

Interim analysis of the APML4 trial incorporating *all-trans* retinoic acid, idarubicin, and intravenous arsenic trioxide as initial therapy in acute promyelocytic leukaemia

An Australasian Leukaemia & Lymphoma Group study

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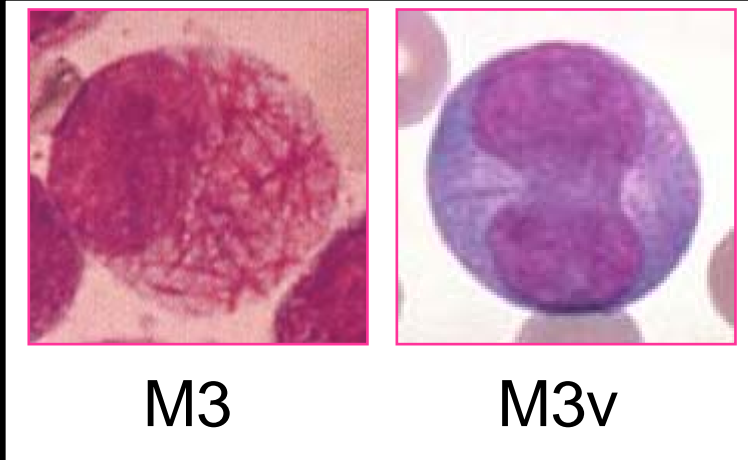
for the



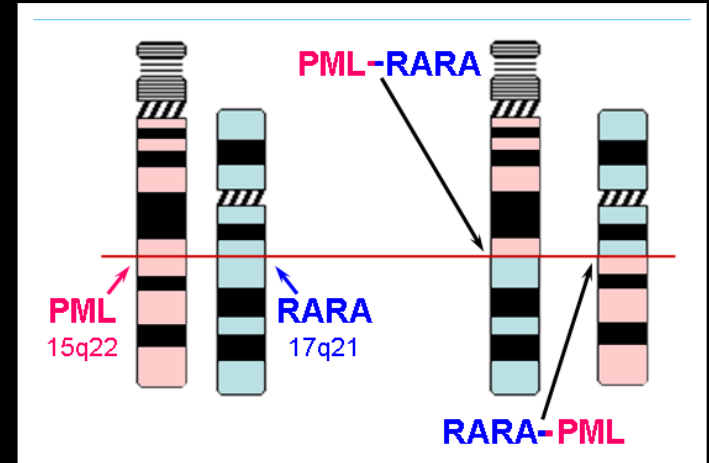
Royal Prince Alfred Hospital (NSW) • St Vincent's Hospital Melbourne (VIC) • Wesley Medical Centre (QLD)
Royal Melbourne Hospital (VIC) • Westmead Hospital (NSW) • St Vincent's Hospital Sydney (NSW)
Calvary Mater Hospital (NSW) • Mater Hospital Brisbane (QLD) • Gosford Hospital (NSW)
Nepean Hospital (NSW) • Royal Adelaide Hospital (SA) • Peter MacCallum Cancer Institute (VIC)

Distinguishing features of APL

characteristic morphology



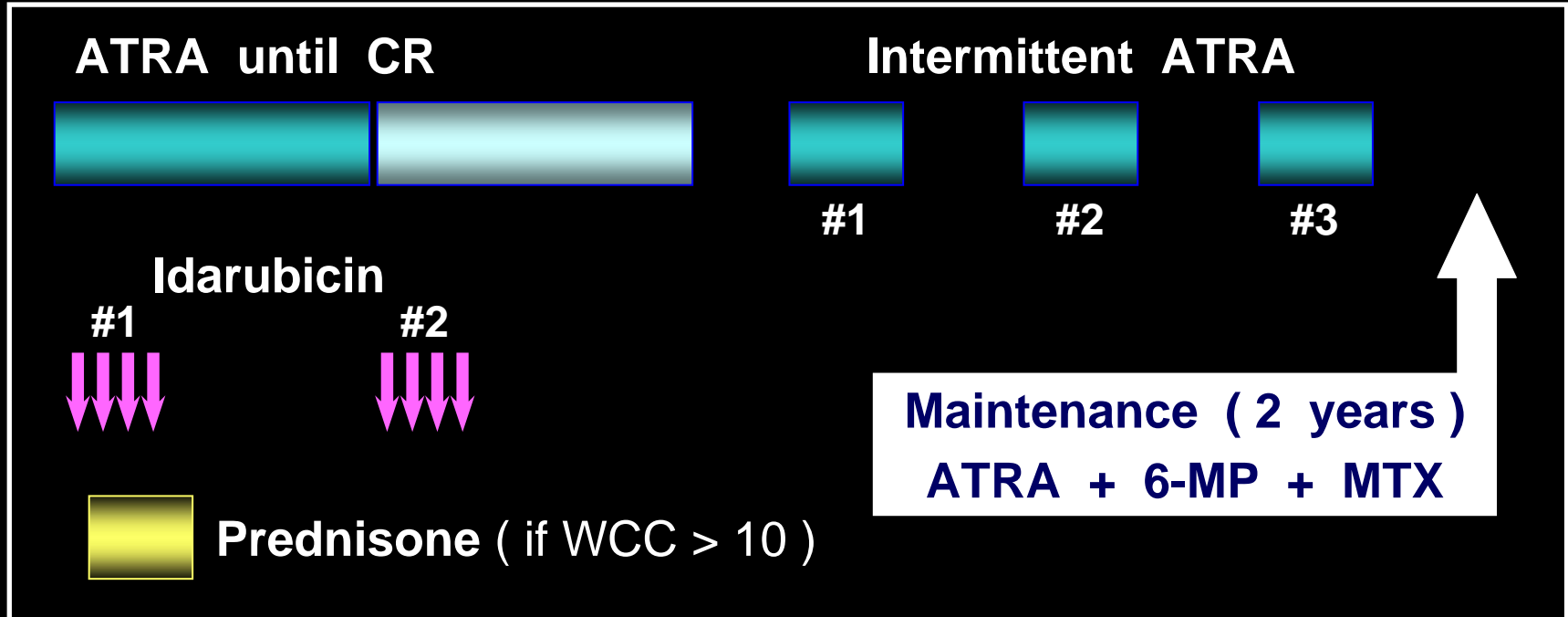
t(15;17) → PML-RARA



- young, pancytopenic, coagulopathic
- high risk of **haemorrhagic death** during induction with conventional chemotherapy
- enhanced anthracycline responsiveness
- unique sensitivity to ATRA & As₂O₃

ALLG APL3: 1997 – 2002

Amended to include maintenance



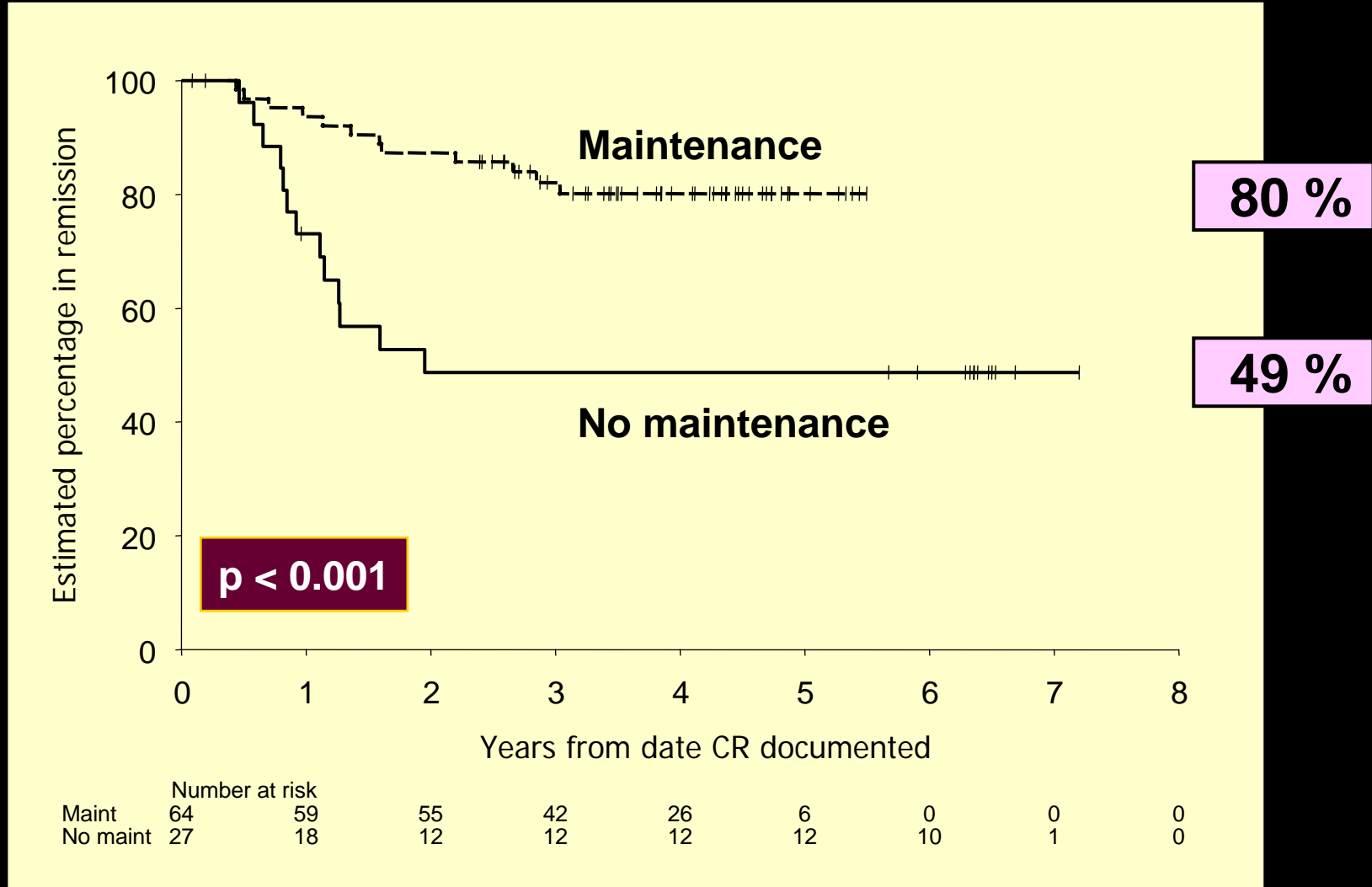
PML-RARA Molecular Monitoring (3 years)

Negative → **Observe**

Positive → **Salvage Therapy ± Transplant**

APML3

Relapse-free survival: 71% at 4 years



Use of Arsenic Trioxide (As_2O_3) in the Treatment of Acute Promyelocytic Leukaemia (APL): II. Clinical Efficacy and Pharmacokinetics in Relapsed Patients

By Zhi-Xiang Shen, Guo-Qiang Chen, Jian-Hua Ni, Xiu-Shong Li, Shu-Min Xiong, Qian-Yao Qiu, Jun Zhu, Wei Tang, Guan-Lin Sun, Kan-Qi Yang, Yu Chen, Li Zhou, Zhi-Wen Fang, Yan-Ting Wang, Jun Ma, Peng Zhang, Ting-Dong Zhang, Sai-Juan Chen, Zhu Chen, and Zhen-Yi Wangy

- **CR in 90% - 100% of relapsed APL**
- **Active in ATRA-resistant and chemorefractory APL**
- **Confirmed in the US Multicenter Study**
[Soignet *et al*, JCO 19:3852, 2001]
- **Combination with ATRA superior to either drug alone in de novo APL**
[Shen ZX *et al*, PNAS 101:5328, 2004]

Induction

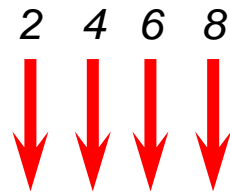
ATRA

45mg/m²/d



Idarubicin

12mg/m²/d



Age-adjusted idarubicin: 61-70: 9mg/m²
>70: 6mg/m²

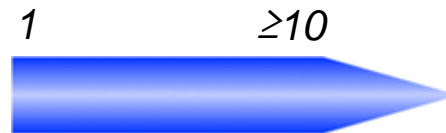
As₂O₃

0.15mg/kg/d



Prednisone

1mg/kg/d



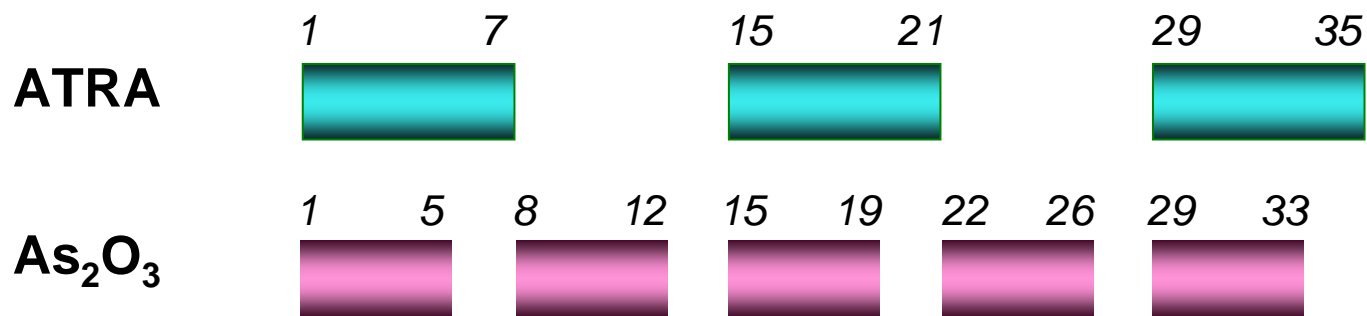
+ Aggressive haemostatic support

- platelets $\geq 30 \times 10^9/L$
- normal PT, APTT, and fibrinogen $> 1.5g/L$

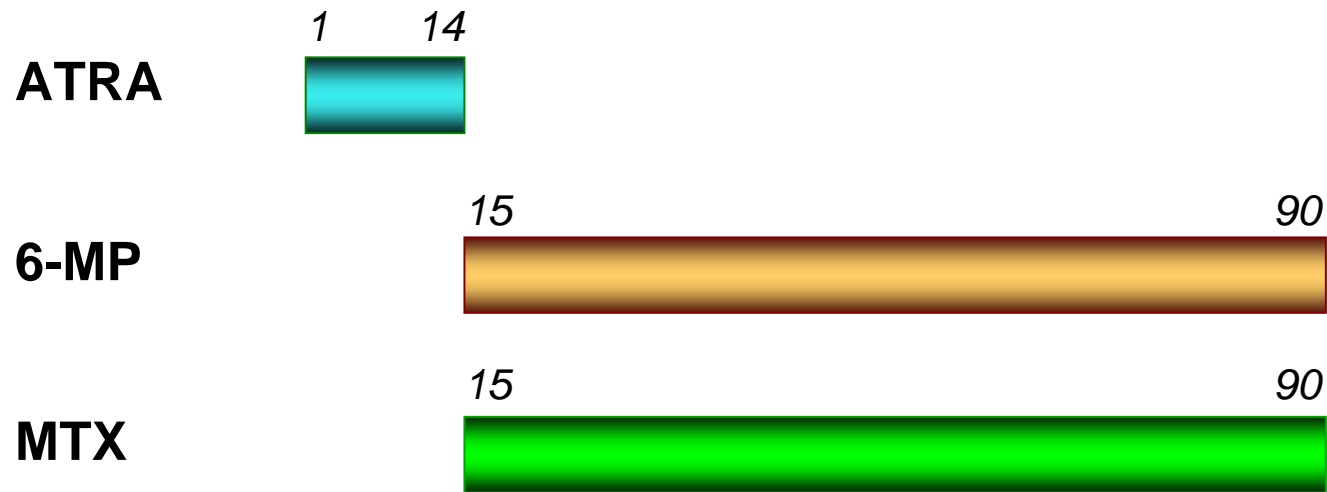
Consolidation #1



Consolidation #2



Maintenance (every 3 months for 2 years)



+ Molecular monitoring by quantitative RT-PCR

- *Ipsogen Cancer Profiler FusionQuant kits*
- *BM every 3 months for 3 years after consolidation*


APML4 Patients

Eligibility	<ul style="list-style-type: none">• De novo APL• PML-RARA or t(15;17) +ve• Age \geq 1
Accrual	10 Nov 2004 - 28 Sep 2009
Number registered	129
Number eligible & evaluable	124 <ul style="list-style-type: none">• 2 PML-RARA & t(15;17) -ve• 1 refused treatment• 1 PRKAR1A-RARA +ve• 1 major protocol violation
Median potential followup time	24 months (2 – 63)

Demographics

		APML3	APML4
Age	median	40	44
	(range)	(19 – 73)	(3 – 78)
Sex	male (%)	52%	50%
	female (%)	48%	50%
Sanz risk category	high (WCC > 10)	23%	21%
	intermediate + low	77%	79%

Early deaths (up to day 36)

124 evaluable for assessment
 **4** early deaths (3.2%)

day of death	cause of death
1	myocardial infarct
3	cerebral haemorrhage
7	cerebral haemorrhage
30	seizures

APML4 vs APML3: $p = 0.073$

Molecular complete remission by the end of consolidation

129 registered
 - 5 inevaluable
 - 1 data not available

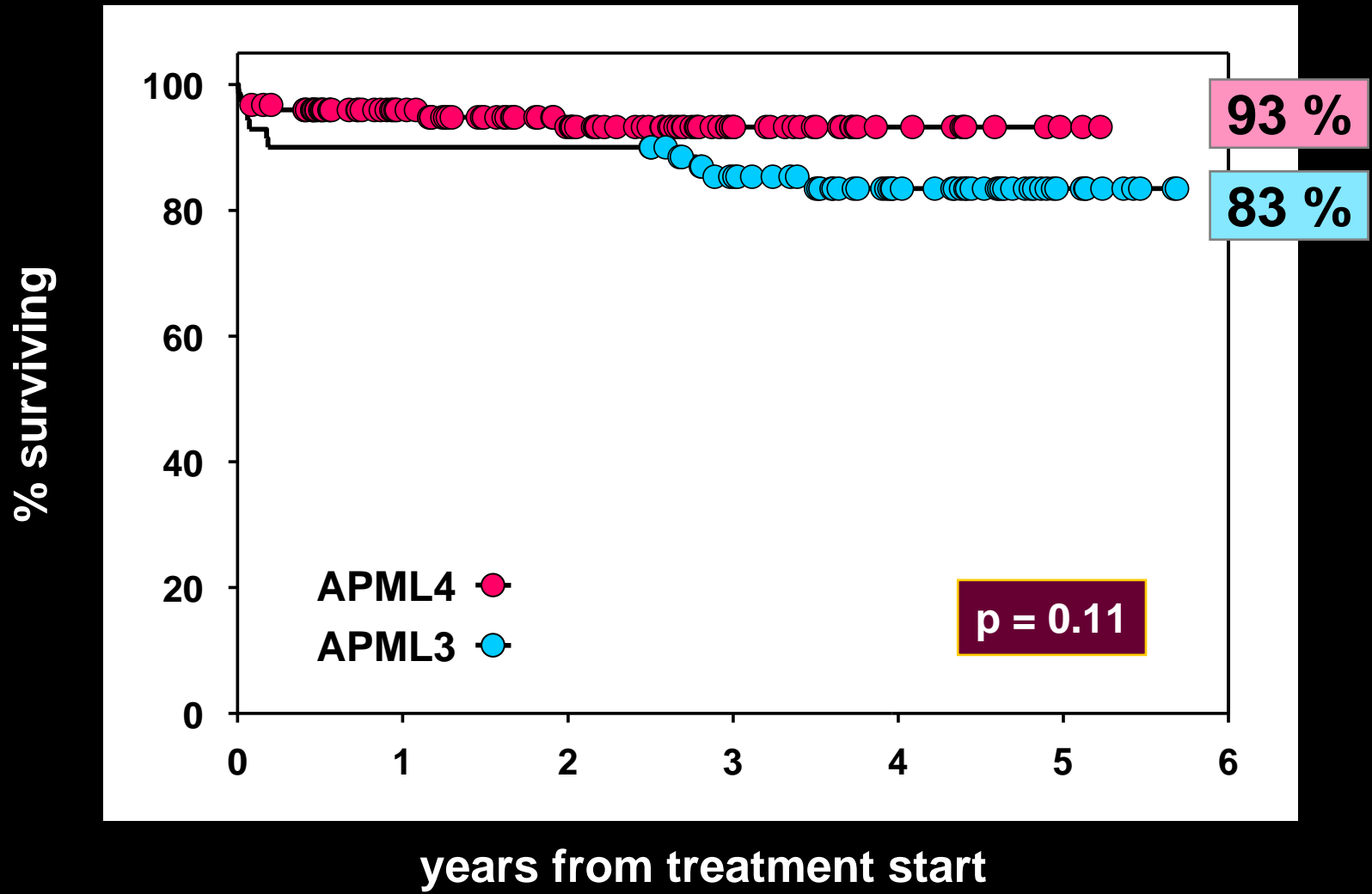
123 evaluable for MCR assessment
 - 4 death before MCR assessment
 - 5 withdrawn before MCR assessment

93 % → 114 completed consolidation → **100 %**
 114 **molecular CR**
 0 **minimal residual disease**

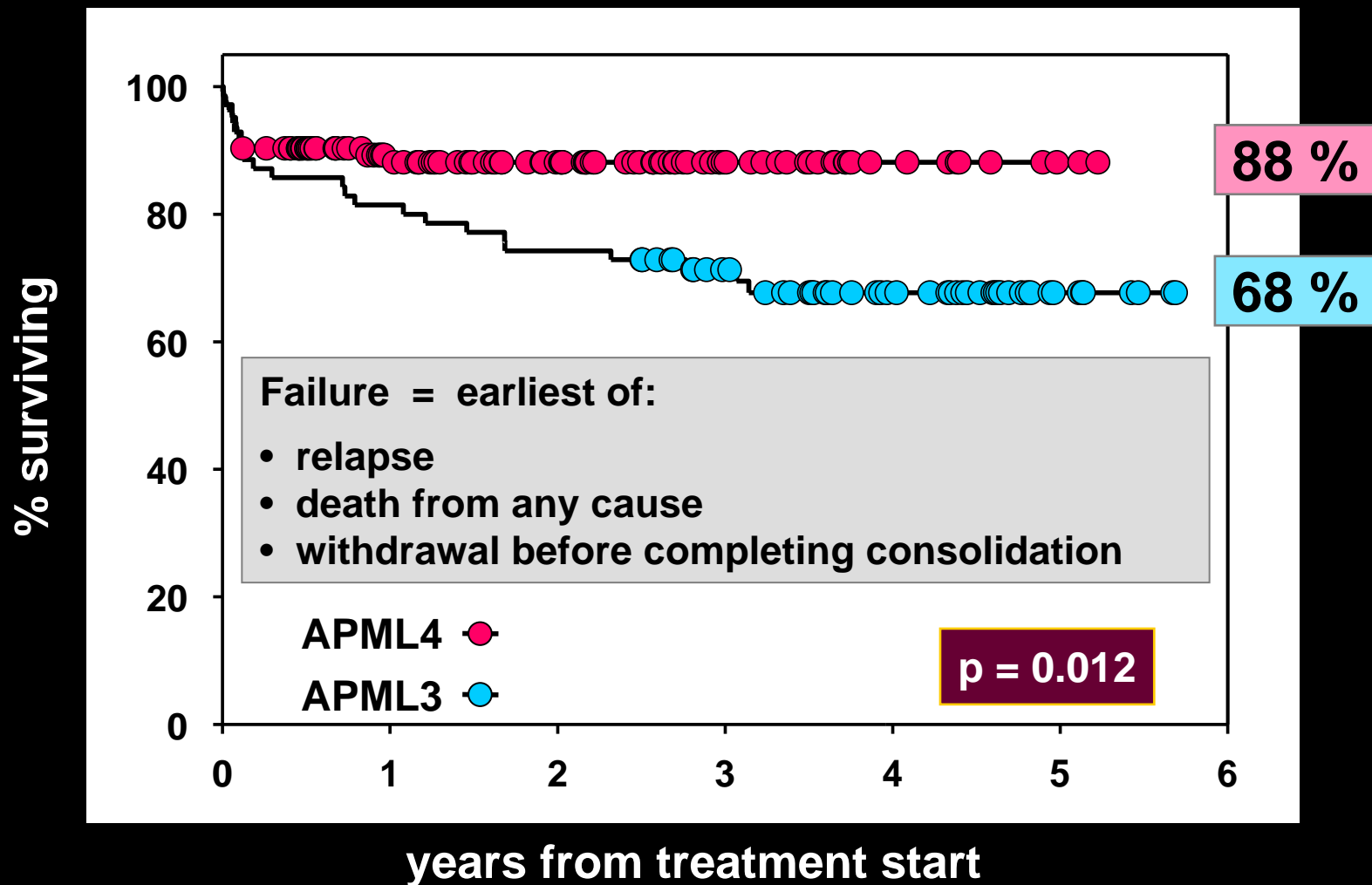
Relapses

Type of relapse	Outcome
simultaneous CNS & molecular BM	death due to progressive disease
molecular BM	death due to sepsis during salvage chemotherapy

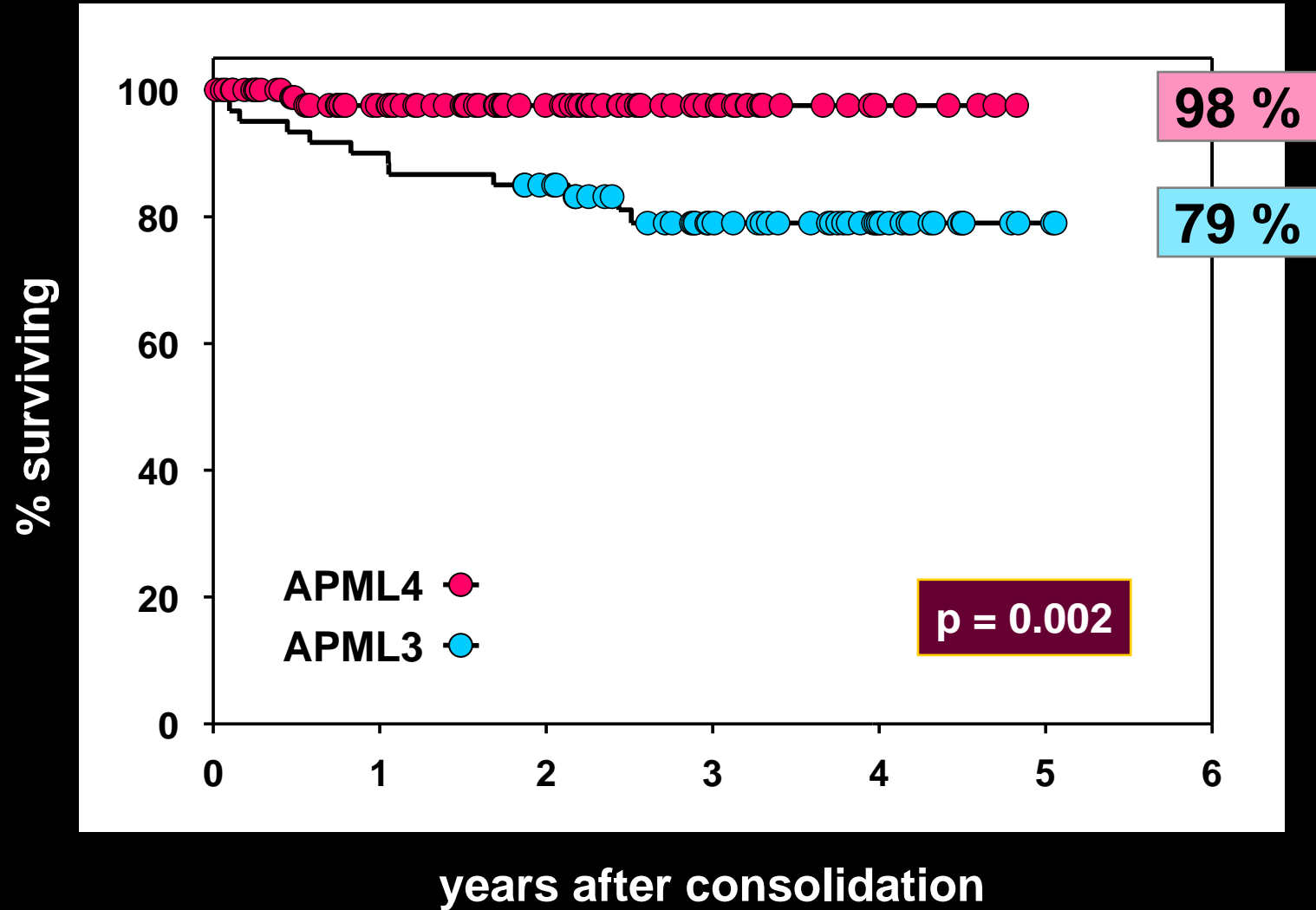
Overall survival by protocol



Failure free survival by protocol



Relapse free survival by protocol



Toxicity (Induction)

APL differentiation syndrome:

- 10 grade 3
- 6 grade 4 (life-threatening)
- 0 fatal

Prolonged Q-Tc > 500msec: n = 14 (12%)

- 0 torsades de pointes / severe arrhythmias
- 1 severe T-wave inversion

Myocardial infarct:

- n = 2; both on day 1
- 1 fatal

Toxicity (Induction)

Cutaneous toxicity:

- grade 3 – 4
- grade 4 – 1

Neurotoxicity

- seizures – 1 (fatal)
- grade 3 neuropathy – 2
- grade 3 headaches – 4

Biochemical hepatotoxicity

- grade 3-4 in approximately 30% (reversible)

Gastrointestinal toxicity

- grade 3 in approximately 20%

Toxicity (Consolidation)

	#1	#2
APL differentiation syndrome	nil	nil
prolonged Q-Tc > 500msec	10% (1 unsustained VT)	4%
grade 3-4 neutropenia	49%	22%
hepatotoxicity	~ 10%	2%
neurotoxicity	anxiety (1) visual defect (1)	nil
cutaneous toxicity	1%	nil
gastrointestinal toxicity	2%	1%

Long-term efficacy and safety of *all-trans* retinoic acid/arsenic trioxide-based therapy in newly diagnosed acute promyelocytic leukemia

PNAS
106:3342, 2009

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Induction

- ATRA then ATO
Hydroxyurea or IDA + AraC if WCC > 10

Consolidation x 3

- DNR + AraC
- intermediate dose AraC
- Homoharringtonine + AraC

Maintenance x 5

- ATRA then ATO then 6MP or MTX

	CR	OS	EFS	RFS
(5 yr)	94%	92%	89%	95%
APML4 (3 yr)	93%	93%	88%	98%

Conclusions

- The APML4 protocol combines As_2O_3 with AIDA-style induction, and omits chemotherapy from consolidation. Steroids and aggressive haemostatic support are used to minimise early deaths
- Induction toxicity is comparable with standard AIDA-based inductions, and consolidation toxicity is minimal
- Overall survival exceeds 90%, relapses have occurred in < 5% of patients who achieve molecular remission, and there have been no deaths during consolidation with ATRA and As_2O_3
- ATRA + As_2O_3 based therapy combined with minimal anthracycline is safe and highly effective for previously untreated APL

Acknowledgements

Investigators

B Augustson	F Firkin	N Patton
J Bashford	C Fraser	M Pidcock
K Bavishi	T Frost	I Prosser
R Bell	J Gibson	W Rasheed
W Benson	P Giri	A Roberts
R Bird	M Greenwood	J Robilliard
K Bradstock	A Grigg	D Ross
P Campbell	M Hertzberg	P Rowlings
P Cannell	J Ho	M Seldon
D Carney	L Ho	A Spencer
K Cartwright	C Hui	M Stevens
L Coyle	H Iland	W Stevenson
P Crispin	I Irving	J Szer
G Cull	A Johnston	J Taper
I Cunningham	I Kerridge	K Taylor
J Curnow	J Koutts	P Thompson
M Dean	H Lai	C Tiley
S Deveridge	S Larsen	J Trotman
S Dunkley	G Lieschke	C Turtle
P Eliadis	R Lowenthal	H Uwe
A Enjeti	S Milliken	C Ward
A Enno	J Moore	A Watson
J Estell	E Morris	A Wei
H Fairweather	J Morton	D Westerman
K Fay	H Nandurkar	
R Filshie	J Norman	

Molecular Haematology (RPAH)

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Phebra

Provided arsenic trioxide

Clinical trial nurses

Data managers