SUPPLEMENTAL DATA

Supplemental Table 1: Characteristics of patients with complete molecular response after induction with CPX-351

	n = 8	% or range
Age, median (years)	67	31-70
Sex		
Male	3	38
Female	5	62
AML subtype		
MRC-AML	4	50
MDS-AML	1	25
CMML-AML	0	0
t-AML	4	50
Median number of WBC (G/L)	4	0-6
Hyperleukocytosis	0	0
Cytopenias	7	88
1	1	13
2	5	62
3	1	13
Karyotype		
Complex	4	50
Monosomal	2	25
Prior HMA	0	0
2017 ELN genetic risk stratification		
Favorable	0	0

Intermediate	2	25
Adverse	6	75
	n = 6	% or range
Median number of mutations	2	2-7
Lindsley's classifier		
de novo/pan-AML	0	0
Secondary-type mutations AML	4	67
TP53 mutated AML	2	33
Functional group		
Epigenetic modifications	5	83
Spliceosome complex	1	17
Signaling and kinase pathway	3	50
Cohesin complex	1	17
Transcription factors	1	17

Supplemental Table 2: Comparison of different classifications of secondary AML

	Clinical classification			Lindsley's classifier				2017 ELN genetic risk stratification			
	MRC-AML	t-AML	*p* value	de novo/ pan-AML	Secondary-type mutations AML	*TP53* mutated AML	*p* value	Favorable	Intermediate	Adverse	*p* value
	n = 74	n = 27		n = 21	n = 37	n = 22		n =2	n = 39	n = 61	
Age – years											
Median (range)	67 (20-82)	65 (31-83)		71 (34-83)	67 (20-82)	63 (49-75)		71 (68-73)	70 (31-83)	66 (20-79)	
AML subtype – n (%)											
MRC-AML	74 (100)	-		13 (62)	32 (86)	13 (59)		1 (50)	31 (79)	41 (67)	
MDS-AML	35 (47)	-		4 (31)	17 (53)	8 (62)		-	13 (42)	21 (51)	
CMML-AML	9 (12)	-		2 (15)	5 (16)	-		1 (100)	7 (23)	1 ()	
t-AML	-	27 (100)		8 (38)	5 (14)	8 (36)		1 (50)	8 (21)	18 (30)	
Others*	-	-		-	-	1 (5)		-	-	2 (3)	
Number of WBC (G/L)											
Median (range)	3 (0-156)	4 (0-116)		3 (0-156)	4 (0-85)	2 (0-14)		44 (4-85)	3 (0-156)	3 (0-119)	
Karyotype – n (%)											
Complex	22 (30)	11 (41)		4 (19)	3 (8)	19 (86)		-	-	35 (57)	
Monosomal	19 (26)	8 (30)		1 (5)	6 (16)	15 (68)		-	-	28 (50)	
2017 ELN risk – n (%)											

Favorable	1/73 (1)	1/27 (4)	1/21 (5)	1/36 (3)	-	2/2 (100)	-	-
Intermediate	31/73 (43)	8/27 (30)	13/21 (62)	17/36 (47)	-	-	39/39 (100)	-
Adverse	41/73 (56)	18/27 (66)	7/21 (33)	18/36 (50)	22/22 (100)	-	-	61/61 (100)
Mutation – n (%)								
FLT3-ITD	5/70 (7)	4/26 (15)	4/21 (19)	4/37 (11)	1/22 (5)	-	3/38 (8)	6/58 (10)
FLT3-TKD	2/71 (3)	4/27 (15)	3/21 (14)	2/37 (5)	1/22 (5)	-	2/38 (5)	4/60 (7)
NPM1	5/72 (7)	2/27 (7)	3/21 (14)	3/37 (8)	1/22 (5)	1/2 (50)	4/38 (11)	2/61 (3)
IDH1	5/70 (7)	2/26 (8)	-	3/37 (8)	1/22 (5)	-	2/38 (5)	5/57 (9)
IDH2	2/70 (3)	1/26 (4)	1/21 (5)	-	-	-	2/38 (5)	1/57 (2)
DNMT3A	9/54 (17)	4/19 (21)	3/21 (14)	6/37 (16)	4/22 (18)	-	3/38 (8)	10/41 (24)
TET2	13/54 (24)	3/19 (16)	3/21 (14)	11/37 (30)	3/22 (14)	1/2 (50)	8/38 (21)	8/41 (20)
RUNX1	19/54 (35)	3/19 (16)	3/21 (14)	19/37 (51)	-	-	-	14/41 (34)
ASXL1	14/54 (26)	4/19 (21)	-	18/37 (49)	-	-	-	9/41 (22)
TP53	13/54 (24)	8/21 (38)	-	-	22/22 (100)	-	-	22/46 (48)
EVI1	3/63 (5)	3/23 (13)	-	3/37 (8)	-	-	-	6/51 (12)
Number of mutations								
Median (range)	3 (0-7)	2 (0-7)	1 (0-5)	4 (2-7)	2 (1-4)	1 (3-5)	2 (0-7)	3 (0-7)
Functional group								
Epigenetic modifications	31/54 (57)	10/19 (53)	6/21 (29)	29/37 (78)	7/22 (32)	1/2 (50)	18/30 (60)	23/41 (56)

Spliceosome complex	22/54 (41)	2/19 (11)		-	23/37 (62)	1/22 (5)		1/2 (50)	11/30 (37)	11/41 (29)	
Signaling/kinase pathway	19/54 (35)	10/19 (53)		9/21 (43)	17/37 (46)	3/22 (14)		2/2 (100)	12/30 (40)	15/41 (37)	
Cohesin complex	10/54 (19)	1/19 (5)		1/21 (5)	9/37 (24)	1/22 (5)		-	5/30 (17)	6/41 (17)	
Transcription factors	23/54 (43)	6/19 (32)		4/21 (19)	25/37 (68)	-		-	10/30 (33)	18/41 (44)	
Overall response – n (%)	40 (54)	19 (70)	0.01	18 (86)	20 (54)	9 (41)	0.009	2 (100%)	25 (64)	33 (54)	0.26
CR – n (%)	37 (50)	19 (70)		16 (76)	20 (54)	9 (41)		2 (100%)	22 (56)	32 (52)	
CRi – n (%)	3 (4)	-		2 (10)	-	-			3 (8)	1 (2)	
Overall survival											
Median (month)	Not reached	9.4 (3.6-15.1)	0.28	not reached	not reached	8.5 (6.1-10.9)	0.02	Not reached	Not reached	Not reached	0.22

*Two patients were treated post-myeloproliferative neoplasm AML: 1 with prior essential thrombocythemia (ET) and 1 with myelofibrosis secondary to ET.

Supplemental Table 3: Univariate and multivariate analysis of factors influencing OS

	Univariate analysis	Multivariate analysis		
	p-value	Hazard ratio	95% CI	*p*-value
Monosomal karyotype	0.04		-	
***DNMT3A* mutation**	0.02		-	
***TP53* mutation**	0.02		-	
Spliceosome complex	0.02	0.31	0.1-0.96	0.04

Supplemental Table 4: Characteristics and therapy response in patients with MRC-AML or t-AML (a comparison with a historical cohort)

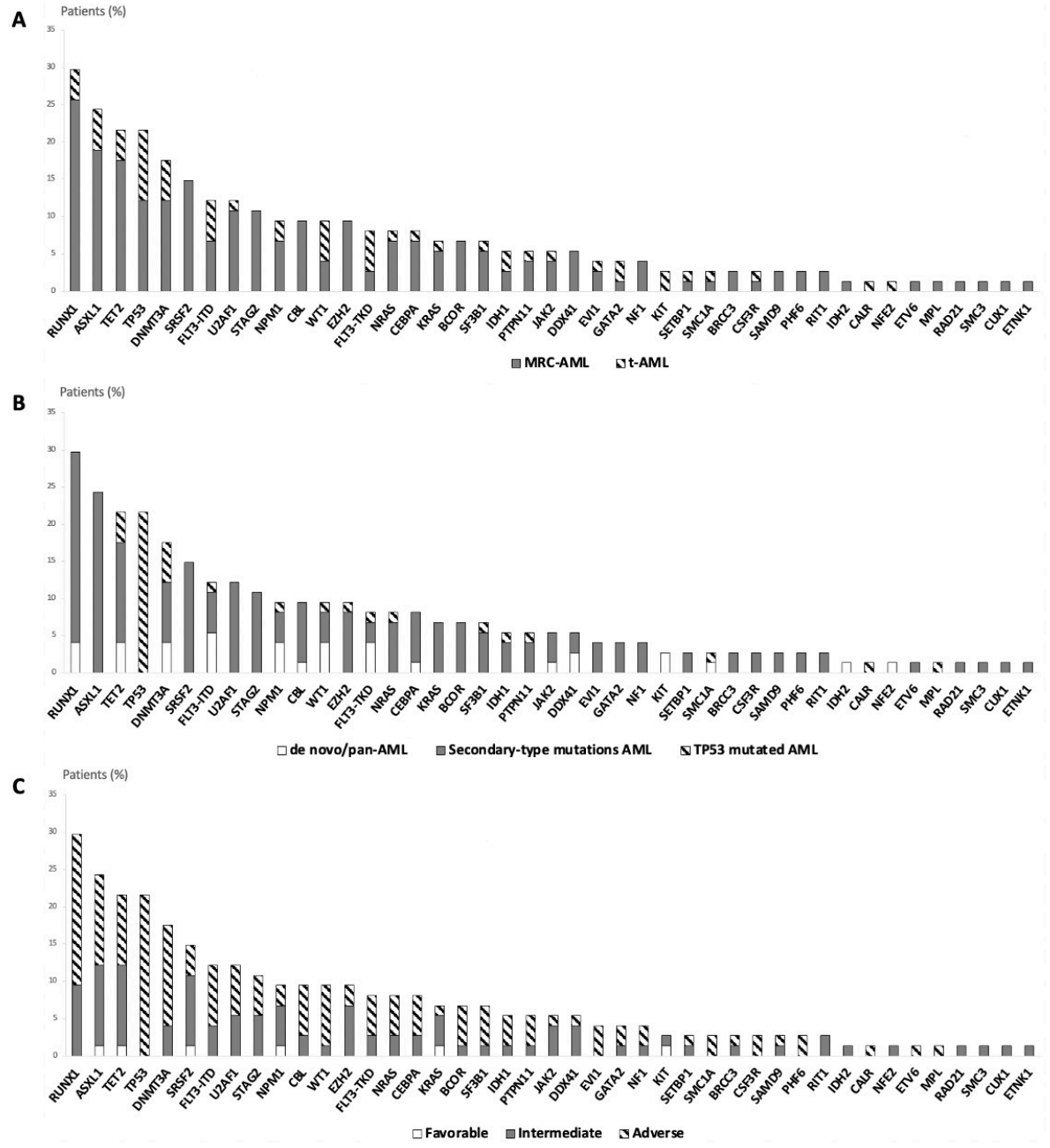
	CPX-351	IC	HMA	*p* value
	n = 103	n = 233	n = 120	
Age – years				
Median (range)	67 (20-83)	62 (19-78)	76 (52-93)	<0.001
Sex – n (%)				
Male	54 (52)	103 (44)	62 (52)	0.264
Female	49 (48)	130 (56)	58 (48)	
AML subtype – n (%)				
MRC-AML	74 (72)	178 (76)	93 (78)	
t-AML	27 (26)	55 (24)	27 (22)	0.113
Other	2 (2)*	0	0	
Number of WBC (G/L)				
Median (range)	3 (0-156)	5.3 (0.5-352)	2.5 (0.4-123)	<0.001
Karyotype – n (%)				
Complex	35/103 (34)	52/230 (23)	52/114 (46)	<0.001
Monosomal	28/103 (27)	43/230 (19)	47/114 (41)	<0.001
2017 ELN genetic risk – n (%)				
Favorable	2/102 (2)	31/223 (14)	2/100 (2)	
Intermediate	38/102 (37)	80/223 (36)	17/100 (17)	<0.001
Adverse	62/102 (61)	112/223 (50)	81/100 (81)	
Mutation – n (%)				
FLT3-ITD	9/98 (9)	21/180 (12)	2/54 (4)	0.274
FLT3-TKD	6/100 (6)	4/135 (3)	2/47 (4)	0.522

NPM1	7/101 (7)	27/183 (15)	2/52 (4)	0.027
CEBPA	6/90 (7)	5/147 (3)	1/34 (3)	0.447
IDH1	7/98 (7)	10/167 (6)	6/76 (8)	0.845
IDH2	3/98 (3)	21/168 (13)	13/76 (17)	0.008
DNMT3A	13/74 (18)	23/124 (19)	5/39 (13)	0.71
TET2	17/74 (23)	9/83 (11)	0/6 (0)	0.022
RUNX1	22/74 (30)	14/81 (17)	2/6 (33)	0.049
ASXL1	18/74 (24)	14/95 (15)	3/33 (9)	0.094
NRAS	6/74 (8)	9/82 (11)	1/6 (17)	0.851
KRAS	5/74 (7)	5/82 (6)	0/6 (0)	0.727
WT1	7/74 (9)	5/84 (6)	2/7 (29)	0.104
KIT	2/74 (3)	1/84 (1)	1/9 (11)	0.186
TP53	22/76 (29)	16/88 (18)	12/17 (71)	<0.001
Chemotherapy – n (%)				
Dau-AraC		55/233 (24)		
Ida-AraC		58/233 (25)		
Ida-AraC-Lomustine		119/233 (51)		
Other		1/233 (<1)		
Number of cycles				
Median (range)			5 (1-41)	
Overall response (CR-CRi) – n (%)	61/103 (59)	160/218 (73)	19/101 (19)	<0.001
CR – n (%)	57/103 (55)	120/218 (55)	11/101 (11)	
CRi – n (%)	4/103 (4)	40/218 (18)	8/(8)	
ASCT – n (%)	36/103 (35)	93/218 (43)	2/111 (2)	<0.001

*Two patients were treated post-myeloproliferative neoplasm AML: 1 with prior essential thrombocythemia (ET) and 1 with myelofibrosis secondary to ET.

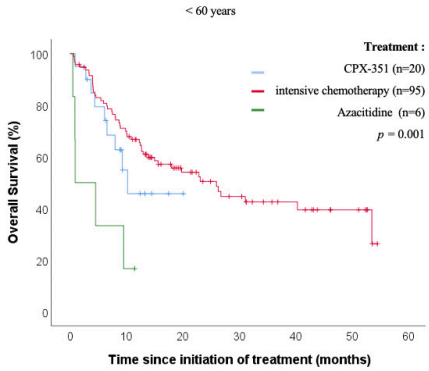
Supplemental Figure 1: Frequencies of mutated genes by different classifications

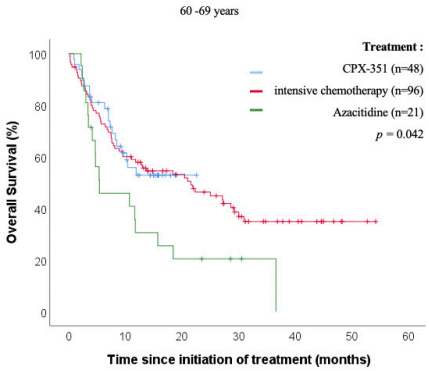
74 patients treated with CPX-351 were assessed by NGS and classified according to AML subtypes (A), Lindsley's molecular classes (B) and 2017 ELN genetic risk stratification (C).

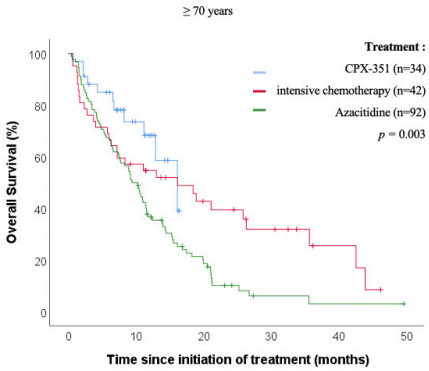


Supplemental Figure 2: Median overall survival in patients treated by CPX-351 (n=103), intensive chemotherapy (n=233) or azacitidine (n=120) according to age and 2017 ELN genetic risk stratification

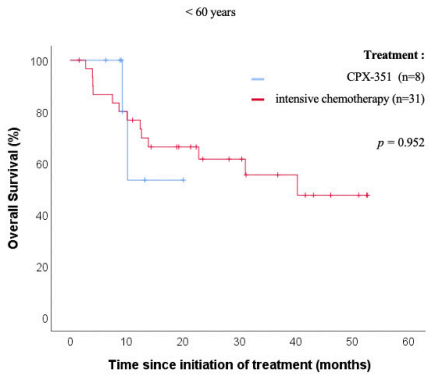
All patients

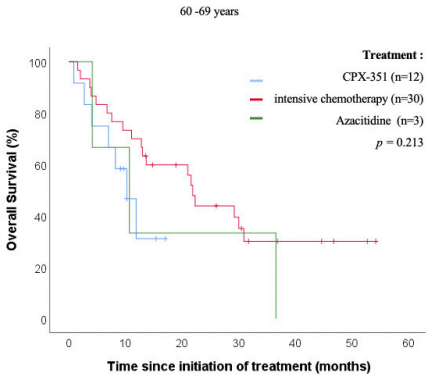


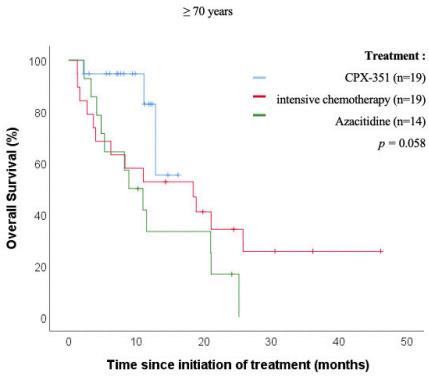




Patients with intermediate 2017 ELN risk







Patients with adverse 2017 ELN risk