Recent results from the prospective studies on APL in the Japan Adult Leukemia Study Group (JALSG)

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the Japan Adult Leukemia Study Group (JALSG)

Summary of the study for APL studies in JALSG

	APL92	APL97	APL204	APL212
	Mar 92 - Aug 96	May 1997 - Jun 2002	Jun 2004 - Dec 2010	July 2012 -
Study design	Pilot	Phase 3	Phase 3	Phase 2
Pts registered	198	302	347	220
New Drugs or Strategies Applied	ATRA	Multi-agent chemotherapy for maintenance	New retinoid Am80 for maintenance	ATO & GO for consolidation Am80 for maintenance
Endpoint	CR rate & EFS	RFS after maintenance period	RFS after maintenance period	EFS
Results	Improved CR rate & EFS	Multi-agents maintenance Cx is not effective	Am80 during maintenance improved EFS in high risk group	In follow-up period

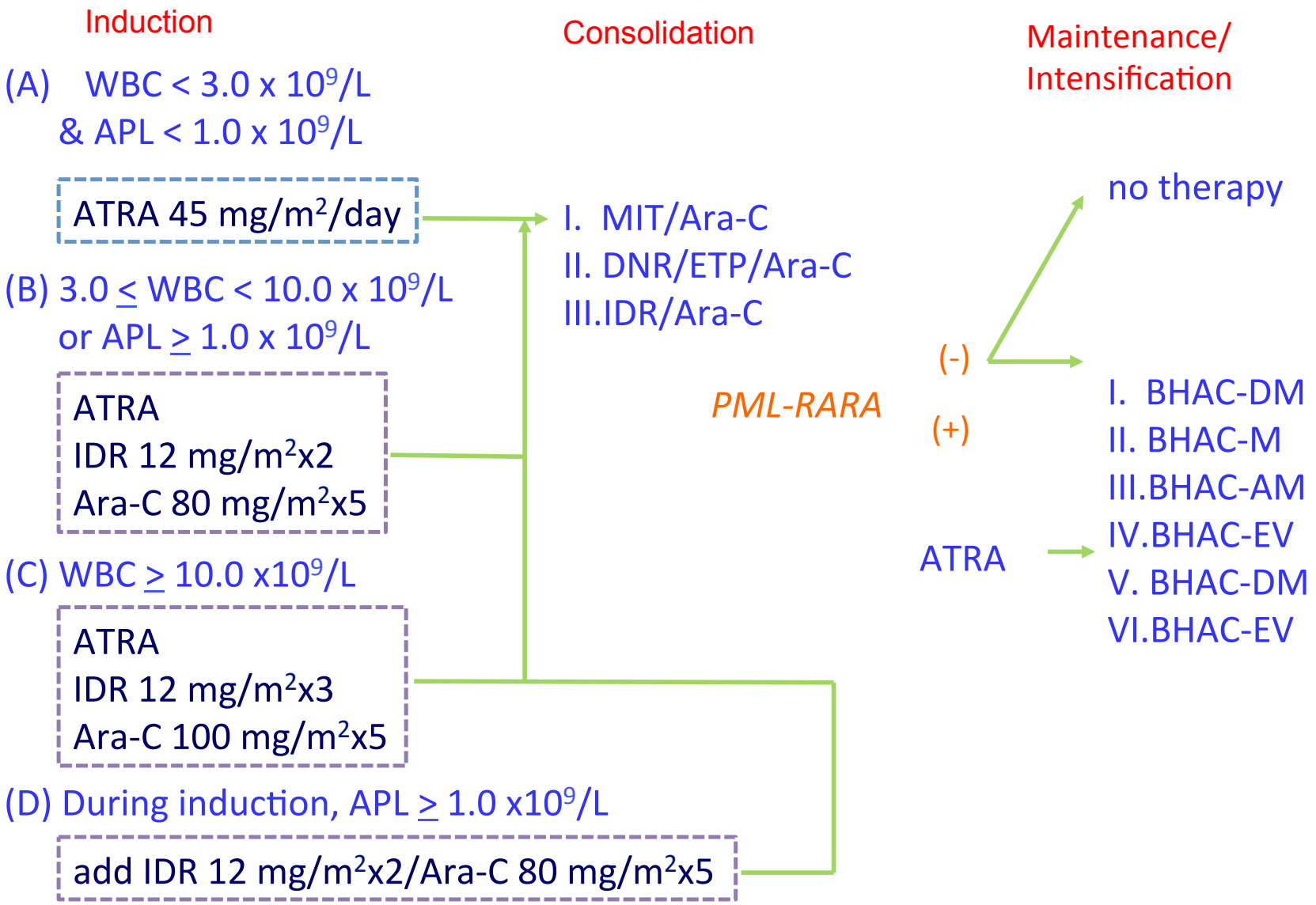
*The combination of ATRA and ATO has been eagerly awaited, but it has not been approved in Japan, yet.

Significance of heavier chemotherapy in maintenance for newly diagnosed APL

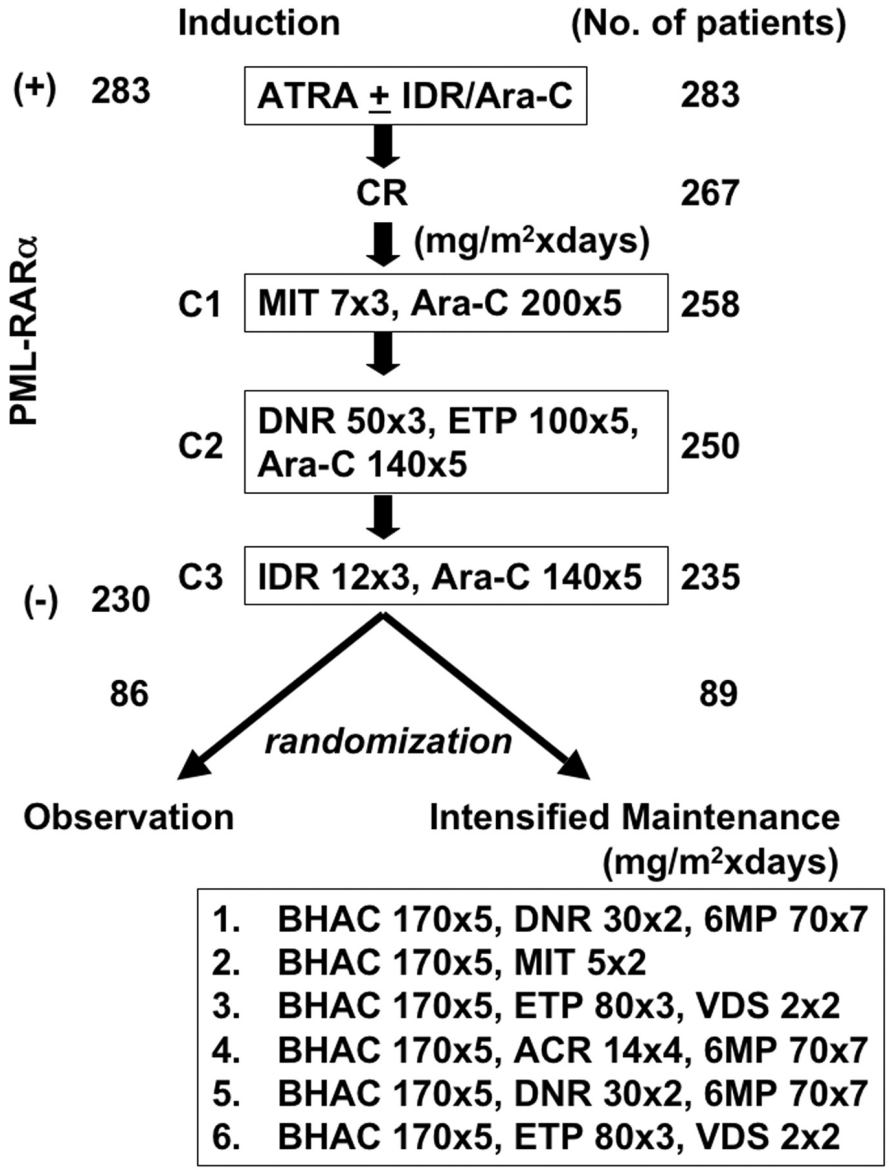
JALSG APL97 study

May 1997 - Jun 2002

JALSG APL97 protocol



JALSG-APL97 Study design



- ✓ 283 patients had t(15;17) and/or the *PML-RARA* transcript at the time of diagnosis.
- ✓ 230 patients were negative for *PML-RARA* at the end of 3 courses of consolidation .
- ✓ 175 patients who showed absence of *PML-RARA* transcript were randomized either to receive 6 courses of intensified maintenance chemotherapy or to observation.

Asou N, et al. Blood, 2007

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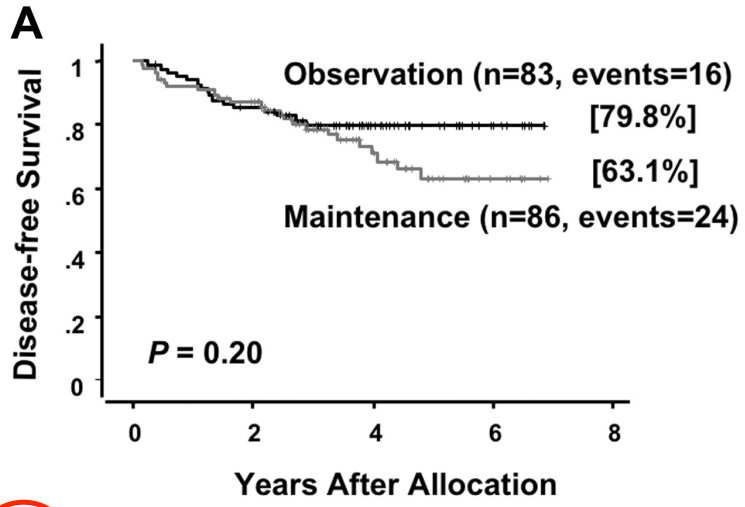
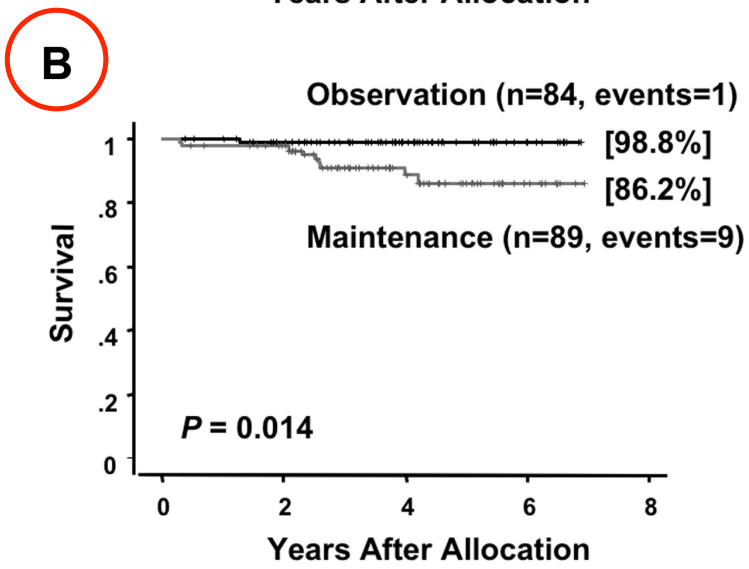
DFS and OS of randomized patients in the maintenance phase in the JALSG APL97

Disease-free survival



Overall survival



estimated from the date of randomization.

Asou N, et al. Blood, 2007

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Tamibarotene as Maintenance Therapy for APL: Phase III Randomized Controlled Trial

Results of Long Time (10-year) Observation

JALSG APL204L study

Jun 2004 - Dec 2010

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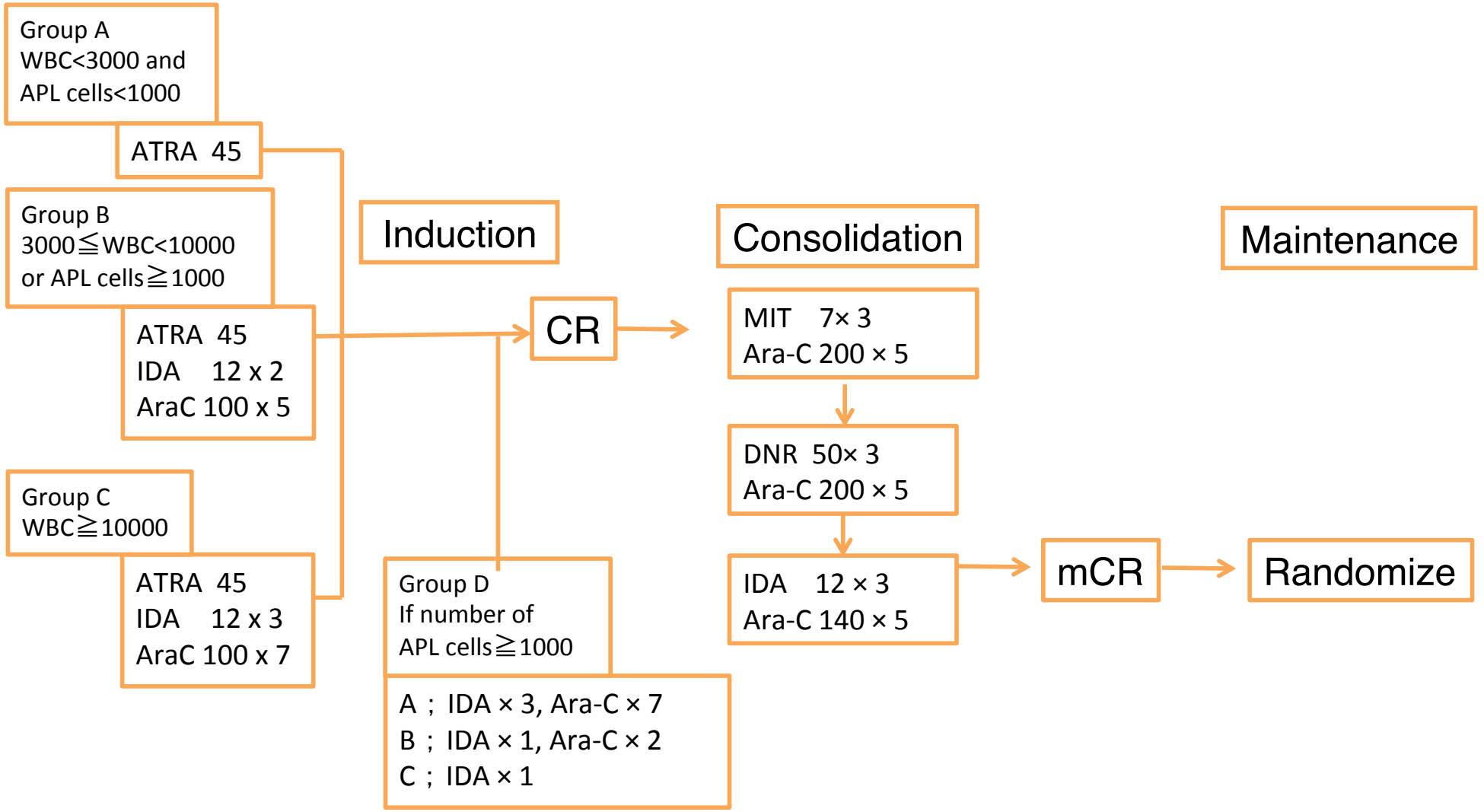
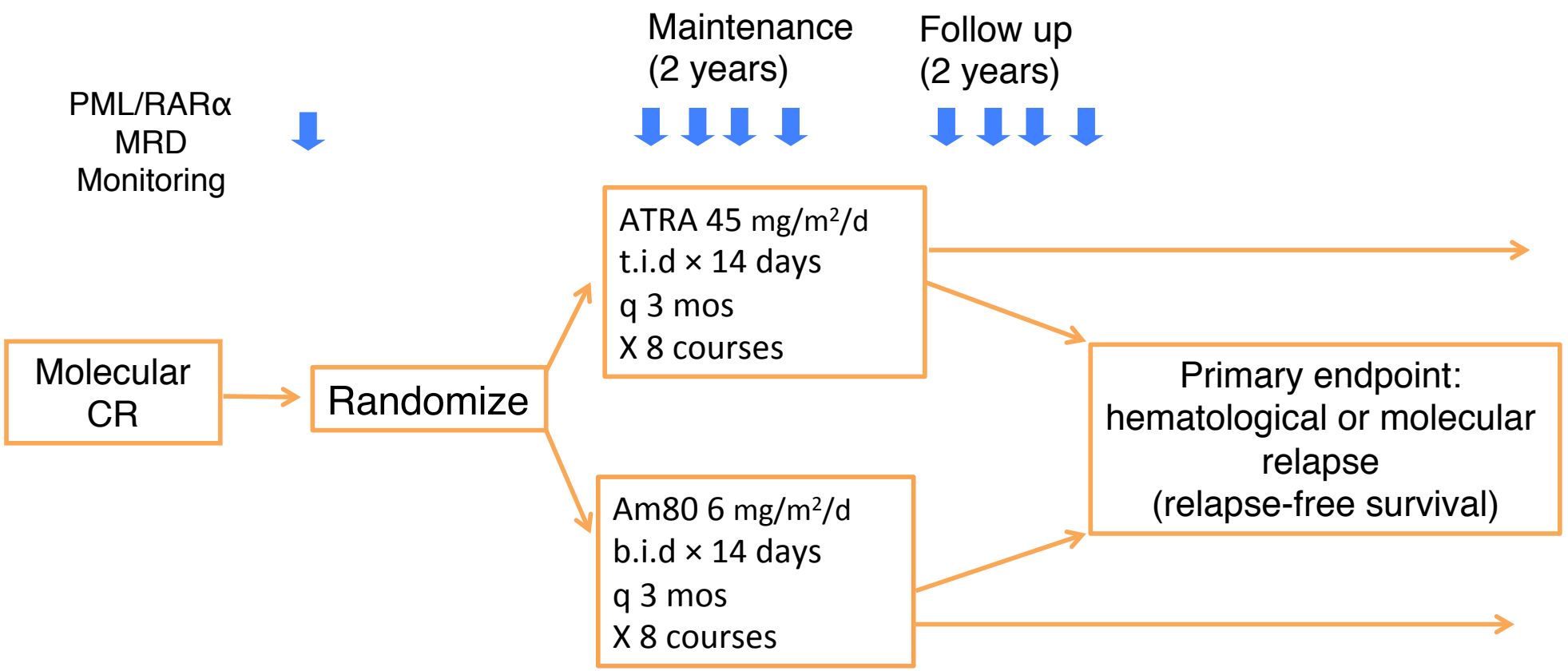
JALSG APL204 Study



JALSG APL204 Study



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(Japan UMIN-CTR　Registration ID : C000000154)

Patients characteristics of 344 cases

Characteristics	No. of Patients (n = 344)
Age, years	
median	48
range	15-70
Gender	
male	183
female	161
Performance status	
0	188
1	126
2	19
3	11
White blood cell count x10^9	
median	1.4
range	0.1-127
Platelet count x10^9	
median	3.1
range	0.1-47.1
Sanz' risk category	
low	115
intermediate	151
high	70
unknown	8
Morphology	
M3	323
M3v	21
Induction therapy group	
A	112
B	48
C	70
D	114

Abbreviations: M3v, M3 variant

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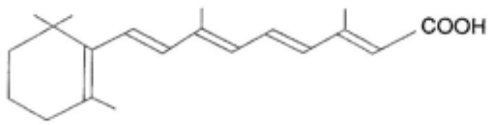
Tamibarotene (Am80)

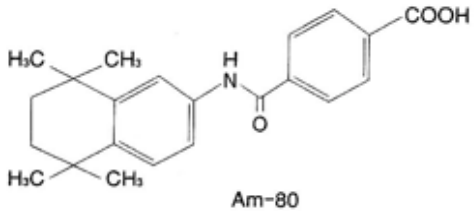
- New synthetic retinoid invented by Shudo K et al. (University of Tokyo) in 1984.
- Differentiation potential is several times higher than ATRA.
- Low affinity to CRABP and no binding to RAR-γ.
- More stable to light, heat, and oxidation than ATRA.
- No decrease of Cmax and AUC even in daily administration, even at end of the treatment.
- Second CR was achieved in 58% of relapsed APL patients by the single treatment of Am80 (Ann Intern Med, 1996; Blood, 1997).
- Am80 was approved in Japan in 2005.
- The efficacy of Am80 was studied by JALSG-APL204 study. the earlier results suggested us Am80 might effective in high-risk group (JCO, 2014).

ATRA



All-*trans* retinoic acid

Am80

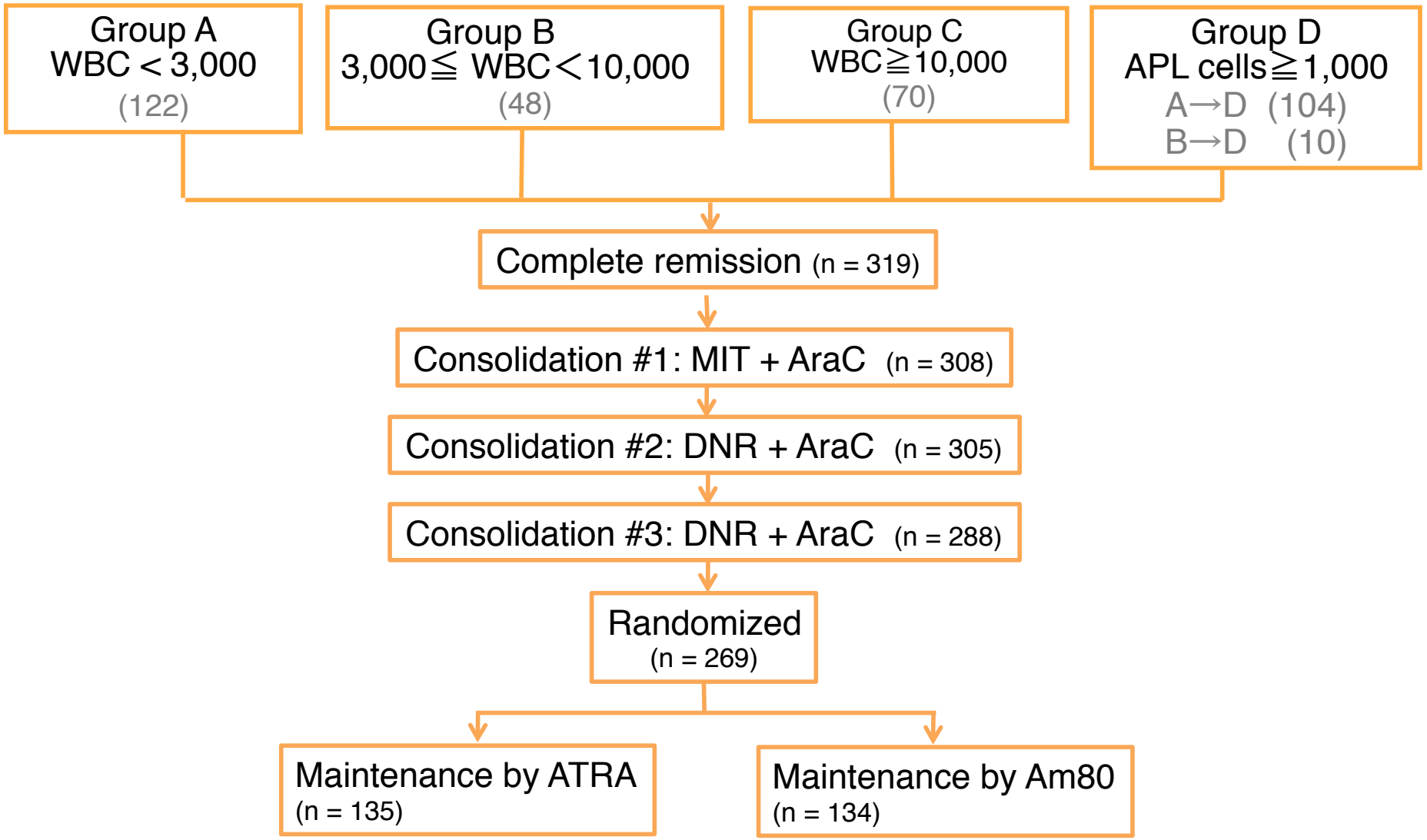


Am-80

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid

$C_{22}H_{25}NO_3$=351.44

Consort diagram and treatment schema



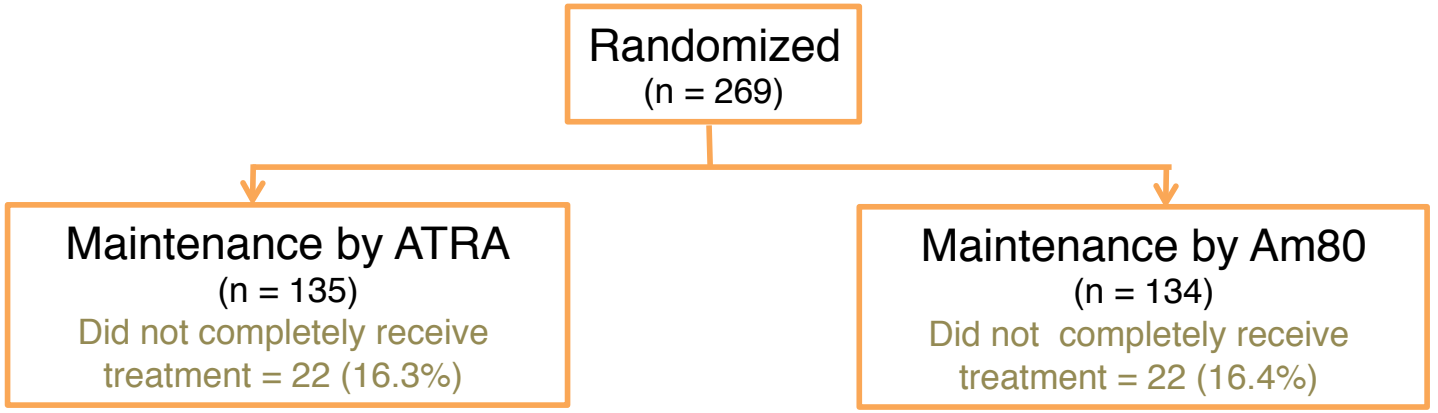
Number of patients achieving CR and CR rates

Enrollment:347; evaluable:344,
Median age (range): 48 (16-68)

Risk Group	N	Death during Induction, N (%)	CR rate (%)
A WBC < 3000	112	2	109 (97.3)
B 3000≦ WBC＜10000	48	4	44 (91.7)
C WBC≧10000	70	9	61 (87.1)
D Add Cx in case of APL cells≧1000	114 A→D 104 B→D 10	6	104 (91.2)
Total	344	21	318 (92.4)

16 patients died within 30 days after starting the treatment. 14 patients died of hemorrhagic complications.
DS: grade 1-, 59 (17.2%), grade 3- (5,2%) [ex: grade 1, 14, grade 2, 27; grade 3, 12, grade 4, 6]

Consort diagram and treatment schema



Discontinued maintenance (n = 22)

- Relapse (n = 12)
- Adverse effect (n = 4)
- Withdrew consent (n = 2)
- Investigator decision (n = 0)
- Other malignancy (n = 3)
- Lost of follow-up (n = 0)
- Unknown reason (n = 1)

Analyzed (n = 135)

- Hematopoietic diseases (n = 4)
- Other malignancy (n = 7)
- Cardiac disease (>grade 3) (n = 3)

Discontinued maintenance (n = 22)

- Relapse (n = 5)
- Adverse effect (n = 7)
- Withdrew consent (n = 6)
- Investigator decision (n = 1)
- Other malignancy (n = 1)
- Lost of follow-up (n = 2)
- Unknown reason (n = 0)

Analyzed (n = 134)

- Hematopoietic diseases (n = 4)
- Other malignancy (n = 1)
- Cardiac disease (>grade 3) (n = 1)

Clinical Characteristics of Patients Randomly Assigned for Maintenance Therapy

Characteristic	No. of patients ATRA (n = 135)	Am80 (n = 134)	
Age (years)			0.597
median	46	46	
range	16-76	16-69	
Gender			0.807
male	70	72	
female	65	62	
Performance status			0.840
0	72	78	
1	50	43	
2	8	8	
3	5	5	
WBC			0.841
median	1.3	1.4	
range	0.2 - 111	0.2 - 88.5	
Platelet count			0.343
median	2.8	3.3	
range	0.2 - 20.8	0.1 - 47.0	
Sanz's risk category			0.636
low	46	44	
intermediate	59	63	
high	26	26	
unkown	4	1	
Morphlogy			0.597
M3	126	128	
M3v	9	6	
Indction treatment group			0.986
A	47	45	
B	18	20	
C	26	26	
D	44	43	

Abbreviations: ATRA, all-trans-retinoic acid; Am80, tamibarotene; M3v, M3 variant

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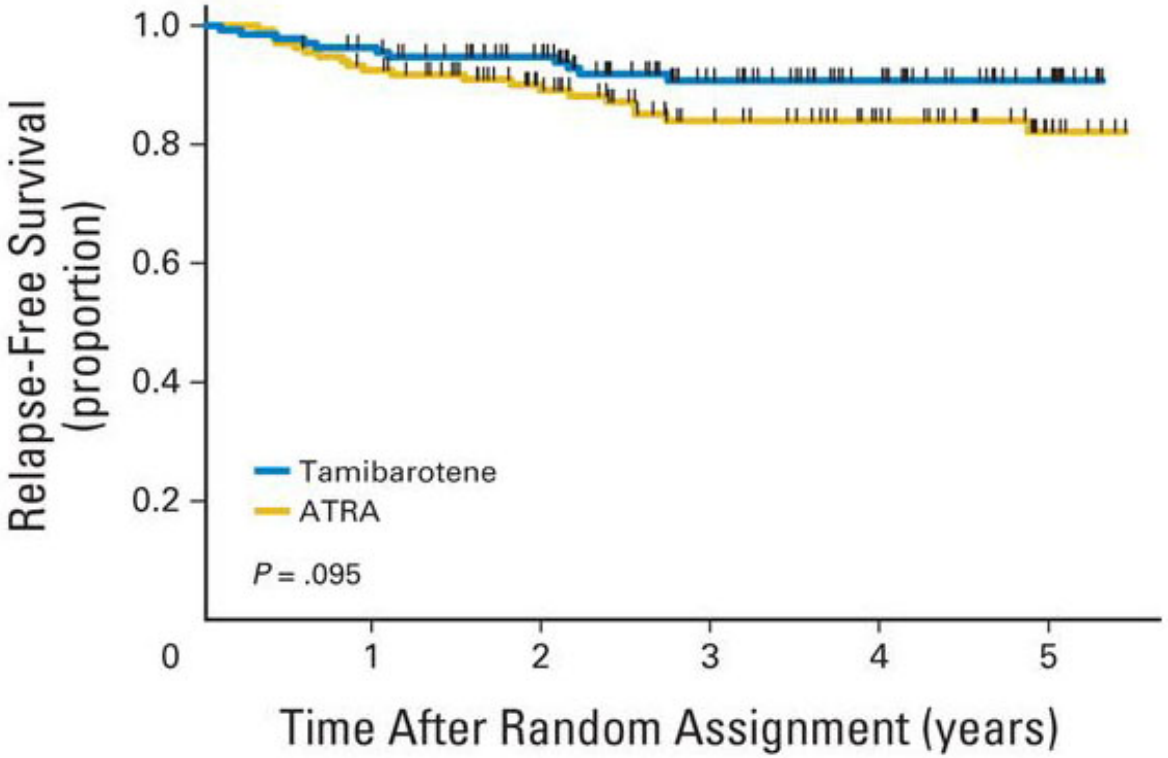
Results of JALSG APL204 Study

5-year RFS

Comparison between patients treated ATRA and tamibarotene



Kaplan-Meier curves for relapse-free survival in relation to maintenance therapy random assignment for all patients (N = 269)

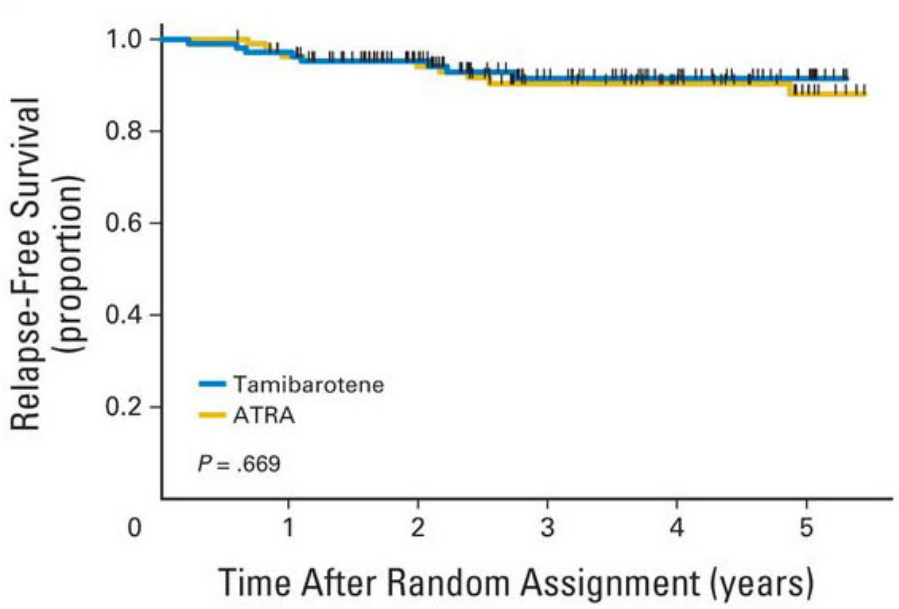
Shinagawa I, Yanada M, et al, JCO, 2014

Results of JALSG APL204 Study

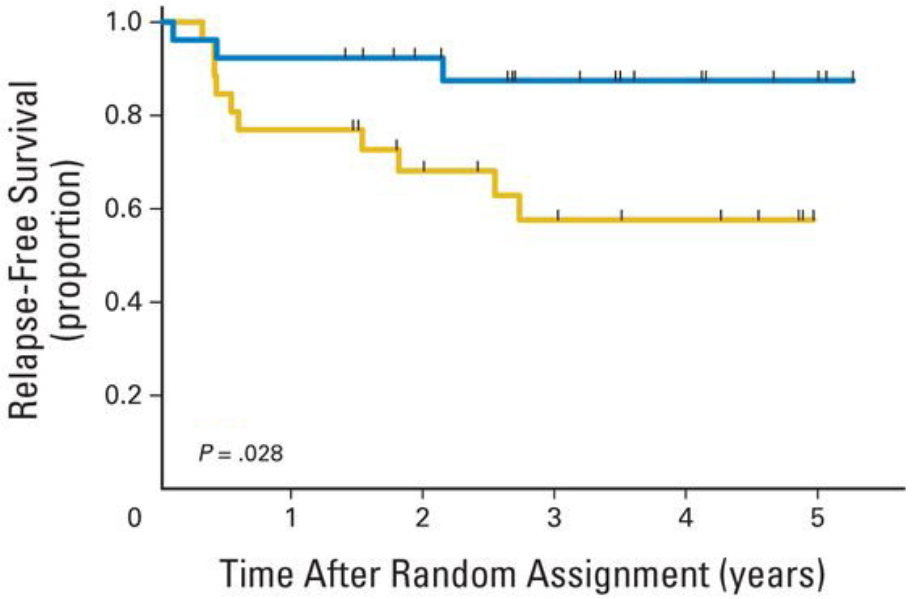
5-year RFS in 'low & intermediate risk group' *and* 'high risk group'

Comparison between patients treated ATRA and tamibarotene

WBC < 10.0 x 10^9 /μL



WBC ≥ 10.0 x 10^9 /μL



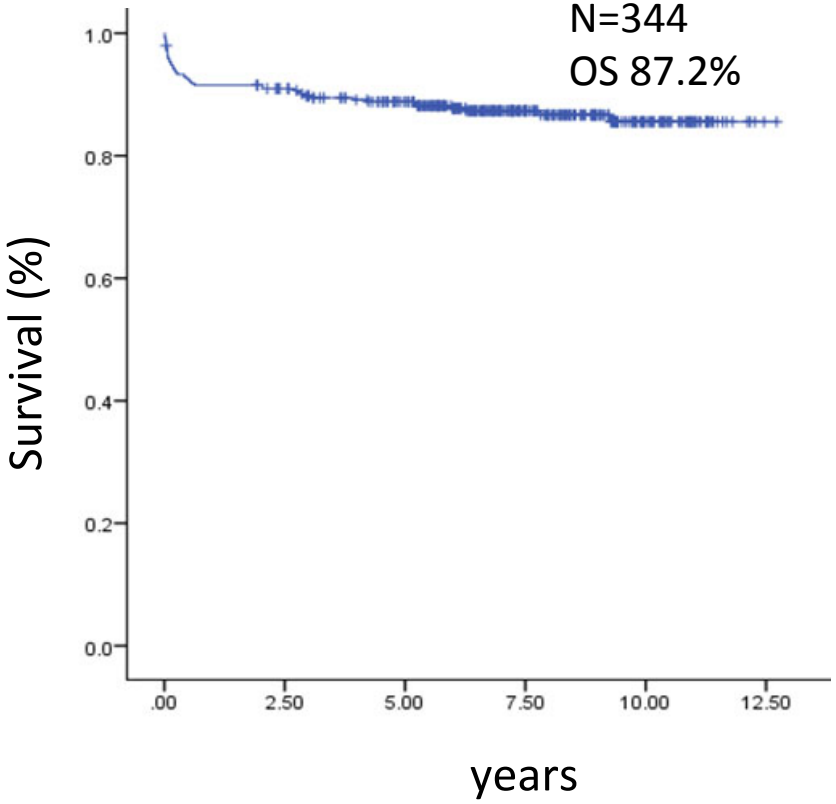
Kaplan-Meier curves RFS in relation to maintenance therapy random assignment for with an initial WBC count of ≥ 10.0 x 10^9/L (n = 52), and for patients with an initial WBC count less than 10.0 x 10^9/L (n = 217).

Shinagawa I, Yanada M, et al, JCO, 2014

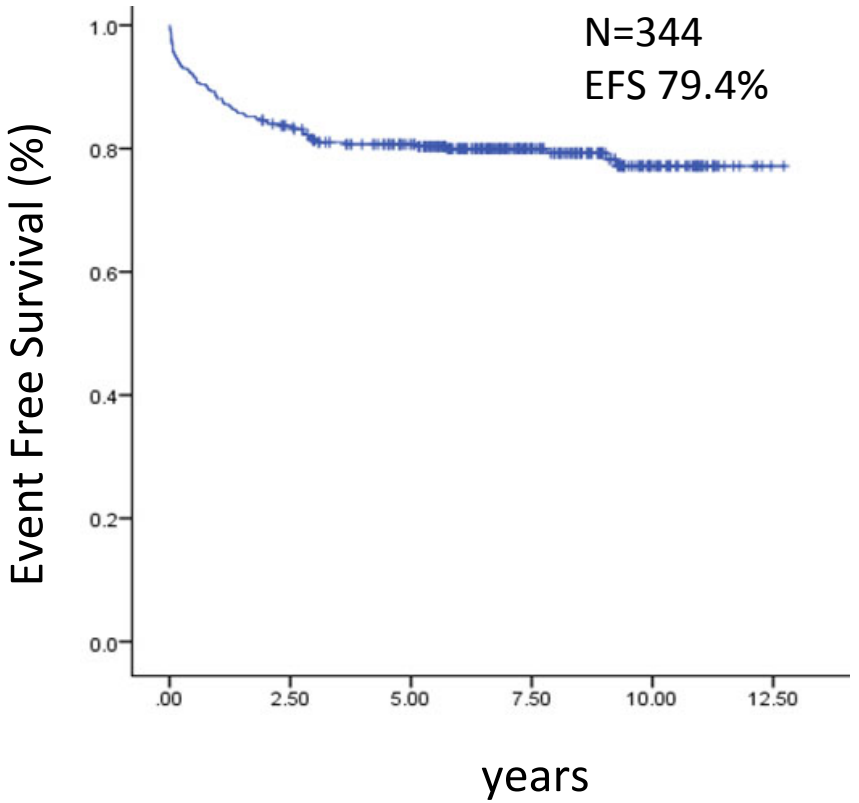
Results of JALSG APL204L Study

10-year OS, EFS for all patients

OS

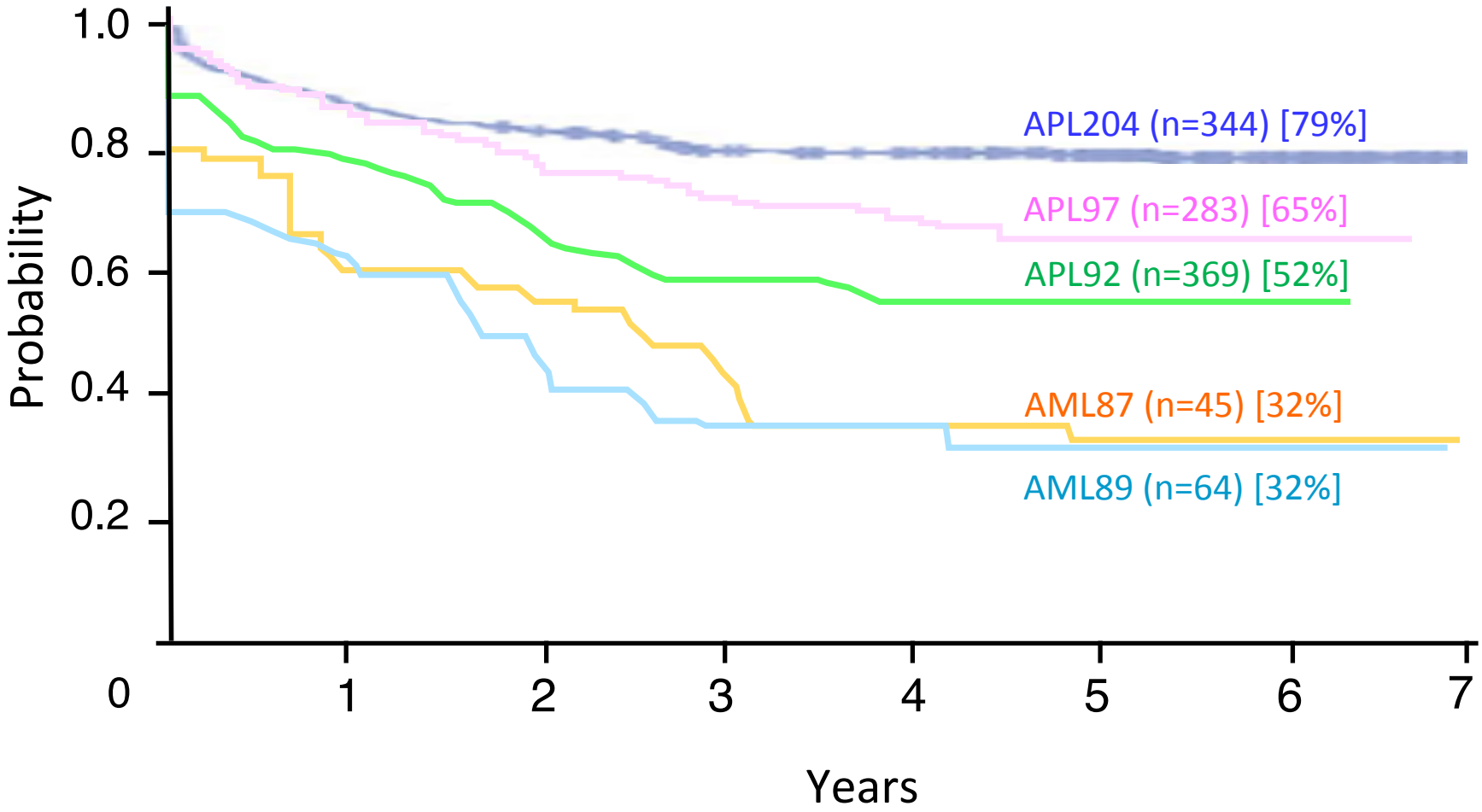


EFS



Follow up period 11.2 years at May 31, 2017

EFS of the 5 previous JALSG-APL studies



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Relapse or Died After Randomization for Maintenance Therapy

	N	Relapse (after R)			Death (after R)		
ATRA	135	21 (15.5%)	A (47) WBC < 3000	5	6	A	1
			B (18) 3000≦ WBC＜10000	2		B	1
			C (26) WBC≧10000	10		C	3
			D (44) Add Cx in case of APL cells≧1000	4		D	1
Am80	134	8 (5.9%)	A (45)	1	3	A	0
			B (20)	1		B	1
			C (26)	3		C	2
			D (43)	3		D	0
Total	269	29 (10.8%)			9 (3.3%)		

Median follow up period 10 years

Grade 2 or Higher Drug-related Adverse Events Reported in More Than 5% of Patients in Either Maintenance Arm

	ATRA (n = 135)						Am80 (n = 134)					
	grade 2		grade 3		grade 4		grade 2		grade 3		grade 4	
Adverse event	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
TG ↑	25	19	17	13	6	4.4	28	21	28	21	0	4.5
TC ↑	11	8.1	0	0	2	1.5	20	15	3	2.2	0	0
Skin eruption	2	1.5	1	0.7	0	0	19	14	0	0	0	0
AST/ALT↑	6	4.4	1	0.7	0	0	8	6	3	2.2	0	0
Headache	6	4.4	2	1.5	0	0	4	3	0	0	0	0

Measures for adverse effect of ATRA
- Dose reduction, 0
- Change to Am80, 0
- Discontinuation, 4

Withdrew consent after randomization, 2

Measures for adverse effect of Am80
- Dose reduction, 1
- Change to ATRA, 7
- Discontinuation, 4

Withdrew consent after randomization, 5 (economical reason, etc)

Results of APL204L study

- Totally, CR rate was 92%, but 87% in high risk group mainly due to hemorrhagic events.
- Tamibarotene is significantly also effective in high risk group as WBC $\geq$ 10,000/μl. It may be notable after the introduction of ATO + retinoid treatment.
- Secondary hematopoietic disorders and malignancies were observed in 12 patients and 9 patients, respectively. These should be considered in APL, which has improved survival.
- In the future, the efficacy of Am80 should be studied in induction setting for untreated APL.

Japan Adult Leukemia Group (JALSG)

was established in 1987

The 30th Anniversary International Symposium of JALSG was held on June, 2017. We have been supported by many people. We would like to express our sincere appreciation to the people having supported us continuously.

Acknowledgements

- All JALSG members,
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Members from 225 institutions