Prise en Charge des LAM-3

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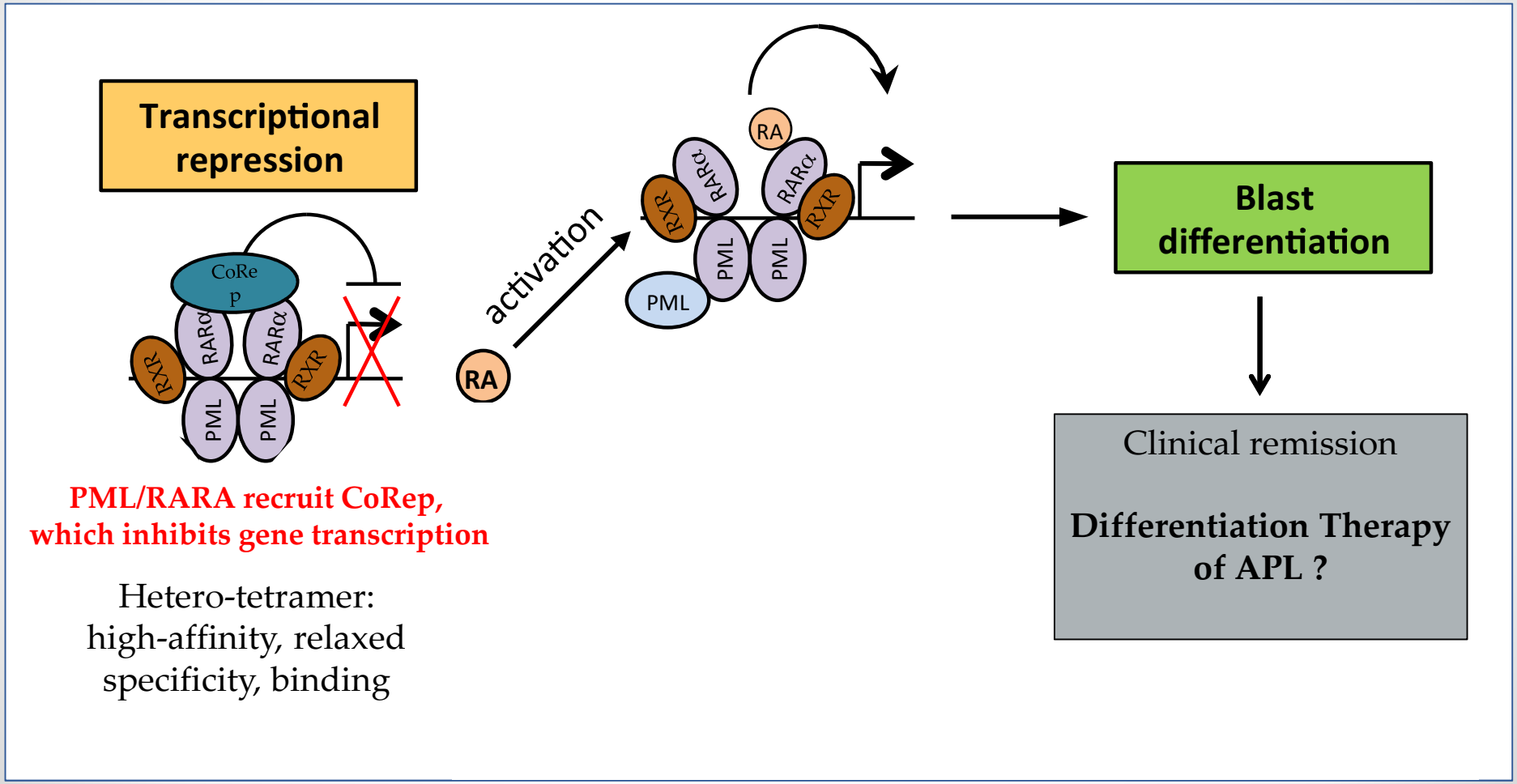
Université Paris Diderot

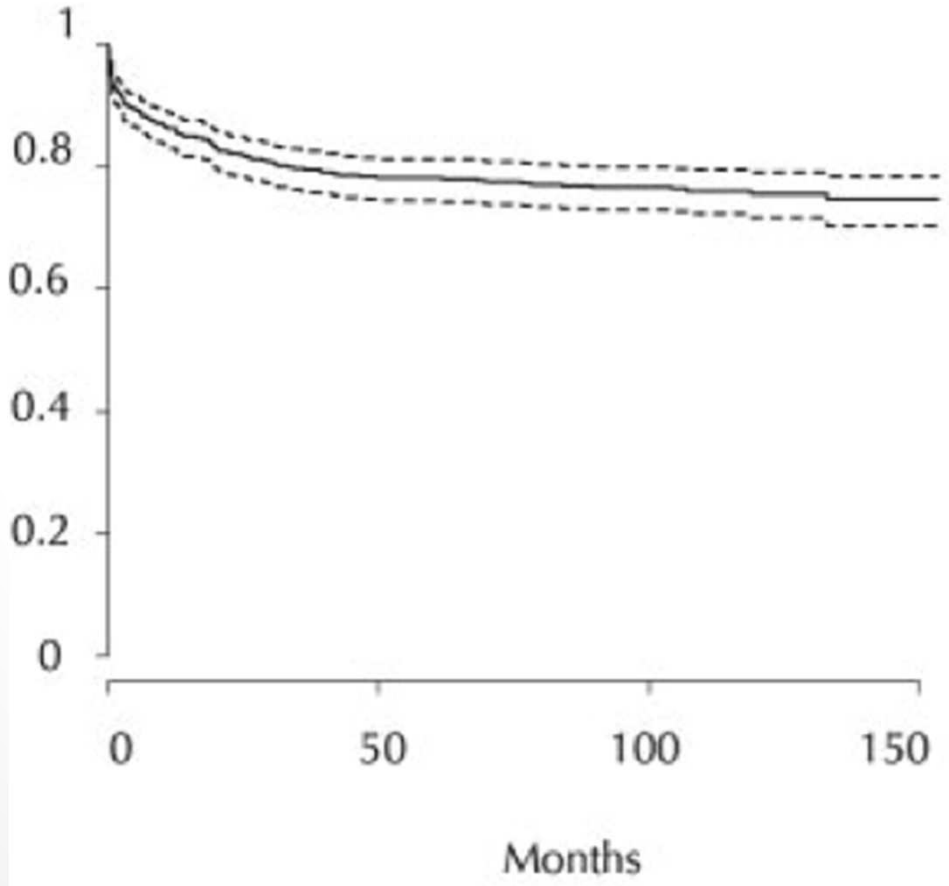
Basal transcription therapy by ATRA



de Thé, Cell, 1991; Kastner, Blood 1999; Lin, Minucci, Mol Cell 2000

APL-93

- *OS, 77% at 10 years*



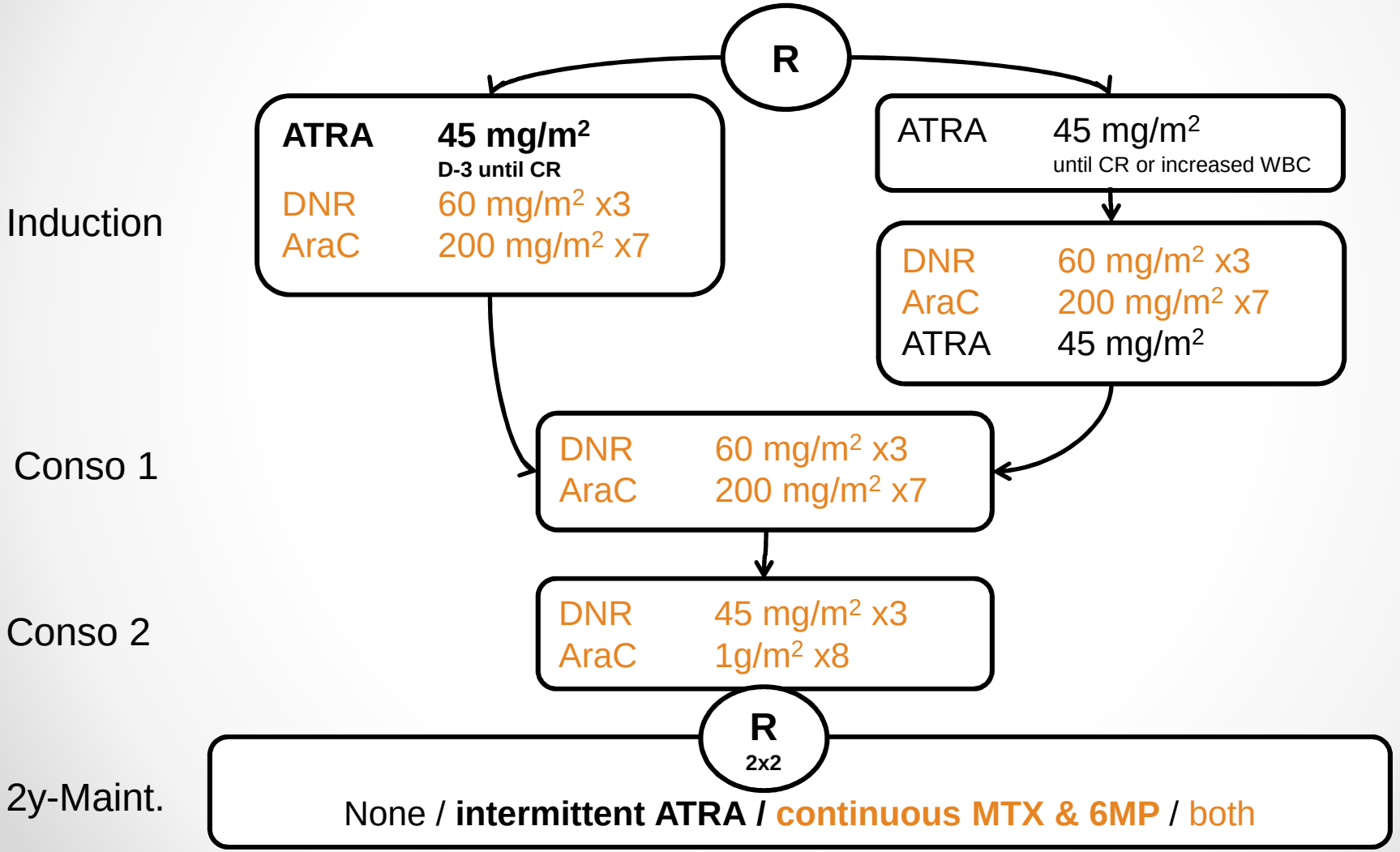
Ades et al. Blood 2010

APL in 2014

- **Too much chemotherapy in standard-risk patients?**
  - *Hospitalizations*
  - *Long-term events*
- **Place for arsenic trioxide (ATO)?**
  - *Biological effects of ATO*
  - *ATO therapy*
    - *Standard-risk patients: « no-chemo treatment »*
    - *High-WBC patients*
    - *Elderly patients*
- **Optimal management of high-WBC patients?**
  - *Early deaths*

Reduce CTx intensity in standard-risk patients

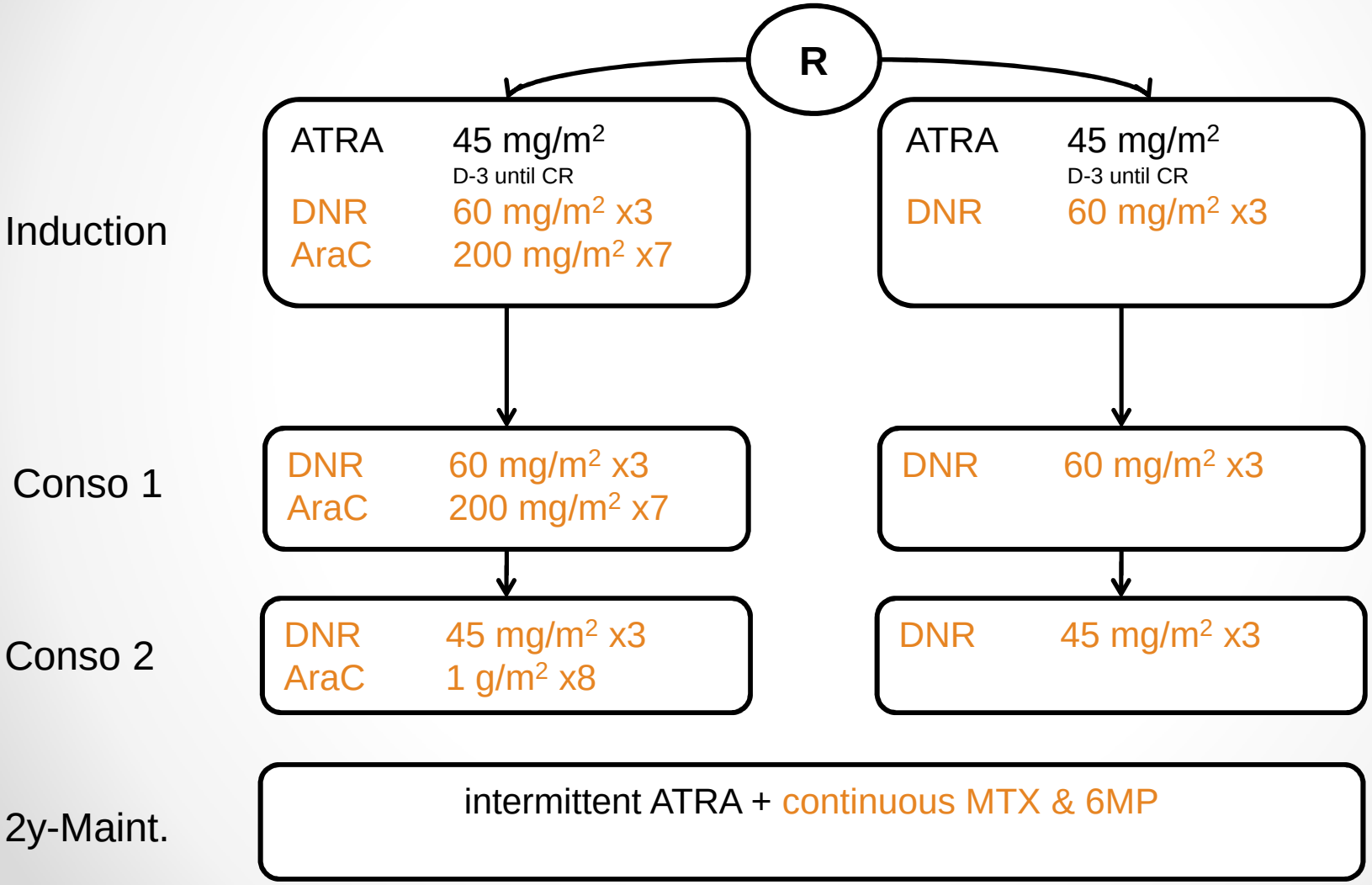
APL-93 standard-risk



APL trials without AraC

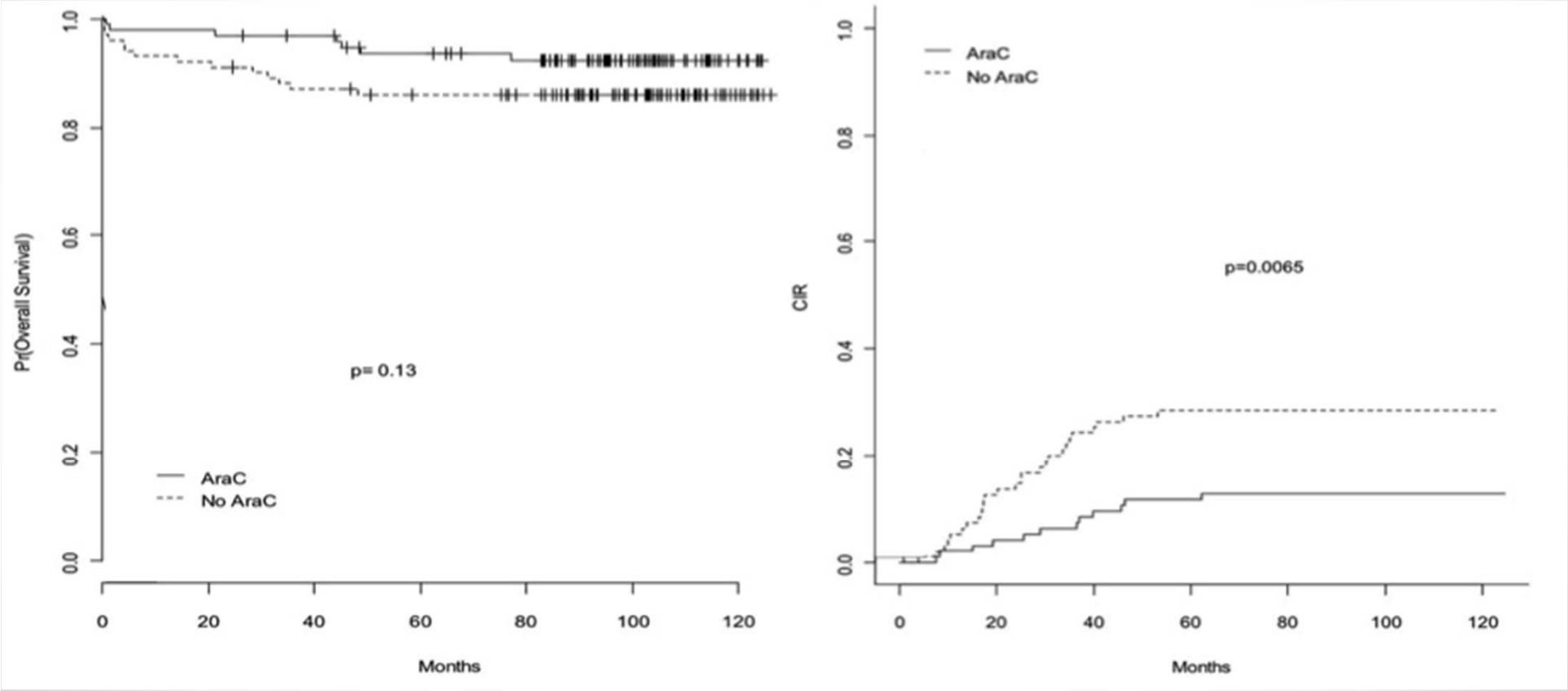
- *GIMEMA*
  - *Lo-Coco F, Avvisati G, Vignetti M, et al.*
    Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: Results of the AIDA-2000 trial of the GIMEMA Group.
    Blood 2011;116:3171–3179.
- *PETHEMA*
  - *Sanz MA, Montesinos P, Rayon C, et al.*
    Risk-adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: Further improvements in treatment outcome.
    Blood 2010;115:5137–5146.

APL-2000 standard-risk



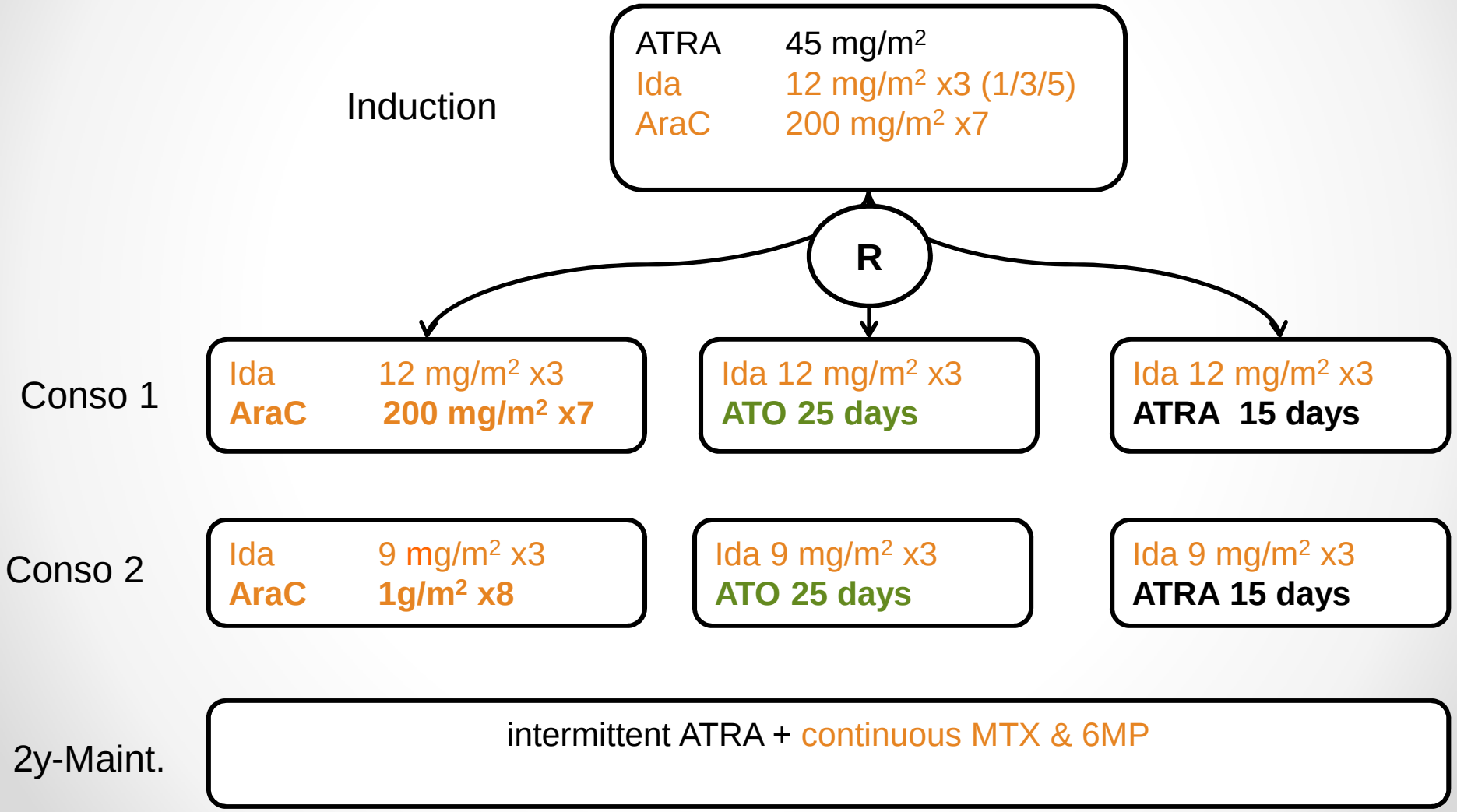
APL-2000 standard-risk

- *Closed after the first interim analysis*



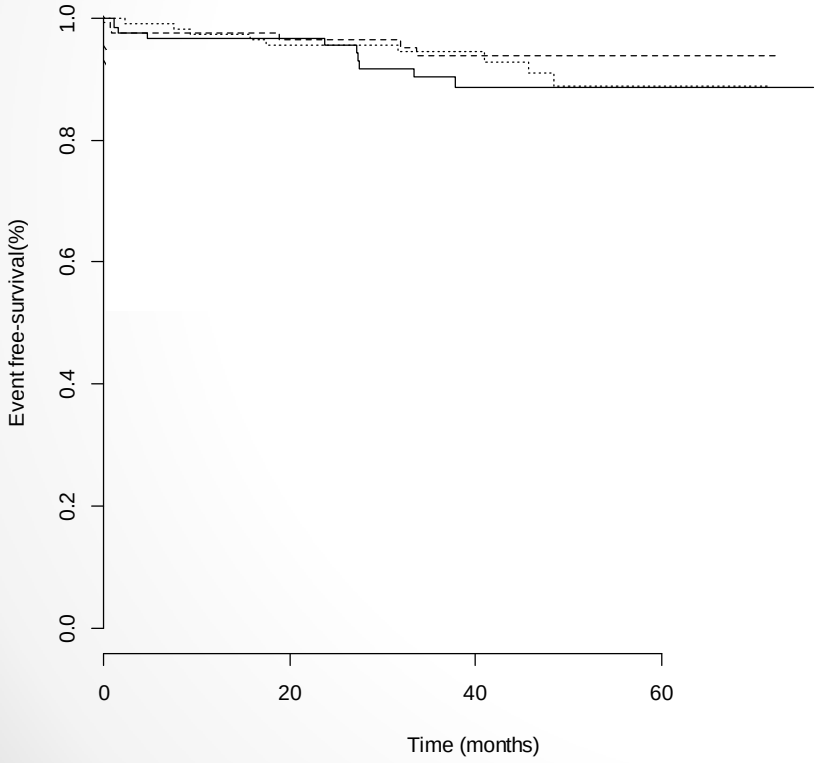
Ades et al. Am J Hematol 2013

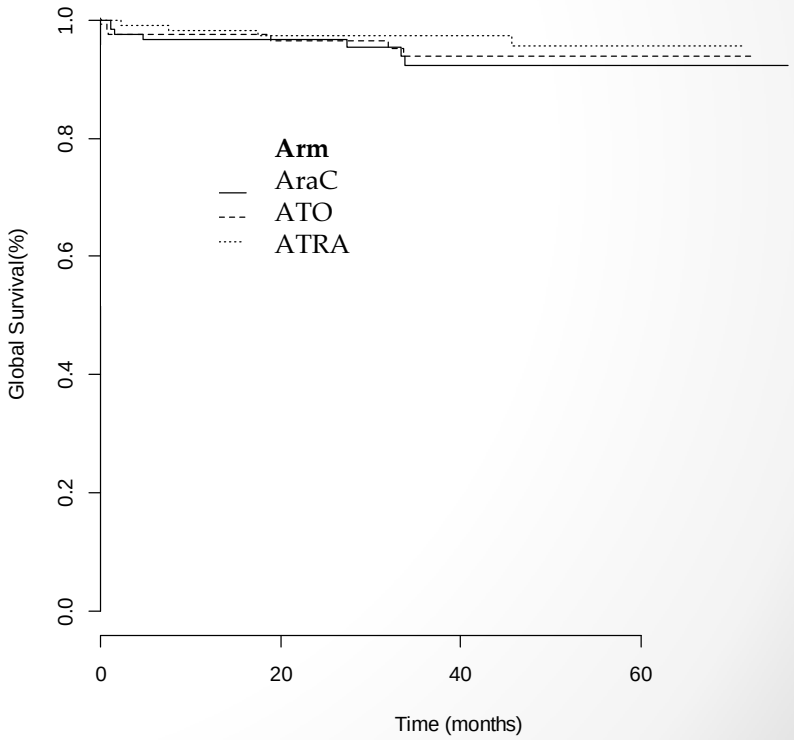
APL-2006 standard-risk



APL-2006 standard-risk

- *Standard-risk patients (<70y, WBC<10 G/L)*

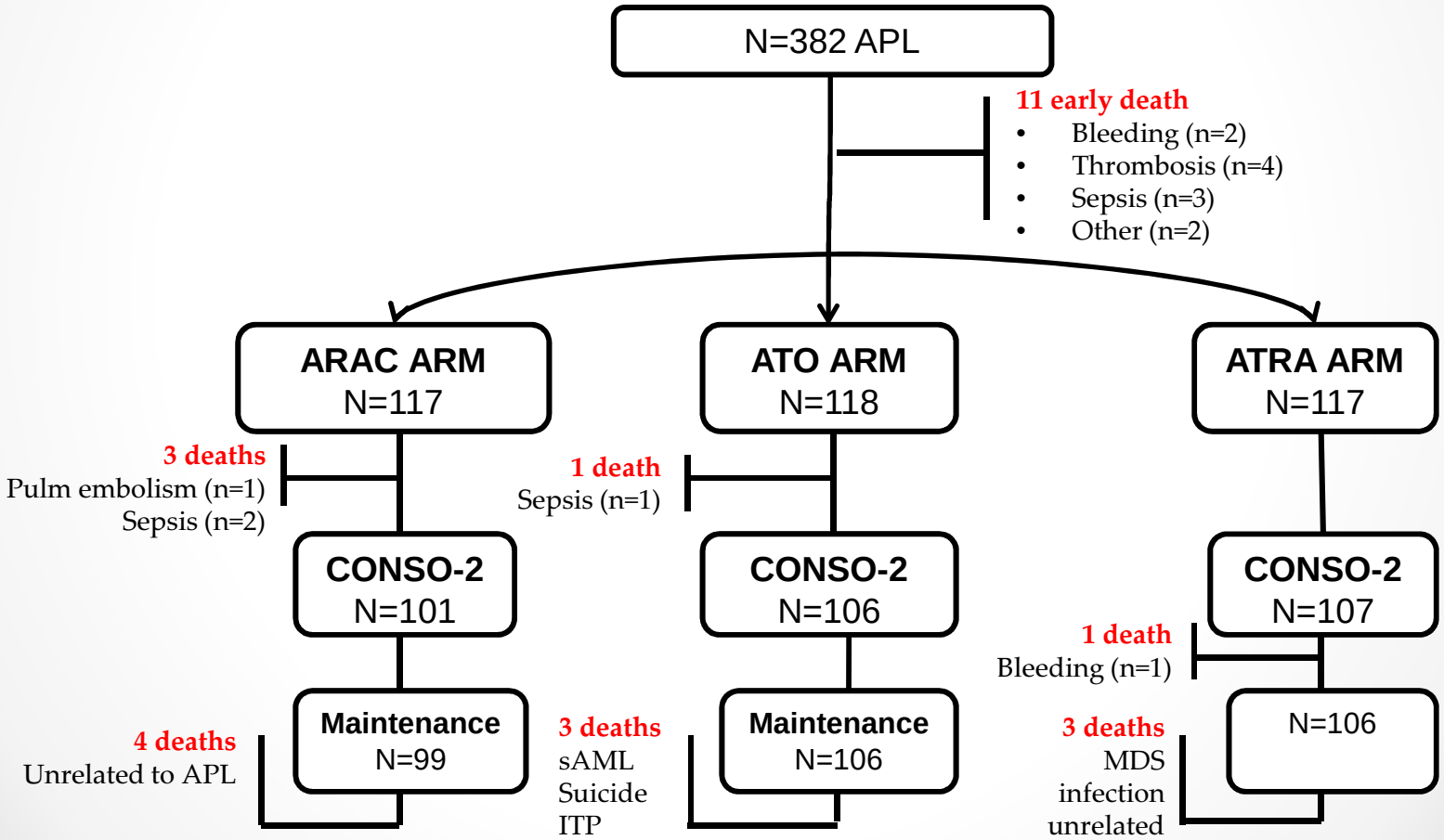




Ades et al. ASH 2013

APL-2006 standard-risk

- *Deaths during Tx*

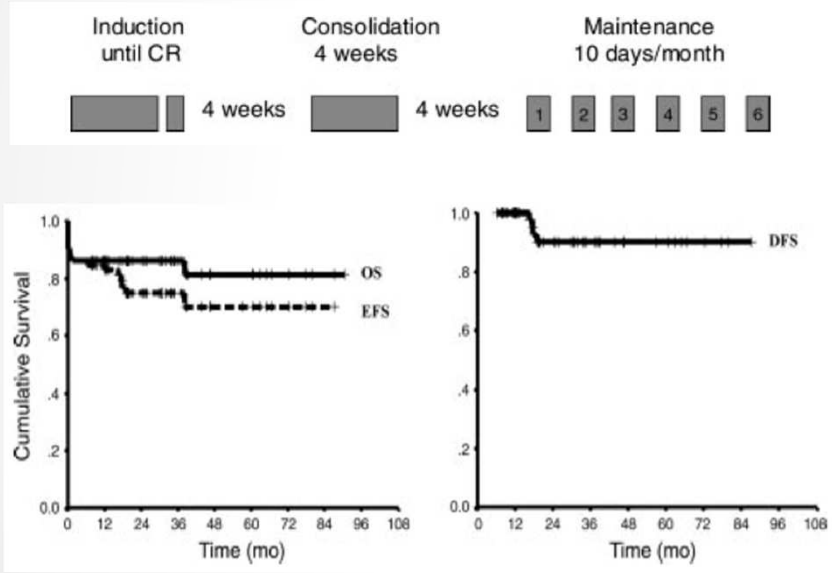


Ades et al. ASH 2013

Introduce ATO during front-line Tx

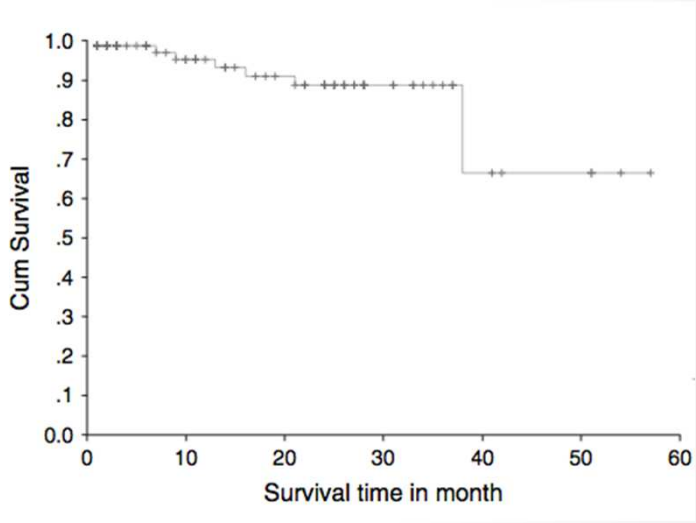
ATO alone

- *India*



Mathews et al. Blood 2006

- *Iran*
  - *2 ATO cycles only*

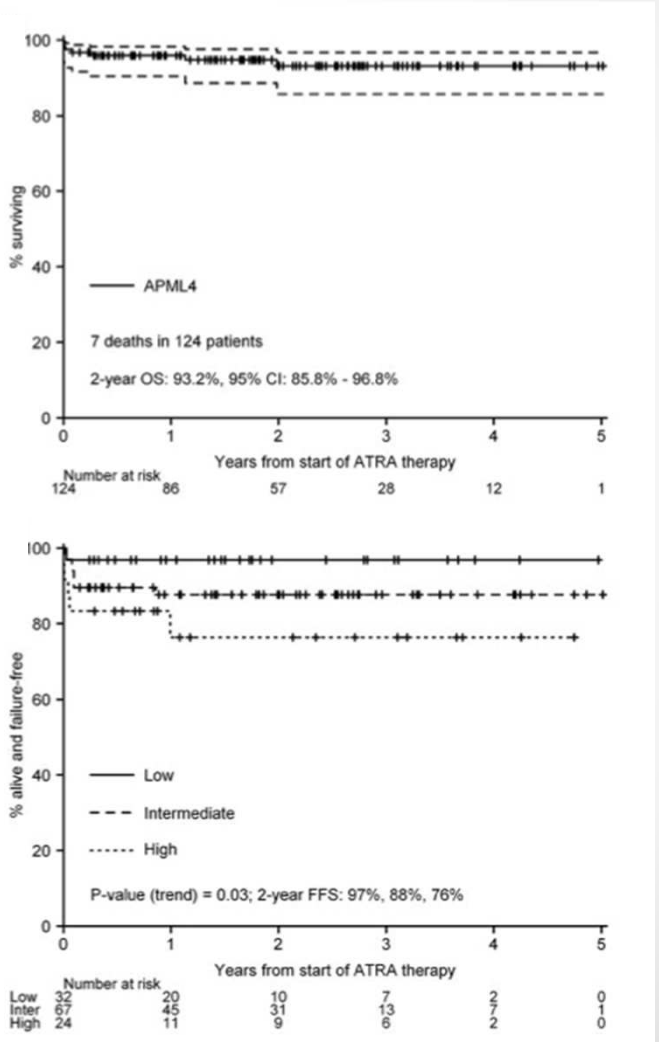


Ghavamzadeh et al. Ann Oncol 2006

ATO-ATRA-Ida

- Australasian Leukaemia and Lymphoma Group

Induction	
ATRA	45 mg/m²/d PO
Idarubicin	12 mg/m²/d IV (ages 1-60) 9 mg/m²/d IV (ages 61-70) 6 mg/m²/d IV (ages > 70)
ATO	0.15 mg/kg/d IV
Prednisone	1 mg/kg/d PO
Hemostatic support	Products administered once or twice daily as required to achieve specified targets
Consolidation cycle 1 (3-4 wks after the end of induction)	
ATRA	45 mg/m²/d PO
ATO	0.15 mg/kg/d IV
Consolidation cycle 2 (3-4 wks after the end of consolidation cycle 1)	
ATRA	45 mg/m²/d PO
ATO	0.15 mg/kg/d IV
Maintenance: 8 cycles (3-4 wks after the end of consolidation cycle 2)	
ATRA	45 mg/m²/d PO
MTX	5-15 mg/m²/wk PO
6MP	50-90 mg/m²/d PO



Iland et al. Blood 2012

ATRA-ATO

standard-risk patients

The NEW ENGLAND JOURNAL of MEDICINE

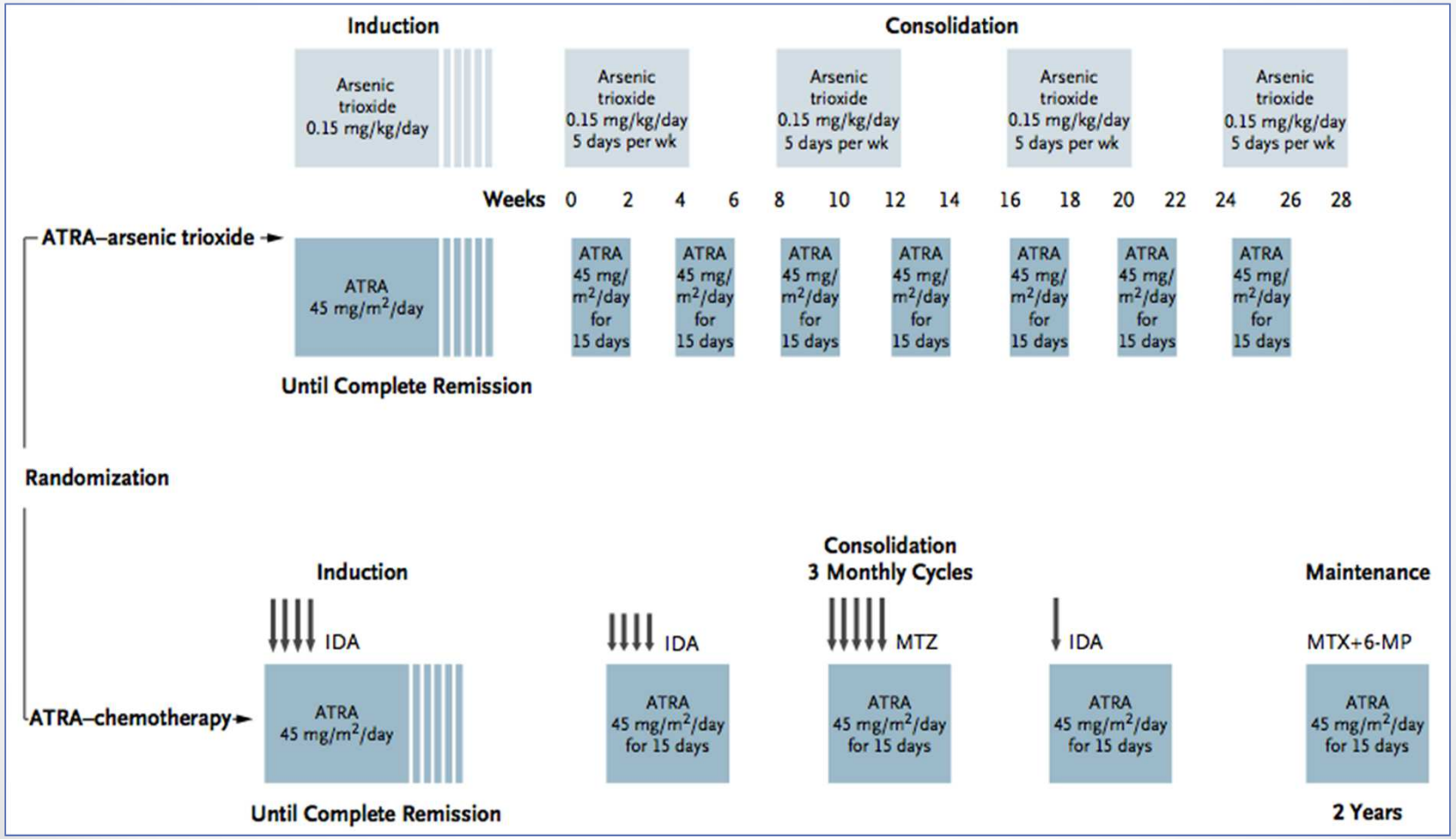
ESTABLISHED IN 1812 JULY 11, 2013 VOL. 369 NO. 2

Retinoic Acid and Arsenic Trioxide for Acute Promyelocytic Leukemia

F. Lo-Coco, G. Avvisati, M. Vignetti, C. Thiede, S.M. Orlando, S. Iacobelli, F. Ferrara, P. Fazi, L. Cicconi, E. Di Bona, G. Specchia, S. Sica, M. Divona, A. Levis, W. Fiedler, E. Cerqui, M. Breccia, G. Fioritoni, H.R. Salih, M. Cazzola, L. Melillo, A.M. Carella, C.H. Brandts, E. Morra, M. von Lilienfeld-Toal, B. Hertenstein, M. Wattad, M. Lübbert, M. Hänel, N. Schmitz, H. Link, M.G. Kropp, A. Rambaldi, G. La Nasa, M. Luppi, F. Ciceri, O. Finizio, A. Venditti, F. Fabbiano, K. Döhner, M. Sauer, A. Ganser, S. Amadori, F. Mandelli, H. Döhner, G. Ehninger, R.F. Schlenk, and U. Platzbecker for Gruppo Italiano Malattie Ematologiche dell'Adulto, the German–Austrian Acute Myeloid Leukemia Study Group, and Study Alliance Leukemia

ATRA-ATO

standard-risk patients



Lo Coco et al. NEJM 2013

ATRA-ATO

standard-risk patients

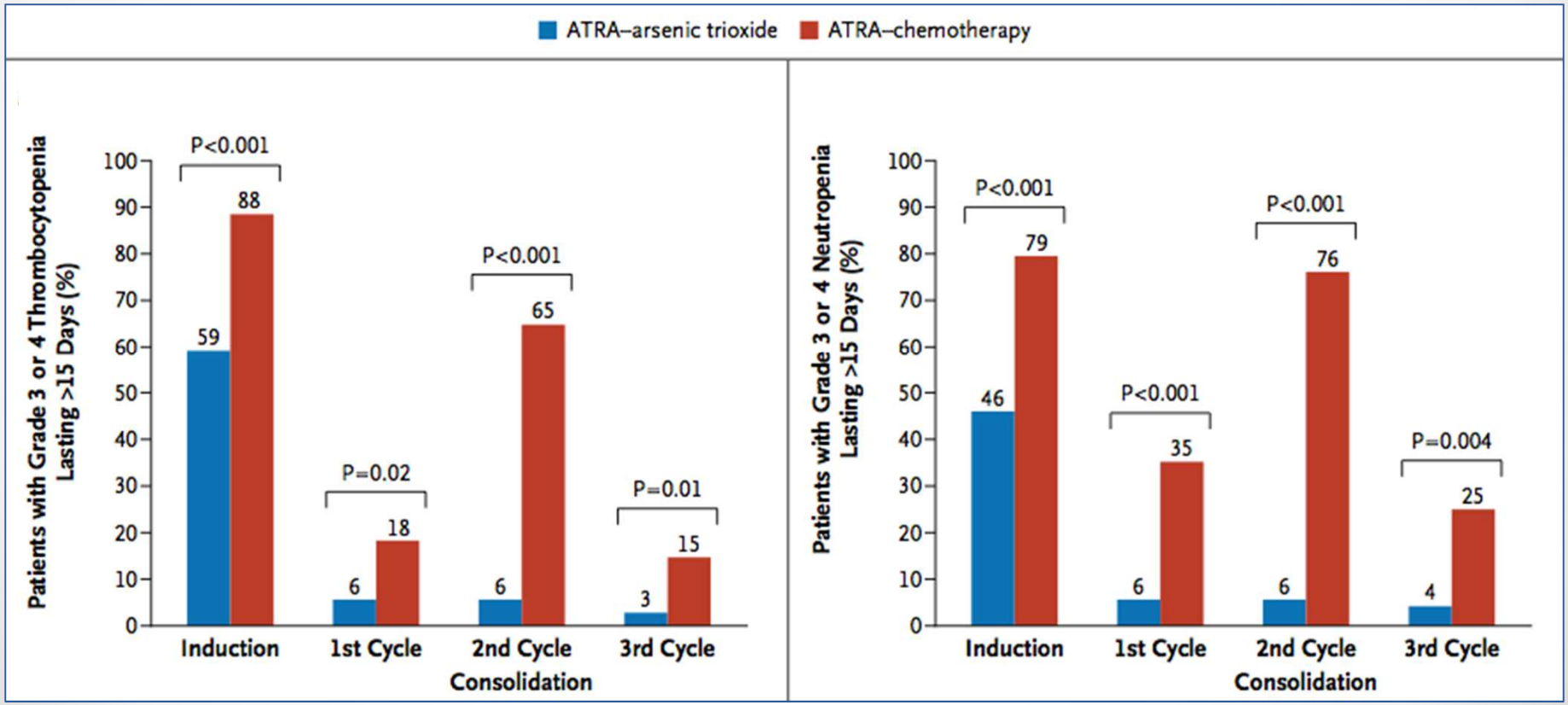
- ATRA-ATO, 100% CR
- ATRA-CTx, 95% CR, 5% ED

- More hepatic toxicities in the ATRA-ATO group (63% vs 6%).
- QTc prolongation in the ATRA-ATO group (16%)
- Differentiation syndrome occurred in 15 patients in the ATRA–ATO group (19%) and in 13 patients in the ATRA–CTx group (16%)
- Severe differentiation syndrome occurred in 10 patients (5 in each group) and was fatal in 2 patients assigned to ATRA–CTx

Lo Coco et al. NEJM 2013

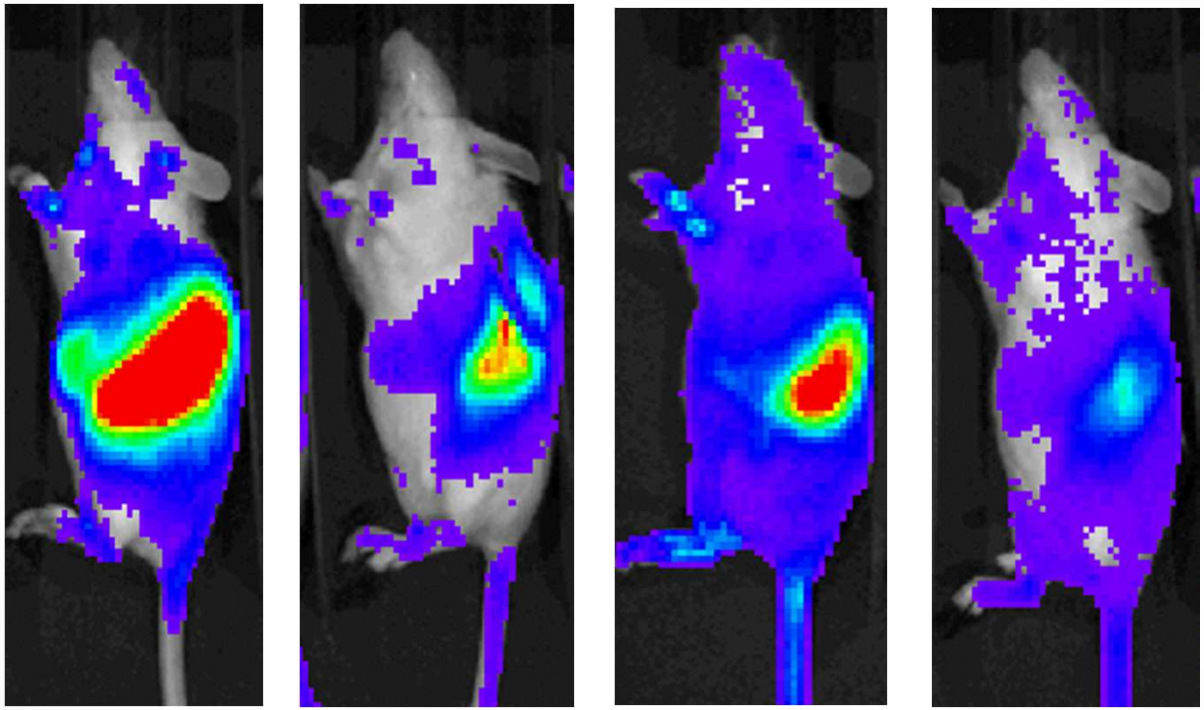
ATRA-ATO

standard-risk patients



Lo Coco et al. NEJM 2013

ATRA & Arsenic synergy

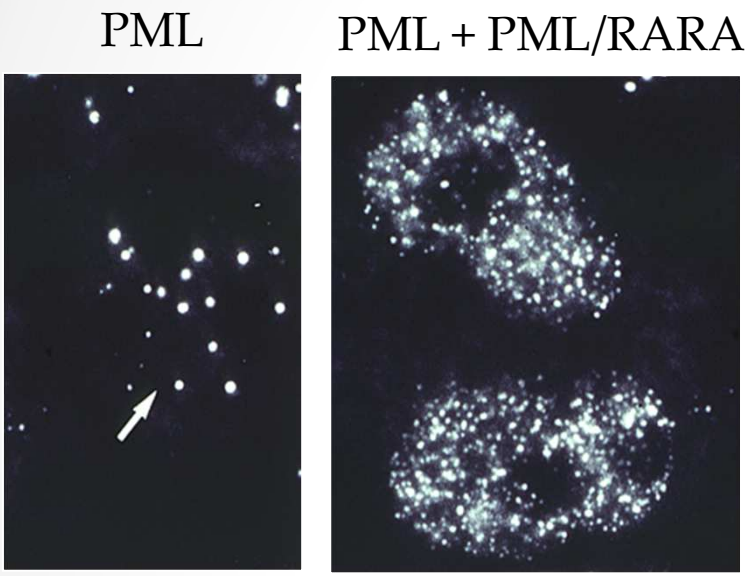


Control ATRA As2O3 ATRA+As2O3

Seen in different APL models

Lallemand, JEM 1999; Rego PNAS 2000; Nasr, Nat Med 2008

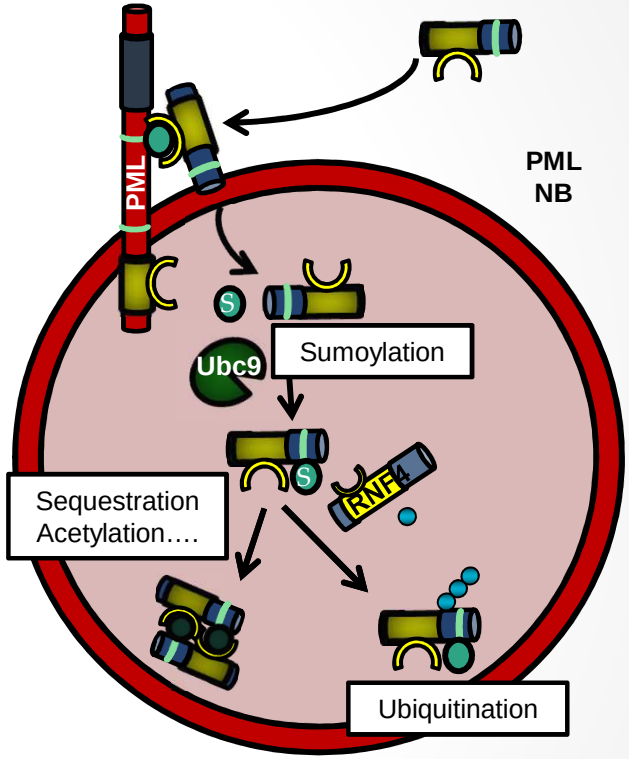
PML NBs are disrupted in APL



PML titration

**PML/RARA recruit PML,
which disrupts PML nuclear bodies**

No effect of PLZF/RARA
on NBs assembly



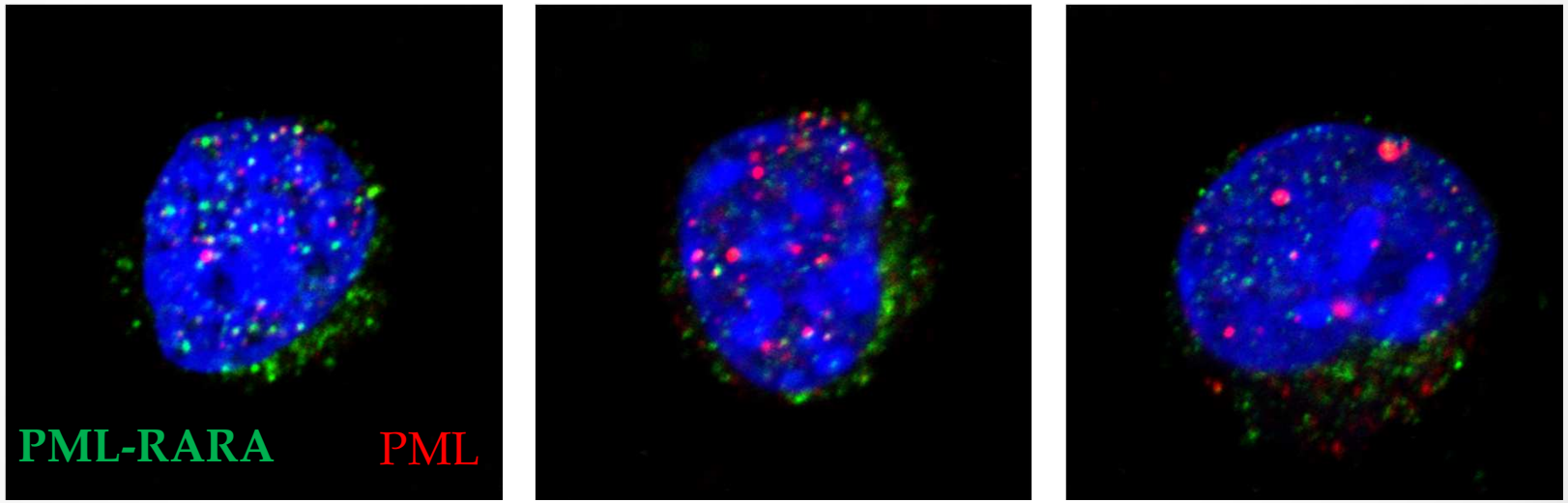
- PML NBs facilitate several post-translational modifications (PTM).
- PML NBs regulates P53 (Senescence).

Daniel, Blood 1993, Koken EMBO J 1994, Weiss, Dyck Cell 1994, Sahin JCB 2014

ATRA & Arsenic restore NBs

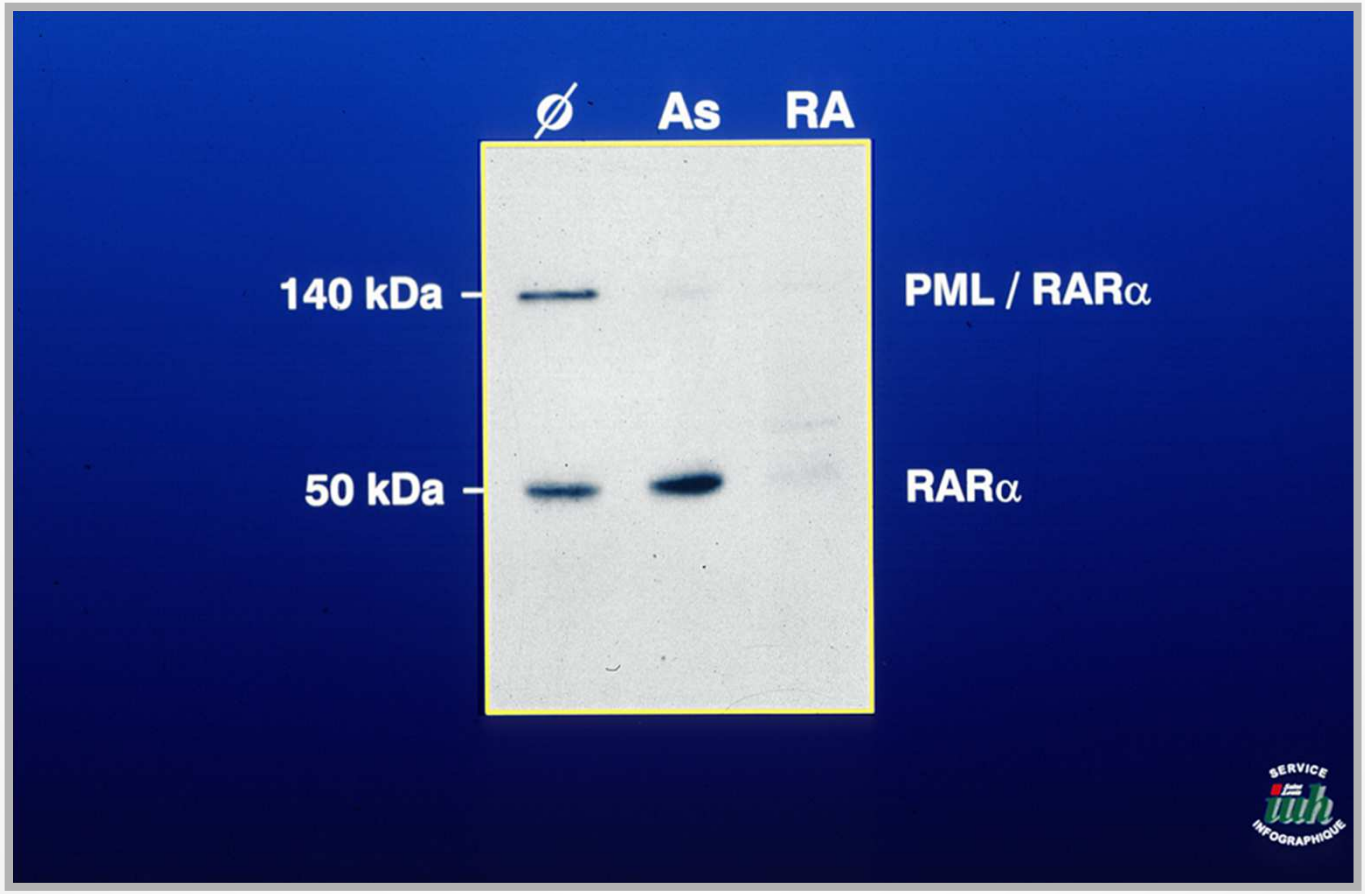
6h *in vivo* treatment

Untreated RA RA/As



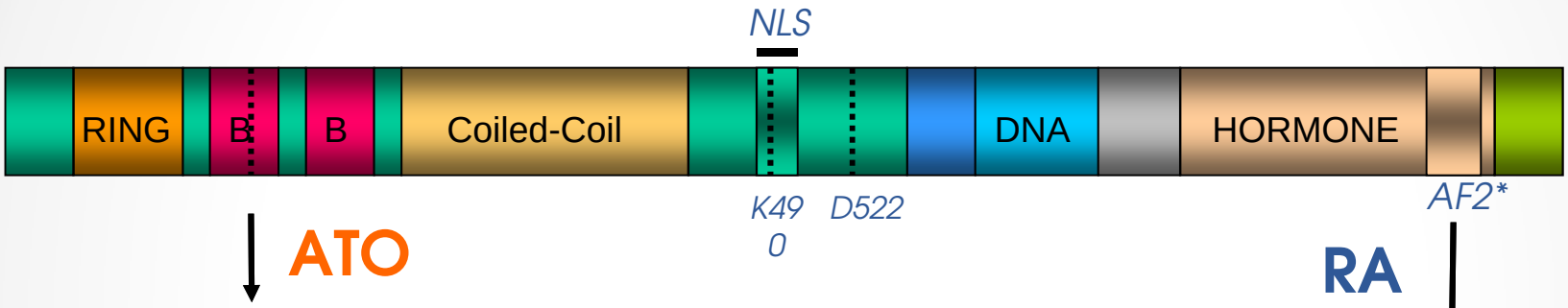
Daniel, Blood 1993; Koken, EMBO J 1994; Weiss, Dyck, Cell 1994

ATRA o& Arsenic degrade PML/RARA



Zhu PNAS 1997, 1999, Lallemand JEM 1999

PML/RARA degradation pathways



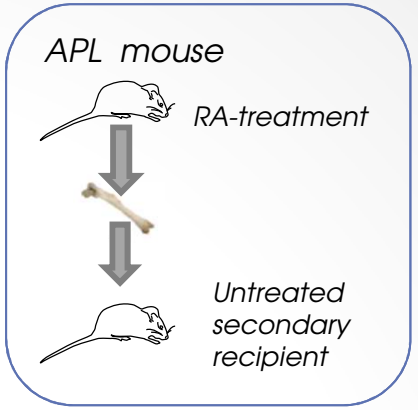
- Binding + Dimerization
- **NB reformation**
- SUMO conjugation
- RNF4-induced poly-ubiquitination

- **Conformation change**
- Dose-dependent 26S proteasome association

Proteasome-dependent DEGRADATION

Zhu PNAS 1997, 1999, Lallemand JEM 2001, Nat Cell Biol 2008, Jeanne Cancer Cell, Zhang Science 2010

Recent findings



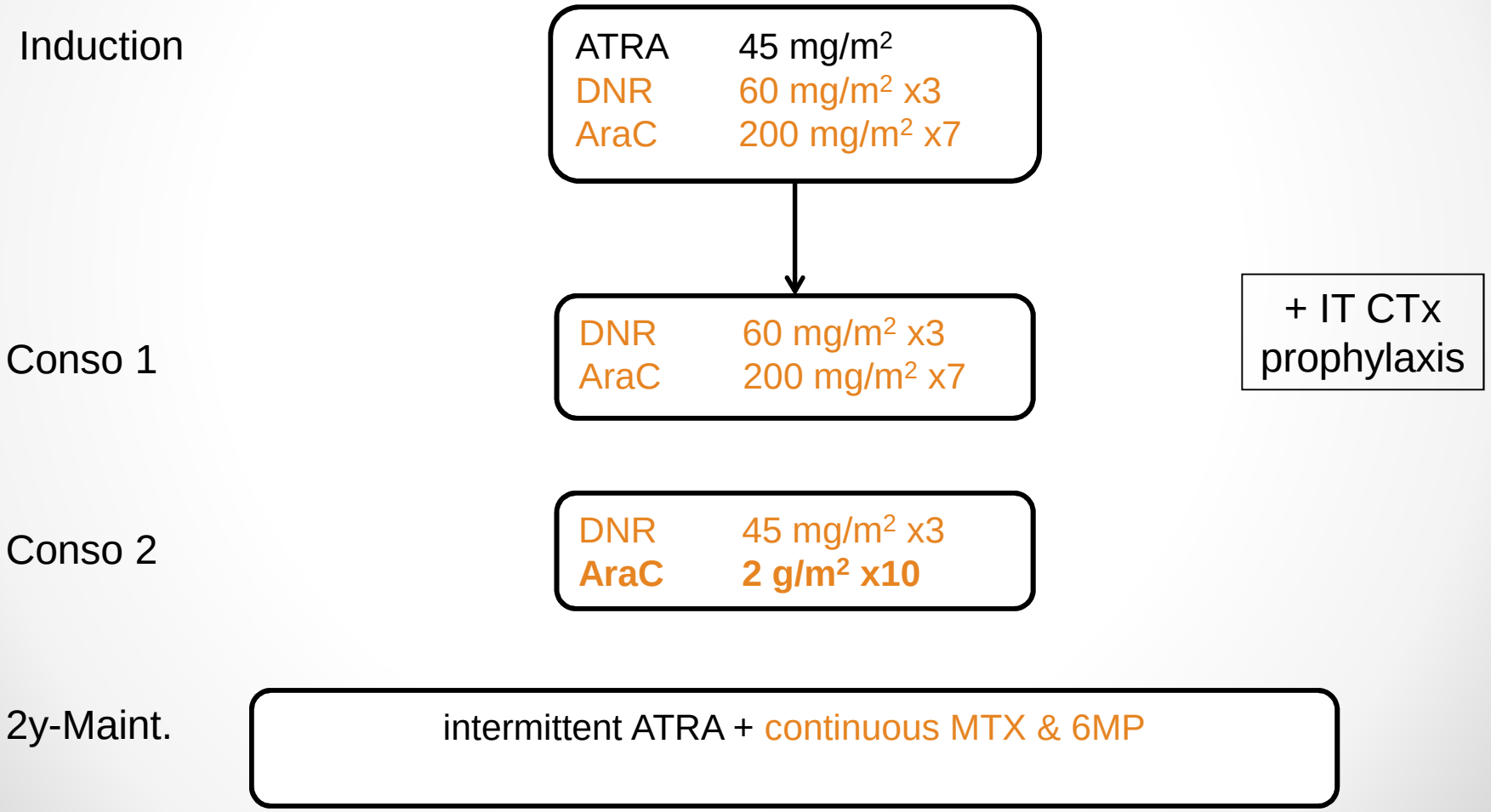
1. *Differentiation reflects transcriptional activation, but does not suffice for cure*
   - *Other retinoids, which activate transcription but do not degrade RARA, can differentiate APL, but never cure mice.*
   - *In PLZF-RARA models, RA induces differentiation but does not clear APL nor induce loss of clonogenic activity.*

2. *PML-RARA degradation re-activates a* **PML-P53 axis**, *which is responsible for cure*
   - *Genes selectively induced by high-dose RA are associated with cell cycle arest and are P53 targets.*
   - *PML drives P53 activation, APL clearance, and loss of clonogenic activity*

Ablain, JEM 2013, Nat Med 2014

Manage high WBC APL patients

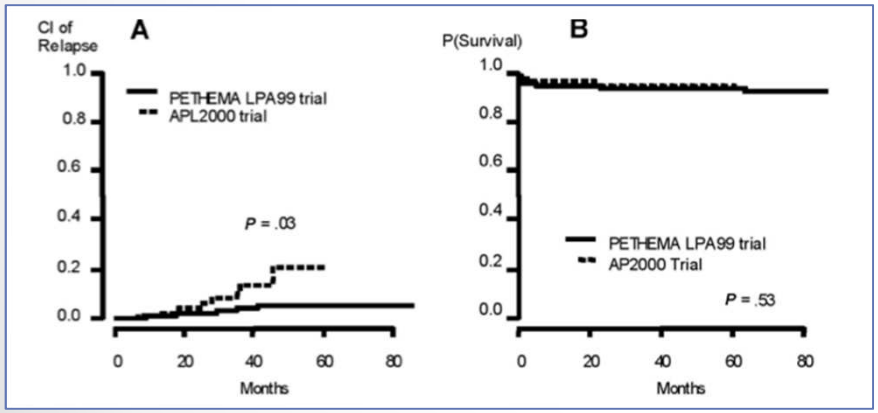
APL-2000 high-risk



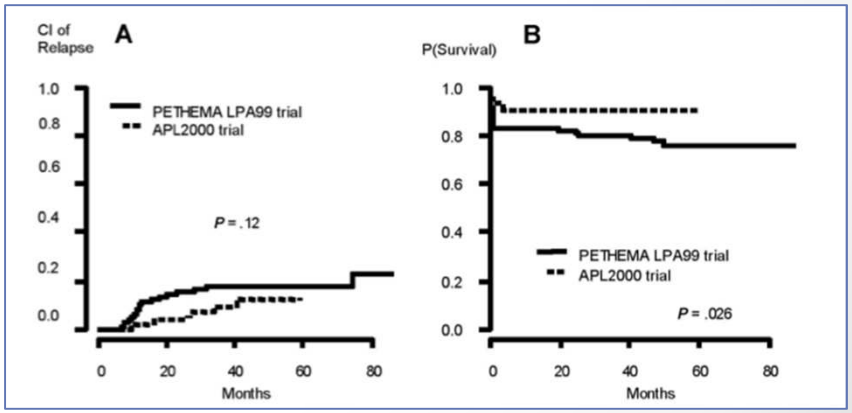
APL *versus* PETHEMA

- *PETHEMA LPA99*
  - *IDA, MTZ*
  - *No AraC*
- *APL-2000 with AraC*
  - *DNR*
  - *AraC*
  - *ID-AraC (conso 2)*
    - *1g x 8 to 2g x 10*

Standard-risk

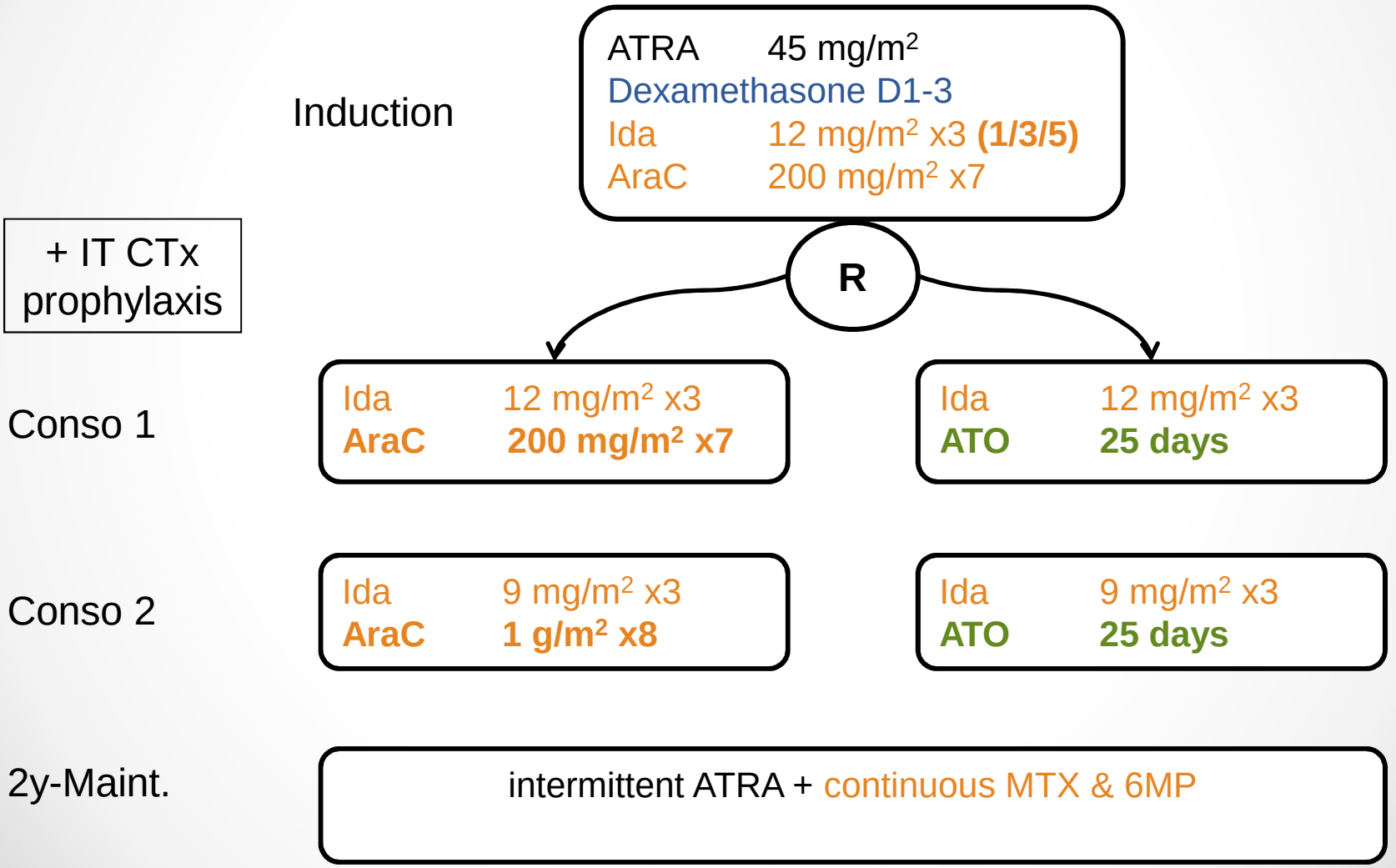


High WBC



Ades, Sanz et al. Blood 2008

APL-2006 high-risk



Single-center experience

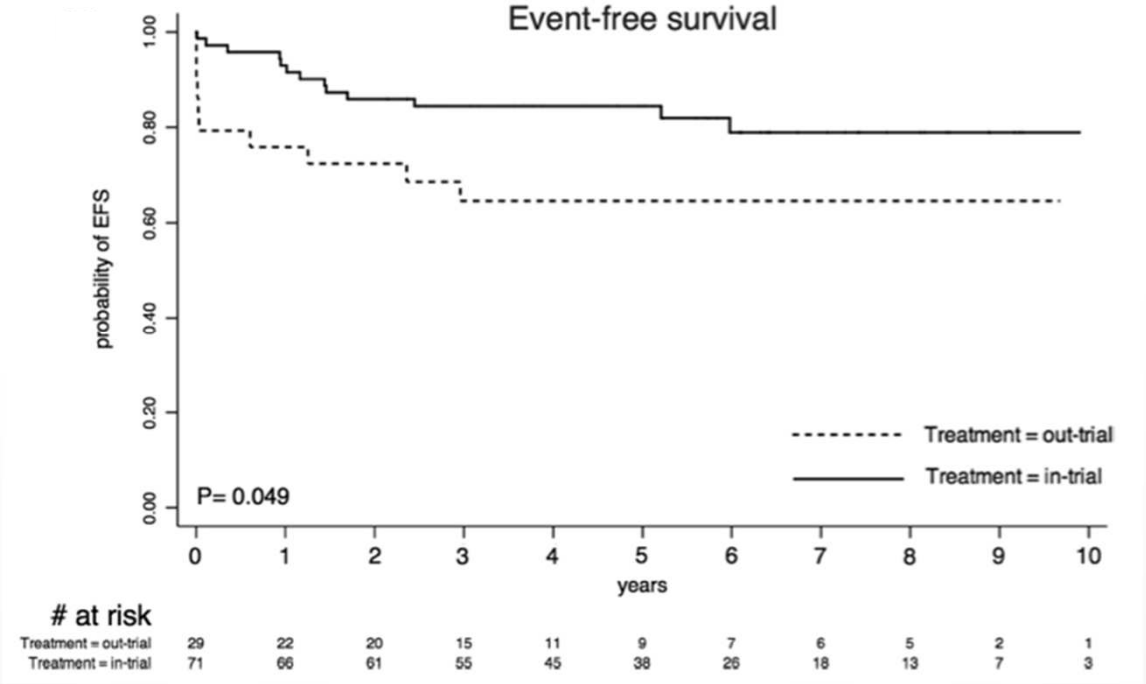
- *N= 100 APL patients*
  - *29 not included in a clinical trial (41% treated in ICU)*

Characteristics	Enrolled ($n = 71$)		Non-enrolled ($n = 29$)		p
	No	%	No	%	
Age, years					
Median	46		40		.97
Range	4–81		4–79		
Sex					
Male	36	51	14	48	.99
Female	35	49	15	52	
Fever					
Yes	35	49	23	79	.007
No	36	51	6	21	
Admission					
Direct	34	48	3	10	<.001
Transfer	37	52	26	90	
WBC count > 10×10^9/L					
Yes	22	31	15	52	.07
No	49	69	14	48	
WBC count > 50×10^9/L					
Yes	6	8	9	31	.01
No	65	92	20	69	
Platelets count < 40×10^9/L					
Yes	46	65	28	97	.001
No	25	35	1	3	
Fibrinogen level < 1 g/L					
Yes	12	17	5	17	.99
No	59	83	24	83	
Creatinine level > 1.4 mg/dL					
Yes	5	7	7	24	.04
No	66	93	22	76	
Microgranular variant					
Yes	8	11	11	38	.004
No	63	89	18	62	

Micol et al. Eur J Cancer 2014

Single-center experience

- *Early death is still a problem, underestimated in clinical trials*



Micol et al. Eur J Cancer 2014

Conclusions

- *In the clinical setting, ATO or ATO + ATRA may be sufficient for cure (not possible with ATRA alone)*
  - *This is currently used to decrease front-line CTx, and even suppress it in standard-risk patients.*
  - *Oral ATO formulations should permit oral APL Tx in the very next future.*
  - *Long-term effects of ATO remain to be defined.*
- *Early events remain the main APL issue*
  - *Very early hemorrhagic deaths.*
  - *Differentiation syndrome during induction.*