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Session 619
Abstract no. 223

Revumenib as Pre-emptive Therapy for Measurable Residual Disease in *NPM1* Mutated or *KMT2A*-rearranged AML: A Domain of The Multi-Arm ALLG AMLM26 INTERCEPT Platform Trial

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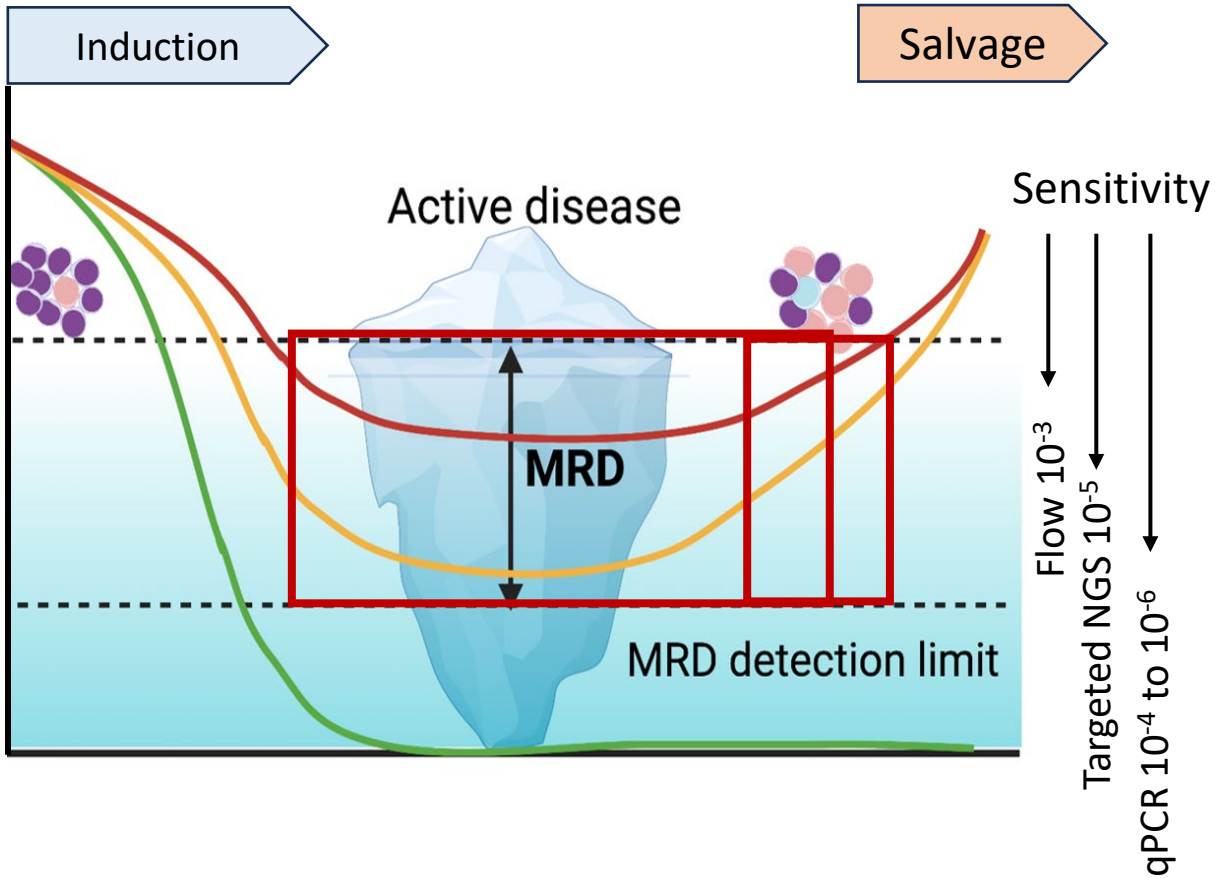
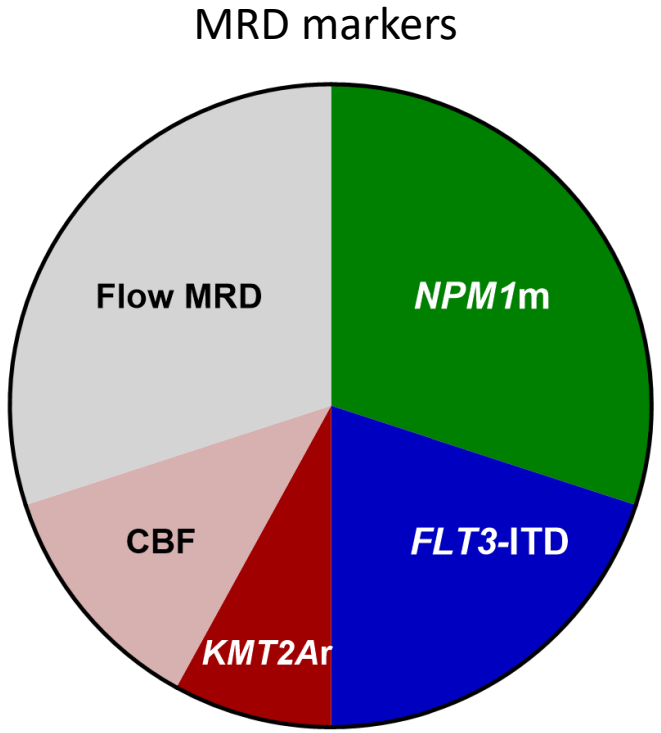
ALLG
Australasian Leukaemia & Lymphoma Group

Rationale for measuring residual disease in acute myeloid leukemia

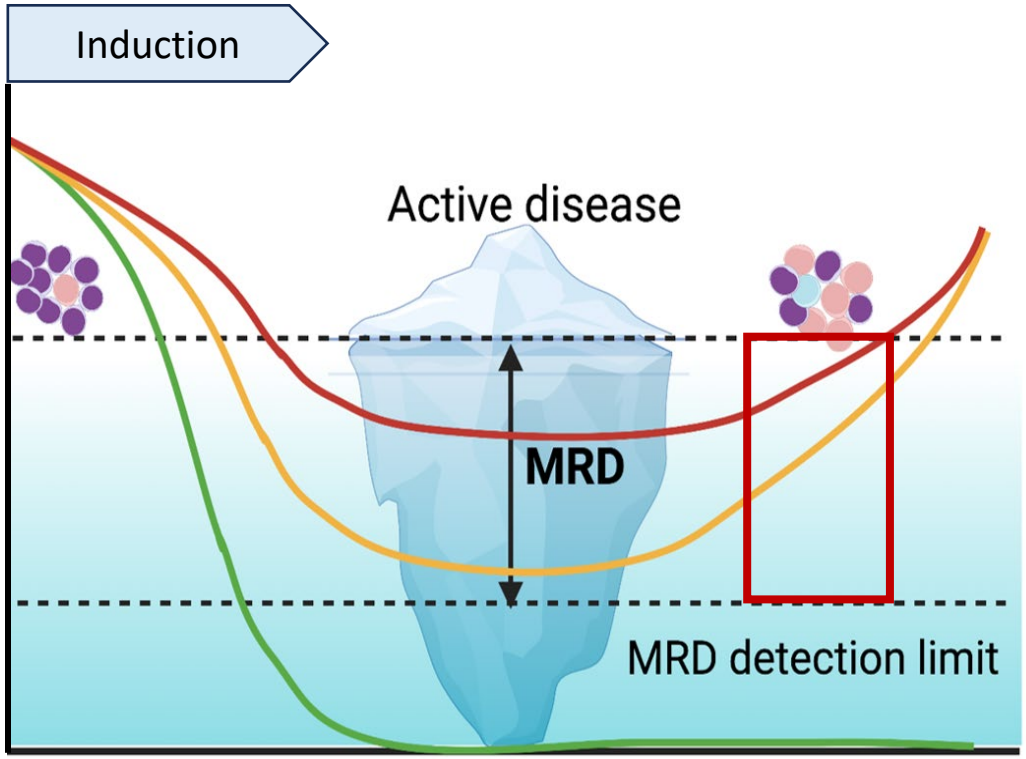




Heuser, Blood 2021

CBF, core binding factor; NGS, next generation sequencing; qPCR, *NPM1*m, *NPM1* mutation; quantitative polymerase chain reaction.

Pre-emptive MRD-directed therapy- evolving options



Treatment	N	MRD clearance	Survival
Azacitidine	53	36%	1y OS 75%
Venetoclax-LDAC	26	46%	2y OS 67%
FLT3 inhibitors	56	45%	2y OS 80%
Venetoclax-HMA/LDAC	79	71%	2y OS 67%

Platzbecker, Lancet Oncol 2018; Tiong, JCO 2024; Othman, Leukemia 2023; Jimenez-Chillon, Blood Adv 2024

HMA, hypomethylating agent; LDAC, low dose cytarabine; OS, overall survival; RFS, relapse-free survival

Revumenib in relapsed/refractory *NPM1* mutant or *KMT2A*-rearranged AML

Treatment	N	CR/CRh	Median OS
KMT2Ar	57	22.8%	8 mo
*NPM1*m	64	23%	ND

Rationale for MRD intervention

Less cytopenia

Fewer hematologic complications

Reduced need for concomitant medications

?Enhanced potential for MRD response

?More durable remission

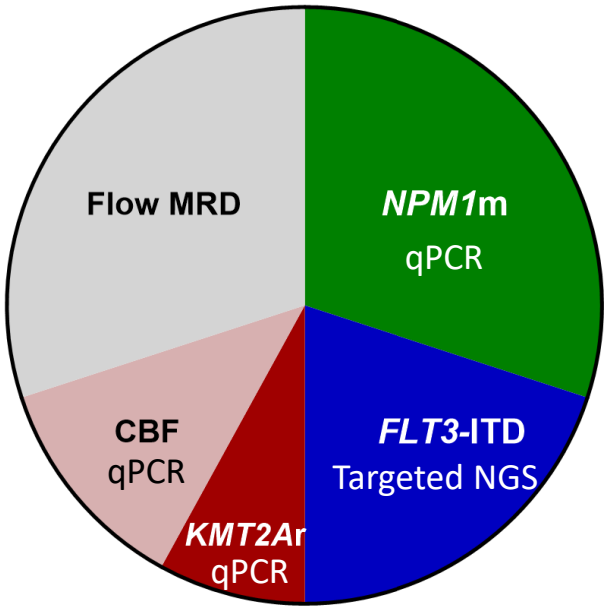
Issa, JCO 2024; Syndax Pharmaceuticals, Inc. press release (12 Nov 2024)

CR, complete remission; CRh, CR with partial hematologic recovery; mo, months; ND, not determined; OS; overall survival.

AMLM26 INTERCEPT

Investigating Novel Therapy to Target Early Relapse and Clonal Evolution as Pre-emptive Therapy in AML

Remission	Relapse	Salvage therapy
	Relapse >15% blasts →	Conventional salvage
	Oligoblastic relapse 5-15% blasts	AMLM26 INTERCEPT therapy
	MRD relapse (≥1 $\log_{10}$ rise in molecular MRD or flow MRD ≥0.1%)	



MRD domains	Treatment options
FLT3/CBL	Gilteritinib + VEN
NPM1	LDAC + VEN
KMT2Ar NPM1	**Revumenib**
IDH1	Ivosidenib + VEN
Flow MRD	AZA + Sabatolimab

Harmonised MRD monitoring

Central MRD relapse confirmation

Central MRD monitoring

14 sites

ASH Trial in Progress (INTERCEPT), 2022 (doi.org/10.1182/blood-2022-167837)

ALLG AMLM26 INTERCEPT revumenib treatment arm

Key eligibility

Adults with AML in first or second remission with:

- MRD relapse: ≥1 $\log_{10}$ rise in *NPM1*m *or KMT2A*r qPCR MRD (confirmed by central lab), OR
- Oligoblastic relapse (5-15% bone marrow blasts)

Primary objective

To assess the efficacy of revumenib in *NPM1*m or *KMT2A*r with MRD or oligoblastic relapse

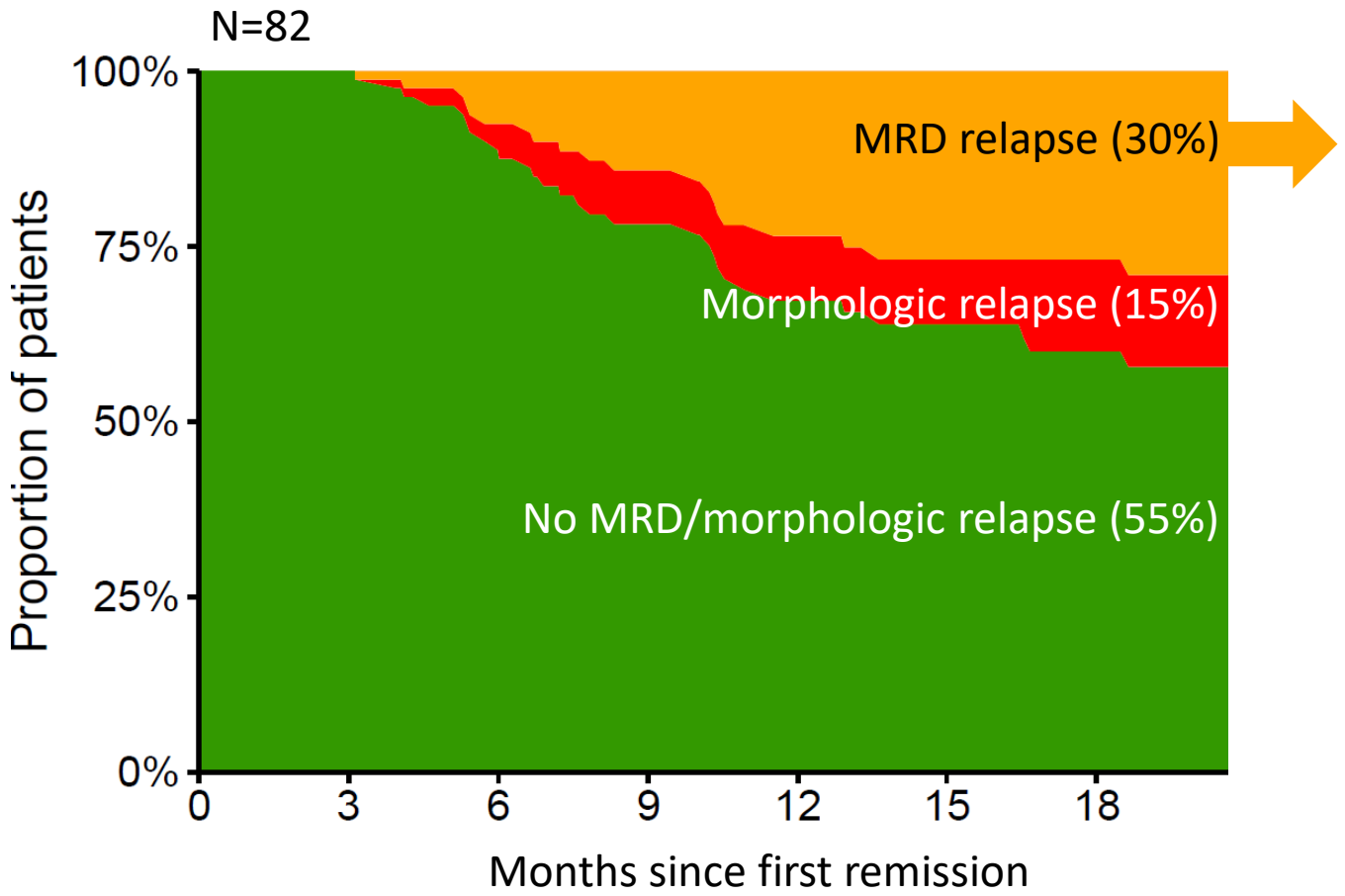
- Target *NPM1*m MRD clearance rate ≥30%
- Target *KMT2A*r MRD clearance rate ≥20%

Key secondary objective

Confirm tolerability of revumenib RP2D (276mg twice a day) in patients with MRD relapse

qPCR, quantitative polymerase chain reaction; RP2D, recommended phase 2 dose.

Fate of patients enrolled to INTERCEPT monitoring with *NPM1* mutation



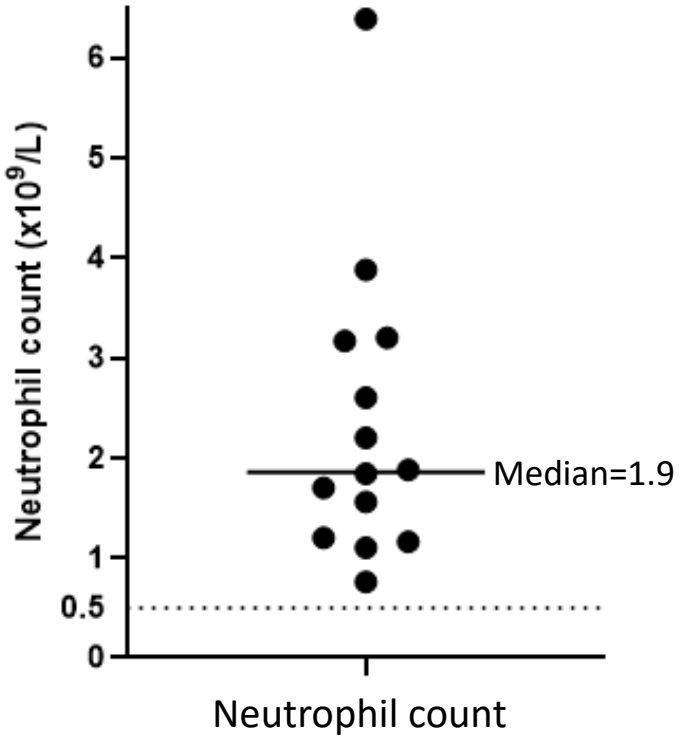
At MRD relapse:
64% enrolled to INTERCEPT treatment
12% currently in screening
24% received off study treatment

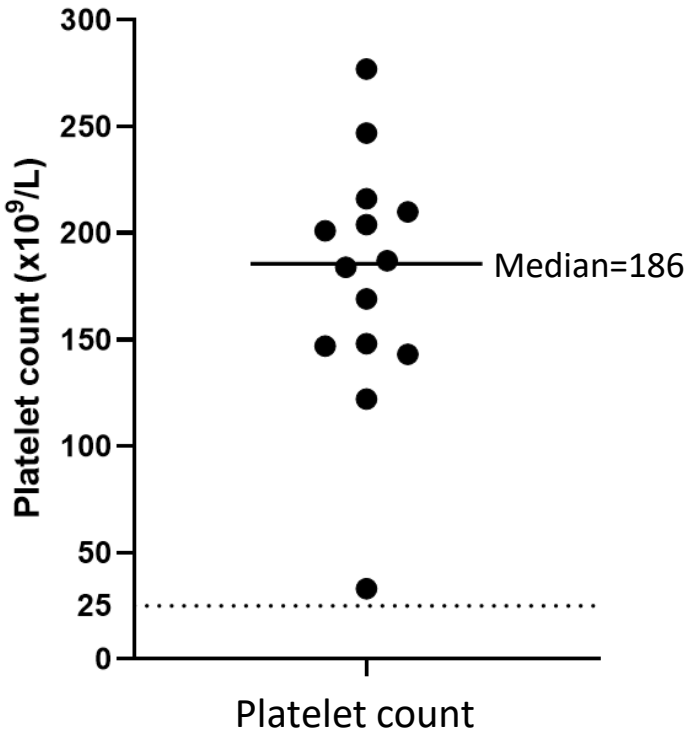
Generated in combination with data from the ALLG National Blood Cancer Registry (NBCR)

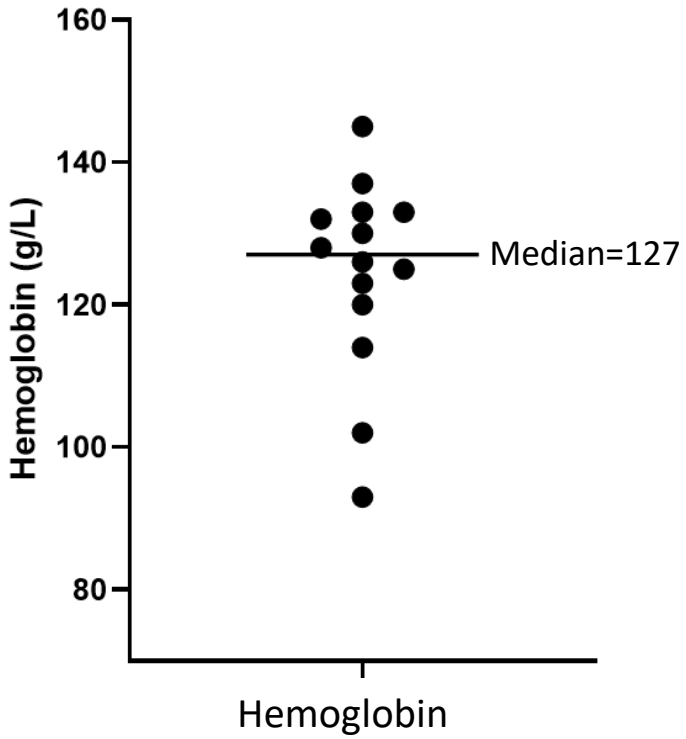
Baseline characteristics of MRD relapse cohort

Variables, n (%) unless specified	**N=14**
Median age (range)	**56 (19-86)**
Female	9 (64)
Ethnicity White Asian Aboriginal Australian	 11 (79) 2 (14) 1 (7)
NPM1 mutation *KMT2A*-rearrangement	**13 (93)** 1 (7)
First remission Second remission	**12 (86)** 2 (14)
Prior frontline treatment • Intensive treatment • Venetoclax-based low intensity treatment	 **12 (86)** 2 (14)
Prior hematopoietic stem cell transplant	3 (21)
Time from MRD failure to first day of cycle, days (range)	**54 (34-107)**

Baseline hematology at MRD relapse prior to revumenib treatment







Treatment-emergent adverse events

Adverse event	N=14			
	All grades	Grade 3	Grade 4	≥Grade 3*
Neutropenia	7	1	6	50%
Thrombocytopenia	9	3	3	43%
QTcF interval prolongation	6	2	-	14%
Anemia	2	1	-	7%
Skin infection	2	1	-	7%
Febrile neutropenia	1	1	-	**7%**
Nausea	5	-	-	-
Vomiting	2	-	-	-
Diarrhea	4	-	-	-
Constipation	2	-	-	-
Dysgeusia	3	-	-	-
Headache	4	-	-	-
Fatigue	3	-	-	-
Upper respiratory tract infection	5	-	-	-
Rash	3	-	-	-
Infection and infestations	2	-	-	-

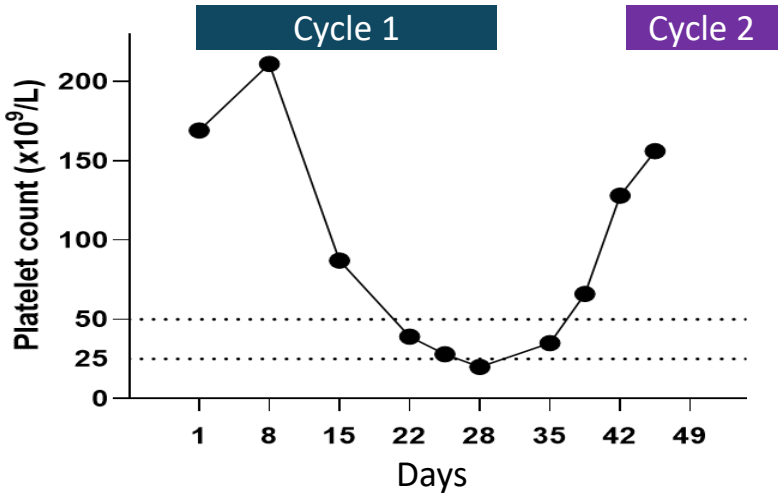
No AE reports of differentiation syndrome

*No grade 5 events

TEAE, treatment emergent adverse event; QTcF; QT with Fridericia correction

Patterns of thrombocytopenia during revumenib therapy

ALF016



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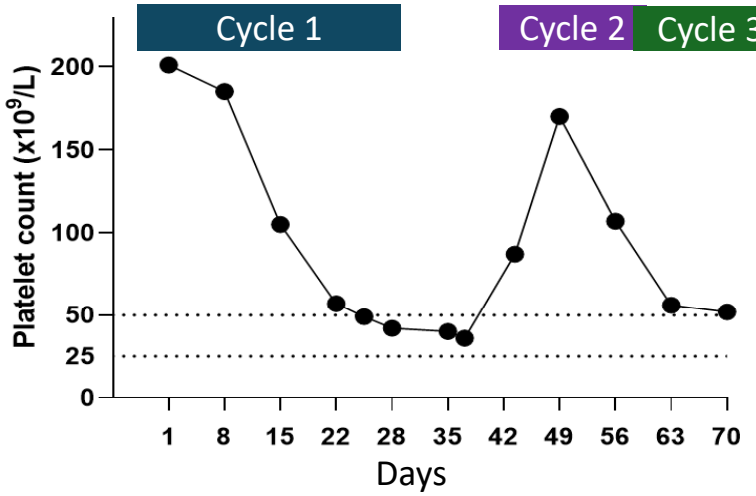

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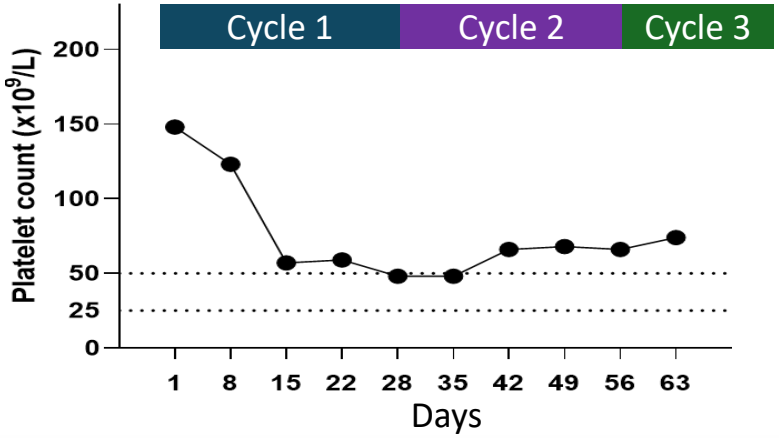

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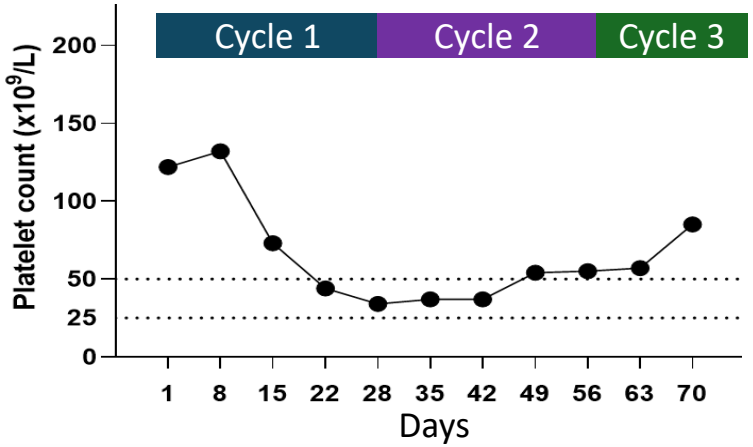

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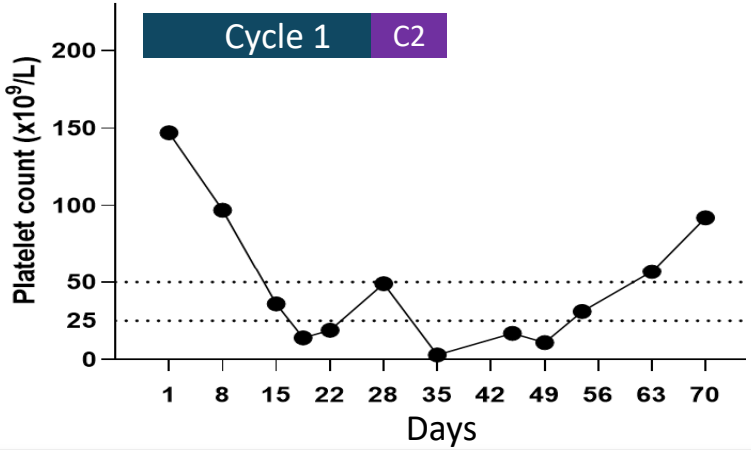
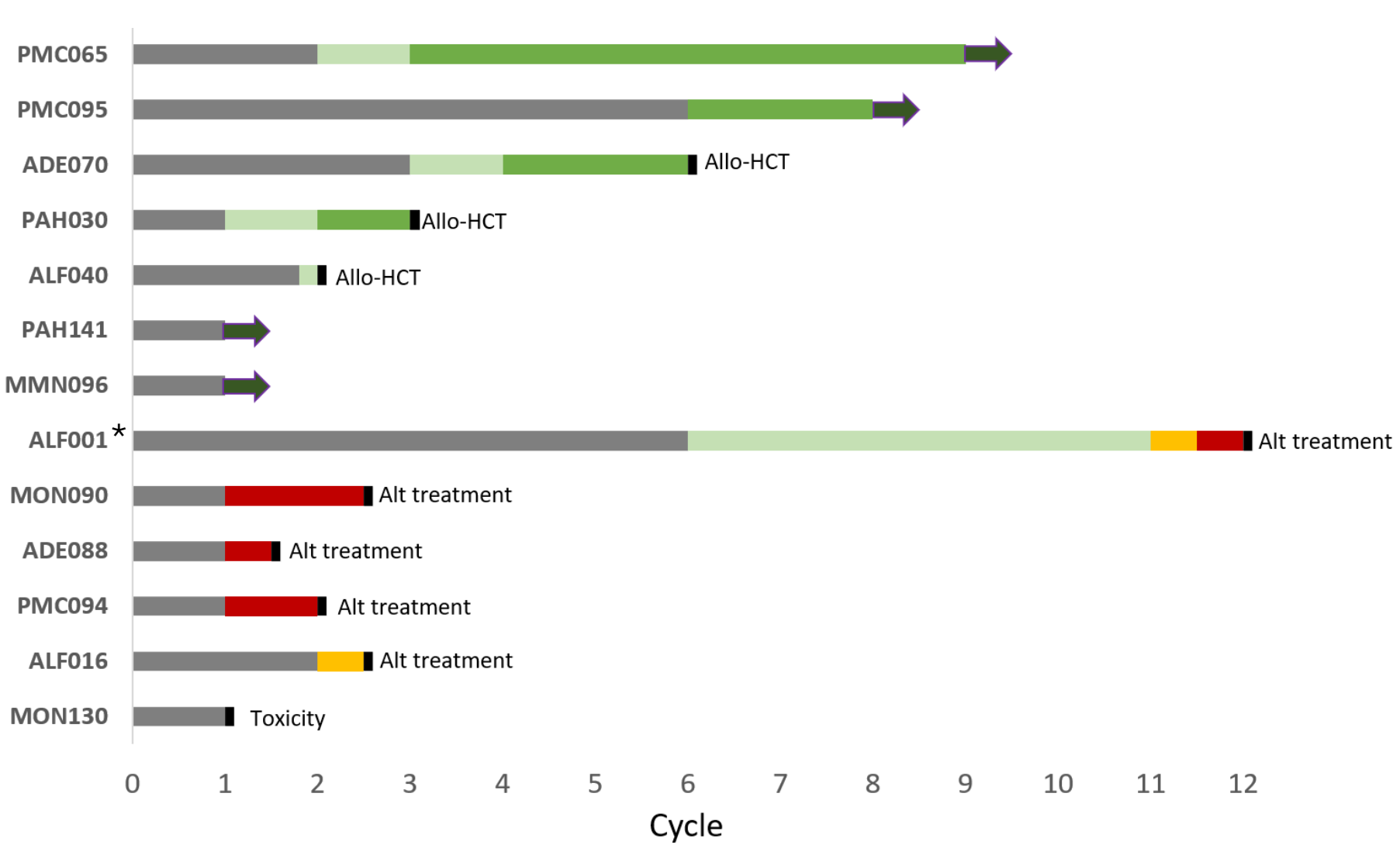


Response and disposition of 13 patients with *NPM1*m



Response

- No response
- ≥ 1 $\log_{10}$ decline
- MRD clearance
- MRD relapse
- Morphologic relapse

Disposition

- Ongoing study treatment
- Off treatment

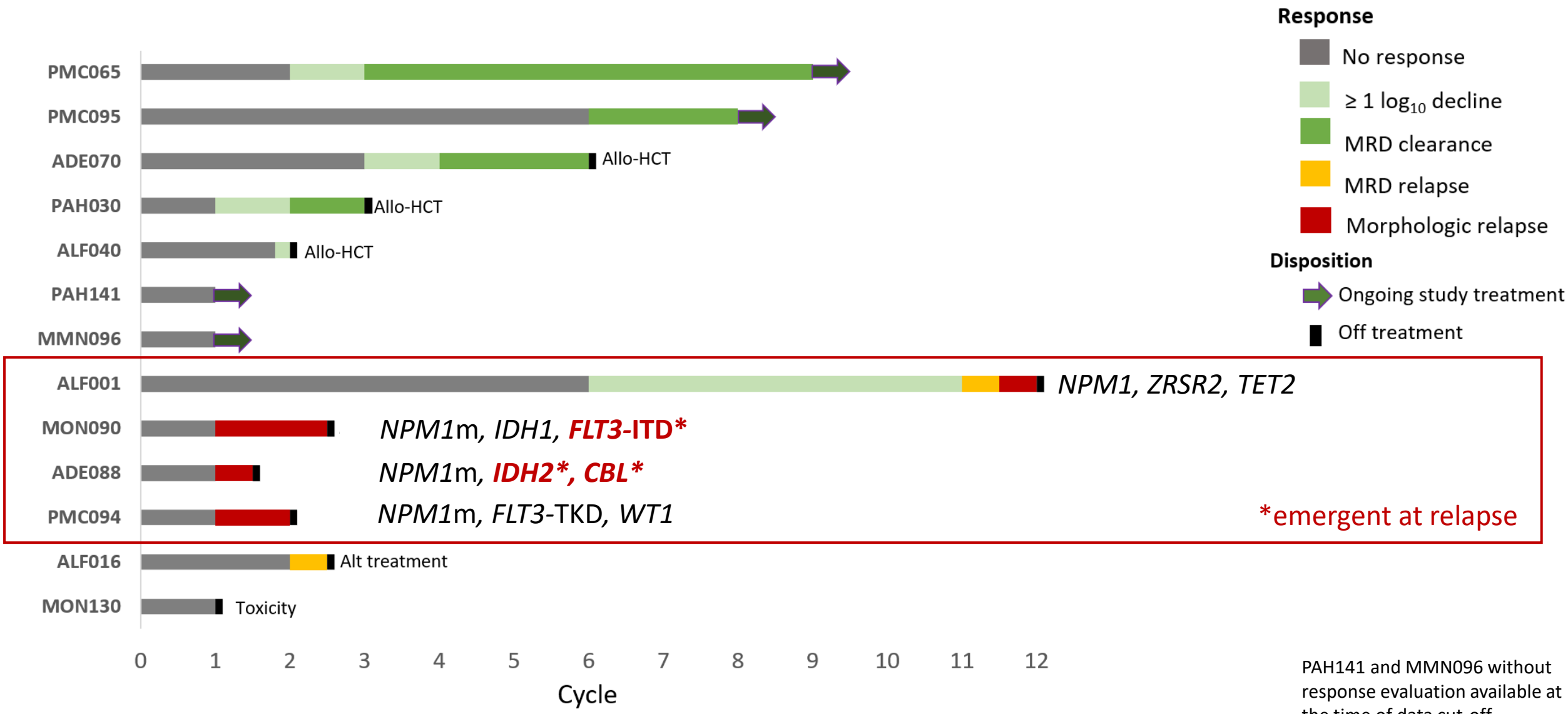
Median cycles: 2 (1-12)

*Treated with MRD relapse in CR2, prior exposure to VEN

PAH141 and MMN096 without response evaluation available at the time of data cut-off

Allo-HCT; allogeneic hematopoietic cell transplant; Alt, alternate.

At relapse, no *MEN1* variants (VAF>0.5%) seen to date

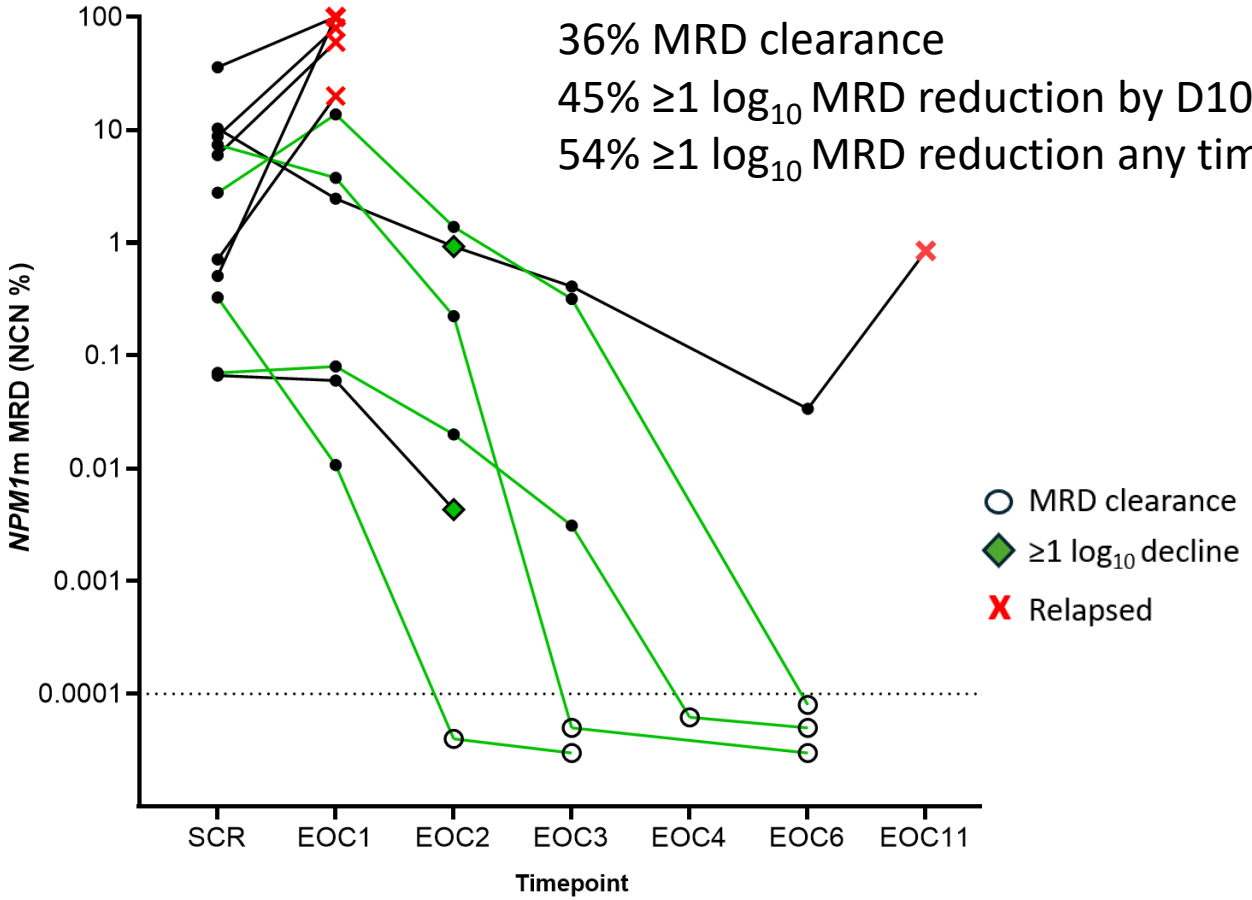


PAH141 and MMN096 without response evaluation available at the time of data cut-off

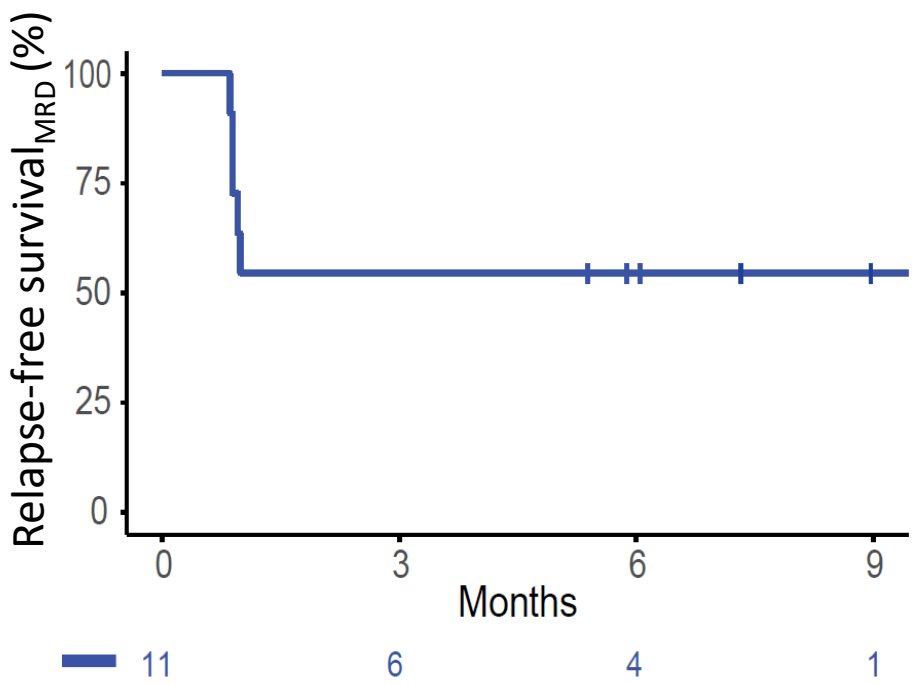
Allo-HCT; allogeneic hematopoietic cell transplant; Alt, alternate.

*NPM1*m MRD response and RFS_{MRD} after revumenib therapy in 11 efficacy evaluable patients

_NPM1_m MRD response



Relapse-free $survival_{MRD}$



Median follow-up time 6.7 months

EOC, end of cycle

Summary

- Revumenib 276mg BD at MRD relapse – tolerable with a low rate of febrile neutropenia (7%)

- Revumenib at *NPM1*m MRD relapse
  - MRD reduction ≥1 log in 54%
  - MRD clearance in 36% (time to clearance 2-6 cycles)
  - No *MEN1* variants seen at relapse to date

- Recruitment and follow-up are ongoing with target recruitment of 92 patients

- AMLM26 INTERCEPT is a novel MRD-directed AML platform trial

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Trial coordinators and team

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