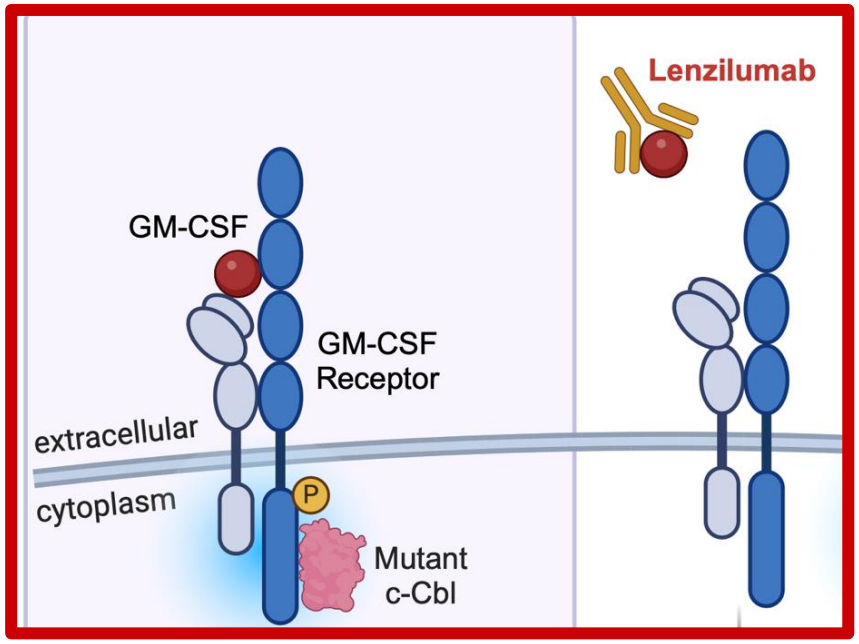
Durable Responses Observed in Proliferative CMML Treated with LENZ/AZA with Suppression of *RAS* & *CBL* subclones



Daniel Thomas **MD PhD FRACP FRCPA Hons**
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PREcision Approach to CHronic Myelomonocytic Leukaemia Study Investigators

D Hiwase, D Ross, D Yeung, J Reynolds, A Yong, T Hughes, S Lane

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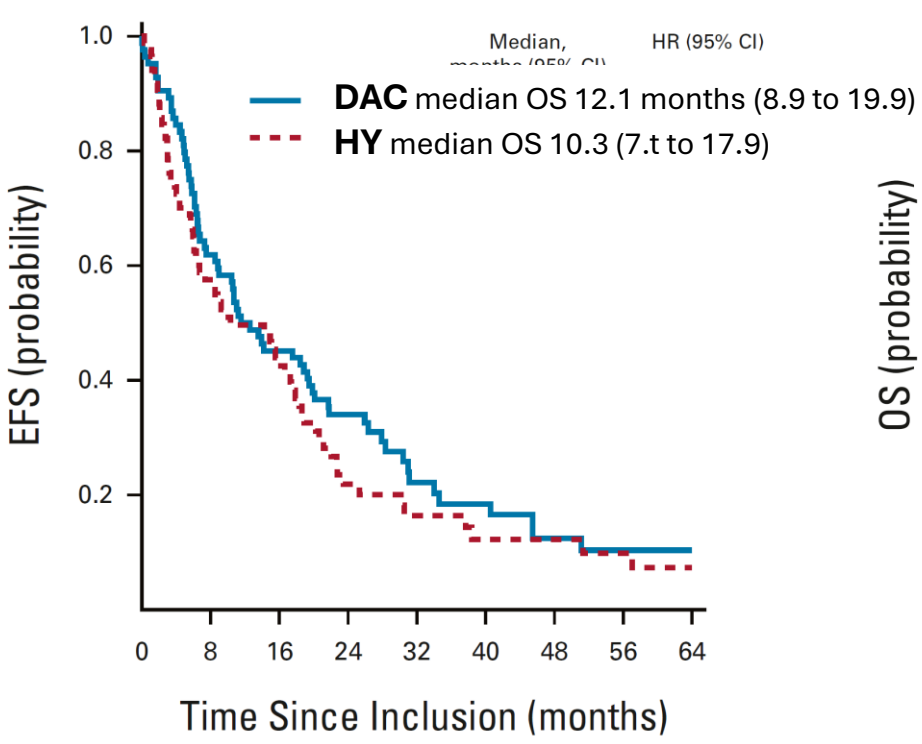
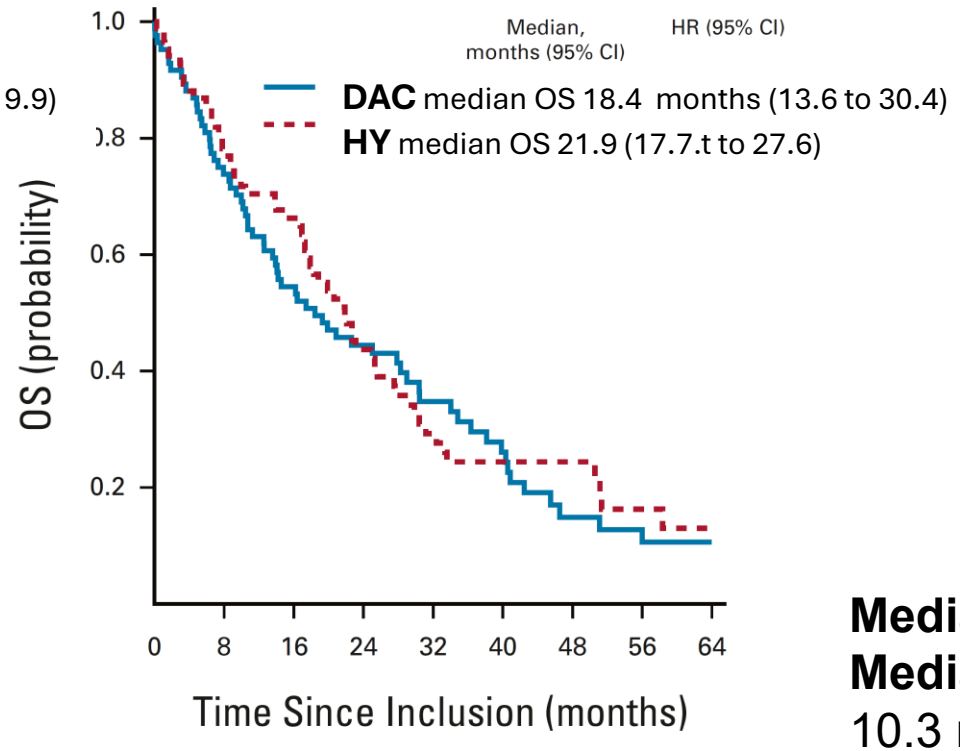
Poor outcome with single agent HMA in Proliferative CMML





Responses at 6 months (IWG 2006 Criteria)

CR	7 (8%) vs 0 (0%)
PR	6 (7%) vs 12 (14%)
mCR+HI	(11%) vs 2(2%)
mCR, no HI	0 (0%) vs 9 (11%)
SD	12 (14%) vs 9 (11%)
PD	6 (7%) vs 12 (14%)
ORR	27 (32%) vs 15(17%)

Median cycles: Five DAC vs. six HY
Median EFS: 12.1 months DAC vs. 10.3 months HY

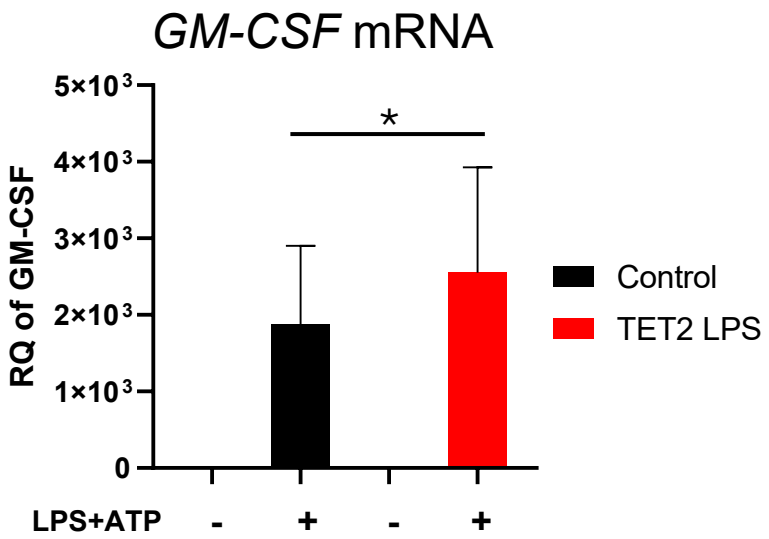
Inclusion Criteria: CMML-1 or 2, WCC ≥ 13 + at least 2 of following: blasts >5%, Cytogenetic abnormality, Hb <10, platelet <100, ANC>16, spleen > 5cm below CM
Primary Endpoint: Event-free Survival
Treatment: IV Decitabine 20 mg/m^2/d D1-5 OR 1-4g/d Hydroxyurea

Compared with HY, frontline treatment with DAC **did not** improve EFS in patients with advanced myeloproliferative CMML

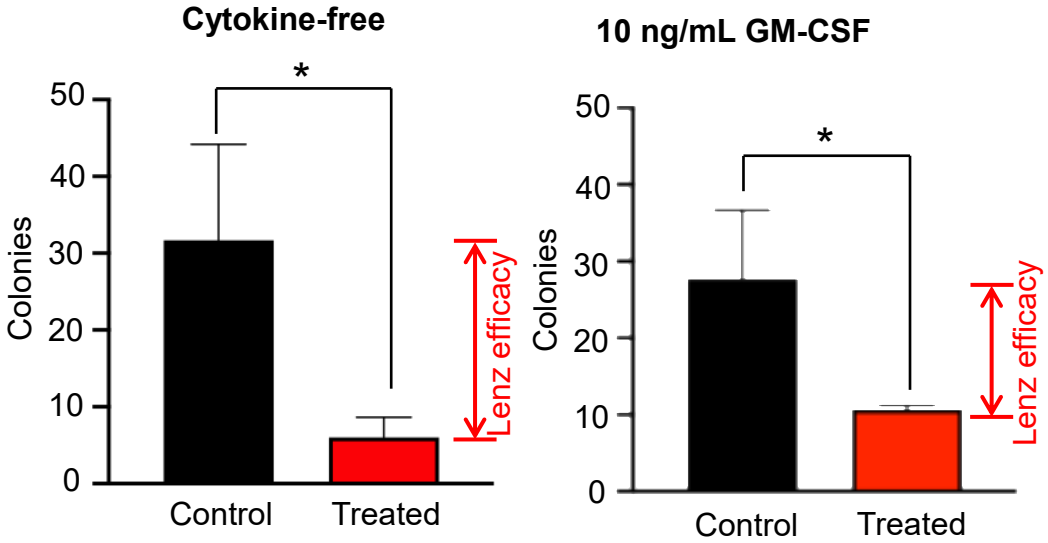
Itsykson *et al*, 2023 *JCO*

Rationale: pro-inflammatory autocrine GM-CSF production

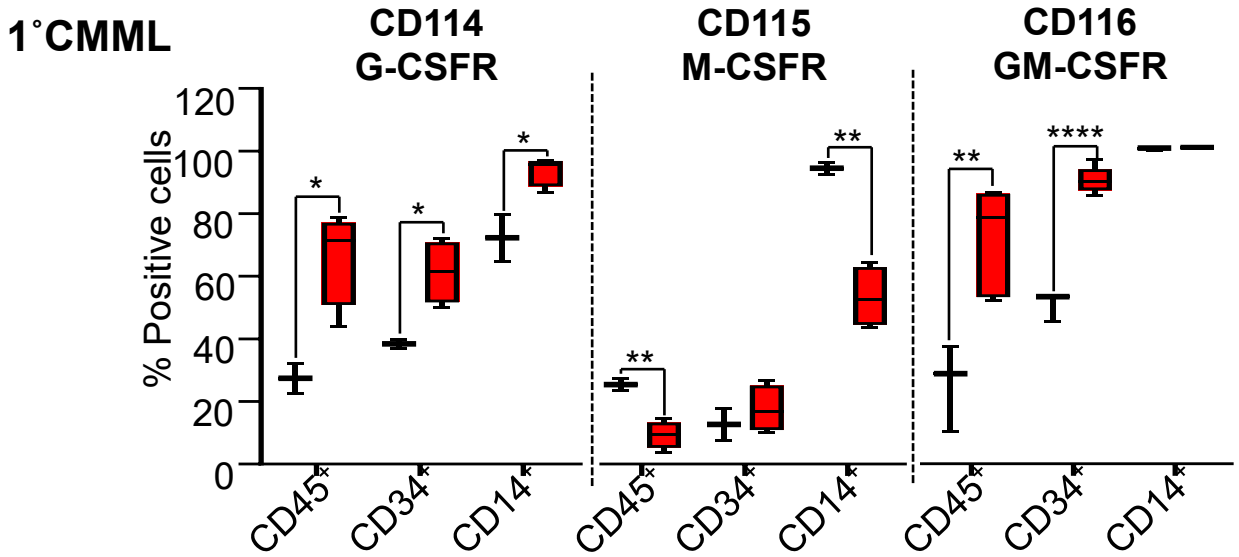
1˚ CRISPRed Human MØ

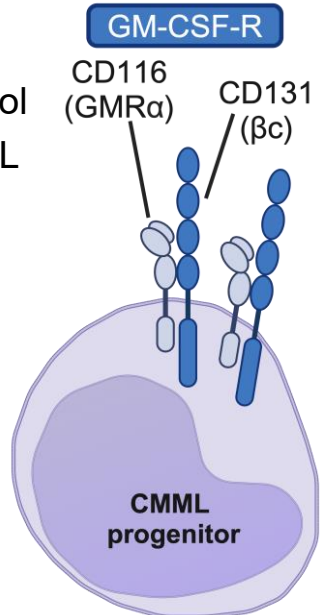


1˚CMML



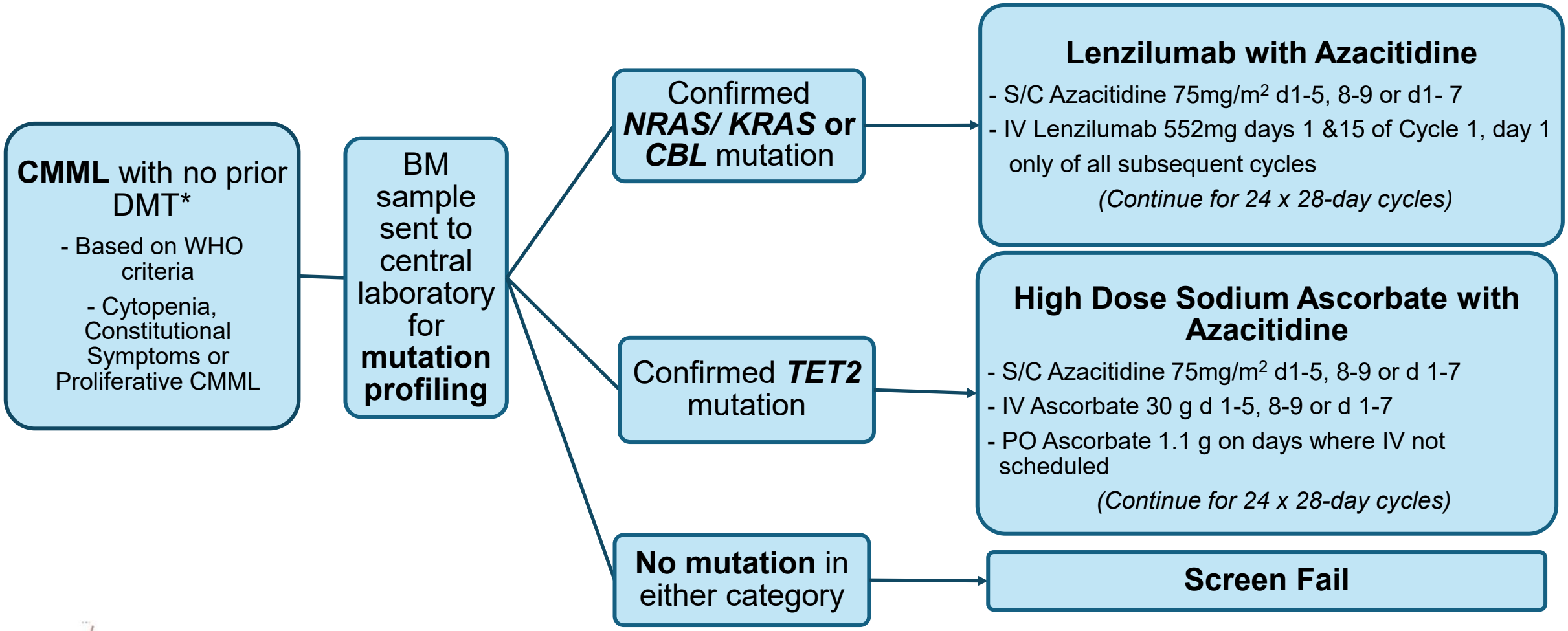
1˚CMML





Lim et al (2024)

PREACH-M Trial Design: Molecularly Informed Phase IIb



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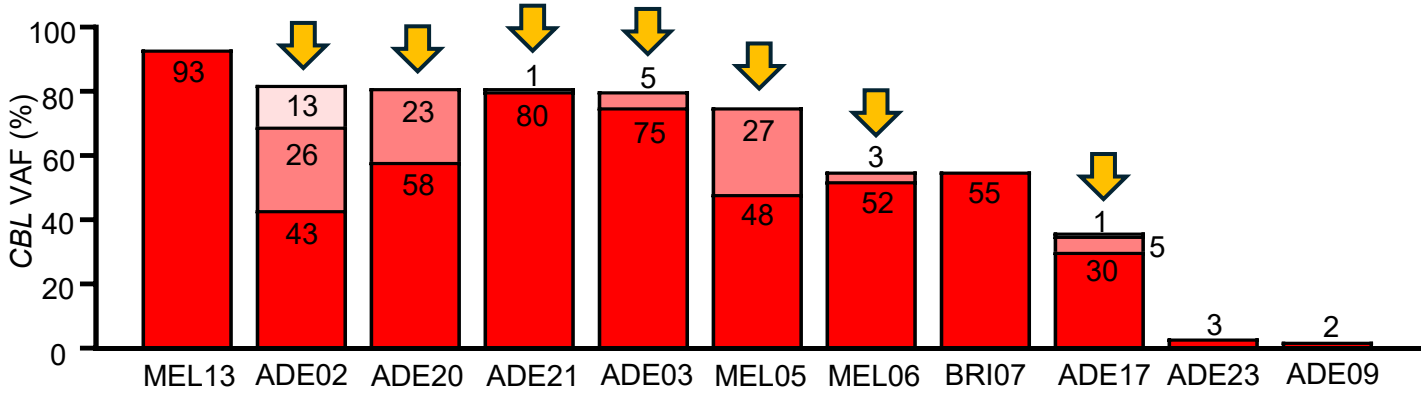
*DMT: Disease modifying therapies

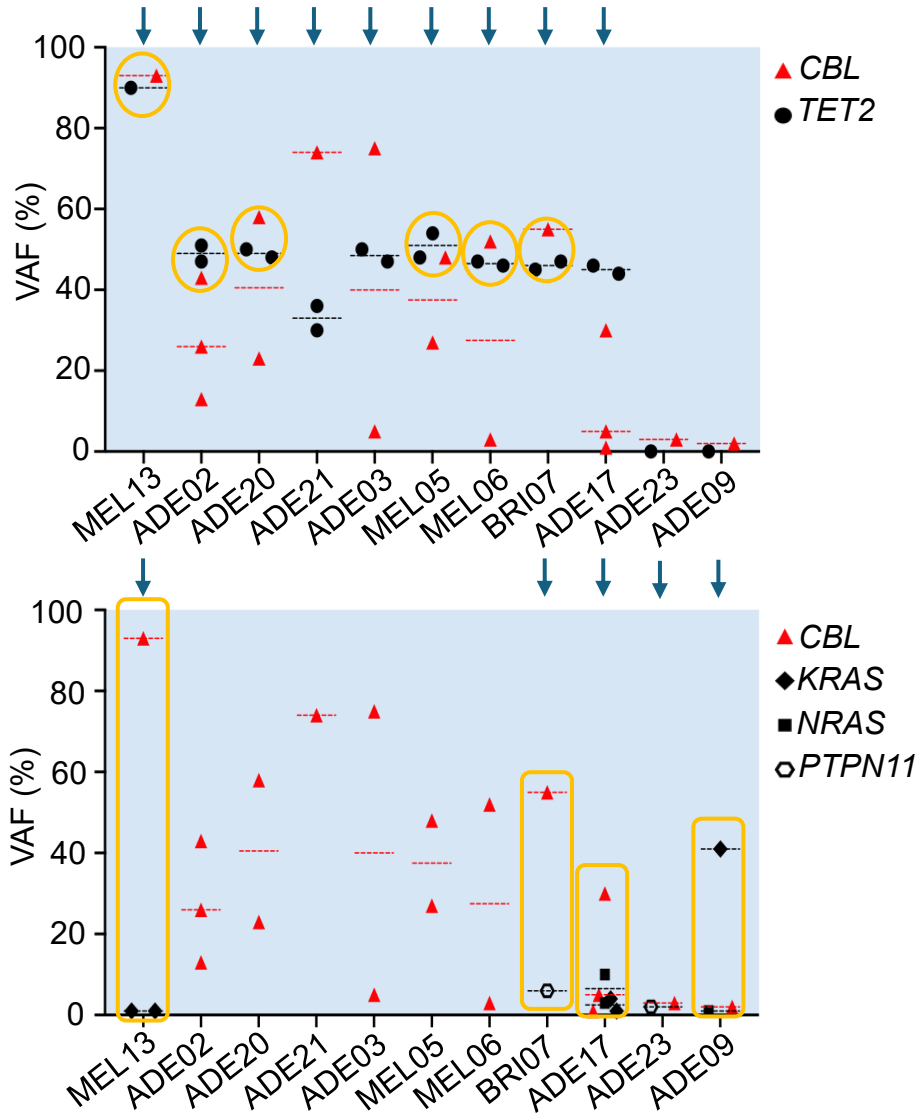
Baseline data (Updated May 2025)

Lenzilumab cohort (n=32)		
Age (Median)		73 years
Sex (n)	M/F	11 (50%) / 11 (50%)
CMML low,Int-1, Int-2, High (n)		4 (12.5%), 7 (21.88%), 21 (65.63%)
Median Haemoglobin (Median)	g/L	108 (82-148)
Median Platelet count (Median)	x10^9/L	74 (18-430)
Median Marrow Blasts (Median)	(%)	7 (1-17)
Median WCC (Median)	x10^9/L	19.96 (4.14-103.3)
Median Monocytes (Median)	x10^9/L	5 (0.7-47.5)
Median Spleen size (Median)	cm	13.25 (9.8-20.6)
Red cell transfusion dependent (n)		2 (6.25%)

Multiple *CBL* sub-clones co-occurring with *TET2*



	MEL13	ADE02	ADE20	ADE21	ADE03	MEL05	MEL06	BRI07	ADE17	ADE23	ADE09
Variant 1	G415S	C419S	L380P	int8 snv	M374K	L380P	I423N	Y371C	C384R	Y371C	C404Y
Variant 2	-	int7 del	C384Y	C416S	I423N	R718*	R343*	-	R420L	-	-
Variant 3	-	C384Y	-	-	-	-	-	-	int7 snv	-	-



Interim Analysis: Response within 12 months (Updated May 25)

- **40 subjects were enrolled overall**
  - **32 subjects were enrolled in the LENZ/AZA arm with 22 evaluable**
  - 8 subject enrolled in ASCORBATE/AZA arm

IWG 2006 Criteria (n=22)

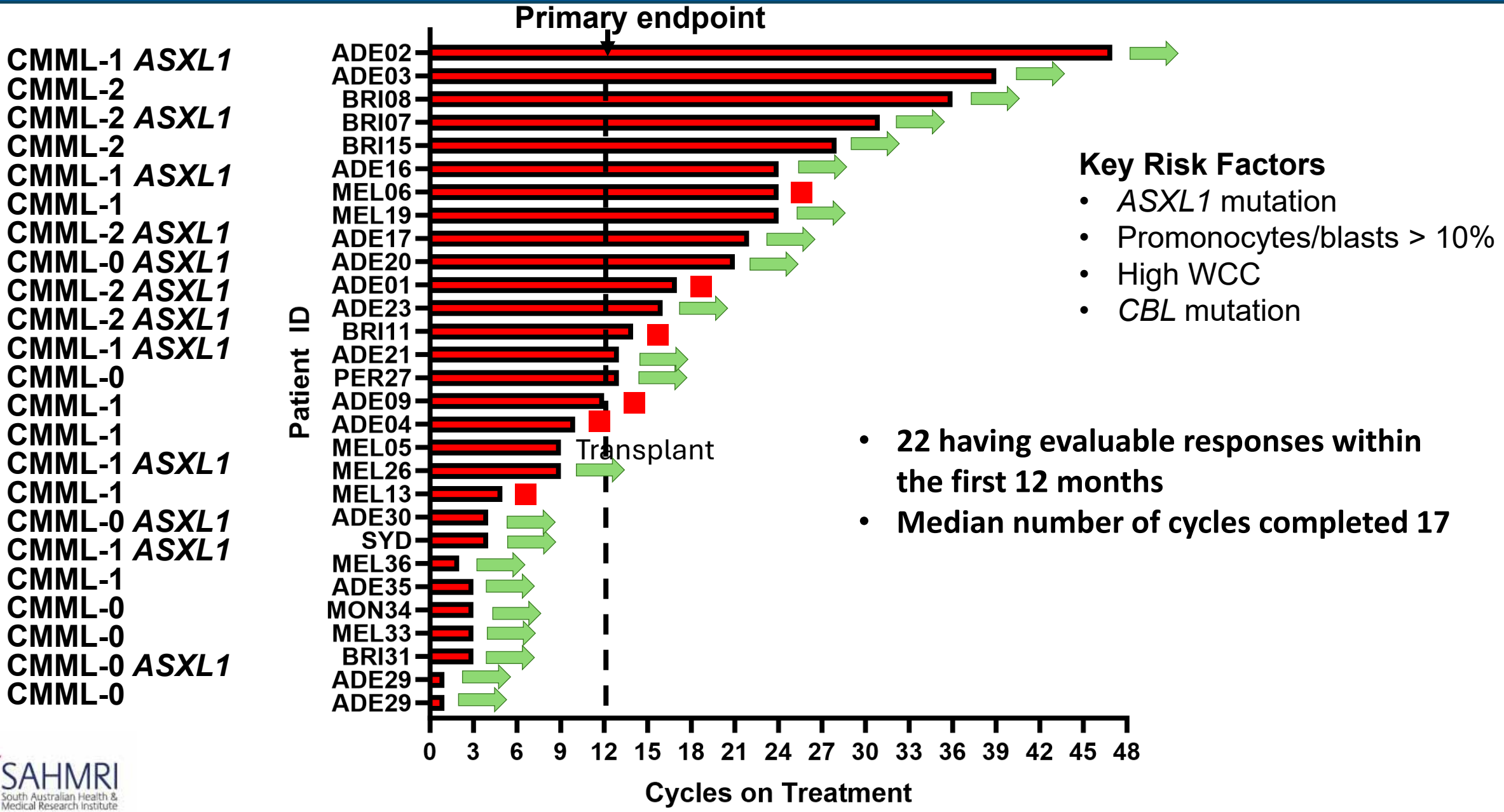
CR	9 (41%)
mCR	10 (45%)
PR	2 (9%)
PD	1 (5%)
CR+mCR	19 (86%)

Savona Criteria (n=22)

Complete Response*	6 (27%)
Optimal Marrow Response	13 (59%)
Partial Marrow Response	2 (9%)
Progressive Disease	1 (5%)
CR + Optimal MR	19 (86%)

83% Patients achieving CR/mCR within 3 months were still on study without progression at 12 months

Swimmer Plot for LENZ-AZA arm (updated May 30 2025)



Key Risk Factors

- *ASXL1* mutation
- Promonocytes/blasts > 10%
- High WCC
- *CBL* mutation

- **22 having evaluable responses within the first 12 months**
- **Median number of cycles completed 17**

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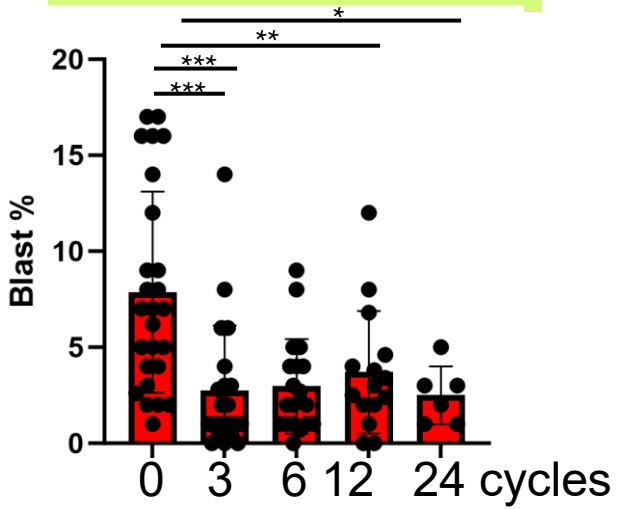
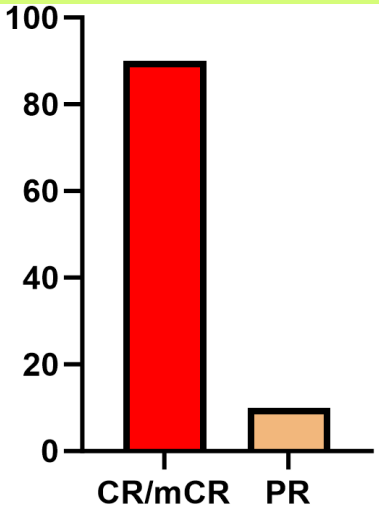
LENZ and AZA shows durable response

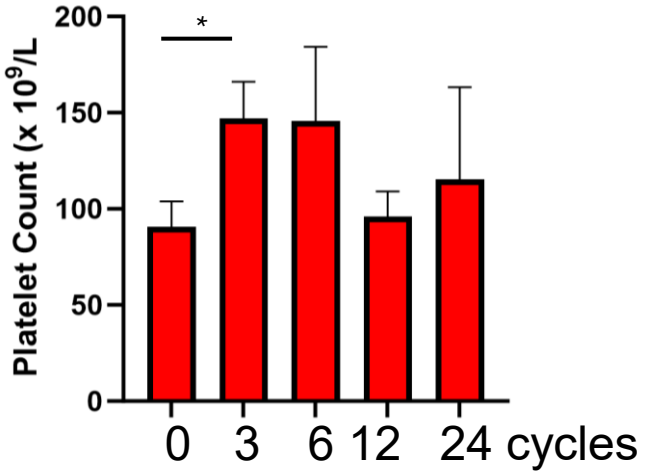
Bone marrow blasts



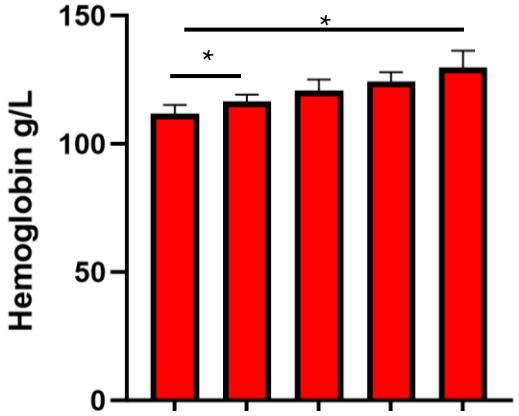
TET2-CBL highly responsive



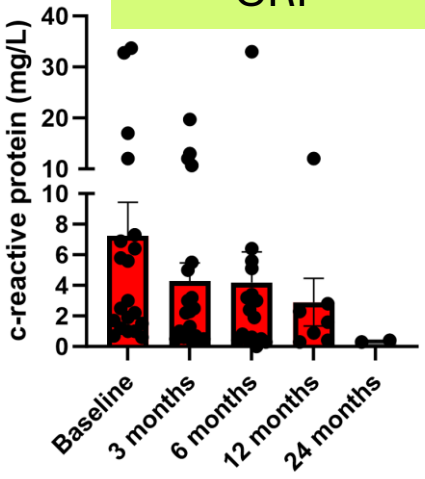
Platelets



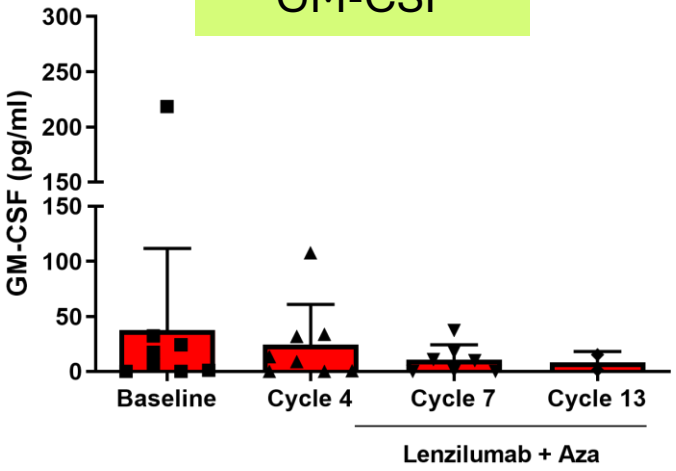
Hemoglobin



CRP



GM-CSF



*P<0.05, ***P<0.0001

Safety Profile

Any-grade TEAEs that occurred in ≥25% of patients (n=32)

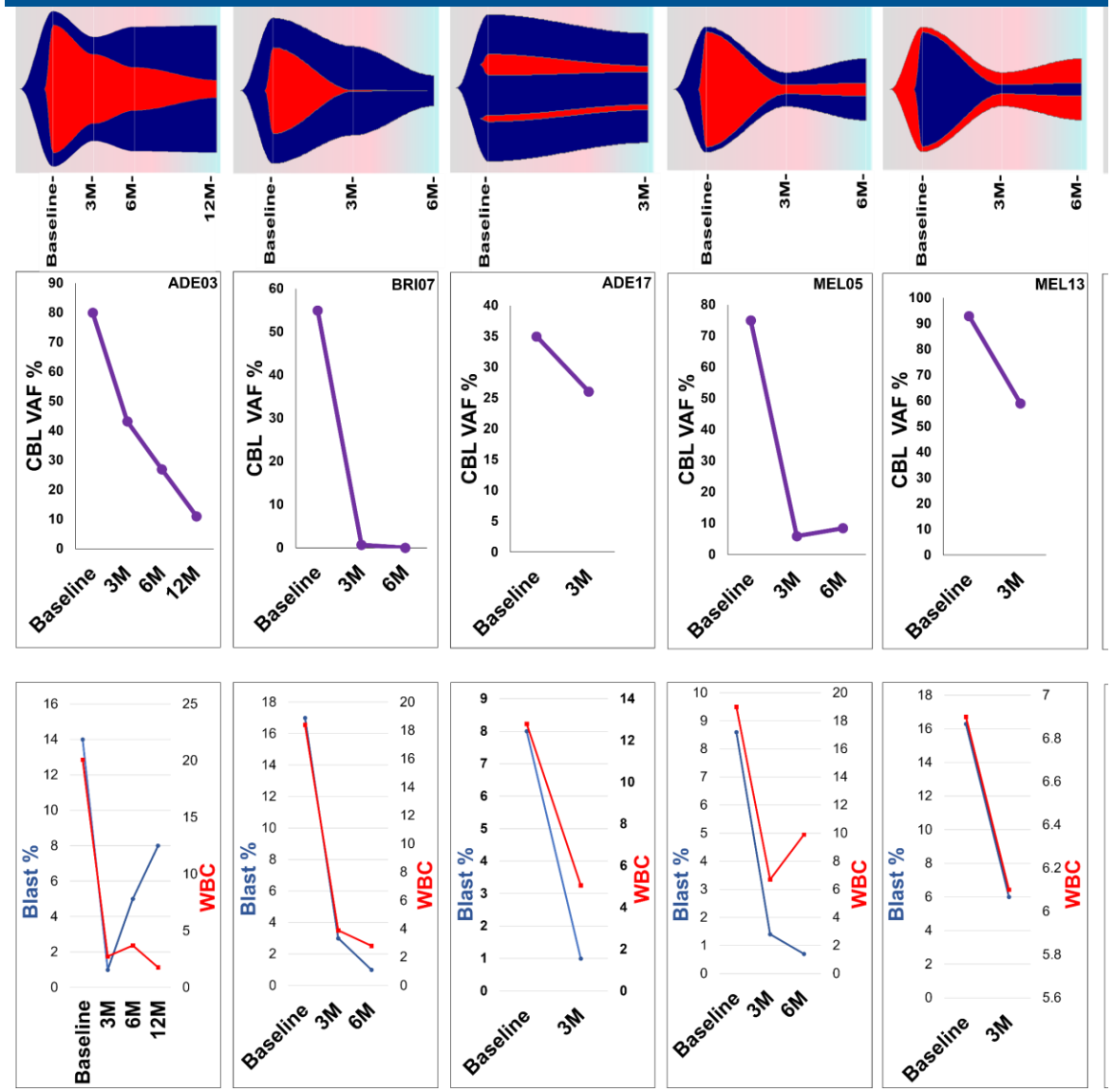
All terms	Events (% total)	n (% total)
Thrombocytopenia	87(14)	18 (56)
Neutropenia	69 (11)	22 (69)
Constipation	25 (4)	21 (66)
Nausea	21 (3)	17 (53)
Anaemia	20 (3)	13 (41)
Injection site reaction	17 (3)	15 (47)
Diarrhoea	16 (3)	10 (31)

Grade ≥3 TEAEs that occurred in ≥10% of patients (n=32)

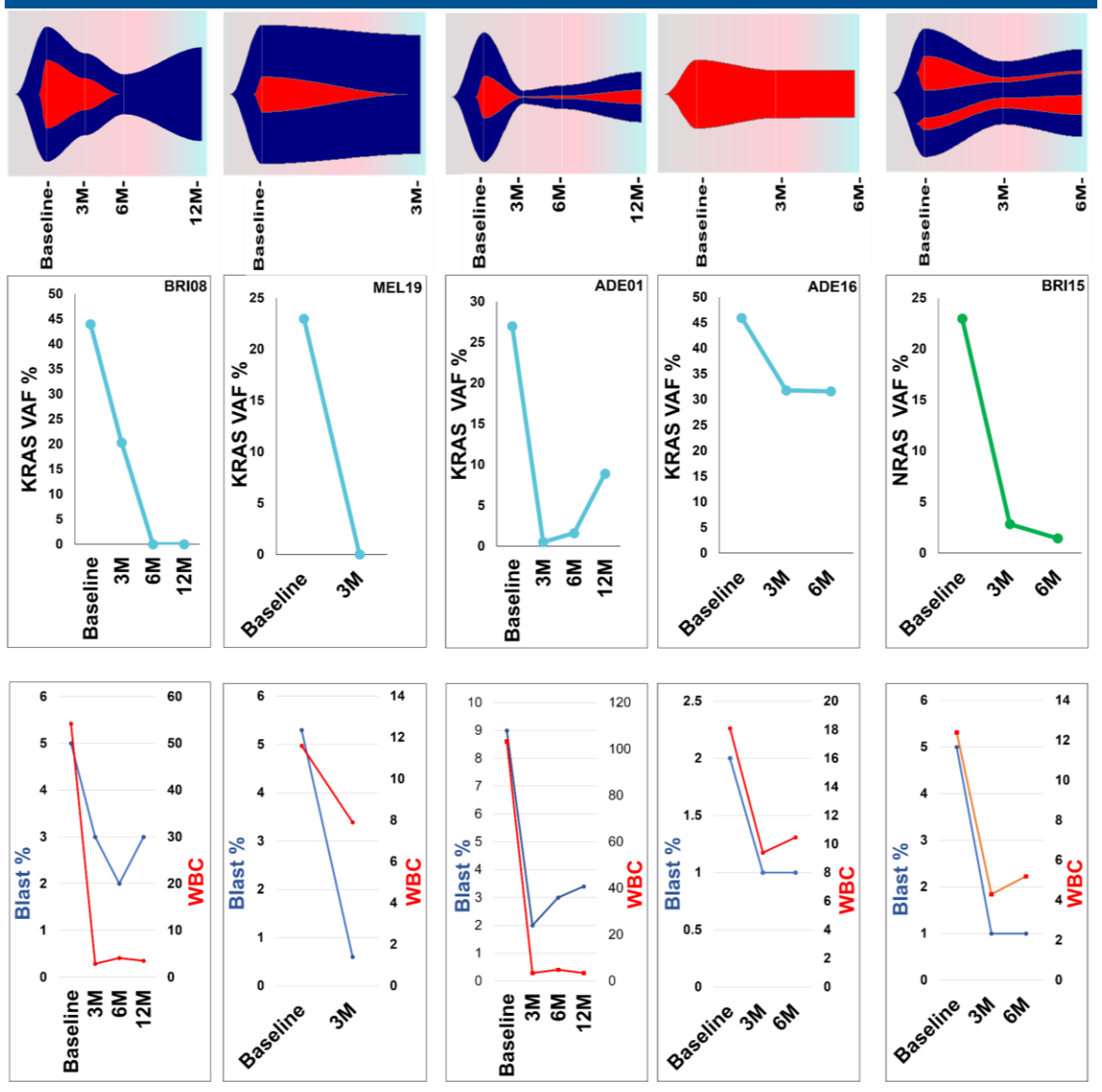
All terms	Events (% total)	n (% total)
Thrombocytopenia	59 (35)	29 (73)
Neutropenia	48 (29)	18 (45)
Anaemia	12 (7)	8 (20)

Decrease in *CBL* and *KRAS* mutant clones by LENZ-AZA

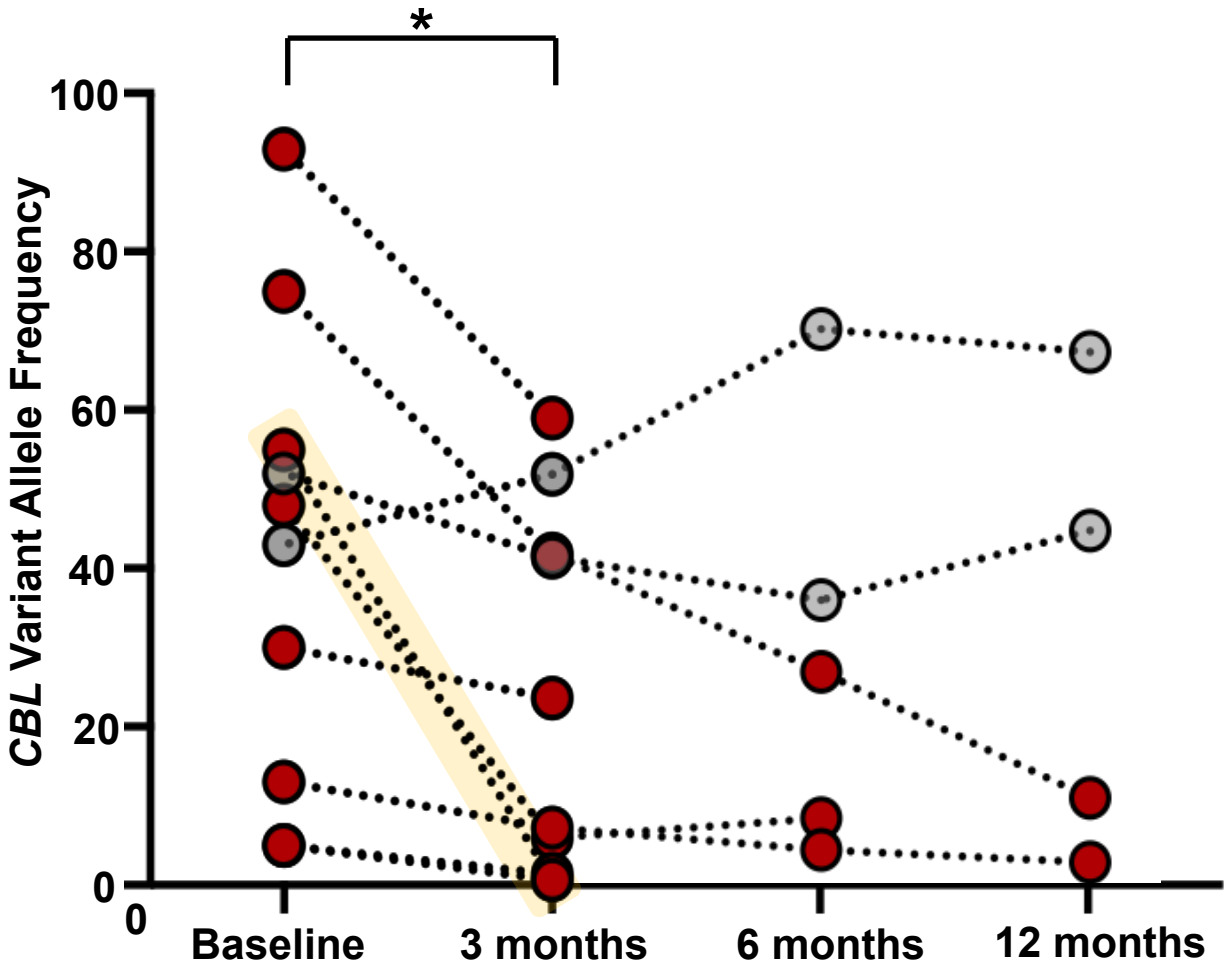
CBL-mutated CMML



RAS-mutated CMML



Durable decreases in *CBL* clones over 12 months



- Some durable beyond 6 months

10 variants, 7 subjects, paired t-test *P<0.05

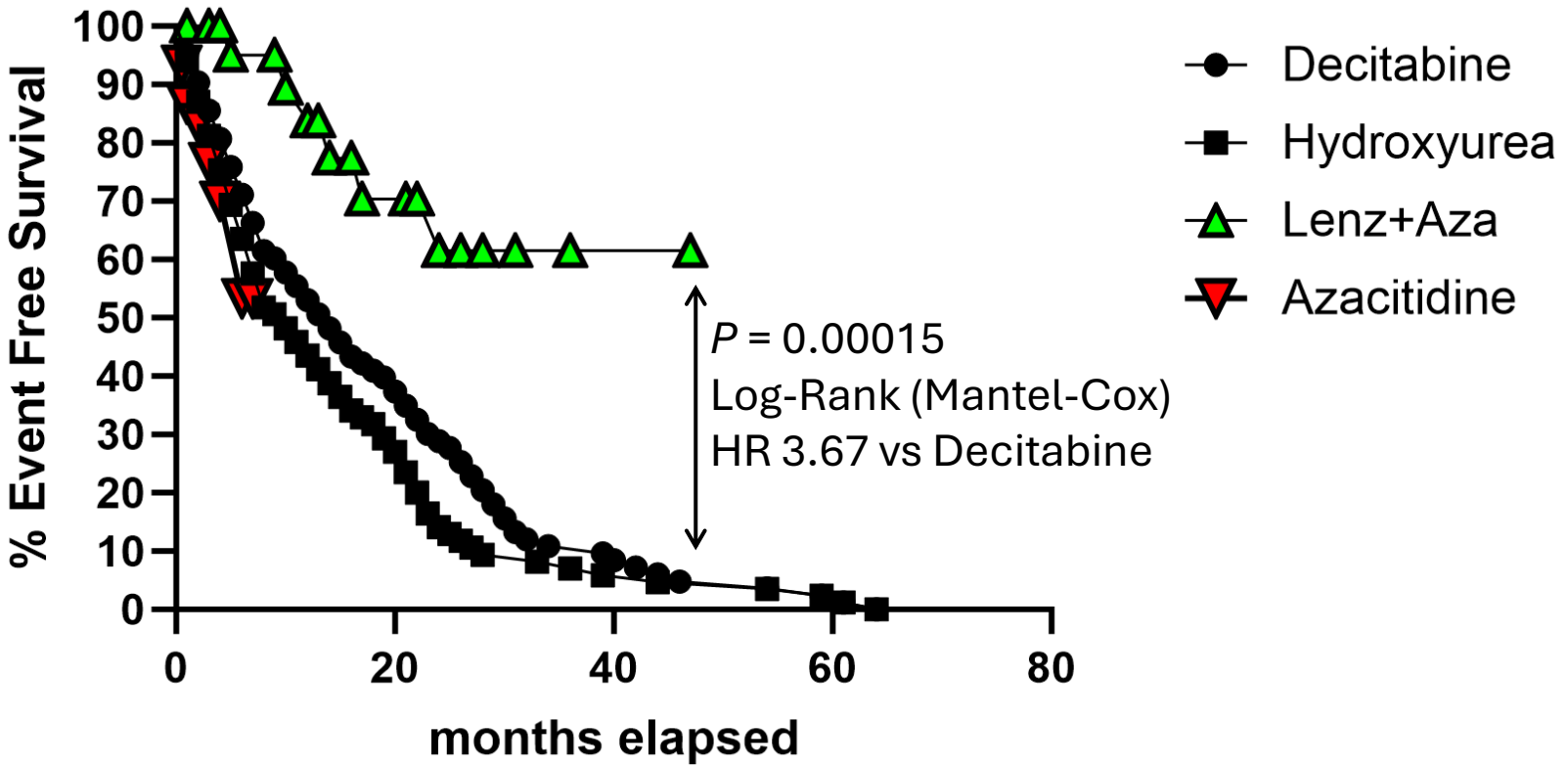
Historical Comparison: LENZ/AZA vs DACOTA vs UK Phase II

EMSCO Inclusion Criteria: CMML-1 or 2, WCC ≥ 13 + at least 2 of following: blasts > 5%, Cytogenetic abnormality, Hb < 10, platelet < 100, ANC>16 or spleen > 5cm

Primary Endpoint: Event-free Survival
Treatment: IV Decitabine 20mg/m2/d D1-5 OR 1-4g/d Hydroxyurea

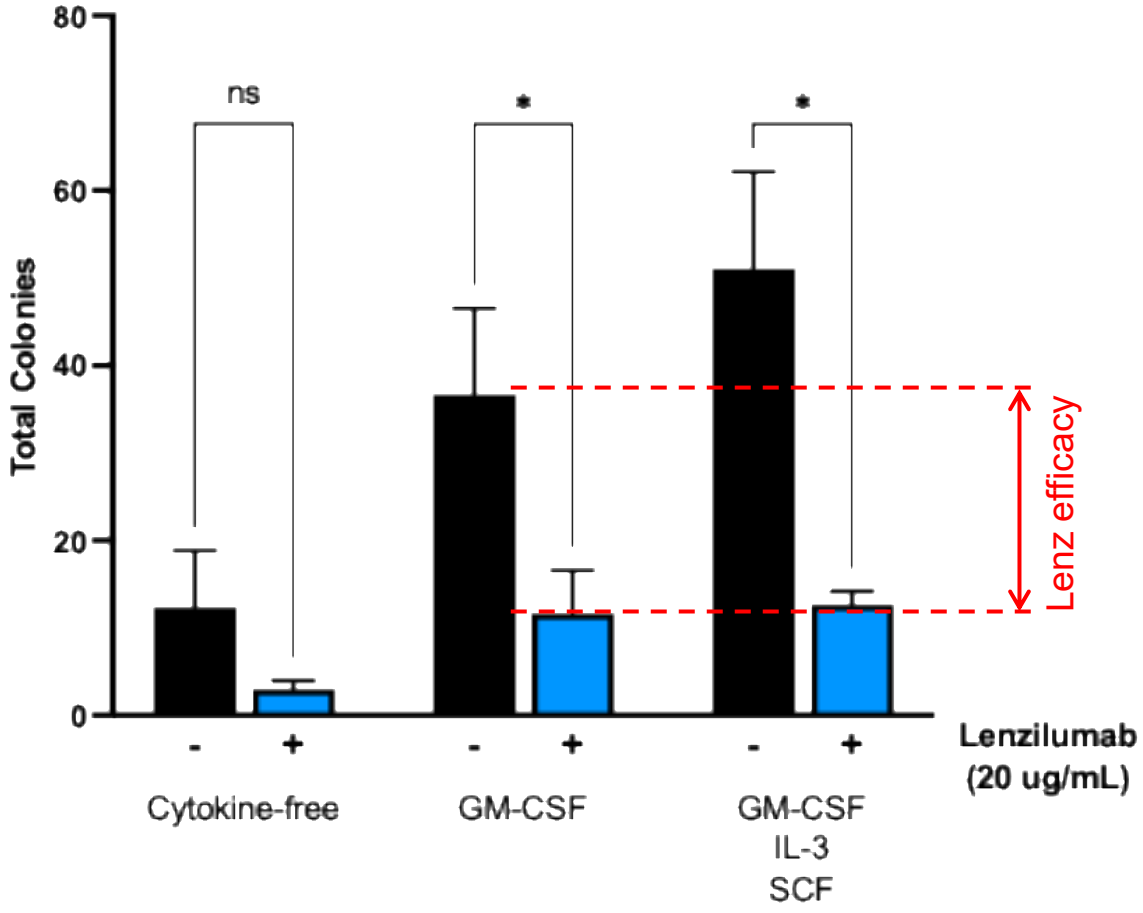
PREACH-M Inclusion Criteria: Constitutional symptoms OR Hb< or Platelet<100 or ANC<1.8 OR WCC>13 AND RAS pathway mutation >3% VAF
Primary Endpoint: Best response in first 12 months (Savona Criteria)
Treatment: Lenzilumab IV 552mg monthly + 75mg/m2 Aza D1-7
Graph: Progression or death as of August 2024; n = 20 recruited to date

UK Phase II Drummond et al
Inclusion Criteria: CMML-2 and CMML-1 patients with cytopenia or proliferative disease, intermediate or high Dusseldorf score (for WCC >12) or int-2 or high IPSS score (for WCC<12) and/or splenomegaly or systemic symptoms or extramedullary disease (8% had *CBL*, 5% *NRAS* mutations)
Graph: No. of cycles AZA received from Supplementary Table 2

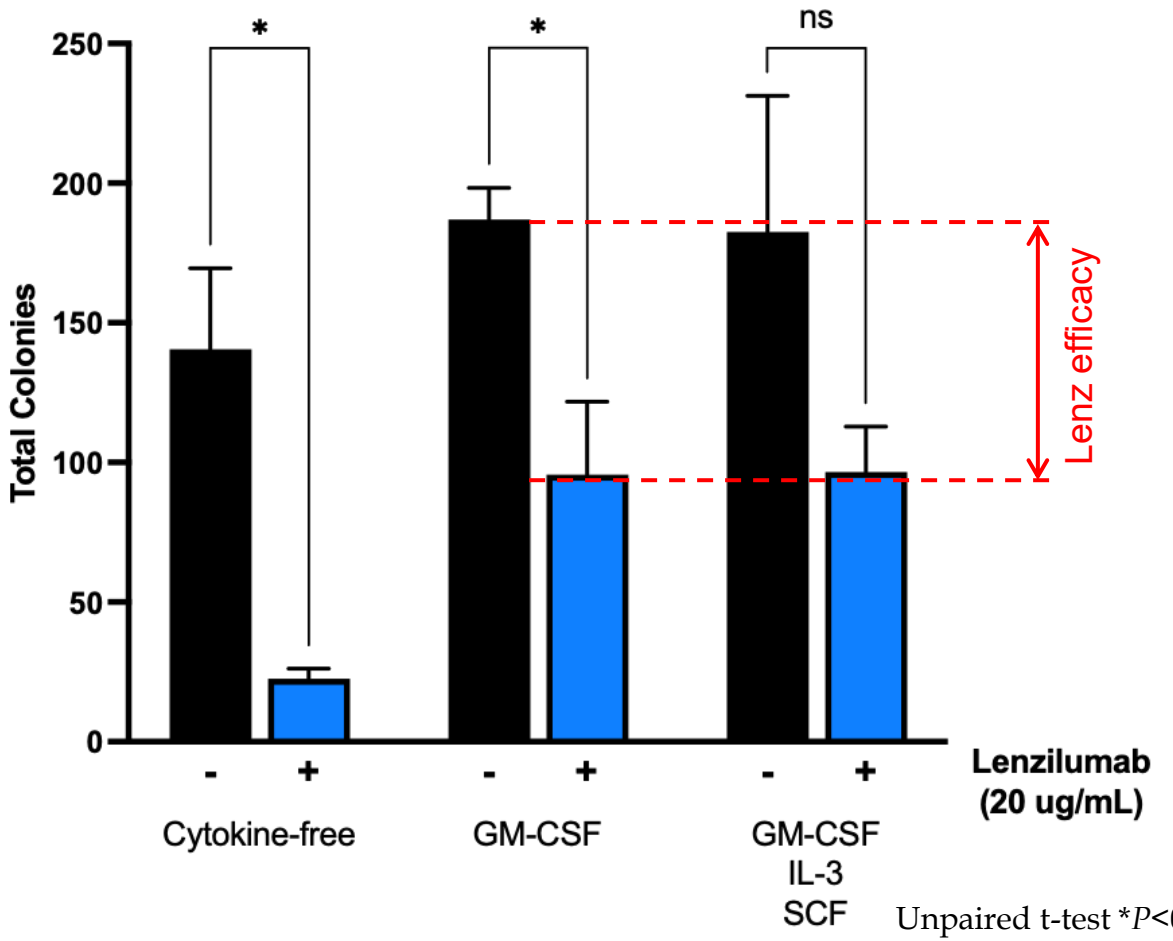


Secondary AML from CMML: Sensitive to LENZ

2°AML (Case 1)
TET2, SRSF2, KRAS



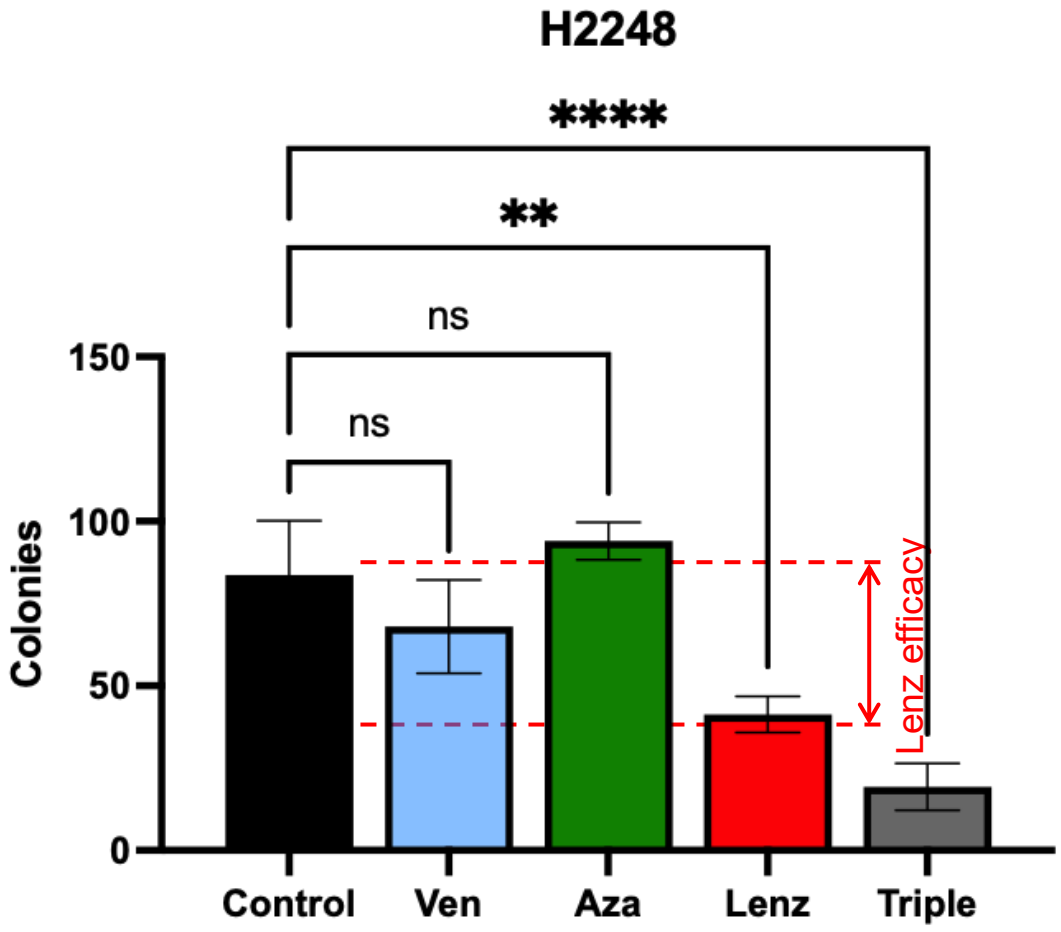
2°AML (Case 2)
CBL*, *NRAS, KRAS, ASXL1, IDH2



Unpaired t-test *P<0.05

Clinical Benefit in AML resistant to VEN

2°AML from CMML (Case 3)

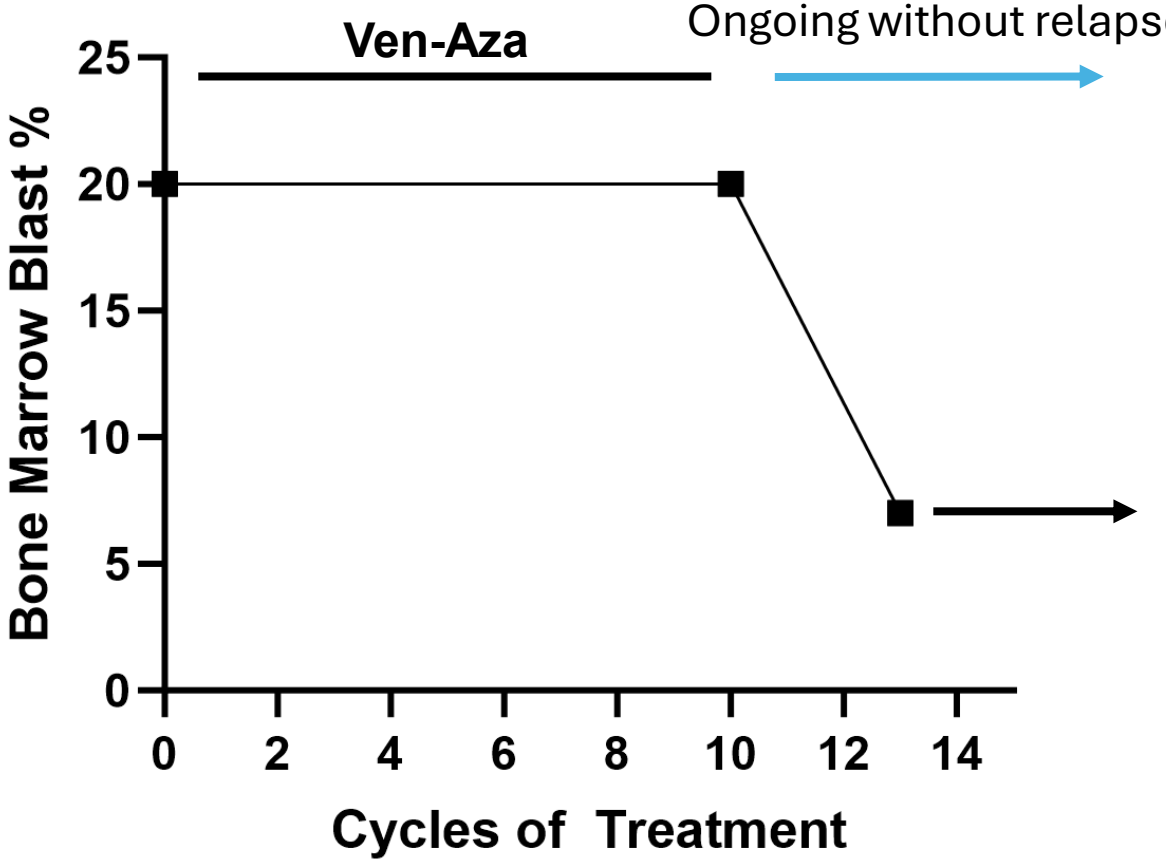


Ordinary 1-way ANOVA, *P>0.05

2°AML (Case 1) clinical data
TET2, SRSF2, KRAS

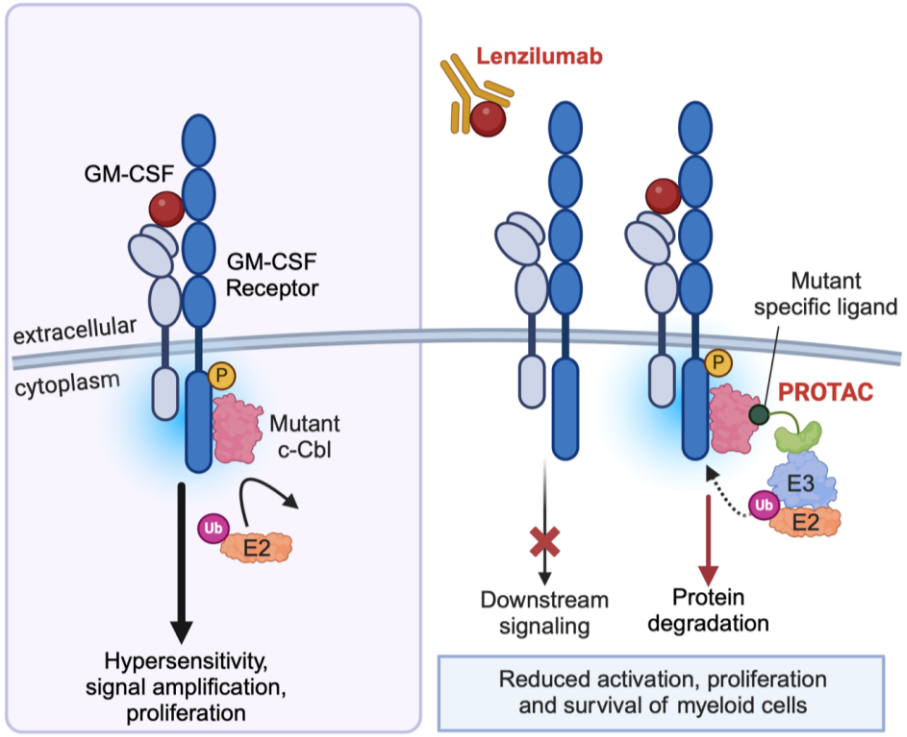
LENZ-Ven-Aza

8 cycles of tripleRx
Ongoing without relapse



- No excessive hematological toxicity

Conclusions



- **Multiple high-risk subgroups show durable responses to LENZ-AZA including CMML-2, *ASXL1, CBL***
- ***TET2+CBL* show excellent early CR and mCR**
- **Decrease in RAS pathway subclones in multiple patients**
- **Durable responses including CR and mCR**
- **LENZ Triplet therapy shows early signal of efficacy in 2˚ AML**

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Kamel et al, (2023) *Blood #1852*; Kamel et al (2024) Blood #
Kutyna et al (2023) *Blood #1847;* Lim et ak (2024) Blood #3196
Hiwase et al (2023) *Blood #3223;* Hiwase et al (2024) Blood #1006;
Lim et al (2024) *PLOS One;* Nakauchi et al, (2022) *Blood Cancer Discovery*