

An operational definition of primary refractory acute myeloid leukemia allowing early identification of patients who may benefit from allogeneic stem cell transplantation

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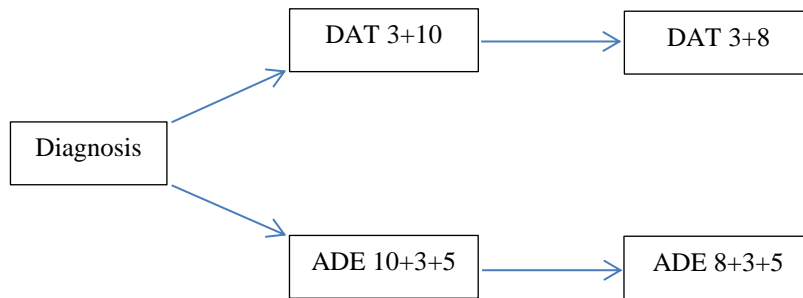
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Supplementary Material

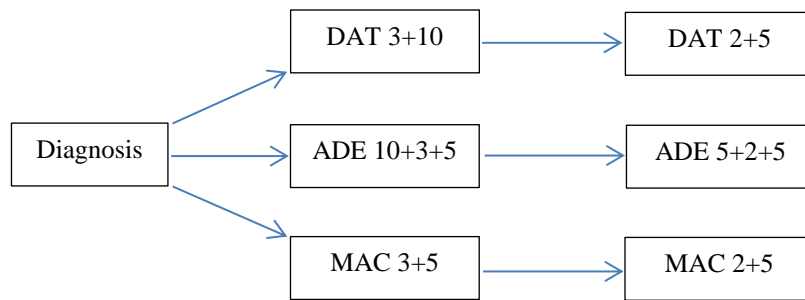
Supplementary Figure 1: Randomisation and treatment arms with drug doses and scheduling for MRC/NCRN AML Trials a) AML 10 b) AML 11 c) AML 12 rota A (Pre-protocol amendment) d) AML 12 rota B (Post-protocol amendment) e) AML 14 f) AML 15 g) AML 16.

a) AML 10



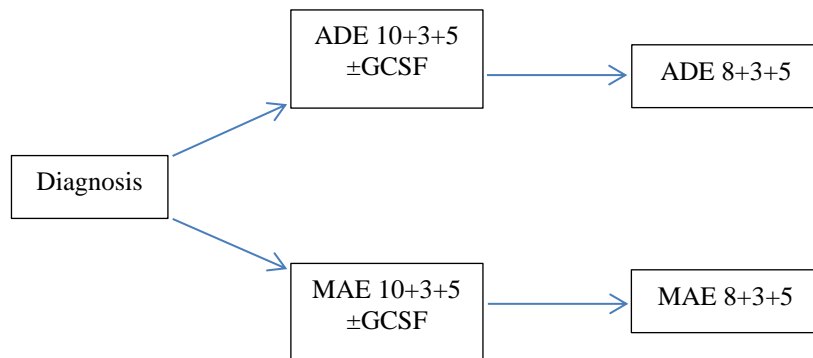
Regimen	Dose(mg/m ²)	Timing
DAT 3+10		
Daunorubicin	50	Daily, Days 1, 3, 5
Cytarabine	100	Every 12h, Days 1-10
Thioguanine	100	Every 12h, Days 1-10
DAT 3+8		
Daunorubicin	50	Daily, Days 1, 3, 5
Cytarabine	100	Every 12h, Days 1-8
Thioguanine	100	Every 12h, Days 1-8
ADE 10+3+5		
Cytarabine	100	Every 12h, Days 1-10
Daunorubicin	50	Daily, Days 1, 3, 5
Etoposide	100	Daily, Days 1-5
ADE 8+3+5		
Cytarabine	100	Every 12h, Days 1-8
Daunorubicin	50	Daily, Days 1, 3, 5
Etoposide	100	Daily, Days 1-5

b) AML 11



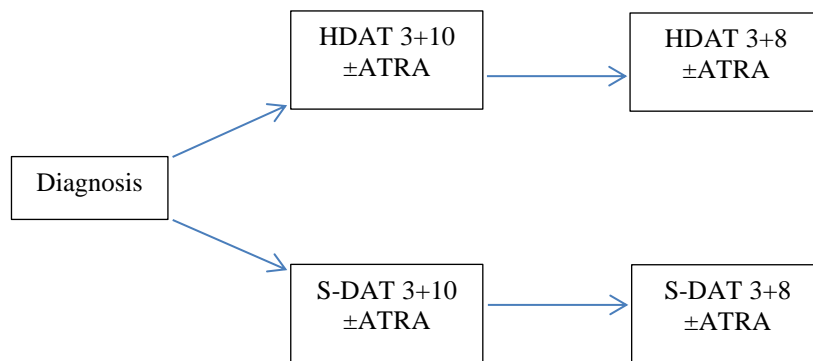
Regimen	Dose(mg/m ²)	Timing
DAT 3+10		
Daunorubicin	50	Daily, Days 1, 3, 5
Cytarabine	100	Every 12h, Days 1-10
Thioguanine	100	Every 12h, Days 1-10
DAT 2+5		
Daunorubicin	50	Daily, Days 1, 3
Cytarabine	100	Every 12h, Days 1-5
Thioguanine	100	Every 12h, Days 1-5
ADE 10+3+5		
Cytarabine	100	Every 12h, Days 1-10
Daunorubicin	50	Daily, Days 1, 3, 5
Etoposide	100	Daily, Days 1-5
ADE 5+2+5		
Cytarabine	100	Every 12h, Days 1-5
Daunorubicin	50	Daily, Days 1, 3
Etoposide	100	Daily, Days 1-5
MAC 3+5		
Mitoxantrone	12	Daily, Days 1-3
Cytarabine	100	Every 12h, Days 1-5
MAC 2+5		
Mitoxantrone	12	Daily, Days 1-2
Cytarabine	100	Every 12h, Days 1-5

c) AML 12 Rota A (Pre-protocol amendment)



Regimen	Dose(mg/m ²)	Timing
ADE 10+3+5		
Cytarabine	100	Every 12h, Days 1-10
Daunorubicin	50	Daily, Days 1, 3, 5
Etoposide	100	Daily, Days 1-5
ADE 8+3+5		
Cytarabine	100	Every 12h, Days 1-8
Daunorubicin	50	Daily, Days 1, 3, 5
Etoposide	100	Daily, Days 1-5
MAE 10+3+5		
Mitoxantrone	12	Daily, Days 1-3
Cytarabine	100	Every 12h, Days 1-10
Etoposide	100	Daily, Days 1-5
MAE 8+3+5		
Mitoxantrone	12	Daily, Days 1-3
Cytarabine	100	Every 12h, Days 1-10
Etoposide	100	Daily, Days 1-5

d) AML rota B (Post-protocol amendment)

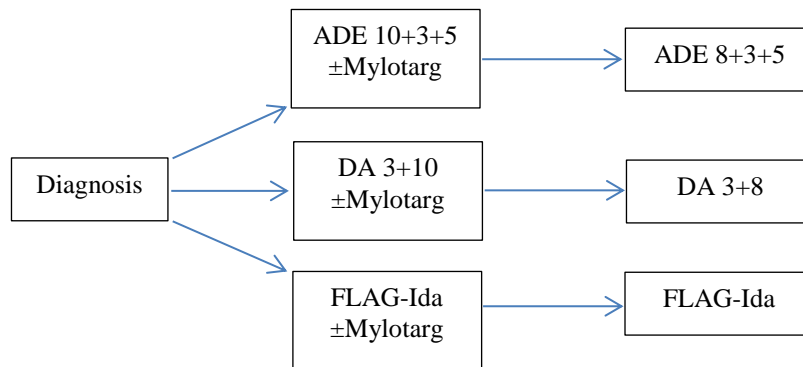


Regimen	Dose(mg/m ²)	Timing
H-DAT 3+10		
Daunorubicin	50	Daily, Days 1, 3, 5
Cytarabine	200	Every 12h, Days 1-10
Thioguanine	100	Every 12h, Days 1-10
H-DAT 3+8		
Daunorubicin	50	Daily, Days 1, 3, 5
Cytarabine	200	Every 12h, Days 1-8
Thioguanine	100	Every 12h, Days 1-8
S-DAT 3+10		
Daunorubicin	50	Daily, Days 1, 3, 5
Cytarabine	100	Every 12h, Days 1-10
Thioguanine	100	Every 12h, Days 1-10
S-DAT 3+8		
Daunorubicin	50	Daily, Days 1, 3, 5
Cytarabine	100	Every 12h, Days 1-8
Thioguanine	100	Every 12h, Days 1-8

e) AML 14

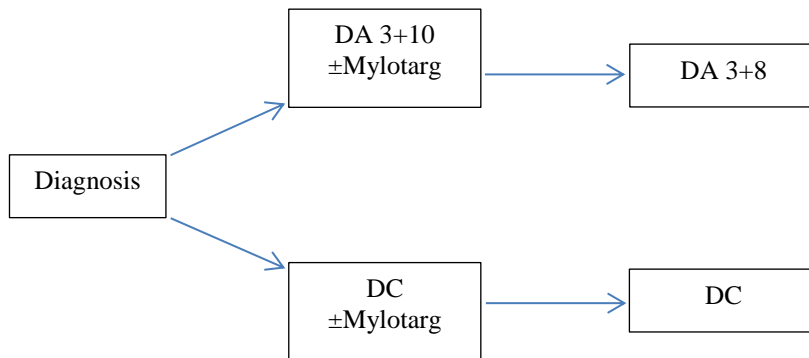
Regimen	Dose(mg/m²)	Timing
Course 1		
DAT 3+10		
Daunorubicin	35 or 50	Daily, Days 1, 3, 5
Cytarabine	200 or 400	Every 12h, Days 1-10
Thioguanine	100	Every 12h, Days 1-10
±PSC 833	2mg/kg + 10mg/kg/24hr	Days 1-3
Course 2		
DAT 3+8		
Daunorubicin	35 or 50	Daily, Days 1, 3, 5
Cytarabine	200 or 400	Every 12h, Days 1-8
Thioguanine	100	Every 12h, Days 1-8
±PSC 833	2mg/kg + 10mg/kg/24hr	Days 1-3

f) AML 15



Regimen	Dose(mg/m ²)	Timing
ADE 10+3+5		
Cytarabine	100	Every 12h, Days 1-10
Daunorubicin	50	Daily, Days 1, 3, 5
Etoposide	100	Daily, Days 1-5
ADE 8+3+5		
Cytarabine	100	Every 12h, Days 1-8
Daunorubicin	50	Daily, Days 1, 3, 5
Etoposide	100	Daily, Days 1-5
DA 3+10		
Daunorubicin	50	Daily, Days 1, 3, 5
Cytarabine	100	Every 12h, Days 1-10
DA 3+8		
Daunorubicin	50	Daily, Days 1, 3, 5
Cytarabine	100	Every 12h, Days 1-8
FLAG-Ida		
Fludarabine	30	Daily, Days 2-6
Cytarabine	2000	Daily, Days 2-6
GCSF (Lenograstim)	263µg STAT	Daily, Days 1-7
Idarubicin	8	Daily, Days 4-6
Mylotarg		
Gemtuzumab ozogamicin	3	Day 1

g) AML 16



Regimen	Dose(mg/m ²)	Timing
DA 3+10		
Daunorubicin	50	Daily, Days 1, 3, 5
Cytarabine	100	Every 12h, Days 1-10
DA 3+8		
Daunorubicin	50	Daily, Days 1, 3, 5
Cytarabine	100	Every 12h, Days 1-8
DC		
Daunorubicin	50	Daily, Days 1, 3, 5
Clofarabine	100	Daily, Days 1-5
Mylotarg		
Gemtuzumab ozogamicin	3	Day 1

Table 1: Demographics of patients in the defined cohorts studied.

Category	RES	PR	REF 1	REF2
Total	2548	1746	802	473
Trial				
AML10	374 (15%)	263 (15%)	111 (14%)	100 (21%)
AML11	412 (16%)	261 (15%)	151 (19%)	96 (20%)
AML12	500 (20%)	350 (20%)	150 (19%)	61 (13%)
AML14	274 (11%)	196 (11%)	78 (10%)	30 (6%)
AML15	514 (23%)	392 (22%)	182 (23%)	97 (21%)
AML16	414 (16%)	284 (16%)	130 (16%)	89 (19%)
Age				
16-29	216 (8%)	160 (9%)	56 (7%)	50 (11%)
30-39	258 (10%)	167 (10%)	91 (11%)	44 (9%)
40-49	381 (15%)	275 (16%)	06 (13%)	71 (15%)
50-59	540 (21%)	367 (21%)	173 (22%)	88 (19%)
60-69	832 (33%)	556 (32%)	276 (34%)	155 (33%)
70+	321 (13%)	221 (13%)	100 (12%)	65 (14%)
Median (range)	58 (16-82)		58 (16-80)	58 (16-79)
Sex				
Female	1129 (44%)	803 (46%)	326 (41%)	192 (41%)
Male	1419 (56%)	943 (54%)	476 (59%)	281 (59%)
Diagnosis				
De Novo	2094 (82%)	1419 (81%)	675 (84%)	390 (82%)
Secondary	454 (18%)	327 (19%)	127 (16%)	83 (18%)
Performance Status				
WHO 0	1333 (52%)	910 (52%)	423 (53%)	232 (49%)
WHO 1	737 (29%)	496 (28%)	241 (30%)	132 (28%)
WHO 2	321 (13%)	226 (13%)	95 (12%)	77 (16%)
WHO 3	138 (5%)	103 (6%)	35 (4%)	26 (5%)
WHO 4	19 (1%)	11 (1%)	8 (1)	6 (1%)
WBC				
0-9.9	861 (34%)	604 (35%)	257 (32%)	113 (24)
10-49.9	764 (30%)	528 (30%)	236 (29%)	139 (29)
50-99.9	866 (34%)	575 (33%)	291 (36%)	212 (45)
100+	57 (2%)	39 (2%)	18 (2%)	9 (2)
Unknown	0	0	0	0
Median (range)	30.9 (0.3-454)		30.9 (0.6-454)	30.9 (0.6-291)
Cytogenetics				
Favourable	73 (3%)	66 (5%)	7 (1%)	4 (1%)
Intermediate	1479 (70%)	1070 (73%)	409 (62%)	267 (68%)

Adverse Unknown	571 (27%) 425	328 (22%) 282	243 (37%) 143	119 (31%) 83
ITD mutation				
WT	765 (78%)	517 (77%)	248 (80%)	133 (77%)
Mutant	219 (22%)	158 (23%)	61 (20%)	39 (22)
Unknown	1564	1071	493	301
NPM mutation				
WT	740 (79%)	489 (75%)	251 (87%)	138 (84%)
Mutant	198 (21%)	161 (25%)	37 (13%)	26 (16%)
Unknown	1610	1096	514	309
Status post C1				
Not "refractory (Ref 1b)"	1375 (63%)			226 (52%)
"Refractory"				208 (48%)
Not known	802 (37%) 371			39