Supplementary material: Incidence and risk factors for development of cardiac toxicity in adult patients with newly diagnosed acute myeloid leukemia

Supplementary Table S1. Baseline cardiac characteristics in all patients

Characteristic	Overall cohort	
	Median (range)	Number of patients n=571 (%)
Relevant cardiac comorbidity		571
Yes		82 (14)
No		489 (86)
All cardiac comorbidity		571
Yes		215 (38)
No		356 (62)
Baseline cardiac medication		571
Yes		265 (46)
No		306 (54)
Baseline cardiac medication	0 (0-9)	571
0		306 (54)
1-2		176 (31)

3-4		73 (13)
>4		16 (3)
Baseline electrocardiogram		571
Normal		278 (49)
Abnormal non clinically significant		128 (22)
Abnormal clinically significant		17 (3)
Not available		148 (26)
Baseline QTcF electrocardiogram	421 (347-556)	409
QTcF <450		359 (88)
QTcF 450-480		38 (9)
QTcF 481-500		7 (2)
QTcF >500		5 (1)
Baseline echocardiogram		571
Normal		242 (42)
Abnormal		70 (12)
Not available		259 (45)
Baseline ejection fraction	66 (35-92)	221
LVEF <50		6 (3)
LVEF ≥50		215 (97)

Heart failure at diagnosis		571
Yes		39 (7)
No		532 (93)
Baseline NYHA	0 (0-4)	571
0		532 (93)
1		12 (2)
2		11 (2)
3		13 (2)
4		3 (1)
Cardioischemic signs or symptoms at diagnosis		571
Yes		11 (2)
No		560 (98)

Supplementary Table S2. Demographic, clinical, and biological characteristics of AML patients at diagnosis according to therapeutic approach (Intensive vs HMA vs LDAC-based vs Trial vs BSC).

Characteristic	Intensive		HMA		LDAC-based		Intensive trial		Non intensive trial		BSC		P value
	Median (range)	n (%)	Median (range)	n (%)	Median (range)	n (%)	Median (range)	n (%)	Median (range)	n (%)	Median (range)	n (%)	

N		218 (46%)		7 (1%)		68 (13%)		67 (13)		165 (31%)		46 (9%)	
Age, years	54 (18-68)	218	69 (49-78)	7	71 (51-91)	68	63 (29-72)	67	74 (57-98)	165	77 (54-94)	46	<0.001
<65		210 (96)		3 (43)		7 (10)		40 (60)		4 (2)		8 (17)	<0.001
≥65-<75		8 (4)		1 (14)		35 (51)		27 (40)		79 (48)		10 (22)	
≥75		0		3 (43)		26 (38)		0		82 (50)		28 (61)	
Gender		218		7		68		67		165		46	
Male		121 (56)		5 (71)		42 (62)		40 (60)		97 (59)		26 (57)	0.897
Female		97 (45)		2 (29)		26 (38)		27 (40)		68 (41)		20 (43)	
ECOG	1 (0-4)	218	1 (0-2)	7	1 (0-4)	68	0 (0-3)	67	1 (0-4)	165	3 (0-4)	46	<0.001
0		101 (46)		3 (43)		16 (24)		35 (52)		47 (28)		2 (4)	<0.001
1		85 (39)		2 (29)		22 (32)		28 (42)		79 (48)		12 (26)	
2		24 (11)		2 (29)		17 (25)		3 (4)		28 (17)		7 (15)	
3		5 (2)		0		6 (10)		1 (1)		10 (6)		11 (24)	
4		3 (1)		0		7 (10)		0		1 (1)		14 (30)	
ECOG Group		218		7		68		67		165		46	
0-1		186 (85)		5 (71)		38 (56)		63 (94)		126 (76)		14 (30)	<0.001
≥2		32 (15)		2 (29)		31 (44)		4 (6)		39 (24)		32 (70)	
Comorbidities		218		7		68		67		165		46	
Yes		108 (50)		5 (71)		52 (76)		40 (60)		131 (79)		42 (91)	<0.001
No		110 (50)		2 (29)		16 (24)		27 (40)		34 (21)		4 (9)	
Type of AML		217		7		67		66		164		46	
De novo		158 (73)		1 (14)		31 (46)		44 (67)		94 (57)		20 (43)	<0.001
Secondary to MDS/MPS		25 (12)		6 (86)		21 (31)		14 (21)		48 (29)		18 (39)	
Therapy related		34 (16)		0		15 (22)		8 (12)		22 (13)		8 (17)	

FAB subtype		204		6		64		48		134		35	
M0		10 (5)		0		5 (8)		2 (4)		10 (7)		2 (6)	0.002
M1		35 (17)		0		6 (9)		16 (33)		14 (10)		1 (3)	
M2		42 (21)		0		11 (17)		4 (8)		27 (20)		4 (11)	
M4		36 (18)		0		9 (14)		8 (17)		23 (17)		7 (20)	
M5		28 (14)		0		7 (11)		6 (13)		10 (7)		4 (11)	
M6		10 (5)		1 (17)		2 (3)		1 (2)		8 (6)		0	
M7		2 (1)		0		0		0		2 (1)		1 (3)	
NA/other		41 (20)		5 (83)		24 (38)		11 (23)		40 (30)		16 (46)	
WHO 2016		218		7		68		67		164		46	
AML-RGA		91 (42)		0		14 (21)		23 (34)		24 (15)		2 (4)	<0.001
AML-NOS		29 (13)		0		8 (12)		5 (7)		23 (14)		3 (7)	
AML-MRC		62 (28)		6 (86)		30 (44)		26 (39)		86 (52)		30 (65)	
Myeloid sarcoma		1 (0.5)		0		0		0		1 (1)		0	
t-AML		18 (8)		0		13 (19)		5 (7)		11 (7)		5 (11)	
Ambiguous lineage		4 (2)		0		1 (1)		1 (1)		2 (1)		0	
BPDCN		0		0		0		0		2 (1)		0	
Not available		13 (6)		1 (14)		2 (3)		7 (10)		15 (9)		6 (13)	
Extramedullary disease		217		7		68		67		164		46	
Yes		48 (22)		0		9 (13)		11 (16)		27 (16)		5 (11)	0.213
No		169 (78)		7 (100)		59 (87)		56 (84)		137 (84)		41 (89)	
WBC, $\times 10^9$/L	10 (0.4-434.3)	218	2.7 (0.5-75)	7	8.9 (0.4-317.9)	68	6.8 (0.3-246.4)	67	5.7 (0.6-223.6)	165	13.7 (0.3-202)	46	0.041
≤ 5		87 (40)		5 (71)		27 (40)		30 (45)		82 (50)		10 (22)	0.07

5-10		22 (10)		1 (14)		10 (15)		8 (12)		18 (11)		9 (20)	
10-50		62 (28)		0		15 (22)		14 (21)		45 (27)		17 (37)	
> 50		47 (22)		1 (14)		16 (24)		15 (22)		20 (12)		10 (22)	
Neutrophil count, $\times 10^9$/L		204		5		66		52		142		38	
≤ 0.5		69 (34)		2 (40)		20 (30)		20 (38)		37 (26)		10 (26)	0.27
0.5-1		38 (19)		2 (40)		11 (17)		5 (10)		24 (17)		3 (8)	
> 1		97 (48)		1 (20)		35 (53)		27 (52)		81 (57)		25 (66)	
Hemoglobin, g/dL	8.8 (3.8-15.5)	218	8.8 (6.9-14.3)	7	8.9 (4.8-13.9)	68	9.1 (5.3-13.1)	67	8.6 (3.8-14.2)	165	8.6 (2.9-12.7)	46	0.53
≤ 10		159 (73)		5 (71)		52 (76)		49 (73)		134 (81)		35 (76)	0.55
> 10		59 (27)		2 (29)		16 (24)		18 (27)		31 (19)		11 (24)	
Platelet count, $\times 10^9$/L	53 (2-1442)	218	54 (9-816)	7	42 (1-599)	68	73 (9-330)	67	54 (7-708)	165	32 (5-613)	45	0.004
≤ 20		34 (16)		2 (29)		21 (31)		7 (10)		30 (18)		15 (33)	0.004
> 20		184 (84)		5 (71)		47 (69)		60 (90)		135 (82)		30 (67)	
PB blasts, %		214		7		68		67		163		44	
≤ 50		146 (68)		6 (86)		49 (72)		46 (69)		137 (84)		33 (75)	0.016
> 50		68 (32)		1 (14)		19 (28)		21 (31)		26 (16)		11 (25)	
BM blasts, %	58 (0-100)	216	28 (21-90)	7	57 (8-100)	67	50 (18-99)	67	38 (1-100)	165	37 (20-99)	37	<0.001
≤ 30		47 (22)		4 (57)		16 (24)		17 (25)		60 (36)		14 (38)	0.021
>30-≤70		94 (44)		2 (29)		30 (45)		25 (37)		71 (43)		12 (32)	
> 70		75 (35)		1 (14)		21 (31)		25 (37)		34 (21)		11 (30)	
Creatinine, mg/dL	0.8 (0.1-6.9)	218	0.9 (0.6-3.6)	6	0.9 (0.4-3.2)	68	0.8 (0.4-7.4)	67	0.9 (0.4-3)	165	1.1 (0.3-5.4)	46	<0.001
≤ 1.3		201 (92)		5 (83)		55 (81)		59 (88)		135 (82)		27 (59)	<0.001

> 1.3		17 (8)		1 (17)		13 (19)		8 (12)		30 (18)		19 (41)	
Urea, mg/dL	30 (6-174)	208	33 (21-64)	6	41 (18-149)	66	32 (10-134)	67	41 (12-156)	163	60 (23-158)	44	<0.001
≤ 50		185 (89)		5 (83)		45 (68)		59 (88)		116 (71)		19 (43)	<0.001
> 50		23 (11)		1 (17)		21 (32)		8 (12)		47 (29)		25 (57)	
Uric acid, mg/dL	4.5 (1-14.6)	174	3.6 (1.7-7.6)	5	5.2 (2.3-17.1)	59	4.3 (2.3-29)	61	5.7 (1.3-15.8)	156	6.4 (1.4-15.7)	34	<0.001
≤ 7		152 (87)		4 (80)		45 (76)		55 (90)		121 (78)		21 (62)	0.003
> 7		22 (13)		1 (20)		14 (24)		6 (10)		35 (22)		13 (38)	
Bilirubin, mg/dL	0.6 (0.1-6.2)	212	0.7 (0.5-2.2)	5	0.7 (0.3-2.1)	64	0.6 (0.2-1.8)	67	0.7 (0.1-2.4)	164	0.8 (0.2-4.8)	41	<0.001
≤ 1.2		179 (84)		3 (60)		55 (86)		66 (99)		149 (91)		32 (78)	0.003
> 1.2		33 (16)		2 (40)		9 (14)		1 (1)		15 (9)		9 (22)	
AST, U/L	23 (6-781)	210	23 (14-42)	6	25 (8-88)	66	21 (10-229)	63	20 (7-112)	159	26 (7-1085)	45	0.036
≤ 50		181 (86)		6 (100)		57 (86)		58 (92)		147 (92)		33 (73)	0.008
> 50		29 (14)		0		9 (14)		5 (8)		12 (8)		12 (27)	
ALT, U/L	21 (3-714)	217	16 (8-37)	6	17 (5-120)	67	21 (7-306)	67	15 (3-146)	165	15 (6-593)	44	<0.001
≤ 50		185 (85)		6 (100)		59 (88)		56 (84)		158 (96)		40 (91)	0.017
> 50		32 (15)		0		8 (12)		11 (16)		7 (4)		4 (9)	
AP, U/L	72 (26-1158)	191	77 (52-126)	6	79 (39-472)	60	73 (27-542)	65	73 (30-416)	162	76 (39-326)	29	0.6
≤ 150		170 (89)		6 (100)		54 (90)		57 (88)		148 (91)		23 (79)	0.46
> 150		21 (11)		0		6 (10)		8 (12)		14 (9)		6 (21)	
Albumin, g/dL	3.7 (1.6-5.1)	196	3.5 (3-4.4)	5	3.5 (2-4.8)	58	3.8 (2.4-5.2)	65	3.9 (2.2-5.2)	160	3.6 (1.7-4.9)	34	<0.001

≤ 3.5		85 (43)		3 (60)		30 (52)		21 (32)		48 (30)		17 (50)	0.011
> 3.5		111 (57)		2 (40)		28 (48)		44 (68)		112 (70)		17 (50)	
LDH, U/L	618 (138-19670)	213	383 (152-1306)	6	637 (201-11380)	65	309 (101-1496)	66	426 (143-3845)	164	941 (149-42630)	44	<0.001
≤ 600		100 (47)		5 (83)		33 (51)		49 (74)		105 (64)		16 (36)	<0.001
> 600		103 (53)		1 (17)		32 (49)		17 (26)		59 (36)		28 (64)	
Fibrinogen	467 (34-1150)	215	485 (287-658)	4	454 (238-831)	64	537 (274-944)	64	504 (145-1002)	157	517 (93-867)	44	0.128
≤ 170		3 (1)		0		0		0		1 (1)		2 (5)	0.24
> 170		212 (99)		4 (100)		64 (100)		64 (100)		156 (99)		42 (95)	
Dimer-D, ng/ml	740 (39-128400)	136	394 (394-394)	1	959 (142-99000)	34	1632 (4-1828000)	62	1271 (11-523300)	114	3358 (22-79630)	20	0.001
≤ 500		50 (37)		0		7 (21)		7 (11)		23 (20)		3 (15)	<0.001
> 500		86 (63)		1 (100)		27 (79)		55 (89)		91 (80)		17 (85)	
Prothrombin time		186		5		63		62		144		41	
Prolonged		64 (34)		0		24 (38)		19 (31)		46 (32)		22 (54)	0.065
Normal		122 (66)		5 (100)		39 (62)		43 (69)		98 (68)		19 (46)	
APTT		211		6		66		64		150		44	
Prolonged		41 (19)		2 (33)		11 (17)		2 (3)		12 (8)		5 (11)	0.002
Normal		170 (81)		4 (67)		55 (83)		62 (97)		138 (92)		39 (89)	
Cytogenetics		218		7		68		67		165		46	
Normal		82 (38)		4 (57)		35 (51)		26 (39)		60 (36)		5 (11)	<0.001
Abnormal		115 (53)		1 (14)		28 (41)		37 (55)		85 (52)		26 (57)	
No metaphases		18 (8)		2 (29)		4 (6)		4 (6)		15 (9)		4 (9)	

Not available		3 (1)		0		1 (1)		0		5 (3)		11 (24)	
MRC Cytogenetic risk		201		5		66		63		147		35	
Favorable		23 (11)		0		1 (2)		2 (3)		1 (1)		0	<0.001
Intermediate		119 (59)		4 (80)		45 (69)		41 (65)		86 (59)		12 (34)	
Adverse		59 (29)		1 (20)		20 (30)		20 (32)		60 (41)		23 (66)	
FLT3-ITD		200		3		56		67		159		32	
0-0.06		168 (84)		3 (100)		51 (91)		50 (75)		149 (94)		31 (97)	0.016
0.06-0.5		9 (5)		0		3 (5)		7 (10)		4 (3)		1 (3)	
0.5-0.8		10 (5)		0		1 (2)		7 (10)		5 (3)		0	
>0.8		13 (7)		0		1 (2)		3 (4)		1 (1)		0	
FLT3-TKD		199		3		56		66		158		32	
Positive		11 (6)		0		2 (4)		5 (8)		5 (3)		3 (9)	0.058
Negative		186 (93)		3 (100)		52 (93)		60 (91)		152 (96)		26 (81)	
Not available		2 (1)		0		2 (4)		1 (2)		1 (1)		3 (9)	
NPM1		201		3		56		67		156		31	
Positive		66 (33)		0		12 (21)		19 (28)		21 (13)		2 (6)	<0.001
Negative		135 (67)		3 (100)		44 (79)		48 (72)		135 (87)		29 (94)	
CEBPA		218		7		68		67		165		46	
Positive		6 (3)		0		2 (3)		1 (1)		5 (3)		0	<0.001
Negative		98 (45)		1 (14)		27 (40)		51 (76)		122 (74)		18 (39)	
Not available		114 (52)		6 (86)		39 (57)		15 (23)		38 (23)		28 (61)	
IDH		218		7		68		67		165		46	
IDH1 positive		5 (2)		0		1 (1)		7 (10)		9 (5)		1 (2)	<0.001
IDH2 positive		19 (9)		0		4 (6)		9 (13)		20 (12)		2 (4)	
Negative		111 (51)		1 (14)		20 (29)		39 (58)		83 (50)		12 (26)	
Not available		83 (38)		6 (86)		43 (63)		12 (18)		53 (32)		31 (67)	

KIT		218		7		68		64		164		46	
Positive		6 (3)		0		0		0		1 (1)		0	<0.001
Negative		38 (17)		1 (14)		8 (12)		47 (73)		60 (37)		3 (7)	
Not available		174 (80)		6 (86)		60 (88)		17 (27)		103 (63)		43 (93)	
Relevant Cardiac comorbidity		218		7		68		67		165		46	
Yes		19 (9)		2 (29)		11 (16)		9 (13)		32 (19)		9 (20)	0.043
No		199 (91)		5 (71)		57 (84)		58 (87)		133 (81)		37 (80)	
Previous anthracycline		218		7		68		67		165		46	
Yes		5 (2)		1 (14)		6 (9)		4 (6)		4 (2)		7 (15)	0.001
No		213 (98)		6 (86)		62 (91)		63 (94)		161 (98)		39 (85)	

Supplementary Table S3. Overall cohort: Multivariate analyses of prognostic factors for development of fatal cardiac events

Covariate	Unfavorable category	Univariate Analysis	Multivariate Analysis	P value
		P value	HR (95% CI)	
Age	≥65	0.247	1.1 (0.3-4.7)	0.88
ECOG	>2	0.56	1.3 (0.4-4)	0.66
Relevant cardiac antecedents	Yes	<0.001	1.9 (2.8-16.6)	<0.001
Front-line therapy	Intensive	0.37	2 (0.4-9.4)	0.4
Front-line clinical trial	Yes	0.062	2.4 (0.1-1.2)	0.095
Use of FLT3 inhibitors	Yes	0.757	2.3 (0.1-2.9)	0.38

Abbreviations: HR: hazard ratio; CI: confidence interval

Supplementary Table S4. Overall cohort: Multivariate analyses of prognostic factors for development of non-fatal cardiac events

Covariate	Unfavorable category	Univariate Analysis	Multivariate Analysis	P value
		P value	HR (95% CI)	
Age	≥65	<0.001	2.2 (1.5-3.3)	<0.001
ECOG	>2	0.626	1.1 (0.8-1.5)	0.54
Relevant cardiac antecedents	Yes	0.004	1.4 (1.1-2)	0.023
Front-line therapy	Non-intensive	0.17	1.8 (1.2-2.8)	0.004
Front-line clinical trial	Yes	<0.001	1.2 (0.6-1.1)	0.21
Use of FLT3 inhibitors	Yes	0.28	1.0 (0.6-1.7)	0.89

Abbreviations: HR: hazard ratio; CI: confidence interval

Supplementary Table S5. 1L study cohort (from index date to last follow-up): First line Intensive chemotherapy patients only. Crude incidence of first cardiac events (Grade 1-2 vs grade 3-4 vs grade 5 vs no cardiac event) according to time of occurrence (before starting therapy, during induction cycle, consolidation, after stem cell transplant, off therapy/follow-up)

Characteristic	N	No cardiac event	Grade 1-2	Grade 3-4	Grade 5
		n (%)	n (%)	n (%)	n (%)
N	285	165 (57.9)	40 (14)	76 (26.7)	4 (1.4)
Before starting therapy	285	276 (96.8)	1 (0.4)	8 (2.8)	0 (0)
Induction	285	222 (77.9)	20 (7)	42 (14.7)	1 (0.4)
Consolidation	169	142 (84)	11 (6.5)	14 (8.3)	2 (1.2)
Allogeneic HSCT	65	58 (89.2)	3 (4.6)	4 (6.2)	0 (0)
Off therapy/ follow-up	163	149 (91.4)	5 (3.1)	8 (4.9)	1 (0.6)

Supplementary Table S6. Intensive chemotherapy patients only: Crude and cumulative incidence of cardiac events (Fatal vs non-fatal vs no cardiac event) according to demographic, clinical, and biological characteristics of intensive chemotherapy patients at diagnosis.

	No cardiac event	P value*	Fatal				Non-fatal			
Characteristic	N (%)		Crude incidence N (%)	Cumulative incidence			Crude incidence N (%)	Cumulative incidence		
				At 6 months, %	At Last FU,%	P value		At 6 months, %	At Last FU, %	P value
N	125 (43.9)		10 (3.5)	1.9	6.3		150 (52.6)	42.5	54.7	
Age	125		10				150			
<65 years	117 (46.8)	0.022	9 (3.6)	1.7	6.2	0.79	124 (49.6)	38.7	51.5	<0.001
≥65 years	8 (22.9)		1 (2.9)	3.6	3.6		26 (74.3)	69.4	75.6	
Relevant cardiologic antecedents	125		10				150			
No	120 (46.7)	<0.001	6 (2.3)	1.3	5	<0.001	131 (51)	40.3	52.4	0.02
Yes	5 (17.9)		4 (14.3)	7.4	18.5		19 (67.9)	64.4	74.4	
Previous anthracycline treatment	125		10				150			
No	120 (44.8)	0.11	8 (3)	1.2	5.8	0.008	140 (52.2)	42.1	54.1	0.27
Yes	5 (29.4)		2 (11.8)	13.4	13.4		10 (58.8)	50.4	57.8	
ECOG at diagnosis	125		10				150			
<2	109 (43.8)	0.76	8 (3.2)	1.7	6.1	0.34	132 (53)	42.9	55.1	0.79
≥2	16 (44.4)		2 (5.6)	2.8	6.8		18 (50)	39.8	52.6	
FLT3-ITD status	117		10				140			

Negative	91 (42.5)	0.56	9 (4.2)	2.5	7.5	0.46	114 (53.3)	43.6	55.8	0.66
Positive	26 (49.1)		1 (1.9)	0	2.3		26 (49.1)	39.6	49.3	
Inclusion in clinical trial	125		10				150			
No	103 (47.3)	0.11	7 (3.2)	1.5	5.8	0.36	108 (49.5)	37.9	51.1	0.011
Yes	22 (32.8)		3 (4.5)	3.2	5.2		42 (62.7)	57.7	64.2	
Use of FLT3 inhibitors	125		10				150			
No	111 (44.8)	0.67	9 (3.6)	2.2	3.9	0.89	128 (51.6)	40.8	53.4	0.20
Yes	14 (37.8)		1 (2.7)	0	3.1		22 (59.5)	54.1	59.7	

*This P value compares the crude incidence between the 3 groups

Supplementary Table S7. Non-intensive chemotherapy patients only: Crude and cumulative incidence of cardiac events (Fatal vs non-fatal vs no cardiac event) according to demographic, clinical, and biological characteristics of intensive chemotherapy patients at diagnosis.

Characteristic	**No cardiac event**	**P value***	**Fatal**				**Non-fatal**			
	N (%)		**Crude Incidence N (%)**	**Cumulative incidence**			**Crude Incidence N (%)**	**Cumulative incidence**		
				At 6 months, %	**At Last FU, %**	**P value**		**At 6 months, %**	**At Last FU, %**	**P value**
N	93 (38.8)		9 (3.8)	2.2	6.8		138 (57.5)	45.2	59.6	
Age	93		9				138			
<65 years	11 (78.6)	0.007	0	0	0	0.54	3 (21.4)	21.4	21.4	0.059
≥65 years	82 (36.3)		9 (4)	2.4	7.2		135 (59.7)	46.6	62	

Relevant cardiologic antecedents	93		9				138			
No	82 (42.1)	0.003	4 (2.1)	1.1	3.7	0.002	109 (55.9)	43.8	57.3	0.1
Yes	11 (24.4)		5 (11.1)	7.1	22.1		29 (64.4)	51.4	70.6	
Previous anthracycline treatment	93		9				138			
No	87 (38.8)	0.7	9 (4)	2.4	7.2	0.42	128 (57.1)	44.8	59.1	0.94
Yes	6 (37.5)		0	0	0		10 (62.5)	50	56.3	
ECOG	93		9				138			
<2	64 (37.9)	0.83	7 (4.1)	2.4	7.4	0.84	98 (58)	43.9	60.3	0.66
≥2	29 (40.9)		2 (2.8)	1.5	4.8		40 (56.3)	48.3	57.6	
FLT3-ITD status	80		9				129			
Negative	70 (36.1)	0.86	8 (4.1)	2.2	7.5	0.82	116 (59.8)	44.9	62.1	0.94
Positive	10 (41.7)		1 (4.2)	4.8	4.8		13 (54.2)	51.3	55.8	
Inclusion in clinical trial	93		9				138			
No	37 (49.3)	0.047	1 (1.3)	0	8	0.24	37 (49.3)	36	48	0.071
Yes	56 (33.9)		8 (4.9)	3.2	7.1		101 (61.2)	49.4	63.9	
Use of FLT3 inhibitors	93		9				138			
No	93 (38.9)	0.69	9 (3.8)	2.2	6.8	0.86	137 (57.3)	44.9	59.5	NA
Yes	0		0	0	0		1 (100)	NA	NA	

*This P value compares the crude incidence between the 3 groups

Supplementary Table S8. Overall study cohort: Crude and cumulative incidence of QTcF prolongation events (grade 0 vs grade 1-2 vs grade 3-4 vs grade 5) according to demographic, clinical, and biological characteristics of patients at diagnosis.

	No QTcF prolongation	P value*	Grade 1-2 QTcF prolongation				Grade 3-4 QTcF prolongation**			
Characteristic	N (%)		Crude incidence N (%)	Cumulative incidence			Crude incidence N (%)	Cumulative incidence		
				At 6 months, %	At Last FU,%	P value		At 6 months, %	At Last FU,%	P value
N	452 (86)		59 (11.2)	8.4	11.6		14 (2.7)	1.5	3.1	
Age	452		59				14			
<65 years	234 (88.6)	0.01	20 (7.6)	6.1	7.6	0.007	10 (3.8)	1.5	4.3	0.16
≥65 years	218 (83.5)		39 (14.9)	10.8	16		4 (1.5)	1.5	1.5	
Relevant cardiologic antecedents	452		59				14			
No	397 (87.8)	0.015	44 (9.7)	7.3	10.2	0.008	11 (2.4)	1.8	2.5	0.38
Yes	55 (75.3)		15 (20.6)	15.1	20.9		3 (4.1)	0	6	
Previous anthracycline treatment	452		59				14			
No	425 (86.4)	0.75	54 (11)	8.1	11.2	0.49	13 (2.6)	1.4	3.1	0.87
Yes	27 (81.8)		5 (15.2)	12.1	12.1		1 (3)	3.3	3.3	
ECOG at diagnosis	452		59				14			
<2	356 (85.2)	0.48	50 (12)	8.9	12.4	0.29	12 (2.9)	1.4	3.4	0.56
≥2	96 (89.7)		9 (8.4)	6.6	8.6		2 (1.9)	1.9	1.9	
FLT3-ITD status	416		57				12			
Negative	347 (85.1)	0.5	51 (12.5)	9.1	13	0.26	10 (2.5)	1.2	3	0.96
Positive	69 (89.6)		6 (7.8)	6.5	7.9		2 (2.6)	1.3	2.7	

Treatment chemotherapy	452		59				14			
Intensive	245 (86)	0.38	30 (10.5)	8.4	10.6	0.59	10 (3.5)	1.4	4.1	0.24
Non-intensive	207 (86.3)		29 (12.1)	8.4	12.9		4 (1.7)	1.7	1.7	
Inclusion in clinical trial	452		59				14			
No	268 (91.5)	<0.001	17 (5.8)	4.4	5.8	<0.001	8 (2.7)	1	2.6	0.87
Yes	184 (79.3)		42 (18.1)	13.4	20.5		6 (2.6)	2.2	3.1	
Use of FLT3 inhibitors	452		59				14			
No	424 (87.1)	0.041	50 (10.3)	7.6	10.6	0.008	13 (2.7)	1.4	2.6	0.95
Yes	28 (73.7)		9 (23.7)	18.4	24.4		1 (2.6)	2.6	2.6	

*This P value compares the crude incidence between the 3 groups; ** All were grade 3

Supplementary Table S9. Overall cohort: Crude and cumulative incidence of arrhythmia (grade 0 vs grade 1-2 vs grade 3-4 vs grade 5) according to demographic, clinical, and biological characteristics of patients at diagnosis.

	No arrhythmia	P value*	Grade 1-2 arrhythmia				Grade 3-4 arrhythmia				Grade 5 arrhythmia			
Characteristic	N (%)		Crude incidence N (%)	Cumulative incidence			Crude incidence N (%)	Cumulative incidence			Crude incidence N (%)	Cumulative incidence		
				At 6 months, %	At Last FU,%	P value		At 6 months, %	At Last FU,%	P		At 6 months, %	At Last FU,%	P value
N	461 (89)		10 (1.9)	1.2	2.3		48 (9.1)	7.3	9.2		6	0.4	1	
Age	461		10				48				6			
<65 years	242 (91.7)	0.045	3 (1.1)	0.4	1.7	0.15	16 (6.1)	4.9	6.1	0.013	3 (1.1)	0.8	2.3	0.61
≥65 years	219 (83.9)		7 (2.7)	2	2.9		32 (12.3)	9.6	12.4		3 (1.1)	0.8	1.2	

Relevant cardiologic antecedents	461		10				48							
No	402 (88.9)	0.12	9 (2)	1.3	2.1	0.69	37 (8.2)	6.2	8.2	0.055	4 (0.9)	0.5	1.8	0.14
Yes	59 (80.8)		1 (1.4)	0	1.9		11 (15.1)	13.7	15.1		2 (2.7)	2.8	2.8	
Previous anthracycline treatment	461		10				48							
No	433 (88)	0.71	9 (1.8)	1.2	2.2	0.63	45 (9.2)	7.1	9.2	0.96	5 (1)	0.6	1.8	0.21
Yes	28 (84.8)		1 (3)	0	3.4		3 (9.1)	9.1	9.1		1 (3)	3.0	3.0	
ECOG at diagnosis	461		10				48							
<2	375 (89.7)	0.043	7 (1.7)	1.2	2.1	0.39	31 (7.4)	5.3	7.5	0.005	5 (1.2)	0.7	2.1	0.93
≥2	86 (80.4)		3 (2.8)	1	3.4		17 (15.9)	15	16		1 (0.9)	1	1	
FLT3-ITD status	425		8				46							
Negative	358 (87.7)	0.63	6 (1.5)	1.3	1.9	0.47	38 (9.3)	7.4	9.3	0.77	6 (1.5)	1.0	2.4	0.3
Positive	67 (87)		2 (2.6)	1	2.8		8 (10.4)	7.8	10.6		0	0	0	
Treatment chemotherapy	461		10				48							
Intensive	259 (90.9)	0.10	3 (1.1)	0.4	1.6	0.1	20 (7)	5.6	7	0.062	3 (1)	0.7	2.3	0.49
Non-intensive	202 (84.2)		7 (2.9)	2.1	3.1		28 (11.7)	9.2	11.8		3 (1.2)	0.9	1.3	
Inclusion in clinical trial	461		10				48							
No	261 (89.1)	0.40	3 (1)	0.3	1.4	0.067	26 (8.9)	7.9	8.9	0.82	3 (1)	0.7	1.9	0.54
Yes	200 (86.2)		7 (3)	2.2	3.2		22 (9.5)	6.5	9.6		3 (1.3)	0.9	1.3	
Use of FLT3 inhibitors	461		10				48							
No	425 (87.3)	0.54	10 (2.1)	1.3	1.9	0.39	46 (9.5)	7.6	9.5	0.38	6 (1.2)	0.8	1.9	0.52

Yes	36 (94.7)		0	0	0		2 (5.3)	2.6	5.3		0	0	0	

*This P value compares the crude incidence between the 4 groups

Supplementary Table S10. Overall study cohort: Crude and cumulative incidence of heart failure and related events (grade 0 vs grade 1-2 vs grade 3-4 vs grade 5) according to demographic, clinical, and biological characteristics of patients at diagnosis.

	No cardiac failure event	P value*	Grade 1-2 cardiac failure event				Grade 3-4 cardiac failure event				Grade 5 cardiac failure event			
Characteristic	N (%)		Crude incidence N (%)	Cumulative incidence			Crude incidence N (%)	Cumulative incidence			Crude incidence N (%)	Cumulative incidence		
				At 6 months, %	At Last FU, %	P value		At 6 months, %	At Last FU,%	P value		At 6 months, %	At Last FU, %	P value
N	428 (81.5)		7 (1.3)	1	1.4		79 (15)	12.2	15.3		11 (2.1)	1	2.4	
Age	428		7				79				11			
<65 years	217 (82.2)	0.23	6 (2.3)	1.5	2.4	0.071	36 (13.6)	11	13.9	0.32	5 (1.9)	0.4	2.2	0.58
≥65 years	211 (80.8)		1 (0.4)	0.4	0.4		43 (16.5)	13.5	16.7		6 (2.3)	1.6	2.8	
Relevant cardiologic antecedents	428		7				79				11			
No	376 (83.2)	0.008	6 (1.3)	0.9	1.4	0.93	64 (14.2)	11.3	14.4	0.13	6 (1.3)	0.7	1.6	0.001
Yes	52 (71.2)		1 (1.4)	1.4	1.4		15 (20.6)	18.1	21		5 (6.9)	2.8	8	
Previous anthracycline treatment	428		7				79				11			
No	403 (81.9)	0.65	7 (1.4)	1	1.5	0.5	72 (14.6)	12	14.9	0.34	10 (2)	0.8	2.4	0.57
Yes	25 (75.8)		0	0	0		7 (21.2)	15.4	21.7		1 (3)	3.1	3.1	
ECOG at diagnosis	428		7				79				11			

<2	349 (83.5)	0.06	6 (1.4)	1	1.5	0.76	54 (12.9)	10.1	13.2	0.005	9 (2.2)	1.2	2.5	0.99
≥2	79 (73.8)		1 (0.9)	0.9	0.9		25 (23.4)	20.6	23.6		2 (1.9)	0	2.7	
FLT3-ITD status	395		7				72				11			
Negative	334 (81.9)	0.81	5 (1.2)	1	1.3	0.36	60 (14.7)	11.8	14.9	0.79	9 (2.2)	1	2.6	0.79
Positive	61 (79.2)		2 (2.6)	1.3	2.8		12 (15.6)	13	15.7		2 (2.6)	1.3	2.8	
Treatment chemotherapy	428		7				79				11			
Intensive	230 (80.7)	0.42	6 (2.1)	1.4	2.2	0.1	43 (15.1)	12.3	15.4	0.99	6 (2.1)	0.7	2.5	0.93
Non-intensive	198 (82.5)		1 (0.4)	0.4	0.4		36 (15)	12.2	15.2		5 (2.1)	1.3	2.4	
Inclusion in clinical trial	428		7				79				11			
No	238 (81.2)	0.23	6 (2.1)	1.4	2.1	0.12	45 (15.4)	12.3	15.5	0.93	4 (1.4)	0	1.7	0.12
Yes	190 (81.9)		1 (0.4)	0.5	0.5		34 (14.7)	12.2	14.9		7 (3)	2.2	3.2	
Use of FLT3 inhibitors	428		7				79				11			
No	398 (81.7)	0.18	5 (1)	0.8	1.1	0.15	74 (15.2)	12.4	15.4	0.81	10 (2.1)	1.1	2.4	0.74
Yes	30 (79)		2 (5.3)	2.6	5.6		5 (13.2)	10.5	13.3		1 (2.6)	0	3	

*This P value compares the crude incidence between the 4 groups

Supplementary Table S11. Overall study cohort: Crude and cumulative incidence of cardioischemic events (grade 0 vs grade 1-2 vs grade 3-4 vs grade 5*) according to demographic, clinical, and biological characteristics of patients at diagnosis.

	No cardioischemic event	P value*	Grade 1-2 cardioischemic event	Grade 3-4 cardioischemic event

Characteristic	N (%)		Crude incidence N (%)	Cumulative incidence			Crude incidence N (%)	Cumulative incidence		
				At 6 months, %	At Last FU,%	P value		At 6 months, %	At Last FU,%	P value
N	505 (96.2)		11 (2.1)	1.5	2.1		9 (1.7)	1.9	4.1	
Age	505		11				9			
<65 years	255 (96.6)	0.62	4 (1.5)	1.1	1.6	0.35	5 (1.9)	1.5	3.8	0.52
≥65 years	250 (95.8)		7 (2.7)	1.9	2.7		4 (1.5)	2.3	4.3	
Relevant cardiologic antecedents	505		11				9			
No	436 (96.5)	0.7	9 (2)	1.3	2	0.69	7 (1.6)	1.5	3.9	0.48
Yes	69 (94.5)		2 (2.7)	2.7	2.7		2 (2.7)	4.1	5.5	
Previous anthracycline treatment	505		11				9			
No	474 (96.3)	0.77	10 (2)	1.4	2.1	0.69	8 (1.6)	1.8	4	0.48
Yes	31 (93.9)		1 (3)	3.1	3.1		1 (3)	3	6.1	
ECOG at diagnosis	505		11				9			
<2	400 (95.7)	0.5	10 (2.4)	1.9	2.4	0.34	8 (1.9)	2.2	4.7	0.21
≥2	105 (98.1)		1 (0.9)	0	1		1 (0.9)	0.9	1.9	
FLT3-ITD status	468		10				7			
Negative	392 (96.1)	0.38	10 (2.5)	2	2.5	0.17	6 (1.5)	2	4.2	0.28
Positive	76 (98.7)		0	0	0		1 (1.3)	1.3	1.3	
Treatment chemotherapy	505		11				9			

Intensive	274 (96.1)	0.99	6 (2.1)	1.4	2.2	0.99	5 (1.8)	1.4	4.3	0.98
Non-intensive	231 (96.3)		5 (2.1)	1.7	2.1		4 (1.7)	2.5	3.8	
Inclusion in clinical trial	505		11				9			
No	279 (95.2)	0.35	7 (2.4)	1.4	2.4	0.62	7 (2.4)	1.7	5	0.31
Yes	226 (97.4)		4 (1.7)	1.7	1.7		2 (0.9)	2.2	2.8	
Use of FLT3 inhibitors	505		11				9			
No	468 (96.1)	0.68	10 (2.1)	1.4	2.1	0.76	9 (1.9)	1.8	4.1	0.84
Yes	37 (97.4)		1 (2.6)	2.6	2.6		0	2.6	2.6	

*This P value compares the crude incidence between the 3 groups

Supplementary Table S12. 1L cohort (from index date to first refractory/relapse): Crude and cumulative incidence of cardiac events (Fatal vs Non-fatal vs No cardiac event) according to demographic, clinical, and biological characteristics of patients at diagnosis

	No cardiac event	P value*	Fatal cardiac event				Non-fatal cardiac event			
Characteristic	**N (%)**		**Crude incidence N (%)**	**Cumulative incidence**			**Crude incidence N (%)**	**Cumulative incidence**		
				At 6 months, %	**At Last FU, %**	**P value**		**At 6 months, %**	**At Last FU, %**	**P value**
N	296 (56.4)		7 (1.3)	1.2	2.8		222 (42.3)	37.8	43.3	
Age	296		7				222			

<65 years	165 (62.5)	0.013	4 (1.5)	1.2	3.1	0.92	95 (36)	31.3	37.2	0.001
≥65 years	131 (50.2)		3 (1.2)	1.2	1.2		127 (48.7)	44.4	49.4	
Relevant cardiologic antecedents	296		7				222			
No	270 (59.7)	<0.001	2 (0.4)	0.3	1.9	<0.001	180 (39.8)	35.6	40.5	0.002
Yes	26 (35.6)		5 (6.9)	7.4	7.4		42 (57.5)	51.8	61	
All cardiologic antecedents	296		7				222			
No	215 (65.6)	<0.001	2 (0.6)	0.4	1.9	0.02	111 (33.8)	30.2	34.6	<0.001
Yes	81 (41.1)		5 (2.5)	2.7	2.7		111 (56.4)	50.6	58.4	
Previous anthracycline treatment	296		7				222			
No	278 (56.5)	0.05	5 (1)	0.8	2.4	0.005	209 (42.5)	37.8	43.3	0.91
Yes	18 (54.6)		2 (6.1)	7.9	7.9		13 (39.4)	37.4	37.4	
ECOG at diagnosis	296		7				222			
<2	240 (57.4)	0.59	5 (1.2)	1	2.7	0.4	173 (41.4)	36.3	42.6	0.17
≥2	56 (52.3)		2 (1.9)	1.9	1.9		49 (45.8)	43.5	46.4	
FLT3-ITD status	269		7				209			
Negative	222 (54.4)	0.33	7 (1.7)	1.6	3.5	0.25	179 (43.9)	38.6	45.2	0.55
Positive	47 (61)		0	0	0		30 (39)	37.7	39	
Treatment chemotherapy	296		7				222			
Intensive	166 (58.3)	0.62	4 (1.4)	1.2	3.1	0.8	115 (40.4)	36	41.6	0.24
Non-intensive	130 (54.2)		3 (1.3)	1.3	1.3		107 (44.6)	39.9	45.1	
Inclusion in clinical trial	296		7				222			
No	185 (63.1)	0.002	3 (1)	0.7	2.4	0.28	105 (35.8)	31.5	36.6	<0.001

Yes	111 (47.8)		4 (1.7)	1.9	1.9		117 (50.4)	45.7	51.8	
Use of FLT3 inhibitors	296		7				222			
No	277 (56.9)	0.49	7 (1.4)	1.3	2.8	0.49	203 (41.7)	37	42.6	0.25
Yes	19 (50)		0	0	0		19 (50)	47.4	50	

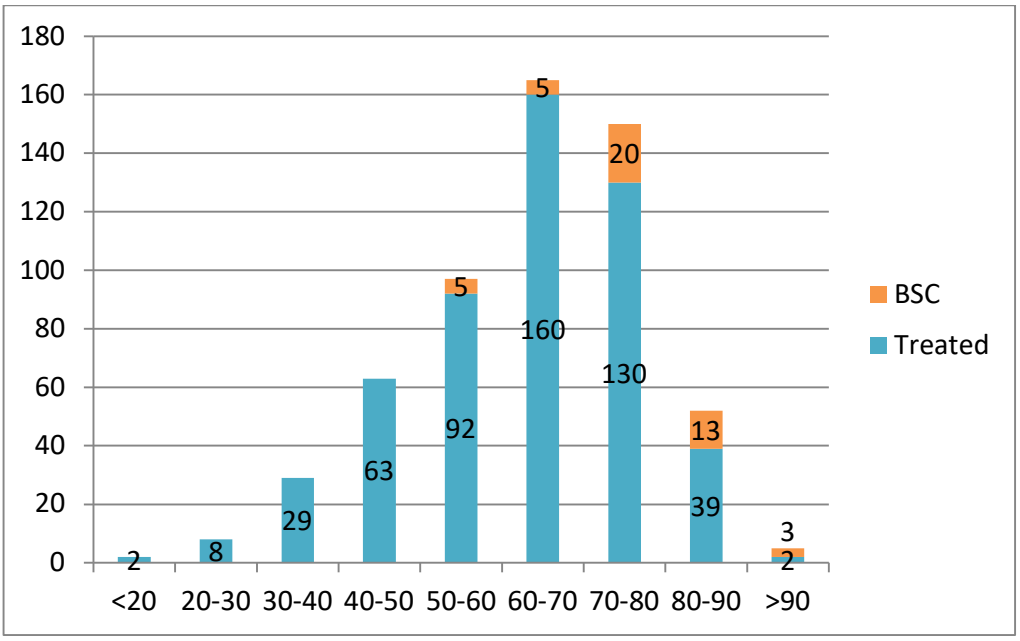
*This P value compares the crude incidence between the 3 groups

Supplementary Table S13. 1L cohort: Multivariate analyses of prognostic factors for development of non-fatal cardiac events

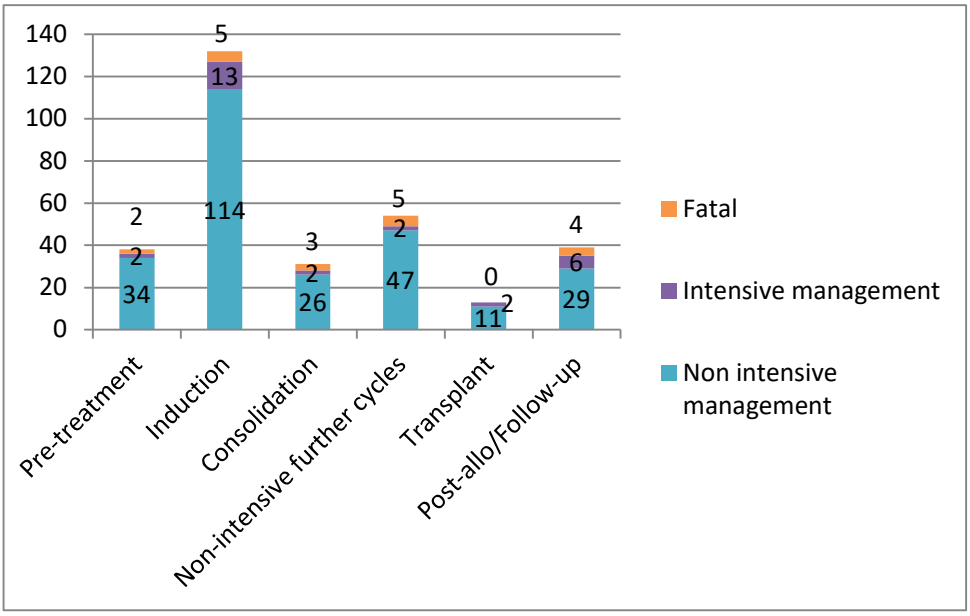
Covariate	Unfavorable category	Univariate Analysis	Multivariate Analysis	
		P value	HR (95% CI)	P value
Age	**≥65**	0.001	1.8 (1.2-2.9)	0.007
ECOG	**>2**	0.17	1.3 (1-1.9)	0.08
Relevant cardiologic antecedents	**Yes**	<0.001	1.9 (1.4-2.6)	<0.001
Front-line treatment	**Non-intensive**	0.24	1.9 (1.2-3)	0.005
Clinical trial	**Yes**	<0.001	1.2 (0.6-1.2)	0.41
Use of FLT3 inhibitors	**Yes**	0.25	1.3 (0.7-2.2)	0.37

Abbreviations: HR: hazard ratio; CI: confidence interval

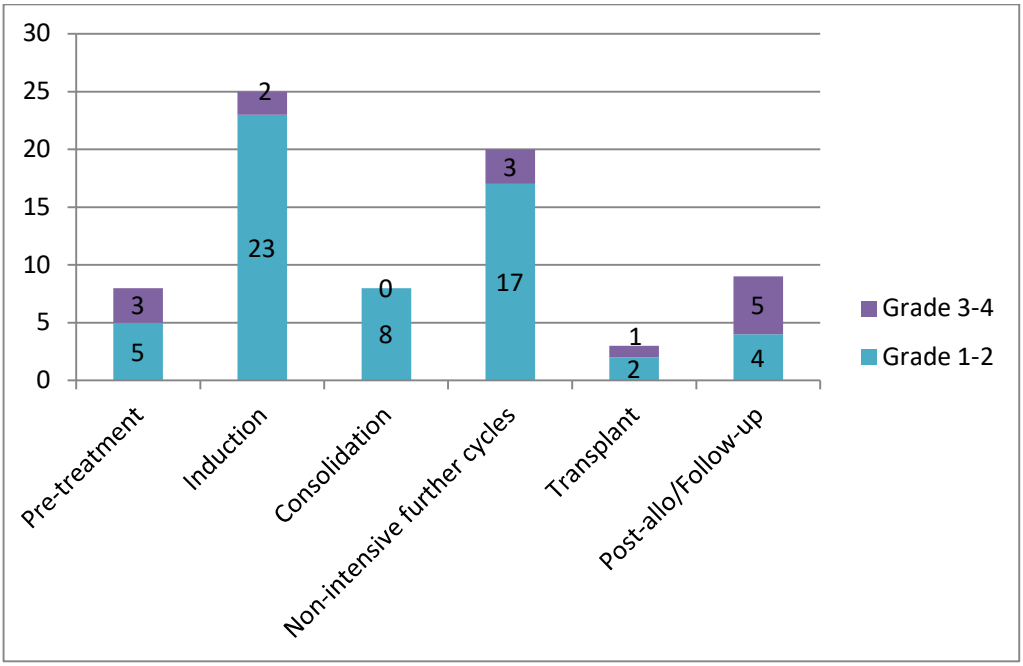
Supplementary Figure S1. Distribution of age at baseline AML diagnosis (diagnosed patients from HULaFe; n=571).



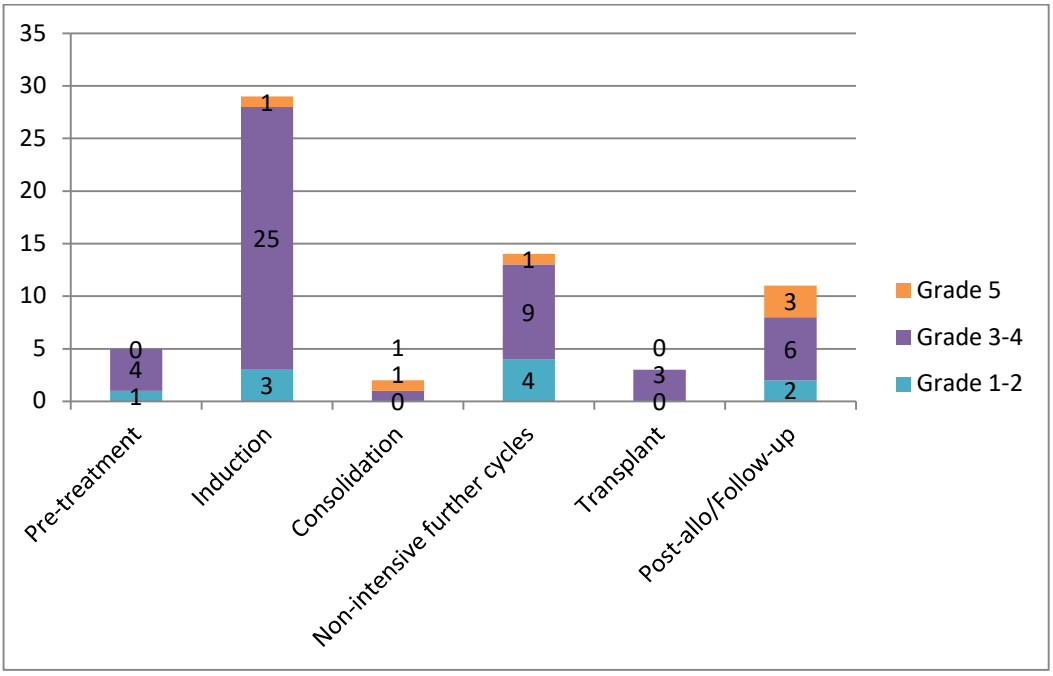
Supplementary Figure S2. Timing of life-threatening (requiring intensive management) cardiac events in the overall cohort.



Supplementary Figure S3. Timing of QTcF prolongation events in the overall cohort.



Supplementary Figure S4. Timing of arrhythmia events in the overall cohort.



Supplementary Figure S5. Timing of heart failure events in the overall cohort.