

SUPPLEMENTAL APPENDIX

Measurable Residual Disease Monitoring in AML With *FLT3*-ITD Treated With Intensive Chemotherapy Plus Midostaurin

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***FLT3*-ITD detection by Next-Generation Sequencing**

Next-generation sequencing: After enrichment for mononuclear cells by Ficoll gradient centrifugation genomic DNA of purified cells was isolated using the AllPrep Mini Kit (Qiagen, Hilden, Germany) according to the manufacturers' instructions. *FLT3* exons 14–15 were amplified by PCR, using 50ng of genomic sample DNA, 20 μ L of 2x KAPA HiFi HotStart ReadyMix (KAPA Biosystems, Wilmington, Massachusetts, USA) and 1.2 μ L of 10 μ M forward and reverse primer (forward primer: 5'-TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGA-3' + 5'-GCAATTTAGGTATGAAAGCCAGCTAC-3', reverse primer: 5'-GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGA-3' + 5'-CTTTCA GCATTTTGACGGCAACC-3', each consisting of *FLT3* locus-specific sequence and the required sequencing adapter). The PCR comprised an initial denaturation step (95°C 3min), 30 amplification cycles (denaturation 98°C 20s, annealing 65°C 30s, elongation 72°C 1min) and a final elongation step (72°C 5min). Amplicons from the first step PCR were purified using Agencourt AMPure XP beads (Beckman Coulter, Fullerton, CA, USA). A second PCR was performed using primers from the Illumina Nextera XT Index Kit for sample multiplexing and the 2x KAPA HiFi HotStart ReadyMix (Kapa Biosystems, Wilmington, MA, USA) with the following thermocycling condition: 95°C for 3 minutes, 8 cycles of 30 second at 95°C (denaturation), 30 seconds at 55°C (annealing), and 30 seconds at 72°C (elongation) and a final extension for 5 minutes at 72°C. The libraries were purified with Agencourt AMPure XP beads (Beckman Coulter, Fullerton, CA, USA). PCR products were prepared for sequencing as detailed in the Illumina 16S Metagenomics Sequencing Protocol (16S Metagenomic Sequencing Library Preparation, Illumina, San Diego, California, USA). The libraries were sequenced with high-coverage on the Illumina MiSeq using 300bp paired-end reads (600-cycles MiSeq Reagent Kit V3, Illumina) and 10% PhiX control spike-in (Kit V3, Illumina; coverage range: 0.806–4.844 million, mean 1.975 million paired-end reads).

Supplemental Table T1. Logistic regression for achievement of *FLT3*-ITD MRD^{neg} after Cy2

	OR (95% CI)	P value
Total <i>FLT3</i>-ITD VAF at diagnosis (log2)	0.46 (0.21-1.03)	.058
Age (10y-increase)	1.43 (0.92-2.22)	.113
Female	0.89 (0.30-2.59)	.824
WBC (log10)	0.31 (0.10-0.92)	.035
BM blasts	1.02 (1.00-1.05)	.098
<i>NPM1</i> mutation	10.45 (3.40-32.07)	<.001
<i>FLT3</i>-ITD high AR (≥0.5)	1.58 (0.39-6.39)	.519
Induction II[§]	0.19 (0.06-0.58)	.004

Abbreviations: ITD, internal tandem duplication; after Cy2, after two cycles intensive chemotherapy; OR, odds ratio; CI, confidence interval; VAF, variant allele frequency; WBC, white blood cell count; BM, bone marrow; AR, allelic ratio determined by Genescan

[§] administered to patients achieved only partial remission after induction I

Supplemental Table T2: Risk of relapse and death on univariate analysis

	CIR		OS	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Age (10y-increase)	1.15 (0.88-1.51)	.312	1.37 (1.07-1.76)	.014
Female	0.47 (0.29-0.84)	.011	0.56 (0.34-0.94)	.028
WBC (log10)	1.13 (0.70-1.85)	.617	0.91 (0.60-1.38)	.669
BM blasts	1.00 (0.95-1.01)	.945	1.00 (0.99-1.01)	.976
<i>NPM1</i> mutation	0.29 (0.16-0.53)	<.001	0.58 (0.34-0.98)	.042
<i>FLT3</i>-ITD high AR (≥ 0.5)	0.88 (0.49-1.57)	.669	1.02 (0.61-1.72)	.932
<i>FLT3</i>-ITD VAF at diagnosis (log2)	0.95 (0.78-1.17)	.646	1.15 (0.92-1.42)	.218
Induction II[§]	1.56 (0.83-2.92)	.169	1.03 (0.57-1.85)	.921
HCT in CR1 (time dependent)	0.28 (0.15-0.50)	<.001	0.60 (0.35-1.04)	.067
<i>FLT3</i>-ITD VAF reduction (log10) after Cy2	0.56 (0.43-0.71)	<.001	0.75 (0.60-0.93)	.010
<i>FLT3</i>-ITD VAF $\geq 0.1\%$	4.78 (2.36-9.76)	<.001	2.14 (1.07-4.30)	.032
<i>FLT3</i>-ITD MR^{3.0} after Cy2	0.31 (0.16-0.62)	<.001	0.58 (0.30-1.10)	.097
<i>FLT3</i>-ITD MRD^{neg} after Cy2	0.33 (0.17-0.64)	.001	0.47 (0.26-0.85)	.012
<i>NPM1</i> MRD^{neg} after Cy2 (PB)	0.27 (0.08-1.00)	.050	0.72 (0.33-1.58)	.416

Abbreviations: CIR, cumulative incidence of relapse; OS, overall survival; HR, hazard ratio; CI, confidence interval; WBC, white blood cell count; BM, bone marrow; ITD, internal tandem duplication; AR, allelic ratio determined by Genescan; VAF, variant allele frequency; HCT in CR1, allogeneic hematopoietic cell transplantation in first complete remission; after Cy2, after two cycles of intensive chemotherapy; MR^{4.0}, ≥ 4.0 -log₁₀ reduction of VAF; MRD, measurable residual disease; PB, peripheral blood

[§] administered to patients achieved only partial remission after induction I

Supplemental Table T3: Multivariable analyses determining the prognostic significance of *FLT3*-ITD MRD log₁₀ reduction, *FLT3*-ITD VAF <0.1%, and *FLT3*-ITD MR^{3.0} after Cy2

	CIR		OS	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
<i>FLT3</i>-ITD MRD log₁₀ reduction				
Age (10y-increase)	0.95 (0.70-1.29)	.739	1.39 (1.04-1.86)	.028
Female	0.57 (0.28-1.16)	.119	0.62 (0.35-1.18)	.112
WBC (log10)	1.05 (0.57-1.91)	.884	0.62 (0.36-1.06)	.080
BM blasts	1.01 (0.99-1.03)	.178	1.01 (0.99-1.03)	.229
<i>NPM1</i> mutation	0.23 (0.10-0.50)	<.001	0.75 (0.39-1.45)	.386
<i>FLT3</i> -ITD high AR (≥0.5)	1.00 (0.48-2.10)	.994	1.12 (0.59-2.11)	.730
HCT in CR1 (time dependent)	0.10 (0.05-0.24)	<.001	0.68 (0.37-1.25)	.211
<i>FLT3</i> -ITD MRD log ₁₀ reduction	0.53 (0.39-0.72)	<.001	0.72 (0.55-0.94)	.014
<i>FLT3</i>-ITD VAF <0.1%				
Age (10y-increase)	0.84 (0.62-1.17)	.255	1.33 (1.01-1.77)	.047
Female	0.52 (0.26-1.07)	.076	0.59 (0.33-1.06)	.080
WBC (log10)	0.91 (0.47-1.75)	.775	0.61 (0.35-1.07)	.082
BM blasts	1.02 (1.00-1.04)	.087	1.01 (1.00-1.03)	.187
<i>NPM1</i> mutation	0.21 (0.09-0.47)	<.001	0.69 (0.36-1.32)	.263
<i>FLT3</i> -ITD high AR (≥0.5)	0.88 (0.42-1.85)	.743	1.02 (0.54-1.91)	.960
HCT in CR1 (time dependent)	0.11 (0.05-0.25)	<.001	0.68 (0.36-1.26)	.222
<i>FLT3</i> -ITD VAF <0.1%	0.16 (0.06-0.38)	<.001	0.38 (0.17-0.87)	.021

Achievement of MR ^{3.0}				
Age (10y-increase)	0.84 (0.62-1.14)	.262	1.30 (0.98-1.73)	.073
Female	0.51 (0.25-1.02)	.058	0.60 (0.34-1.07)	.084
WBC (log10)	1.24 (0.67-2.31)	.499	0.69 (0.41-1.08)	.179
BM blasts	1.02 (0.99-1.04)	.169	1.01 (0.99-1.03)	.236
<i>NPM1</i> mutation	0.23 (0.10-0.49)	<.001	0.67 (0.35-1.29)	.226
<i>FLT3</i>-ITD high AR (≥0.5)	0.85 (0.40-1.82)	.680	1.02 (0.53-1.94)	.960
HCT in CR1 (time dependent)	0.11 (0.05-0.25)	<.001	0.64 (0.34-1.20)	.164
<i>FLT3</i>-ITD MR^{3.0} after Cy2	0.27 (0.11-0.62)	.002	0.57 (0.27-1.20)	.137

Abbreviations: CIR, cumulative incidence of relapse; OS, overall survival; HR, hazard ratio; CI, confidence interval; WBC, white blood cell count; BM, bone marrow; ITD, internal tandem duplication; AR, allelic ratio determined by Genescan; HCT in CR1, allogeneic hematopoietic cell transplantation in first complete remission; MR^{3.0}, ≥3.0- \log_{10} reduction of variant allele frequency; after Cy2, after two cycles of intensive chemotherapy

Supplemental Table T4: Multivariable analysis on relapse-free survival determining the prognostic significances of *FLT3*-ITD MRD and *NPM1*^{mut} MRD interaction status after Cy2

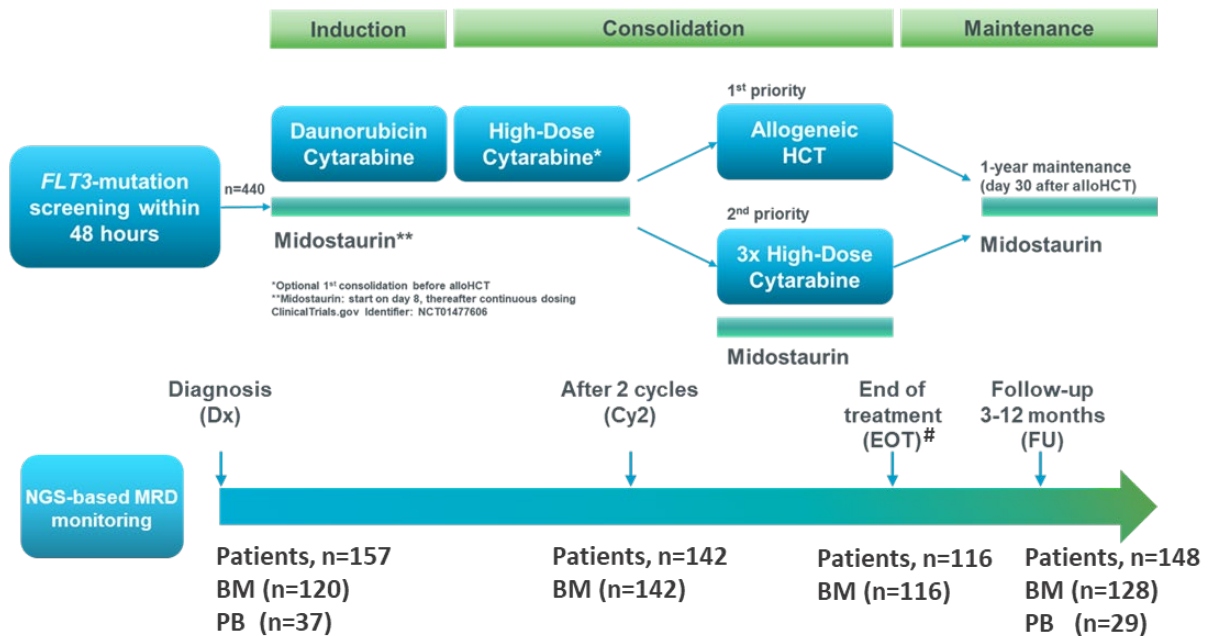
	RFS	
	HR (95% CI)	<i>P</i>
Age (10y-increase)	1.56 (0.97-2.51)	.069
Female	0.51 (0.22-1.17)	.111
WBC (log10)	0.50 (0.23-1.07)	.074
BM blasts	1.01 (0.99-1.03)	.384
<i>FLT3</i> -ITD ^{high}	1.08 (0.44-2.65)	.867
HCT in CR1 [§]	0.46 (0.18-1.16)	.099
<i>FLT3</i> -ITD MRD ^{neg} / <i>NPM1</i> ^{mut} MRD ^{neg}	1	
<i>FLT3</i> -ITD MRD ^{neg} / <i>NPM1</i> ^{mut} MRD ^{pos}	1.52 (0.59-3.96)	.388
<i>FLT3</i> -ITD MRD ^{pos} / <i>NPM1</i> ^{mut} MRD ^{pos}	7.89 (2.34-26.58)	<.001

Abbreviations: RFS, relapse-free survival; HR, hazard ratio; CI, confidence interval; WBC, white blood cell count; BM, bone marrow; mut, mutated; *FLT3*-ITD^{high}, *FLT3*-internal tandem duplication with allelic ratio ≥ 0.5 ; HCT in CR, allogeneic hematopoietic cell transplantation in first complete remission; MRD, measurable residual disease; neg, negative; mut, mutated

[§]as time dependent variable

Supplemental Figure F1

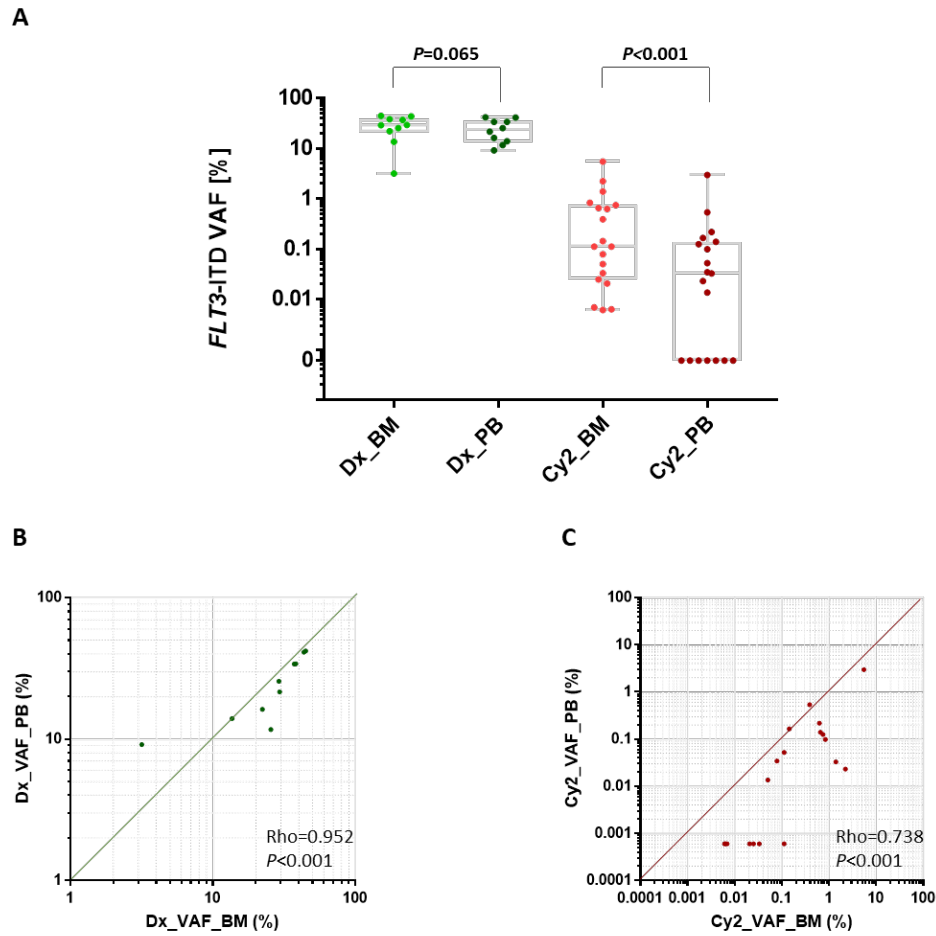
***FLT3*-ITD MRD assessment at defined time-points.** AMLSG 16-10 study design and time-points for *FLT3*-ITD MRD assessment.



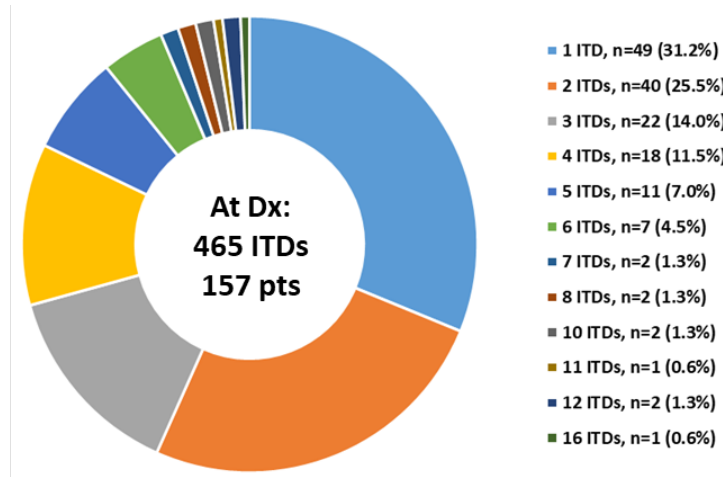
EOT was defined as response assessment on day 35 to 42 after last consolidation cycle or HCT (for HCT median day +34).

Supplemental Figure F2

Paired BM and PB Analysis at diagnosis and after Cy 2. (A) Comparison of total ITD VAF at diagnosis and after Cy2 in BM and PB, respectively. Correlation of *FLT3*-ITD VAF assessed in BM and PB at diagnosis (B) and after Cy2 (C).



	Dx (n=10)		Cy2 (n=19)	
	BM	PB	BM	PB
MRDpos, n (%)	10 (100)	10 (100)	19 (100)	12 (63)
Median <i>FLT3</i> -ITD VAF [%], range	29.24 (3.16-44.73)	23.59 (9.15-42.01)	0.112 (0.006-5.476)	0.033 (0.0-2.969)
Median Log_{10} difference PB/BM (range)	0.04 (-0.46-0.34)		0.9 (-0.14-2.27)	

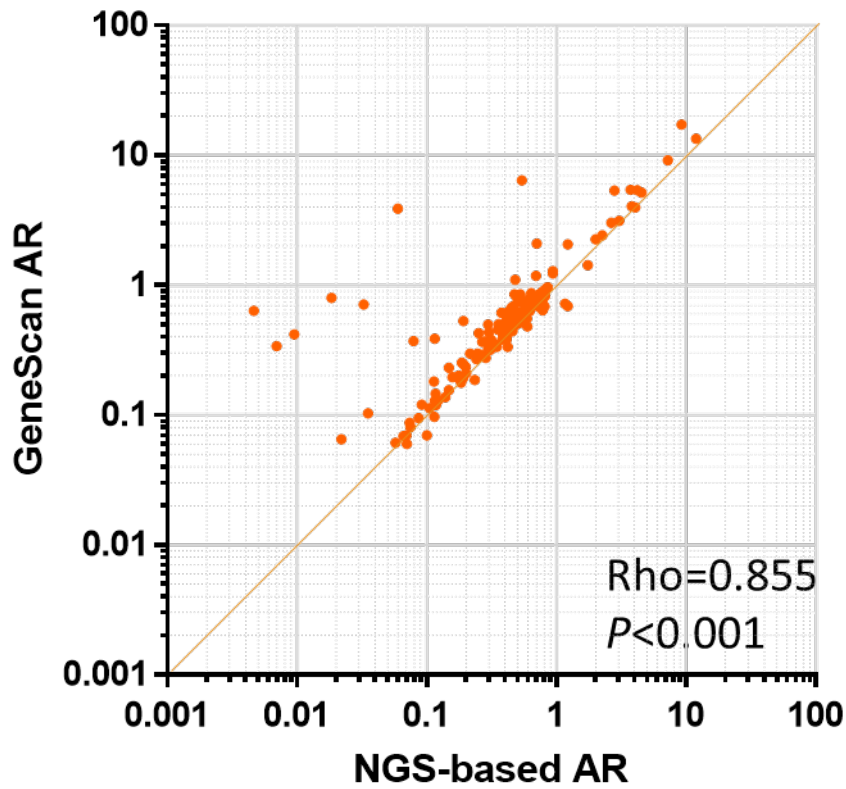
Supplemental Figure F3**Molecular characterization of the 465 ITDs identified in 157 *FLT3*-ITD^{pos} AML at diagnosis.***FLT3*-ITD characteristics at diagnosis

Median number of ITDs, n (range)	2 (1-16)
>1 ITD, n (%)	108 (69)
Median length, nt (range)	51 (9-285)
Median Variant allele frequency (VAF), % (range)	0.312 (0.006-92.256)
Median total VAF per pt*, % (range)	31.543 (0.461-92.256)
Median calculated allelic ratio (AR) per pt*, % (range)	0.461 (0.005-11.913)

*Total *FLT3*-ITD VAF/AR calculated over all ITDs per pt

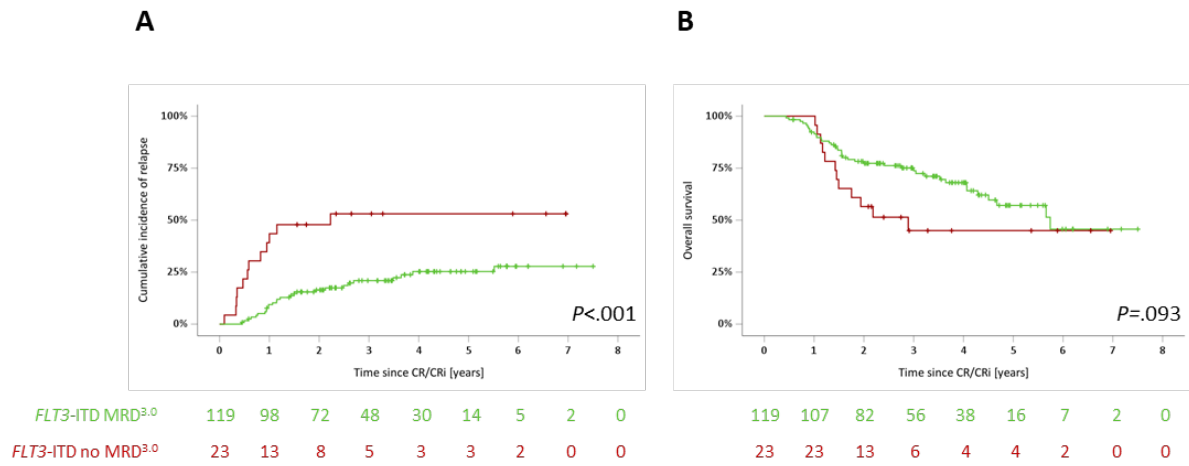
Supplemental Figure F4

Correlation of *FLT3*-ITD allelic ratio at diagnosis. Correlation of NGS-based allelic ratio (AR) per patient, calculated as $\sum \text{VAF}/(100-\sum \text{VAF})$, with AR determined by Genescan.



Supplemental Figure F5:

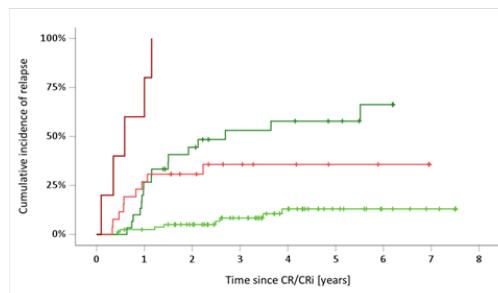
Outcome according to *FLT3*-ITD MR^{3.0}. Cumulative Incidence of relapse (A) and Overall Survival (B) according to achievement of *FLT3*-ITD MR^{3.0} after Cy2.



Supplemental Figure F6:

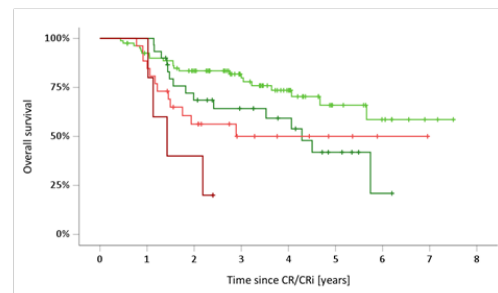
Outcome according to *FLT3*-ITD MRD status after Cy2 and post-remission therapy (conventional consolidation vs HCT in CR1). Cumulative Incidence of relapse (A) and Overall Survival (B) according to various *FLT3*-ITD MRD status after Cy2 and post-remission therapy. Results of pairwise comparisons are provided below the x-axis.

A



<i>FLT3</i> -ITD MRD ^{neg} /HCT_CR1	81	72	57	39	23	11	5	2	0
<i>FLT3</i> -ITD MRD ^{neg} /no HCT_CR1	30	22	13	8	5	4	1	0	0
<i>FLT3</i> -ITD MRD ^{pos} /HCT_CR1	26	16	10	6	4	2	1	0	0
<i>FLT3</i> -ITD MRD ^{pos} /no HCT_CR1	5	1	0	0	0	0	0	0	0

B



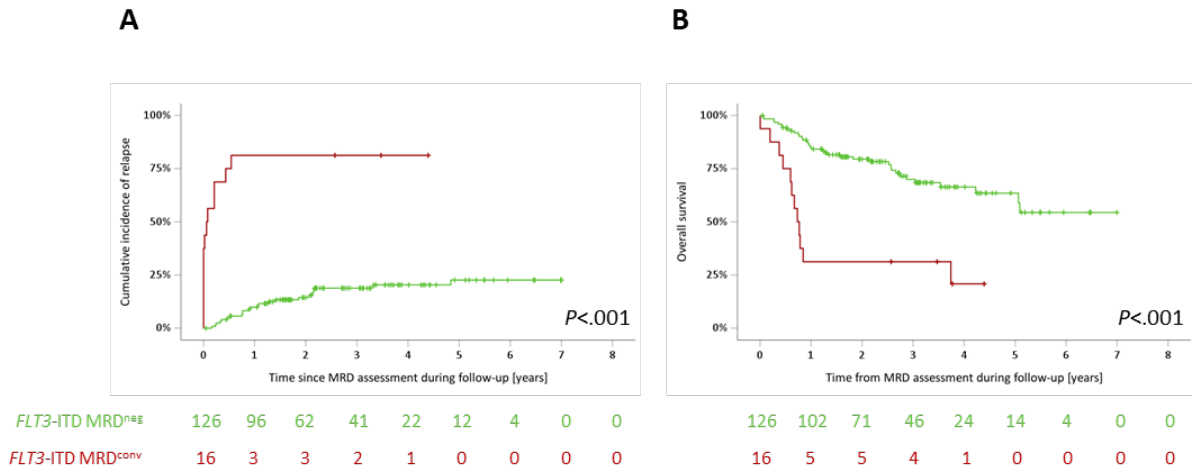
<i>FLT3</i> -ITD MRD ^{neg} /HCT_CR1	81	72	61	41	26	12	7	2	0
<i>FLT3</i> -ITD MRD ^{neg} /no HCT_CR1	30	30	19	14	11	5	1	0	0
<i>FLT3</i> -ITD MRD ^{pos} /HCT_CR1	26	23	13	7	5	3	1	0	0
<i>FLT3</i> -ITD MRD ^{pos} /no HCT_CR1	5	5	2	0	0	0	0	0	0

<i>FLT3</i> -ITD	MRD ^{neg} / no HCT_CR1	MRD ^{pos} / HCT_CR1	MRD ^{pos} / no HCT_CR1
MRD ^{neg} /HCT_CR1	<0.001	0.001	<0.001
MRD ^{neg} /no HCT_CR1	-	0.231	<0.001
MRD ^{pos} /HCT_CR1	0.231	-	0.001
MRD ^{pos} /no HCT_CR1	<0.001	0.001	-

MRD ^{neg} / no HCT_CR1	MRD ^{pos} / HCT_CR1	MRD ^{pos} / no HCT_CR1
0.042	0.027	<0.001
-	0.716	0.011
0.716	-	0.183
0.011	0.183	-

Supplemental Figure F7:

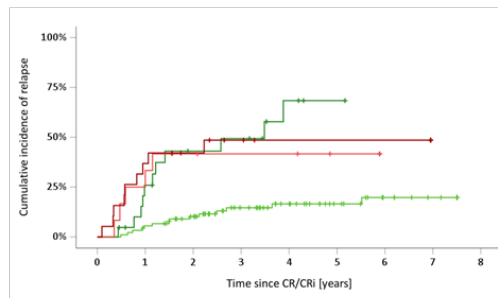
Outcome according to *FLT3*-ITD MRD status during follow up. Cumulative incidence of relapse (A) and Overall survival (B). MRD^{neg}, MRD negative; MRD^{conv}, MRD conversion (MRD^{neg} to MRD^{pos})



Supplementary Figure F8:

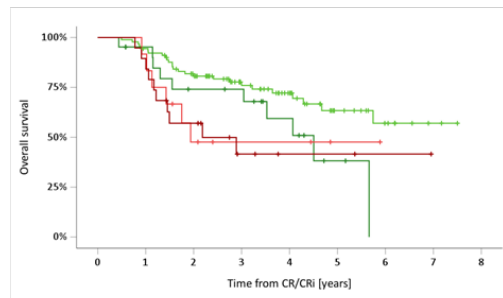
Outcome according to *FLT3*-ITD MRD status and concurrent *NPM1* mutation (*NPM1*^{mut}) status after Cy2. Cumulative Incidence of relapse (A) and Overall Survival (B). Results of pairwise comparisons are provided below the x-axis.

A



<i>FLT3</i> -ITD MRD ^{neg} / <i>NPM1</i> ^{mut}	90	80	61	39	26	14	6	2	0
<i>FLT3</i> -ITD MRD ^{neg} / <i>NPM1</i> ^{WT}	21	14	9	8	3	1	0	0	0
<i>FLT3</i> -ITD MRD ^{pos} / <i>NPM1</i> ^{mut}	12	7	4	3	3	1	0	0	0
<i>FLT3</i> -ITD MRD ^{pos} / <i>NPM1</i> ^{WT}	19	10	6	3	1	1	1	0	0

B



<i>FLT3</i> -ITD MRD ^{neg} / <i>NPM1</i> ^{mut}	90	84	67	43	30	15	8	2	0
<i>FLT3</i> -ITD MRD ^{neg} / <i>NPM1</i> ^{WT}	21	18	13	12	7	2	0	0	0
<i>FLT3</i> -ITD MRD ^{pos} / <i>NPM1</i> ^{mut}	12	11	5	3	3	1	0	0	0
<i>FLT3</i> -ITD MRD ^{pos} / <i>NPM1</i> ^{WT}	19	17	10	4	2	2	1	0	0

<i>FLT3</i> -ITD	MRD ^{neg} / <i>NPM1</i> ^{WT}	MRD ^{pos} / <i>NPM1</i> ^{mut}	MRD ^{pos} / <i>NPM1</i> ^{WT}
MRD ^{neg} / <i>NPM1</i> ^{mut}	<0.001	0.010	<0.001
MRD ^{neg} / <i>NPM1</i> ^{WT}	-	0.560	0.959
MRD ^{pos} / <i>NPM1</i> ^{mut}	0.560	-	0.725
MRD ^{pos} / <i>NPM1</i> ^{WT}	0.959	0.725	-

MRD ^{neg} / <i>NPM1</i> ^{WT}	MRD ^{pos} / <i>NPM1</i> ^{mut}	MRD ^{pos} / <i>NPM1</i> ^{WT}
0.071	0.072	0.008
-	0.798	0.441
0.798	-	0.904
0.441	0.904	-