Pevonedistat, a first-in-class NEDD8-activating enzyme (NAE) inhibitor, combined with azacitidine, in patients with AML

Supplemental information

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Supplemental information

Supplemental table 1A. List of 116 genes included in the targeted NGS panel

PHF6	CARD11	FGFR2	JAK2	NRAS	SOCS1	CIITA	P2RY8	UNC5D	PSMB10
MLL	CBL	FGFR3	JAK3	PAX5	TET2	ETV6	PASD1	XPO1	PSMB5
APC	CDKN2A	FLT3	KDM6A	PDGFRA	TNFAIP3	GNA13	PCLO	CCND1	PSMB6
EGFR	CEBPA	GATA1	KIT	PIK3CA	TP53	HIST1H1C	PIM1	ERN1	PSMB8
MET	CREBBP	GATA2	KRAS	PRDM1	WT1	HIST1H3B	POU2F2	MAP3K7 (TAK1)	PSMB9
STK11	CRLF2	GNAS	MPL	PTEN	ACTB	HLA-A	SOCS1	TNFRSF11A (RANK)	TRAF3
ABL1	CSF1R	HRAS	MT-ND4	PTPN11	B2M	KRTAP5-5	STAT3	TRAF2	AKT2
AKT1	CTNNB1	IDH1	MYD88	RB1	BTG1	LOC153328	SYK	TRAF5	FGFR1
ASXL1	DNMT3A	IDH2	NF1	RUNX1	CCND3	MEF2B	SYN2	XBP1	
ATM	EP300	IKZF1	NOTCH1	SF3B1	CD58	MLL2	TMSL3	IKBa	
ATRX	EZH2	IL7R	NOTCH2	SMAD4	CD70	NFKBIA	TNFRSF14	NFKB2	
BRAF	FBXW7	JAK1	NPM1	SMARCB1	CD79B	OR6K3	UBE2A	PSMB1	

Supplemental table 1B. List of 38 frequently mutated genes with mutations identified using the targeted NGS panel

Gene	Amino acid ranges*	Truncating ranges*
ASXL1	None	327-1540
DNMT3A	290-374;626-910	All
EZH2	1-340;428-476;502-611;617-738;	All
GATA1	ExACFreq<0.01	All
GNAS	844-844;201-201	None
IDH1	126-138	None
IDH2	134-146;164-180	None
IKZF1	142-196	All
JAK2	505-547;617-617;683-683;867-867;873-873;933-933	None
KRAS	ExACFreq<0.01	None
MPL	500-520	None
NOTCH1	1530-1795;	2061-2555
NPM1	None	All
NRAS	ExACFreq<0.01	None
PHF6	197-353;	All
RUNX1	ExACFreq<0.01	All
SF3B1	600-780;	None
TET2	1104-1481;1843-2002;	All
TP53	ExACFreq<0.01	All

*The accepted amino acid changes and truncating ranges used for mutation calling from NGS sequence data in frequently-mutated genes. 'None' indicates that no amino acid changes or truncating mutations are accepted. 'ExAcFreq<0.01' indicates that all mutations are accepted if the allele is present in less than 1% of the ExAC population. 'All' indicates that all of the truncating mutations are accepted.

Supplemental table 2: Response based on treatment cycles

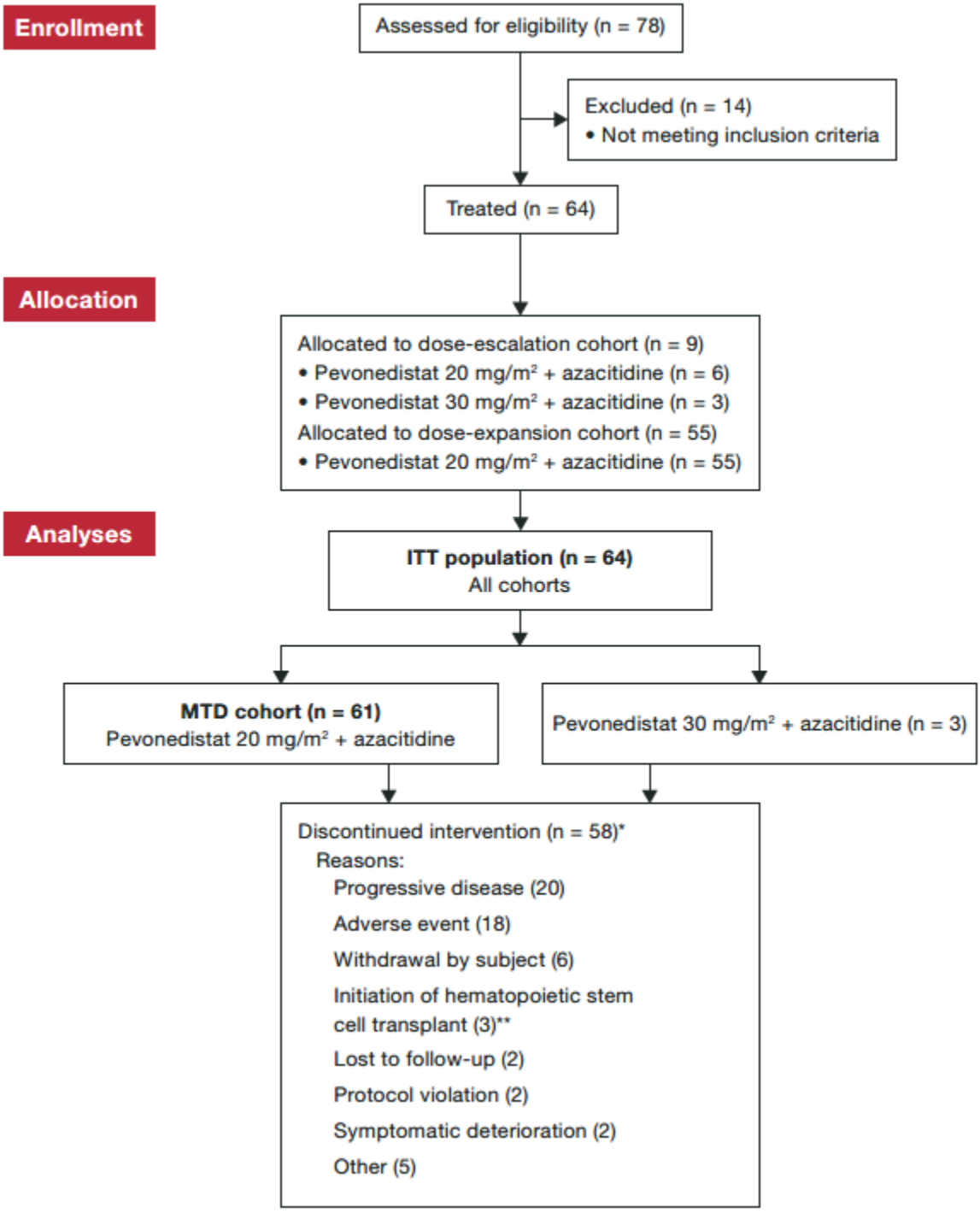
Number of cycles treated with AZA+PEV	Responses observed at Cycle 1	Responses observed at Cycle 2	Responses observed at Cycle 4	Responses observed at Cycle 7	Total pts with objective responses	Patients
<6 cycles	7	~~4~~5	1	0	13	41
≥6 cycles	6	2	8	3	19	23
Total	13	7	9	3	32	64

Supplemental table 3. Baseline characteristics for de novo AML versus secondary AML

Characteristics	De novo AML (n = 36)	Secondary AML (n = 28)
Median age, years (range)	77 (66–89)	73 (61–84)
Median haemoglobin, g/dL (range)†	9.8 (8.2–12.4)	10.5 (7.3–12.4)
ECOG PS, n (%)		
0	12 (33)	15 (54)
1	16 (44)	7 (25)
2	8 (22)	6 (21)
Cytogenetics, n (%)		
Adverse	13 (36)	5 (18)
Intermediate	17 (47)	15 (54)
Favorable	1 (3)	1 (4)
Unclassified	4 (11)	5 (18)
Not available	1 (3)	2 (7)

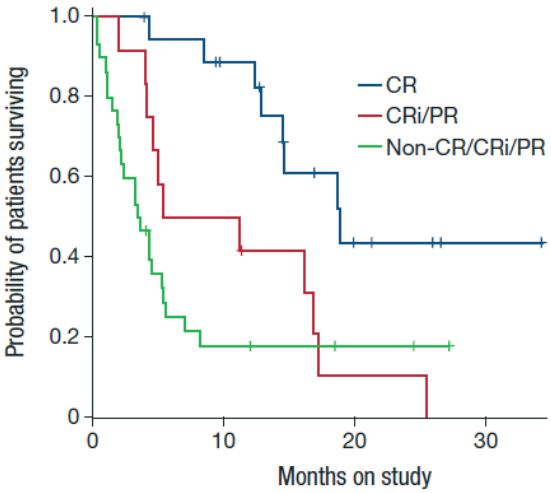
†p=0.01; all other categories p= >0.05.

Supplemental figure 1. Study CONSORT diagram and patient disposition



* At the time of submission of manuscript, 6 patients remained active on study
**Three patients received HSCT: one patient had secondary AML and achieve CRi at treatment cycle 6 prior to HSCT; another patient had de novo AML and achieved CR at treatment cycle 4 prior to transitioning into HSCT; the third patient with de novo AML had achieved SD at treatment cycle 4 prior to HSCT

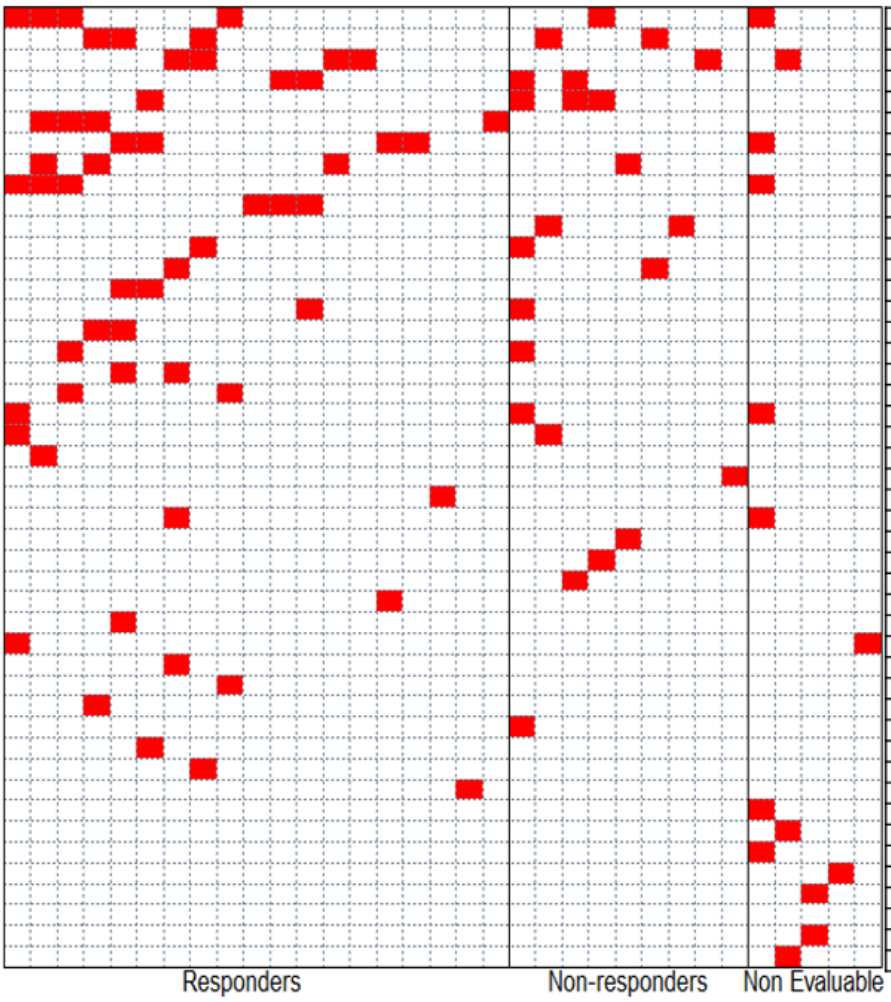
Supplemental figure 2. Kaplan-Meier survival analysis based on best response achieved in the MTD cohort



Number of patients at risk:							
CR	19	17	14	8	4	3	1
CRi/PR	12	7	6	4	1	1	0
Non-CR/CRi/PR	30	10	5	3	2	1	0

N=61, log-rank p-value <0.05. Median overall survival for CR group: 18.8 months (95%CI: 13.0, NE); median overall survival for CRi/PR group: 8.3 months (95% CI: 4.0, 17.0)

Supplemental figure 3. Heatmap showing mutational status of all 46 mutated genes and response data for patients in the MTD cohort



Gene name	Mutation frequency	Number of responders/ number of NGS-evaluable patients with mutation
DNMT3A	15	4/5
KMT2D	15	3/5
TP53	15	4/5
IDH2	12	2/4
NKFB2	12	1/4
NRAS	12	4/4
TET2	12	4/4
TNFRSF14	12	3/4
KRAS	9	3/3
RUNX1	9	3/3
ASXL1	6	0/2
CCND1	6	1/2
CCND3	6	1/2
EGFR	6	2/2
GNA13	6	1/2
IKZF1	6	2/2
JAK1	6	1/2
JAK2	6	2/2
MAP3K7	6	2/2
TNFRSF11A	6	1/2
TRAF2	6	1/2
EZH2	3	1/1
GATA1	3	0/1
GNAS	3	1/1
HIST1H3H	3	1/1
HRAS	3	0/1
IDH1	3	0/1
KDM6A	3	0/1
MPL	3	1/1
NOTCH1	3	1/1
NPM1	3	1/1
PHF6	3	1/1
POU2F2	3	1/1
SF3B1	3	1/1
SOCS1	3	0/1
STK11	3	1/1
TRAF5	3	1/1
UNC5D	3	1/1
CEPBA	0	0/0
FLT3	0	0/0
KIT	0	0/0
MEF2B	0	0/0
NF1	0	0/0
PTEN	0	0/0
TNFAIP3	0	0/0
WT1	0	0/0

Genetic mutation data identified by targeted NGS for all 46 genes that were found to be mutated in the 33 patients in MTD cohort are shown. Each column represents a single patient, and each row represents a single gene. Presence of a mutation in any gene is denoted as a red box in red.

*Mutation frequency = (# of patients with mutation/ # of NGS-evaluable patients) * 100.

^Responders = CR + CRi + PR.