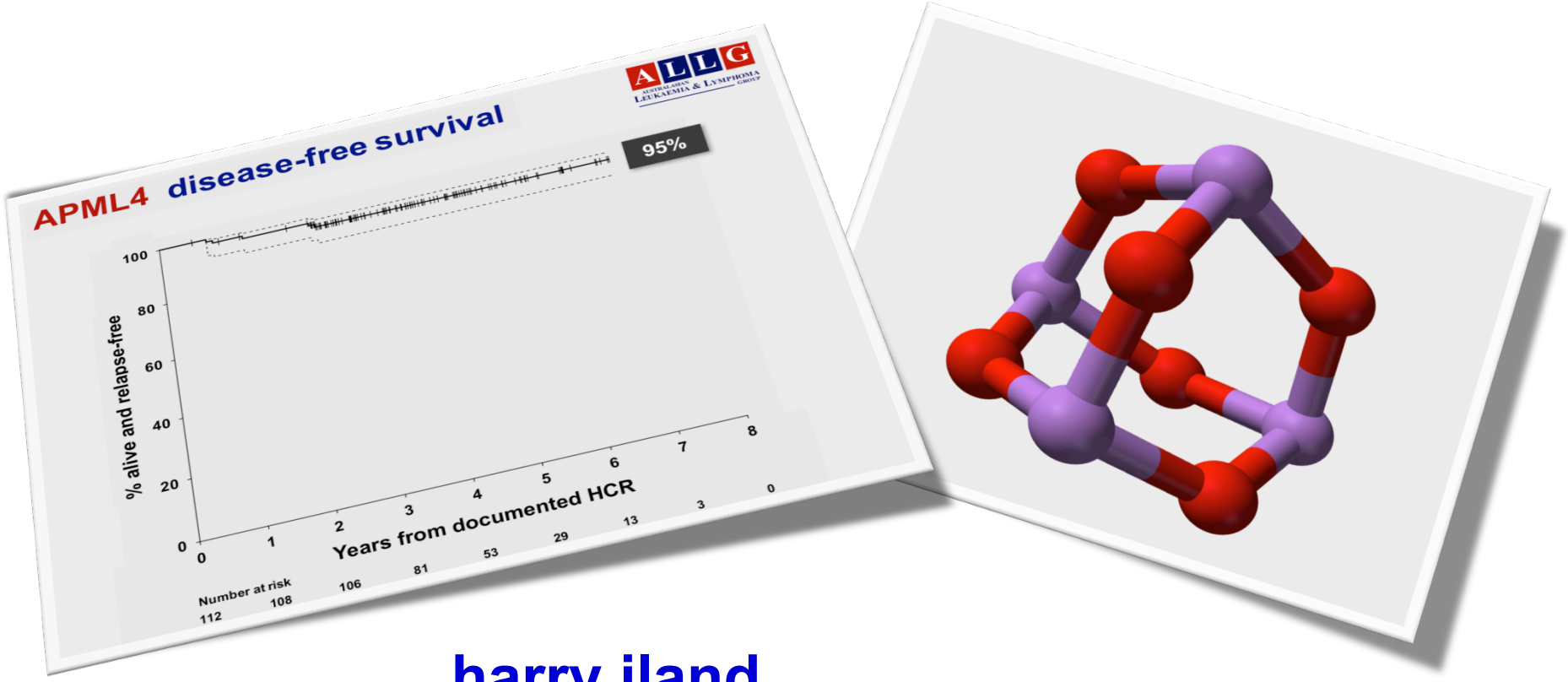
The ALLG approach to incorporating arsenic trioxide

APML4
final analysis

and

APML5
encapsulating therapy



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ALLG
AUSTRALASIAN LEUKAEMIA & LYMPHOMA GROUP

Disclosures of Harry Iland

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NONE							

Background to APML4

AIDA
Avvisati *et al*
Blood 88:1390; 1996

AIDA (all-trans retinoic acid + idarubicin) in newly diagnosed acute promyelocytic leukemia: a GIMEMA pilot study

GIMEMA AIDA: a triumphal march

Induction

ATRA

45mg/m^2/d until CR [max 90 days]

Idarubicin

12mg/m^2/d x4 (days 2,4,6,8)

Avvisati *et al,* Blood 88:1390, 1996 • Mandelli *et al,* Blood 90:1014, 1997

Induction

ATRA 45mg/m^2/d
until CR [max 90 days]

Idarubicin
12mg/m^2/d x4

Consolidation

Idarubicin
12mg/m^2/d x1

Idarubicin
7mg/m^2/d x4

Mitoxantrone
10mg/m^2/d x5

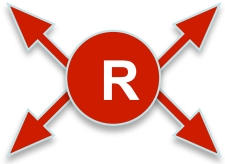
Cytarabine
150mg/m^2 q8h x5

Cytarabine
1g/m^2/d x4

Etoposide
100mg/m^2/d x5

6-Thioguanaine
70mg/m^2 q8h x5

Maintenance



ATRA x15 — every 3 months for 2 years

6-MP 50mg/m^2/d

MTX 15mg/m^2/wk

Avvisati *et al,* Blood 88:1390, 1996 • Mandelli *et al,* Blood 90:1014, 1997

Background to APML4

AIDA Avvisati *et al* Blood 88:1390; 1996	AIDA (all-trans retinoic acid + idarubicin) in newly diagnosed acute promyelocytic leukemia: a GIMEMA pilot study
APML3 Iland *et al* Haematologica 97:227; 2012	Results of the APML3 trial incorporating all-trans-retinoic acid and idarubicin in both induction and consolidation as initial therapy for patients with acute promyelocytic leukemia

APML3 accrued 1997-2002

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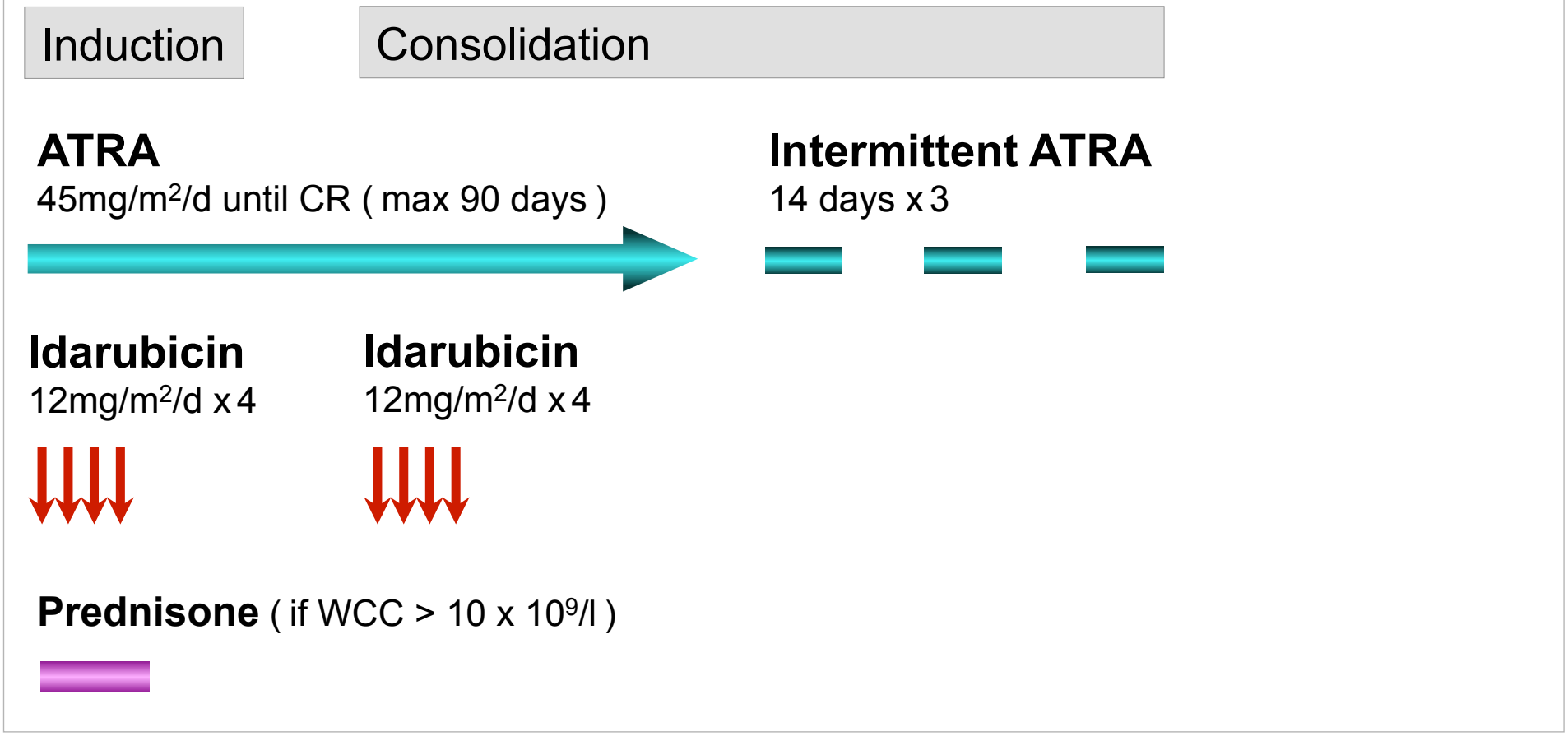

Iland *et al,* Haematologica 97:227, 2012

APML3 accrued 1997-2002
maintenance added June 2000

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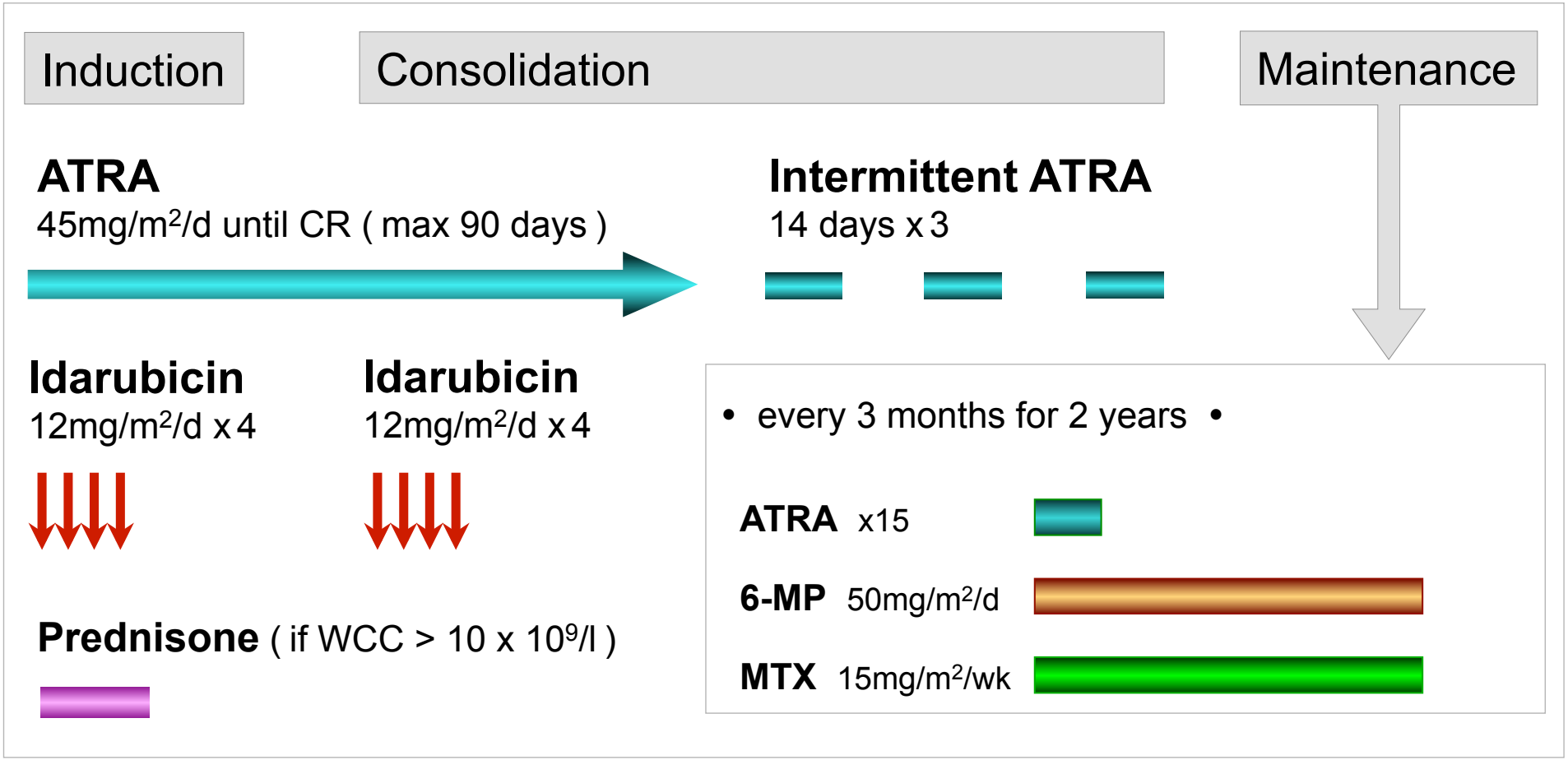
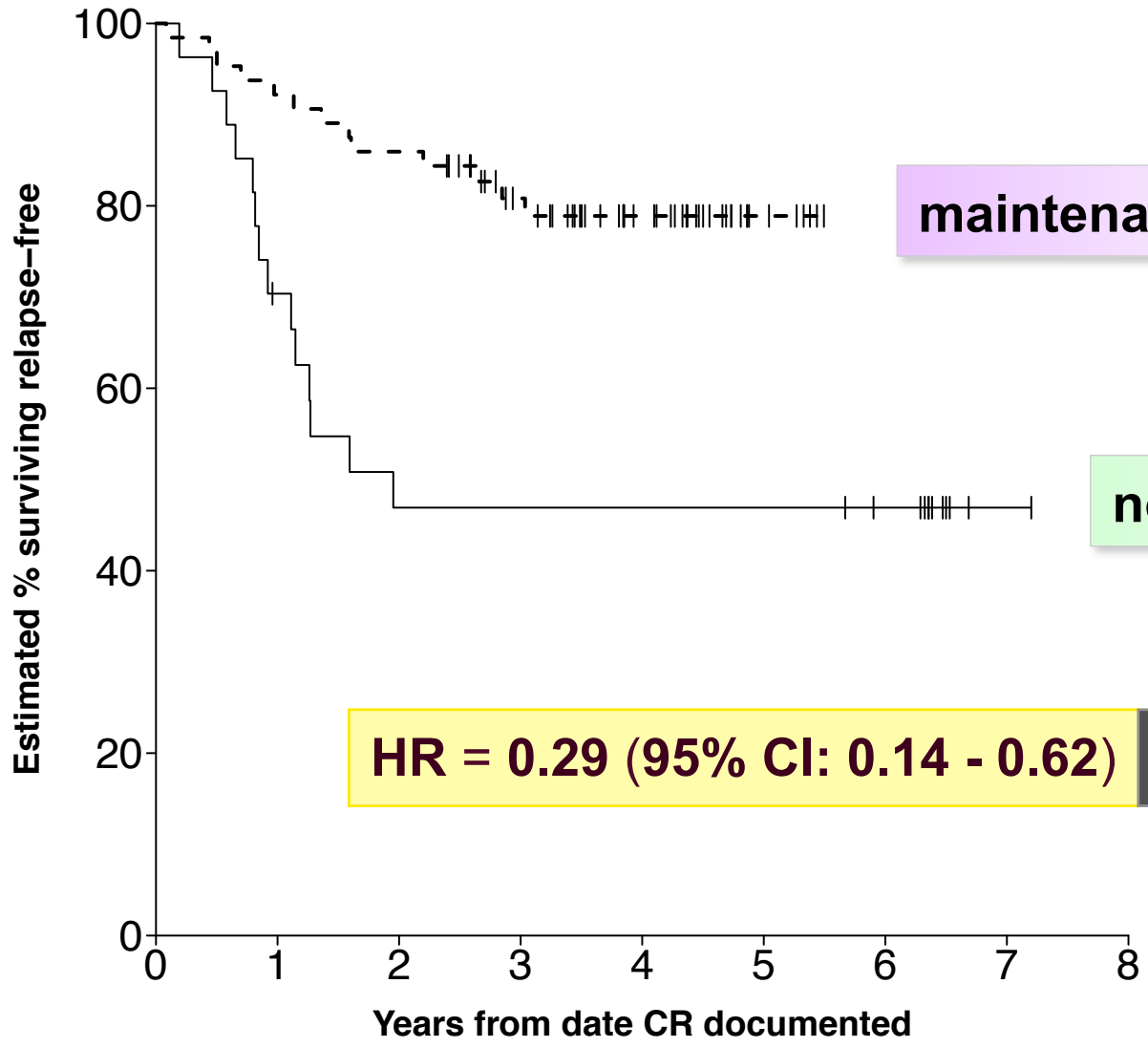


Iland *et al,* Haematologica 97:227, 2012

APML3 disease-free survival



maintenance 79%

no maintenance 47%

HR = 0.29 (95% CI: 0.14 - 0.62) *P* < .001

Number at risk

No maint	27	18	12	12	12	12	10	1	0
Maint	64	59	55	42	26	6	0	0	0

Background to APML4

AIDA Avvisati *et al* Blood 88:1390; 1996	AIDA (all-trans retinoic acid + idarubicin) in newly diagnosed acute promyelocytic leukemia: a GIMEMA pilot study
APML3 Iland *et al* Haematologica 97:227; 2012	Results of the APML3 trial incorporating all-trans-retinoic acid and idarubicin in both induction and consolidation as initial therapy for patients with acute promyelocytic leukemia
ATRA + arsenic Shen *et al* PNAS 101:5328; 2004	All-trans retinoic acid/As_2O_3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia

ATRA + ATO as initial therapy

Induction

ATRA

25mg/m^2/d until CR

ATO

0.16mg/kg/d until CR

WCC > 10x10^9/l

- **Hydroxyurea**
  20-40mg/kg/d

or

- **Idarubicin + cytarabine**
  6mg/m^2/d x3 100mg/m^2/d x3-5

Shen *et al,* PNAS 101:5328, 2004

Induction

ATRA
25mg/m^2/d until CR

ATO
0.16mg/kg/d until CR

WCC > 10x10^9/l

- **Hydroxyurea**
  20-40mg/kg/d

or

- **Idarubicin + cytarabine**
  6mg/m^2/d x3 100mg/m^2/d x3-5

Consolidation

#1 **Daunorubicin + cytarabine**
45mg/m^2/d x3 100mg/m^2/d x7

#2 **Cytarabine**
1.5-2.5g/m^2/d x3

#3 **Homoharringtonine + cytarabine**
2-3mg/m^2/d x3 100mg/m^2/d x7

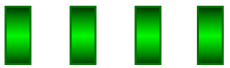
Maintenance

3 months x 5 cycles

ATRA + **ATO** + **6-MP**
25mg/m^2/d x30 0.16mg/kg/d x30 100mg/d x30

or

MTX
15mg/wk x4



Shen *et al,* PNAS 101:5328, 2004

APML4 induction

AUSTRALASIAN LEUKAEMIA & LYMPHOMA GROUP

Induction

ATRA
45mg/m^2/d x36

1 — 36

Idarubicin
12mg/m^2/d x4

2 4 6 8

Age-adjusted idarubicin: 61-70: 9mg/m^2
>70: 6mg/m^2

ATO
0.15mg/kg/d x28

9 — 36

Prednisone
1mg/kg/d x10

1 — ≥10

+ Aggressive hemostatic support

- platelets ≥ 30 x 10^9/l
- normal PT and APTT
- fibrinogen > 1.5g/l

APML4 consolidation

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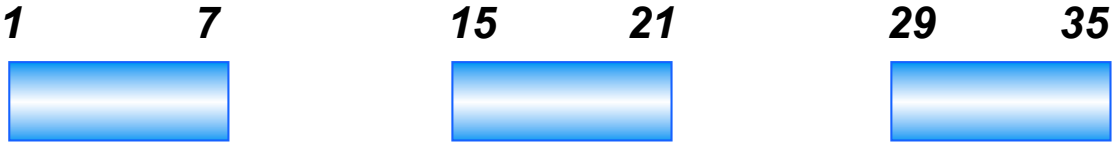
Consolidation #1

ATRA
45mg/m^2/d x28

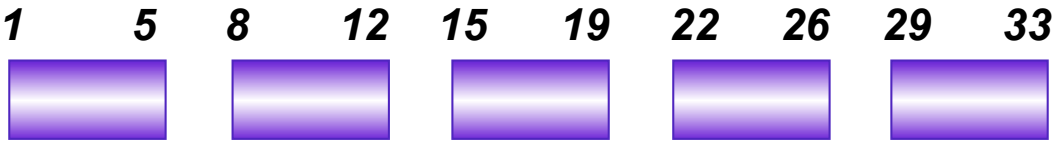
ATO
0.15mg/kg/d x28

Consolidation #2

ATRA
45mg/m^2/d x21



ATO
0.15mg/kg/d x25



APML4 maintenance

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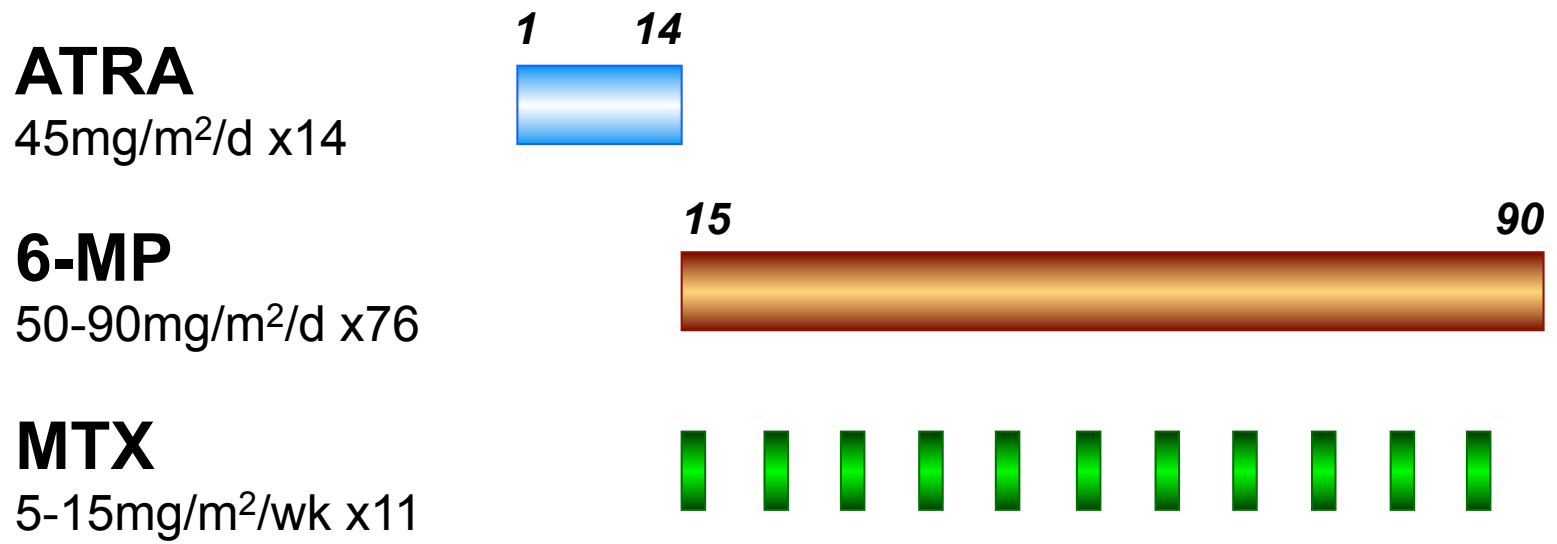
Maintenance (every 3 months for 2 years)



+ Molecular monitoring by quantitative RT-PCR

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

APML4 patients

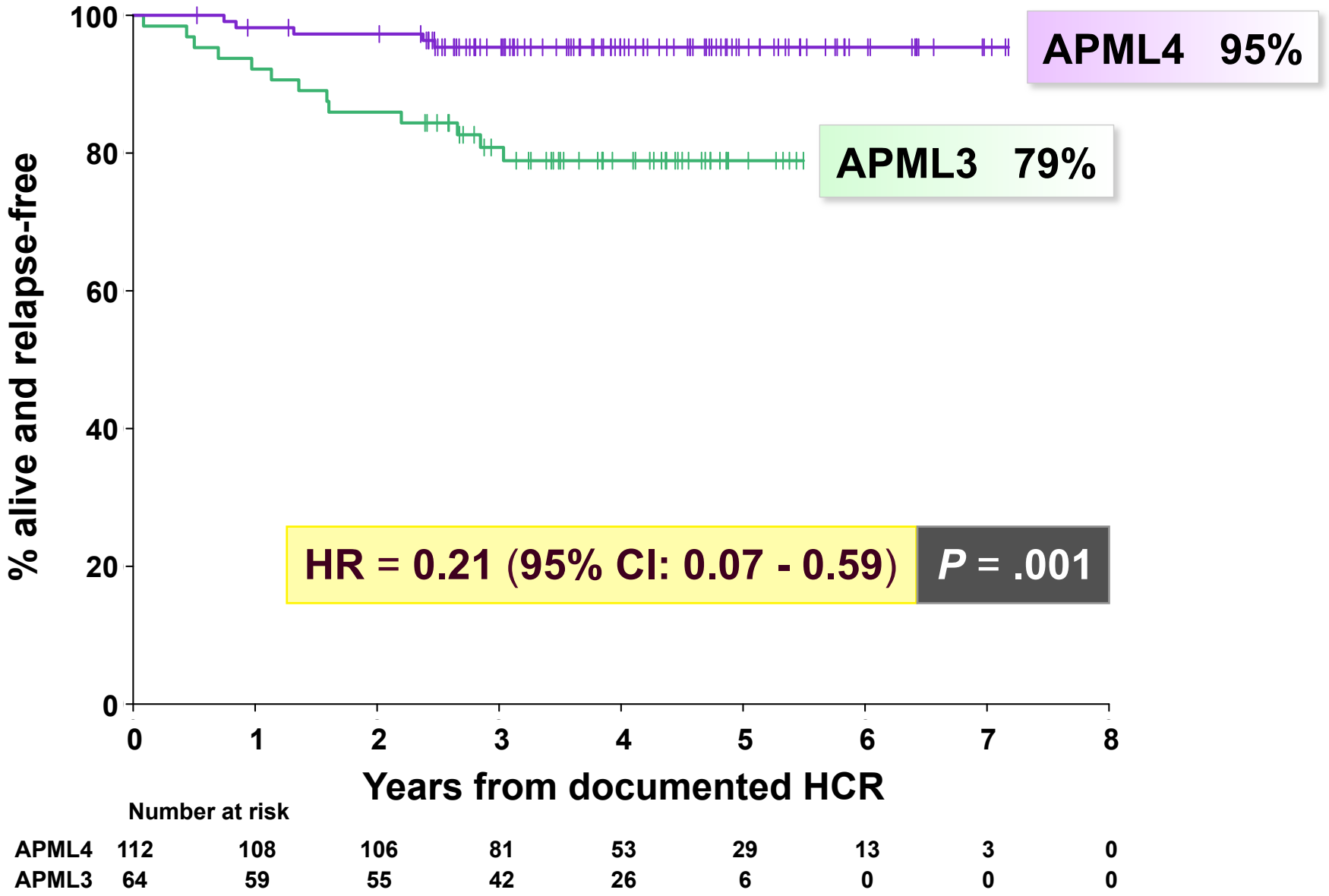
accrued	Nov 2004 - Sep 2009
evaluable patients	n = 124 (27 sites)
median age	44 (3 – 78)
median white cell count	2.4 x 10^9/L (0.1 - 85.8)
high risk	23
standard risk	101
median follow-up	4.2 years
early deaths (to day 36)	4 (3.2%)

APML4 early deaths up to day 36

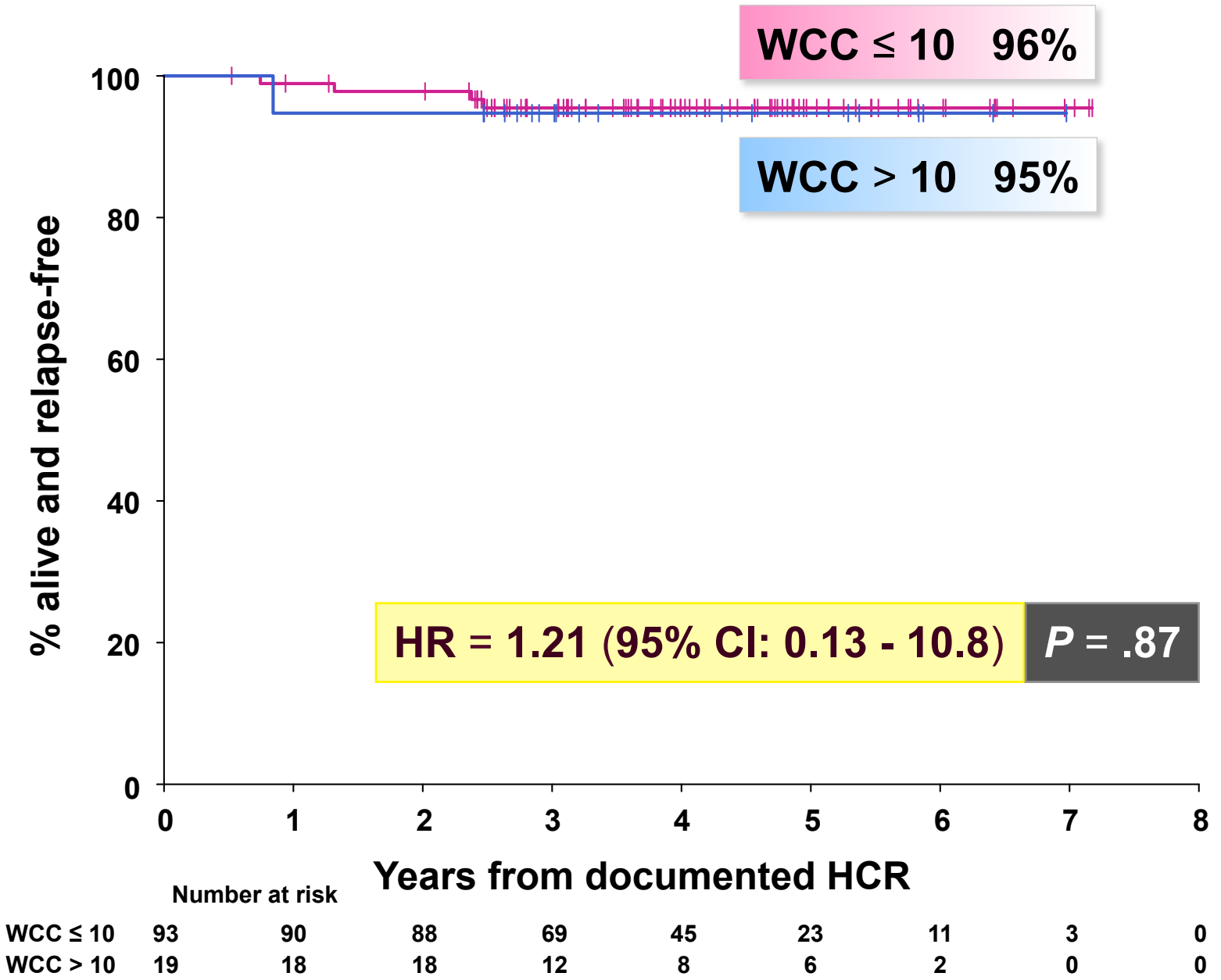
Age ≤ 70 (n = 117)	Age > 70 (n = 7)	*P*
2 (1.7%)	2 (28.6%)	0.02

WCC ≤ 10 (n = 101)	WCC > 10 (n = 23)	*P*
2 (2.0%)	2 (8.7%)	0.16

APML4 vs APML3 DFS



APML4 DFS - white cell count



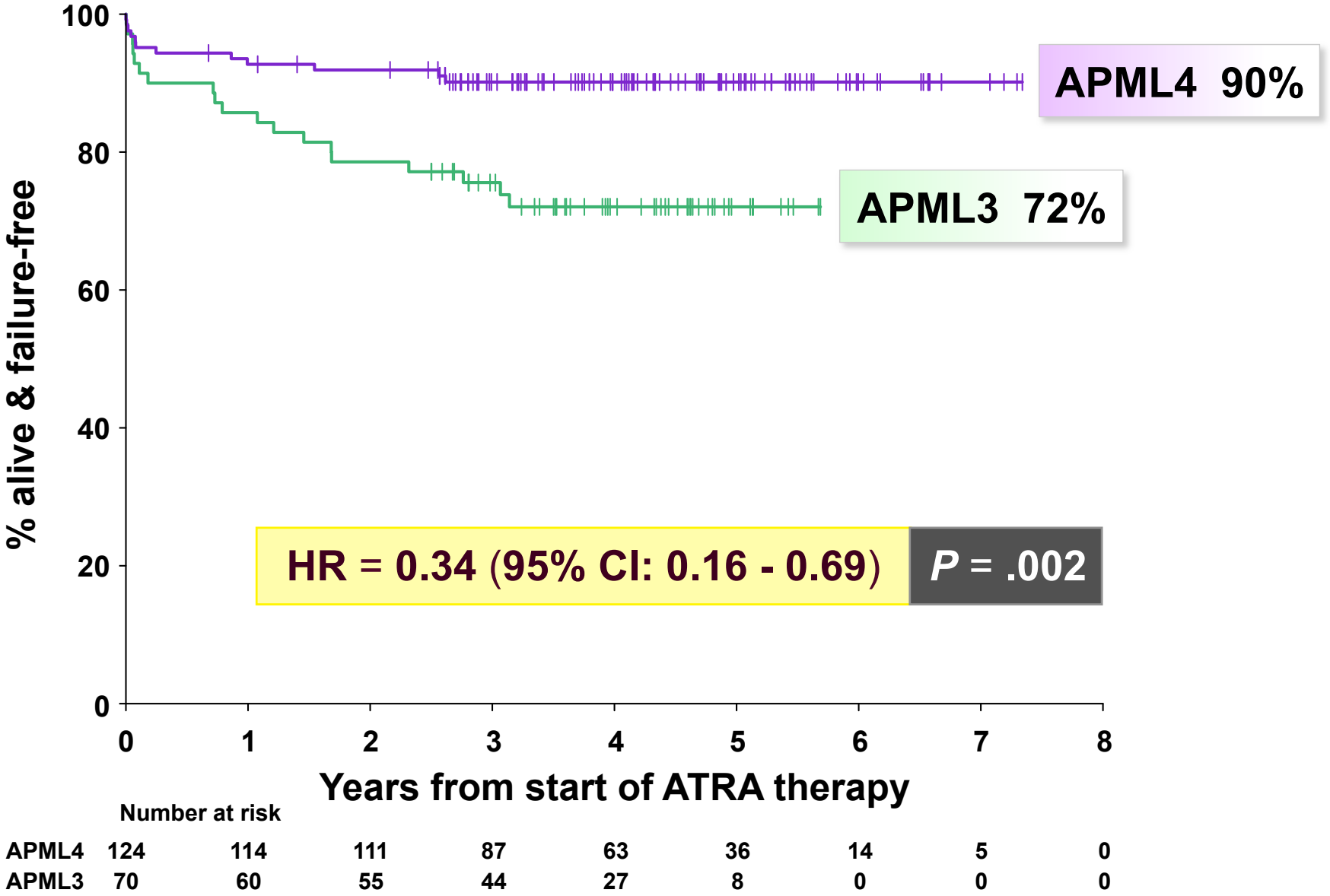
APML4 cumulative incidence of relapse

Competing risks:

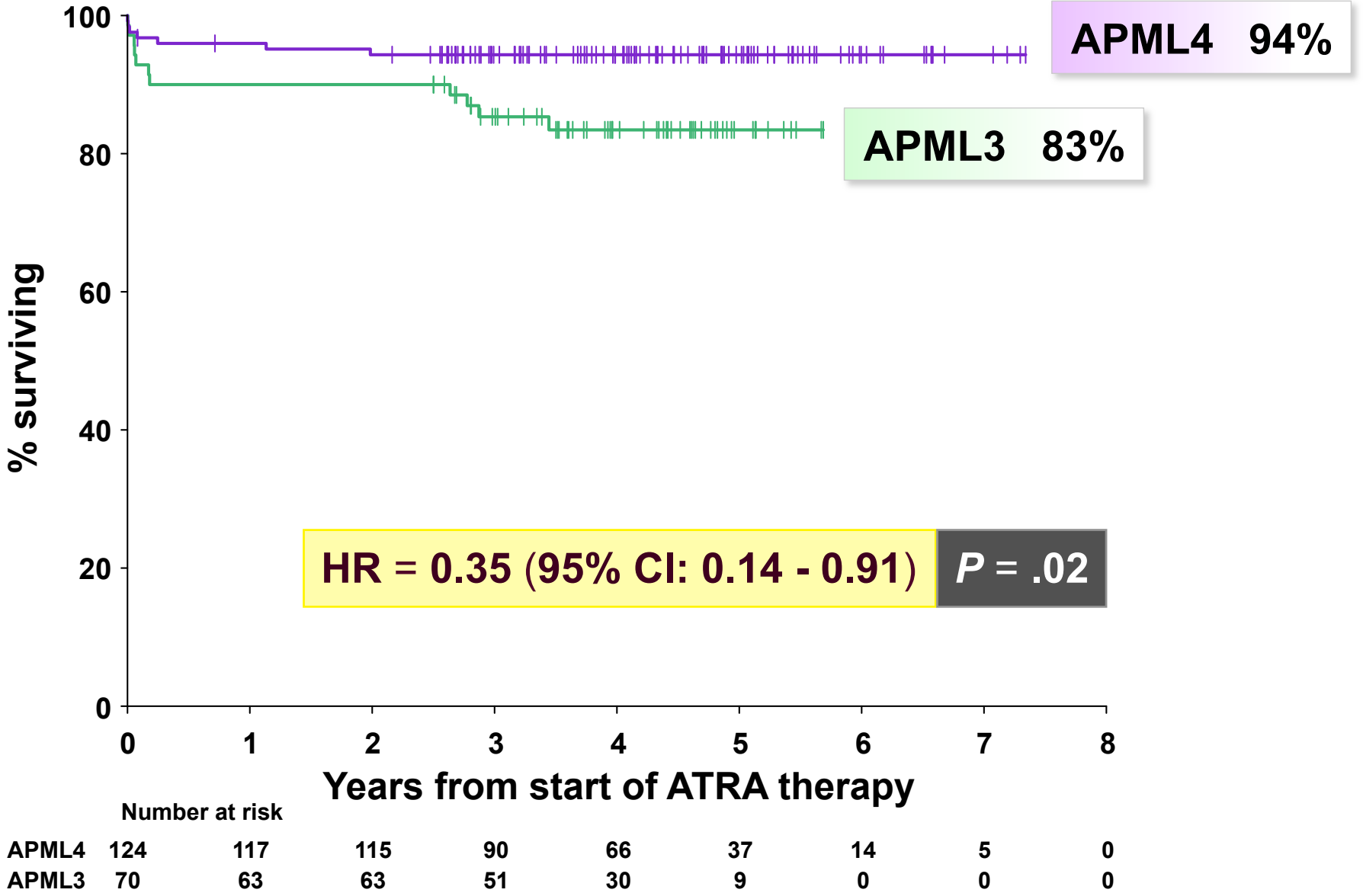
- **relapse**
- **death in remission**
- **failure to achieve molecular CR**

CIR at 5 years (± SEM)	all patients	4.6% ± 2.0%
	WCC ≤ 10 x 10^9/L	4.5% ± 2.2%
	WCC > 10 x 10^9/L	5.3% ± 5.1%

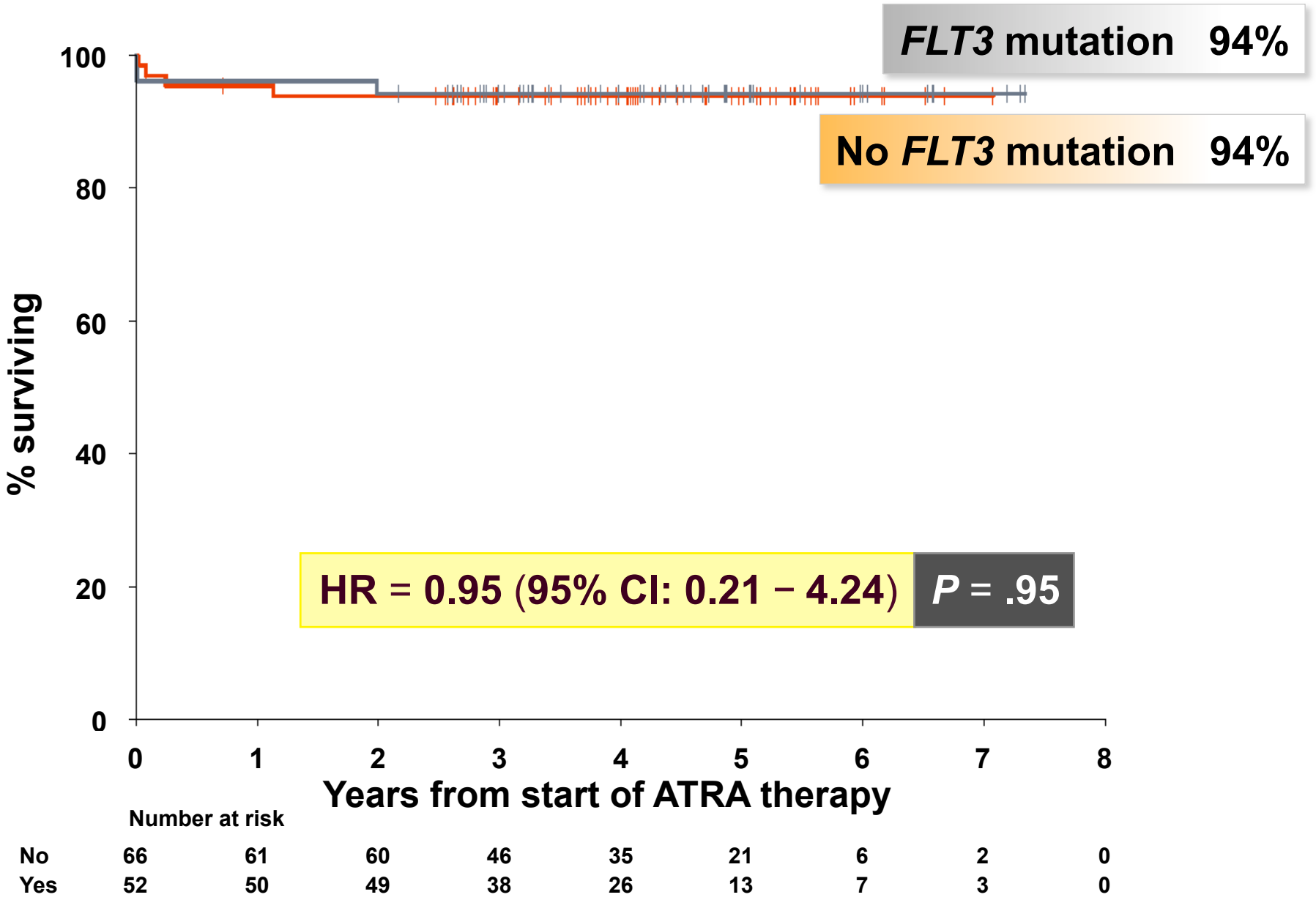
APML4 vs APML3 EFS



APML4 vs APML3 OS



APML4 OS - *FLT3* mutations



APML4 multifactor analysis

	Factor	HR	*P*
EFS	Age > 70	51.3 (8.48, 311)	**.0002**
	Sanz	trend	**.003**
OS	Age > 70	31.5 (3.77, 264)	**.005**
	Sanz	trend	**.02**
DFS	≥ 2 additional cytogenetic abnormalities	5.19 (0.87, 31.1)	**.04**

Post-hoc comparison of outcomes stratified by disease risk category

standard risk

	Protocol	Number at risk	Survival at 5 yrs	Hazard ratio	*P*
EFS	APML4	100	92%	0.34 (0.14, 0.84)	**.015**
	APML3	55	77%	-	
OS	APML4	100	96%	0.30 (0.09, 1.04)	**.045**
	APML3	55	87%	-	
DFS	APML4	92	95%	0.31 (0.09, 1.05)	**.046**
	APML3	50	85%	-	

Post-hoc comparison of outcomes stratified by disease risk category

high risk

	Protocol	Number at risk	Survival at 5 yrs	Hazard ratio	*P*
EFS	APML4	23	83%	0.36 (0.11, 1.24)	**.091**
	APML3	15	-	-	
OS	APML4	23	87%	0.53 (0.12, 2.36)	**.40**
	APML3	15	-	-	
DFS	APML4	19	95%	0.11 (0.01, 0.88)	**.011**
	APML3	14	-	-	

blood

All-*trans*-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4)

Iland *et al*, Blood 120:1570, 2012

CME article

THE LANCET Haematology

Volume 2 · Issue 9 · September 2015 www.thelancet.com/haematology

Use of arsenic trioxide in remission induction and consolidation therapy for acute promyelocytic leukaemia in the Australasian Leukaemia and Lymphoma Group (ALLG) APML4 study: a non-randomised phase 2 trial

Iland *et al,* Lancet Haematol 2:e357, 2015

Recommended for high-risk APL
NCCN Guidelines Acute Myeloid Leukemia Version 3.2017
Canadian guidelines Seftel *et al*, Curr Oncol 21:234, 2014

ATO in Australia	
TGA:	Front-line indication - 2015
PBS:	Funded for front-line indication - 2016

High-risk APL

ATRA + risk-adapted chemo vs APML4

Series	Number	Median follow-up (months)	IDA equivalent[6] (mg/m^2)	araC (g/m^2)	Death in CR	DFS	CIR	OS
PETHEMA LPA2005[1]	118	28	122	5.8	3.1%	82% at 4 yrs	14%	79%
European APL2000[2,3]	74 (≤ 60 yrs)	103	99	22.8	3.8%	-	7% at 7 yrs	88%
GIMEMA AIDA2000[4]	129 (≤ 61 yrs)	59	122	6.3	5.1%	85% at 6 yrs	9%	83%
ALLG APML4[5]	**23**	**50**	**48**	**0**	**0%**	**95% at 5 yrs**	**5%**	**87%**

[1] Sanz, Blood 115:5137, 2010 • [2] Adès, Blood 111:1078, 2008 • [3] Adès, Am J Hematol 88:556, 2013
[4] Lo Coco, Blood 116:3171, 2010 • [5] Iland, Lancet Haem 2:e357, 2015 • [6] Sanz, Best Pract Res Clin Haematol 16:433, 2003

Arsenic administration

IV

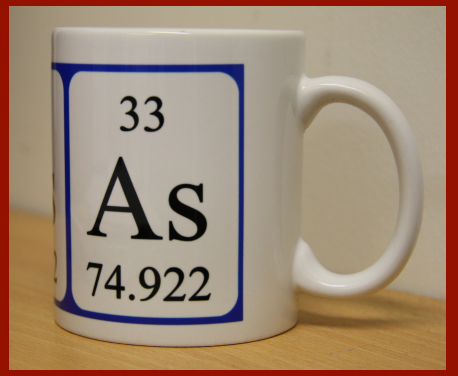
patient time commitment

hospital resources

prolonged IV access

? higher Cmax
→ more cardiotoxicity
(↑QTc)

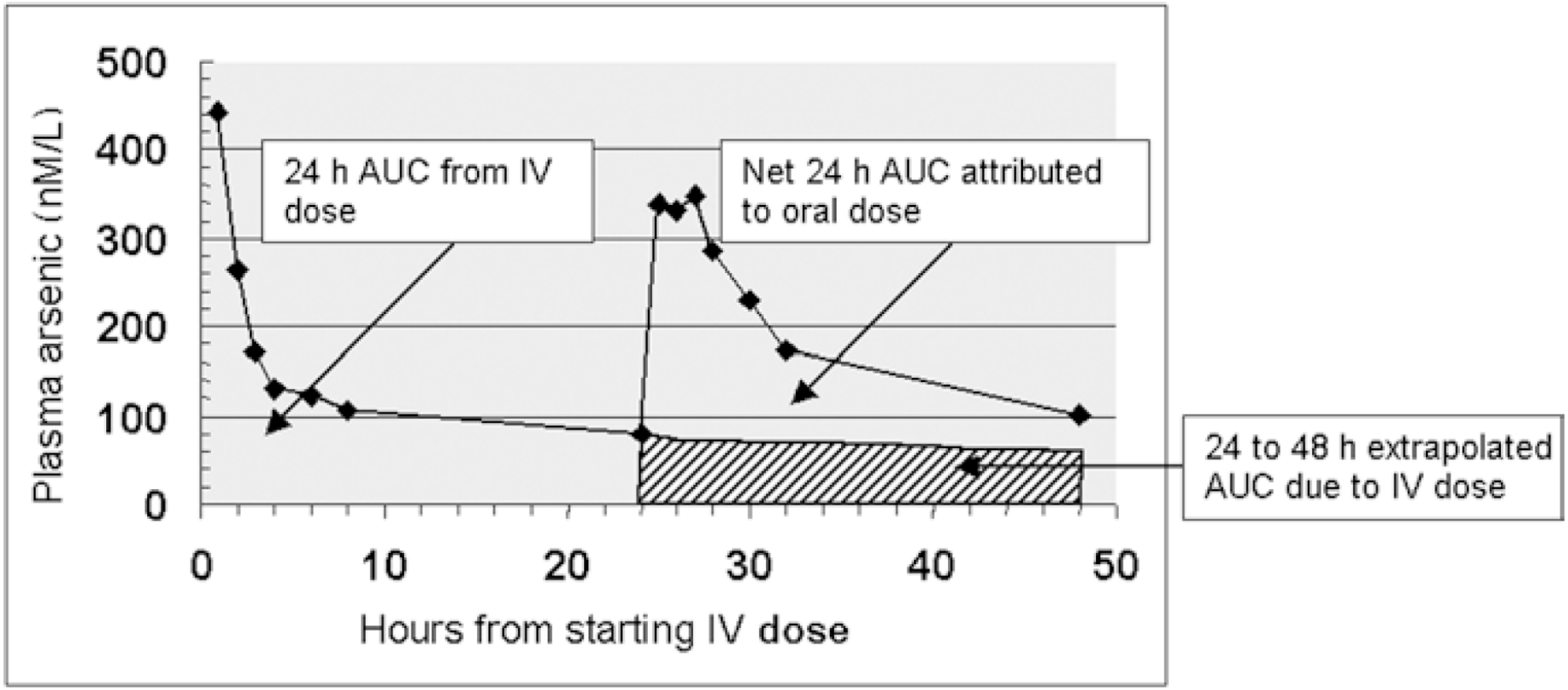
Oral



? food restrictions

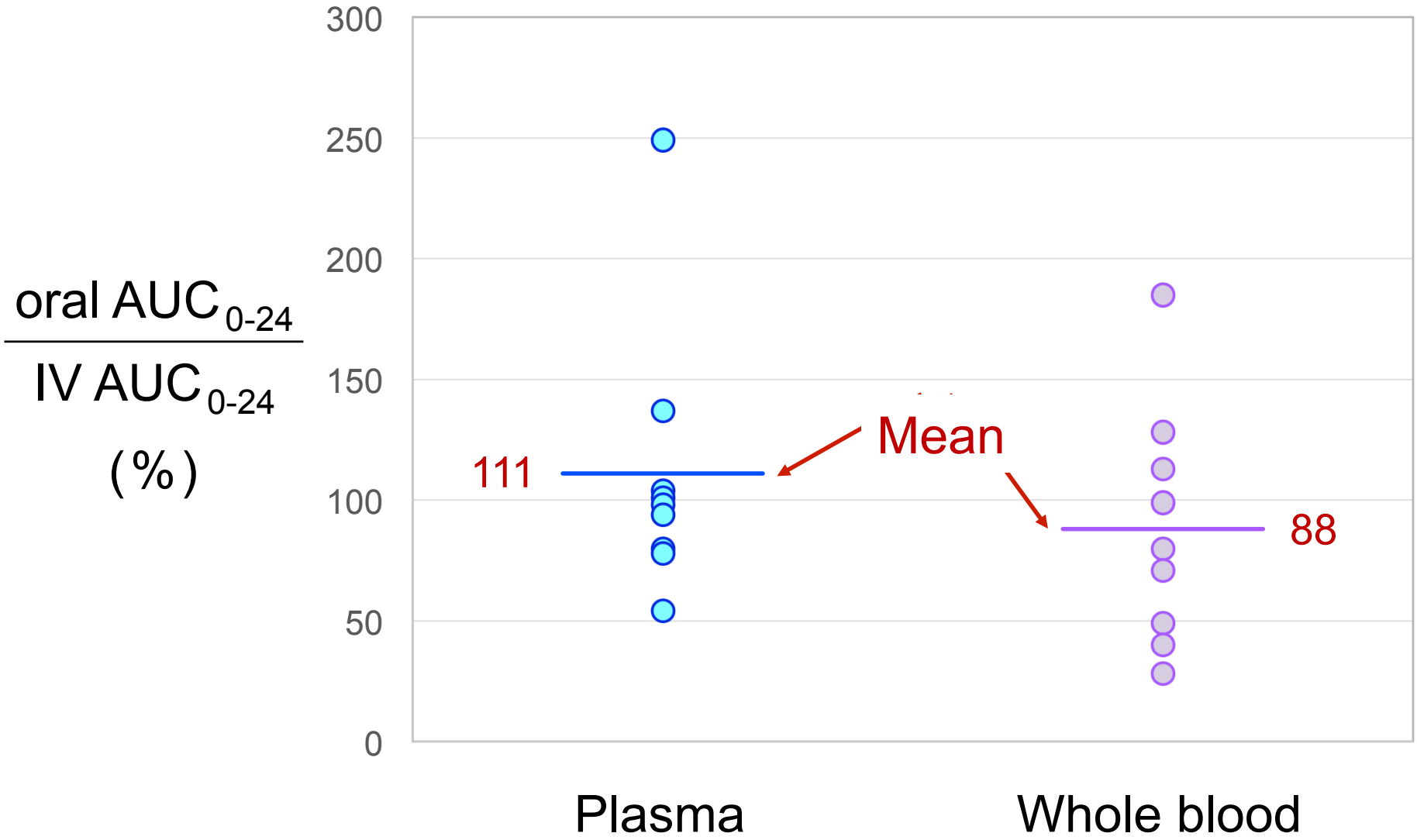
? poorer compliance

Systemic availability of oral arsenic trioxide solution



Kumana *et al*, Eur J Clin Pharmacol 58:521, 2002

Comparison of derived oral and IV AUC_{0-24}



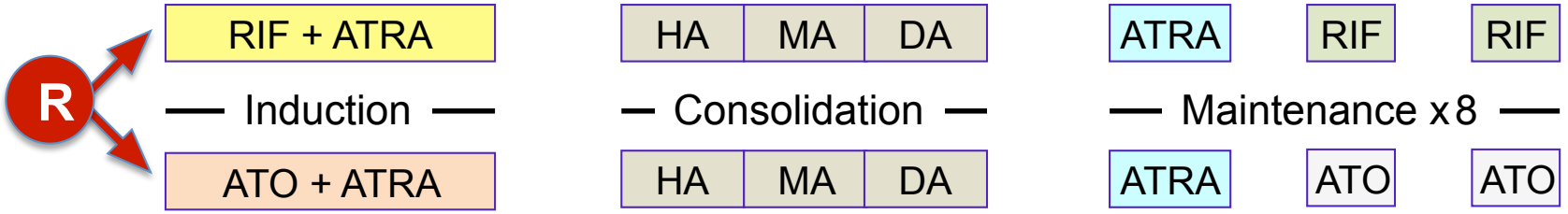
Kumana *et al*, Eur J Clin Pharmacol 58:521, 2002

Realgar-*Indigo naturalis* formula

- Realgar [As_4S_4]
- *Indigo naturalis* [indirubin]
- *Radix salviae miltiorrhizae* [tanshinone IIA]
- *Radix pseudostellariae*

Bioavailability of realgar-derived arsenic ~ 2-3%

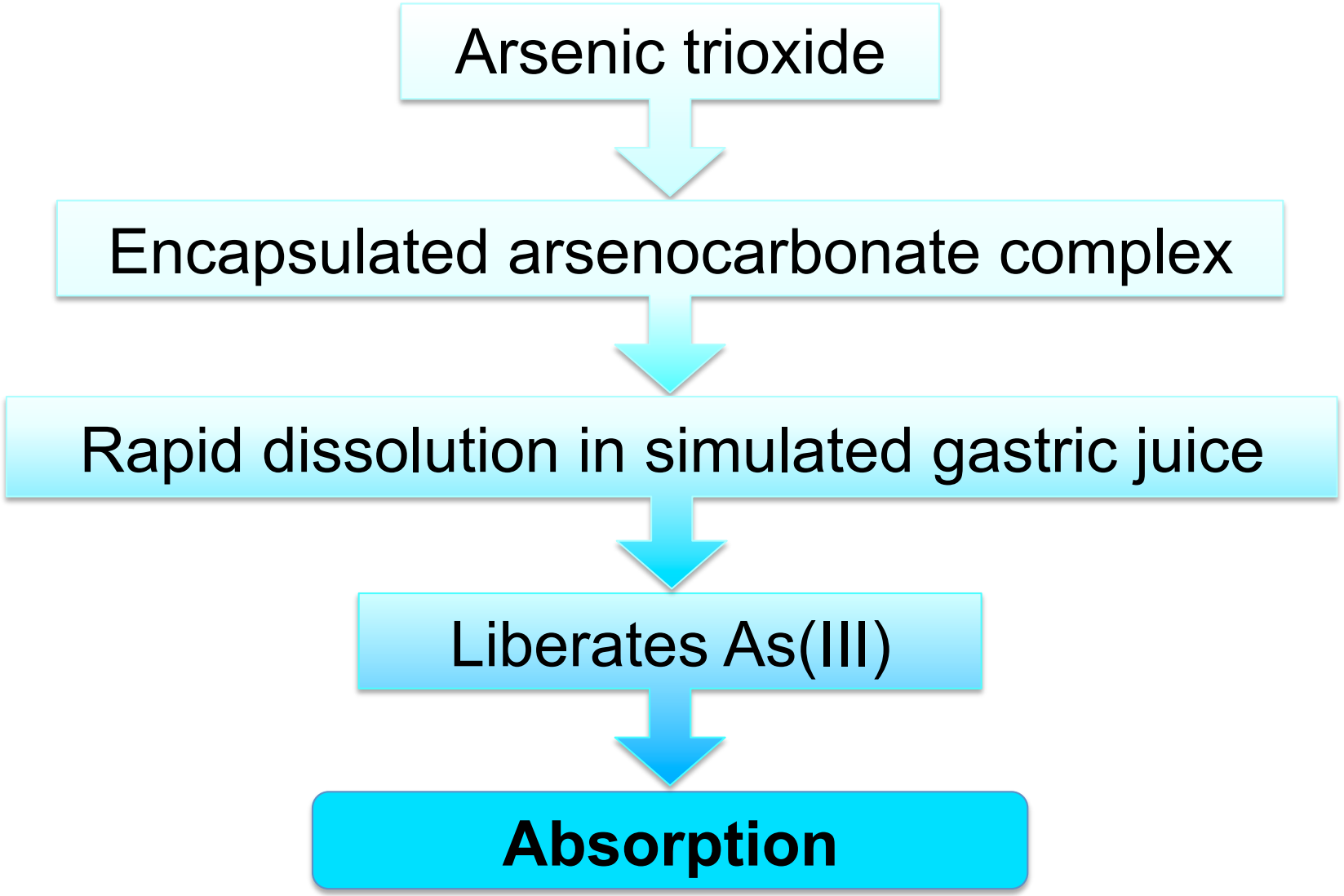
Chinese APL Cooperative Group APL07



RIF non-inferior to IV ATO

Zhu *et al*, J Clin Oncol 31:4215, 2013 • Zhu et al, Br J Haematol 174:820, 2016

Eupharma/Phebra oral arsenic



APML5

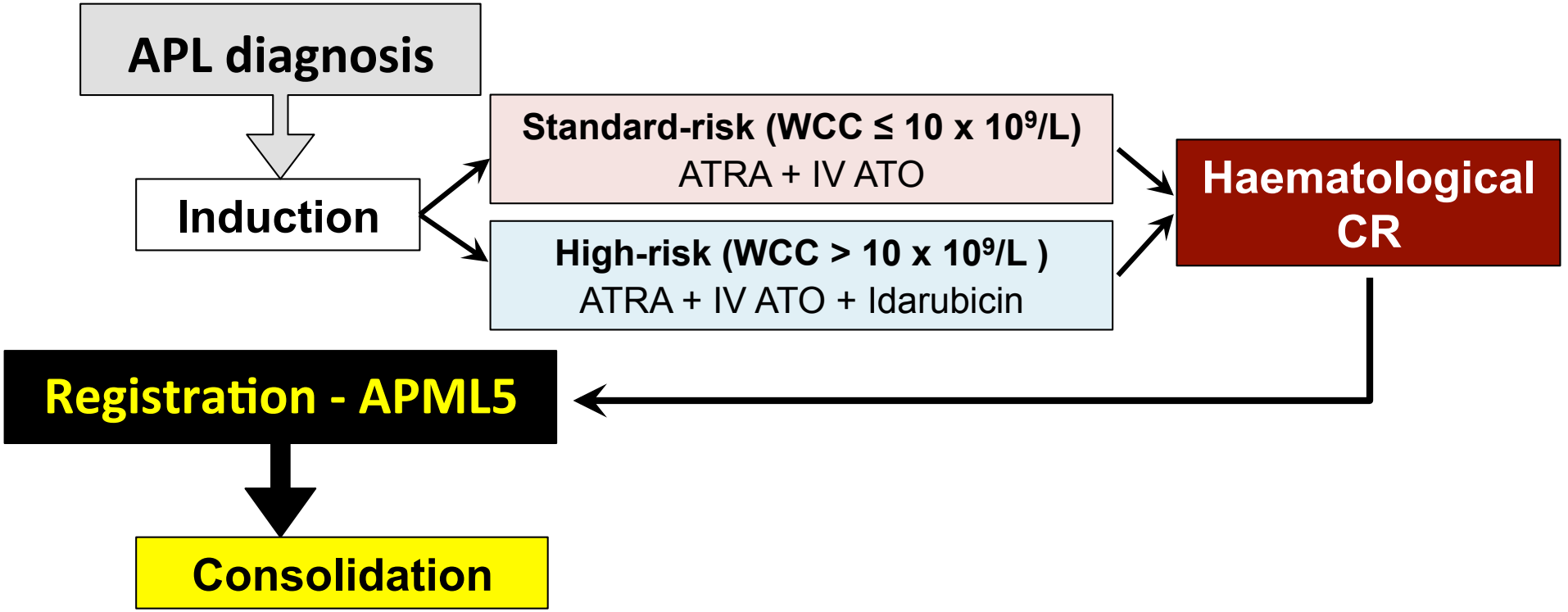
ALLG
AUSTRALASIAN LEUKAEMIA & LYMPHOMA GROUP

A phase I pharmacokinetic evaluation of oral ATO in previously untreated patients with APL

Oral ATO – Eupharma / Phebra

1mg, 5mg, 10mg capsules

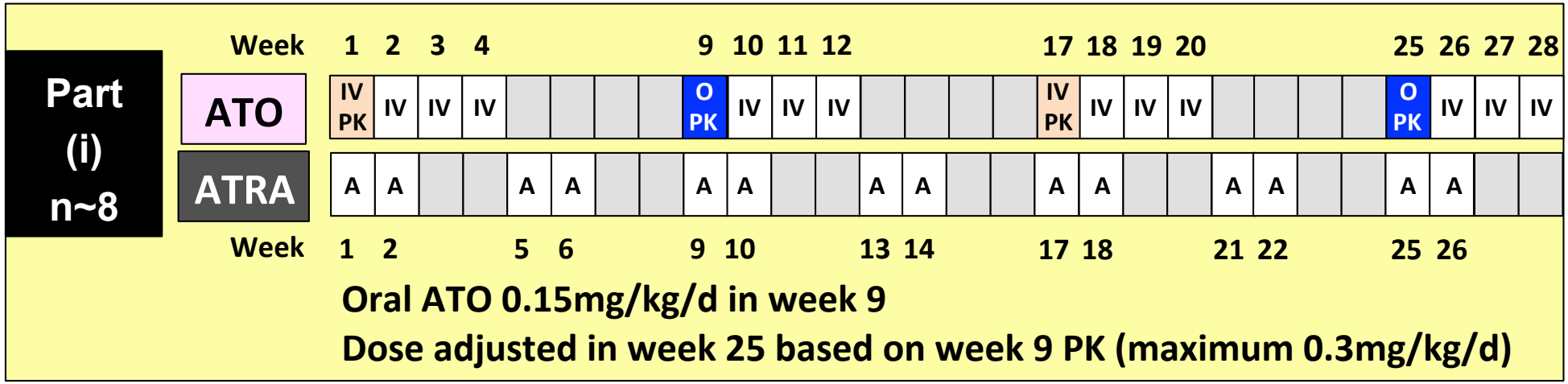
APML5 bioavailability study

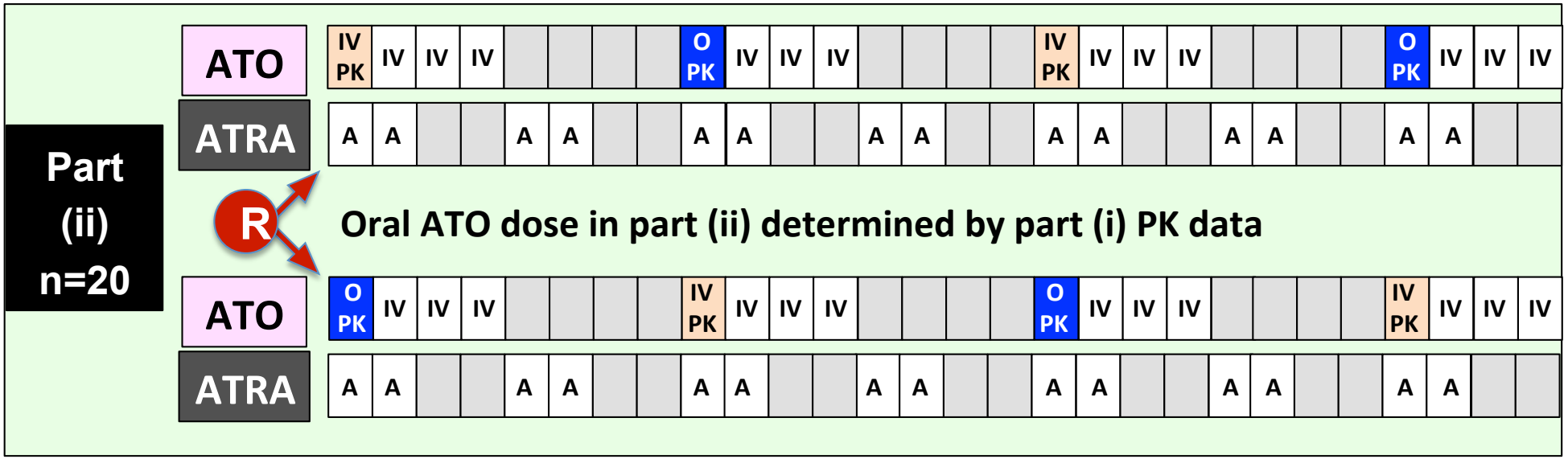


- **4 cycles of ATO**
  (cycle = 5 days/week for 4 weeks; 4 weeks between cycles)

- **7 cycles of ATRA**
  (cycle = 7 days/week for 2 weeks; 2 weeks between cycles)

APML5 bioavailability study - consolidation





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IV PK IV ATO with PK

O PK oral ATO with PK

IV IV ATO

A ATRA

APML5 bioavailability study - PK sampling

Day of the week	Mon 1	Tue 2	Wed 3	Thu 4	Fri 5
ATO	IV / PO	IV / PO	IV / PO	IV / PO	IV / PO

PK samples (hours)

0 0.5 1 2 4 6-8 — 24

0 0.5 1 2 4 6-8 — 24

24-hour urine collection

0 – 24

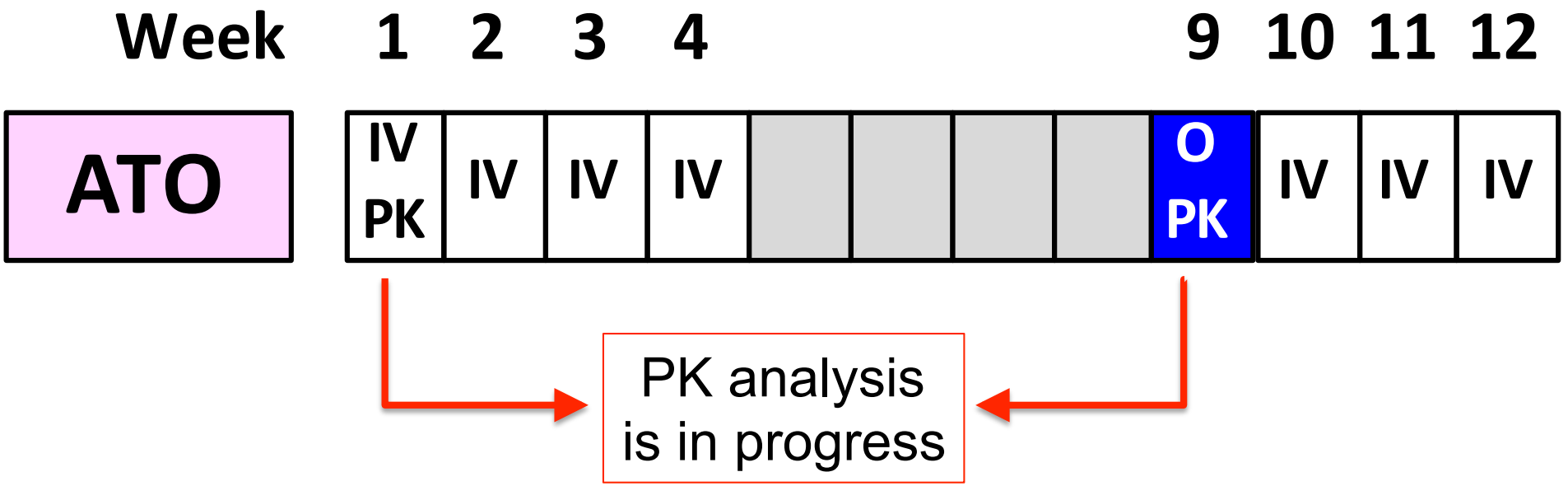
AUSTRALASIAN LEUKAEMIA & LYMPHOMA GROUP

APML5 current status

Trial registered: ACTRN12616001022459

First patient enrolled: 26 June 2017

Completed first 2 ATO cycles



Conclusions

- APML4 is highly effective, with a low early death rate and absence of deaths in remission
- All survival endpoints are statistically significantly superior to APML3 (ATRA + IDA)
- Compared to risk-adapted protocols for high-risk disease, APML4 allows substantial reduction in anthracycline exposure and eliminates the need for high-dose cytarabine
- Our results support the inclusion of ATO in both induction and consolidation as the standard of care for the initial therapy of patients with high-risk APL

Current aim

To develop an oral ATO regimen that:

- is as effective as IV ATO
- is at least as safe as IV ATO
- improves the overall treatment experience
- is acceptable to regulatory agencies worldwide

Acknowledgements

Institute of Haematology
Royal Prince Alfred Hospital

Molecular Haematology Lab

Colleagues

Patients

ALLG
AUSTRALASIAN
LEUKAEMIA & LYMPHOMA
GROUP

APML3 • APML4 • APML5

Local investigators

Registrars & nurses

Trial support staff

Statisticians

Phebra / Eupharma

Lab & pharmacy support staff