JPLSG Studies for AML

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On behalf of the AML committee,
the Japanese Pediatric Leukemia/Lymphoma Study group (JPLSG)

COI

- Nothing to disclose

Estimated number of patients in Japan

Total population of Japan: 120 million
Population less than 15 year of age in Japan: 18 million

ALL	500 /year
AML	150 /year

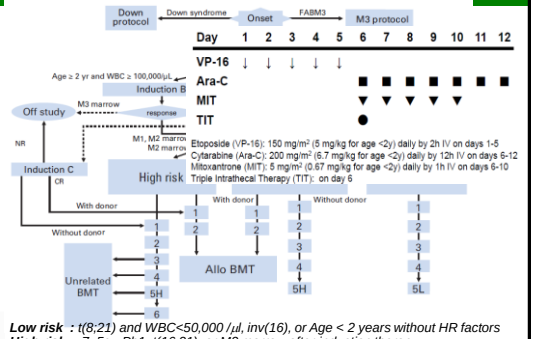
(de novo AML, APL, AML-DS)

Major concepts of AML studies in Japan

Improve the outcome of children with AML by …

1. *Intensifying post-remission therapy with high dose Ara-C*
2. *Reducing the cumulative doses of anthracyclines*
3. *Limiting the indication of allogeneic hematopoietic stem cell transplantation (HSCT) in 1CR*

AML99 (2000-02): Treatment schema



***Low risk* :** *t(8;21) and WBC<50,000 /μl, inv(16), or Age < 2 years without HR factors*
***High risk* :** *-7, 5q-, Ph1, t(16;21), or M2 marrow after induction therapy*
***Intermediate risk* :** *other than LR and HR*

Tsukimoto I, et al. *J Clin Oncol* 2009

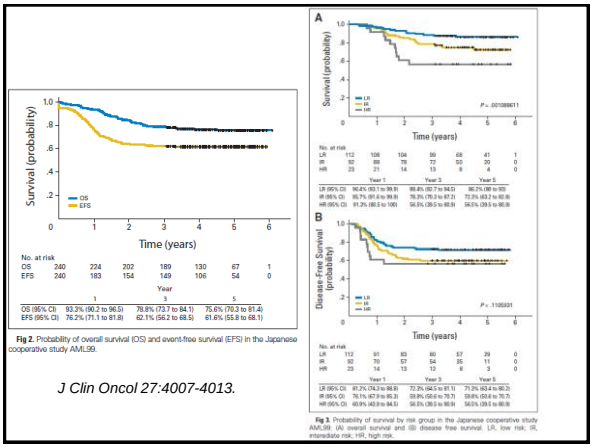


Fig 2. Probability of overall survival (OS) and event-free survival (EFS) in the Japanese cooperative study AML99.

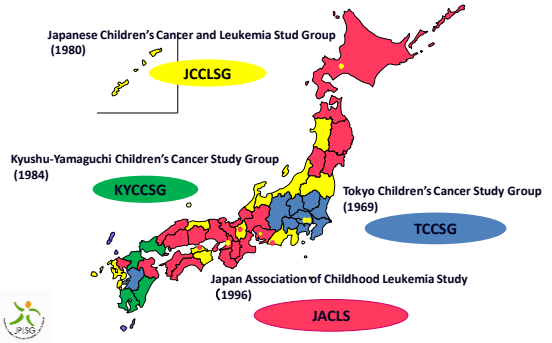
J Clin Oncol 27:4007-4013.

Childhood AML : Recent results of major study groups

Study	N	CR	# of courses	Allo SCT	pEFS (y)	pOS (y)
Japan AML99 2000-2002	240	94 %	6	19 %	61 % (5)	75 % (5)
SJCRH AML02 2002-2008	230	94 %	5	27 %	63 % (3)	71 % (3)
MRC AML12 1995-2002	455	92 %	4 – 5	7 %	56 % (5)	66 % (5)
BFM2004 2004-2009	566		4 – 5 + maintenance	NA	54 % (5)	72 % (5)
NOPHO93 1993-2000	243	92 %	6 – 7	23 %	48 % (5)	65 % (5)
CCG2961 1996-2002	901	88 %	3	18 %	42 % (5)	52 % (5)

Japanese Pediatric Leukemia/Lymphoma Study Group

Established in Nov. 2003



JPLSG AML-05 trial

- **The first "all Japan" AML trial excluding APL & DS-ML**
- **Nov, 2006 – Dec, 2010**
- **Main study objectives**

  To evaluate an efficacy of the post-remission chemotherapy consisted of 3 courses (total 5 courses) with reduced cumulative doses of anthracyclines and etoposide.

  To evaluate an efficacy of the post-remission chemotherapy consisted of 3 courses (total 5 courses) without allo-HSCT in 1CR

  To evaluate an efficacy of allo-HSCT in 1CR.

AML-05 : Study endpoints

- ***Primary endpoint***

  3-year EFS for each risk groups

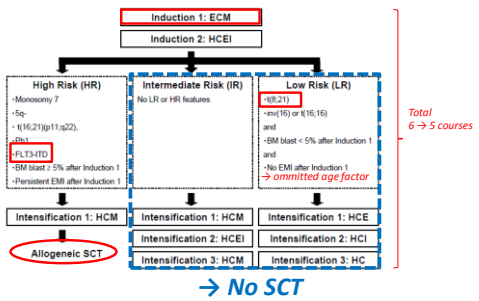
- ***Secondary endpoint***

  By risk group : 3-year OS
  Grade 3&4 AEs（CTCAEv3.0）
  Feasibility of the protocol regimen

  Overall : 3yeas EFS&OS
  CR rate
  CR rate after Induction-1
  Feasibility of the protocol regimen

AML-05: Treatment schema

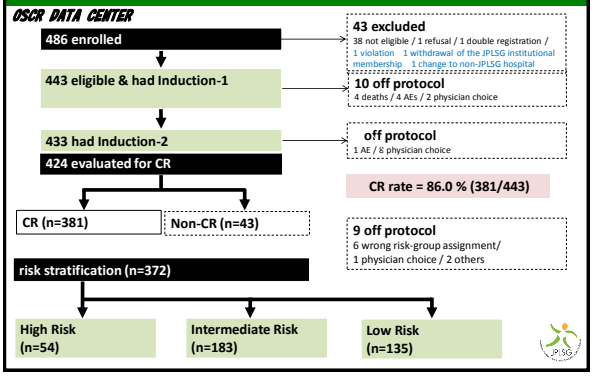
De novo AML (including AML with MLD), age ≤18yrs



→ No SCT

C, ara-C; HC, HD ara-C; M, mitoxantrone; I, Idarubicin; E, etoposide

AML-05 : Study flow chart



AML-05 : Patient characteristics (1)

Total, N=443	N	%
Age at diagnosis, years		
0-<1	45	10.1%
1-<2	58	13.1%
2-<10	167	37.7%
10-<15	143	32.3%
≥15	30	6.8%
Sex		
Male	238	53.7%
Female	205	46.3%
WBC at diagnosis, /μL		
– 10K	156	35.2%
10K – 50K	165	37.2%
50K – 100K	58	13.1%
100K –	64	14.5%

AML-05 : Patient characteristics (2)

FAB classification, N=443	N	%
M0	8	1.8%
M1	57	12.9%
M2	117	26.4%
M3	1	0.2%
M4	47	10.6%
M4Eo	15	3.4%
M5a	75	16.9%
M5b	19	4.3%
M6	10	2.3%
M7	48	10.8%
RAEB-T	39	8.8%
RAEB	3	0.7%
ND	4	0.9%

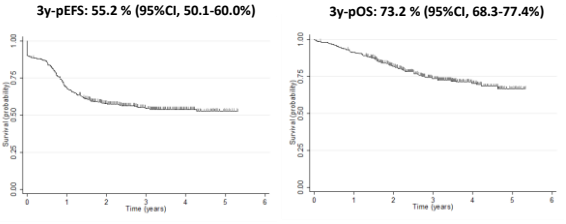
AML-05 : Patient characteristics (3)

Total, N=443	N	%
Cytogenetics		
t(8;21)(q22;q22)	122	27.5%
inv(16)(p13.1q22) or t(16;16)(p13.1;q22)	32	7.2%
t(9;11)(p22;q23)	39	8.8%
Other 11q23 abnormalities	30	6.8%
t(6;9)(p23;q34)	3	0.7%
inv(3)(q21q26.2) or t(3;3)(q21;q26.2)	2	0.5%
Normal karyotype	80	18.0%
Others	132	29.8%
ND	3	0.7%
FLT3-ITD		
Positive	47	10.6%
Negative	395	89.2%
ND	1	0.2%

AML-05 : Patient characteristics (4)

WHO classification 2008, N=443	N	%
AML with recurrent genetic abnormalities		
t(8;21)(q22;q22)/*RUNX1-RUNX1T1*	122	27.5%
inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB-MYH11*	32	7.2%
t(9;11)(p22;q23)/*MLL-MLLT3(AF9)*	39	8.8%
Other 11q23/*MLL* abnormalities	30	6.8%
t(6;9)(p23;q34)/*DEK-NUP214*	3	0.7%
inv(3)(q21q26.2) or t(3;3)(q21;q26.2)/*RPN1-EVI1*	2	0.5%
t(1;22)(p13;q13)/*RBM15-MKL1*	3	0.7%
AML with myelodysplasia-related changes	93	21.0%
AML, NOS		
AML with minimal differentiation	9	2.0%
AML without maturation	29	6.6%
AML with maturation	17	3.8%
Acute myelomonocytic leukemia	13	2.9%
Acute monoblastic and monocytic leukemia	20	4.5%
Acute erythroid leukemia	2	0.5%
Acute megakaryoblastic leukemia	21	4.7%
Mixed phenotype acute leukemia, B/myeloid, NOS	1	0.2%
Mixed phenotype acute leukemia, T/myeloid, NOS	7	1.6%

AML-05 : 3y-pEFS & pOS



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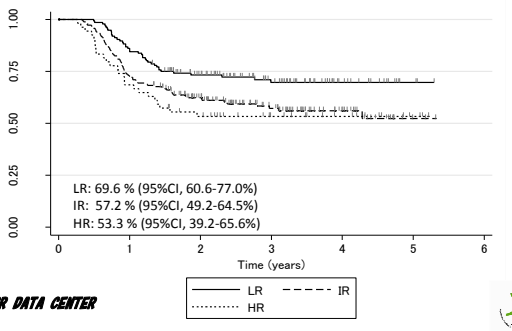
AML-05 : 3y-pEFS by risk groups



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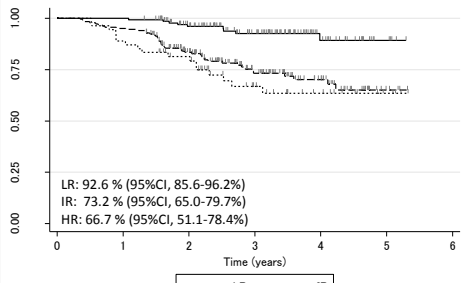
AML-05 : 3y-pOS by risk groups



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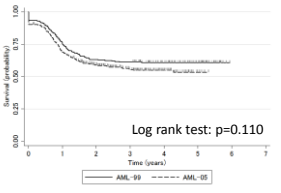
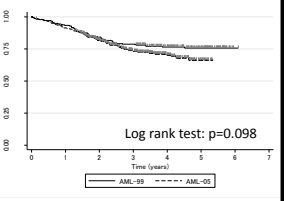
AML-05 vs AML99 : 3y-pEFS & pOS

3y-pEFS
AML99: 61.2% (95%CI, 54.7-67.0%)
AML-05: 55.2% (95%CI, 50.1-60.0%)



3y-pOS
AML99: 78.7% (95%CI, 73.0-83.4%)
AML-05: 73.2 % (95%CI, 68.3-77.4%)



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2012 ASH Annual Meeting and Exposition

December 8-11, 2012

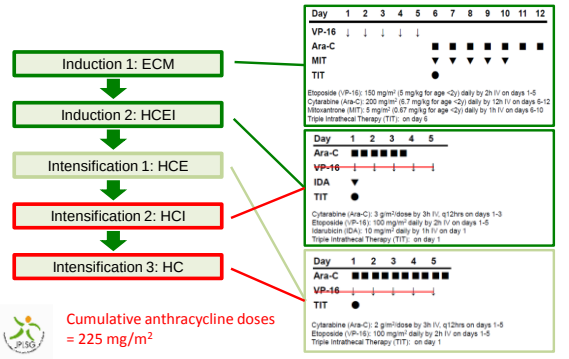
■ Oral presentation

- Tomizawa D, *et al*. Excess Reduction of Anthracyclines Results in Inferior Event-Free Survival in Core Binding Factor Acute Myeloid Leukemia in Children; A Report From the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG)

■ Poster presentation

- Hasegawa D, *et al*. Attempts to optimize post-induction treatment in childhood acute myeloid leukemia without core binding factors: a report from the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG)
- Kinoshita A, *et al*. Myelodysplasia-related changes have adverse prognostic significance in children with acute myeloid leukemia; a report from the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG)
- Tomizawa D, *et al*. Appropriate Dose Modification in Induction Therapy Is Essential for the Treatment of Infants with Acute Myeloid Leukemia; A Report From the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG)

AML-05: LR chemotherapy regimen



Cumulative anthracycline doses
= 225 mg/m^2

AML-05 : Study flow chart

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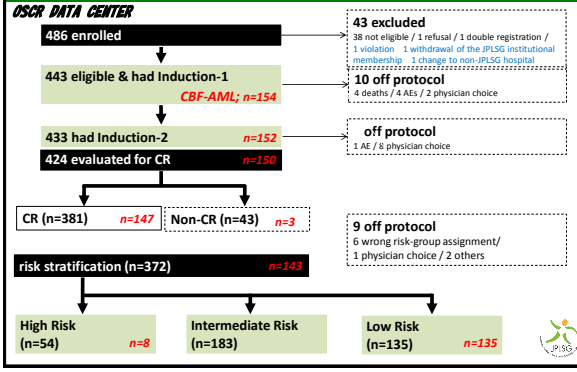

t(8;21) : Patient characteristics

		AML-05, n=122		AML99, n=77		p
		n	%	n	%	
Age at diagnosis, years	0-<2	1	0.8%	2	2.6%	
	2-<10	70	57.4%	43	55.8%	
	≥10	51	41.8%	32	41.6%	0.603
Sex	Male	72	59.0%	46	59.7%	
	Female	50	41.0%	31	40.3%	0.919
WBC at diagnosis, /μL	– 10K	62	50.8%	34	44.2%	
	10K – 50K	53	43.5%	34	44.2%	
	50K –	7	5.7%	9	11.6%	0.283
FAB classification	M1	16	13.1%	8	10.4%	
	M2	78	64.0%	63	81.8%	
	M4	2	1.6%	6	7.8%	
	M5a	1	0.8%	0	0.0%	
	RAEB-T	24	19.7%	0	0.0%	
	ND	1	0.8%	0	0.0%	<0.001
FLT3-ITD	Positive	3	2.5%	2	2.6%	
	Negative	119	97.5%	44	57.2%	
	ND	0	0.0%	31	40.3%	0.893

inv(16) : Patient characteristics

		AML-05, n=32		AML99, n=12		p
		n	%	n	%	
Age at diagnosis, years	0-<2	7	21.9%	1	8.3%	
	2-<10	10	31.2%	5	41.7%	
	≥10	15	46.9%	6	50.0%	0.555
Sex	Male	20	62.5%	7	58.3%	
	Female	12	37.5%	5	41.7%	0.800
WBC at diagnosis, /μL	– 10K	5	15.6&	1	8.3%	
	10K – 50K	6	18.8%	3	25.0%	
	50K –	21	65.6%	8	66.7%	0.775
FAB classification	M1	0	0.0%	2	16.7%	
	M2	4	12.5%	0	0.0%	
	M4	12	37.5%	3	25.0%	
	M4Eo	14	43.8%	4	33.3%	
	M5	1	3.1%	3	25.0%	
	RAEB-T	1	3.1%	0	0.0%	0.07
FLT3-ITD	Positive	2	6.2%	0	0.0%	
	Negative	30	93.8%	7	58.3%	
	ND	0	0.0%	5	41.7%	0.789

Core binding factor (CBF)-AML
AML-05 vs AML99 : Initial treatment response

	AML-05, n=154	AML99, n=89	p
BM blast < 5% after Ind-1	144 (93.5 %)	84 (95.4 %)	0.532
CR rate (after Ind-2)	147 (95.4 %)	87 (97.7 %)	0.361
Early death (≤ 42d)	1 (0.6 %)	0 (0.0 %)	0.446
Non-response	3 (1.9 %)	2 (2.2 %)	
Others*	3	0	

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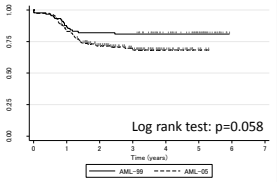
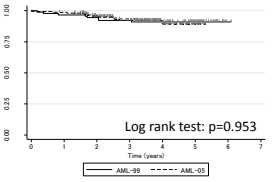
Core binding factor (CBF)-AML
AML-05 (n=154) vs AML99 (n=89) : 3y-pEFS & pOS

3y-pEFS
AML99: 80.9% (95%CI, 71.0-87.6%)
AML-05: 68.3% (95%CI, 59.9-75.4%)



3y-pOS
AML99: 92.1% (95%CI, 84.2-96.1%)
AML-05: 92.1 % (95%CI, 85.7-95.7%)



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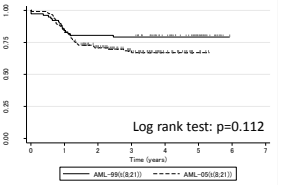
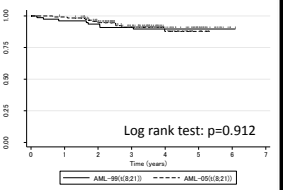
t(8;21)(q22;q22)
AML-05 (n=122) vs AML99 (n=77) : 3y-pEFS & pOS

3y-pEFS
AML99: 79.2% (95%CI, 68.3-86.7%)
AML-05: 67.0% (95%CI, 57.4-74.9%)



3y-pOS
AML99: 90.9% (95%CI, 81.8-95.5%)
AML-05: 91.0 % (95%CI, 83.3-95.3%)



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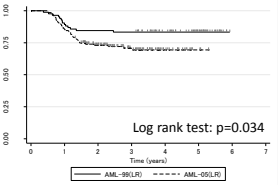
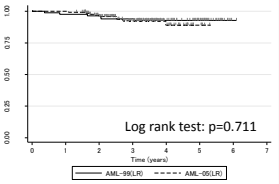
Low risk group (in AML-05 definition)
AML-05 (n=135) vs AML99 (n=84) : 3y-pEFS & pOS

3y-pEFS
AML99: 83.3% (95%CI, 73.4-89.7%)
AML-05: 69.6% (95%CI, 60.6-77.0%)



3y-pOS
AML99: 94.0 % (95%CI, 86.2-97.4%)
AML-05: 92.5 % (95%CI, 85.4-96.2%)



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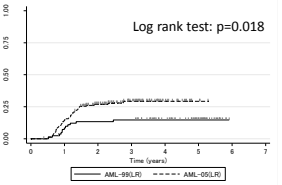
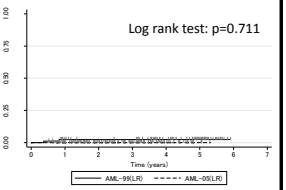
Low risk group (in AML-05 definition)
AML-05 (n=135) vs AML99 (n=84) : 3y-RR & Non-relapse mortality

3y-Relapse rate
AML99: 14.6% (95%CI, 8.5-24.2%)
AML-05: 29.1% (95%CI, 22.0-37.9%)



Non-relapse mortality
AML99: 0.0 %
AML-05: 2.4 % (95%CI, 0.6-9.3%)



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Low risk group (in AML-05 definition)
Univariate & multivariate analyses

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Protocol: AML-05 (vs. AML99*)	1.815 (0.984 – 3.350)	0.056	1.963 (1.061 – 3.632)	0.032
Age: ≥ 10 yrs (vs. < 10 yrs)	0.494 (0.272 – 0.899)	0.021	0.499 (0.274 – 0.909)	0.023
Sex: Female (vs. Male)	1.220 (0.711 – 2.091)	0.471	1.196 (0.696 – 2.056)	0.517
WBC: ≥ 50K/μL (vs. < 50K/μL)	0.892 (0.420 – 1.893)	0.776	1.632 (0.622 – 4.281)	0.319
Cytogenetics: inv(16) [vs. t(8;21)]	0.532 (0.228 – 1.245)	0.146	0.382 (0.128 – 1.138)	0.084

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Comparison of treatment for CBF-AML

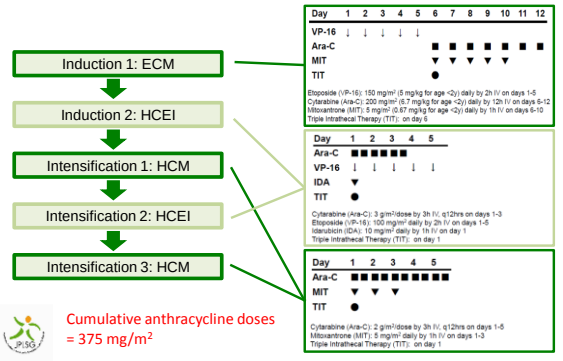
Study	# of courses	Ara-C (g/m²)	Anthracyclines (mg/m²)	EFS (yrs)	OS (yrs)
AML-BFM 98 1998-2003	4 – 5 + maintenance	41-47	420	t(8;21): 84 (5) inv(16): 70 (5)	t(8;21): 91 (5) inv(16): 87 (5)
MRC AML12 1995-2002	4 – 5	10.6-34.6	550-610	75 % (5) *DFS from CR	84 % (5) *OS from CR
NOPHO-AML 2004 2004-2009	6 – 7 ± GO	49.3	480	+GO: 38 (5) -GO: 50 (5)	NA
SJCRH AML02 2002-2008	5	51.6-67.6	550	85.8 (3)	90.6 (3)
CCG2961 1996-2002	3 ± IL-2 (No donor)	27.2-33.19	360	61 (5)	72 (5)
Japan AML99 2000-2002	6	78.4 (59.4, if IR)	300 (375, if IR)	80.9 (3)	92.1 (3)
JPLSG AML-05 2006-2010	5	77.4	225	69.3 (3)	92.2 (3)

Conversion rate of 5:1 was used to compare the cumulative dose of Daunorubicin and Mitoxantrone/Idarubicin.

Conclusions

- The pEFS of children with CBF-AML treated with very low cumulative dose of anthracyclines were inferior to the historical control even treated with intensive use of HD Ara-C.
- Caution is needed to reduce cumulative anthracycline doses to below 300mg/m².
- However, the fact that nearly 70% of the CBF-AML patients are cured with lower dose of anthracyclines suggest the presence of underlying biological factors to be identified for future stratification of CBF-AML in children.

AML-05: IR/HR chemotherapy regimen



Cumulative anthracycline doses = 375 mg/m²

Table 1. characteristics of non-CBF AML pts in AML-05 and AML99

		Non-CBF AML in AML-99 (n=151)		Non-CBF AML in AML-05 (n=289)		p
		N	%	N	%	
Age at diagnosis (years: mean±SD)		5.7±4.9		6.4±5.5		0.18
Sex (Male/Female)		75 / 76		146 / 143		0.87
WBC at diagnosis(/μL) (mean±SD)		62253.8±97601.0		57675.8±99091.0		0.64
WBC at diagnosis (/μL: <10x10³/≥10x10³)		122/29		237/52		0.76
FAB type	M0	10	(6.6%)	8	(2.8%)	0.02
	M1	26	(17.2%)	41	(14.2%)	
	M2	21	(13.9%)	35	(12.1%)	
	M3	0	(0.0%)	1	(0.4%)	
	M4	25	(16.5%)	33	(11.4%)	
	M4Eo	1	(0.7%)	1	(0.4%)	
	M5a	26	(17.2%)	74	(25.6%)	
	M5b	15	(9.9%)	18	(6.2%)	
	M6	3	(2.0%)	10	(3.5%)	
	M7	20	(13.3%)	48	(16.6%)	
	RAEB-T	0	(0.0%)	14	(4.8%)	
	RAEB	0	(0.0%)	3	(1.0%)	
	ND	4	(2.7%)	3	(1.0%)	
Cytogenetics	t(8;21)	0	(0.0%)	0	(0.0%)	0.054
	inv(16)	0	(0.0%)	0	(0.0%)	
	t(9;11)	15	(9.9%)	39	(13.5%)	
	11q23	26	(17.2%)	30	(10.4%)	
	Normal	53	(35.1%)	80	(27.7%)	
	Others	55	(36.4%)	137	(47.4%)	
	ND	2	(1.3%)	3	(1.0%)	
FLT3-ITD	negative	67	(44.4%)	246	(85.1%)	0.41
	positive	15	(9.9%)	42	(14.5%)	
	ND	69	(45.7%)	1	(0.4%)	

Table 2. comparison of outcome of non CBF-AML between AML-05 and AML99.

	AML99		AML-05		*p*-value
	N	%	N	%	
CR rate (after ind-1)	125/148	84.5	225/289	77.9	0.102
CR rate (after ind-2)	137/151	90.7	234/289	81.0	0.008
Early death (<42d)	3/151	2.0	6/289	2.1	0.950
Non-relapse mortality	11/151	7.3	44/289	15.2	0.017
Early death (<42d) in infant (<1yr)	1/26	3.8	5/44	11.4	0.13
HSCT in 1st CR	**40/151**	**26.4**	**47/289**	**16.3**	**0.011**

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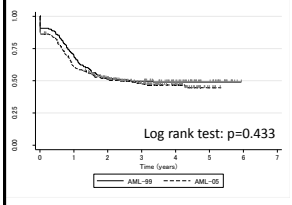
Non CBF-AML
AML-05 vs AML99 : 3y-pEFS & pOS

3y-pEFS
AML99: 49.6% (95%CI, 41.4-57.3%)
AML-05: 47.5% (95%CI, 41.1-53.5%)



3y-pOS
AML99: 70.8% (95%CI, 62.9-77.4%)
AML-05: 62.8 % (95%CI, 56.2-68.6%)

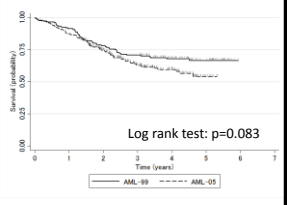


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Table 3. Multivariable analysis for event-free survival and overall survival

variable	Event-free survival			Overall survival		
	HR	95%CI	p	HR	95% CI	p
age 1-10y	0.94	0.57-1.56	0.82	0.67	0.36-1.23	0.19
age≥10y	0.89	0.53-1.50	0.66	0.83	0.45-1.56	0.57
female	0.75	0.54-1.04	0.08	0.87	0.58-1.29	0.48
WBC≥100,000/μl	1.46	0.98-2.19	0.07	1.26	0.76-2.08	0.37
FLT3-ITD	1.14	0.71-1.83	0.60	1.60	0.93-2.76	0.09
Unfavorable cytogenetics	1.16	0.69-1.97	0.57	1.80	0.98-3.33	0.06
CR after ind-1	0.26	0.18-0.38	<0.001	0.40	0.26-0.62	<0.001

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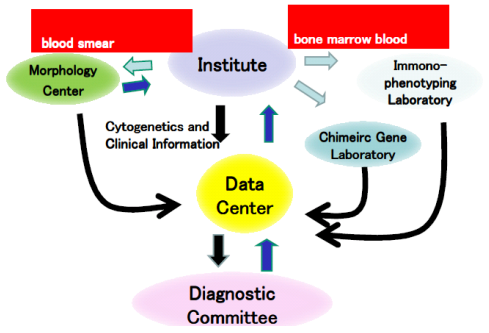
The Integrated Dagnosis in JPLSG AML-05



Final diagnosis according to the 2001 WHO classification

Table 1.Breakdown by WHO classification

Categories	Number of cases
AML with recurrent chromosomal abnormalities	**235(52.7%)**
AML-MRC	**93(20.8%)**
MLD,sole	**34**
Myelodysplasia rerated cytogenetics,sole	**53**
MLD+Myelodysplasia rerated cytogenetics	**6**
A previous history of myelodysplastic syndrome	**0**
AML-NOS	**111(24.8%)**
Mixed phenotype acute leukemia	**7(1.6%)**
Total	**446**

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40

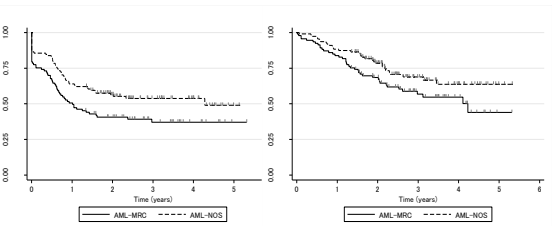
Table 2.Patient Characteristics

		AML-MRC	AML-NOS	P
n		93	111	
Age (years; mean±SD)		5.8±5.6	8.0±5.4	0.005
Sex	Male/Female	48/45	57/54	0.970
WBC at diagnosis	>10K/<10K	10/83	26/85	0.018
Karyotype	normal	22	63	
	Complex karyotype	46	0	
	Complex karyotype + -7	1	0	
	Complex karyotype + 5q-	6	0	
	Complex karyotype + 9q-	1	0	
	-7	6	0	
	9q-	4	0	
	others	9	45	
	unknown	0	3	
FLT3-ITD	Negative/Positive	83/10	83/27	0.011

Figure 1.AML-MRC vs AML-NOS: 3y-pEFS & pOS

3y-pEFS
AML-MRC(n=93): 37.1% (95%CI, 26.9-47.3%)
AML-NOS(n=111): 53.8% (95%CI, 43.8-62.8%)
Log rank test: p=0.017

3y-pOS
AML-MRC(n=93): 56.8% (95%CI, 45.2-66.8%)
AML-NOS(n=111): 66.9 % (95%CI, 58.2-77.4%)
Log rank test: p=0.053



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42

Table 3. Univariate analysis and multivariate analysis of risk factors for EFS

variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR(95% CI)	P
Age 1-10 years	0.79 (0.36-1.72)	0.55	0.86 (0.39-1.89)	0.70
Age>10 years	0.70 (0.31-1.61)	0.40	0.70 (0.26-1.87)	0.48
Female	0.68 (0.40-1.16)	0.16	0.63 (0.36-1.10)	0.10
WBC>10K	1.43 (0.65-3.15)	0.38	1.78 (0.75-4.20)	0.19
FLT3-ITD	1.83 (0.86-3.88)	0.12	2.13 (0.89-5.15)	0.09
High risk cytogenetics	1.23 (0.70-2.15)	0.47	1.32 (0.70-2.15)	0.39
MLD	0.61 (0.34-1.11)	0.11	0.17 (0.02-1.24)	0.08
MDS-related cytogenetics	1.22 (0.67-2.24)	0.52	0.23(0.03-1.86)	0.17
MLD +MDS-related cytogenetics	0.20 (0.03-1.43)	0.11	-	-

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43

Table 4. Univariate analysis and multivariate analysis of risk factors for OS

variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR(95% CI)	P
Age 1-10 years	0.47 (0.20-1.13)	0.09	0.42 (0.17-1.01)	0.05
Age>10 years	0.73 (0.30-1.79)	0.49	0.54 (0.20-1.49)	0.24
Female	0.73 (0.39-1.36)	0.32	0.83 (0.43-1.62)	0.59
WBC>10K	1.22 (0.48-3.11)	0.68	1.32(0.47-3.73)	0.60
FLT3-ITD	2.61 (1.14-6.00)	0.02	3.00(1.15-7.84)	0.03
High risk cytogenetics	1.42 (0.74-2.73)	0.29	1.83(0.89-3.76)	0.10
MLD	0.63 (0.31-1.28)	0.20	-	-
MDS-related cytogenetics	1.15 (0.56-2.35)	0.71	-	-
MLD+ MDS-related cytogenetics	0.04 (0.00-9.39)	0.25	-	-

AML-05: Early death in infants

Age	AML-05 (11/06 – 4/09)			AML99 (1/00 – 12/02)		
	Total patients	Early death N	Early death rate	Total patients	Early death N	Early death rate
0 - < 1y	32	7*	21.8 %	27	1	3.7 %
≥ 1y	243	2†	0.8 %	213	3	1.4 %
all	275	9	3.2 %	240	4	1.6 %

- Study accrual for patients aged < 1 year was suspended on 4/2/2009.
- The accrual of infants were restarted on 8/11/2009 after study amendment. Since then, no fatal cases are observed.

Patient characteristics (1)

		< 1yr, n=45		1 - < 2yr, n=58		≥ 2yr, n=340		p
		n	%	n	%	n	%	
Sex	Male	20	44%	32	55%	186	55%	
	Female	25	56%	26	45%	154	45%	0.419
WBC at diagnosis, /μL	– 10K	8	18%	20	34%	128	38%	
	10K – 50K	25	56%	23	40%	117	34%	
	50K –	12	26%	15	26%	95	28%	0.051
FAB classification	M0	0	0%	0	0%	8	2%	
	M1	2	5%	3	5%	52	15%	
	M2	1	2%	2	3%	114	34%	
	M3	1	2%	0	0%	0	0%	
	M4	3	7%	4	7%	40	12%	
	M4Eo	1	2%	5	9%	9	3%	
	M5a	15	33%	11	19%	49	14%	
	M5b	4	9%	4	7%	11	3%	
	M6	0	0%	5	9%	5	1%	
	M7	14	31%	21	36%	13	4%	
	RAEB	1	2%	1	2%	1	0.3%	
	RAEB-T	1	2%	2	3%	36	11%	
	ND	2	5%	0	0%	2	0.7%	

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Patient characteristics (2)

	< 1yr, n=45		1 - < 2yr, n=58		≥ 2yr, n=340		p
	n	%	n	%	n	%	
Cytogenetics							
t(8;21)(q22;q22)	0	0%	1	2%	121	36%	<0.001
inv(16)(p13.1q22)	1	2%	6	10%	25	7%	0.282
t(9;11)(p22;q23)	8	18%	9	16%	22	6%	0.006
Other 11q23 abnormalities	11	25%	4	7%	15	4%	<0.001
t(6;9)(p23;q34)	0	0%	0	0%	3	1%	0.586
inv(3)(q21q26.2)	0	0%	0	0%	2	1%	0.737
t(1;22)(p13;q13)	3	7%	0	0%	0	0%	0.009
t(7;12)(q36;p13)	2	4%	1	2%	0	0%	0.041
Normal karyotype	6	13%	6	10%	68	20%	0.143
Others	13	29%	31	53%	82	24%	<0.001
ND	1	2%	0	0%	2	1%	0.544
FLT3-ITD							
Positive	0	0%	3	5%	44	13%	
Negative	44	98%	55	95%	296	87%	
ND	1	2%	0	0%	0	0%	0.011

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Initial treatment response by age

	<1yr, n=45	1-<2yr, n=58	≥2yr, n=340	p
BM blast < 5% after Ind-1	28 (62.2 %)	51 (87.9 %)	290 (85.2 %)	0.001
CR rate (after Ind-2)	33 (73.3 %)	49 (84.4 %)	299 (87.9 %)	0.036
Early death (≤ 42d)	5 (11.1 %)	1 (1.7 %)	1 (0.2 %)	0.000
Non-response	5 (11.1 %)	6 (10.3 %)	32 (9.4 %)	0.922
Others*	2 (4.4 %)	2 (3.4 %)	8 (2.3%)	0.670

Off protocol before CR evaluation

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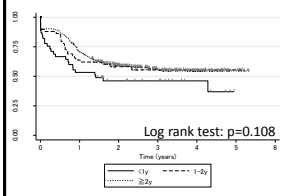
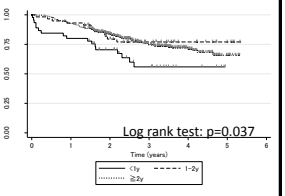
3y-pEFS & pOS by age
Age <1yr (n=45) vs 1-<2y (n=58) vs ≥2yr (n=340)

3y-pEFS
Age <1yr: 46.1% (95%CI, 31.1-59.9%)
Age 1-<2yr: 55.4% (95%CI, 41.2-67.5%)
Age ≥2yr: 55.2% (95%CI, 49.4-60.5%)



3y-pOS
Age <1yr: 55.9% (95%CI, 37.9-70.6%)
Age 1-<2yr: 77.0% (95%CI, 62.7-86.3%)
Age ≥2yr: 74.7% (95%CI, 69.2-79.4%)



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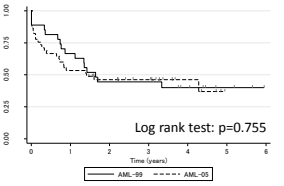
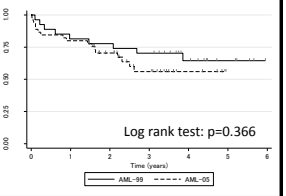
3y-pEFS & pOS in infants
AML-05 (n=45) vs AML99 (n=27)

3y-pEFS
AML-05: 46.1% (95%CI, 31.1-59.9%)
AML99: 44.4% (95%CI, 25.5-61.7%)



3y-pOS
AML-05: 55.9% (95%CI, 37.9-70.6%)
AML99: 70.3% (95%CI, 49.4-83.9%)



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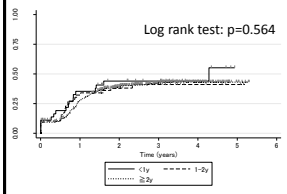
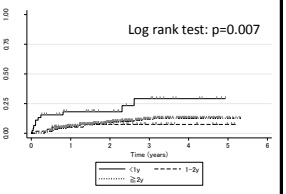
3y-RR & Non-relapse mortality by age
Age <1yr (n=45) vs 1-<2y (n=58) vs ≥2yr (n=340)

3y-Relapse rate
Age <1yr: 44.0% (95%CI, 29.8-61.2%)
Age 1-<2yr: 41.0% (95%CI, 29.0-55.8%)
Age ≥2yr: 42.6% (95%CI, 37.3-48.3%)



3y-Non-relapse mortality
Age <1yr: 29.2% (95%CI, 15.6-50.4%)
Age 1-<2yr: 7.4% (95%CI, 2.8-18.9%)
Age ≥2yr: 11.8% (95%CI, 8.3-16.7%)



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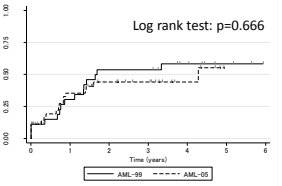
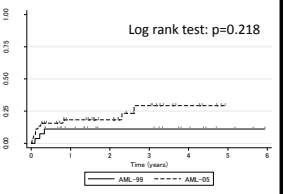
3y-RR & Non-relapse mortality in infants
AML-05 (n=45) vs AML99 (n=27)

3y-Relapse rate
AML-05: 44.0% (95%CI, 29.8-61.2%)
AML99: 53.6% (95%CI, 36.1-73.1%)



3y-Non-relapse mortality
Age <1yr: 29.2% (95%CI, 15.6-50.4%)
Age ≥1yr: 11.3% (95%CI, 8.1-15.7%)



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Infants (age <1yr): initial treatment response
pre- (n=28) vs post-amendment(n=17)

	Pre-, n=28	Post-, n=17	p
BM blast < 5% after Ind-1	16 (57.1 %)	12 (70.5 %)	0.367
CR rate (after Ind-2)	19 (67.9 %)	14 (82.4 %)	0.286
Early death (≤ 42d)	5 (17.9 %)	0 (0.0 %)	0.065
Non-response	2 (7.1 %)	3 (17.6 %)	0.269
Others*	2 (7.1 %)	0 (0.0 %)	0.381

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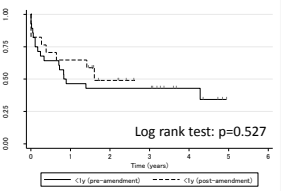
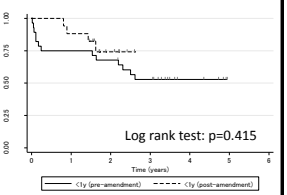
Infants (age <1yr): 2y-pEFS & pOS
pre- (n=28) vs post-amendment(n=17)

2y-pEFS
Pre-: 42.8% (95%CI, 24.5-59.9%)
Post-: 49.0% (95%CI, 13.3-22.0%)



2y-pOS
Pre-: 67.8% (95%CI, 47.3-81.8%)
Post-: 74.1% (95%CI, 44.0-89.6%)



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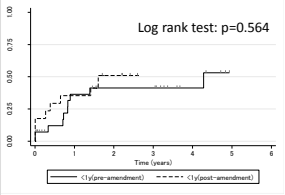
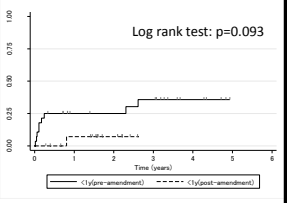
Infants (age <1yr): 3y-RR & Non-relapse mortality
pre- (n=28) vs post-amendment(n=17)

2y-Relapse rate
Pre-: 41.3% (95%CI, 23.8-64.8%)
Post-: 50.9% (95%CI, 28.5-77.9%)



2y-Non-relapse mortality
Pre-: 25.0% (95%CI, 12.7-45.3%)
Post-: 7.1% (95%CI, 1.0-40.9%)



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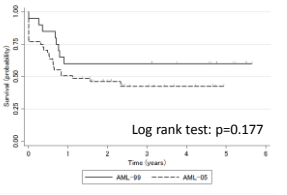
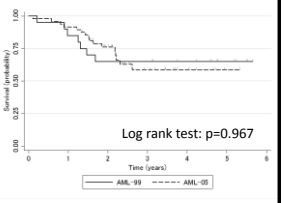
FAB M7
AML-05 vs AML99：3y-pEFS & pOS

3y-pEFS
AML99: 60.0% (95%CI, 35.7-77.6%)
AML-05: 42.4% (95%CI, 27.5-56.6%)



3y-pOS
AML99: 65.0% (95%CI, 40.3-81.5%)
AML-05: 58.7 % (95%CI, 40.4-73.1%)



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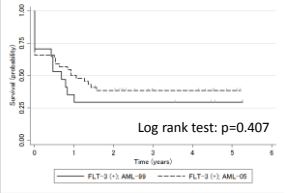
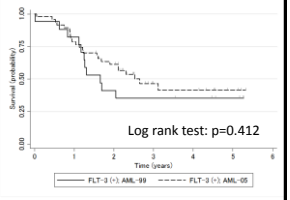
FLT3-ITD
AML-05 vs AML99：3y-pEFS & pOS

3y-pEFS
AML99: 29.4% (95%CI, 10.7-51.1%)
AML-05: 38.5% (95%CI, 24.5-52.3%)



3y-pOS
AML99: 35.2% (95%CI, 14.4-57.0%)
AML-05: 46.4 % (95%CI, 30.2-61.0%)



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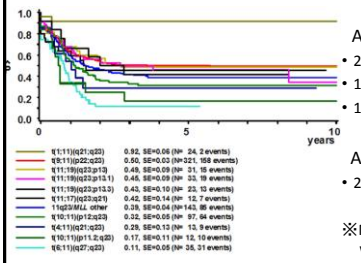
t(6;11)(q27;q23)/*MLL-MLLT4(AF6)*



AML99
- 2 cases both died
- 1case died in 1CR after SCT
- 1 case of IR after relapse (no SCT)

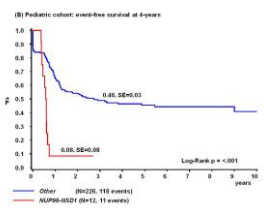
AML-05
- 2 cases (IR) both died after relapse

※MLL-AF10：AML-05； 5/8 alive w/o disease

(Balgobind BV. *Blood* 2009;114:2489-96)

NUP98-NSD1

- Ch11p15; *Nucleoporin* 98kD (*NUP98*) and Ch5q35; *nuclear receptor binding SET domain protein 1* (*NSD1*) translocation
- Crytric translocations
- Ped AML (DCOG/BFM/Paris):
  13/313 (4.2%) , 16.1% in CN-AML



(Hollink IH. *Blood* 2011;118:3645-3656)

【AML99】
- 6 cases（3.8%）
- 4y-OS=33%

【AML-05】
- 10 cases（2.9%）
- 8/10 dead（7cases relapse）
- 6/10 case non CR

Prognostic factors of AML-05 under invetigation

- Poor prognostic factors;

c-Kit mut (t(8;21)), Evi-1 expression(MLL), G-CSFR type IV (relapse rate?), CXCR4(?) DMNT3a (?, rare), survivin (?) Other new mutations (next generation sequencer)

- Favorite prognostic factors;

CEBPA mut(?), NPM mut (? rare)

Standard AML induction therapy: "3 + 7"

- **DNR:** 60 mg/m^2 x 3 days
  or **IDA / MIT:** 10-12 mg/m^2 x 3 days
- **Ara-C:** 100-200 mg/m^2 x 7 days
  continuous or twice daily IV

1. *Role of additional agents, especially etoposide ?*
2. *Optimal duration of induction regimen ?*
3. *Role of HD Ara-C ?*

Induction regimen in ped AML studies

Study Group	No. of Patients	Early Death Rate (%)	CR Rate (%)	Time of Evaluation	CR Rate (%) After One Course of Chemotherapy	Induction Regimen (/m^2)	No. of Courses
EORTC-CLG 58,921[11,12]	177	2	84	After 2 courses	69	Ara-C 100 mg 24 hours cont IV days 1-2; 100 mg/12 hours days 3 to 8; VP-16 150 mg IV day 3-5; MIT or IDA 10 mg days 6 to 8	4 Maintenance
LAME-91[13,14]	247	4	91	After 2 courses	84	Ara-C 200 mg 24h cont IV days 1 to 7; MIT 12 mg IV days 1 to 5	3 Maintenance
BFM-93[15-17]	427	7	83	After 4 courses	ND	Ara-C 100 mg 24 hours cont IV days 1 to 2; 100 mg/12 hours days 3 to 8; VP-16 150 mg IV days 6 to 8; DNR 60 mg or IDA 12 mg IV days 3 to 5	4 Maintenance
BFM-98[18,19]	473	3	88	After 4 or 5 courses	ND	Ara-C 100 mg 24 hours cont IV days 1 to 2, 100 mg/12 hours days 3 to 8; VP-16 150 mg IV days 6 t o 8; IDA 12 mg IV days 3 to 5	4 or 5 Maintenance
MRC-AML10[20,21]	303	4	93	After 4 courses	68	Ara-C 100 mg/12 hours IV days 1 to 10; DNR 50 mg IV days 1, 3, 5; 6-TG 75 mg/12 hours PO days 1 to 10 or VP-16 100 mg IV days 1 to 5	4
MRC-AML12[22,23]	455	4	92	After 4 courses	ND	Ara-C 100 mg/12 hours IV days 1 to 10; VP-16 100 mg IV days 1 to 5; DNR 50 mg IV days 1, 3, 5 or MIT 12 mg IV days 1, 3, 5	4 or 5
NOPHO-AML93[24,25]	223	2	92	After 2 or 3 courses	65	Ara-C 200 mg 24 hours cont IV days 1 to 4; VP-16 100 mg 24 hours cont IV days 1 to 4; DOX 75 mg 6 hours IV day 5; 6-TG 100 mg/12 hours PO days 1 to 4	6-8
POG-8821[26,27]	511	4	77	After 2 courses	ND	Ara-C 100 mg 2 hours cont IV days 1 to 7; DNR 45 mg IV days 1 to 5; 6-TG 100 mg PO days 1 to 7	9
CCG-2891[28,29]	750	4	78	After 2 courses	74	DEX 6 mg/12 hours; Ara-C 200 mg cont IV; 6-TG 100 mg/12 hours; VP-16 100 mg cont IV; DNR 20 mg cont IV days 1 to 4, 10 to 14, or 14 to 18	8
TCCSG AML M91-13 and M96-14[10]	192	3.6	88	ND	ND	Ara-C 200 mg 12 hours cont IV days 6 to 12; VP-16 150 mg 2 hours IV days 1 to 5; MIT 5 mg IV days 6 to 10	7 or 9
AML99	240	1.7	94	After 2 courses	86	Ara-C 200 mg 12 hours cont IV days 6 to 12; VP-16 150 mg 2 hours IV days 1 to 5; MIT 5 mg IV days 6 to 10	6

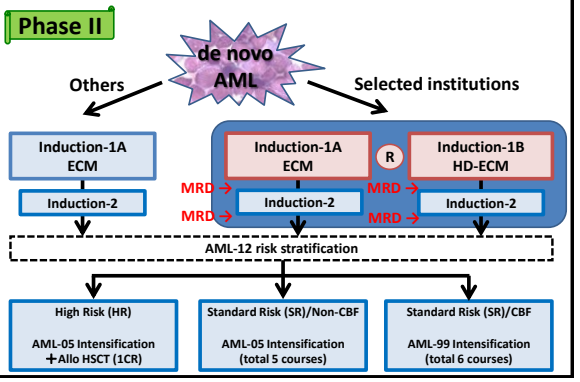
Tsukimoto I, et al. *J Clin Oncol* 2009

HD vs SD Ara-C … from pediatric studies

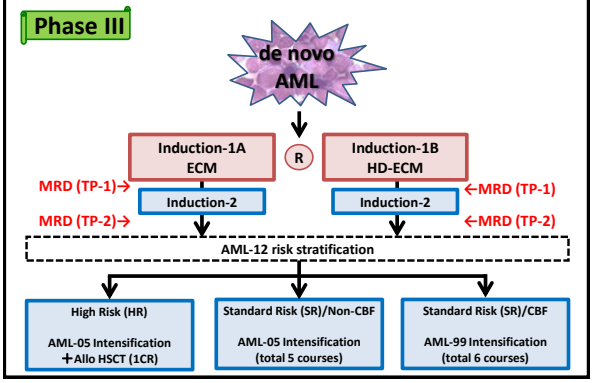
Study	Induction	Results (HDCA vs SDCA)
POG 9421 (1995-1999)	・HD-DAT: **Ara-C 1g/m^2 x2 d1-7** DNR 45mg/m2 d1-3 6TG 100mg/m2 d1-7 ・DAT: **Ara-C 100mg/m^2 x2 d1-7** DNR 45mg/m2 d1-3 6TG 100mg/m2 d1-7	・CR: 91.0% vs 87.9% (P=0.23) ・3yEFS:40.1% vs 35.2% (P=0.28)
SJCRH AML02 (2002-2008)	・HD-ADE: **Ara-C 3g/m^2 x2 d1,3,5** DNR 50mg/m2 d2,4,6 ETP 100mg/m2 d2-6 ・ADE: **Ara-C 100mg/m^2 x2 d1-10** DNR 50mg/m^2 d2,4,6 ETP 100mg/m^2 d2-6	・3yOS: 68.8% vs 73.4% (P=0.41) ・3yEFS:60.2% vs 65.7% (P=0.41) ・MRD% (after 1 course): 34% vs 42% (P=0.17)

Becton D, et al. *Blood* 2006
Rubnitz JEet al. *Lancet Oncol* 2010

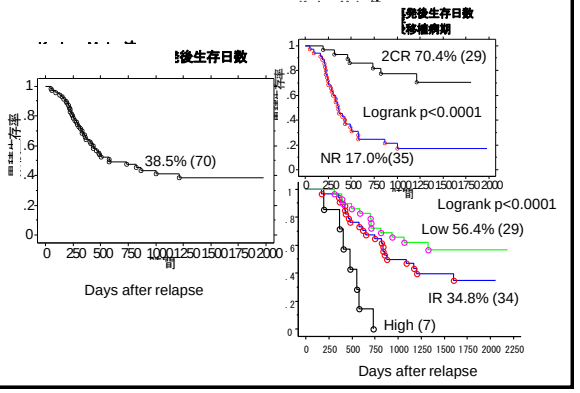
AML-12 : seamless phase II/III study



AML-12 : seamless phase II/III study



Results of relapsed AML99



AML-R11 (relapsed protocol)

Primary endpoint; CR after Induction therapy

Registration

Central review(morphology, FCM),
G－CSF type IV, WT1

Induction1: Ida FLAG

★MRD study
(FCM, WT1)

Intensification (any)

SCT (any)

Acute myeloid leukemia in Down syndrome (AML-DS)

Acute myeloid leukemia in Down syndrome (AML-DS) harbors unique characteristics;
・predominance of acute megakaryoblastic leukemia
・age predilection during the first 4 years of life
・higher sensitivity to chemotherapeutic agents which translate into a good treatment response as well as an increased treatment-related toxicities compared to the non-DS children with AML.

As a result, AML-DS children are treated separately from non-DS counterparts with less intensive treatment on the recent clinical studies in developed countries.

JPLSG AML-D05 study OBJECTIVES:

To evaluate an efficacy and safety of treatment strategy according to the risk stratification based on response to the initial induction therapy on Down syndrome with newly diagnosed childhood AML (excluding APL) and MDS.

Standard Risk group (SR): to evaluate efficacy and safety of the multi-agent combination chemotherapy reducing etoposide compared to AML 99 Down study.

High Risk group (HR): to evaluate efficacy and safety of the multi-agent combination chemotherapy consisted of continuous and high-dose cytarabine.

AML99 Down protocol

Induction

Day	1	2	3	4	5	6	7
cytarabine (100mg/m²1hrDIV)	↓	↓	↓	↓	↓	↓	↓
pirarubicin* (25mg/m² 1hrDIV)	↓	↓					
etoposide(150mg/m²2hrDIV)			↓	↓	↓		

M2 marrow after induction→ repeat induction regimen
M3 marrow after induction→ administer 2/3 dose of AML99 induction regimen A

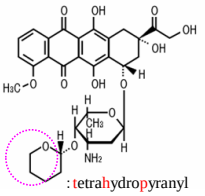
Consolidation
Repeat 4 cycles

CNS prophylaxis
No prophylaxis

* AT-Down protocol
(Kojima et al, Leukemia 14:786, 2000)
Daunorubicin 25mg/m²/day instead of Pirarubicin
Consolidation 5 cycles

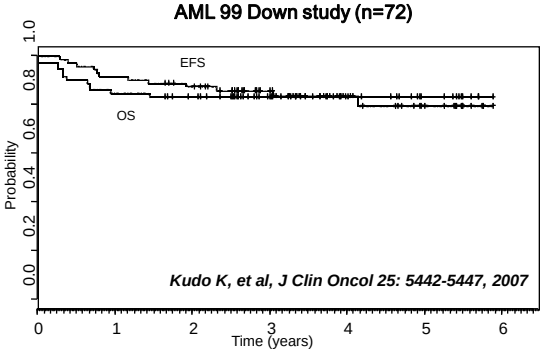
Pirarubicin(TetraHydroPyranyl-Adriamycin)

・A derivative of doxorubicin
・Approval date 1988
・Released in Japan, China, France
・Used for clinical trial of neuroblastoma, hepatoblastoma in Japan



Pirarubicin has shown a high antitumor activity on experimental tumor in mice and a ***lower cardiac toxicity*** in hamsters than other anthracycline antitumor agents.

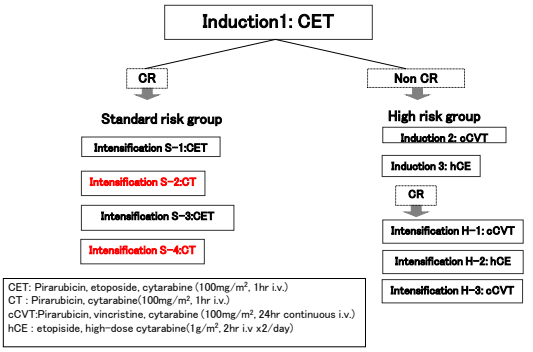
AML 99 Down study (n=72)



Kudo K, et al, J Clin Oncol 25: 5442-5447, 2007

Among the 72 patients, 70 achieved CR. Nine patients relapsed. One patient died from pneumonia during the first CR. Two patients received CBSCT in first CR. Fifty-eight patients remained in first CR. The 3-year OS was 84% and the 3-year EFS 83%, respectively.

JPLSG AML-D05 protocol



CET: Pirarubicin, etoposide, cytarabine (100mg/m², 1hr i.v.)
CT : Pirarubicin, cytarabine(100mg/m², 1hr i.v.)
cCVT:Pirarubicin, vincristine, cytarabine (100mg/m², 24hr continuous i.v.)
hCE : etopiside, high-dose cytarabine(1g/m², 2hr i.v x2/day)

JPLSG AML D05 study -Patients' characteristic-

Resistration Period：Jan 2007-Dec 2010
Patient number：72
21 trisomy Mozaic: Yes 3, No 64, Unknown 5
Male：Female = 36：36
Age：10 - 206 month (Median 20 month)
History of TAM: Yes 35, No 26, Unknown 11
Cardiac Complication：No 21, Yes 48, Unknown 3

Clinical trials for AML-DS in Japan

Study	Registry (Year)	N	Daunorubicin (mg/m²)	Ara-C (mg/m²)	Etoposide (mg/m²)	TRM (%)	OS (%)	EFS (%)
AT/Down	87-97	33	100-400	4200	2700	9	NA	80 (8y)
AML99 DS	00-04	72	250 *	3500	2250	1	84	83 (4y)
JCCLSG 9805DS	98 06	24	190 *	12600	200	12.5	88	83 (5y)
JPLSG AML-D05 (on going)	08-10		170-250 *	3500-12800	1050-1350	NA	NA	NA

*Pirarubicin (a derivative of doxorubicin)

Comparison of recent clinical trials for AML-DS

Study	Registry (Year)	N	Daunorubicin (mg/m²)	Ara-C (mg/m²)	Etoposide (mg/m²)	TRM (%)	OS (%)	EFS (%)
BFM98 for DS	98 03	67	220-240	23-29000	950	5	91	89 (3y)
BFM93	NA	51	220-400	23000	950	4	70	68 (3y)
NOPHO AML93	88 02	41	300	48600	1600	5	NA	85 (8y)
MRC AML10/12	88 02	46	670	10600	NA	15	74	74 (5y)
CCG 2861/2891	89-99	160	320	15800	1600	4	79	77 (6y)
POG 9421	95-99	57	100	20700		0	NA	79 (3y)
LD-cytarabine	90-03	34	0	7400	0	0	77	67(5y)
AT/Down	87-97	33	100-400	4200	2700	9	NA	80 (8y)
AML99 DS	00-04	72	250 *	3500	2250	1	84	83 (4y)
JCCLSG 9805DS	98 06	24	190 *	12600	200	12.5	88	83 (5y)
JPLSG AML D05	**08-10**	**72**	**170-250 ***	**3500-12800**	**1050-1350**	**(1)**	**(80)**	**(81)**

TRM, **treatment-related mortality; OS, overall survival; EFS, event-free survival; NA, not evaluated, *pirarubicin**

Poor prognosis for refractory/relapsed AML-DS

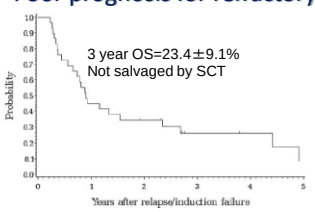


Figure 1. OS curve of R/R ML-DS. The 3-year OS rate was 25.9% ± 8.5%.

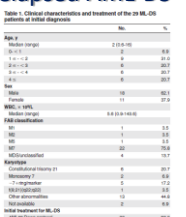


Table 4. Univariate and multivariate analyses of prognostic factors for refractory/relapsed ML-DS patients

Variables	Univariate analysis HR (95% CI)	P	Multivariate analyses Model 1 (baseline) HR (95% CI)	P	Model 2 (relapsed phase) HR (95% CI)	P
Sex: male vs female	0.78 (0.33-1.83)	.56	0.71 (0.30-1.71)	.45	0.85 (0.36-2.05)	.72
Age at initial diagnosis: < 2 y vs > 2 y	1.98 (0.83-4.72)	.12	2.73 (0.89-8.37)	.08	*	
WBC at initial diagnosis: ≥ 10 000/μL vs < 10 000/μL	0.57 (0.22-1.47)	.24	0.43 (0.15-1.19)	.10	0.60 (0.22-1.60)	.30
FAB classification: M7 vs others	1.63 (0.60-4.44)	.34	0.92 (0.27-3.09)	.89	1.88 (0.66-5.37)	.24
Disease status: IF or RL < 6 mo vs RL > 6 mo	2.92 (1.24-6.88)	.01	–		3.14 (1.28-7.67)	.012
Response to *r*-induction therapy: non-CR vs CR	16.54 (4.44-61.59)	< .0001	–		*	

Blood 2012, 120(9): 1810-1815

JPLSG AML-D11 OBJECTIVES:

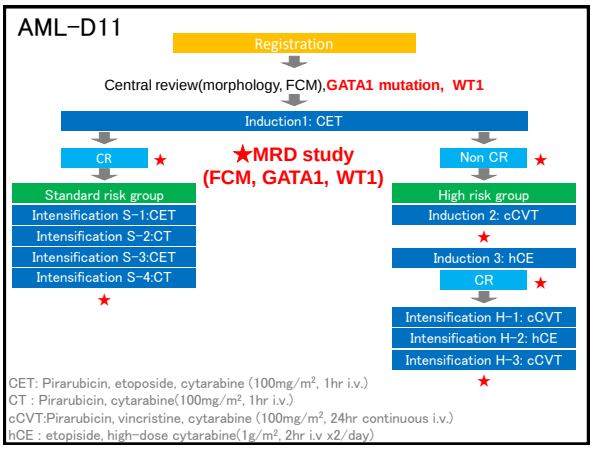
To evaluate a prognostic value of minimal residual disease (MRD) for the patients of myeloid leukemia with Down syndrome in a JPLSG AML-D05 backbone chemotherapy.

Primary end point:

- Rate of MRD positivity with different methods (FCM, GATA1 & WT1 transcript) after induction and at the completion of therapy

Secondary end point:

- Availability of MRD results
- Rate of GATA1 mutation in AML-DS patients
- EFS and OS



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