Clinical interrogation of *TP53* aberrations and its impact on survival in patients with myeloid neoplasms

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Supplemental Data

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Pages: 22
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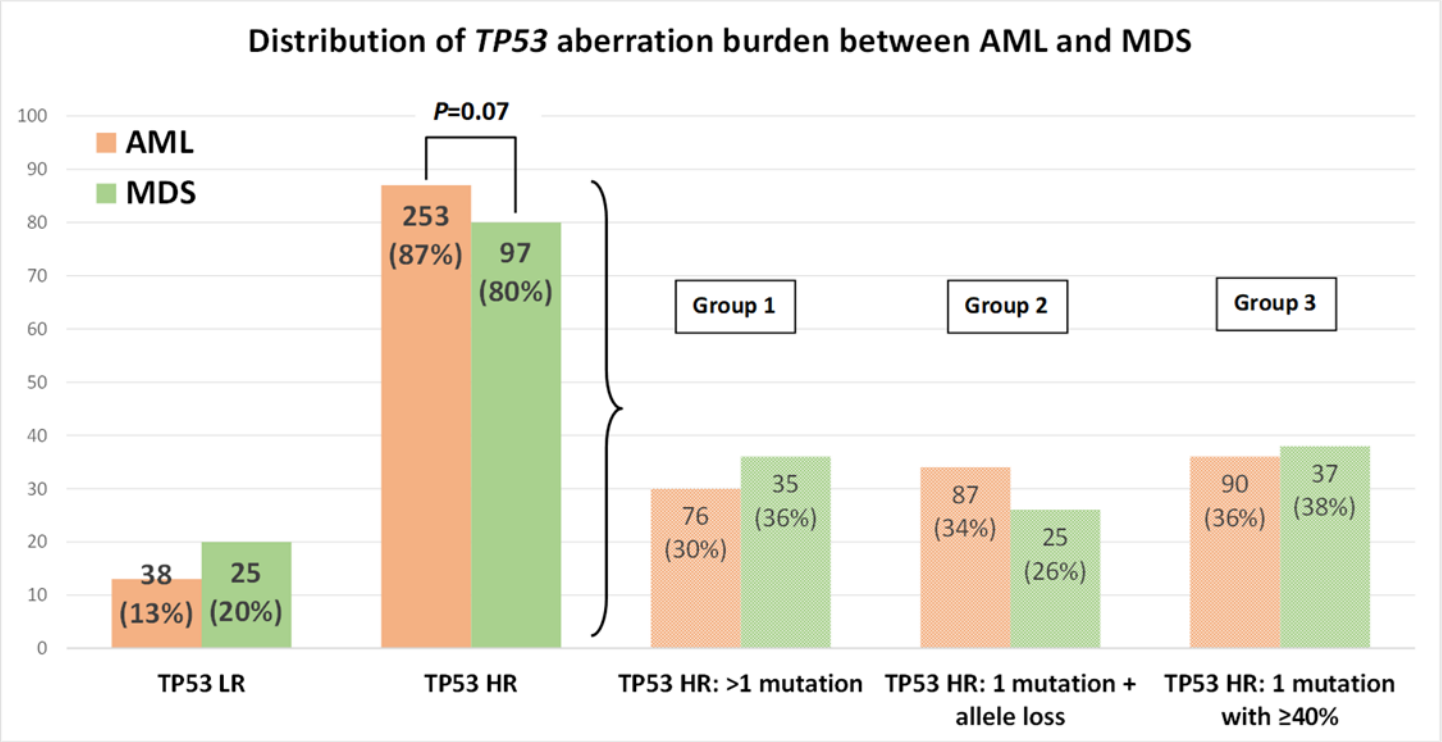
(Sequence of tables and figures in this supplement is according to the appearance in the manuscript)

Figure S1: Types of *TP53* aberration amongst the patients stratified based on the diagnosis of MDS or AML



Abbreviations: LR, low risk; HR, high-risk; VAF, variant allele fraction

Figure S2: Overall survival of patients with multi-hit *TP53* mutations stratified by the sum of VAFs (<50% versus ≥50%)

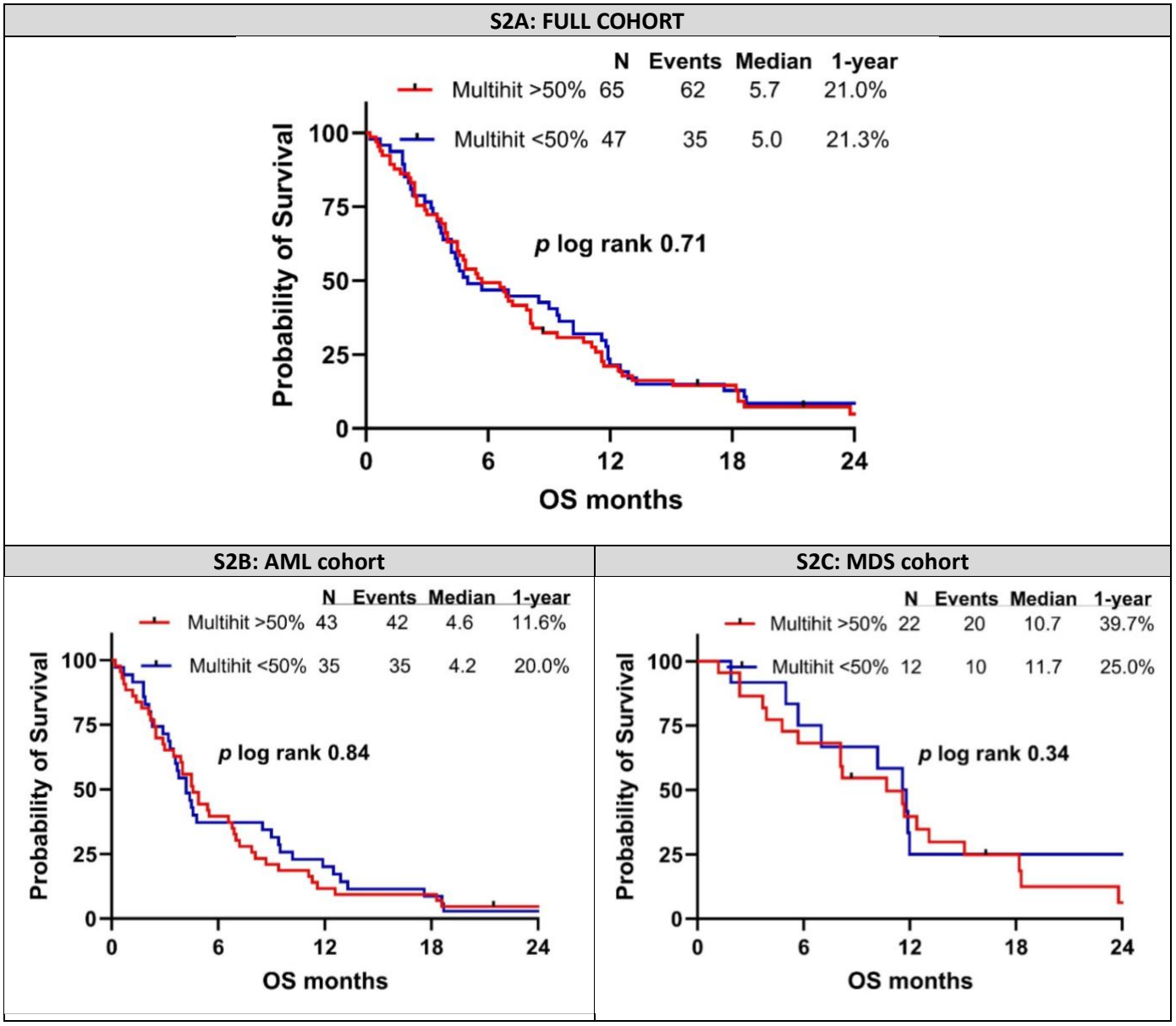


Figure S3: Classification and regression tree (CRT) model predicting the VAF cutoff for inferior survival at 1 year in patients with AML harboring a single-hit *TP53* mutation (n=128); **ROC AUC= 0.68**

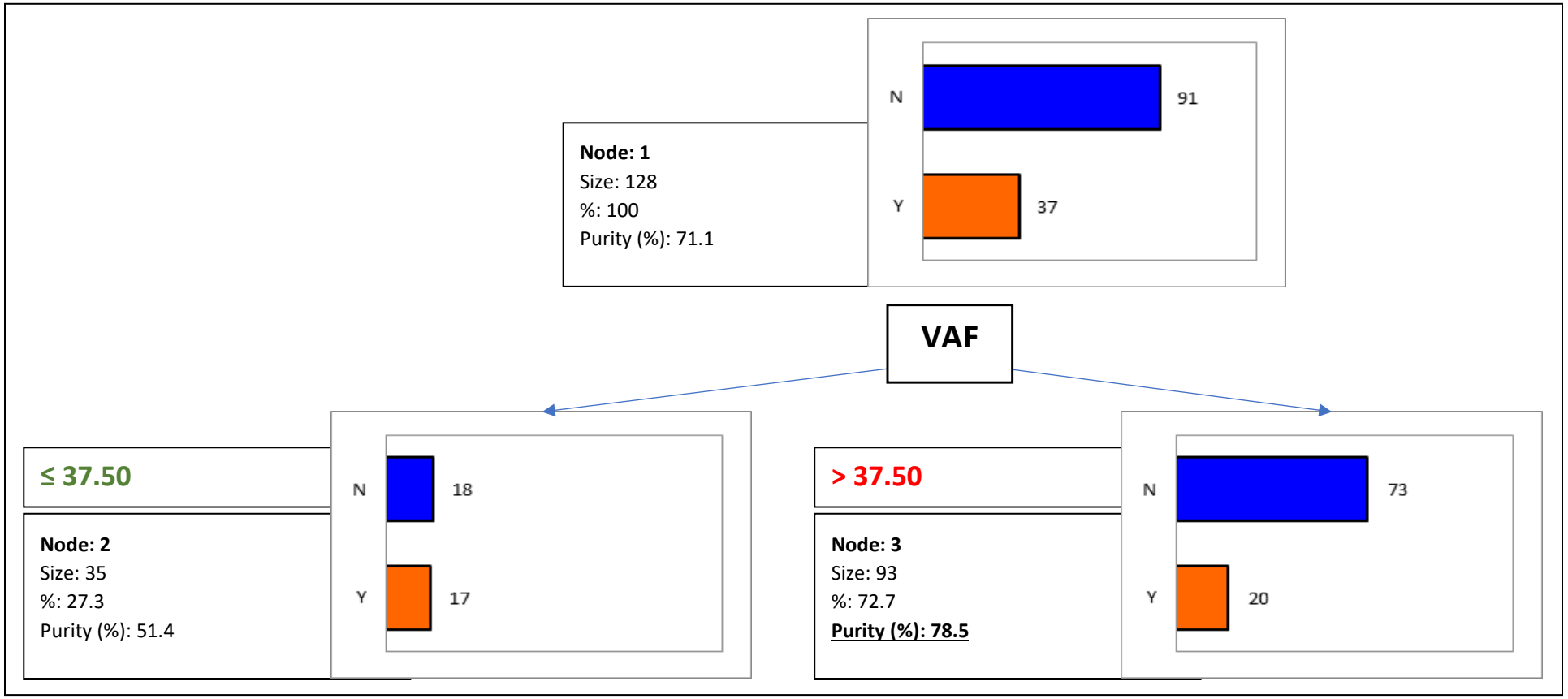


Figure S4: Classification and regression tree (CRT) model predicting the VAF cutoff for inferior survival at 1 year in patients with AML harboring a single-hit *TP53* mutation (n=128); Depth level of 2, **ROC AUC= 0.73**

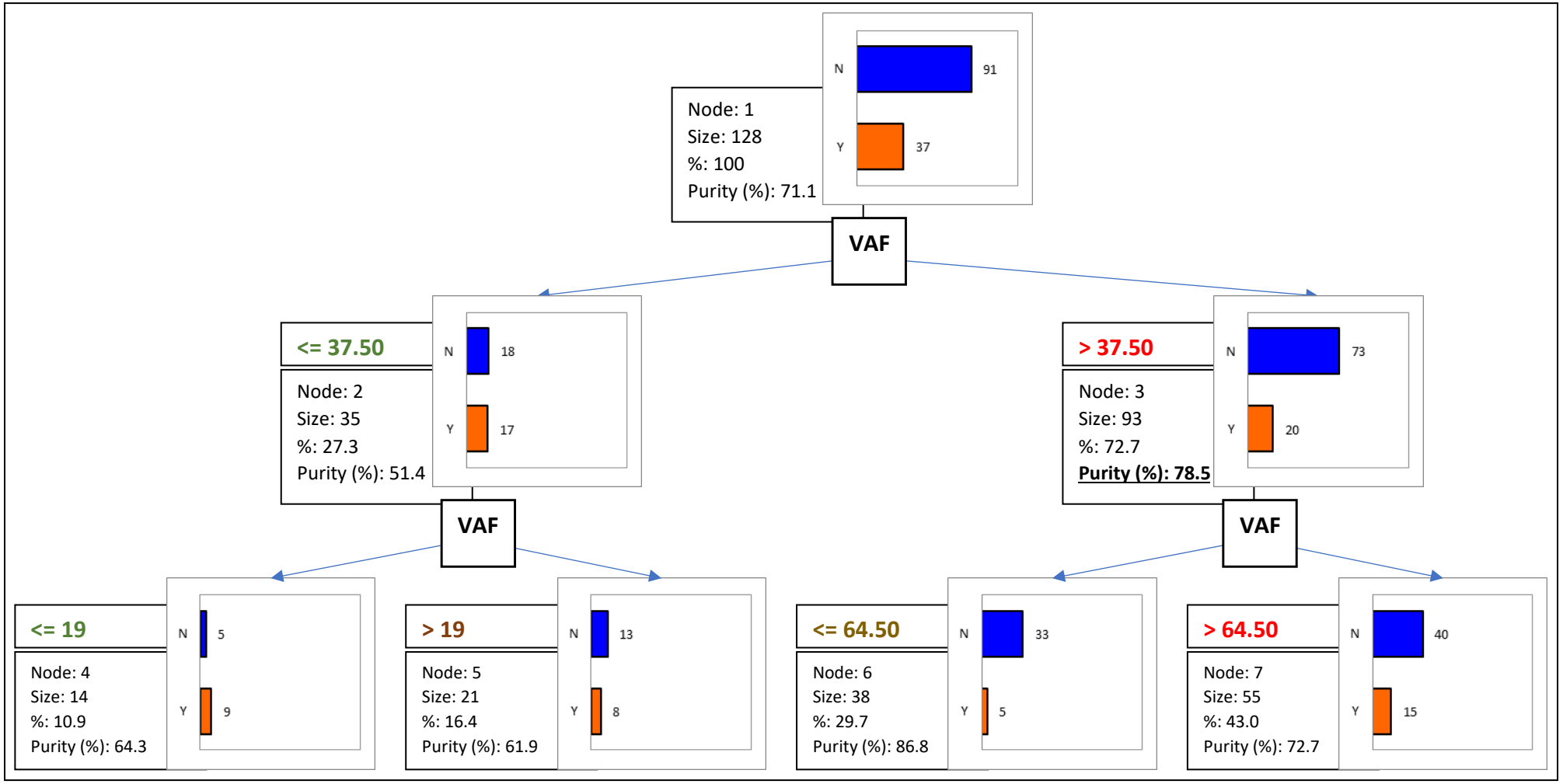


Figure S5: OS of patients with AML harboring a single *TP53* mutation stratified based on VAF cutoffs predicted from the CRT model.

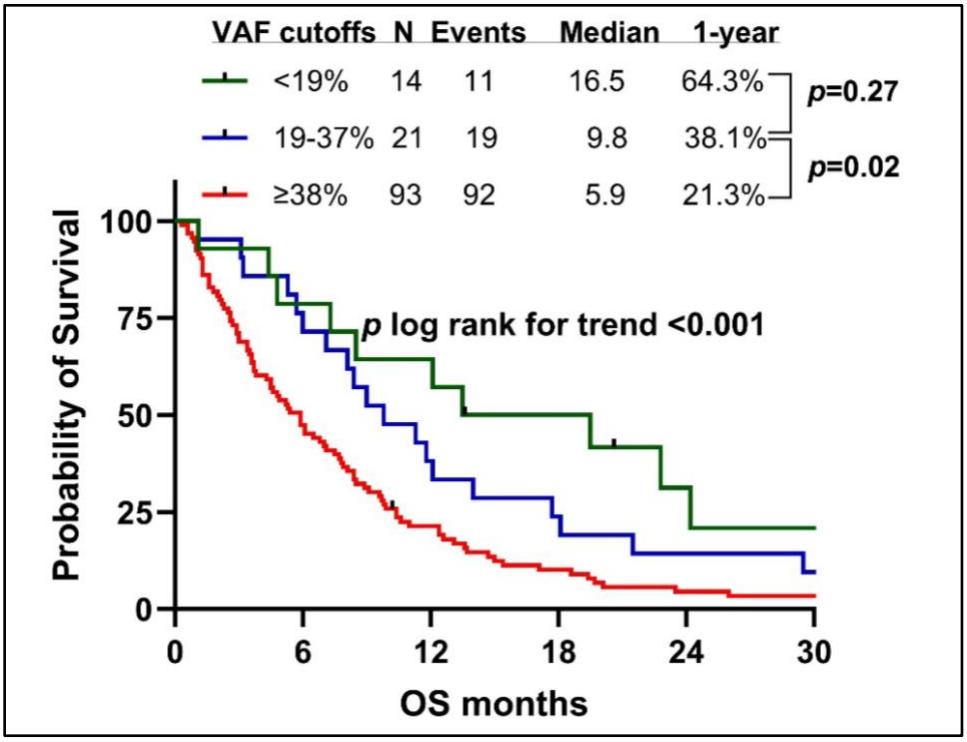


Figure S6: Representation of the type of *TP53* mutation in the full patient cohort

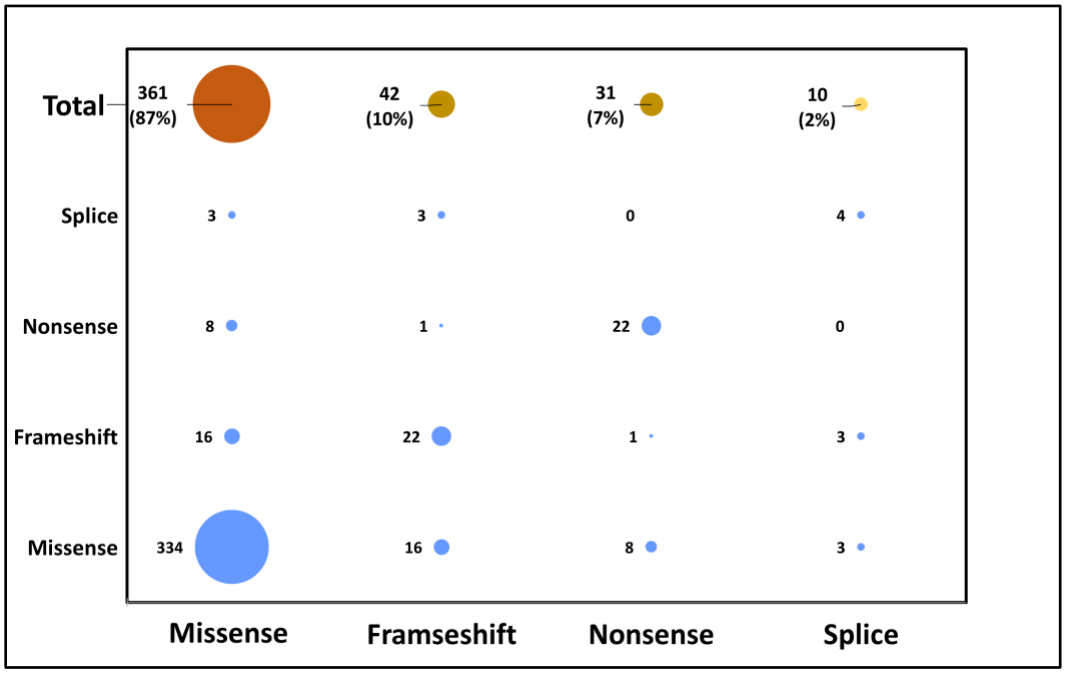


Table S1A-B: Details of treatment regimens

A: AML cohort

With Venetoclax (90/291 [30.9%]); n (%)			
Intensive Chemotherapy (9/90 [10%])		**Low-intensity therapy (81/90 [90%])**	
FLAG/FLAG-IDA	5	Decitabine	58
CLIA	3	CLAD/LDAC	6
MEC	1	AZA	2
		AZA+ APR246	6
		AZA+ Pevenidostat	4
		Aza-Magrolimab	2
		Aza/Decitabine+ FLT3i	2
		Decitabine + GO	1
Without Venetoclax (201/291[69.1%])			
Intensive Chemotherapy (48/201 [23.9%])		**Low-intensity therapy (153/201 [76.1%])**	
CLIA	14	Decitabine*	41
FA/FA-IDA	8	CLAD/LDAC	27
IA + Nivolumab	7	Decitabine + Vosaroxin	13
IA	6	Decitabine + Ruxolitinib	7
CIA	5	Decitabine + SGN-CD33A	2
CPX	4	Decitabine + BP1001	1
		Decitabine+ Clofarabine	1
7+3	2	Guadecitabine (SG110)*	14
CAT/CECA	2	Guadecitabine+ CLAD	7
		AZA*	6
		AZA+ Magrolimab	12
		AZA+ Nivolumab/Pembro	6
		AZA+ Lenalidomide	4
		AZA+ Vorinostat/Pracinostat	4
		AZA+ FLT3i	2
		AZA+ Rigosertib	1
		AZA+ Enasidenib	1
		LDAC + Daunorubicin	1
		LDAC + Omacetaxine	1

Abbreviations: FLAG, fludarabine/intermediate dose cytarabine/G-CSF; IDA, idarubicin; CLIA, cladribine /idarubicin/intermediate dose cytarabine; MEC, mitoxantrone, etoposide, intermediate dose cytarabine; CLAD, cladribine; LDAC, low dose cytarabine; AZA, azacitidine; APR246, eprenetapopt; FLT3i, FMS like tyrosine kinase 3 inhibitor; GO, gemtuzumab ozogamicin; FA, fludarabine. Intermediate dose cytarabine; IA, idarubicin, intermediate dose cytarabine; CIA, clofarabine, idarubicin, intermediate dose cytarabine; 7+3, 7 days of continuous infusion cytarabine and 3 days of daunorubicin; CAT, cyclophosphamide /cytarabine/topotecan; CECA, cyclophosphamide, etoposide, carboplatin; intermediate dose cytarabine; Pembro, pembrolizumab

*These groups denote HMA monotherapy

SGN CD33A: CD33-targeting antibody-drug conjugate using a pyrrolobenzodiazepine dimer

BP1001: Liposomal Grb2 antisense oligonucleotide

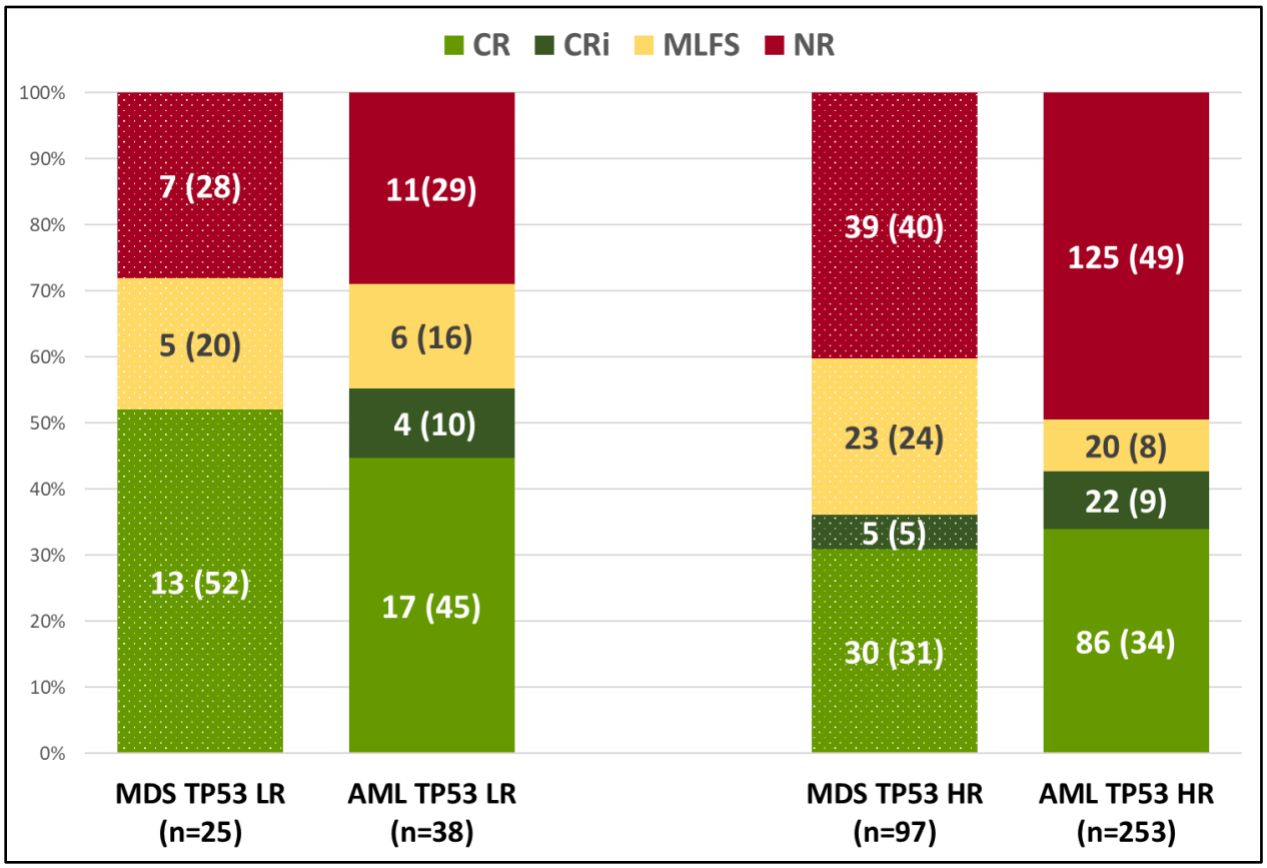
B: MDS cohort

With Venetoclax (7/122 [5.7%])	
Decitabine	6
AZA	1
Without Venetoclax (115/122 [94.3%])	
Decitabine	24
Guadecitabine (SG110)	22
AZA	12
AZA+ IPI/PEMBRO/NIVO	20
AZA+ Magrolimab/other CD47 blocker	8
AZA+ Lenalidomide	6
AZA+ APR 246	6
AZA+ Pracinostat	4
AZA+ CB839	4
AZA+ Lirilumab	2
AZA+ Rigosertib	1
CLAD/LDAC	4
Lenalidomide	1
FF-10501-01	1

Abbreviations: AZA, azacitidine; IPI, ipilimumab; PEMBRO, pembrolizumab; NIVO, nivolumab; APR246, eprenetapopt; CLAD, cladribine; LDAC, low dose cytarabine

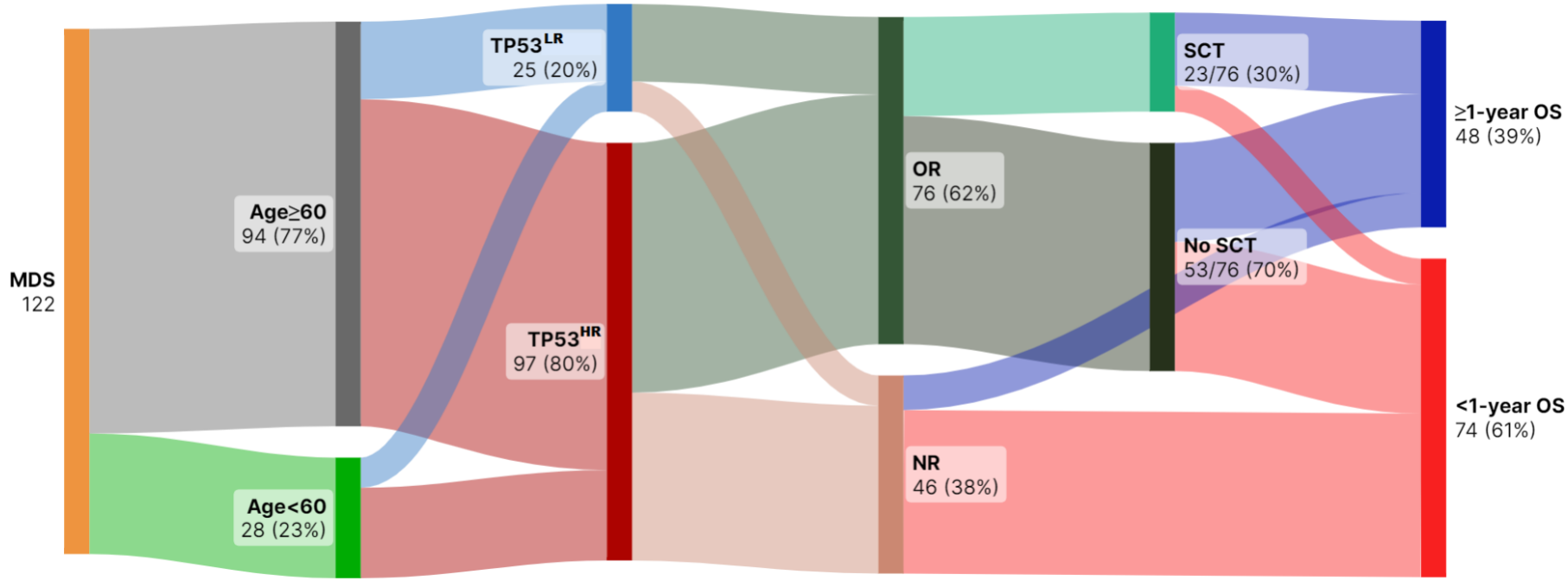
CB839: Glutaminase inhibitor
FF-10501-01: Inosine-5-monophosphate dehydrogenase inhibitor

Figure S7: Response rates in the MDS and AML cohort based on the *TP53* aberration burden.



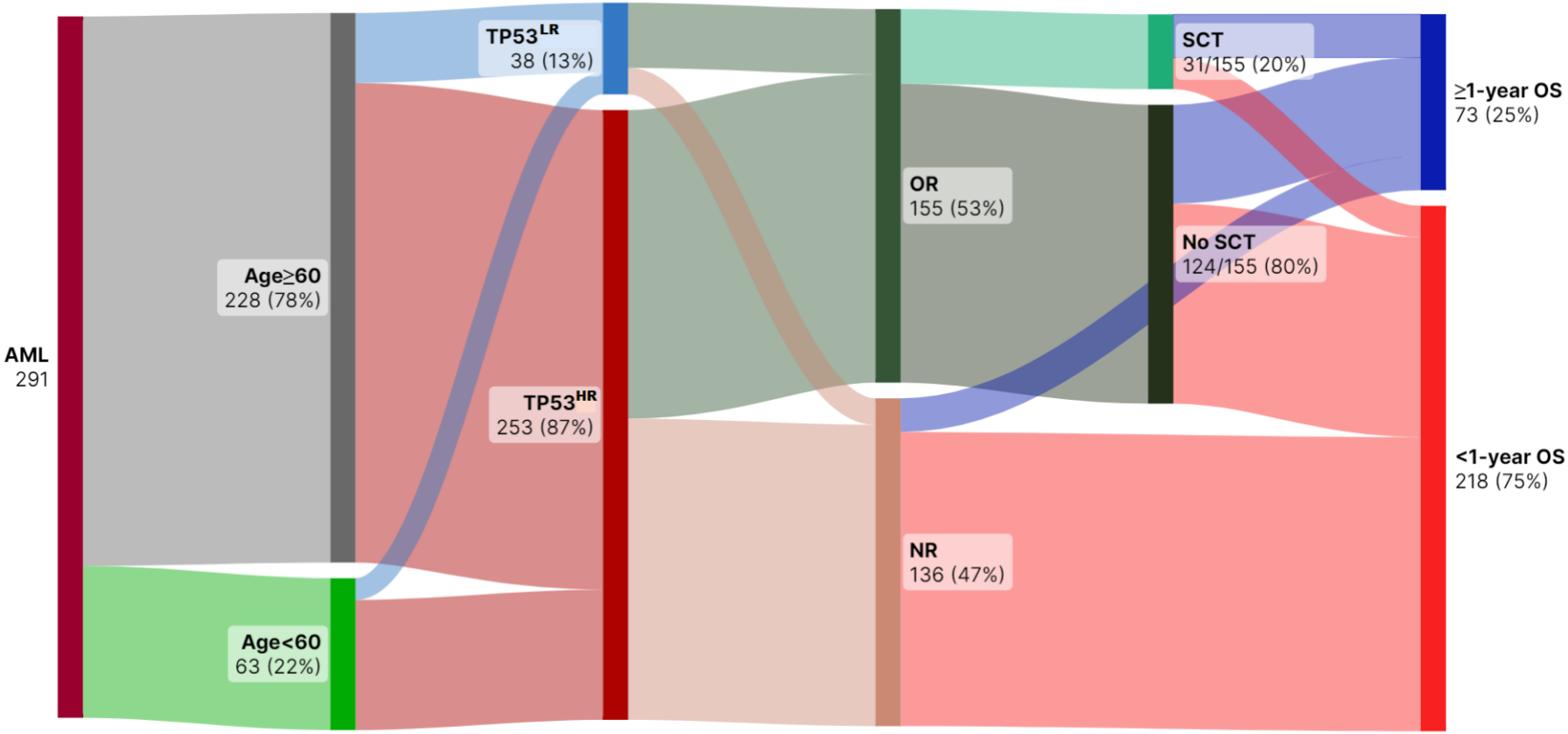
Abbreviations: CR, complete remission; CRi, CR with incomplete counts recovery; MLFS, morphological leukemia free state; NR, no response; TP53 LR, *TP53*^{LR}; TP53 HR, *TP53*^{HR}

Figure S8A: Sankey Diagram of patients with MDS showing age, *TP53* burden, response rates, allogeneic stem cell transplantation and survival at 1 year.



Abbreviations: MDS, myelodysplastic syndrome; OR, overall response; NR, no response, SCT, allogeneic stem cell transplnatation, OS, overall survival

Figure 8B: Sankey Diagram of patients with AML showing treatment intensity, *TP53* burden, response rates, allogeneic stem cell transplantation (SCT)* and survival at 1 year.

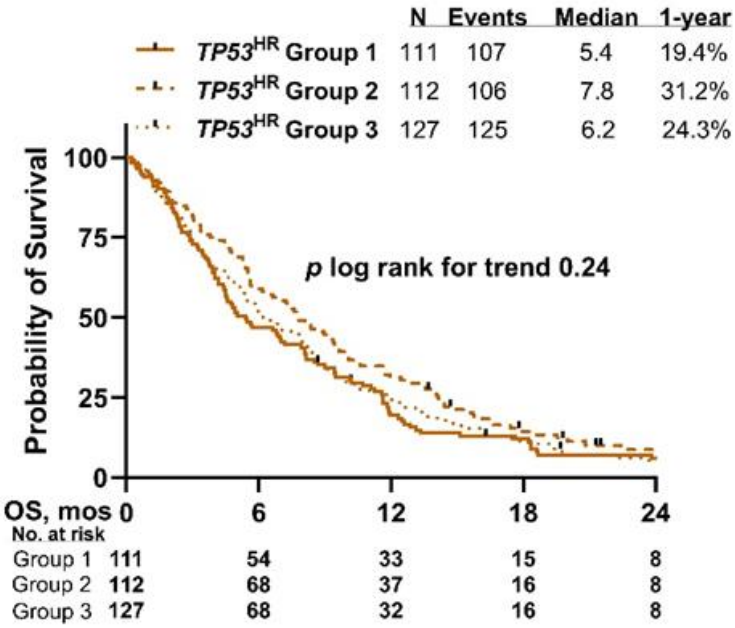


*Total 32 patients with AML underwent SCT, 31 patients after attainment of an OR and one patient with stable disease.

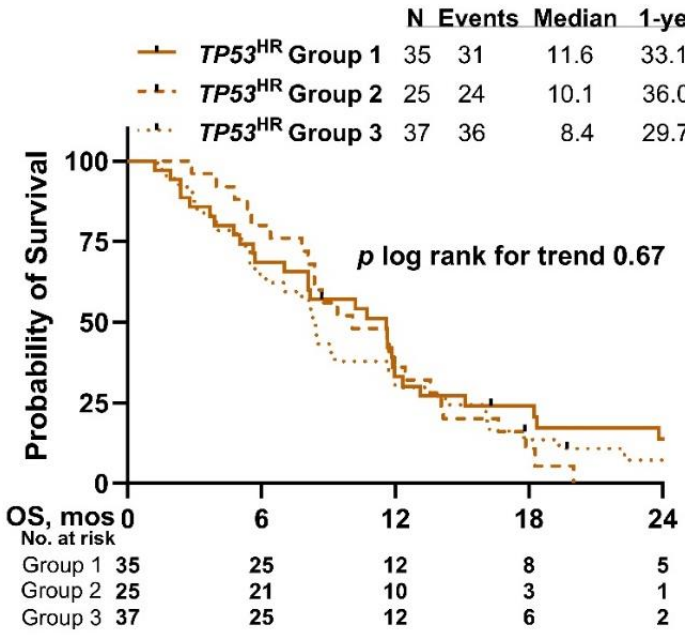
Abbreviations: AML, acute myeloid leukemia; OR, overall response; NR, no response, SCT, allogeneic stem cell transplnatation, OS, overall survival

Figure S9: OS in the *TP53*^{HR} group based on the type of *TP53* aberrations

S9A: OS in the full cohort based on type of *TP53*^{HR} aberration



S9B: OS in the MDS cohort based on *TP53*^{HR} aberration



S9C: OS in the AML cohort based on *TP53*^{HR} aberration

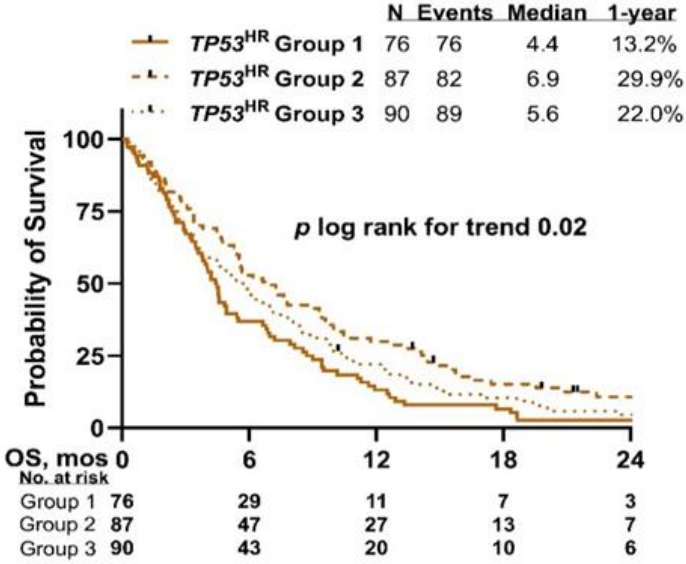
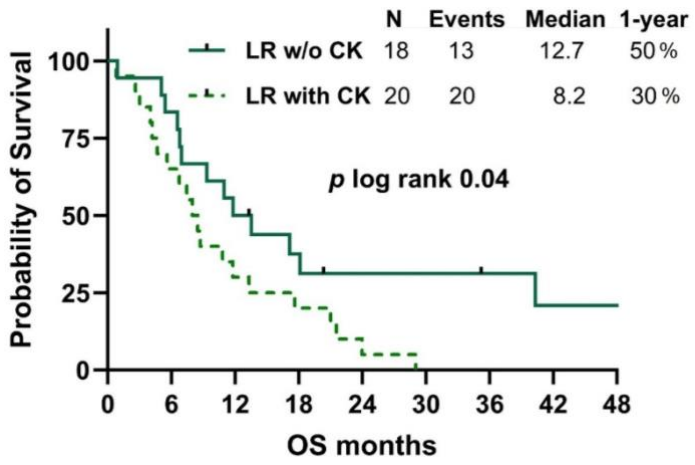
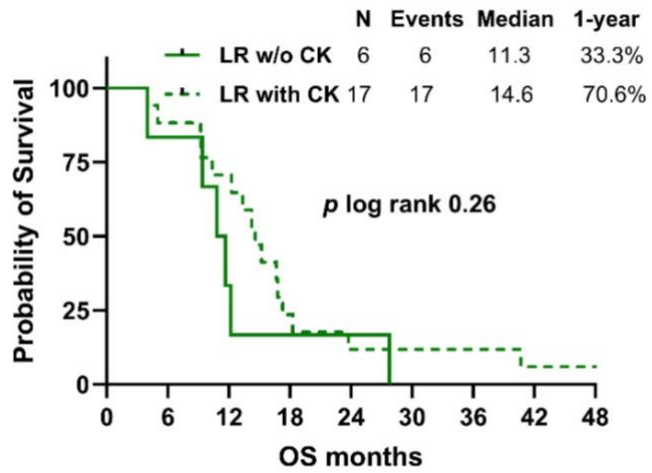


Figure S10: Overall survival (OS) of patients with AML or MDS and *TP53*^{LR} stratified by complex karyotype

S10A: *TP53*^{LR} AML



S10B: *TP53*^{LR} MDS



Abbreviations: LR, *TP53*^{LR}; w/o, without; CK, complex karyotype

Figure S11: Overall survival (OS) of patients with MDS and AML stratified by BM blast percentage

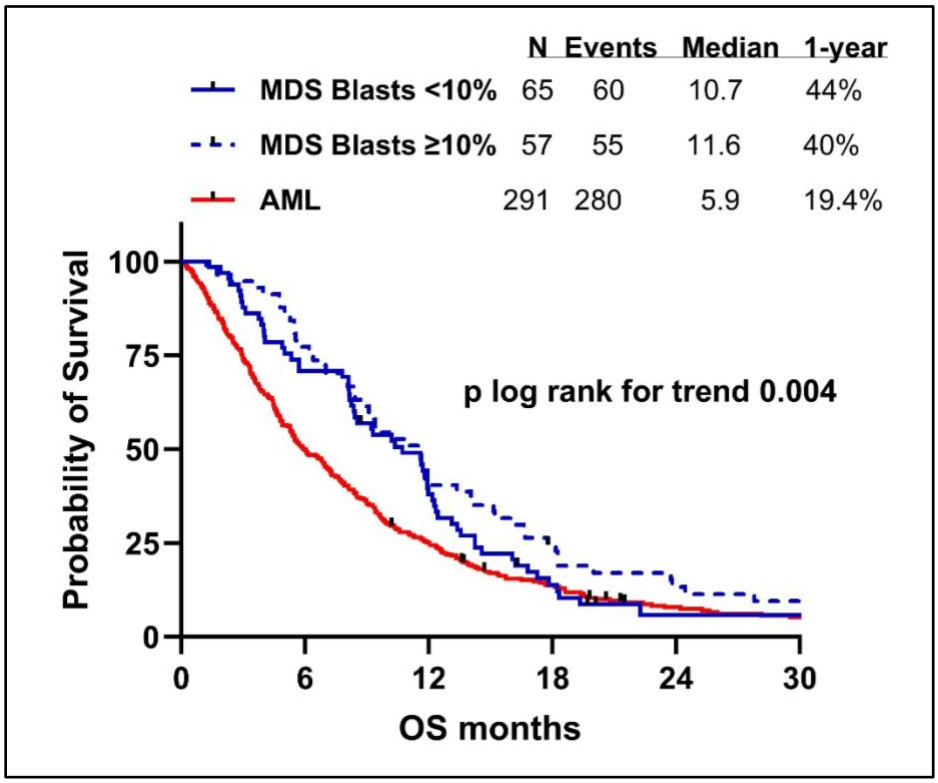


Figure S12: Comparison of OS of patients in the MDS group to the AML group stratified by the *TP53* aberration status.

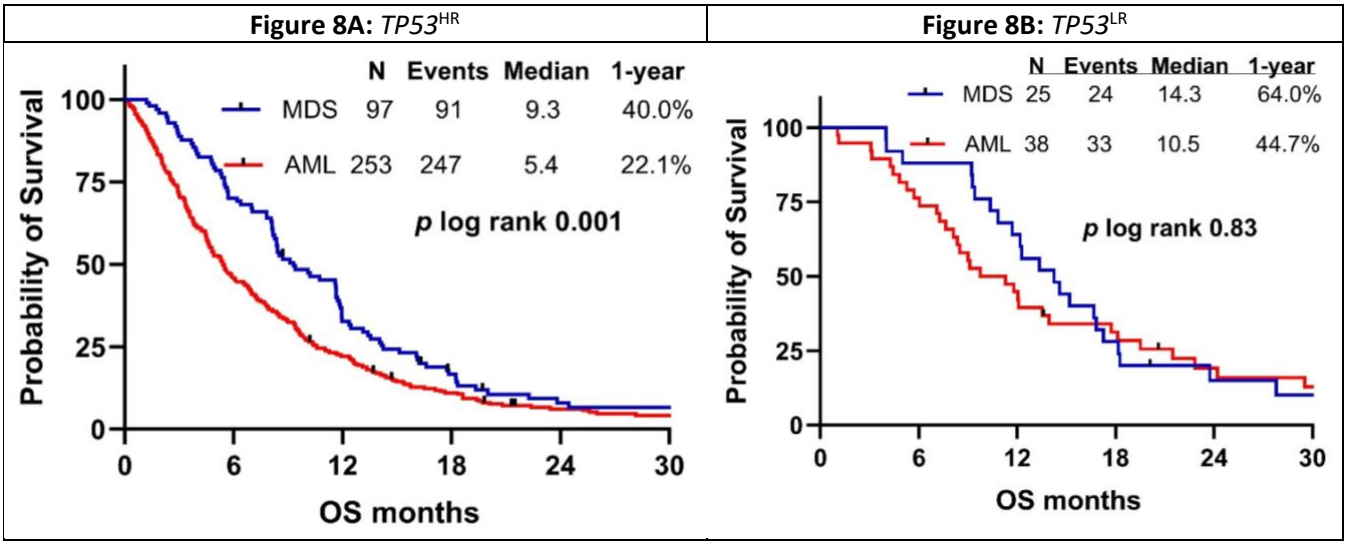


Figure S13: Comparison of OS of patients with MDS versus patients with AML who had *TP53*[HR] and underwent an HSCT.

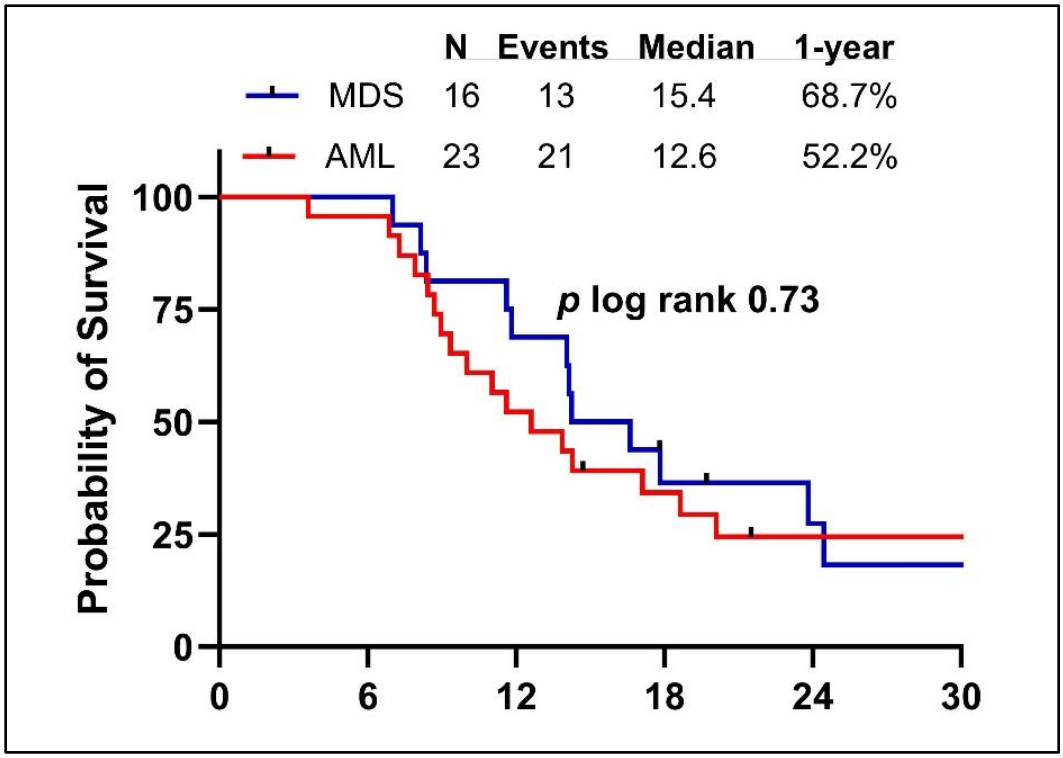


Figure S14: CRT decision tree showing variables affecting survival at 1 year for the full cohort; **ROC AUC 0.69**

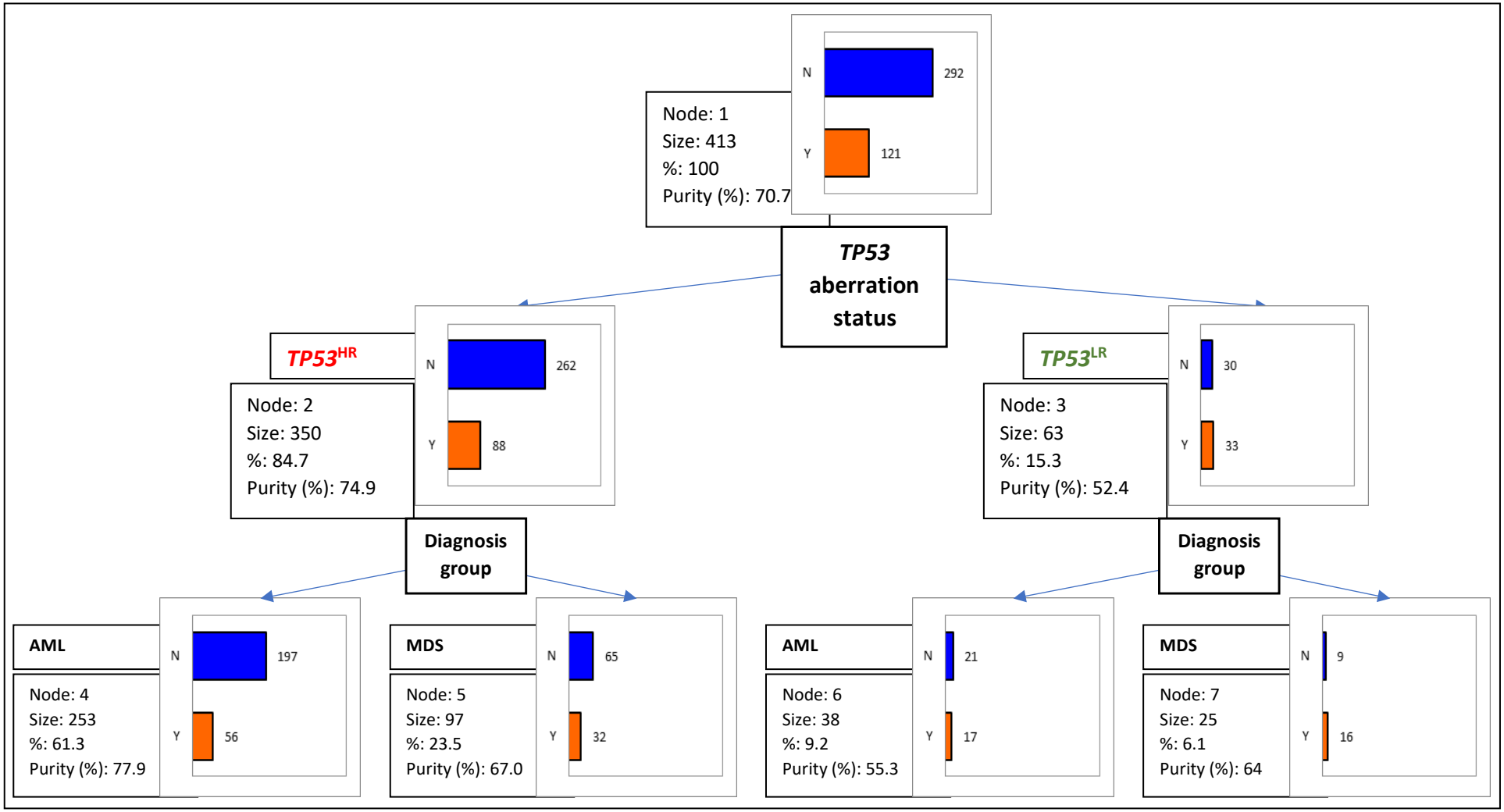


Table S2: Logistic regression analysis of factors affecting overall response in patients with AML.

Univariate Analysis				Multivariate Analysis			
Variable	**Odds ratio**	**95% CI**	**P value**	**Variable**	**Odds ratio**	**95% CI**	**P value**
Age (continuous)	1.01	0.99-1.03	0.35				
Age ≥ 60 years	1.57	0.89-2.77	0.11				
Complex CTG	0.46	0.22-0.91	0.03	**Complex CTG**	0.58	0.26-1.21	0.15
***TP53*^{LR}**	2.40	1.17-5.24	0.02	***TP53*^{LR}**	2.15	0.99-4.95	0.05
Venetoclax	2.08	1.25-3.52	0.005	**Venetoclax**	2.09	1.23-3.59	0.007
Intensive therapy	0.6	0.33-1.07	0.08	**Intensive therapy**	0.69	0.37-1.25	0.22
De novo AML	1.05	0.66-1.67	0.84				

Table S3: Response rates in patients with AML based on treatment intensity.

Full AML Cohort (n=291)										
Treatment intensity	n	Median age [IQR]	Age ≥60 years	P-value	CRc (%)	P-value	ORR (%)	P-value	HSCT (%)	P-value
Low intensity	234	72.2 [66.9-77.5]	213 (91)	<0.001	104 (44)	0.99	130 (56)	0.14	21 (9)	0.03
Intensive	57	56.6 [46.8-60.1]	15 (26)		25 (44)		25 (44)		11 (19)	
AML with *TP53*^{HR} (n=253)										
Low intensity	202	73.2 [67.1-77.7]	185 (91)	<0.001	87 (43)	0.87	107 (53)	0.16	13 (6)	0.01
Intensive	51	57.1 [48.0-60.3]	14 (27)		21 (41)		21 (41)		10 (20)	

Figure S15: Survival outcomes in patients with AML stratified by the treatment intensity.

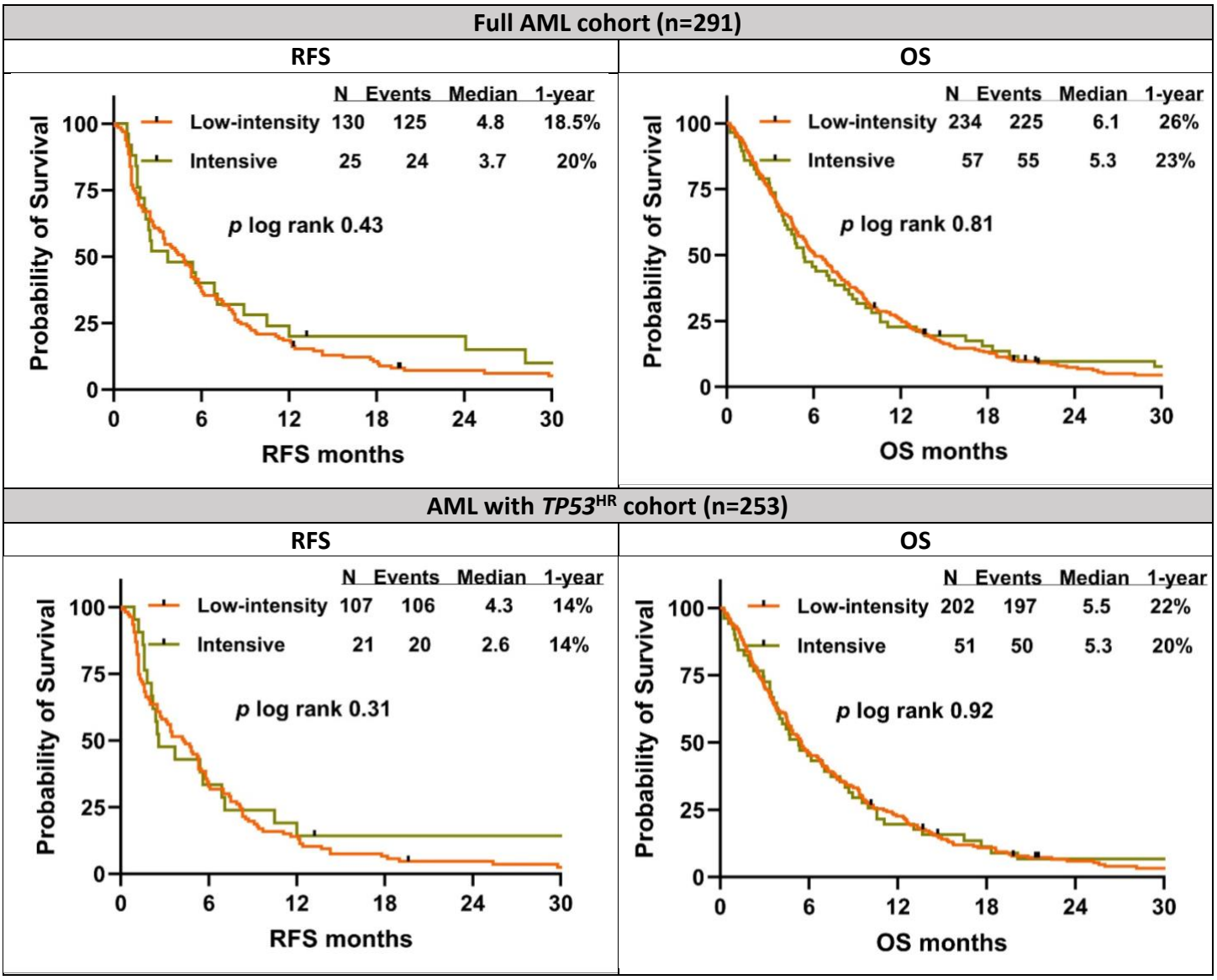


Figure S16: Survival outcomes in patients with AML <60 years of age stratified by the treatment intensity.

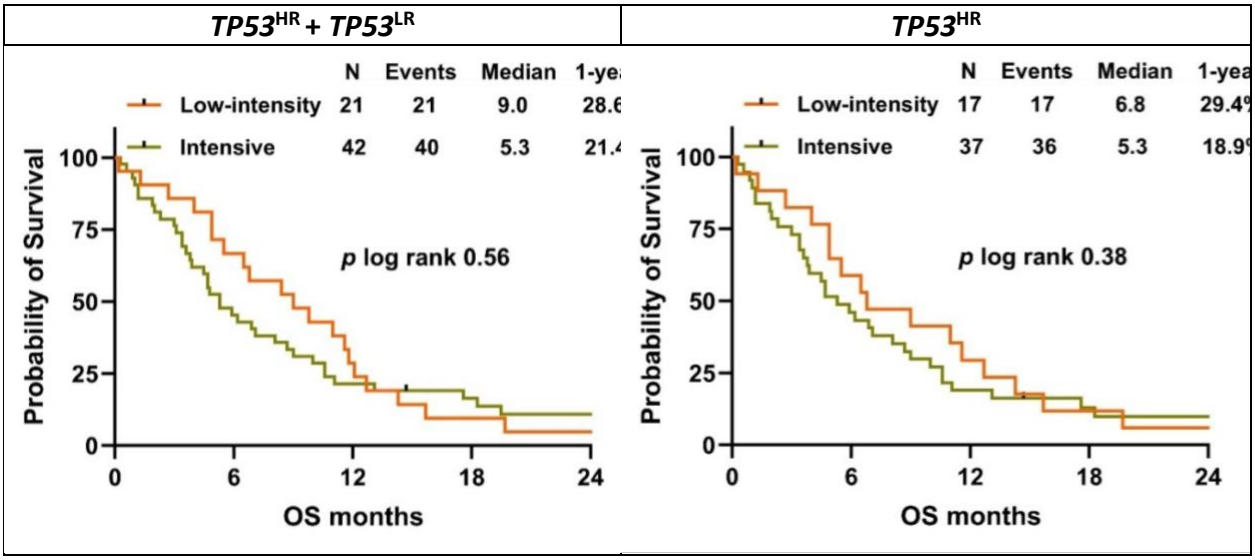


Table S4: Response rates in patients with AML patients based on venetoclax exposure.

Full AML Cohort (n=291)									
Venetoclax	n	Median age [IQR]	Low intensity therapy (%)	CRc (%)	P-value	ORR (%)	P-value	HSCT (%)	P-value
Yes	90	71.3 [64.7-77.5]	81 (90)	49 (54)	0.02	59 (66)	0.005	11 (12)	0.69
No	201	68.8 [59.8-75.7]	153 (76)	80 (40)		96 (48)		21 (10)	
AML with *TP53*^{HR} (n=253)									
Yes	82	72.4 [65.1-77.5]	73 (89)	44 (54)	0.02	52 (63)	0.005	7 (9)	0.99
No	171	69.5 [59.8-75.9]	129 (75)	64 (37)		76 (44)		16 (9)	

Figure S17: Survival outcomes in patients with AML stratified by venetoclax exposure.

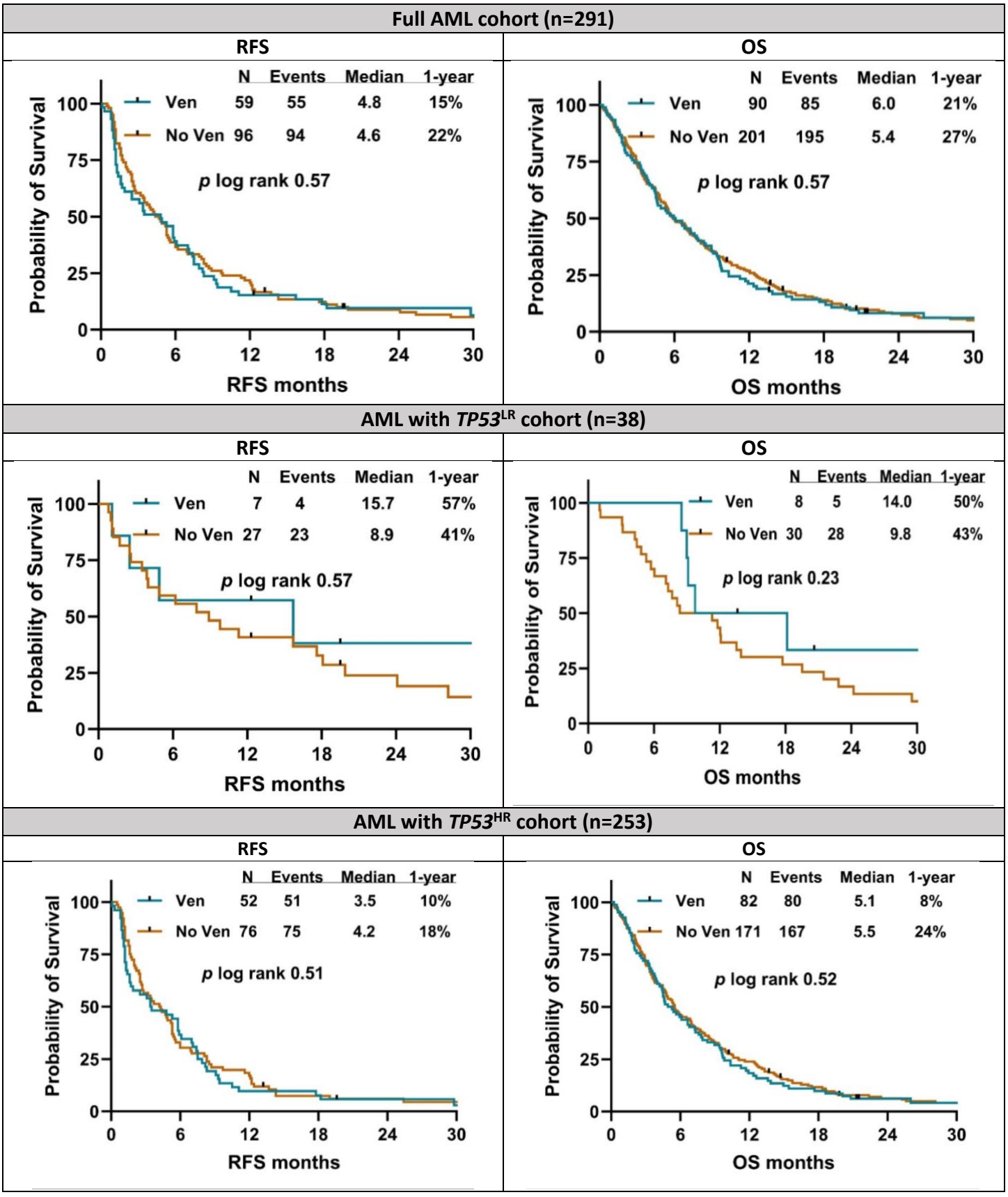


Table S5: Baseline characteristics and outcomes of patients with AML treated with HMA based low-intensity therapy

Variables		HMA monotherapy	HMA+ venetoclax	HMA-non-venetoclax doublets
n		61	75	61
Age (years)		75. 2 [40.8-87.4]	73.6 [37.4-85.6]	70.0 [31.9-82.7]
Age ≥60		52 (85)	72 (96)	53 (87)
***TP53*^{HR}**		51 (84)	63 (84)	44 (72)
Response Rates	CRc ORR	17 (28) 25 (41)	42 (56) 52 (69)	30 (49) 37 (61)
HSCT		2 (3)	7 (9)	6 (10)
Median Follow up (months)		NR	NR	NR
Median OS (months)		5.9	6.1	6.9
Median RFS (months)=ORR		n=25 5.3	n=52 3.5	n=37 4.2

Abbreviations: HMA, hypomethylating agent; CRc, composite complete response; ORR, overall response rate; NR, not reached; OS overall survival; RFS, relapse free revival

Supplemental Methods File

Clinical Interrogation of *TP53* Aberrations and its Impact on Survival in Patients with Myeloid Neoplasms

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1. Assessment of *TP53* mutations:

Next-generation sequencing (NGS) was performed using our clinically validated myeloid panels, interrogating the entire exonic or hotspot regions of 28, 53 or 81 genes (depending on the time of presentation) frequently mutated in myeloid malignancies, including TP53, as described previously[1,2]. Sequencing libraries were prepared using 250 ng of genomic DNA and respective sequencing libraries were subjected to the Illumina MiSeq (Illumina,Inc., San Diego, CA, USA) sequencer. A minimum sequencing coverage of x250 (bidirectional true paired-end sequencing) was required to allow achieving a lower limit of detection of 2% variant allelic frequency in the background of wild-type sequence.

2. Assessment of *TP53* allelic loss/deletion:

Allelic loss/deletion at the TP53 locus was studied using a combination of conventional karyotyping, FISH and aCGH. Allelic loss/deletion was defined as described previously[3,4] : monosomy 17 (-17); isochromosome i(17)(q10); del(17)(pvar(variable)) with pvar centromeric to p13.1; unbalanced translocations involving 17(p), including der(var)t(var;17)(var;qvar),–17; der(var)t(var;17)(var;pvar), –17 with pvar centromeric to p13.1; der(17)t(17;var)(pvar;var)der(17)t(var;17)(var;pvar) with pvar centromeric to p13.1; der(var)t(var;17)(var;qvar) with dicentric der; der(var)t(var;17)(var;pvar) with pvar centromeric to p13.1 and dicentric der; balanced translocation and 17p13 breakpoint: t(17;var)(p13;var) or t(var;17)(var;p13) in the presence of TP53 deletion by FISH; additive material: add(17)(pvar) in the presence of TP53 deletion by FISH; dicentric chromosome dic(var;17)(var;pvar); and ring chromosome r(17)(pvarqvar) with the presence of TP53 deletion by FISH.