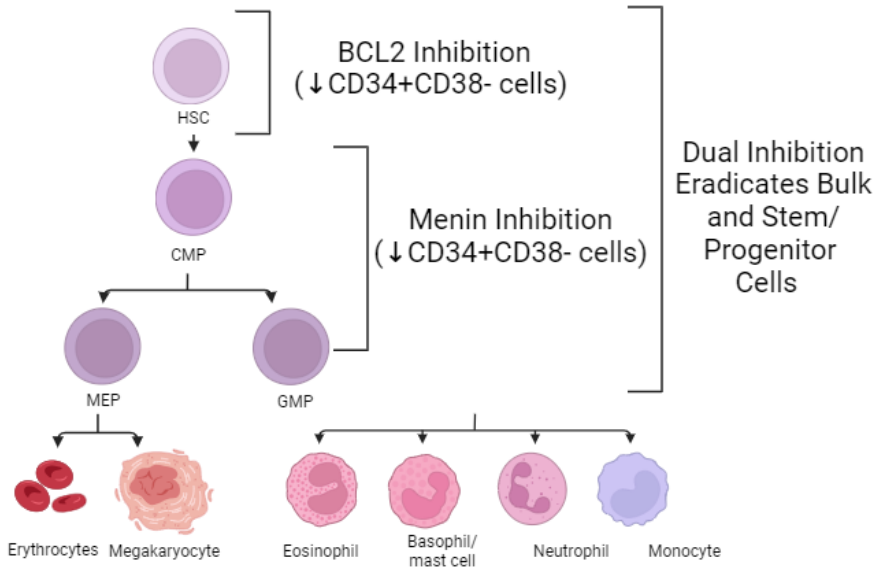
- Menin-KMT2A interaction is a dependency in *KMT2A*r, *NPM1mt* and *NUP98*r leukemias[1-3]
- Revumenib is a potent, oral, selective inhibitor of the menin–KMT2A interaction, FDA approved for adult and pediatric R/R acute leukemia with *KMT2A*r or *NPM1mt*
- Monotherapy with revumenib in R/R *KMT2Ar* or *NPM1mt*: ORR 43-60%, CR/CRh 21-30%, DOR ~ 4-6 months[4-6]
- Need to improve chances of responses and decrease risk of relapse

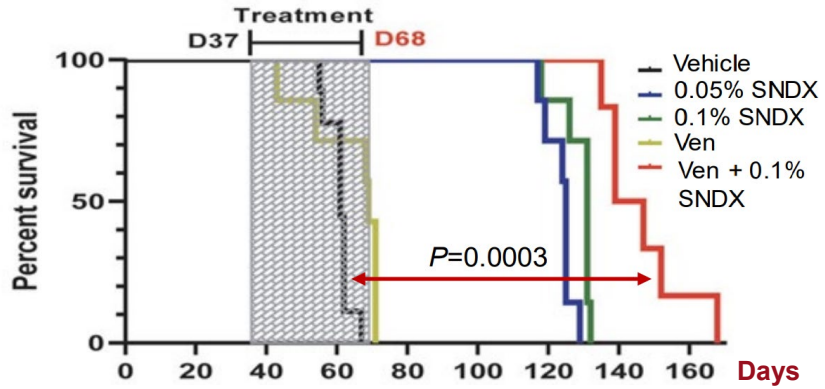


[1]Grembecka J et al. Nat Chem Biol 2012;8:277-84. [2]Uckelmann HJ et al. Science 2020;367:586-90. [3]Heikamp EB et al. Blood 2022;139:894-906. [4]Issa GC et al. Nature. 2023;615:920-924. [5]Issa GC et al. J Clin Oncol. 2025; 43(1):75-84. [6]Arellano ML et al. Blood. 2025;146(9):1065-1077.

Rationale for SAVE combination

- HMA + venetoclax is standard for older/unfit AML
- Oral decitabine/cedazuridine (ASTX727) approved (MDS, CMML, PDUFA for AML: Feb 2026), equivalent efficacy as IV decitabine[1]
- *KMT2Ar* or *NPM1mt* are susceptible BCL2 inhibition[2-5]; Need to improve outcomes
- **BCL2 + menin inhibition** → eradication of bulk and stem/progenitor cells and improved survival in preclinical models[6,7]
- All-oral combination of **S**NDX-5613 + **A**STX727 + **VE**netoclax (**SAVE**)





[1]Garcia-Manero G et al. Lancet Haematol. 2024;11(1):e15-e26. [2]Benito JM et al. Cell reports 2015;13:2715-27. [3]Tiong IS et al. Br J Haematol. 2021;192(6):1026-1030. [4]Lachowiez CA et al. Blood Adv. 2020;4(7):1311-1320. [5]Issa GC et al. Blood Adv. 2023;7(6):933-942. [6]Carter BZ et al. Blood. 2021;138(17):1637-1641. [7]Fiskus W et al. BCJ 2022;12:5.

SAVE Phase I/II Study Design

- Age ≥12 years
- AML or Myeloid MPAL with *KMT2Ar* or *NPM1mt* or *NUP98r*
  - Frontline: not eligible for high-intensity chemo
  - Relapsed/refractory
- ECOG ≤2
- Adequate organ function

Revumenib (SNDX-5613)*
DL 0: 110 mg (+CYP3A4i) or 160 mg (w/o CYP3A4i)
DL 1: 160 mg (+CYP3A4i) or 270 mg (w/o CYP3A4i) (USPI dose)
PO Q12h D1-D28

ASTX727
1 tablet (35 mg decitabine and 100 mg cedazuridine) PO daily D1-D5

Venetoclax
400 mg target dose* with ramp up
PO daily D1-D14
*adjusted with azoles

Primary objectives:
- **Phase I in R/R (3+3 design)**
  Safety, MTD and RP2D
- **Phase II (Frontline and R/R)**
  Efficacy

Secondary objectives:
- Phase II
  OS, RFS, CRD, MRD

Exploratory objectives:
- MRD at 10^{-5}, resistance

Maintenance revumenib post-SCT for 1 year

D14 bone marrow for early response
Amendment: hold revumenib after D21 if D14 BM blasts <5%

*Revumenib: 113 mg capsule = 110 mg tablet; 163 mg capsule = 160 mg tablet. CYP3A4i indicates strong inhibitors: posa; vori.

Baseline Characteristics – SAVE in ND AML

Characteristic	All (N=21)	*NPM1mt* (N=14)	*KMT2Ar* (N=7)
Median age, years [range]	70 [60, 83]	73 [66, 83]	64 [60, 77]
≥70 years, n (%)	11 (52%)	10 (71%)	1 (14%)
Female, n (%)	15 (71%)	9 (64%)	6 (86%)
Secondary AML, n (%)	5 (24%)	2 (14%)	3 (43%)
Diploid CG, n (%)	9 (43%)	9 (64%)	0
Adverse CG, n (%)	7 (33%)	1 (7%)	6 (86%)
Co-mutations, n (%)			
NRAS / KRAS	4 (19%)	2 (14%)	2 (29%)
FLT3	4 (19%)	4 (28%)	0
ITD*	1 (5%)	1 (7%)	0
TKD	3 (14%)	3 (21%)	0
IDH1/2	4 (19%)	3 (21%)	1 (14%)
MDS-associated#	9 (43%)	6 (43%)	3 (43%)

KMT2Ar	n (%)
t(6;11)(q27;q23) *KMT2A::AFDN*	2 (29%)
t(11;19)(q23;p13.1) *KMT2A::ELL*	2 (29%)
t(9;11)(p21;q23) *KMT2A::MLLT3*	1 (14%)
t(X;11)(q13.1;q23.3) *KMT2A::FOXO4*	1 (14%)
t(11;11)(p15.4;q23.3) *KMT2A::NUP98*	1 (14%)

**FLT3*-ITD detected with a frequency of 0.03.
#MDS-associated mutations in the following genes: *ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2,* and/or *RUNX1*.

Adverse events

TEAEs (any grade, >30%)	(N=21)
Vomiting	14 (67%)
Elevated AST/ALT	13 (62%)
↑K+	13 (62%)
Nausea	12 (57%)
↑Phos	11 (52%)
Hyponatremia	11 (52%)
Febrile neutropenia	10 (48%)
Constipation	10 (48%)
QTc prolonged	9 (43%)
Thrombocytopenia	8 (38%)
Headache	7 (33%)
[…]	
Differentiation syndrome	4 (19%)

No Grade ≥3 QT prolongation

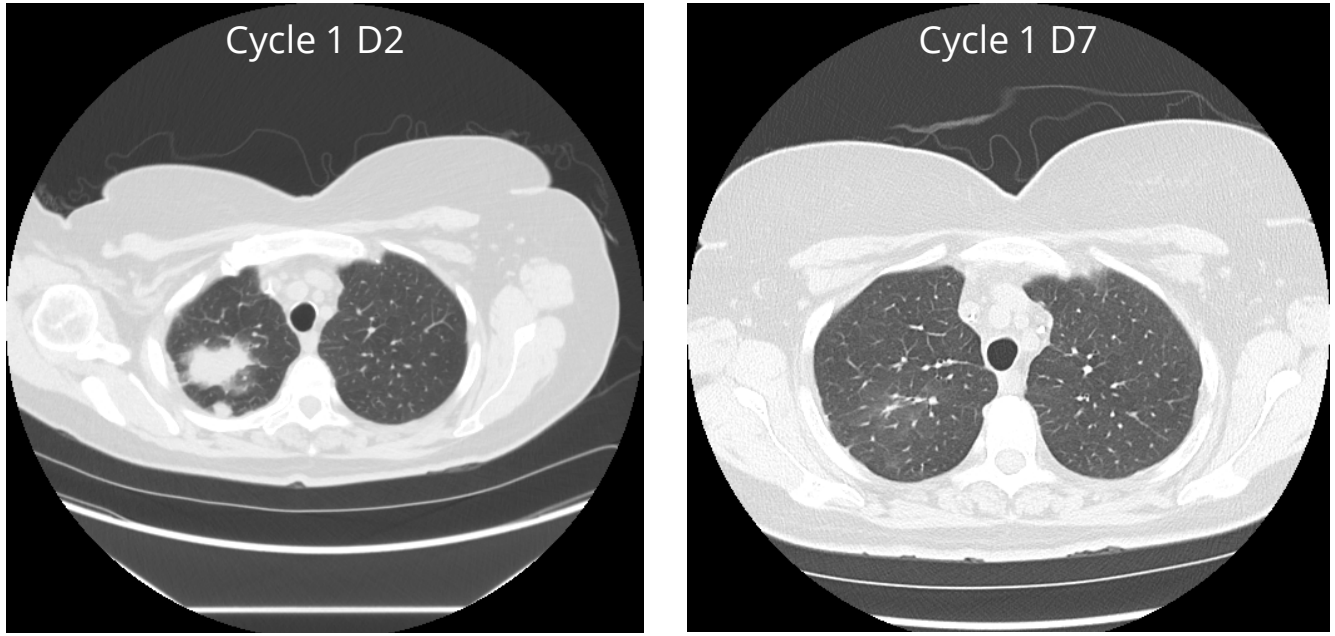
TEAEs (Grade ≥3, any G4-5)	G3	G4	G5	G ≥3
Febrile neutropenia	0	10 (48%)	0	10 (48%)
Thrombocytopenia	2 (10%)	5 (24%)	0	7 (33%)
Neutropenia	2 (10%)	4 (19%)	0	5 (24%)
Bacteremia	2 (10%)	0	2 (10%)	4 (19%)
Lung infection	2 (10%)	1 (5%)	0	3 (14%)
Skin infection	3 (14%)	0	0	3 (14%)
Differentiation syndrome	2 (10%)	0	0	2 (10%)
Respiratory failure	0	2 (10%)	0	2 (10%)
Elevated AST	2 (10%)	0	0	2 (10%)
Elevated ALT	2 (10%)	0	0	2 (10%)
Sepsis	2 (10%)	0	0	2 (10%)
Bronchopulmonary hemorrhage	0	0	1 (5%)	1 (5%)
Skin infection	1 (5%)	0	0	1 (5%)
Intracranial hemorrhage	1 (5%)	0	0	1 (5%)

TEAEs: treatment emergent adverse events regardless of attribution to any of the study drugs.

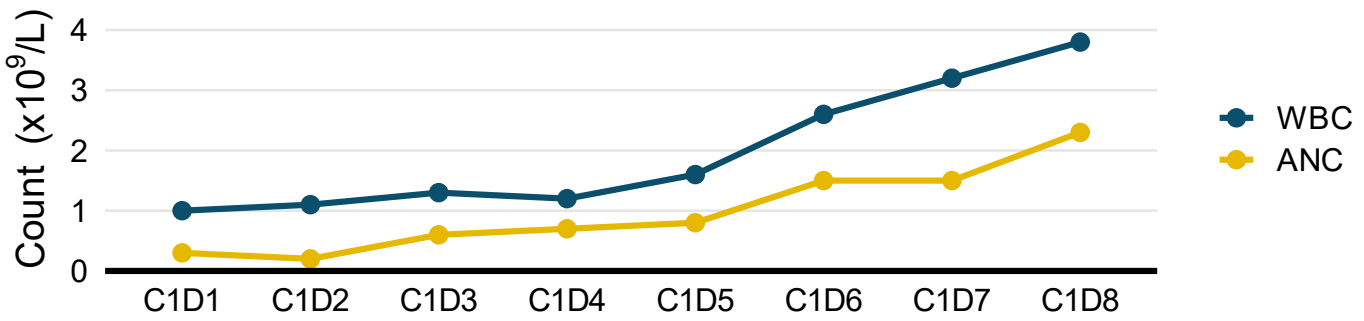
Differentiation Syndrome: Monocytic/high burden

77y AML with *NPM1*, *IDH1*, *FLT3* D835 mutations, leukocytosis at presentation (reduced with hydrea) with monocytosis

- Baseline CT chest prior to starting (not shown): small ground glass opacities
- C1D2 of SAVE, chest tightness, and mild tachypnea, normal oxygen and VS, mild ↑WBC and left shift
- Received high dose steroids, empiric antibiotics, diuresis
- Chest tightness resolved with first dose of steroids. Attained CR, MRD neg by *NPM1* NGS



Dexamethasone 10 mg BID for 3 days followed by taper



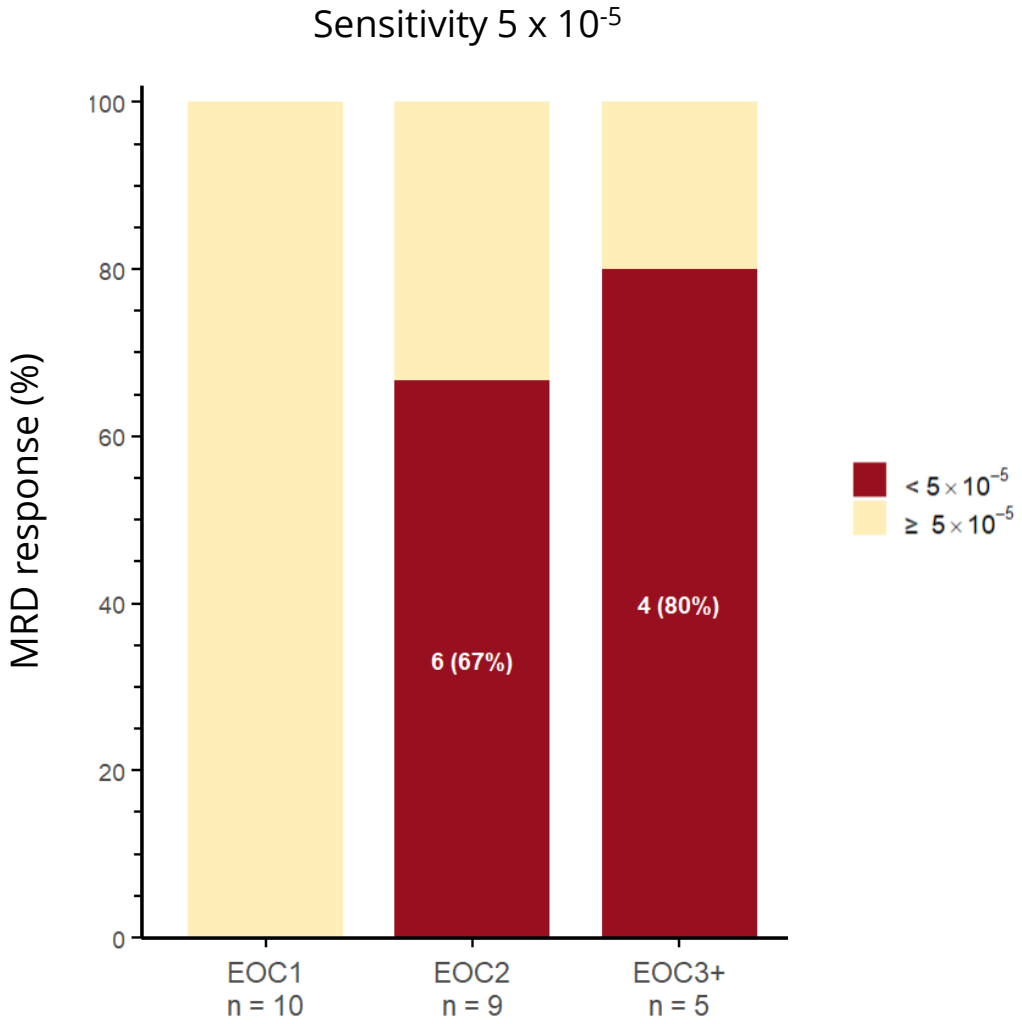
Response rate with SAVE in ND AML

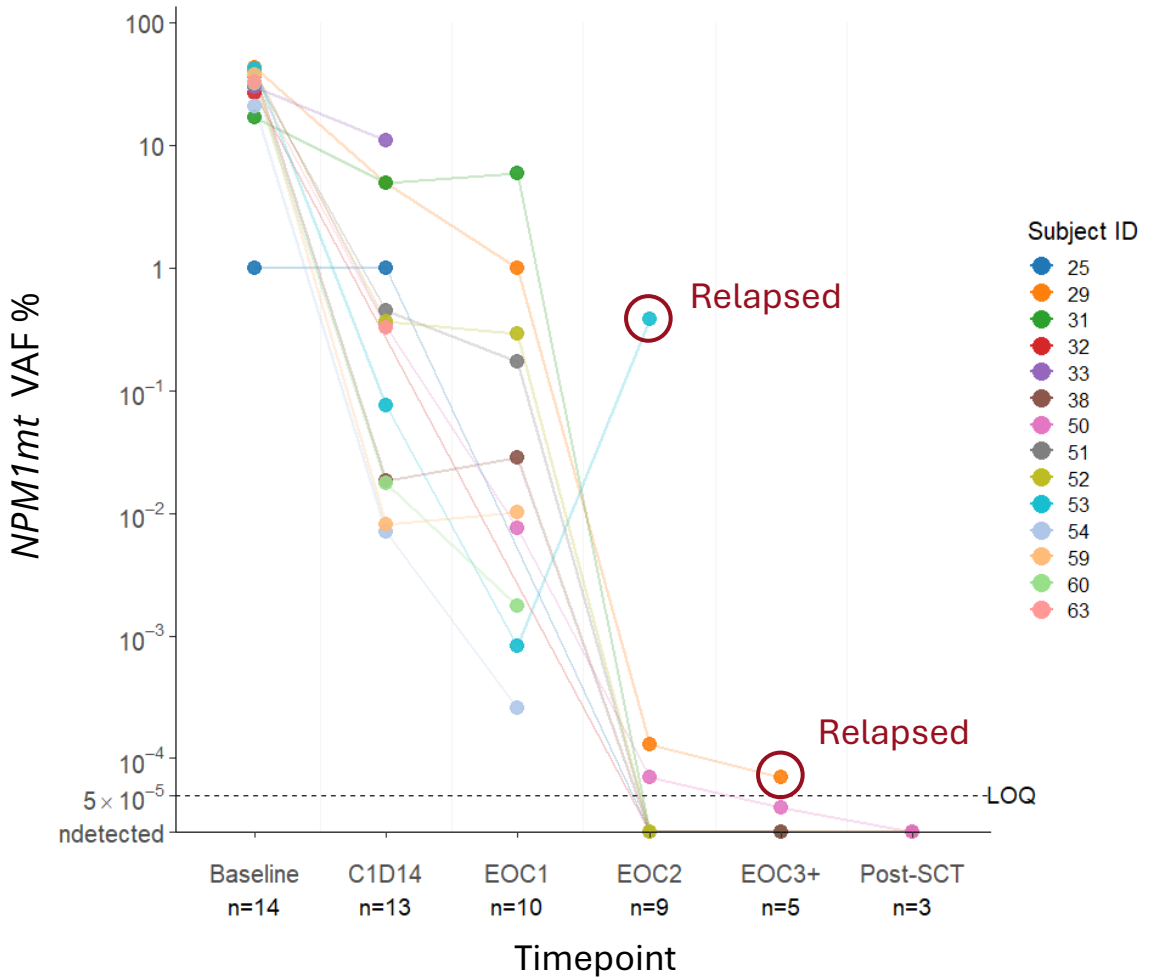
Best Response	All patients (N=21)	*NPM1mt* (N=14)	*KMT2Ar* (N=7)
ORR	18 (86%)	12 (86%)	6 (86%)
CR/CRh	17 (81%)	11 (79%)	6 (86%)
CR	16 (76%)	10 (71%)	6 (86%)
CRh	1 (5%)	1 (7%)	0
CRp	1 (5%)	1 (7%)	0
MLFS	0	0	0
Early death (30-day)	2 (10%)	2 (10%)	0
Not evaluable*	1 (5%)	0	1 (14%)
MRD neg by MFC (10^{-4})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

ORR= CR+CRh+CRp+MLFS. Data Cutoff 11/10/2025.
MFC, multicolor flow cytometry.

*One patient withdrew consent and proceeded to hospice care during week 1 prior to response assessment.

Molecular *NPM1mt* MRD in bone marrow by NGS

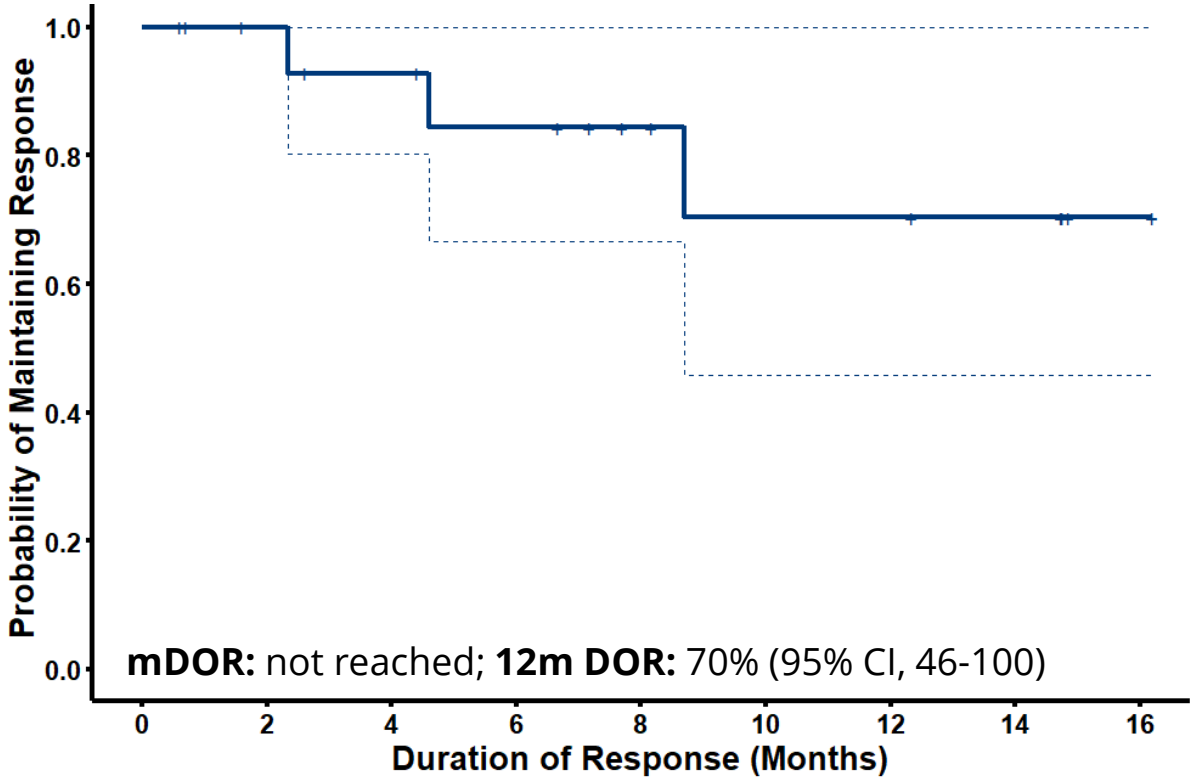




DOR and Survival in ND AML

Median follow-up of 9 months

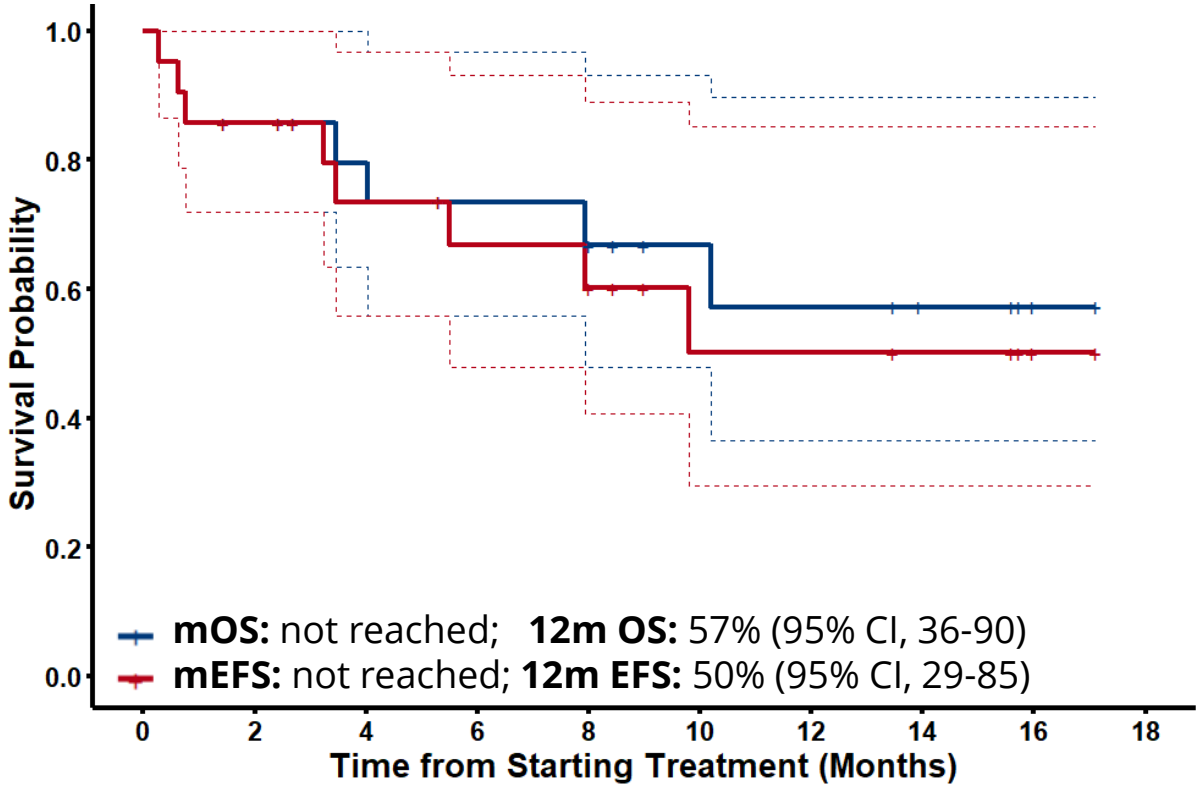
DOR in patients attaining CR or CRh



Number at risk

—	17	14	12	10	7	5	5	4	1

OS and EFS of the entire cohort

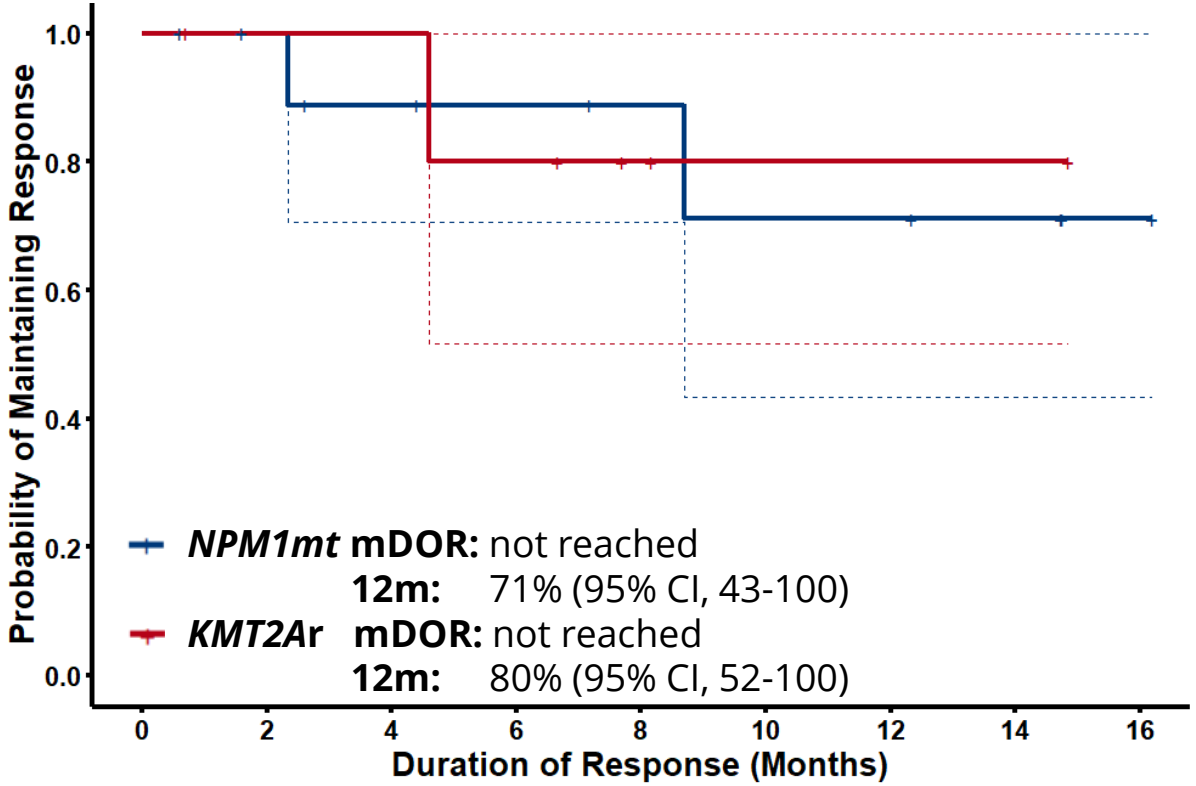


Number at risk

—	21	17	13	11	10	7	6	4	1	0
—	21	17	12	10	9	5	5	4	1	0

DOR and Survival by genotype

DOR in patients attaining CR or CRh

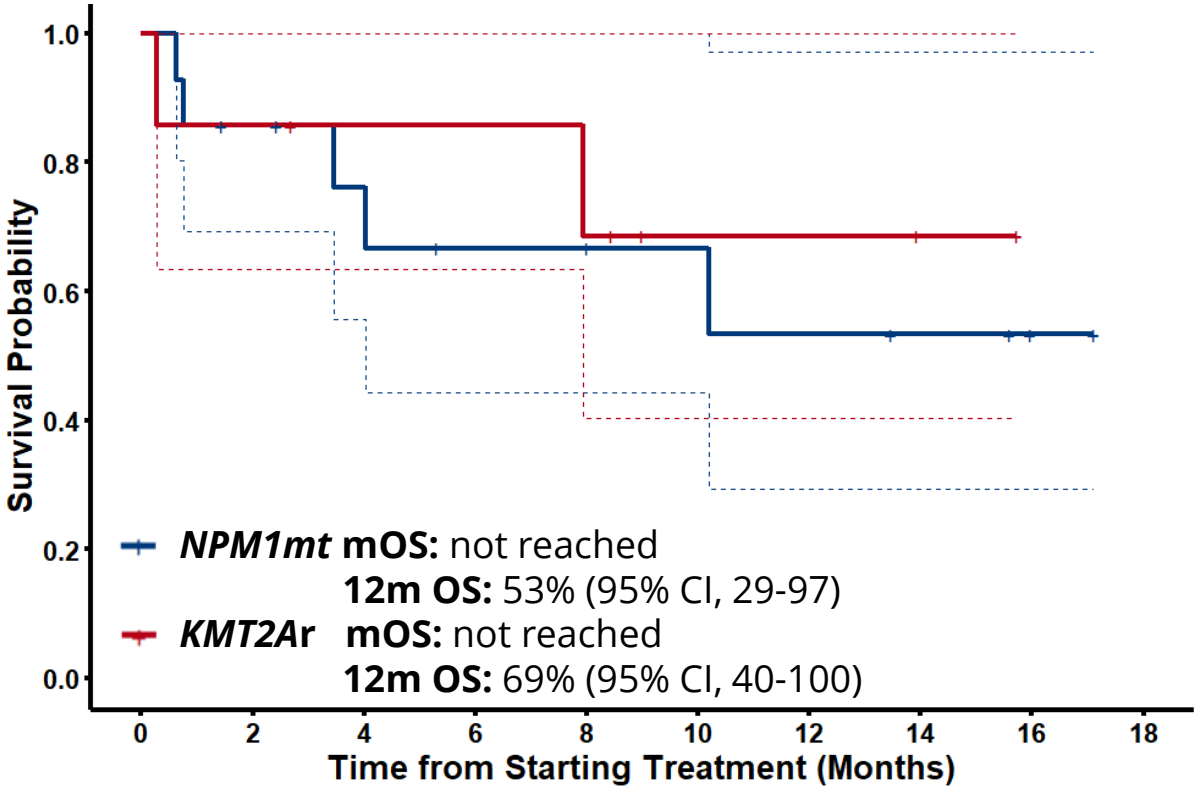


Number at risk

	11	9	7	6	5	4	4	3	1
	6	5	5	4	2	1	1	1	0

Overall Survival

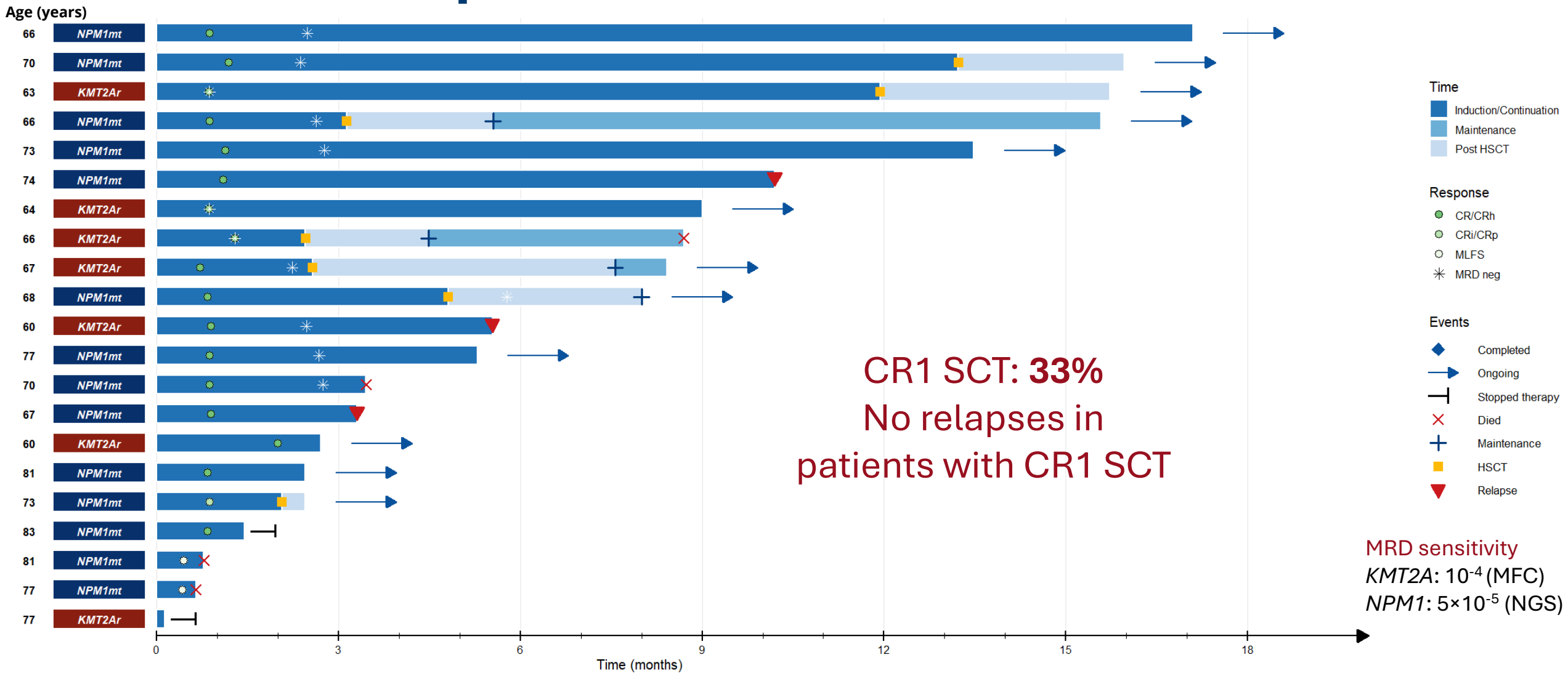
Median follow-up of 9 months



Number at risk

	14	11	8	6	6	5	4	3	1	0
	7	6	5	5	4	2	2	1	0	0

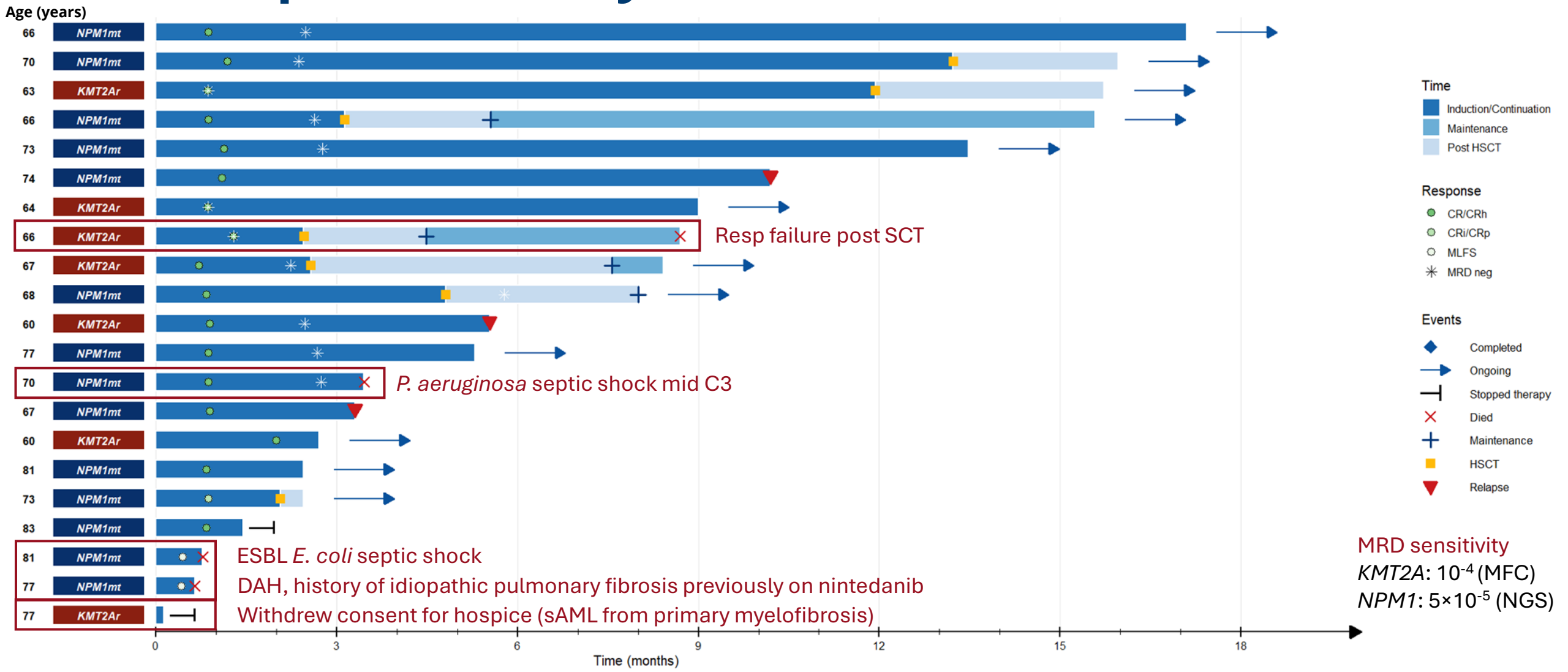
Duration of response: SAVE in ND AML



CR1 SCT: **33%**
No relapses in patients with CR1 SCT

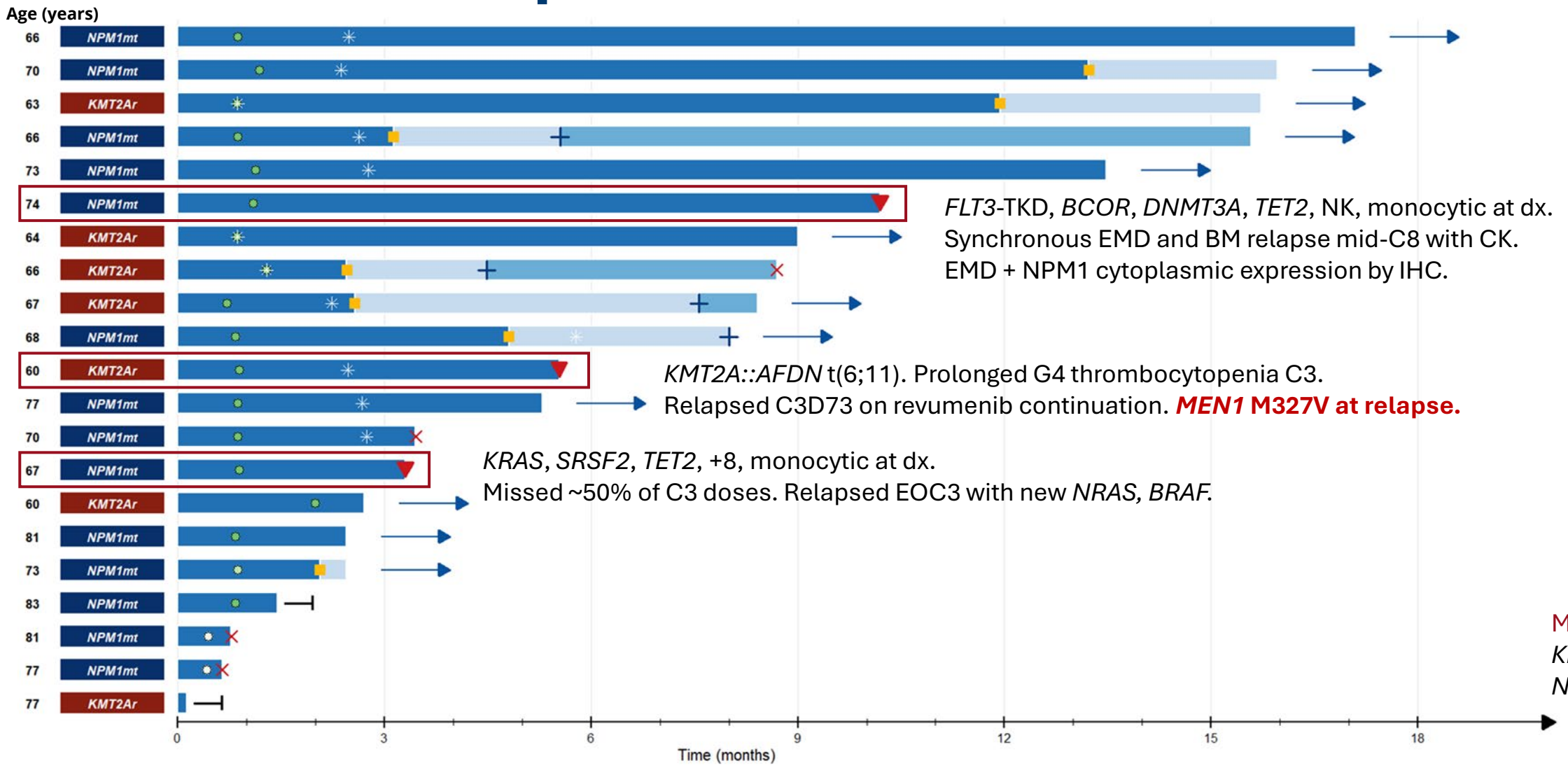
MRD sensitivity
KMT2A: 10^{-4} (MFC)
NPM1: 5×10^{-5} (NGS)

Non-relapse mortality: SAVE in ND AML



MRD sensitivity
KMT2A: 10^{-4} (MFC)
NPM1: 5×10^{-5} (NGS)

Patterns of relapse: SAVE in ND AML



FLT3-TKD, *BCOR*, *DNMT3A*, *TET2*, NK, monocytic at dx.
Synchronous EMD and BM relapse mid-C8 with CK.
EMD + NPM1 cytoplasmic expression by IHC.

KMT2A::AFDN t(6;11). Prolonged G4 thrombocytopenia C3.
Relapsed C3D73 on revumenib continuation. ***MEN1* M327V at relapse.**

KRAS, *SRSF2*, *TET2*, +8, monocytic at dx.
Missed ~50% of C3 doses. Relapsed EOC3 with new *NRAS, BRAF*.

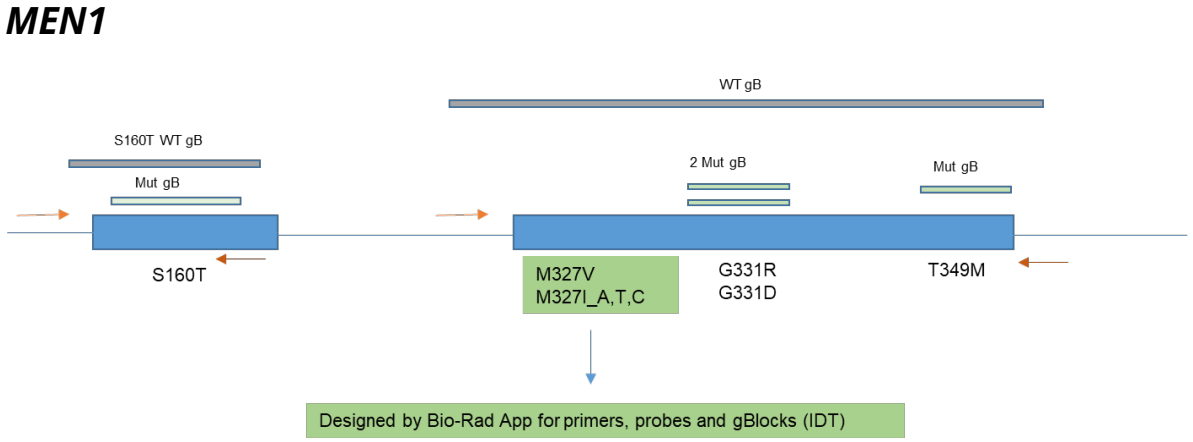
Time
- Induction/Continuation
- Maintenance
- Post HSCT

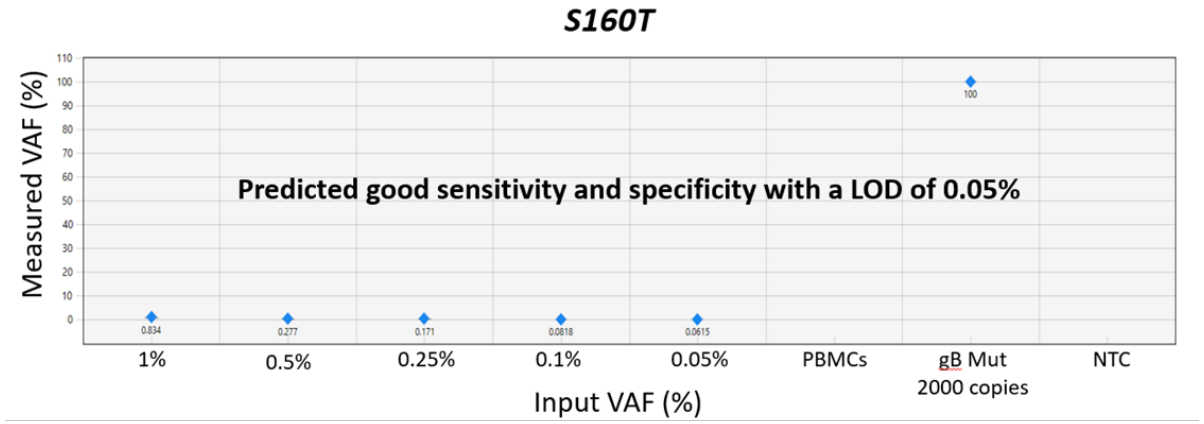
Response
- CR/CRh
- CRi/CRp
- MLFS
- MRD neg

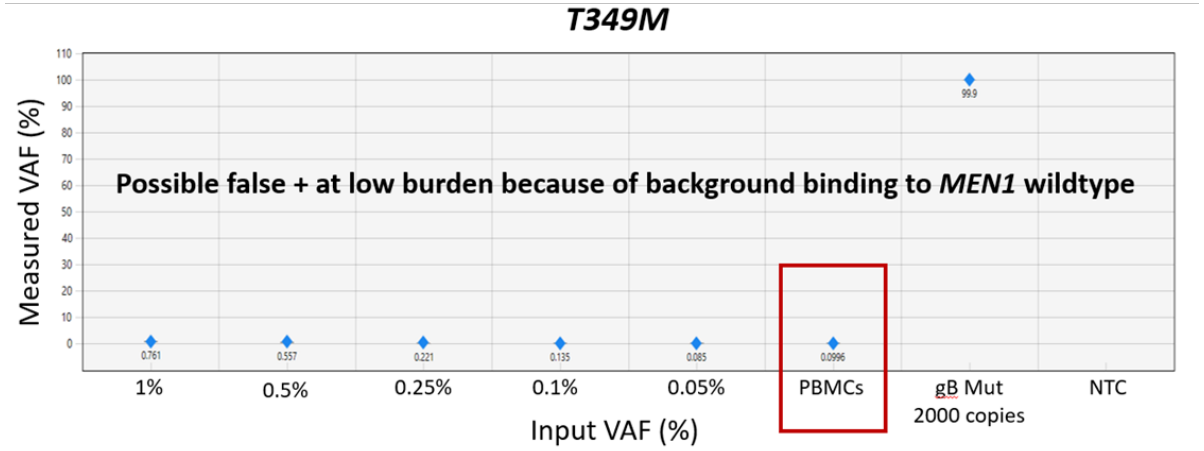
Events
- Completed
- Ongoing
- Stopped therapy
- Died
- Maintenance
- HSCT
- Relapse

MRD sensitivity
KMT2A: 10^{-4} (MFC)
NPM1: 5×10^{-5} (NGS)

Detection of *MEN1* mutations by ddPCR







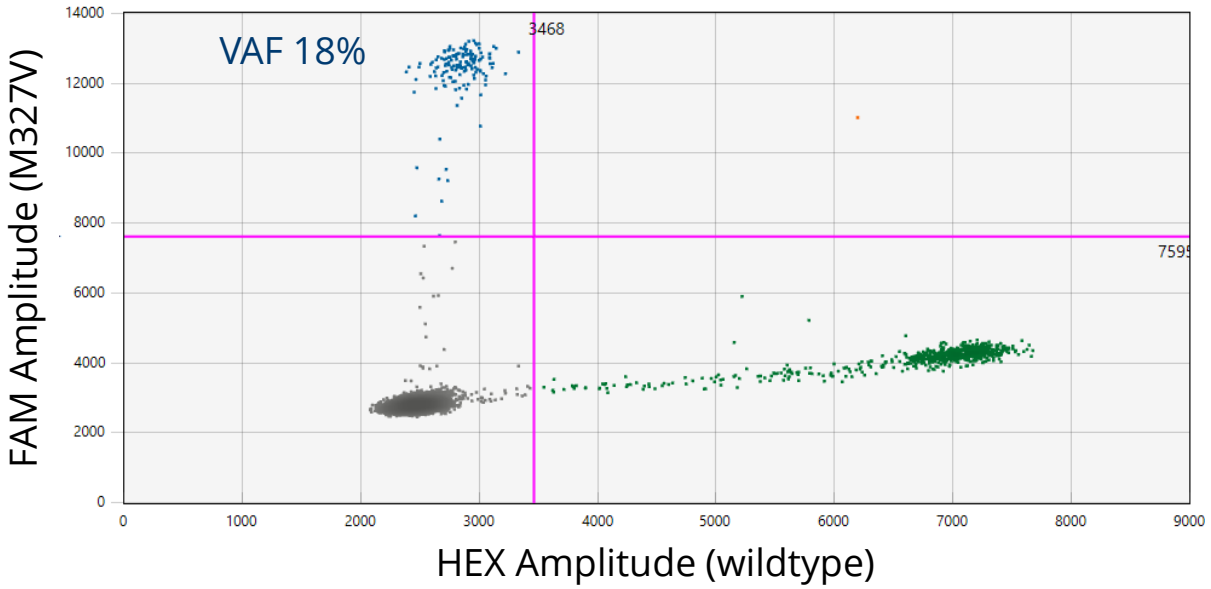
Optimization/validation of ddPCR assay for *MEN1* mutations that disrupt revumenib binding[1]

- LOD (VAFs of 1%, 0.5%, 0.25%, 0.1% and 0.05%) using serial dilution of gBlocks + Ctrls for sen/spe
- **True + vs False + (noise; background binding to *MEN1wt)***

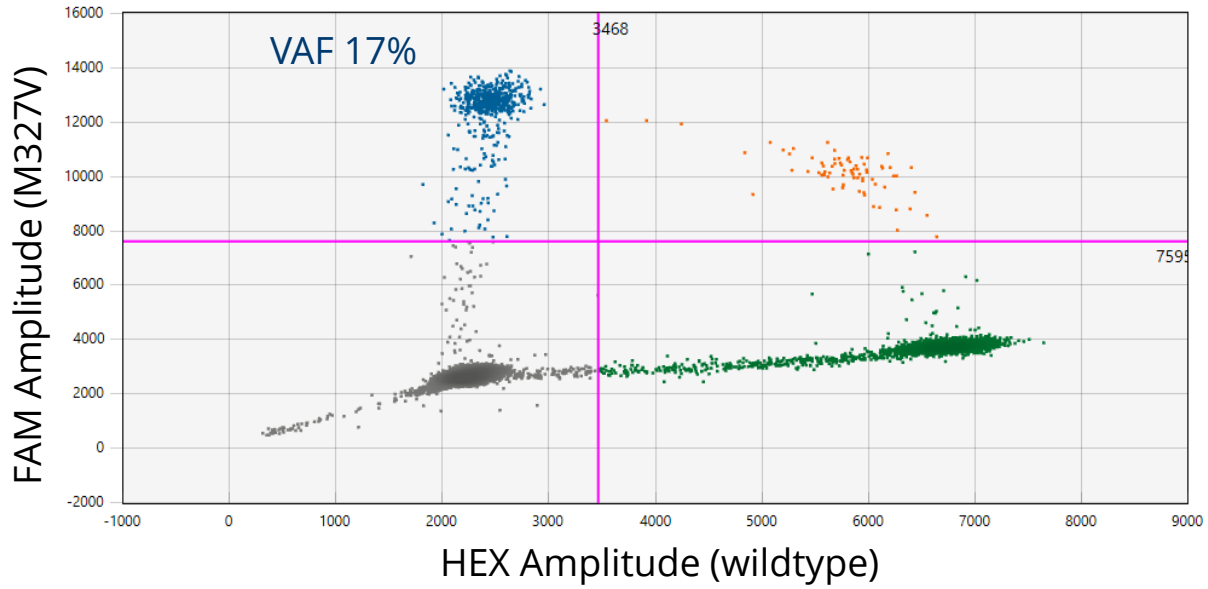
[1]Perner F et al. Nature. 2023 Mar;615(7954):913-919

Detection of *MEN1* M327V at relapse

MDA Seq#36 (BM sample at relapse, 10 ng)



MDA Seq#36 (BM sample at relapse, 25 ng)



MDA Seq#36: 60 y.o female with AML, t(6;11)(q27;q23) or *KMT2A::AFDN*, no other co-mutation (80-gene panel), attained CR, MRD neg by MFC, progression after cycle 3 of SAVE.

Conclusions

- The all-oral SAVE shows high efficacy in newly diagnosed AML susceptible to menin inhibition:
  - High response and MRD-negativity rates in a small cohort, need larger sample and longer follow-up
- Emergent *MEN1* mutation (M327V) was detected at relapse, suggesting this combination may not fully address this mechanism of resistance, though likely additional mechanisms implicated
- Recommend empiric high-dose steroids at earliest suspicion of DS
- Concern for myelosuppression; Need to optimize menin inhibitor combinations to improve the overall benefit–risk, especially in *NPM1mt* AML