Acute promyelocytic leukemia

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University Tor Vergata
Rome, Italy

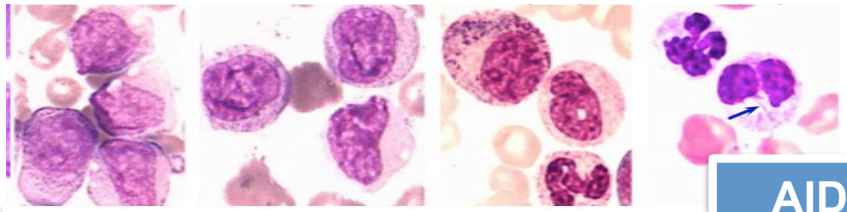
Acute Myeloid Leukemia Meeting

Ravenna, Italy (October 2017)

APL. From highly fatal to curable disease

- Fatal outcome if not recognized and promptly treated
- Coagulopathy and severe bleeding episodes at onset
- Recurrent genetic abnormality *PML-RARA* is unique to APL and is the target of specific APL therapies
- Cure rates >90% with target therapies

Turning points in APL therapy



Differentiation of blasts. CR w
resolution of coagulopathy

AIDA (ATRA+IDA)
Risk-adapted
approaches

>95% of cured
APL

ATRA*

ATRA+CHT

ATO+ATRA
+/-CHT

1980

1990

2000

2010

t(15;17)
J Rowley

Cloning of
PML-RARA

ATO°

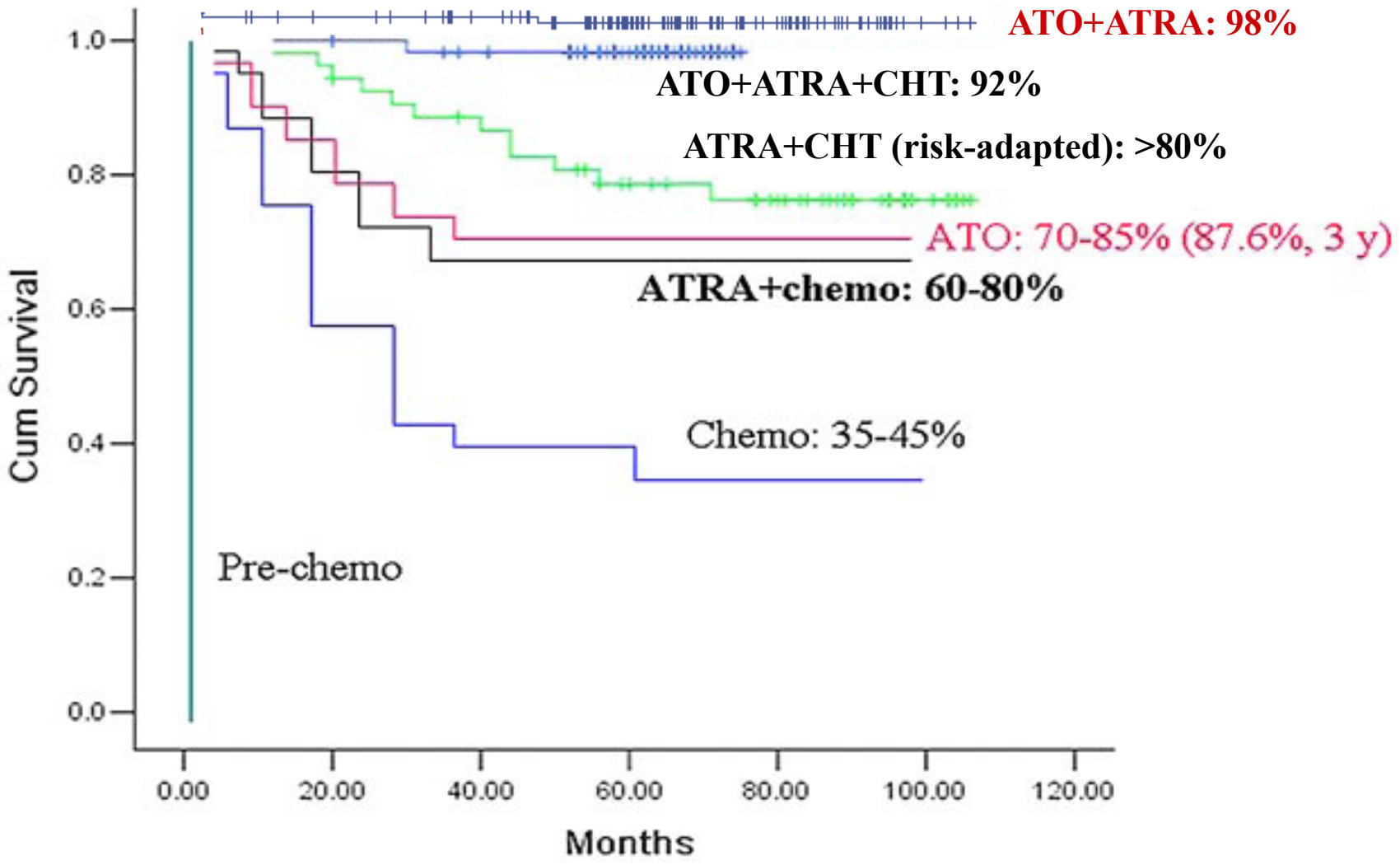
ATO

Most effective singl
agent in APL
(relapsed)

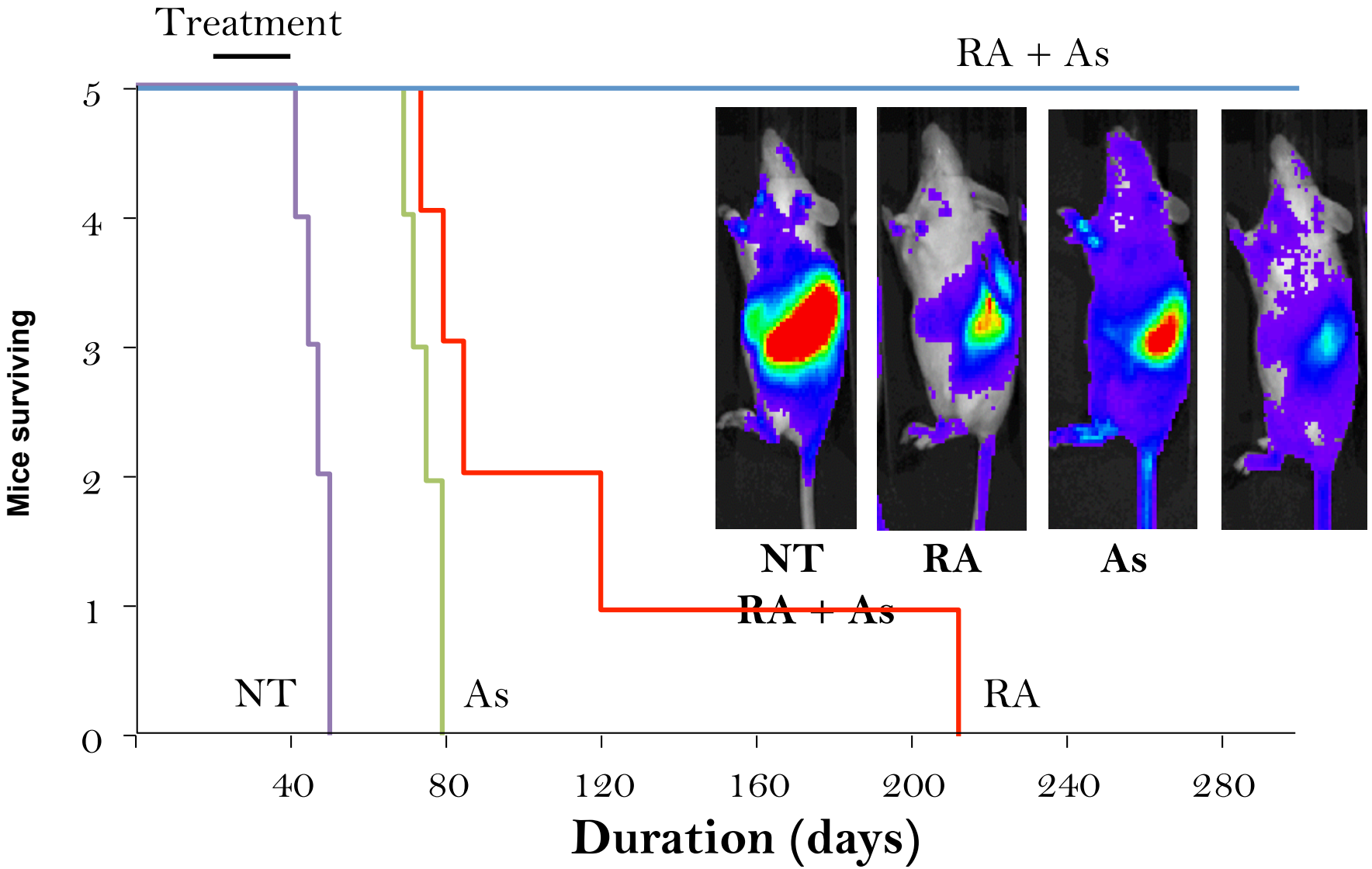
>70% CRm in
front-line APL

*All-*trans* retinoic acid; °arsenic trioxide

Survival improvement in APL



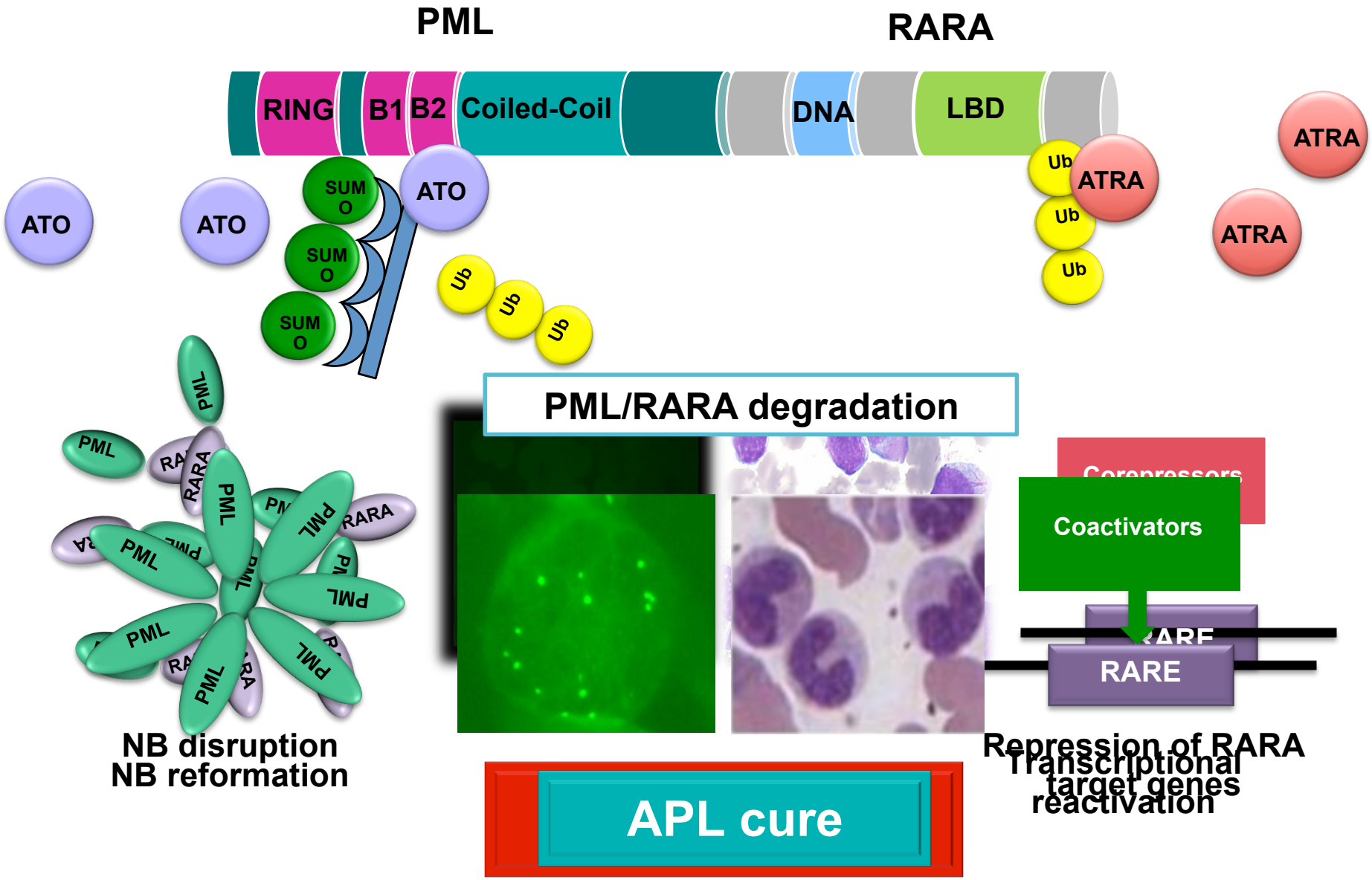
ATO and ATRA synergize for cure



Lallemand-Breitenbach V, et al. J Exp Med. 1999;89:1043-52.
Nasr R, et al. Nat Med. 2008;14:1333-42.

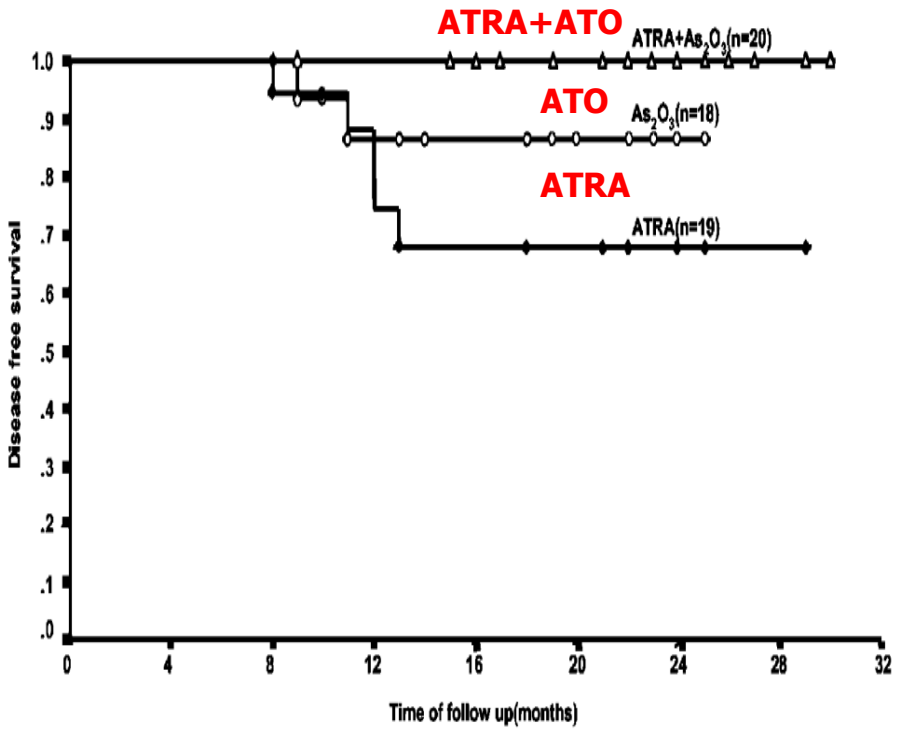
NT, no treatment.

PML-RARA, ATO and ATRA

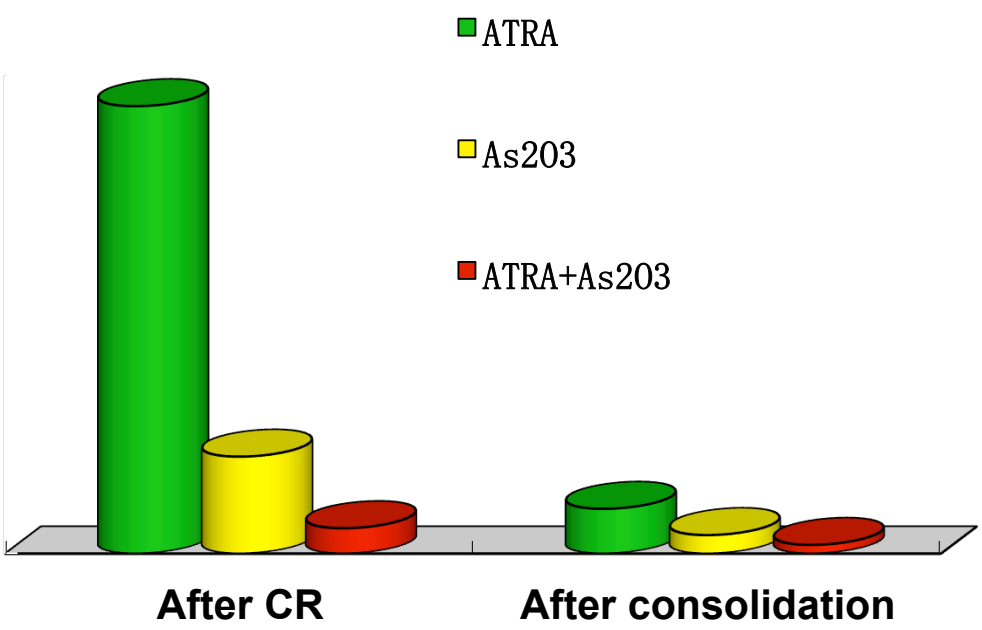


Synergistic Targeting of PML-RARa in Newly Diagnosed APL

Disease free survival N=61



RQ-PCR for PML-RARA



Shen et al. PNAS. 2004, 101(15): 5328-35.

ATO combinations in APL therapy

- Can CHT be minimized by ATO?

1. Shen, et al. *PNAS*. 2004.
2. Powell BL, et al. *Blood.* 2010
3. Iland HJ, et al. *Blood.* 2012
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- Can CHT be substituted by ATO with similar efficacy?

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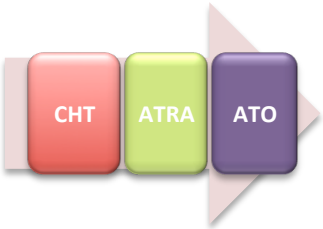


ATO+ATRA+CHT

Australasian APML4 trial

Induction
ATRA + ATO + CHT

Consolidation (2)
ATRA + ATO

Maintenance (5)
ATRA + LD-CHT

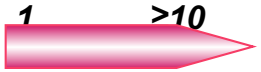
Induction

ATRA
45mg/m²/d x36

Idarubicin
12mg/m²/d x4

ATO
0.15mg/kg/d x28

Prednisone
1mg/kg/d x10



Consolidation #1

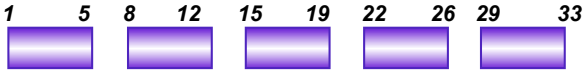
ATRA
45mg/m²/d x28

ATO
0.15mg/kg/d x28

Consolidation #2

ATRA
45mg/m²/d x21

ATO
0.15mg/kg/d x25



Maintenance

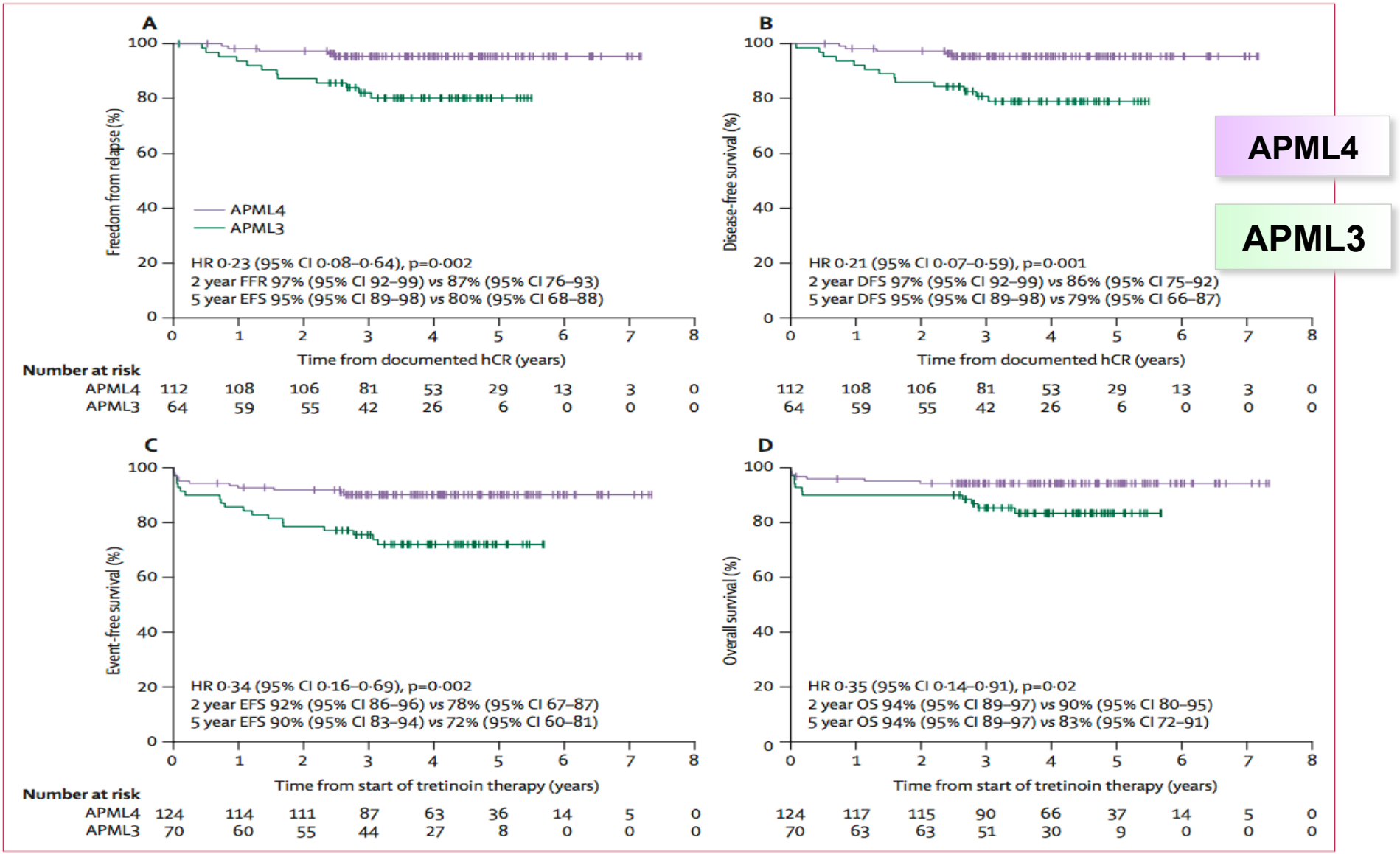
ATRA
45mg/m²/d x14

6-MP
50-90mg/m²/d x76

MTX
5-15mg/m²/wk x11

ATO+ATRA+CHT

Australasian APML4 trial



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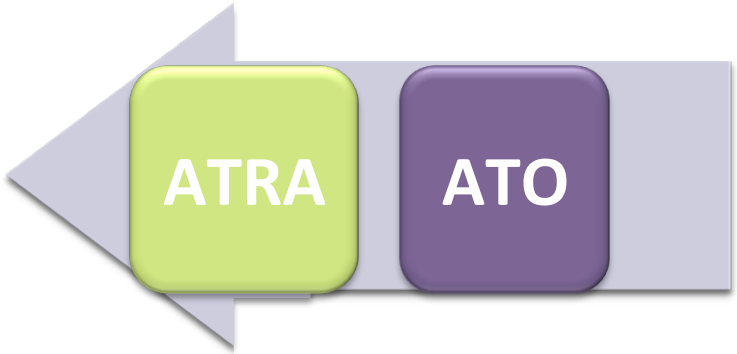

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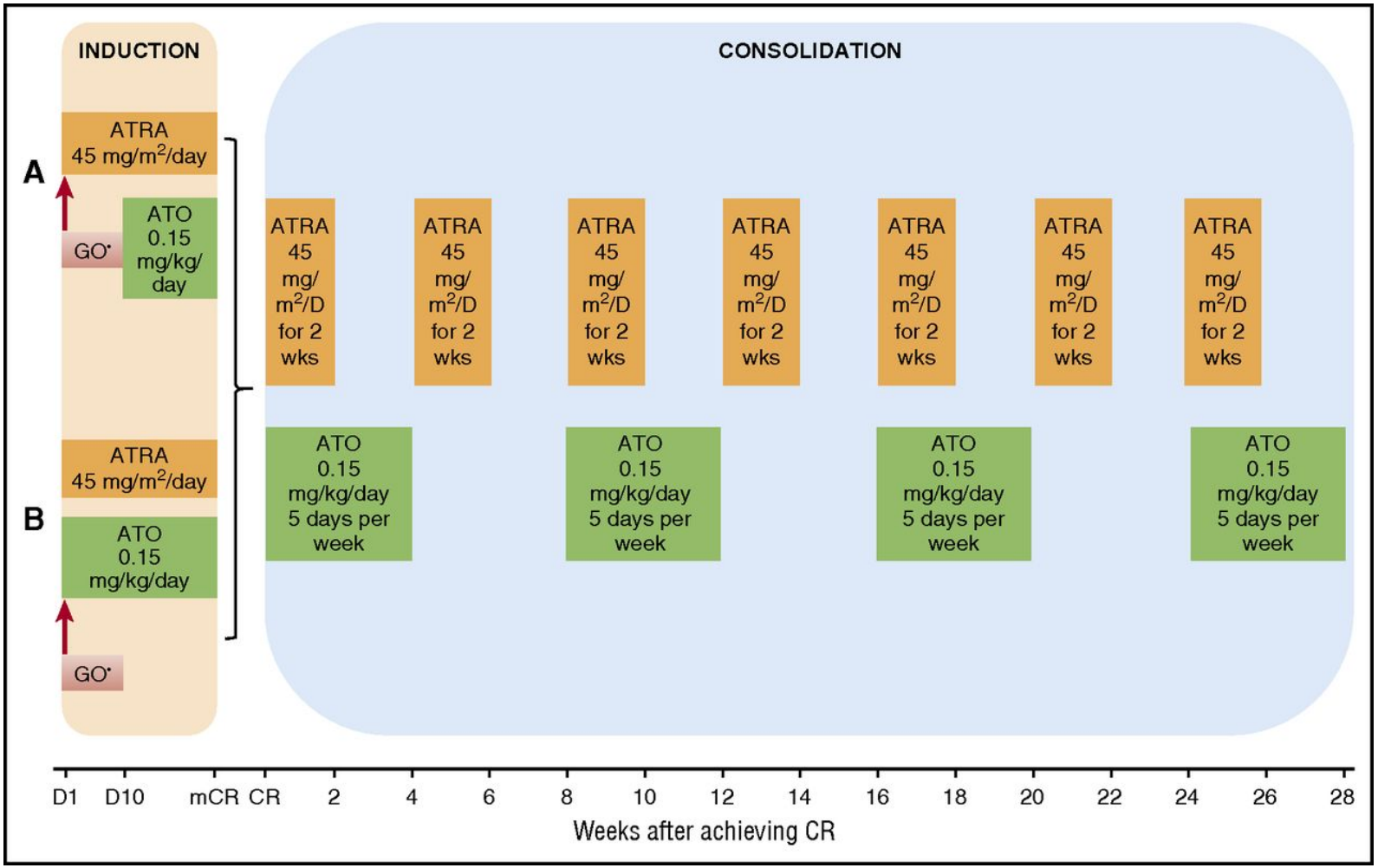
ATRA + ATO ± GO. MDACC Long-term follow-up

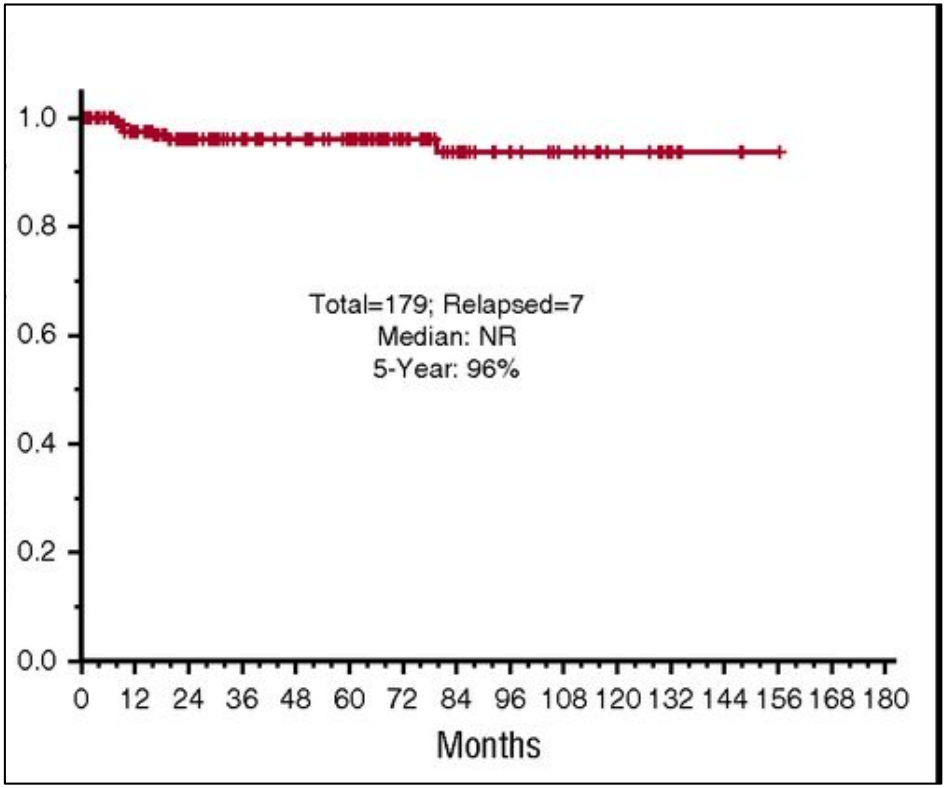


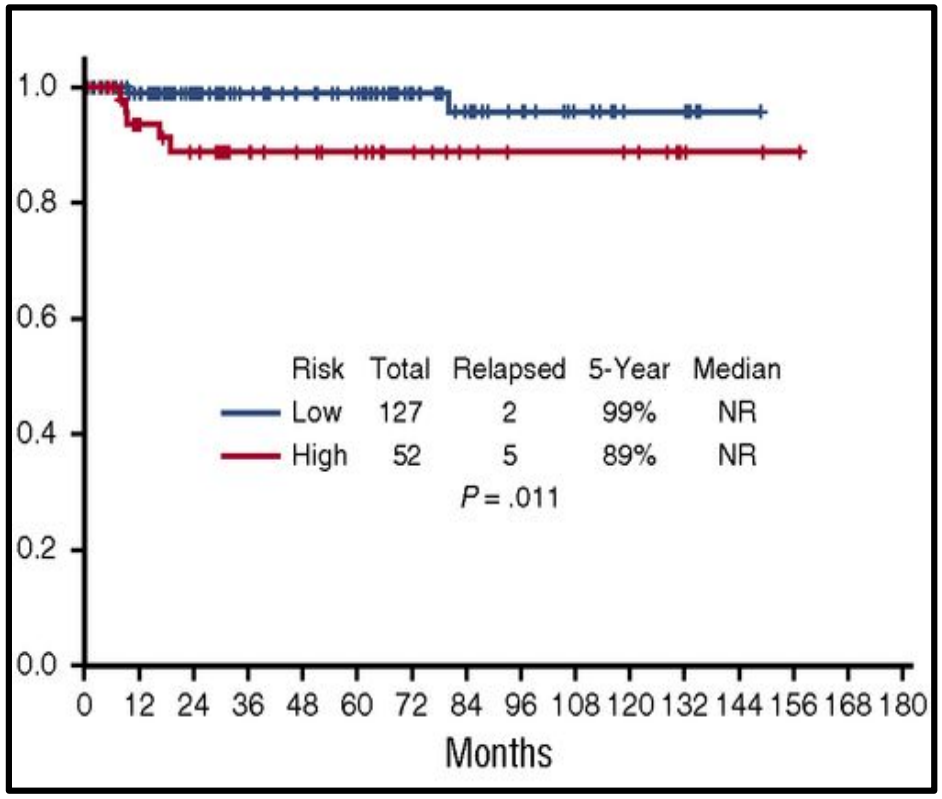
Estey et al., Blood 2006; Abaza Y, et al. Blood 2017

ATRA + ATO ± GO. MDACC
Long-term follow-up

Median F/U 47.6 months, Range 2.7 – 159.7 months

Disease-free survival





Abaza Y, et al. Blood 2017

ATO+ATRA+/- minimal CHT
Randomized Studies

GIMEMA-SAL-AMLSG

APL 0406 Italian-German: Phase III Study

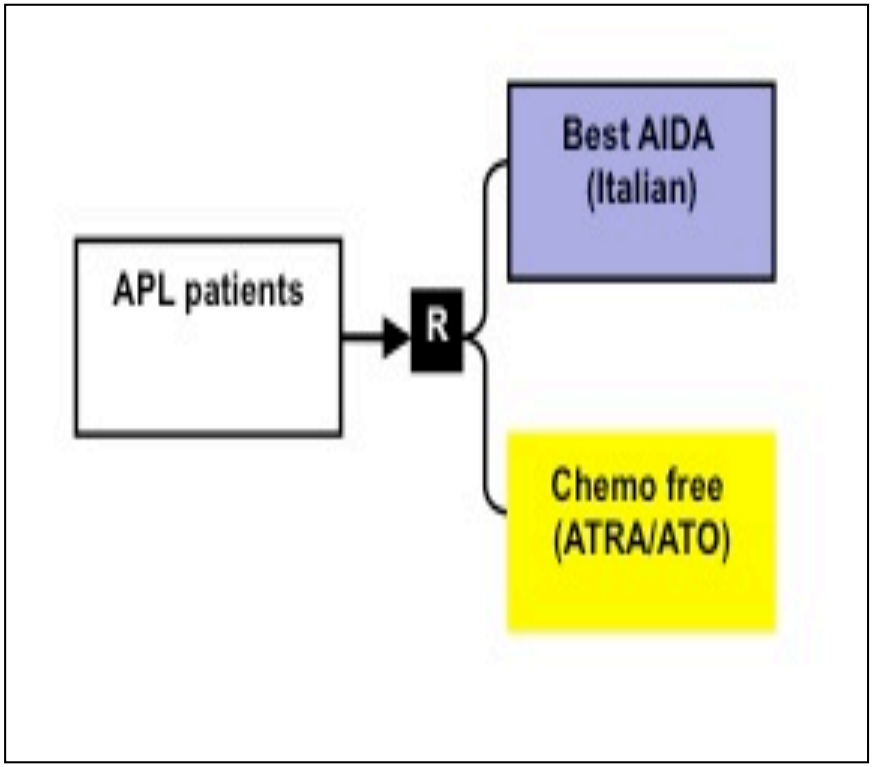
Acute Promyelocytic Leukemia
Low-intermediate risk

R

ATRA + Arsenic Trioxide

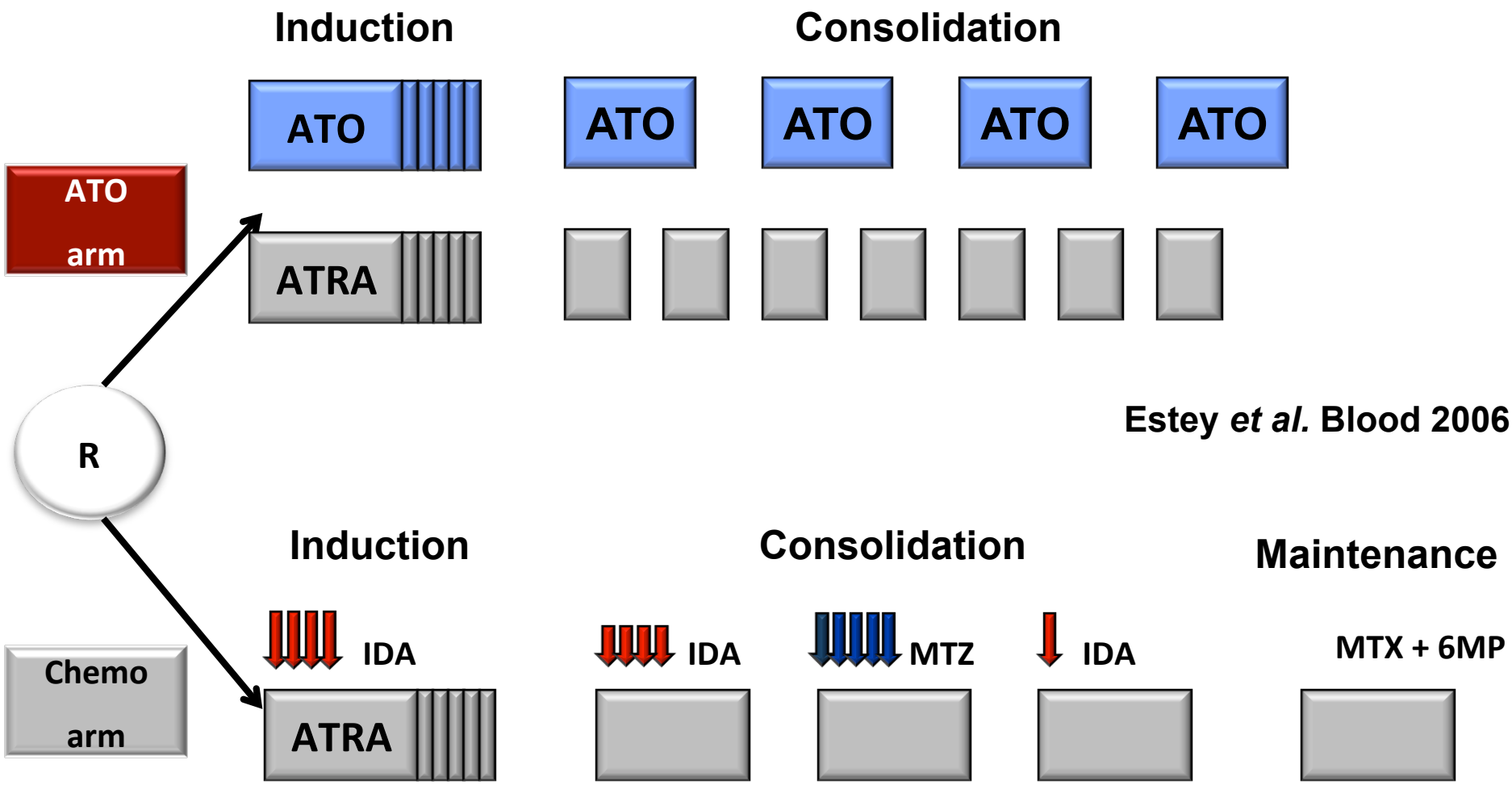
ATRA + Chemotherapy

MRC – AML 17



ATO+ATRA in low-intermediate risk APL

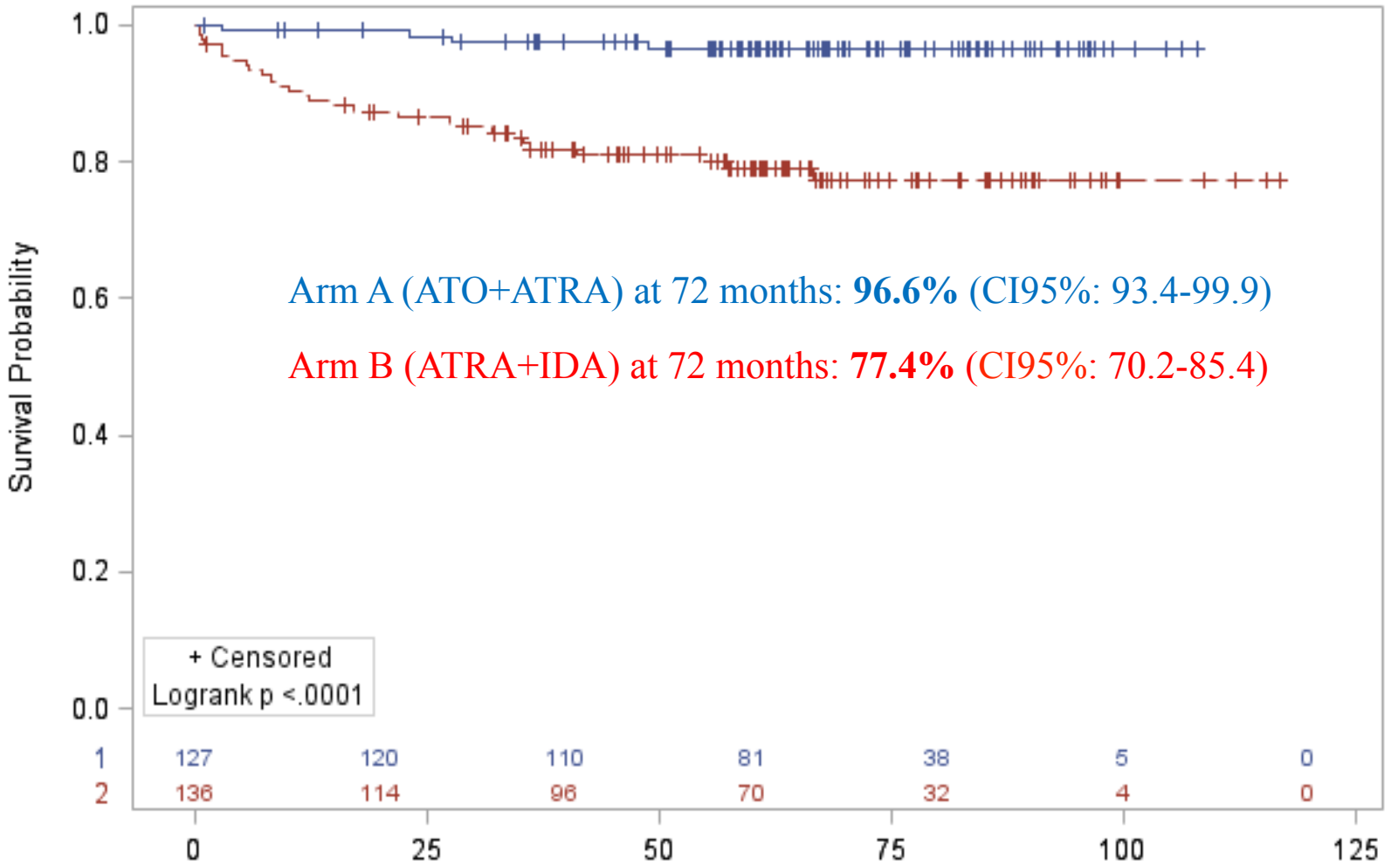
GIMEMA-SAL-AMLSG APL0406 trial



APL0406: Updated and extended series

276 pts; Follow-up 67 mos

Event-free survival



APL2017 conference; G.Avvisati

APL0406: Updated and extended series

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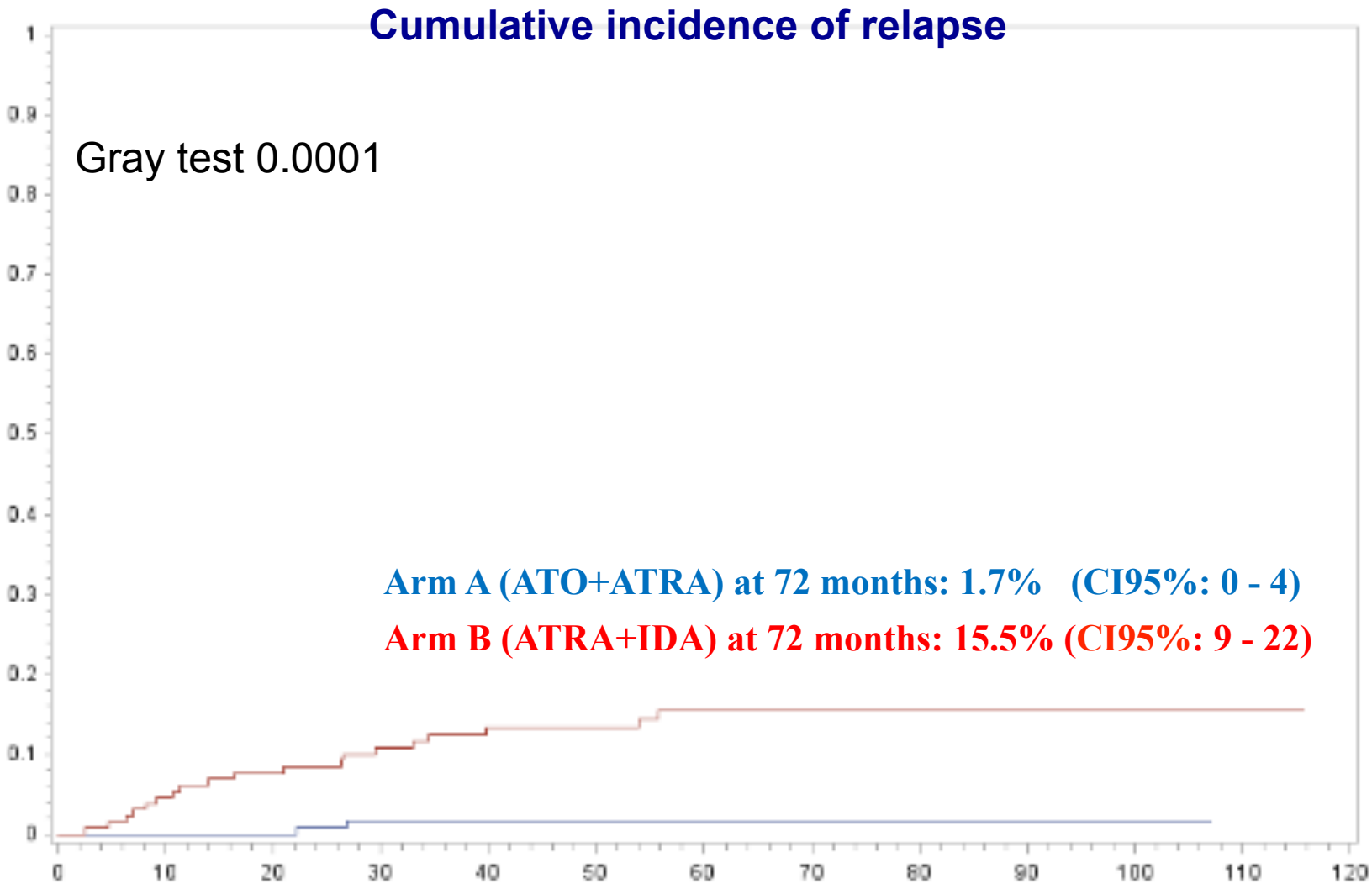


APL2017 conference; G.Avvisati

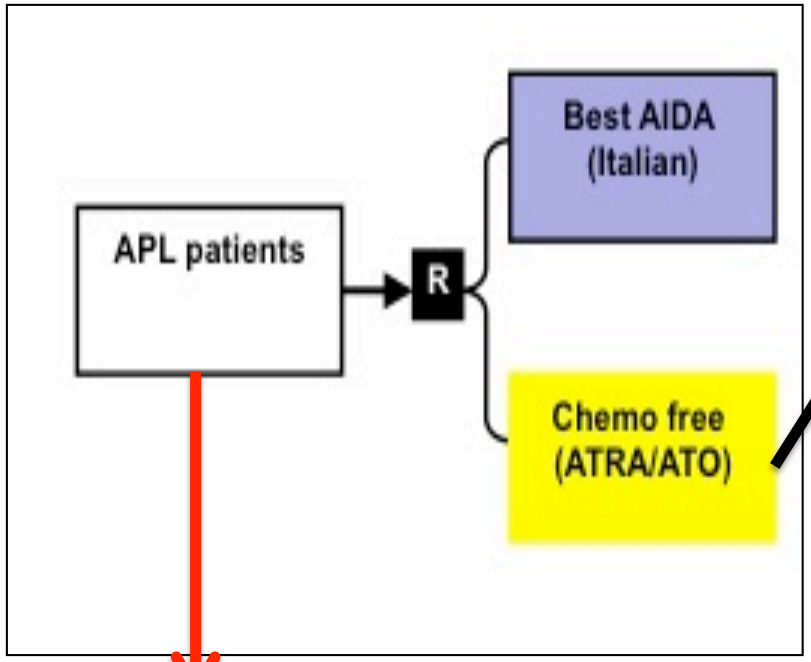
Events in APL0406 protocol

Event	ATRA-ATO	AIDA
Induction Death	0	4
Death in CR	2	5
Molecular resistance	0	2
Relapses	2	17
Secondary AML	0	1
Total	4	29

APL2017 conference; G.Avvisati

ATO + ATRA *vs.* AIDA

UK NCRI - AML 17 trial



High-risk patients

GO 6 mg/m^2 as a single infusion within the first 4 days (on day 1 if possible and on day 4 if necessary).

Induction

- **ATO** 0.3 mg/kg days 1-5 in week 1 **followed by** ATO 0.25 mg/kg twice a week for 7 weeks
- **ATRA** 45 mg/m^2/d 9 weeks

Consolidation (4 courses)

- **ATO** 0.3 mg/kg days 1-5 in week 1 **followed by** ATO 0.25 mg/kg twice a week for 3 weeks
- **ATRA** 45 mg/m^2/d 2 weeks on 2 weeks off

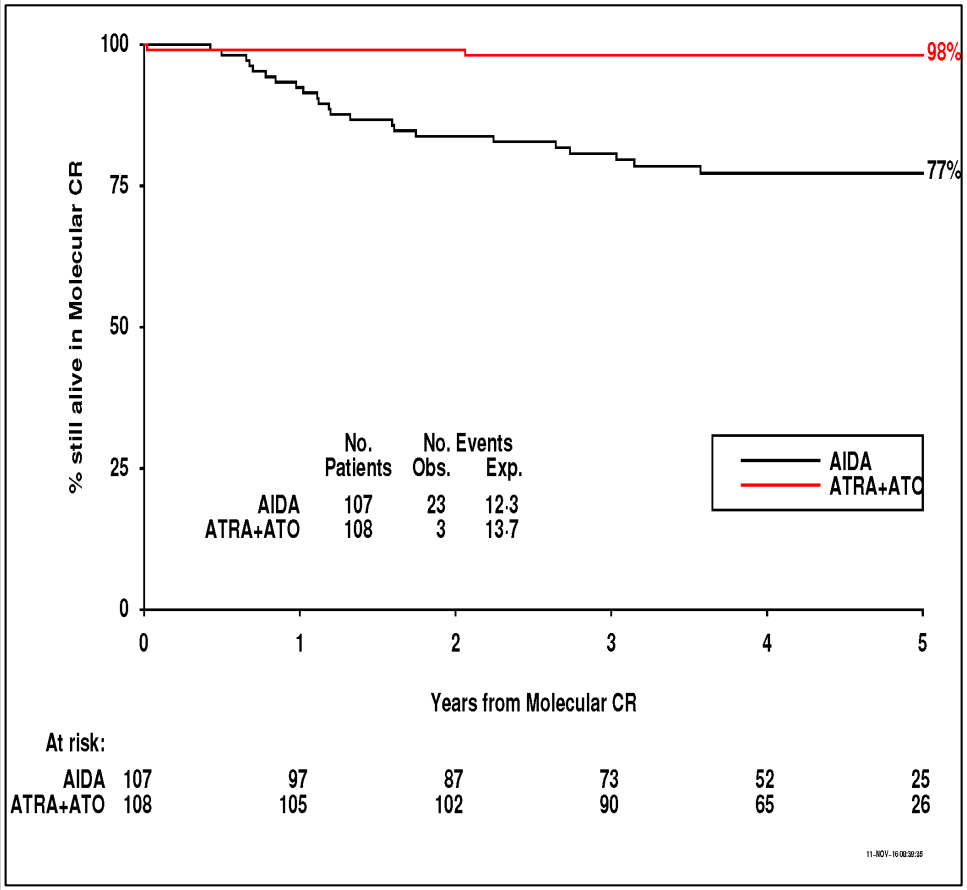
Burnett AK, *et al*. Lancet Oncol 2015;16: 1295–305

AML 17 APL Randomisation: Updated Outcomes

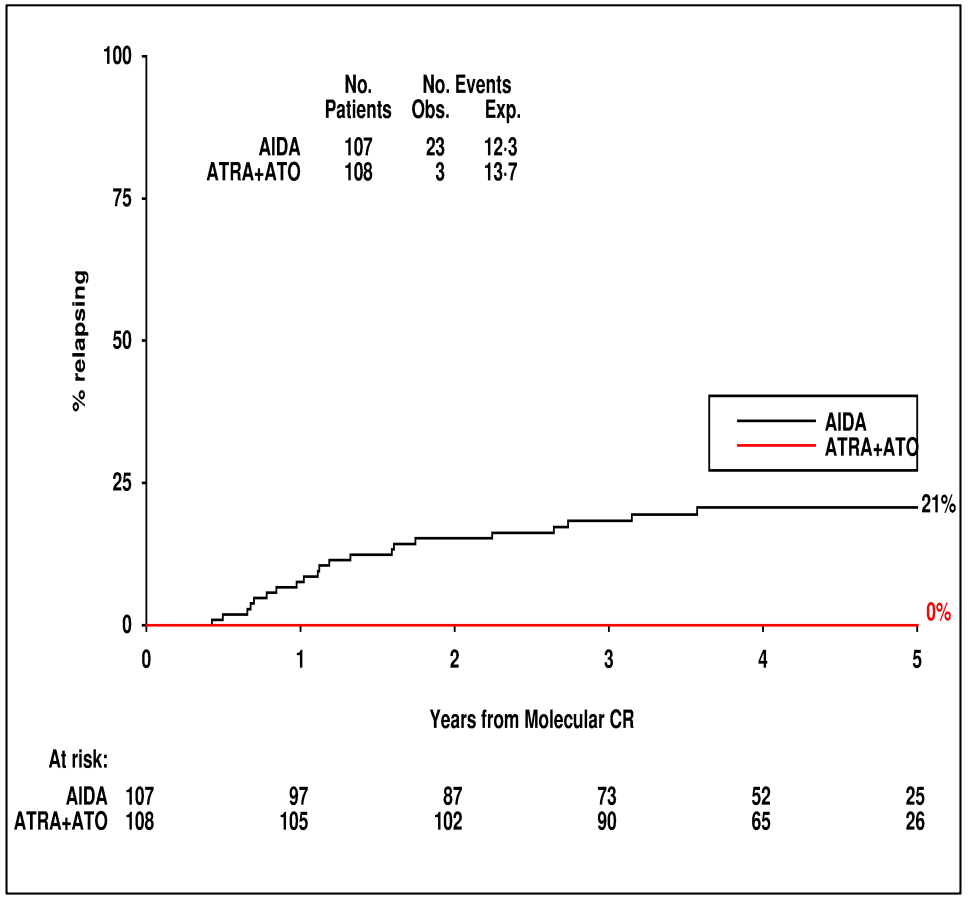
Outcome	AIDA	ATRA+ATO	HR/OR & CI	p-value
CR	91%	96%	0.46 (0.17-1.27)	0.13
Molecular negativity	90%	93%	0.67 (0.27-1.66)	0.4
30-day mortality	6%	4%	0.72 (0.23-2.31)	0.6
Resistant disease	3%	0%	0.14 (0.02-0.97)	0.05
60-day mortality	9%	5%	0.55 (0.21-1.43)	0.2
5-year survival	87%	93%	0.61 (0.27-1.35)	0.2
5-year EFS	79%	93%	0.38 (0.19-0.77)	0.007
5-year Frank RFS	87%	97%	0.33 (0.13-0.85)	0.02
5-year Molecular RFS*	77%	98%	0.19 (0.09-0.41)	<.0001
5-year CIDCR	2%	2%	1.72 (0.18-16.6)	0.6
5-year CIHR	10%	1%	0.16 (0.05-0.48)	0.001
5-year CIMR*	21%	0%	0.12 (0.05-0.30)	<.0001
5-year CITAML	1%	0%	0.15 (0.003-7.48)	0.3

UK NCRI - AML17 trial. Outcomes

Molecular relapse free survival



Cumulative incidence of relapse

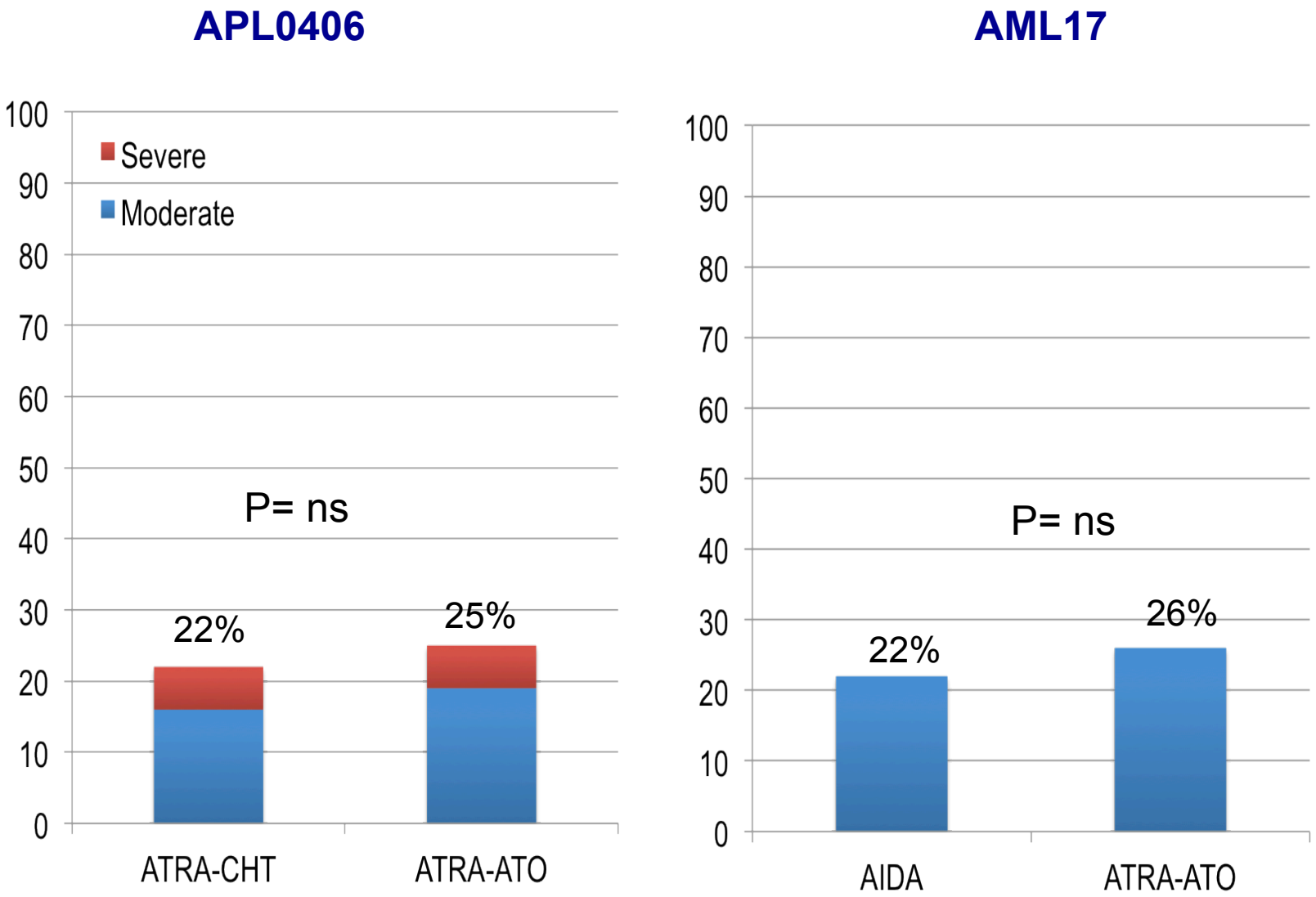


Burnett AK, *et al*. Lancet Oncol 2015;16: 1295–305

ATO-ATRA toxicity profile

	ATRA-chemo	ATRA-ATO
Differentiation syndrome	15-20%	20-25%
Myelosuppression	60-100%	20%
Infections, GI toxicity	+++	+
Hyperleukocytosis	5%	10-40%
Hepatic toxicity (AST/ALT)	5-10%	10-40%
Cardiac toxicity	2-5%	10%

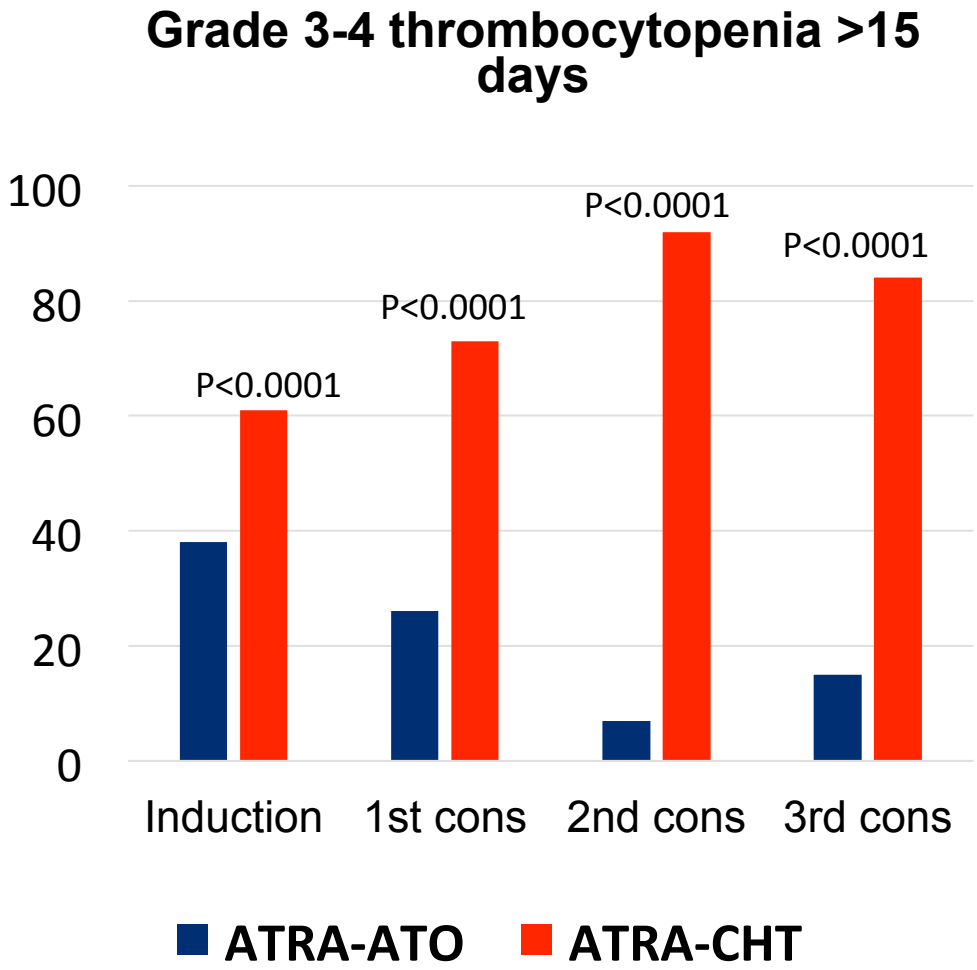
Incidence of differentiation syndrome

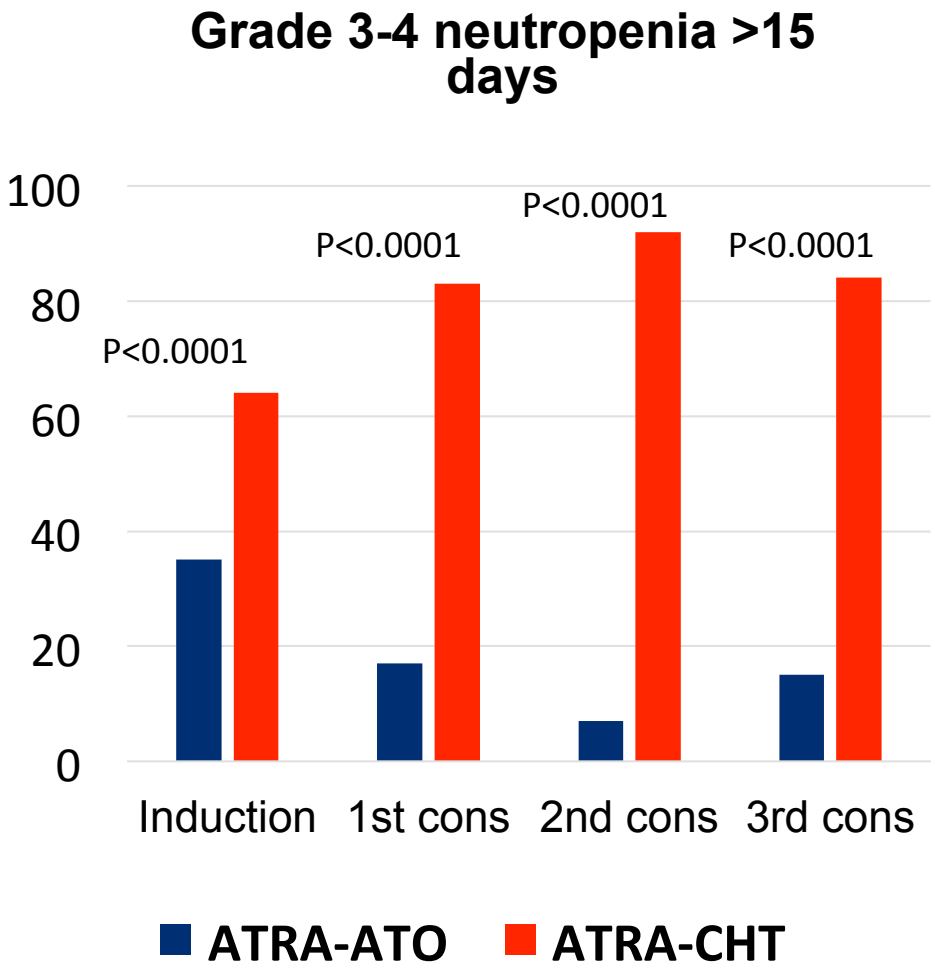


Lo-Coco et al, NEJM 2013; Burnett et al, Lancet Oncol 2015

Hematologic toxicity

(APL0406)

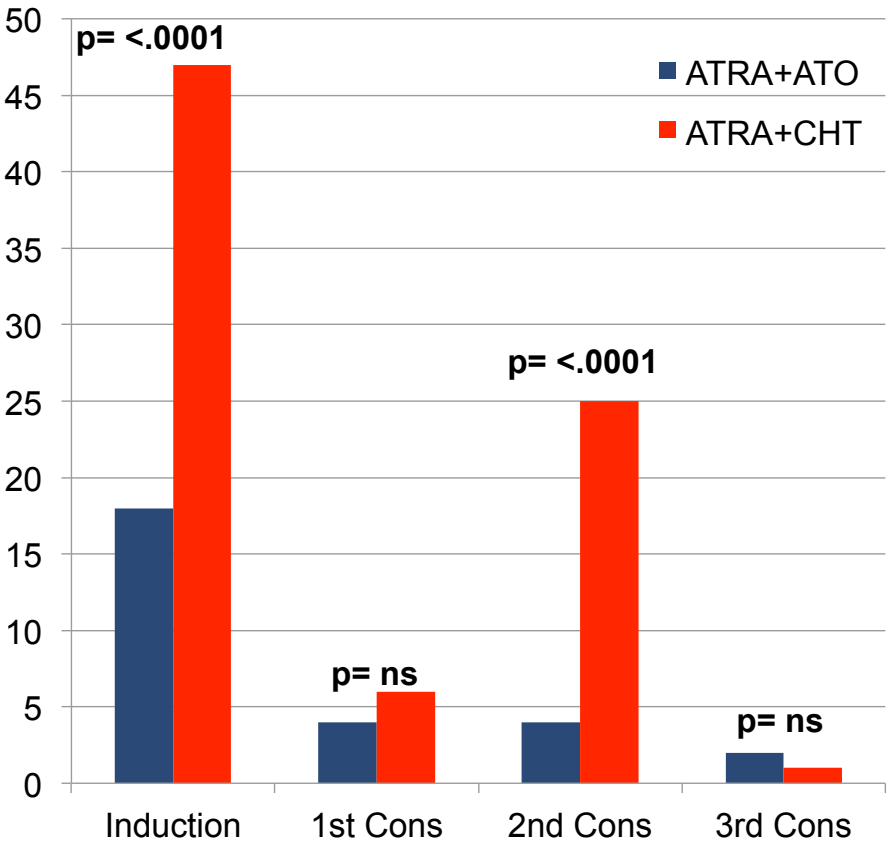




Platzbecker et al., JCO 2016

Infections, supportive care and hospitalization

FUO and infections (APL0406)



Supportive care (AML17)

	ATRA and Idarubicin	ATRA and arsenic trioxide	p value
Blood, units			
Course 1	9·5 (5·1)	5·9 (5·5)	<0·0001
Course 2	1·0 (1·7)	0·1 (0·5)	<0·0001
Platelets, units			
Course 1	12·8 (9·1)	8·8 (10·8)	<0·0001
Course 2	0·3 (1·0)	0 (0)	0·0001
Antibiotics, days			
Course 1	19·2 (9·7)	9·3 (9·4)	<0·0001
Course 2	1·7 (4·2)	0·9 (2·5)	0·40
Hospital stay, days			
Course 1	33·3 (9·6); 34 (29–37)	27·3 (16·5); 25 (15–34)	<0·0001
Course 2	7·9 (8·7); 5 (2–10)	6·5 (9·8); 1 (0–10)	0·01

Lo-Coco et al, NEJM 2013; Burnett et al, Lancet Oncol 2015

ATO-ATRA toxicity profile

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Differentiation syndrome	15-20%	20-25%
Myelosuppression	60-100%	20%
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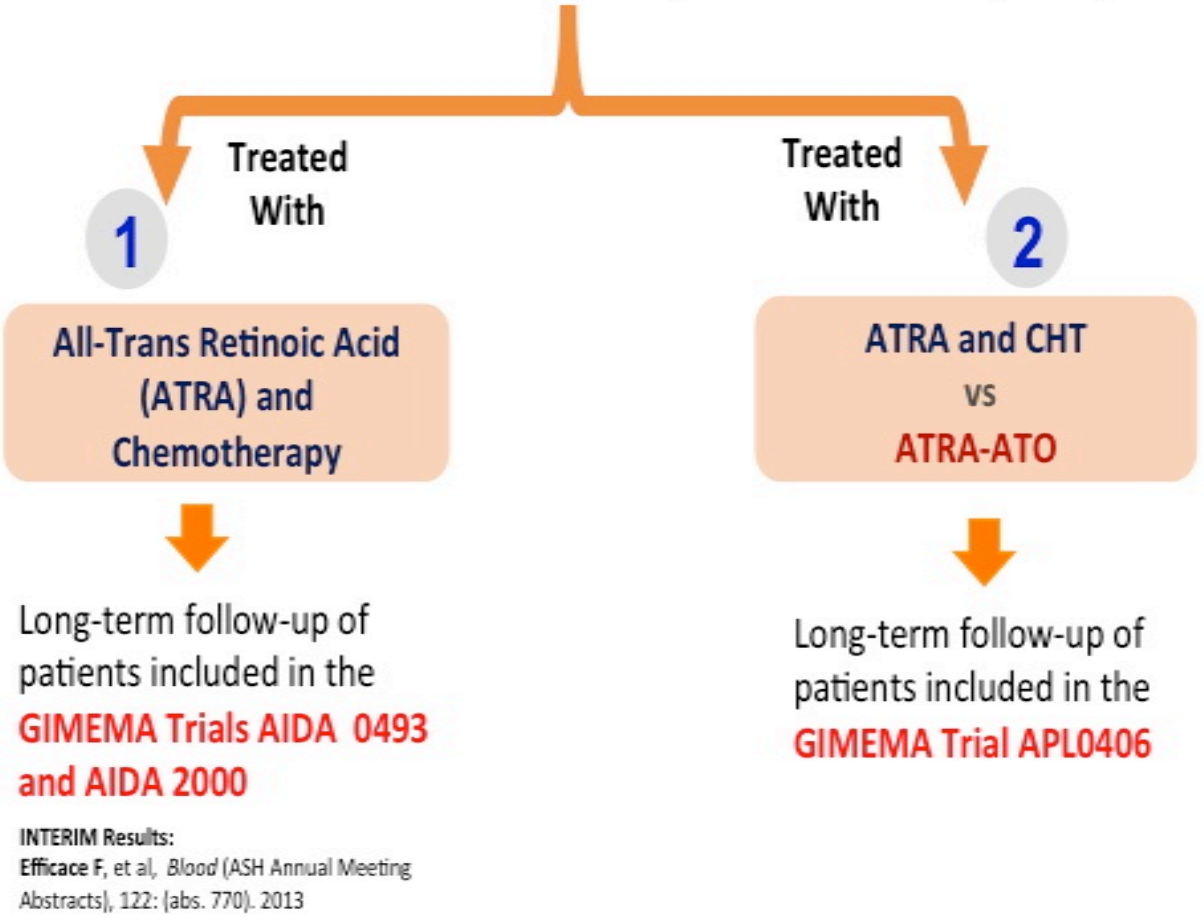
GIMEMA "Long-Term" Outcomes in APL Patients

Long-Term Quality Of Life, Late Adverse Effects and Symptom Burden In Patients With Acute Promyelocytic Leukemia (APL)



Is there room for improvement?

Open areas of investigation

1. Early death in “real-life” APL
2. Improve patient QoL: oral arsenic formulations
3. Optimal management of high-risk disease
4. Biologic basis of ATO resistance

1. Early death

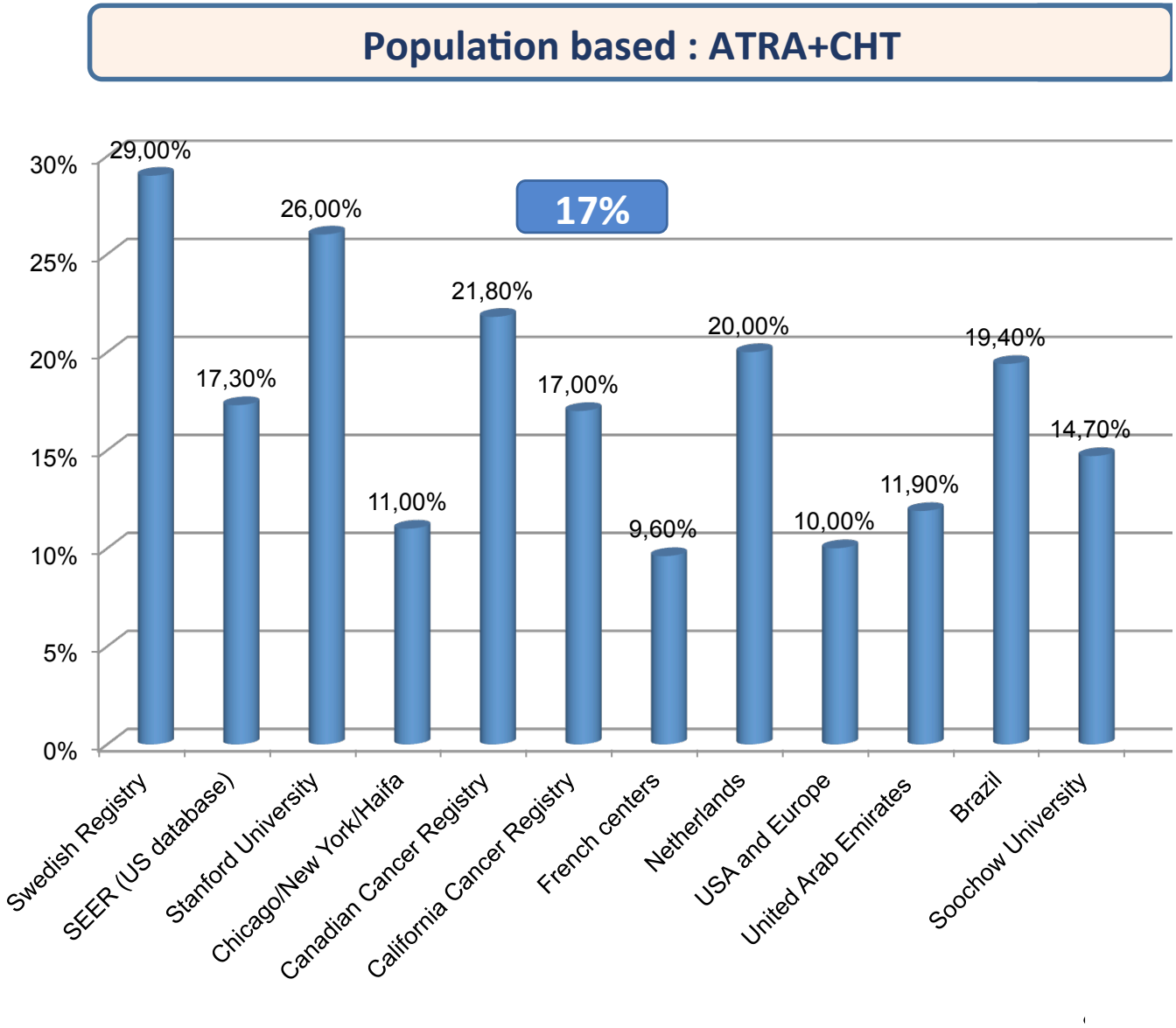
Clinical trials vs. “real-life”data

Recent trials

STUDY	Total Patients	Median Age	Patients died	Percentage
Lengfelder E -2009	142	40	11	7.7
Lo-Coco F - 2010	1020	38.2 - 40.9	70	6.8
Sanz MA - 2010	402	42	30	7.4
Powell BL - 2010	481	--	38	8
Iland H - 2012	124	44	4	3.2
Lo-Coco F - 2013	156	44.6-46.6	4	2.5
Burnett AK -2015	235	47	11	5

Early death

Clinical trials vs. “real-life”data

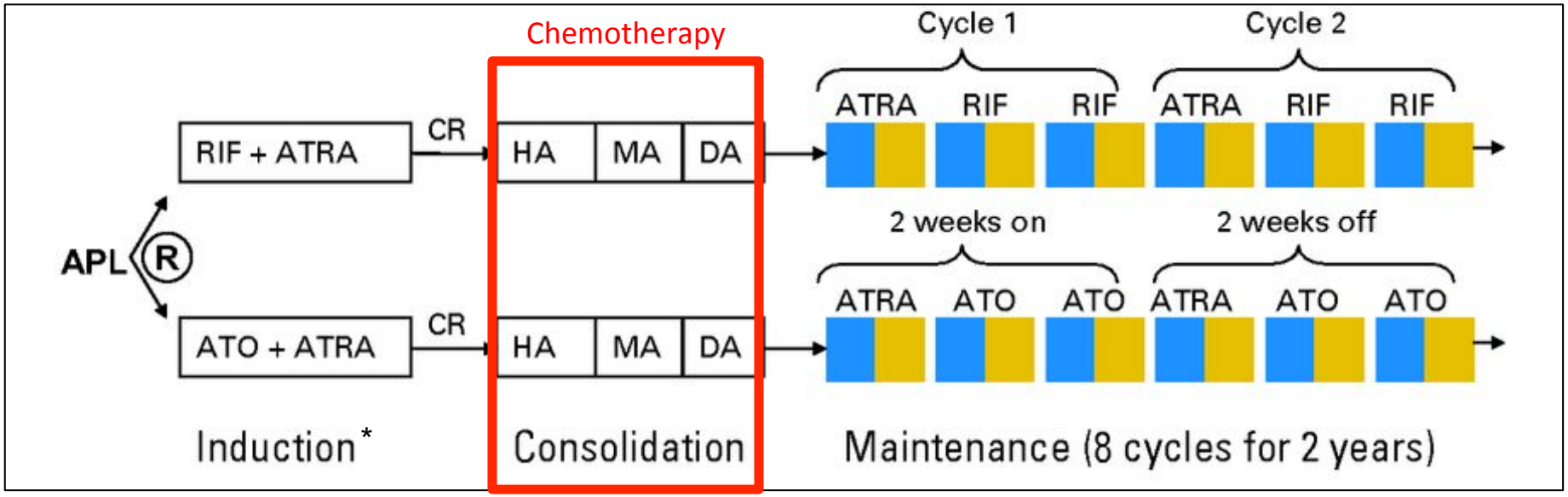


2.Oral arsenic

ATO+ATRA vs. RIF+ ATRA

Chinese APL Cooperative Group

Randomized comparison of oral arsenic derivative *vs*. IV ATO



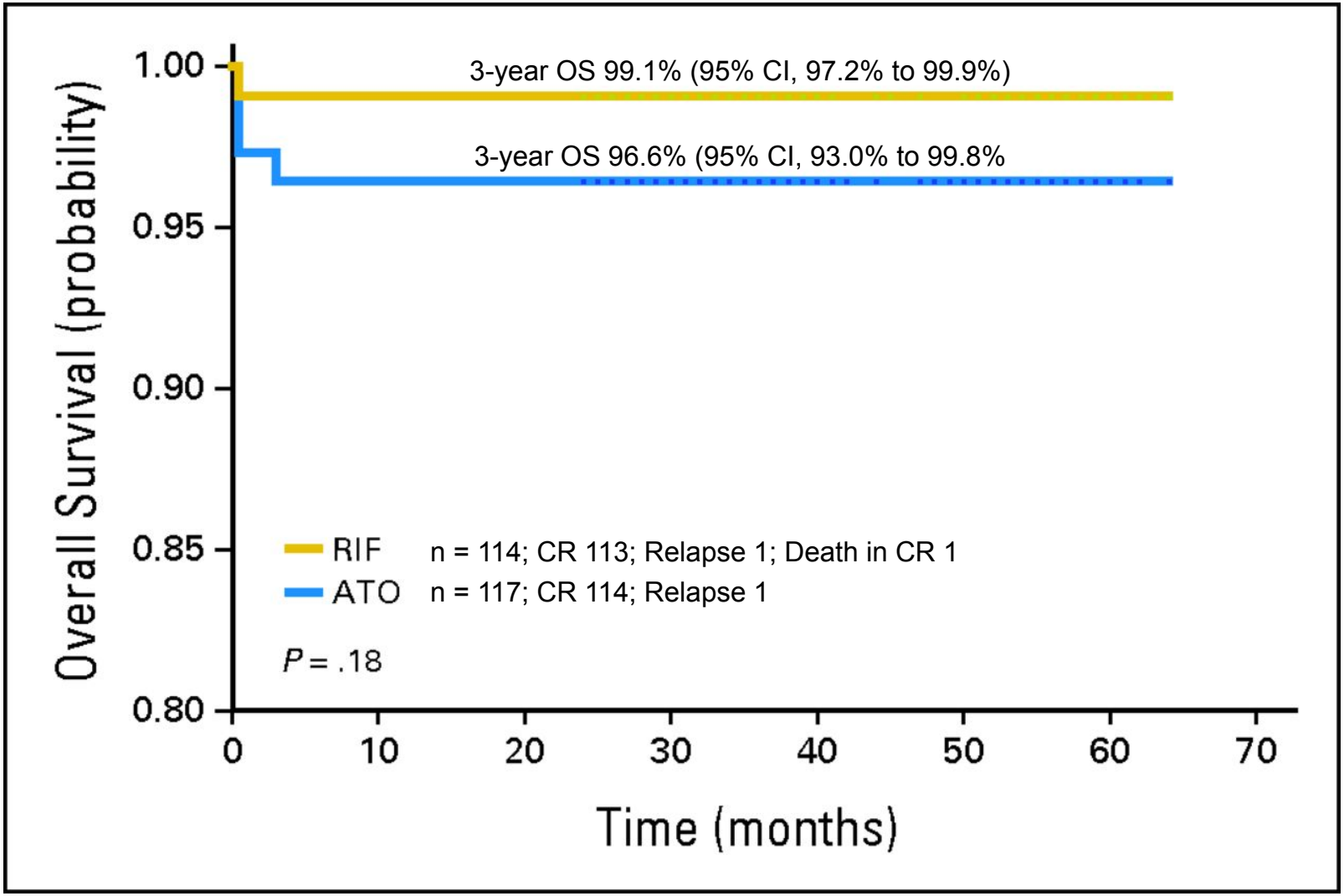
* Mitoxantrone was added at a dose of 1.4 mg/m^2/day on 5 days 4, 5, 6, 7, and 8 (if WBC >10 x 10^9/L start on day 1).

ATRA = all-trans retinoic acid; **ATO** = arsenic trioxide; **RIF** = Realgar-*Indigo naturalis* formula; **HA** = homoharringtonine and cytarabine; **DA** = daunorubicin and cytarabine; **MA** = mitoxantrone and cytarabine

Zhu H et al. JCO 2013;31:4215-4221

Oral arsenic

ATO+ATRA vs. RIF+ ATRA



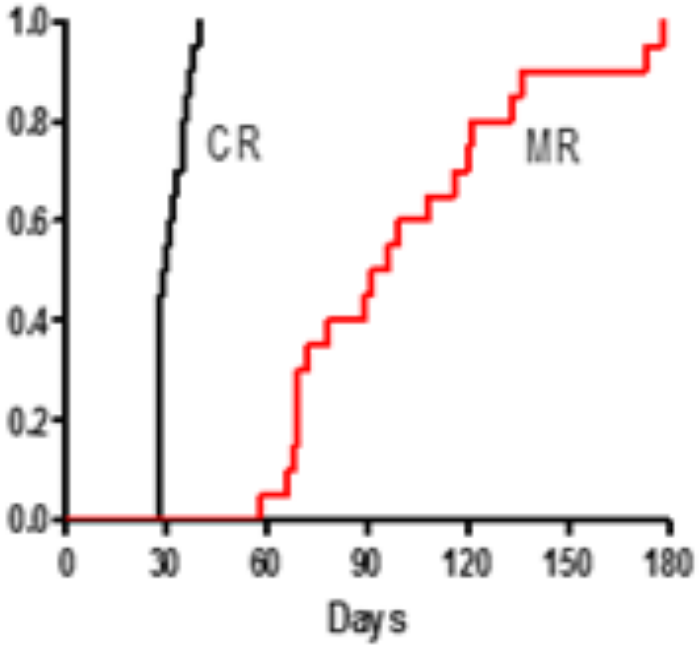
Zhu H et al. JCO 2013;31:4215-4221

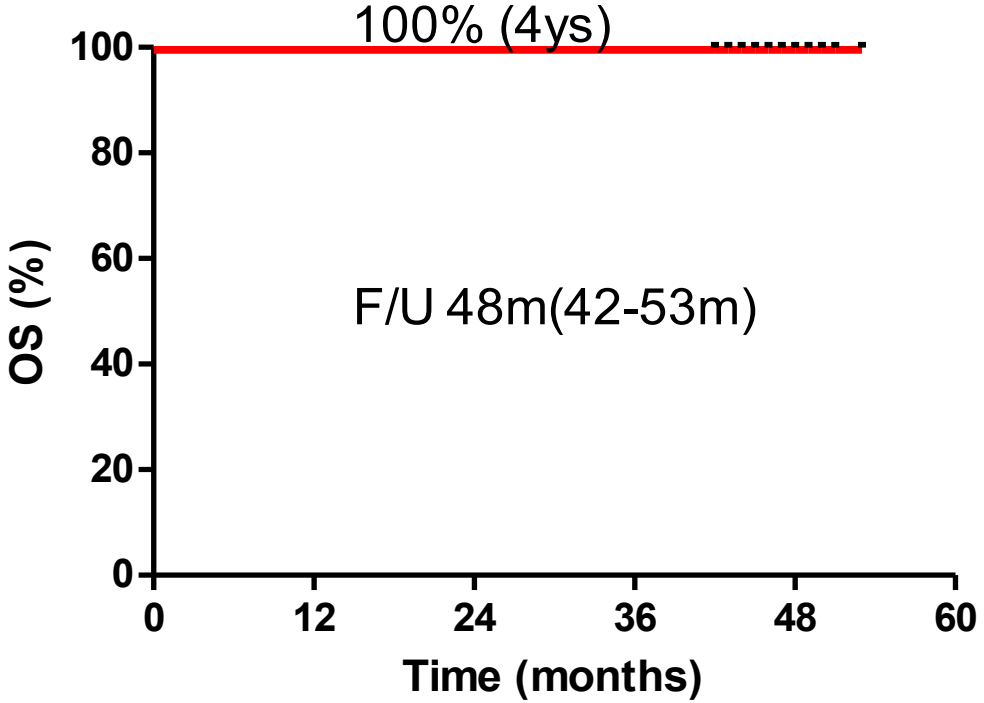
Oral arsenic

ATRA+ oral ATO. Non-high risk

Outpatient Oral Treatment for Acute Promyelocytic Leukemia

TO THE EDITOR: Zhu and Huang (Dec. 4 issue)[1] report excellent, though preliminary, outcome regarded as a rapidly fatal disease, APL is now curable in most cases with the use of targeted

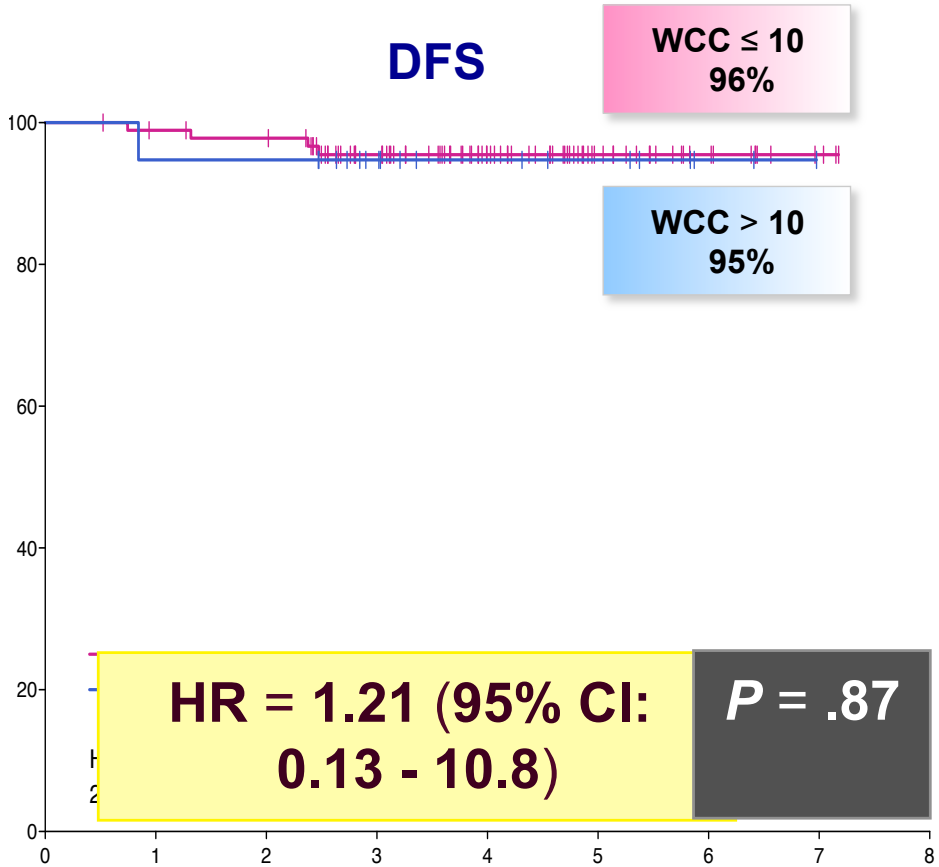




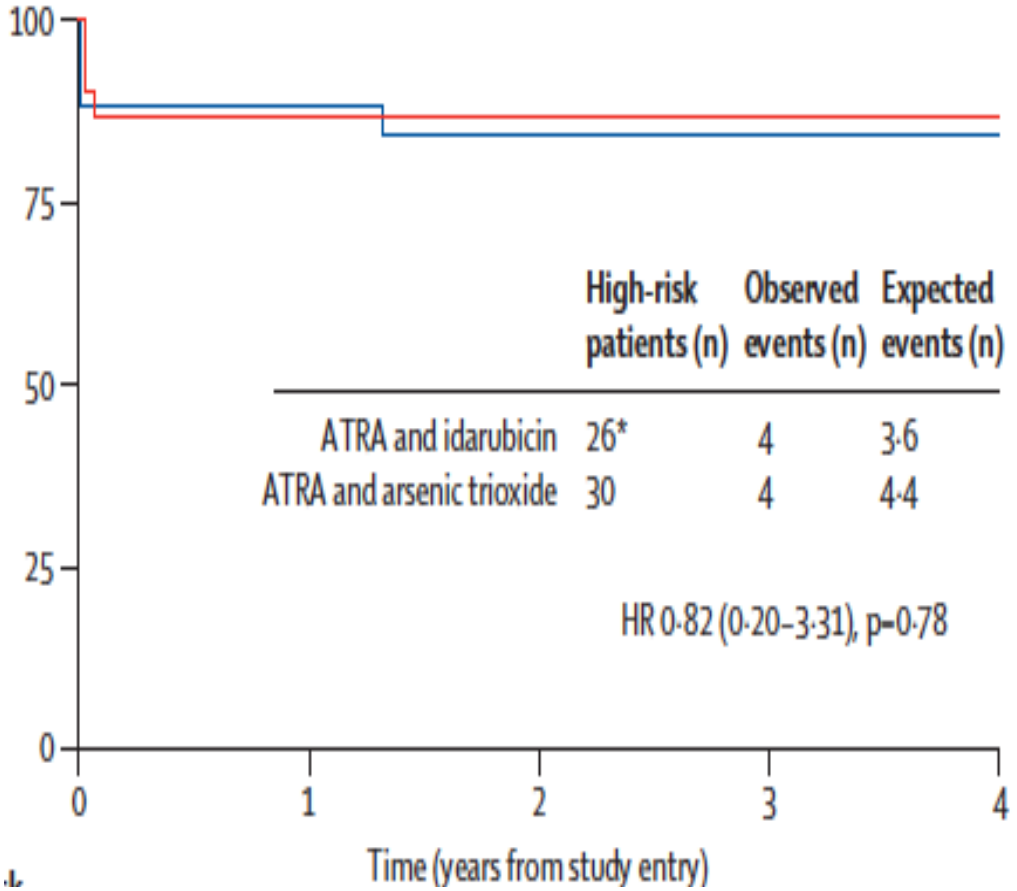
Medical costs: 4,675$
Median hospital stay: 15 months

3. High-risk APL

ATO/ATRA-based trials



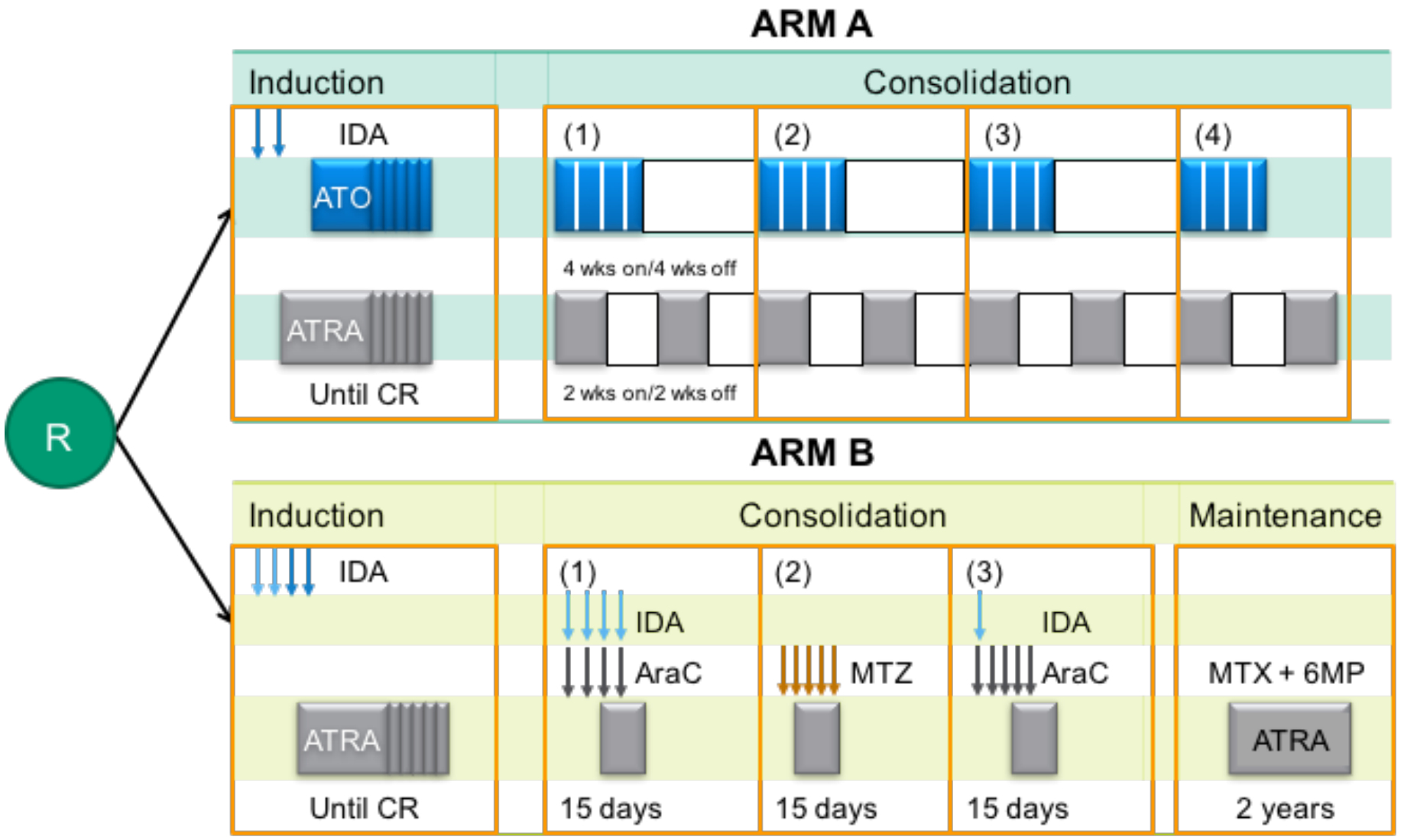
Iland HJ, et al. *Blood.* 2012



Burnett AK, *et al*. Lancet Oncol 2015

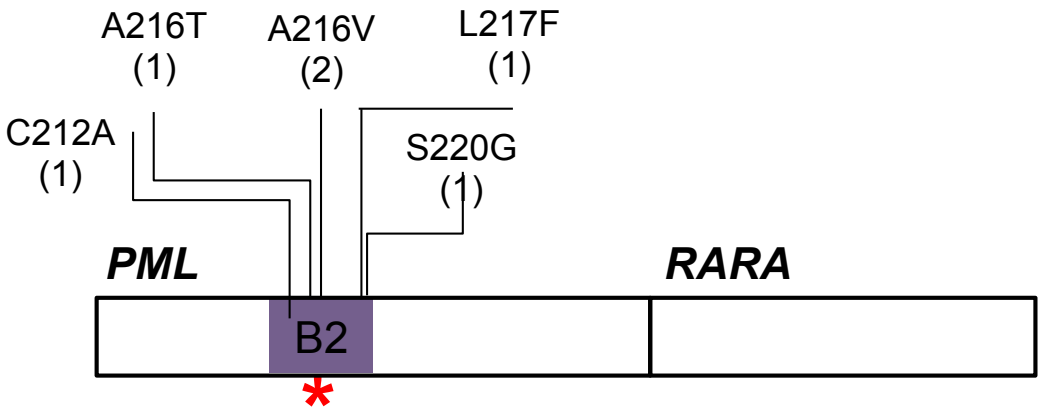
High-risk APL

Pan-European randomized trial in high-risk APL (APOLLO trial)



4. ATO resistance

Role of *PML* mutations



- *PML* mutations within the B2 domain of *PML/RARA* [illegible] ATO resistance and can be found in up to 40% of relapse[illegible]

- Mutations have been described also [illegible] ***ML*** allele and have been proposed as additional mechanism[illegible]sociated with ATO resistance

What happens in 70% of relapsed APL?

Jeanne M., *et al*, Cancer Cell 2010; Lehmann-Che et al, *NEJM* 2014; Iaccarino et al, *BJH* 2016

Conclusions

- ATO-ATRA has become the standard of care in newly diagnosed low/intermediate risk APL
- ATO-ATRA+CHT can be a curative option for high-risk disease but deserves futher investigation
- Early death remains the major obstacle to APL cure
- Despite the low rate of relapses, resistance to ATO should be futher investigated

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