

Article

Azacitidine plus Venetoclax for the Treatment of Relapsed and Newly Diagnosed Acute Myeloid Leukemia Patients

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Supplementary Table S1. Panel of genes Next-generation sequencing (NGS).

<i>ABL1</i>	<i>EZH2</i>	<i>PTPN11</i>
<i>ANKRD26</i>	<i>FBXW7</i>	<i>RAD21</i>
<i>ASXL1</i>	<i>FLT3</i>	<i>RhoA</i>
<i>ASXL2</i>	<i>GATA2</i>	<i>RIT1</i>
<i>ATM</i>	<i>HRAS</i>	<i>RUNX1</i>
<i>BCOR</i>	<i>IDH1</i>	<i>SETBP1</i>
<i>BCORL1</i>	<i>IDH2</i>	<i>SF3B1</i>
<i>BRAF</i>	<i>JAK2</i>	<i>SH2B3</i>
<i>CALR</i>	<i>KDM6A</i>	<i>SMC1A</i>
<i>CBL</i>	<i>KIT</i>	<i>SMC3</i>
<i>CDKN2A</i>	<i>KRAS</i>	<i>SRSF2</i>
<i>CEBPalpha</i>	<i>MPL</i>	<i>STAG2</i>
<i>CREBBP</i>	<i>NF1</i>	<i>STAT3</i>
<i>CSF3R</i>	<i>NOTCH1</i>	<i>SUZ12</i>
<i>CSNK1A1</i>	<i>NOTCH2</i>	<i>TET2</i>
<i>CUX1</i>	<i>NPM1</i>	<i>TNFAIP3</i>
<i>DDX41</i>	<i>NRAS</i>	<i>TP53</i>
<i>DNMT3A</i>	<i>PHF6</i>	<i>U2AF1</i>
<i>ETNK1</i>	<i>PPMD1</i>	<i>WT1</i>
<i>ETV6</i>	<i>PTEN</i>	<i>ZRSR2</i>

Supplementary Table S2. Response rates at Day-28 and Day-56.

	Total		ND AML		R/R AML	
	N	%	N	%	N	%
Response at day-28 (n=77)						
CR	10	13	6	16	4	10
CRi	11	14	7	18	4	10
PR	2	3	1	3	1	3
MLFS	13	17	9	24	4	10
SD/PD	31	40	12	32	19	49
death	9	12	2	5	7	18
unknown	1	1	1	3	-	-
Response at day-56 (n=77)						
CR	17	22	12	32	5	13
CRi	8	10	5	13	3	8
PR	1	1	0	-	1	3
MLFS	10	13	5	13	5	13
SD/PD	27	35	8	21	19	49
death	12	16	6	16	6	15

	unknown	2	3	2	5	0	0
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Supplementary Table S3. Response rates at Day-28 and Day-56 in the group of the VIALE-A eligible patients.

		1st line	
Response at day-28 (n=64)		N	%
	CR	4	14
	CRi	6	21
	PR	1	3
	MLFS	8	28
	SD/PD	8	28
	death	1	3
	unknown	1	3
Response at day-56 (n=64)			
	CR	8	28
	CRi	5	17
	PR	0	0
	MLFS	5	17
	SD/PD	5	17
	death	4	14
	unknown	2	7

Supplementary Table S4. Response rates assessed at day-56 in the cytogenetics and molecular subgroups and according to VEN cycle 1 dose.

cytogenetics		non-adverse		adverse	
Response at day-56 (n=77)		N	%		%
	CR	8	20	9	25
	CRi	5	12	3	8
	PR	1	2	0	0
	MLFS	9	22	2	6
	SD/PD	13	32	13	36
	death	4	10	8	22
	unknown	1	2	1	3
Molecular subgroup		TP53/RAS WT		TP53/RAS mut	
Response at day-56 (n=54)					
	CR	9	28	4	18
	CRi	5	16	2	9
	PR	0	0	0	0
	MLFS	7	22	3	14
	SD/PD	5	16	10	45
	death	4	13	3	14
	unknown	2	6	0	0
VEN cycle 1 dose		>50%		≤50%	
Response at day-56 (n=54)		N	%		
	CR	9	18	7	32
	CRi	6	12	2	9
	PR	0	0	1	5
	MLFS	8	16	3	14
	SD/PD	19	37	6	27

death	8	16	2	9
unknown	1	2	1	5

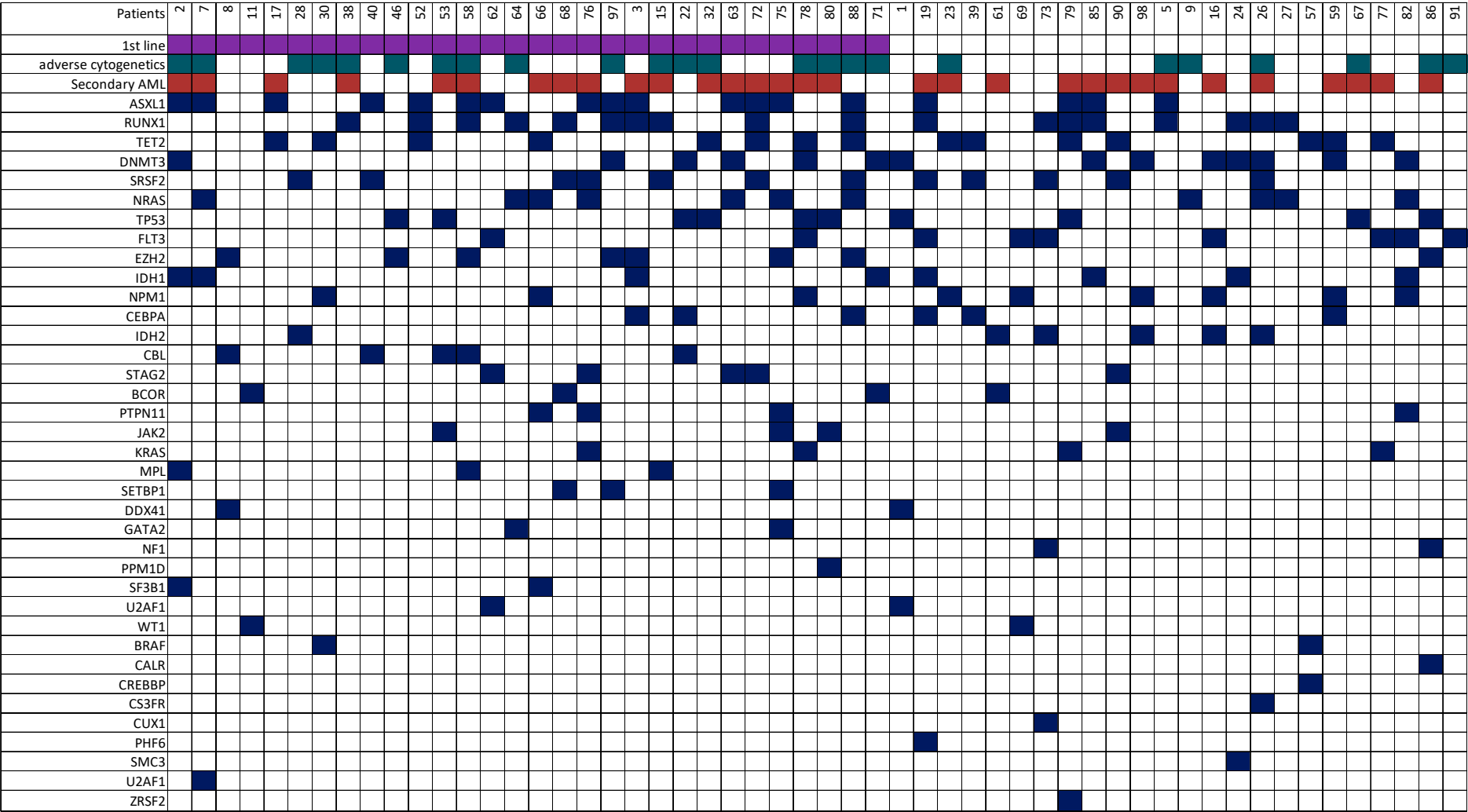
Supplementary Table S5. Factors associated with response in the ND-AML group.

ND-AML	responders		dead/non responders		RR	P value
N, %	22	100	14	100		
male	12	55	10	71	0.76 (0.46-1.27)	0.48
age, median (range)	74	(61-81)	72	(67-79)		0.95
age >75 years	7	32	6	43	0.82 (0.46-1.48)	0.73
Secondary AML	16	73	10	71	0.92 (0.55-1.82)	1
AML-MRC	10	45	3	21		0.17
therapy-related	2	9	2	14		1
post MPN	4	18	5	36		0.26
Previous azacitidine	2	9	3	21	0.62 (0.21-1.87)	0.36
WBC, median (range)	1.8	(0.4-60)	8.8	(0.8-40)		0.47
WBC >10G/L	7	32	5	36	0.97 (0.55-1.73)	1
plt count, median (range)	100	(11-272)	55	(3-200)		0.18
plt <20G/L	3	14	4	29	0.65 (0.27-1.60)	0.39
BM blasts, median (range)	36	(7-70)	36	(12-88)		0.83
BM blasts <30%	9	41	6	43	0.97 (0.57-1.65)	1
Adverse cytogenetics	13	59	8	57	1.03 (0.61-1.76)	1
monosomal	8	36	4	29		1
complex	7	32	6	43		0.83
genomic alteration						
NPM1	2	14	1	7	1.13 (0.49-2.65)	1
FLT3	1	7	1	7	0.83 (0.2-3.4)	1
ITD	0	0	0	0		-
TKD	1	7	1	7		-
IDH (n=37)	5	23	3	21	1.02 (0.56-1.9)	1
IDH1	4	18	3	21		-
IDH2	1	5	0	0		-
TP53 (n=33)	3	14	5	42	0.52 (0.20-1.31)	0.10
JAK2 (n=31)	2	10	5	42	0.39 (0.12-1.31)	0.07
ASXL1 (n=28)	7	39	5	50	0.9 (0.49-1.63)	1
RUNX1 (n=28)	4	22	4	40	0.75 (0.35-1.6)	0.43
TET2 (n=28)	3	17	4	40	0.63 (0.25-1.55)	0.37
DNMT3A (n=28)	2	11	3	30	0.6 (0.2-1.8)	0.34
SFSR2 (n=28)	4	22	3	30	0.89 (0.44-1.84)	1
NRAS (n=28)	4	22	3	30		1
RAS/TP53 (n=28)	4	22	7	70	0.69 (0.33-1.46)	0.41
VEN dose >50% during cycle 1 (n=37)	11	52	9	69	0.86 (0.49-1.49)	0.72

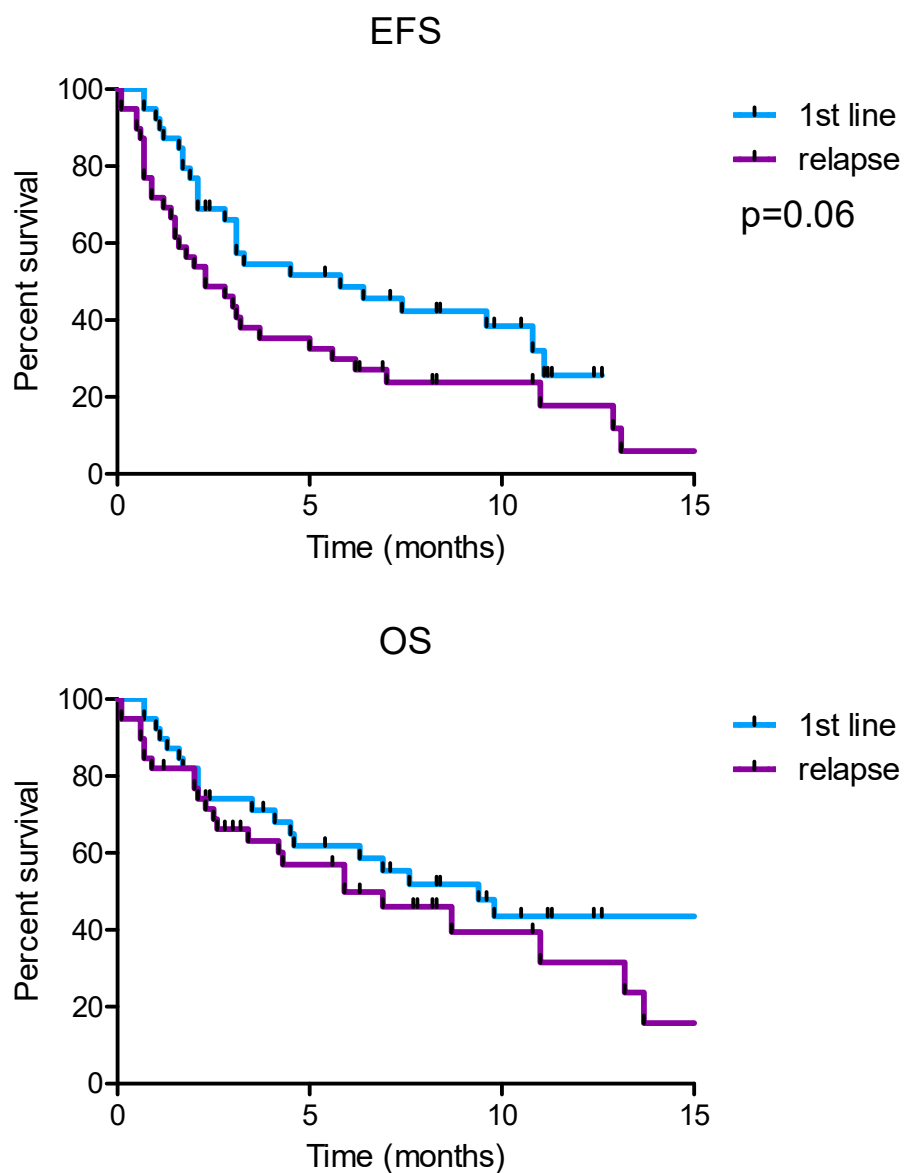
Supplementary Table S6. Factors associated with response in the R/R-AML group.

R/R cohort	responding	death/non responding	RR	P value
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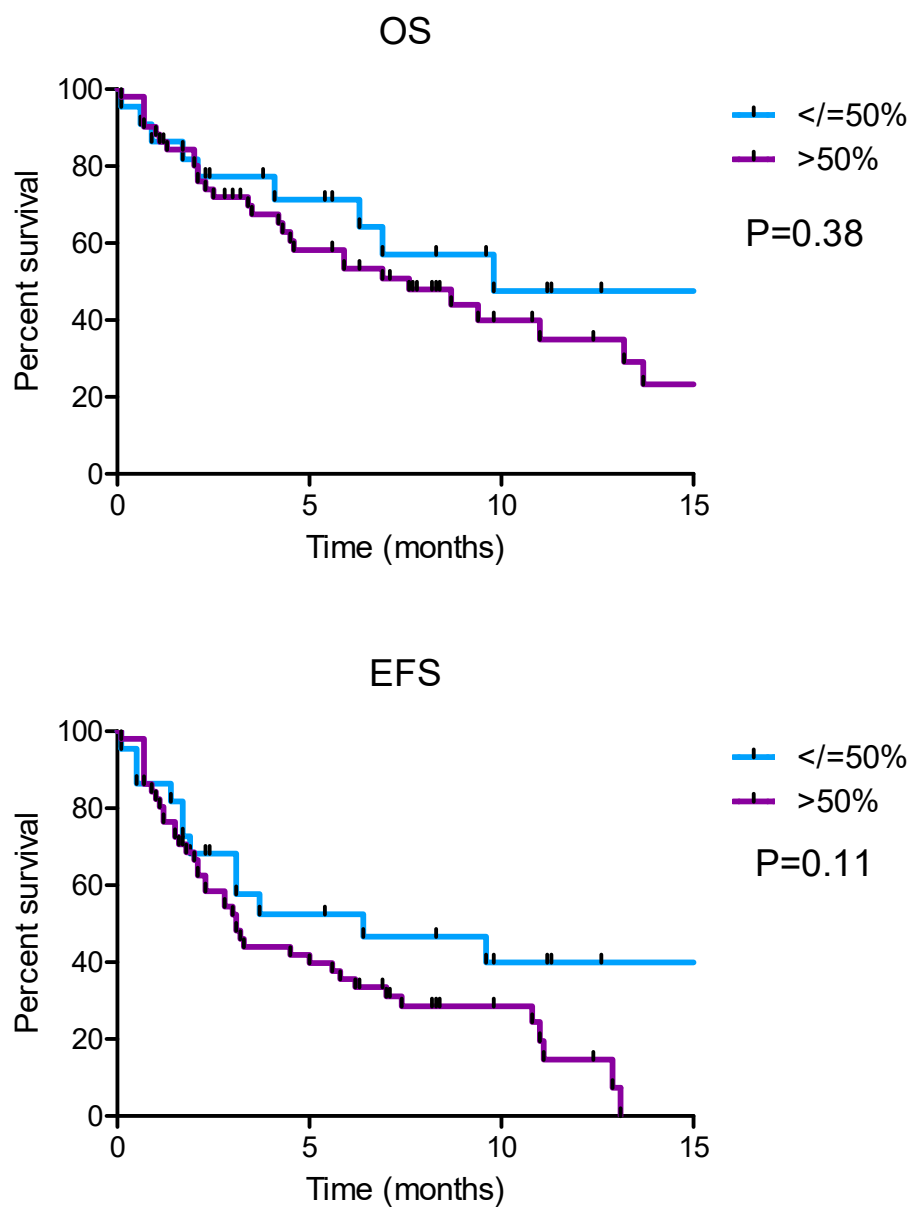
N, %	14	100	25	100		-
male	10	71	14	56	1.56 (0.59-4.09)	0.49
age, median (range)	75	(22-86)	65	(22-77)		0.10
age >75 years	7	50	2	8	3.33 (1.59-6.97)	0.005
Secondary AML	5	36	14	56	0.58 (0.24-1.43)	0.32
AML-MRC	4	29	8	32		1
therapy-related	0	0	3	12		0.54
post MPN	1	7	3	12		1
Previous treatments						
median number of line	2	(1-3)	1	(1-4)		0.63
Azacitidine	3	21	7	28	0.71 (0.26-2.13)	0.72
median cycle (range)	6	(3-20)	4	(3-8)		0.22
chemotherapy	14	100	20	80	0.38 (0.39-15.5)	0.14
allogenic transplantation	3	21	7	28	0.79 (0.28-2.27)	0.72
WBC, median (range)	2	(0.4-13)	4.5	(7-73)		0.21
WBC >10G/L	2	14	7	28	0.56 (0.15-2.54)	0.44
plt count, median (range)	55	(5-757)	21	(0.6-73)		0.26
plt <20G/L	4	29	9	36	0.73 (0.30-2.01)	0.73
BM blasts, median (range)	37	(8-77)	29	(10-92)		0.82
BM blasts <30%	5	36	12	48	0.72 (0.29-1.76)	0.52
Adverse cytogenetics	1	7	13	52	0.13 (0.02-0.90)	0.005
monosomal	0	0	11	44		0.003
complex	0	0	10	40		0.007
genomic alteration						
NPM1	3	21	3	12	1.5 (0.59-3.82)	0.65
FLT3	3	21	4	16	1.25 (0.47-3.32)	0.69
ITD	2	14	4	16		-
TKD	1	7	0	0		-
IDH (n=37)	6	43	4	17	2 (0.95-4.21)	0.13
IDH1	2	14	1	4		-
IDH2	4	29	3	13		-
TP53 (n=32)	2	15	5	26	0.69 (0.20-2.42)	0.68
JAK2 (n=28)	1	8	1	6	1.18 (0.28-5.07)	1
ASXL1 (n=24)	3	27	1	8	1.87 (0.86-4.09)	0.30
RUNX1 (n=24)	4	36	4	31	1.14 (0.47-2.78)	1
TET2 (n=24)	4	36	3	23	1.39 (0.59-3.27)	0.66
DNMT3A (n=24)	3	27	5	38	0.95 (0.38-2.36)	0.68
SFSR2 (n=24)	4	36	1	8	2.17 (1.04-4.52)	0.14
RAS/TP53 (n=28)	2	18	7	54	0.37 (0.10-1.35)	0.10
VEN dose >50% during cycle 1 (n=34)	11	79	19	83	0.86 (0.32-2.27)	1



Supplementary Figure S1. Oncoprint showing the set of gene mutations found in the whole VEN-AZA treated population according to treatment groups, cytogenetics and type of AML.



Supplementary Figure S2. Kaplan-Meier analyses showing overall survival and event-free survival in the ND AML group and the R/R group of patients.



Supplementary Figure S3. Kaplan-Meier analyses showing overall survival (OS) and event-free survival (EFS) according to the percentage of maximum venetoclax dose during the first cycle.