Outcomes after intensive chemotherapy for secondary and myeloid-related changes acute myeloid leukemia patients aged 60 to 75 years old: a retrospective analysis from the PETHEMA registry

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Supplemental material

Supplemental Table 1. Different schedules grouped by therapeutic approach in all patients.

Therapeutic approach	Schedule	Number of patients (n=765)	Dose
"3+7"	IDA + Ara-C (3+7)	374	IDA (10-12 mg/m^2/day), days 1 to 3 + Ara-C (100-200 mg/m^2/day), days 1 to 7
	DNR + Ara-C (3+7)	15	DNR (60 mg/m^2/day), days 1 to 3 + Ara-C (200 mg/m^2/day), days 1 to7
Other intensive therapy	IDA + Ara-C (2+5)	94	IDA (10-12 mg/m^2/day), days 1 to 2 + Ara-C (100-200 mg/m^2/day), days 1 to 5
	FLAG-IDA (FLU + Ara-C + IDA)	101	FLU (30 mg/m^2/day), days 1 to 4 + IDA (10 mg/m^2/day), days 1 to 3 + Ara-C (2000 mg/m^2/day), days 1 to 4 + G-CSF (300 µg/ m^2/day), days -1 to 5
	ICE (IDA + Ara-C + etoposide)	26	IDA (10-12 mg/m^2/day), days 1, 3 and 5 + Ara-C (500 mg/m^2/12h), days 1, 3, 5 y 7 + Etoposide 100 mg/m^2/day, days 1 to 3
	IDA + Ara-C (LMA 98 >65)	62	IDA (8 mg/m^2/day), days 1 to 3 + Ara-C (100 mg/m^2/day), days 1 to 7
	MTZ + intermediate Ara-C	29	MTZ (10mg/m^2), days 1 to 3 + Ara-C (150 mg/m^2), days 1 to 7
	Other intensive chemotherapy	64	Other not previously included schedules

Ara-C: cytarabine; IDA: idarubicin; DNR: daunorubicin; FLU: fludarabine; G-CSF: Granulocyte-Colony Stimulating Factor; HSCT: hematopoietic stem cell transplantation; MTZ: mitoxantrone.

Supplemental Table 2. Other demographic and baseline characteristics of the study population ("3+7" vs Other intensive therapy)

Characteristic	Overall		"3+7"		Other intensive therapy		*P value*
	Median (IQR)	n (%)	Median (IQR)	n (%)	Median (IQR)	n (%)	
Total		765 (100)		389 (100)		376 (100)	
FAB subtype		765 (100)		389 (100)		376 (100)	
M0/M6/M7		113 (15)		51 (13)		62 (16)	0.04
M1/M2		224 (29)		103 (26)		121 (32)	
M4/M5		173 (23)		102 (26)		71 (19)	
Not available		255 (33)		133 (34)		122 (32)	
Hemoglobin, g/dl	9 (7.8-10.4)	660 (100)	9 (7.6-10.4)	331 (100)	9.1 (7.9-17.2)	329 (100)	0.23*
Platelet count, $\times 10^9$/l	54.2 (26-101)	664 (100)	55 (25-107)	332 (100)	53.5 (26-97.5)	332 (100)	0.53*
BM blasts, %	48 (31-70)	631 (100)	48 (32-72)	317 (100)	48 (30-65)	314 (100)	0.50*
Creatinine, mg/dl	0.9 (0.7-1.1)	531 (100)	0.9 (0.7-1.1)	278 (100)	0.9 (0.8-1.1)	253 (100)	0.07*
Urea, mg/dl	36 (27-45)	476 (100)	37 (30-47)	251 (100)	34 (25-44)	225 (100)	0.02*
Uric acid, mg/dL	4.8 (3.5-6.6)	469 (100)	5.1 (3.7-6.7)	249 (100)	4.6 (3.5-6.1)	220 (100)	0.07*
Bilirubin, mg/dL	0.64 (0.45-0.92)	493 (100)	0.61 (0.42-0.9)	258 (100)	0.65 (0.46-0.97)	235 (100)	0.39*
Albumin, g/dl	3.7 (3.2-4.1)	441 (100)	3.7 (3.3-4.1)	220 (100)	3.6 (3.2-4.0)	221 (100)	0.47*
LDH, U/l	440 (262-730)	532 (100)	453 (282-756)	273 (100)	430 (250-714)	259 (100)	0.40*
Fibrinogen, mg/dl	414 (320-530)	441 (100)	420 (327-528)	221 (100)	409 (312-534)	220 (100)	0.86*
Cytogenetics		759 (100)		384 (100)		375 (100)	
Normal		174 (23)		96 (25)		78 (21)	0.34
Abnormal		483 (64)		243 (63)		240 (64)	
No metaphases		34 (4)		14 (4)		156 (7)	

Characteristic	Overall		"3+7"		Other intensive therapy		*P value*
	Median (IQR)	**n (%)**	**Median (IQR)**	**n (%)**	**Median (IQR)**	**n (%)**	
Not available		68 (9)		31 (8)		37 (10)	

IQR: interquartile range; FAB: French - American – British; BM: Bone Marrow; LDH: Lactate dehydrogenase; * *P* compare continuous variables.

Supplemental Table 3. Induction response and OS according to other baseline characteristics.

	Induction response, n (%)				OS					
Variable	**CR/CRi**	**PR/RES**	**Induction death**	***P***	**N (%)**	**Median (95%, CI)**	**At 1 year (95%, CI)**	**At 3 years (95%, CI)**	**At 5 years (95%, CI)**	***P***
Platelets count, ×10^9/l					664 (100)					
≤20	53 (43)	47 (39)	22 (18)	0.18	123 (26)	6.5 (5.1-8.6)	23.5 (16.8-32.8)	10.6 (6-19)	4.7 (1.7-12.96)	0.01
> 20	267 (50)	205 (38)	65 (12)		541 (74)	7.7 (6.6-9.2)	37.7 (33.7-42.2)	14.5 (11.6-18.2)	8.8 (6.3-12.2)	
Creatinine, mg/dl					531 (100)					
≤1.3	227 (51)	166 (37)	56 (12)	0.04	451 (68)	8.6 (7-10)	38.5 (34.1-43.4)	14.8 (11.6-18.9)	8.4 (5.7-12.4)	0.001
>1.3	32 (41)	28 (36)	18 (23)		80 (32)	5.1 (3.4-7.2)	22.3 (14.4-34.5)	7.4 (3.2-17.2)	5.6 (2-15.3)	
Uric acid, mg/dl					469 (100)					
≤7	207 (54)	134 (35)	42 (11)	0.003	385 (82)	8.9 (7.7-10.7)	40.8 (36.1-46.3)	16.4 (12.8-21.1)	8.6 (5.6-13)	0.001
>7	28 (34)	40 (48)	15 (18)		84 (18)	5.1 (3.1-7)	21.8 (14.2-33.5)	8.2 (3.8-17.6)	6.8 (2.9-15.8)	
Albumin, g/dl					441 (100)					
≤3.5	83 (44)	67 (35)	39 (21)	<0.001	190 (43)	6 (4.6-7.8)	28.6 (22.7-36.1)	11 (7.1-17)	6.2 (3.3-11.8)	0.003
>3.5	135 (54)	96 (39)	17 (7)		251 (57)	9.2 (7.6-11.4)	41.2 (35.3-48.1)	14.2 (10-20.2)	8.6 (5-14.9)	
BM blast cells, %					631 (100)					
≤30	87 (56)	46 30)	21 (14)	0.09	156 (25)	8.9 (8.1-11.7)	40.2 (32.9-49.2)	15.7 (10.3-23.8)	10.9 (6.2-19)	0.04

30-70	144 (45)	138 (43)	41 (13)		327 (52)	7.1 (6.3-9.3)	33.7 (28.9-39.4)	11 (7.9-15.4)	6.4 (3.8-10.5)	
>70	69 (47)	56 (38)	22 (15)		148 (23)	4.7 (3.4-6.9)	29.5 (22.8-38.2)	14.9 (9.8-22.8)	7.7 (4-14.8)	

BM: Bome marrow; CI: Confidence Interval; CR: Complete Remission; CRi: CR with incomplete recovery; OS: Overall Survival; PR: partial remission; RES: Resistance.

Supplemental Table 4. Consolidation schedules in patients achieved CR/CRi after one cycle of induction.

Schedule	Number of patients				Dose
	C1 (n=259)	C2 (n=134)	C3 (n=16)	C4 (n=2)	
IDA + Ara-C (3+7)	122	-	-	-	IDA (10-12 mg/m^2/day), days 1 to 3 + Ara-C (100-200 mg/m^2/day), days 1 to 7
DNR + Ara-C (3+7)	6	11	-	-	DNR (60 mg/m^2/day), days 1 to 3 + Ara-C (200 mg/m^2/day), days 1 to7
High dose Ara-C	21	42	9	-	Ara-C (3000 mg/m^2/12h), days 1, 3, 5
Intermediate Ara-C	9	14	4	-	Ara-C (1000-2000 mg/m^2/day, days 1 to 3
	15	15	-	-	Ara-C (100 mg/m^2/day), days 1 to 5 +/- GO (3 mg/m^2/day, day 1
IDA + Ara-C (2+5)	15	-	-	-	IDA (10-12 mg/m^2/day), days 1 to 2 + Ara-C (100-200 mg/m^2/day), days 1 to 5
FLAG-IDA (FLU + Ara-C + IDA)	13	-	-	-	FLU (30 mg/m^2/day), days 1 to 4 + IDA (10 mg/m^2/day), days 1 to 3 + Ara-C (2000 mg/m^2/day), days 1 to 4 + G-CSF (300 µg/ m^2/day), days -1 to 5
IDA + Ara-C (LMA 98 >65)	14	-	-	-	IDA (8 mg/m^2/day), days 1 to 3 + Ara-C (100 mg/m^2/day), days 1 to 7
DA + Ara-C (LMA 98 >65)	-	6	-	-	DA (45 mg/m^2/day), days 5 to 7 + Ara-C (500 mg/m^2/12h), days 1 to 4
MTZ + intermediate Ara-C	18	18	-	-	MTZ (10mg/m^2), days 1 to 3 + Ara-C (150 mg/m^2), days 1 to 7
Carboplatin	-	13	-	-	CBDCA (300 mg/m^2/day), days 1 to 5
Other intensive chemotherapy	21	9	1	2	Other not previously included schedules
Not available	5	6	2	-	Schedule unknown, but intensive

Ara-C: cytarabine; IDA: idarubicin; CBDCA: carboplatin; C1: first consolidation; C2: second consolidation; C3: third consolidation; C4: fourth consolidation; DNR: daunorubicin; FLU: fludarabine; G-CSF: Granulocyte-Colony Stimulating Factor; HSCT: hematopoietic stem cell transplantation; MTZ: mitoxantrone.

Supplemental Table 5. Second induction and consolidation schedules in patients failed to achieve CR/CRi after one cycle of induction.

Schedule	Number of patients						Dose
	I2 (n=43)*	I2 (n=24)#	C1 (n=22)	C2 (n=8)	C3 (n=1)	C4 (n=1)	
IDA + Ara-C (3+7)	26	8	4	-	-	-	IDA (10-12 mg/m^2/day), days 1 to 3 + Ara-C (100-200 mg/m^2/day), days 1 to 7
DNR + Ara-C (3+7)	1	1	-	-	-	-	DNR (60 mg/m^2/day), days 1 to 3 + Ara-C (200 mg/m^2/day), days 1 to7
High dose Ara-C	-	-	7	3	-	-	Ara-C (3000 mg/m^2/12h), days 1, 3, 5
Intermediate Ara-C	1	-	2	-	-	-	Ara-C (1000-2000 mg/m^2/day, days 1 to 3
IDA + Ara-C (2+5)	1	2	-	-	-	-	IDA (10-12 mg/m^2/day), days 1 to 2 + Ara-C (100-200 mg/m^2/day), days 1 to 5
FLAG-IDA (FLU + Ara-C + IDA)	2	2	-	1	-	-	FLU (30 mg/m^2/day), days 1 to 4 + IDA (10 mg/m^2/day), days 1 to 3 + Ara-C (2000 mg/m^2/day), days 1 to 4 + G-CSF (300 µg/ m^2/day), days -1 to 5
IDA + Ara-C (LMA 98 >65)	1	6	1	-	-	-	IDA (8 mg/m^2/day), days 1 to 3 + Ara-C (100 mg/m^2/day), days 1 to 7
MTZ + intermediate Ara-C	2	1	2	-	-	-	MTZ (10mg/m^2), days 1 to 3 + Ara-C (150 mg/m^2), days 1 to 7
Other intensive chemotherapy	8	4	5	4	1	1	Other not previously included schedules
Not available	1	-	1	-	-	-	Schedule unknown, but intensive

*Patients in partial remission after first cycle of induction; #Patients in resistance after first cycle of induction; Ara-C: cytarabine; CBDCA: carboplatin; C1: first consolidation; C2: second consolidation; C3: third consolidation; C4: fourth consolidation; DNR: daunorubicin; FLU: fludarabine; G-CSF: Granulocyte-Colony Stimulating Factor; HSCT: hematopoietic stem cell transplantation; IDA: idarubicin; I2: second induction; MTZ: mitoxantrone.

Supplemental Table 6. Multivariate analysis for overall survival in the overall cohort.

Characteristic	Hazard ratio (CI95)	*P*
Age, years		
≥70	1.29 (1.07-1.55)	0.007
ECOG		
1	1.22 (1.0031-1.48)	0.046
2	1.39 (1.08-1.8)	0.01
3	2.56 (1.66-3.94)	<0.001
4	4.75 (1.75-12.91)	0.002
WBC, $\times 10^9$/L	1.002 (1.0001-1.0043)	0.04
MRC Cytogenetic risk		
Intermediate	0.8 (0.67-0.96)	0.016
***NPM1* mutation present**	0.52 (0.33-0.84)	0.007

ECOG: Eastern Cooperative Oncology Group WBC: White Blood Cells; MRC: Medical Research Council; NPM1: Nucleophosmin1.

Supplemental Table 7. Induction response, HSCT rates, OS and EFS according to therapeutic group in patients included in the CPX-351-like cohort with ECOG PS 0-2, serum creatinine < 2.0 mg/dL and serum total bilirubin < 2.0 mg/dL.

Variable	Overall N (%)	3+7 N (%)	Other N (%)	*P*
All patients	367 (100)	181 (100)	186 (100)	
ORR (CR + CRi)	187 (51)	97 (57)	90 (48)	0.79
CR + CRi after first induction	174 (47)	89 (49)	85 (46)	
CR + CRi after second induction	13 (4)	8 (4)	5 (3)	
PR	29 (8)	14 (8)	15 (8)	
Resistance	110 (30)	50 (28)	60 (32)	
Death	41 (11)	20 (11)	21 (11)	
HSCT in first CR/CRi, n (%)	184 (100)	94 (100)	90 (100)	
Allogeneic HSCT rate, n (%)	45 (24)	27 (29)	18 (20)	0.3
Autologous HSCT rate, n (%)	12 (7)	7 (7)	5 (6)	
No HSCT, n (%)	127 (69)	60 (64)	67 (74)	
OS, n (%)	368 (100)	182 (100)	186 (100)	
Median (CI95), months	7.7 (6.6-9.1)	8.1 (6.5-10.3)	7.7 (6.1-9.3)	0.45
1 year (CI95), %	35.2 (30.6-40.6)	34.5 (28.1-42.5)	35.8 (29.4-43.5)	
3 years (CI95), %	14.1 (10.7-18.5)	16.8 (11.8-24)	11.8 (7.8-18)	
5 years (CI95), %	8.5 (5.6-12.7)	11.3 (6.8-18.8)	6.2 (3.2-11.9)	
EFS, n (%)	360 (100)[#]	176 (100)[#]	184(100)[#]	
Median (CI95), months	2.8 (2-3.9)	3.3 (2.1-4.8)	2.3 (1.6-4.3)	0.72
1 year (CI95), %	22.2 (18.2-27)	21.1 (15.7-28.3)	23.1 (17.7-30.2)	
3 years (CI95), %	10.7 (7.8-14.6)	12.8 (8.5-19.3)	8.9 (5.4-14.4)	
5 years (CI95), %	7 (4.5-10.8)	7.1 (3.8-13.4)	7.1 (4-12.7)	

CR: Complete Remission; CRi: CR with incomplete recovery; HSCT: hematopoietic stem cell transplantation; Non-IC: Non-intensive chemotherapy; EoT: End of treatment; ; Non-IC: Non-intensive chemotherapy; HSCT: hematopoietic stem cell transplantation; NA: not applicable; OS: Overall Survival; CI: Confidence Interval; EFS: Event-Free Survival; [#]patients with available data for EFS analysis.

Supplemental Table 8. Demographic and baseline characteristics of the study population (Allogeneic HSCT vs Autologous HSCT vs no HSCT).

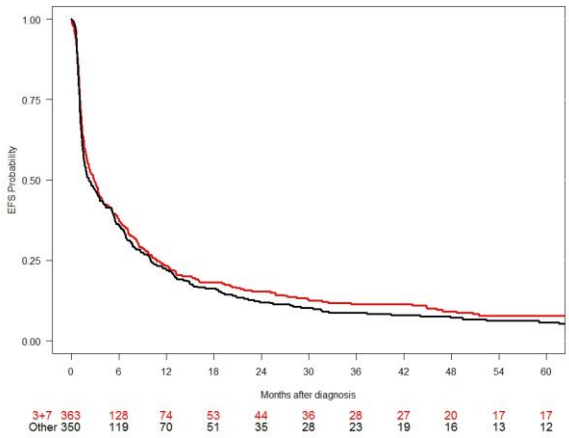
Characteristic	Overall		Allogeneic HSCT		Autologous HSCT		No HSCT		*P value*
	Median (IQR)	n (%)	Median (IQR)	n (%)	Median (IQR)	n (%)	Median (IQR)	n (%)	
Total		350 (100)		73 (100)		28 (100)		249 (100)	
Age, years	65 (63-68)	350 (100)	63 (62-65)	73 (100)	64 (61-66)	28 (100)	67 (64-70)	249 (100)	<0.001*
<70		283 (81)		73 (100)		24 (86)		186 (75)	<0.001
≥70		67 (19)		0 (0)		4 (14)		63 (25)	
Gender		350 (100)		73 (100)		28 (100)		249 (100)	
Male		201 (57)		43 (59)		14 (28)		144 (58)	0.7
Female		149 (43)		30 (41)		14 (28)		105 (42)	
ECOG	1 (0-1)	313 (100)	1 (0-1)	68 (100)	0 (0-1)	24 (100)	1 (0-1)	221 (100)	0.002*
0-2		306 (98)		68 (100)		24 (100)		214 (97)	0.23
3-4		7 (2)		0 (0)		0 (0)		7 (3)	
WBC, $\times 10^9$/L	3.6 (1.9-14)	339 (100)	2.9 (1.5-7.2)	72 (100)	3 (1.8-12.7)	27 (100)	4.1 (2.1-19.4)	240 (100)	0.09*
<20		265 (78)		62 (86)		23 (85)		180 (75)	0.09
≥ 20		74 (22)		10 (14)		4 (15)		60 (25)	
Hemoglobin, g/dL	9.1 (7.8-10.4)	307 (100)	9.4 (8.3-10.4)	68 (100)	10.5 (7.9-12)	21 (100)	9 (7.6-10.3)	210 (100)	0.07*
Platelet count, $\times 10^9$/L	59.2 (29-105)	69 (100)	69 (33-131)	21 (100)	56 (47-130)	219 (100)	54 (27-101)	309 (100)	0.24*
BM blasts, %	45 (30-70)	289 (100)	39 (28-70)	61 (100)	49 (30-84)	19 (100)	45 (30-66)	209 (100)	0.49*
Creatinine, mg/dL	0.9 (0.7-1.1)	253 (100)	0.8 (0.7-1)	59 (100)	0.8 (0.8-1.1)	18 (100)	0.9 (0.8-1.1)	176 (100)	0.01*
< 2		248 (98)		59 (100)		18 (100)		171 (97)	0.33
≥ 2		5 (2)		0 (0)		0 (0)		5 (3)	
Urea, mg/dL	35 (27-44)	229 (100)	33 (28-41)	57 (100)	34 (23-46)	15 (100)	36 (27-45)	157 (100)	0.41*

Characteristic	Overall		Allogeneic HSCT		Autologous HSCT		No HSCT		*P value*
	Median (IQR)	**n (%)**	**Median (IQR)**	**n (%)**	**Median (IQR)**	**n (%)**	**Median (IQR)**	**n (%)**	
Uric acid, mg/dL	4.6 (3.6-6.3)	229 (100)	4.6 (3.7-6.1)	58 (100)	3.9 (3.4 -5.1)	16 (100)	4.8 (3.6-6.4)	155 (100)	0.31*
Bilirubin, mg/dL	0.64 (0.45-0.9)	239 (100)	0.67 (0.5-0.9)	57 (100)	0.54 (0.45-0.9)	17 (100)	0.6 (0.42-0.9)	165 (100)	0.65*
Albumin, g/dL	3.7 (3.4-4.1)	212 (100)	3.8 (3.4-4.3)	53 (100)	3.8 (3.3-4.0)	14 (100)	3.7 (3.4-4)	145 (100)	0.09*
LDH, U/L	401 (224-711)	257 (100)	347 (215-543)	62 (100)	456 (310-714)	18 (100)	443 (238-726)	177 (100)	0.19*
Fibrinogen, mg/dL	420 (328-535)	215 (100)	449 (338-534)	55 (100)	440 (303-677)	16 (100)	408 (329-519)	144 (100)	0.53*
Cytogenetics		348 (100)		72 (100)		28 (100)		248 (100)	
Normal		103 (30)		23 (32)		12 (43)		68 (27)	0.59
Abnormal		210 (60)		43 (60)		15 (54)		152 (61)	
No metaphases		14 (4)		3 (4)		0 (0)		11 (4)	
Not available		21 (6)		3 (4)		1 (4)		17 (7)	
MRC Cytogenetic risk		309 (100)		63 (100)		27 (100)		219 (100)	
Favorable		7 (2)		0 (0)		0 (0)		7 (3)	0.51
Intermediate		157 (51)		31 (49)		15 (56)		111 (51)	
Adverse		145 (47)		32 (51)		12 (44)		101 (46)	
FLT3-ITD		212 (100)		54 (100)		15 (100)		139 (100)	
Positive		15 (7)		2 (3)		3 (20)		10 (7)	0.08
Negative		197 (93)		52 (97)		12 (80)		129 (93)	
NPM1		194 (100)		56 (100)		13 (100)		125 (100)	
Positive		27 (14)		6 (11)		3 (23)		18 (14)	0.49
Negative		167 (86)		50 (89)		10 (77)		107 (86)	
Type of AML		350 (100)		73 (100)		28 (100)		249 (100)	
t-AML		79 (23)		12 (16)		6 (21)		61 (24)	0.01
Previous MDS/CMML		101 (29)		22 (30)		6 (21)		73 (29)	

Characteristic	Overall		Allogeneic HSCT		Autologous HSCT		No HSCT		*P value*
	Median (IQR)	**n (%)**	**Median (IQR)**	**n (%)**	**Median (IQR)**	**n (%)**	**Median (IQR)**	**n (%)**	
MDS-related cytogenetic		111 (32)		30 (41)		5 (18)		76 (31)	
Dysplasia		43 (12)		9 (12)		7 (25)		27 (11)	
Unknown[#]		161 (5)		0 (0)		4 (14)		12 (5)	
Induction treatment		350 (100)		73 (100)		28 (100)		249 (100)	
"3+7"		182 (52)		44 (60)		18 (64)		120 (48)	0.08
Other		168 (48)		29 (40)		10 (36)		129 (52)	

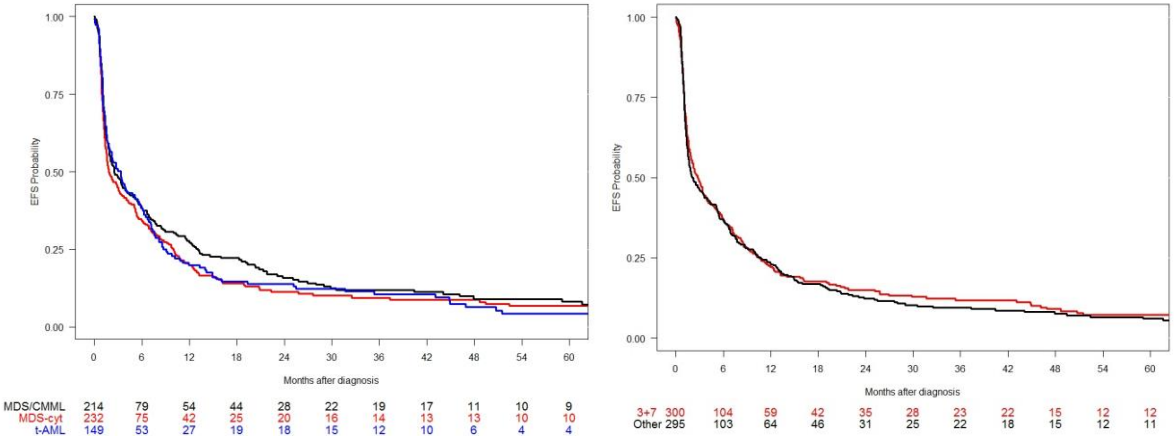
IQR: interquartile range; ECOG: Eastern Cooperative Oncology Group; sAML: secondary Acute Myeloid Leukemia; FAB: French - American – British; WBC: White Blood Cells; BM: Bone Marrow; LDH: Lactate dehydrogenase; MRC: Medical Research Council; FLT3: FMS-like tyrosine kinase 3; HSCH: Hematopoietic stem cell transplantation; ITD: internal tandem duplication; NPM1: Nucleophosmin1; HMA: hypomethylating agents; MDS: myelodisplastic syndrome; * *P* compare continuous variables; [#] this group includes patients with dysplasia but no information regarding previous therapy, neoplastic antecedents or cytogenetics and patients with MDS/CMML- related cytogenetics but no information regarding previous therapy or neoplastic antecedents.

Supplemental Figure 1. Event-free survival according to therapeutic approach ("3+7" vs Other intensive therapy).



Supplemental Figure 2. CPX-351-like cohort. A) Event-free survival according to the type of AML (t-AML, sAML MDS/CMML, sAML MDS-cytogenetics). B) Event-free survival according to therapeutic approach ("3+7" vs Other intensive therapy).

Figure 2A **Figure 2B**



Appendix

Institutions and clinicians participating in the PETHEMA epidemiologic registry of acute myeloid leukemia and acute promyelocytic leukemia:

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