

Supplemental Materials for:

Undetectable Measurable Residual Disease is Associated with Improved Outcomes in AML Irrespective of Treatment Intensity

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Supplemental Table 1. Multivariate analysis for overall survival and cumulative incidence of relapse with exclusion of best response as a factor (censored for SCT)

Covariate	OS		CIR	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Model for all patients				
Age, continuous	1.01 (1.00 - 1.03)	0.060	0.99 (0.97 - 1.00)	0.146
Treatment cohort				
IA	Reference		Reference	
LOW + VEN	1.13 (0.70 - 1.83)	0.605	0.90 (0.52 - 1.54)	0.697
MRD status*				
Negative	Reference		Reference	
Positive	1.65 (1.08 – 2.53)	0.020	1.64 (1.08 - 2.49)	0.020
ELN 2017 risk				
Favorable	Reference		Reference	
Intermediate	1.35 (0.89 – 2.03)	0.153	1.89 (1.23 - 2.91)	0.004
Adverse	2.11 (1.43 – 3.11)	<0.001	2.95 (1.92 – 4.54)	<0.001
Model for patients ≥ 60 years				
Age, continuous	1.00 (0.98 - 1.03)	0.782	0.98 (0.95 - 1.02)	0.318
Treatment cohort				
IA	Reference		Reference	
LOW + VEN	1.63 (0.80 – 3.33)	0.175	1.50 (0.65 – 3.47)	0.343
MRD status*				
Negative	Reference		Reference	
Positive	2.16 (0.77 – 6.04)	0.142	2.19 (0.69 – 6.91)	0.183
ELN 2017 risk				
Favorable	Reference		Reference	
Intermediate	1.43 (0.78 - 2.62)	0.248	2.17 (1.06 – 4.44)	0.034
Adverse	2.12 (1.29 – 3.49)	0.003	2.82 (1.53 – 5.20)	0.001

*An interaction term composed of the product of MRD status and treatment cohort was included in the above model but not found to be significant.

Abbreviations: CI, confidence interval; CIR, cumulative incidence of relapse; ELN, European LeukemiaNet; HR, hazard ratio; IA, idarubicin plus intermediate to high-dose cytarabine; LOW + VEN, low-intensity backbone plus venetoclax; MRD, measurable residual disease; OS, overall survival; SCT, stem cell transplantation.

Supplemental Table 2. Multivariate analysis for overall survival and cumulative incidence of relapse with exclusion of MRD as a factor (censored for SCT)

Covariate	OS		CIR	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Model for all patients				
Age, continuous	1.02 (1.00 - 1.03)	0.029	0.99 (0.98 - 1.01)	0.263
Treatment cohort				
IA	Reference		Reference	
LOW + VEN	1.09 (0.72 - 1.65)	0.681	0.91 (0.58 - 1.44)	0.695
Best response				
CR	Reference		Reference	
CRi	1.67 (1.17 - 2.40)	0.005	2.17 (1.44 - 3.26)	<0.001
MLFS	2.98 (1.79 - 4.96)	<0.001	2.10 (0.91 - 4.84)	0.082
ELN 2017 risk				
Favorable	Reference		Reference	
Intermediate	1.42 (0.94 - 2.13)	0.093	2.07 (1.35 - 3.16)	0.001
Adverse	2.35 (1.62 - 3.42)	<0.001	3.37 (2.24 - 5.09)	<0.001
Model for patients ≥ 60 years				
Age, continuous	1.01 (0.98 - 1.04)	0.355	0.99 (0.96 - 1.03)	0.637
Treatment cohort				
IA	Reference		Reference	
LOW + VEN	1.37 (0.75 - 2.51)	0.302	1.34 (0.66 - 2.71)	0.417
Best response				
CR	Reference		Reference	
CRi	1.72 (1.10 - 2.71)	0.018	2.42 (1.52 - 3.87)	<0.001
MLFS	4.78 (2.58 - 8.87)	<0.001	1.70 (0.62 - 4.67)	0.306
ELN 2017 risk				
Favorable	Reference		Reference	
Intermediate	1.49 (0.81 - 2.73)	0.196	2.44 (1.19 - 5.00)	0.015
Adverse	2.07 (1.26 - 3.41)	0.004	3.24 (1.76 - 5.97)	<0.001

Abbreviations: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; CIR, cumulative incidence of relapse; ELN, European LeukemiaNet; HR, hazard ratio; IA, idarubicin plus intermediate to high-dose cytarabine; LOW + VEN, low-intensity backbone plus venetoclax; MRD, measurable residual disease; MLFS, morphologic leukemia-free state; OS, overall survival; SCT, stem cell transplantation.

Supplemental Table 3. Univariate analysis for overall survival (not censored for SCT)

Variable	events/N (%)	Median (months)	log-rank	HR (95% CI)	p-value
Age, continuous	329/635 (51.8)	28.2	-	1.03 (1.02 - 1.03)	<0.001
Age, categorical			<0.001		
Age < 60 years	167/338 (49.4)	45.1		1.00	-
Age ≥ 60 years	162/297 (54.5)	18.3		1.63 (1.31 - 2.03)	<0.001
Sex			0.867		
Male	168/323 (52.0)	31.1		1.00	-
Female	161/312 (51.6)	27.7		0.98 (0.79 - 1.21)	0.836
Treatment intensity			<0.001		
IA	189/385 (49.1)	45.2		1.00	-
LOW + VEN	140/250 (56.0)	14.0		2.03 (1.62 - 2.55)	<0.001
Best response			<0.001		
CR	252/534 (47.2)	39.2		1.00	-
CRi	58/76 (76.3)	10.9		2.35 (1.76 - 3.13)	<0.001
MLFS	19/25 (76)	7.3		2.78 (1.74 - 4.43)	<0.001
MRD status			<0.001		
Negative	187/426 (43.9)	44.8		1.00	-
Positive	142/209 (67.9)	12.4		2.05 (1.65 - 2.56)	<0.001
ELN 2017 risk			<0.001		
Favorable	62/161 (38.5)	80.9		1.00	-
Intermediate	82/190 (43.2)	56.0		1.23 (0.88 - 1.71)	0.220
Adverse	178/273 (65.2)	13.7		2.43 (1.82 - 3.25)	<0.001
Cytogenetics*					
Diploid	129/307 (42.0)	44.3	-	1.00	-
Other intermediate	42/100 (42.0)	63.5	0.710	0.94 (0.66 - 1.33)	0.710
11q23	20/34 (58.8)	17.0	0.030	1.68 (1.05 - 2.69)	0.032
t(6;9)	1/8 (12.5)	NR	0.056	0.18 (0.03 - 1.30)	0.089
inv(3)	8/10 (80.0)	8.7	0.004	2.76 (1.34 - 5.65)	0.006
-5/5q-	62/76 (81.6)	8.1	<0.001	3.54 (2.59 - 4.83)	<0.001
-7/7q-	56/70 (80.0)	9.5	<0.001	3.07 (2.23 - 4.22)	<0.001
-17/17p-	41/52 (78.8)	8.3	<0.001	3.38 (2.36 - 4.85)	<0.001
Complex	102/136 (75.0)	8.7	<0.001	2.79 (2.14 - 3.62)	<0.001

* Hazard ratios are for individual cytogenetic features compared to diploid as the baseline risk.

Abbreviations: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; ELN, European LeukemiaNet; HR, hazard ratio; IA, idarubicin plus intermediate to high-dose cytarabine; LOW + VEN, low-intensity backbone plus venetoclax; MRD, measurable residual disease; MLFS, morphologic leukemia-free state; NR, not reached; SCT, stem cell transplantation.

Supplemental Table 4. Univariate analysis for cumulative incidence of relapse (not censored for SCT)

Variable	events/N (%)	Median (months)	HR (95% CI)	p-value
Age, continuous	250/635 (39.4)	55.9	1.00 (1.00 - 1.01)	0.410
Age, categorical				
Age < 60 years	140/338 (41.4)	64.2	1.00	-
Age ≥ 60 years	110/297 (37.0)	35.7	1.01 (0.78 - 1.29)	0.960
Sex				
Male	133/323 (41.2)	46.7	1.00	-
Female	117/312 (37.5)	118.6	0.90 (0.70 - 1.15)	0.389
Treatment intensity				
IA	153/385 (39.7)	118.6	1.00	-
LOW + VEN	97/250 (38.8)	26.2	1.21 (0.94 - 1.56)	0.142
Best response				
CR	186/534 (34.8)	118.6	1.00	-
CRi	49/76 (64.5)	7.5	2.55 (1.86 - 3.49)	<0.001
MLFS	15/25 (60.0)	4.5	2.40 (1.29 - 4.47)	0.006
MRD status				
Negative	136/426 (31.9)	118.6	1.00	-
Positive	114/209 (54.5)	9.96	2.25 (1.75 - 2.89)	<0.001
ELN 2017 risk				
Favorable	40/161 (24.8)	NR	1.00	-
Intermediate	71/190 (37.4)	NR	1.79 (1.23 - 2.59)	0.002
Adverse	133/273 (48.7)	17.0	2.77 (1.98 - 3.89)	<0.001
Cytogenetics*				
Diploid	97/307 (31.6)	NR	1.00	-
Other intermediate	36/100 (36.0)	NR	1.12 (0.76 - 1.65)	0.559
11q23	16/34 (47.1)	16.9	1.92 (1.07 - 3.44)	0.030
t(6;9)	3/8 (37.5)	NR	1.04 (0.29 - 3.74)	0.956
inv(3)	8/10 (80.0)	2.9	5.06 (1.89 - 13.56)	0.001
-5/5q-	48/76 (63.2)	7.0	3.25 (2.25 - 4.71)	<0.001
-7/7q-	41/70 (58.6)	8.9	2.71 (1.84 - 3.98)	<0.001
-17/17p-	38/52 (73.1)	6.0	4.24 (2.87 - 6.26)	<0.001
Complex	82/136 (60.3)	7.5	2.82 (2.09 - 3.81)	<0.001

* Hazard ratios are for individual cytogenetic features compared to diploid as the baseline risk.

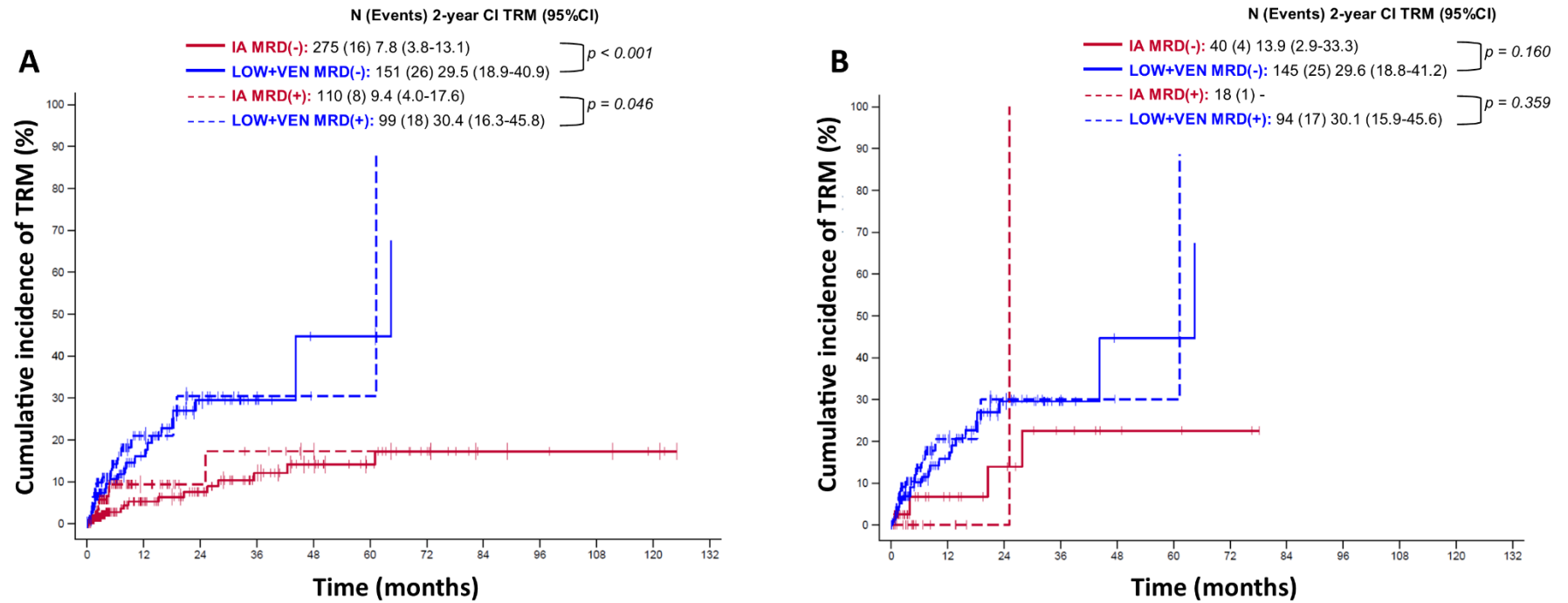
Abbreviations: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; ELN, European LeukemiaNet; HR, hazard ratio; IA, idarubicin plus intermediate to high-dose cytarabine; LOW + VEN, low-intensity backbone plus venetoclax; MRD, measurable residual disease; MLFS, morphologic leukemia-free state; NR, not reached; SCT, stem cell transplantation.

Supplemental Table 5. Multivariate analysis for overall survival and cumulative incidence of relapse (not censored for SCT)

Covariate	OS		CIR	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Model for all patients				
Age, continuous	1.02 (1.00 - 1.03)	0.006	1.00 (0.98 - 1.01)	0.574
Treatment cohort				
IA	Reference		Reference	
LOW + VEN	1.20 (0.86 - 1.66)	0.284	1.01 (0.69 - 1.49)	0.951
Best response				
CR	Reference		Reference	
CRi	1.56 (1.14 - 2.14)	0.005	1.99 (1.42 - 2.80)	<0.001
MLFS	1.99 (1.21 - 3.26)	0.006	1.77 (0.89 - 3.52)	0.106
MRD status				
Negative	Reference		Reference	
Positive	1.41 (1.10 - 1.81)	0.007	1.63 (1.23 - 2.15)	0.001
ELN 2017 risk				
Favorable	Reference		Reference	
Intermediate	1.24 (0.89 - 1.73)	0.208	1.65 (1.13 - 2.41)	0.009
Adverse	1.86 (1.37 - 2.53)	<0.001	2.04 (1.43 - 2.92)	<0.001
Model for patients ≥ 60 years				
Age, continuous	1.03 (1.00 - 1.06)	0.025	1.01 (0.98 - 1.04)	0.575
Treatment cohort				
IA	Reference		Reference	
LOW + VEN	1.43 (0.87 - 2.37)	0.162	1.45 (0.78 - 2.71)	0.240
Best response				
CR	Reference		Reference	
CRi	1.26 (0.81 - 1.96)	0.300	1.75 (1.10 - 2.79)	0.019
MLFS	2.27 (1.23 - 4.17)	0.008	1.14 (0.46 - 2.80)	0.782
MRD status				
Negative	Reference		Reference	
Positive	1.45 (1.01 - 2.08)	0.044	1.77 (1.15 - 2.71)	0.009
ELN 2017 risk				
Favorable	Reference		Reference	
Intermediate	1.27 (0.74 - 2.16)	0.388	1.78 (0.94 - 3.37)	0.076
Adverse	1.83 (1.17 - 2.86)	0.008	2.02 (1.18 - 3.45)	0.010

Abbreviations: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; CIR, cumulative incidence of relapse; ELN, European LeukemiaNet; HR, hazard ratio; IA, idarubicin plus intermediate to high-dose cytarabine; LOW + VEN, low-intensity backbone plus venetoclax; MRD, measurable residual disease; MLFS, morphologic leukemia-free state; OS, overall survival; SCT, stem cell transplantation.

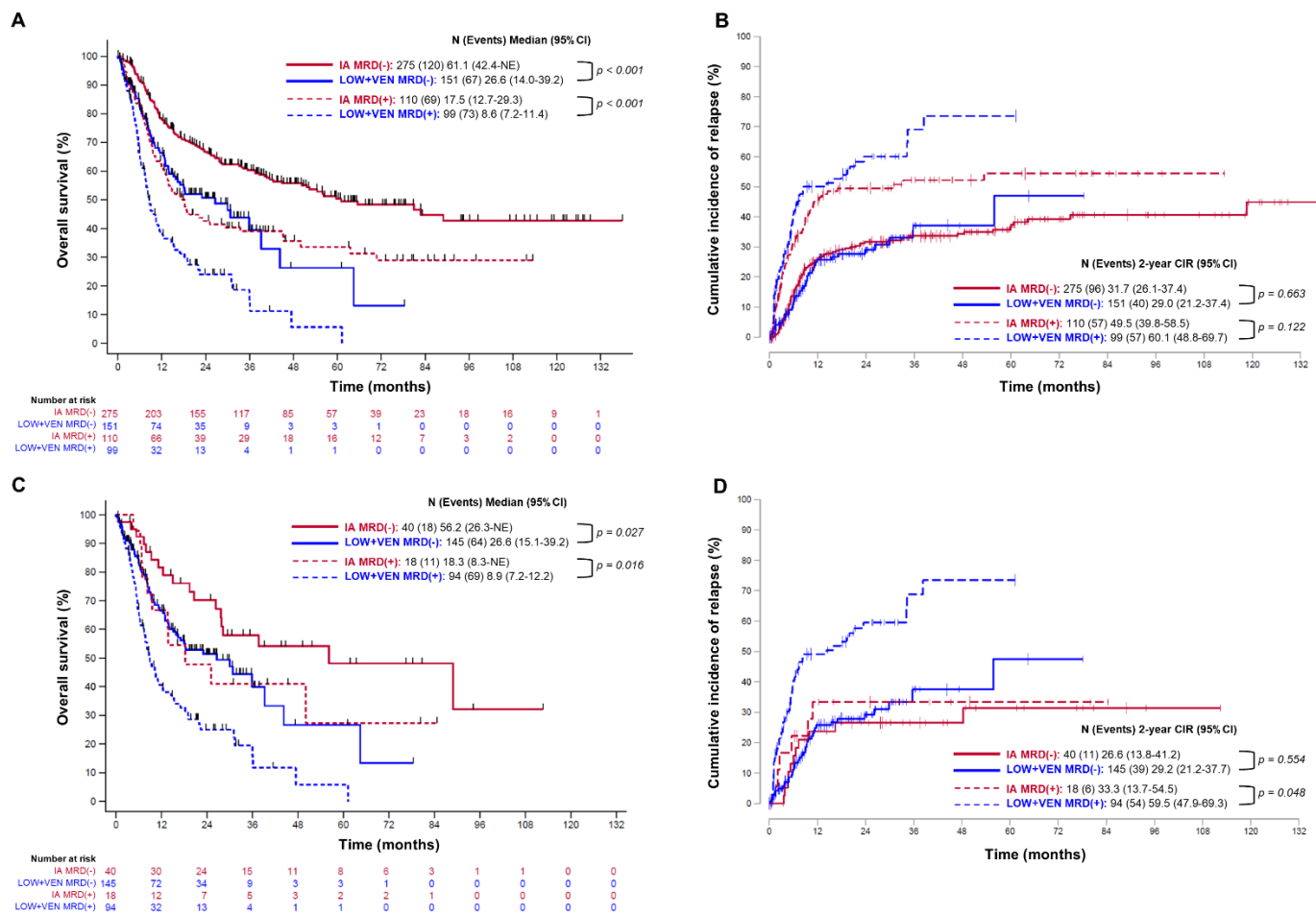
Supplemental Figure 1. Cumulative incidence of treatment-related mortality



(A) CI of TRM stratified by treatment intensity and MRD status, full cohort. (B) CI of TRM stratified by treatment intensity and MRD status, age ≥ 60 years only. Data shown is censored at the time of SCT.

Abbreviations: CI, confidence interval; CI TRM, cumulative of treatment-related mortality; IA, idarubicin plus intermediate to high-dose cytarabine; LOW + VEN, low-intensity backbone plus venetoclax; MRD, measurable residual disease, SCT, stem cell transplantation.

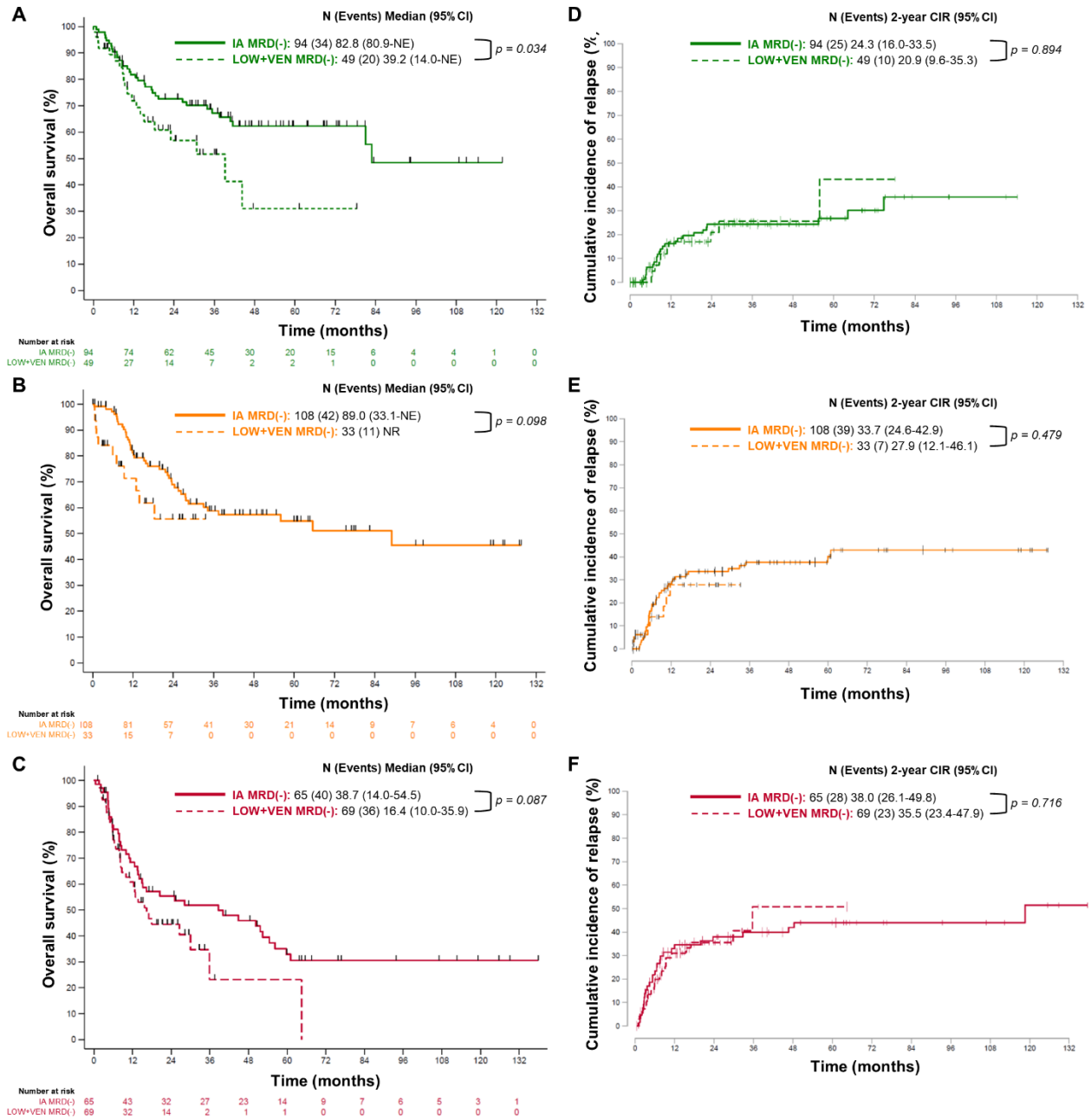
Supplemental Figure 2. Overall survival and cumulative incidence of relapse stratified by treatment intensity and MRD status (not censored for SCT)



(A) OS stratified by treatment intensity and MRD status, full cohort. **(B)** CIR stratified by treatment intensity and MRD status, full cohort. **(C)** OS stratified by treatment intensity and MRD status, age ≥ 60 years only. **(D)** CIR stratified by treatment intensity and MRD status, age ≥ 60 years only.

Abbreviations: CI, confidence interval; CIR, cumulative incidence of relapse; IA, idarubicin plus intermediate to high-dose cytarabine; LOW + VEN, low-intensity backbone plus venetoclax; MRD, measurable residual disease; NE, not estimable; SCT, stem cell transplantation.

Supplemental Figure 3. Overall survival and cumulative incidence of relapse stratified by treatment intensity for patients achieving MRD-negativity within ELN categories (not censored for SCT)



(A) ELN favorable, MRD negative. OS stratified by treatment. (B) ELN intermediate, MRD negative. OS stratified by treatment. (C) ELN adverse, MRD negative. OS stratified by treatment. (D) ELN favorable, MRD negative. CIR stratified by treatment. (E) ELN intermediate, MRD negative. CIR stratified by treatment. (F) ELN adverse, MRD negative. CIR stratified by treatment.

Abbreviations: CI, confidence interval; CIR, cumulative incidence of relapse; IA, idarubicin plus intermediate to high-dose cytarabine; LOW + VEN, low-intensity backbone plus venetoclax; MRD, measurable residual disease; NE, not estimable; NR, not reached; OS, overall survival; SCT, stem cell transplantation.