université PARIS DIDEROT PARIS 7

Acute Promyelocytic Leukemia

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Etiologies

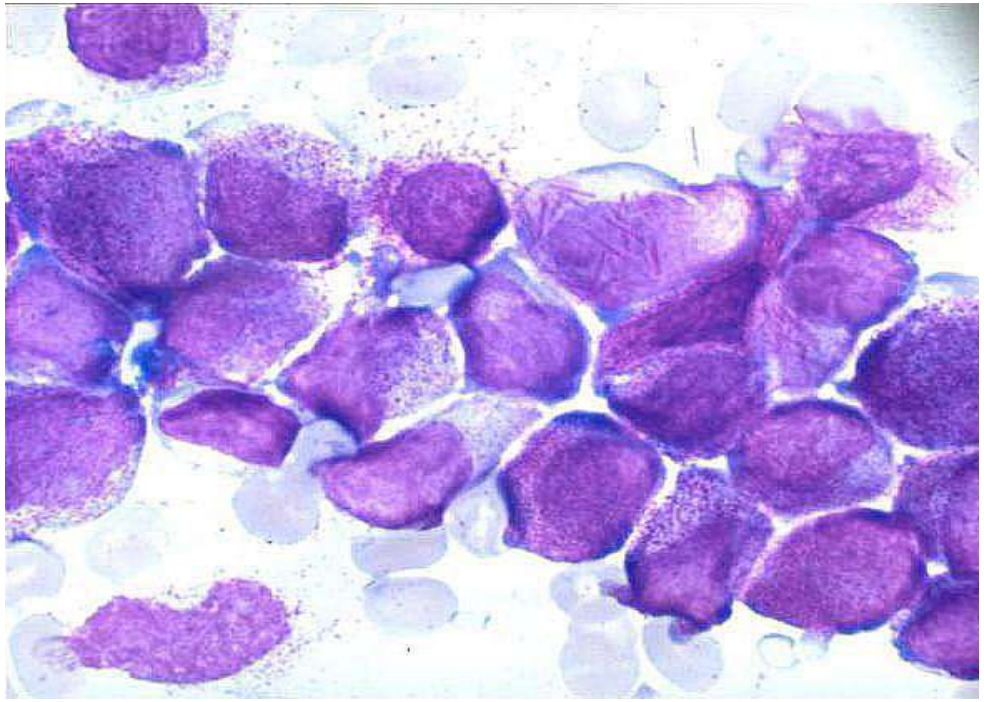
- Moins de 10% des LAM
  - ~2 nouveaux cas / millions l'habitant
  - 150 cas par an en France
- Facteurs ethniques
  - Incidence augmentée chez les 'Latinos' US
  - Le BMI elevé est plus frequent dans les LAP
- Frequement secondaire (15% dans APL2006)
  - Cancer du sein après inhibiteurs de topo II

APL characteristics

- Morphology:M3, M3v
- Cytogenetics: t(15;17) (t(11;17,t(5;17) very rare)
  complex or variant translocations
- molecular biology:PML-RAR (bcr1> bcr2>bcr3)
  others (PLZF-RAR,etc very rare)
- Coagulopathy:DIC+fibrinolysis

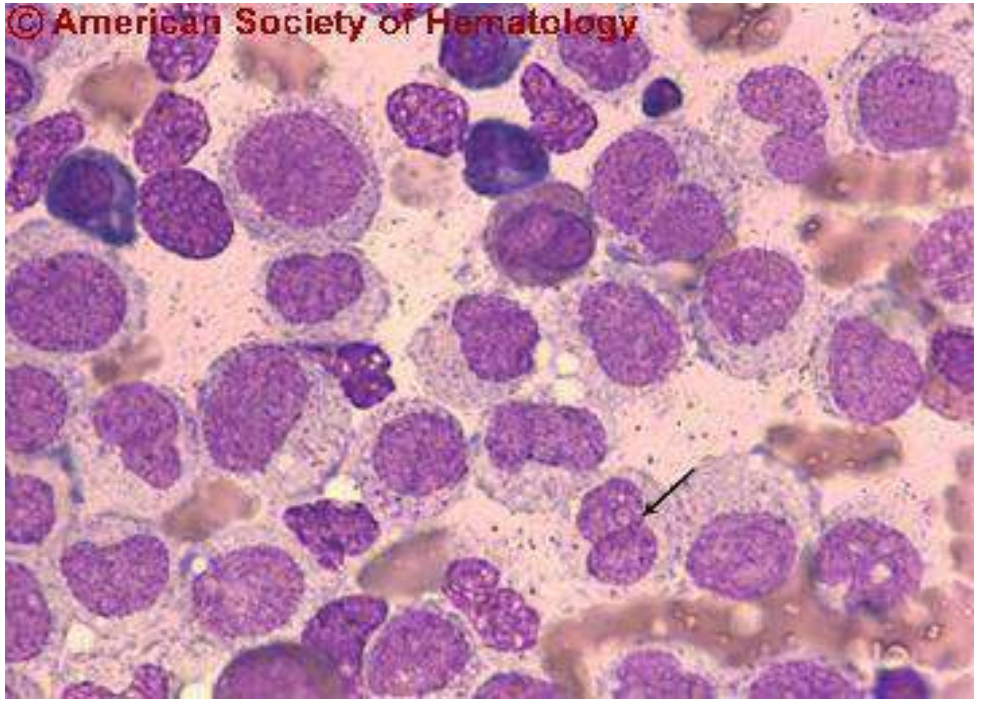
APL characteristics - Morphology

M3 (80%)



Promyelocytes with heavy granulation and Auer rods.

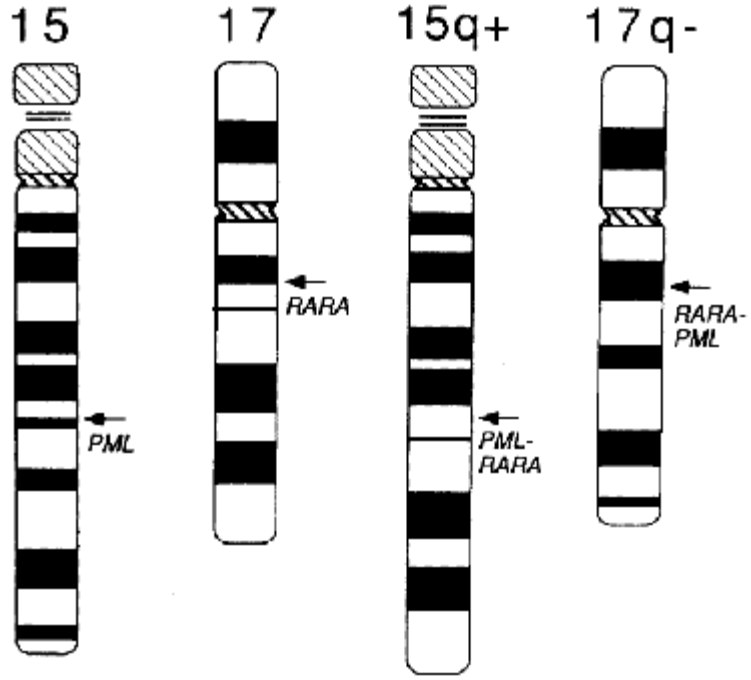
M3 variant (20%)



The granules are less prominent than those seen in the most common form of this disease. The nucleus has a characteristic bilobed, folded appearance (arrow)

Cytogénetique

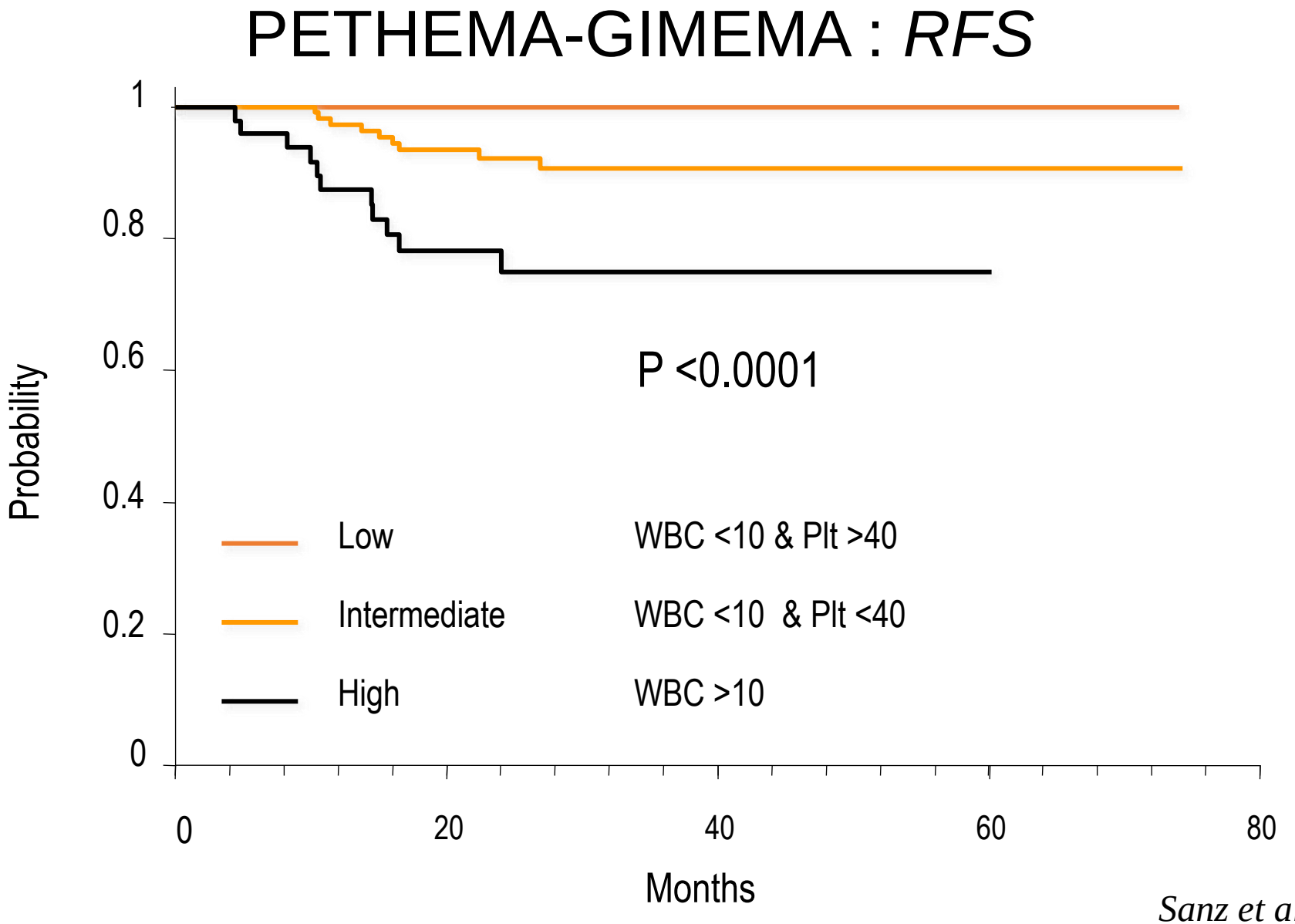
PML-RARα	t(15;17)	> 95%
PLZF-RARα	t(11;17)	1%
NuMA-RARα	t(11;17)	1 case
NPM-RARα	t(5;17)	< 1%
STAT5b-RARα	der(17)	1 case
X-RARα	t(3;17)	1 case



Facteurs pronostiques classiques

- Leucocytes >10.000/mm^3
  - *M3 variant*
  - *bcr (2)-3*
  - *Ftl3 ITD*
- Plaquettes <40.000/mm^3
  - *Sanz index*
- Réponse au traitement
  - *In vitro*
  - *In vivo : la MRD*

Score de Sanz



Sanz et al, Blood 2000

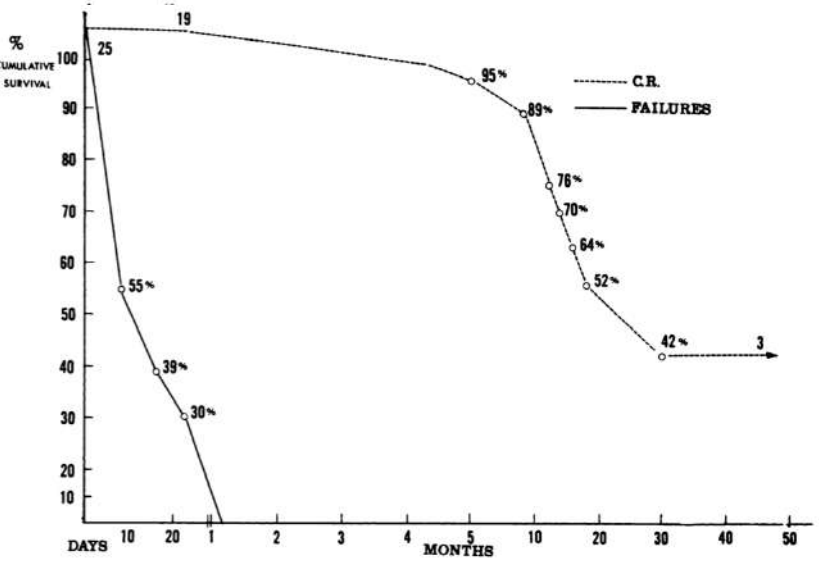
Un peu d'histoire

Anthracyclines alone

BLOOD *The Journal of Hematology*
VOL. XLI, NO. 4 APRIL 1973

Acute Promyelocytic Leukemia: Results of Treatment by Daunorubicin

By Jean Bernard, Marise Weil, Michel Boiron, Claude Jacquillat, Georges Flandrin, and Marie-François Gemon



ATRA alone

Table 1. Data of 24 Patients With APL

Case	Sex	Age	Previous Therapy/Duration	PB WBC ($\times 10^9$/L)	BM Prom (%)	Present Therapy (mg/m²/day)	PR (day)	CR (day)	BM Prom (%)	Further Therapy	Duration of CR (mo)
1	F	5	HOAP/7 days HOP/9 days H/20 days	1.16	78	RA 80	31	68	1.5	(1)	8*
2	M	6	HOP/26 days	1.7	73.5	RA 100	18	28	2.5	(3)	—†
3	F	28	HOA/62 days	1.8	89	RA 60	21	34	2.0	(3)	4‡
4	M	8	HOAP/10 days OH/21 days CR/3 mo Relapse	2.2	33	RA 80	18	43	3.6	(2)	5‡
5	F	38	HOP,HOAP,H CR/1 mo Relapse	7.7	15.5	RA 45	17	20	4.5	(1)	5*
6	F	54	HOP,HOAP CR/30 mo Relapse	4.0	28.5	RA 45	22	22	2.0	(1)	4‡
7	M	54	H/10 days	1.4	94	RA 45	29	38	1.0	(1)	2‡
8	F	69	H/5 days	0.5	48	RA 45	22	44	4.0	(3)	1*
9	M	61	Untreated	1.0	74	RA 45-50	29	36	2.5	(2)	11*
10	M	31	Untreated	1.6	76	RA 50	35	35	1.5	(2)	5‡
11	M	37	Untreated	1.4	65	RA 45	26	43	3.5	(1)	10*
12	F	18	Untreated	0.9	81.5	RA 45-50	21	40	2.5	(4)	8*
13	F	35	Untreated	2.2	70	RA 50	20	39	2.0	(2)	4‡
14	M	45	Untreated	2.1	84.5	RA 45	36	119	1.0	(4)	5*
15	F	57	Untreated	1.9	88.5	RA 45	23	51	2.5	(4)	5*
16	F	20	Untreated	0.9	85.5	RA 50	22	46	2.0	(1)	8*
17	M	32	Untreated	1.1	78	RA 45	29	39	3.0	(4)	4‡
18	M	36	Untreated	1.1	89.7	RA 50	35	52	2.0	(4)	4*
19	F	53	Untreated	15.8	75.5	RA 45	23	39	0	(3)	5*
20	M	30	Untreated	6.5	90	RA 45	46	46	2.5	(4)	3*
21	F	36	Untreated	1.7	91	RA 50	36	50	1.0	(3)	1*
22	M	21	Untreated	1.7	90	RA 45	28	56	1.0	(4)	2*
23	M	45	Untreated	1.4	78	RA 45	25	45	3.0	(4)	1*
24	M	34	Untreated	1.1	30	RA 45 + ara-C 20	60	98	1.5	(4)	3‡

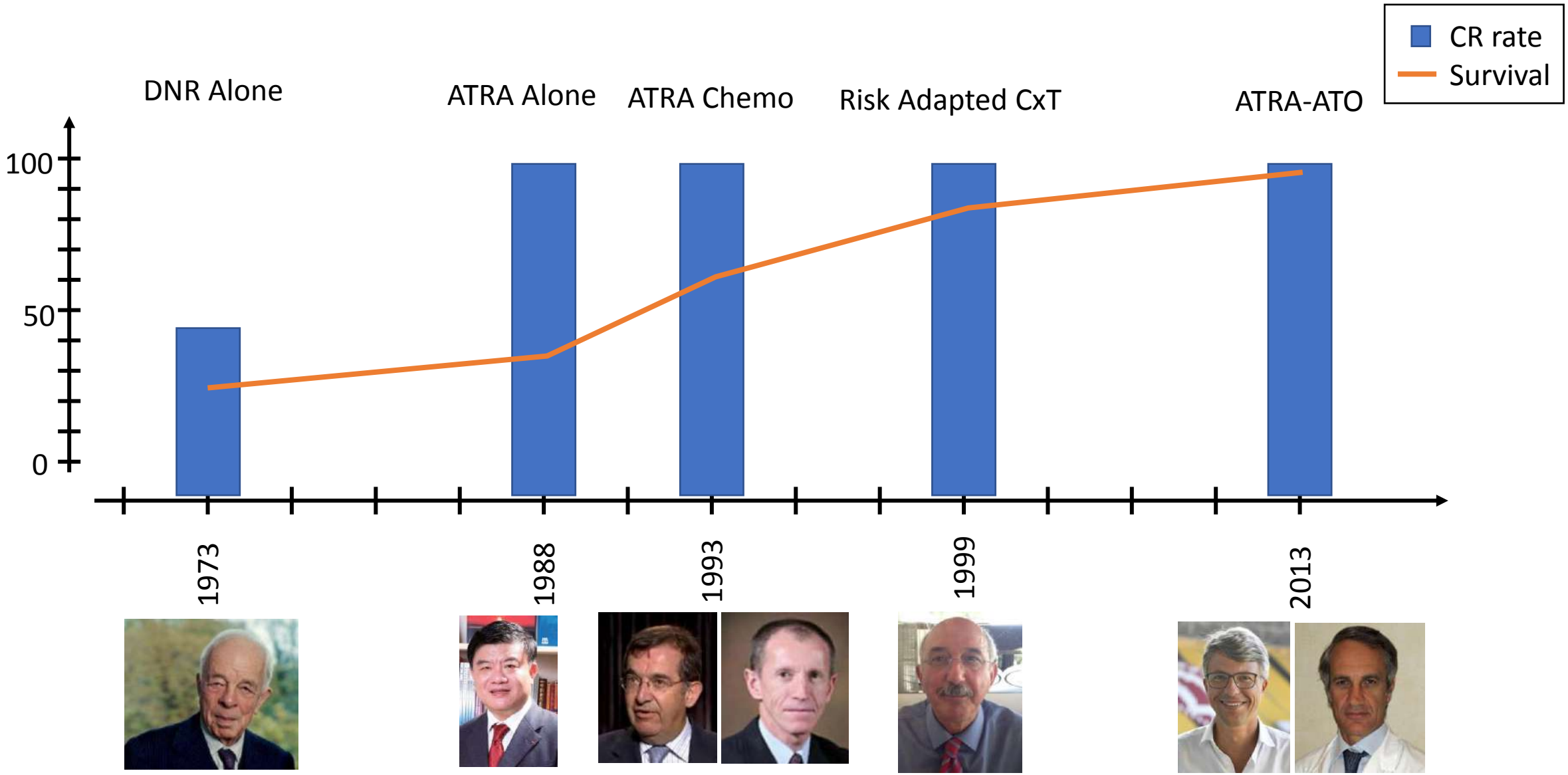
ATO alone

Ref.	n	Induction therapy	CR (%)	ED
Shen	20	ATO 0.16mg/kg	90	7
	21	ATO + ATRA	95	7
Hu	56	ATO 0.16 mg/kg + ATRA	94	6
Matthews	72	ATO 10mg	86	14
Ghavamzadeh	197	ATO 0.16 mg/kg	86	14
Estey/Ravandi	82	ATO 0.15 mg/kg (GO in HR) + ATRA	91 (95/81)	9

Jean Bernard, Blood 1973

Shen *et al.* PNAS 2004 , Hu *et al.* Blood 2005/PNAS2009, Mathews *et al.* Blood 2005/JCO 2010, Ghavamzadeh *et al.* Ann Oncol. 2006/JCO2011, Estey/Ravandi *et al.* Blood 2006/JCO 2009

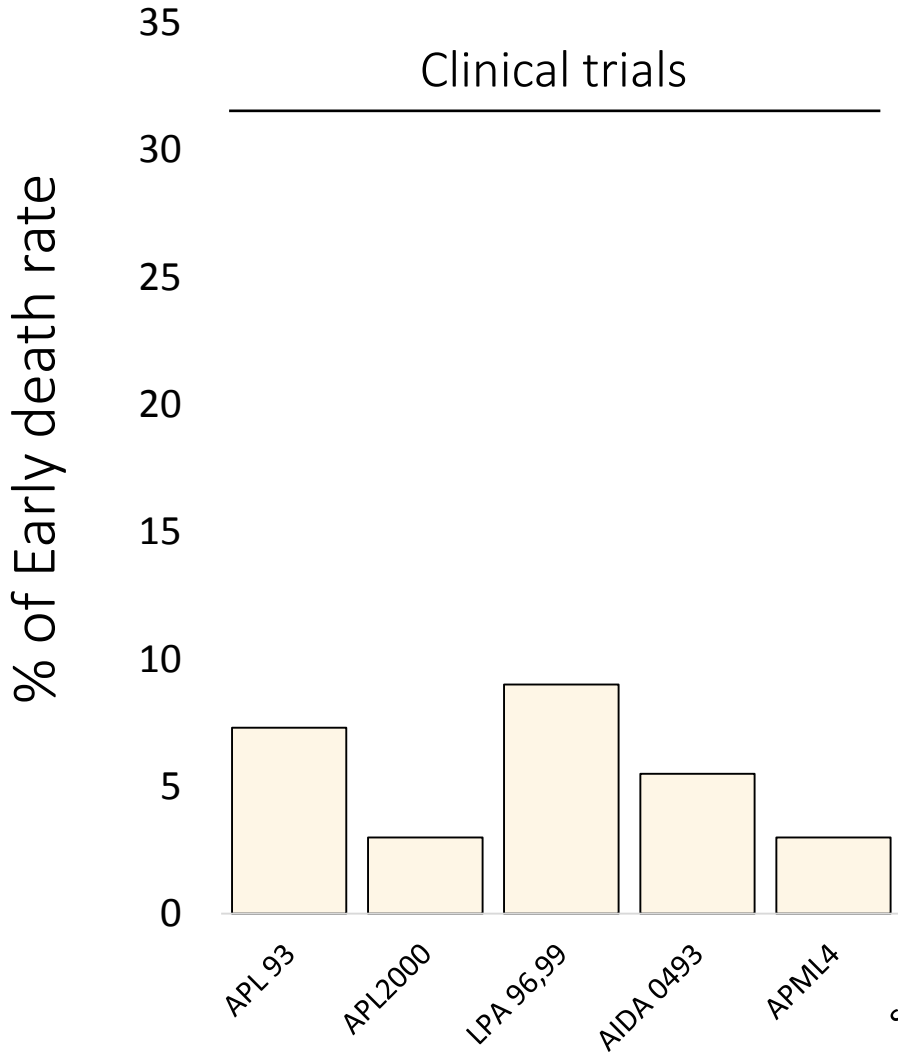
Milestones in APL



Are all APL patients Cured ?

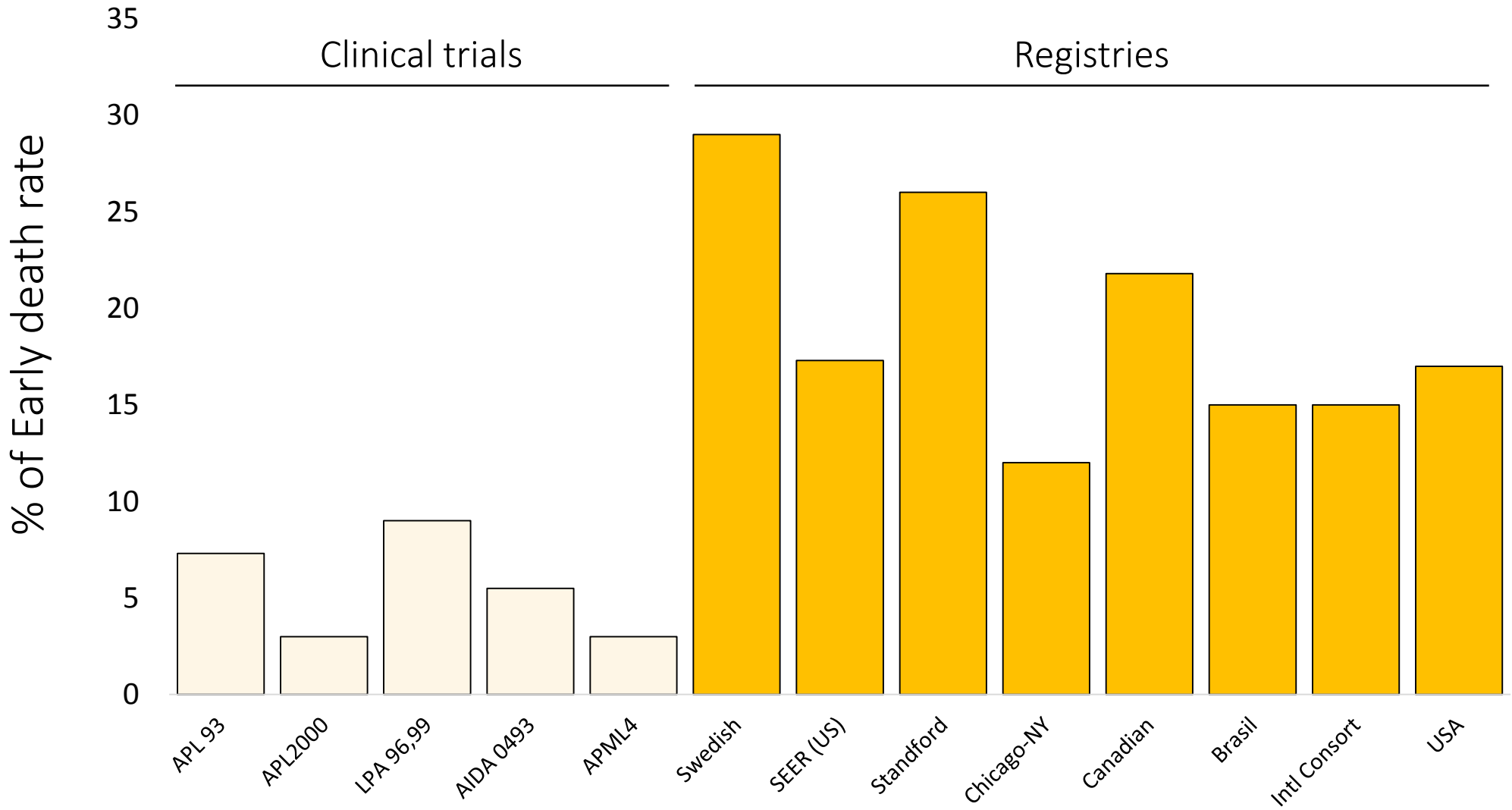
The 1st Issue in APL : Early Death rate

Incidence of early death with ATRA-CxT

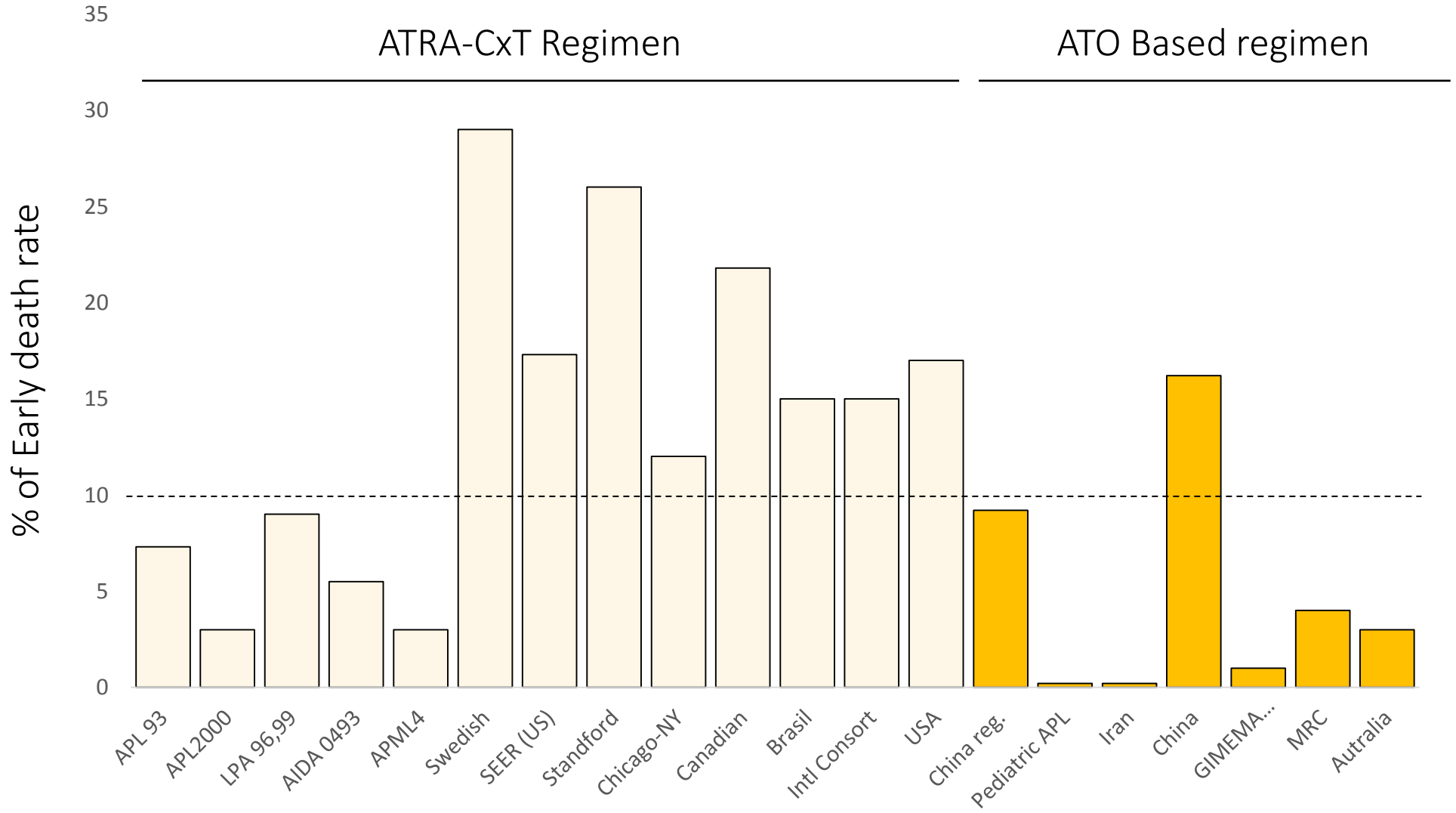


Limited early death rate in patients with APL
Enrolled within clinical trials

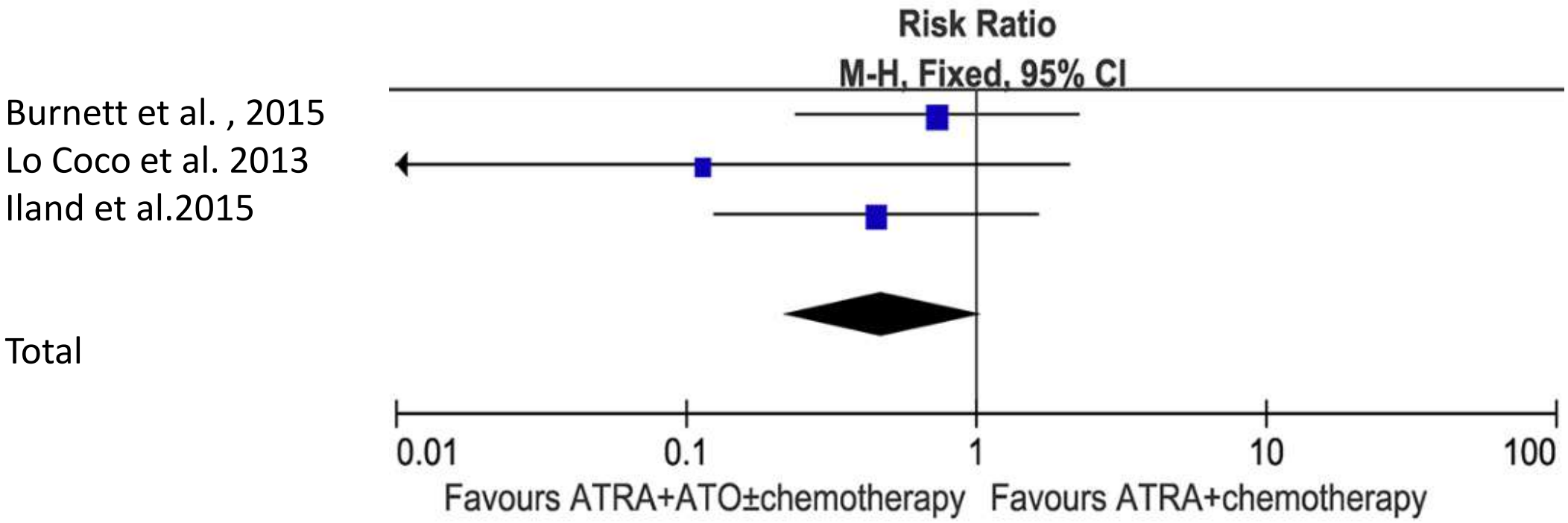
Cause of early death over time with ATRA-CxT



Cause of early death CxT vs ATO



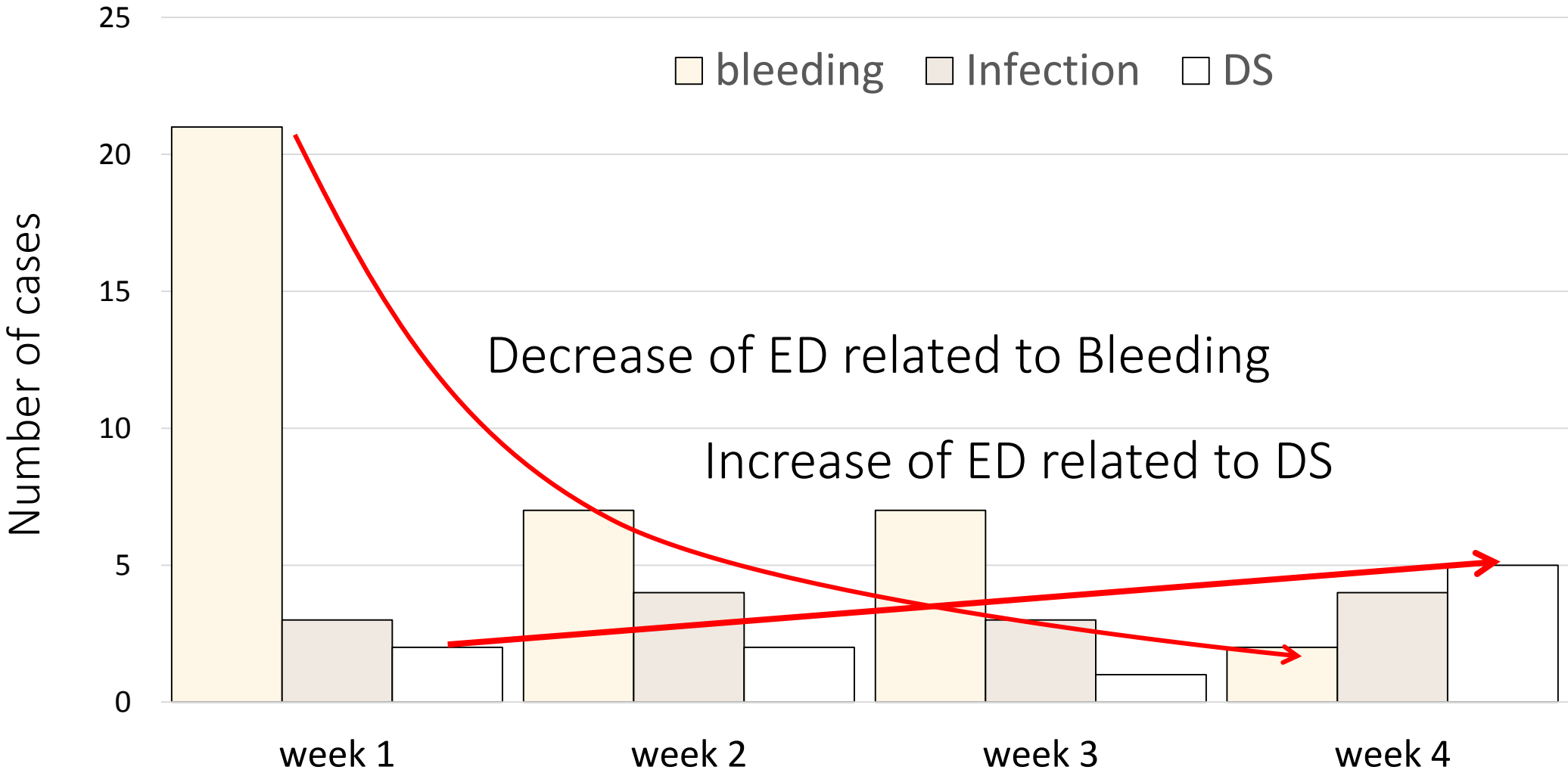
Early death rate in Randomized studies with ATO – A meta-analysis



A trend for lower ED death with ATO but
No l significant difference between the two groups (RR = 0.48; 95% CI: 0.22–1.05; p = 0.07)

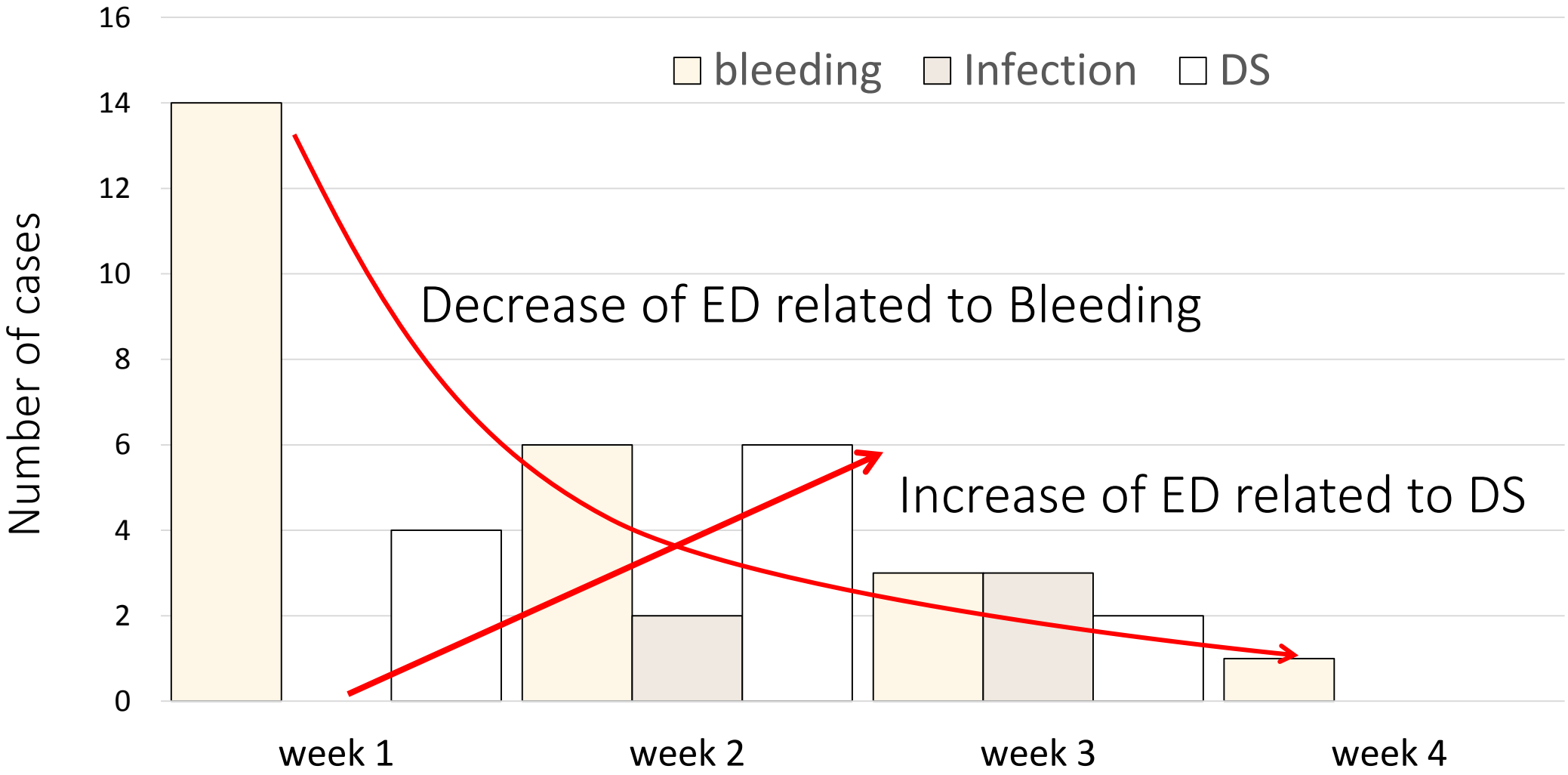
Ma Y et al. PLoS One. 2016 Jul 8;11(7):e0158760

Cause of early death over time with ATRA-CxT



De La Serna, Blood 2008

Cause of early death over time with ATO



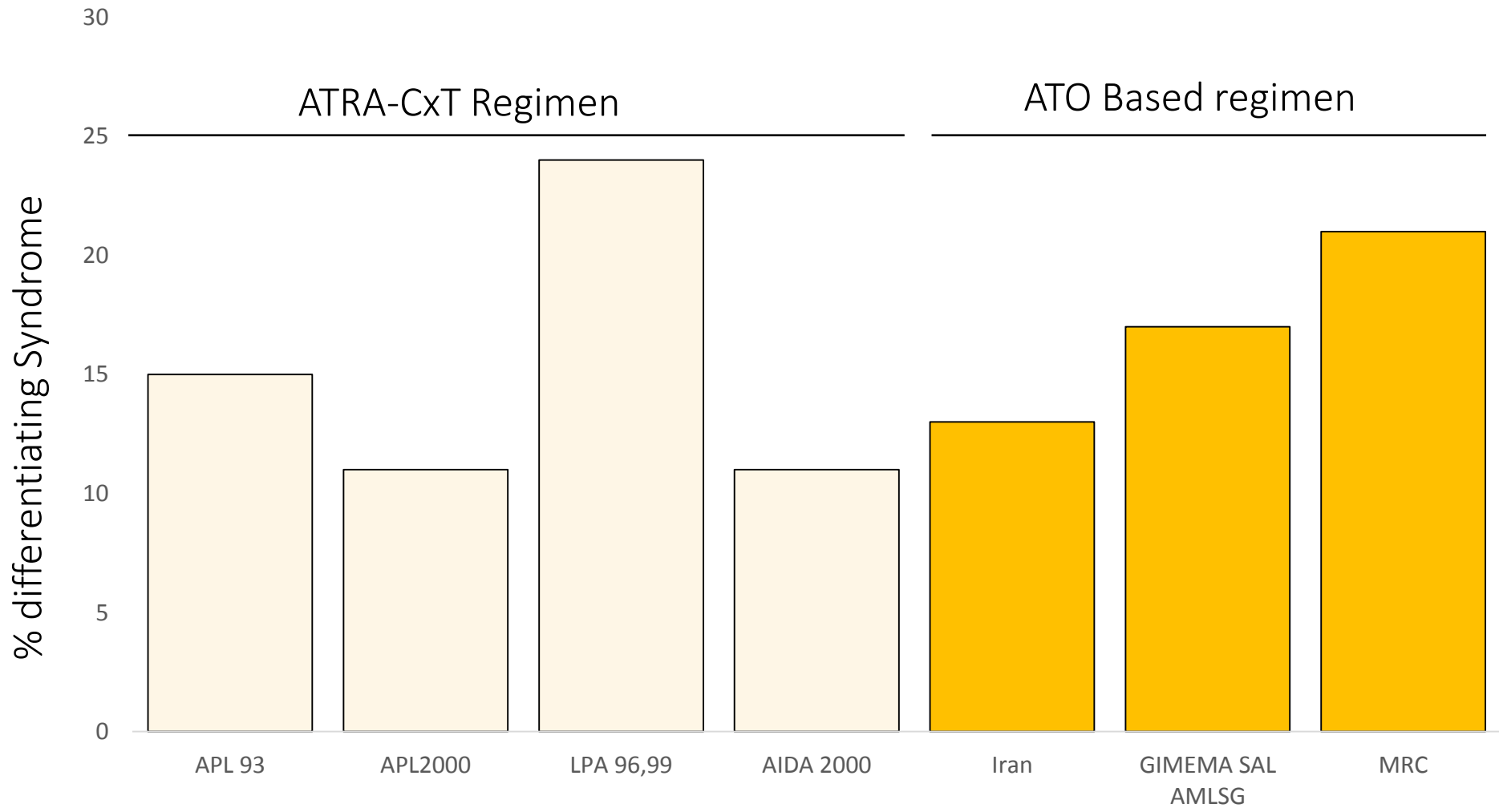
Ann Hematol. 2017 Dec;96(12):2005

Recommendations to prevent ED

- APL : immediately hospitalized and managed as a medical emergency
- Even before diagnosis confirmation ATRA and measures to counteract the coagulopathy should be begun based solely on clinical suspicion of APL :
  - maintaining the fibrinogen > 100-150 mg/dL
  - maintaining the platelet > 50×10^9/L

The 2nd Issue in APL : Differentiating syndrome

Incidence of Differentiating syndrome



Preventing DS in low risk APL ?

study	#patients	therapy	Early death From DS	Prophylaxis
Lo Cocco et al. [1]	445	ATRA-CxT	1%	Yes
Lo Cocco et al. [2]	636	**ATRA-CxT**	1%	Yes
Adès et al.[3]	356	ATRA-CxT	0%	No
Sanz et al. [4]	561	ATRA-CxT	1.4%	Yes
Lendfelder et al. [5]	142	ATRA-CxT	0.7%	No
Mathews et al. [6]	72	ATO	1.4%	No
Iland et al. [7]		ATO-ATRA		
Lo Cocco et al.[8]		ATO-ATRA	0%	Yes
Burnett et al. [9]		ATO-ATRA	0%	No

1 Blood. 2010;116(17):3171-3179.
2 N Engl J Med. 2013;369(2):111-121.
3 J Clin Oncol. 2006;24(36): 5703-5710.
4 Blood. 2010;115(25): 5137-5146.
5 Leukemia. 2009;23(12): 2248-2258.
6 J Clin Oncol. 2010; 28(24):3866-3871.
7 Blood. 2012;120(8): 1570-1580
8
9

No Randomized trial for Steroids use in LR APL

- **Using ATRA-CxT Based therapy**
- LAP 96 trial (no Prophylaxis) vs LPA99 trial (5-day prophylaxis with prednisone)
- Reduction of the incidence of severe DS (11.3% vs 16.6%; P =0.07)
- But No significant improvement in the DS mortality rate (1.1% vs 1.4%)

Blood. 2014 May 1;123(18):2777-82

Recommendations for DS #1

- Prophylactic use of steroids remain controversial in Standard risk APL
  - Prophylaxis was done in the GIMEMA-SAL-AMLSG trial
  - Not done in the MRC trial
  - With similar incidence of DS
- But administration of high-dose dexamethasone at the onset of the first sign of DS have reduced the mortality associated with this syndrome from 30% to <2%

Recommendations for DS #2

- Temporary discontinuation of ATRA or ATO is indicated in the case of DS with very poor clinical condition or severe organ dysfunction
- Dexamethasone should be maintained until complete disappearance of signs and symptoms, and then ATRA / ATO should be resumed.

Recommendations for Hyperleucocytosis During treatment

- Still an unanswered question
- Various recommendations
  - Use of Idarubicin 12 mg/m^2 1d [1]
  - Use of GO 9 mg/m^2 1d [1]

45% of LR APL required Ida/GO
in the MDA experience of ATRA-ATO

  - Use of HU [3]

47% of LR APL required HU
in the GIMEMA-AMLSG-SAL trial of ATRA-ATO

Yasmin Abaza et al. Blood 2017
Lo Coco et al. , NEJM 2013

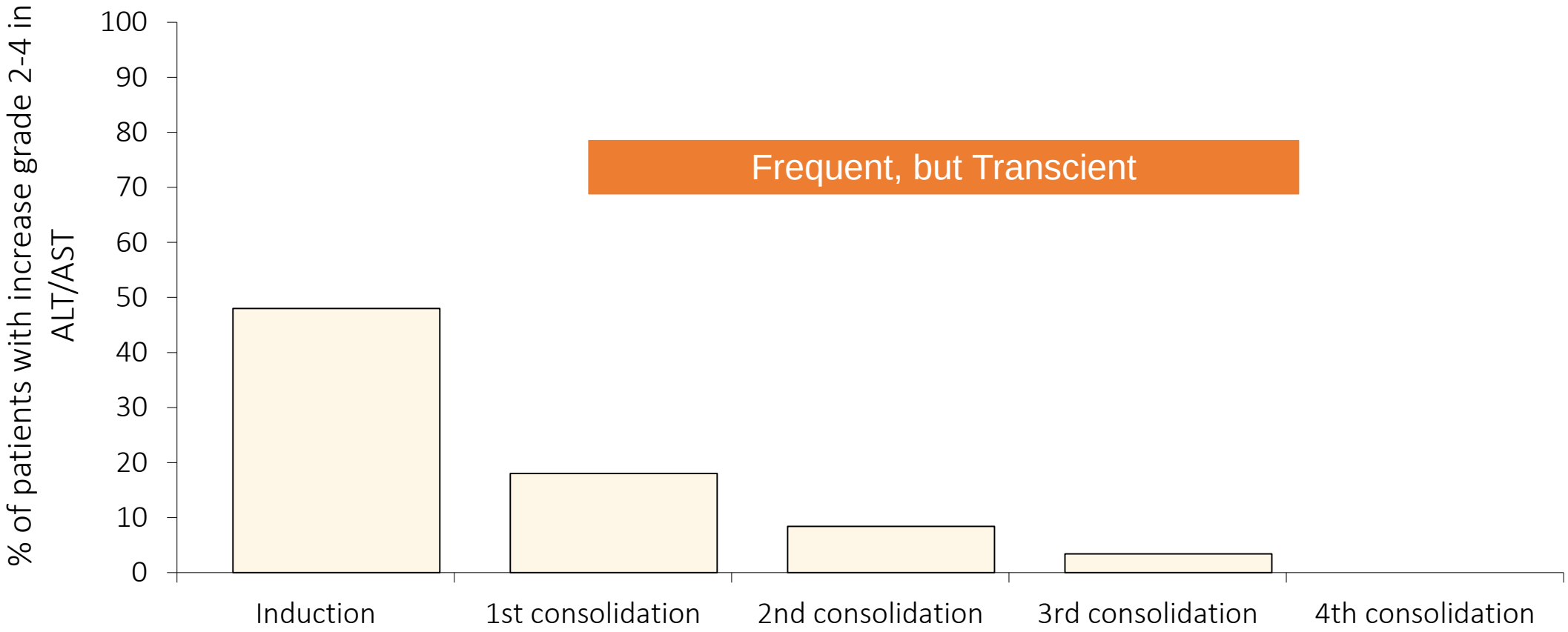
The 4th Issue in APL : side effects of ATO

Non Hematological toxicites

		Induction	p-value	1st cons	p-value	2nd cons	p-value	3rd cons	p-value
Hepatic toxicity	ATRA-ATO	62(48%)	-	22(19%)	-	10(8.5%)	-	4(3.2%)	-
QTc prolongation	ATRA-ATO	11(8.5%)	0.0022	3(2%)	0.11	3(2%)	0.11	2(1.5%)	0.23
	ATRA-CHT	1(0.7%)		0		0		0	
Cardiac function (grade 3-4)	ATRA-ATO	0	0.06	0		0		0	
	ATRA-CHT	5 (3.7%)		0		0		0	
Neurotoxicity	ATRA-ATO	1(0.7%)	0.48	5(4.2%)	0.02	6(5%)	0.01	7(5.9%)	0.006
	ATRA-CHT	0		0		0		0	
Gastrointestinal toxicity (grade 3-4)	ATRA-ATO	3(2%)	<0.0001	0	1	0	0.03	0	1
	ATRA-CHT	25(18.2%)		1(0.8%)		6(4.9%)		0	
Hypercholesterolemia	ATRA-ATO	14(10%)	0.55	19(16%)	0.13	19 (16%)	0.14	16(14%)	0.27
	ATRA-CHT	12(8.7%)		12(9.6%)		12 (9.7%)		11(9%)	
Hypertrigliceridemia	ATRA-ATO	29(22%)	0.76	22(18.4%)	0.49	17(14.4%)	0.12	16(14%)	0.5
	ATRA-CHT	29(22%)		19(15.2%)		10(8%)		13(11%)	

Courtesy of U. Platzbecker

Hepatic toxicity in the ATRA-ATO arm



Adapted from U. Platzbecker

ATO : Any long term toxicities ?

- 112 patients with newly diagnosed APL treated with ATRA and ATO
- 12-year follow-up

  - 15.2% grade 1 liver dysfunction
  - 42.9% hepatic steatosis
  - → **But No long term liver fibrosis**

  - 7% skin pigmentation issue, transcient

  - **No common signs of chronic arseniasis** (cardiovascular events, chronic renal insufficiency, diabetes, or neurological dysfunction)
  - **No long term arsenic retention**

Zhu et al. Blood. 2016 Sep 15;128(11):1525-8.

QTc Prolongation with ATO

study	#patients	therapy	QTc prolongation	Outcome
Lo Cocco et al. NEJM 2013	68	ATRA-ATO	16%	1 **Discontinuation**
Burnett Lancet Hematol 2015	114	ATRA-ATO	22%	2 **Discontinuations**
Mathews 2010 JCO	72	ATO	?	?
Gavamzadeh JCO 2010	197	ATO	?	2 cardiac arrest
Powell Blood 2010	244	ATO during conso	0 grade 3-4	0
Roboz JCO 2014	113	ATO (non APL)	26%	No cardiac death

QTc Prolongation and ATO

- QTc prolongation is not equivalent to the occurrence of torsades de pointes or any other cardiac event
- The incidence of fatal torsades de pointes approaches zero when there is :
  - appropriate ECG surveillance
  - and attentive repletion of magnesium and potassium

- It is crucial that, if at all possible, patients receive the optimal number of doses of ATO

Recommendation in APL

- Treatment with ATO requires careful monitoring to maintain electrolytes in the normal range
  - keeping the serum potassium above 4.0 mEq/L
  - serum magnesium above 1.8 mg/dL.

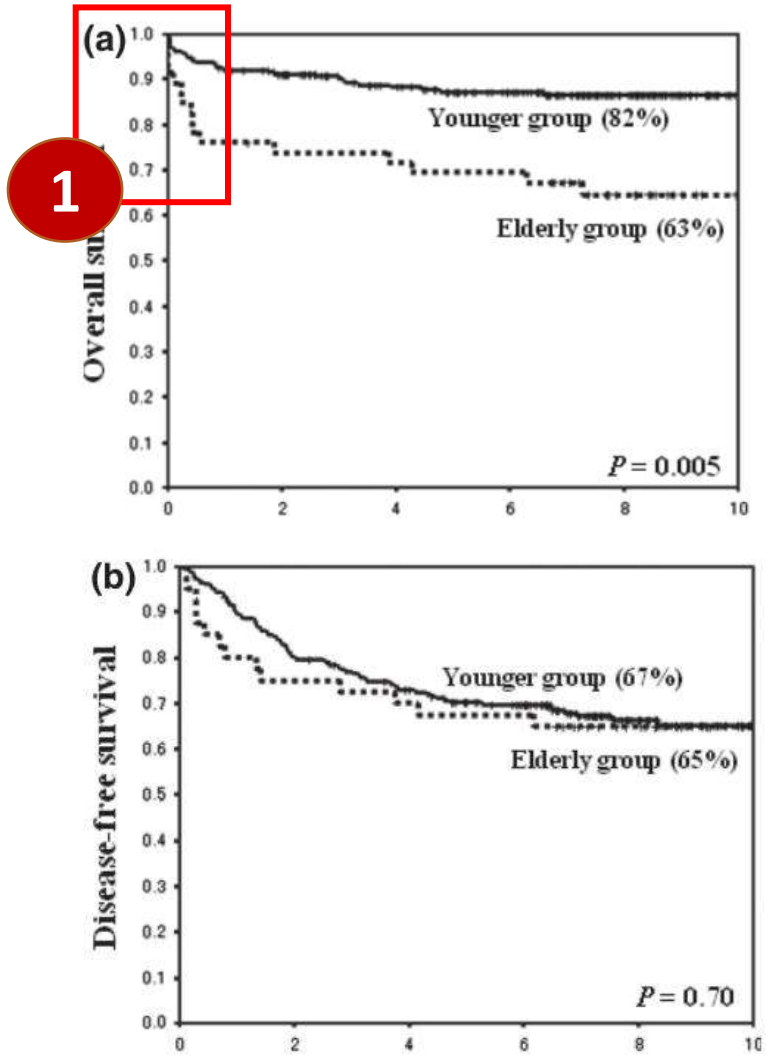
- Treatment with ATO requires careful monitoring of the QT/QTc interval
  - For routine ECG surveillance of QT interval prolongation, alternative rate adjustment formulas other than the classical Bazett correction (e.g. Friedericia, Hodges or Sagie) should be used.
  - If the QTc (interval is prolonged longer than 500 milliseconds, ATO should be withheld, the electrolytes repleted (potassium and magnesium), and other medications that may cause prolonged QTc interval searched for and ideally discontinued.
  - Once the QT/QTc returns to approximately 460 milliseconds, and the electrolytes are repleted, ATO may be resumed.

The 5th Issue in APL : Elderly patients

Different OS but similar Relapse rate

In the elderly, the treatment of APL with conventional ATRA-anthracycline based CT regimens is associated with :

1. A relatively high early death rate

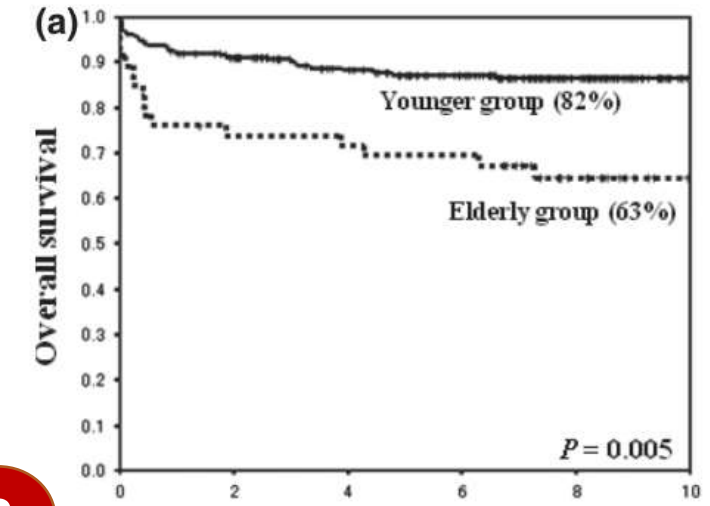


Takaaki Ono et al. , Cancer Science 2012

Different OS but similar Relapse rate

In the elderly, the treatment of APL with conventional ATRA-anthracycline based CT regimens is associated with :

1. A relatively high early death rate
2. Limited number of relapses



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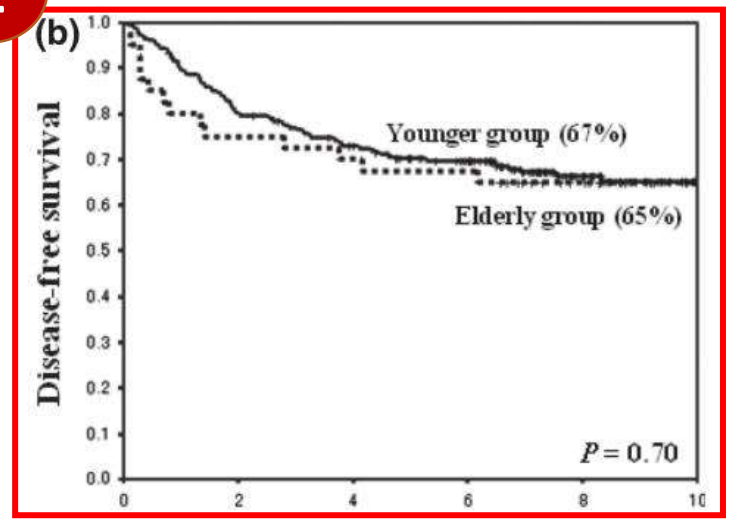
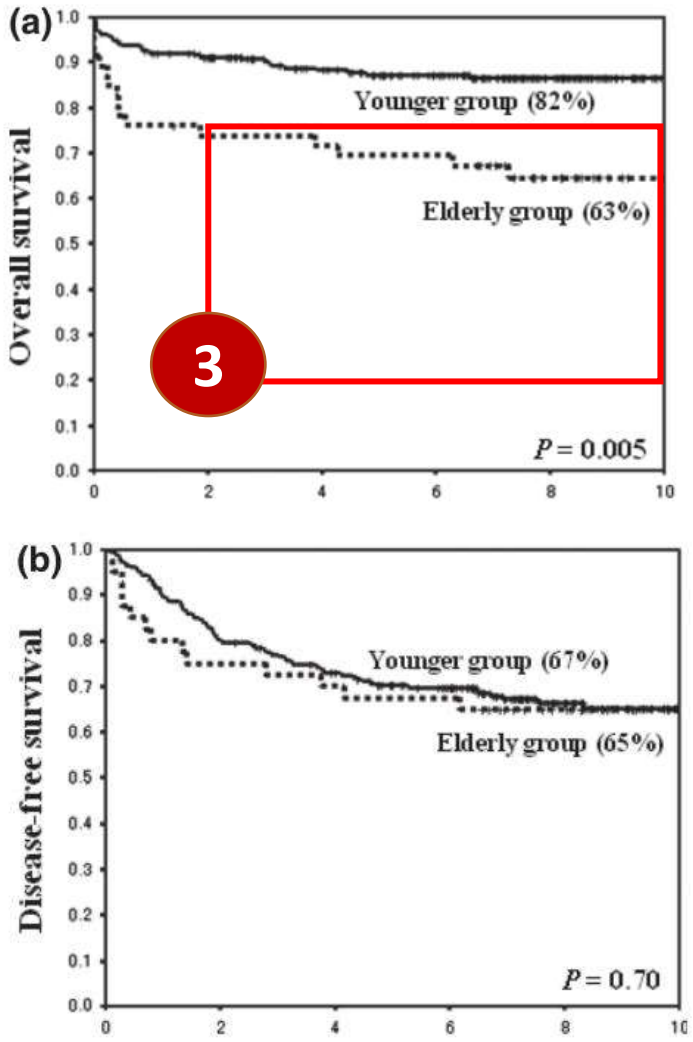


Takaaki Ono et al. , Cancer Science 2012

Different OS but similar Relapse rate w/ CxT

In the elderly, the treatment of APL with conventional ATRA-anthracycline based CT regimens is associated with :

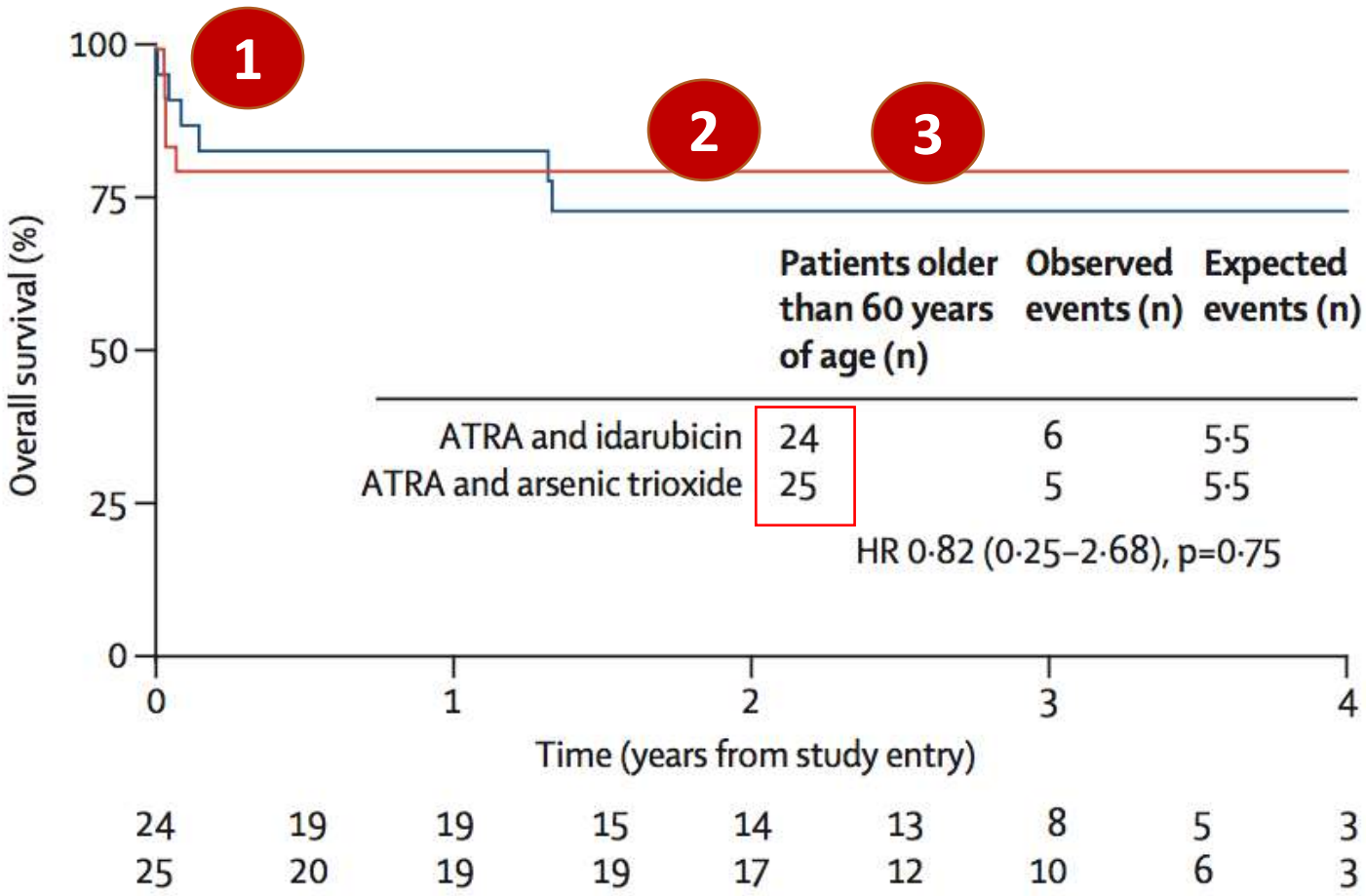
1. A relatively high early death rate
2. Limited number of relapses
3. and a high rate of deaths in CR



Takaaki Ono et al. , Cancer Science 2012

Limited experience with ATO-ATRA

APL older than 60 y



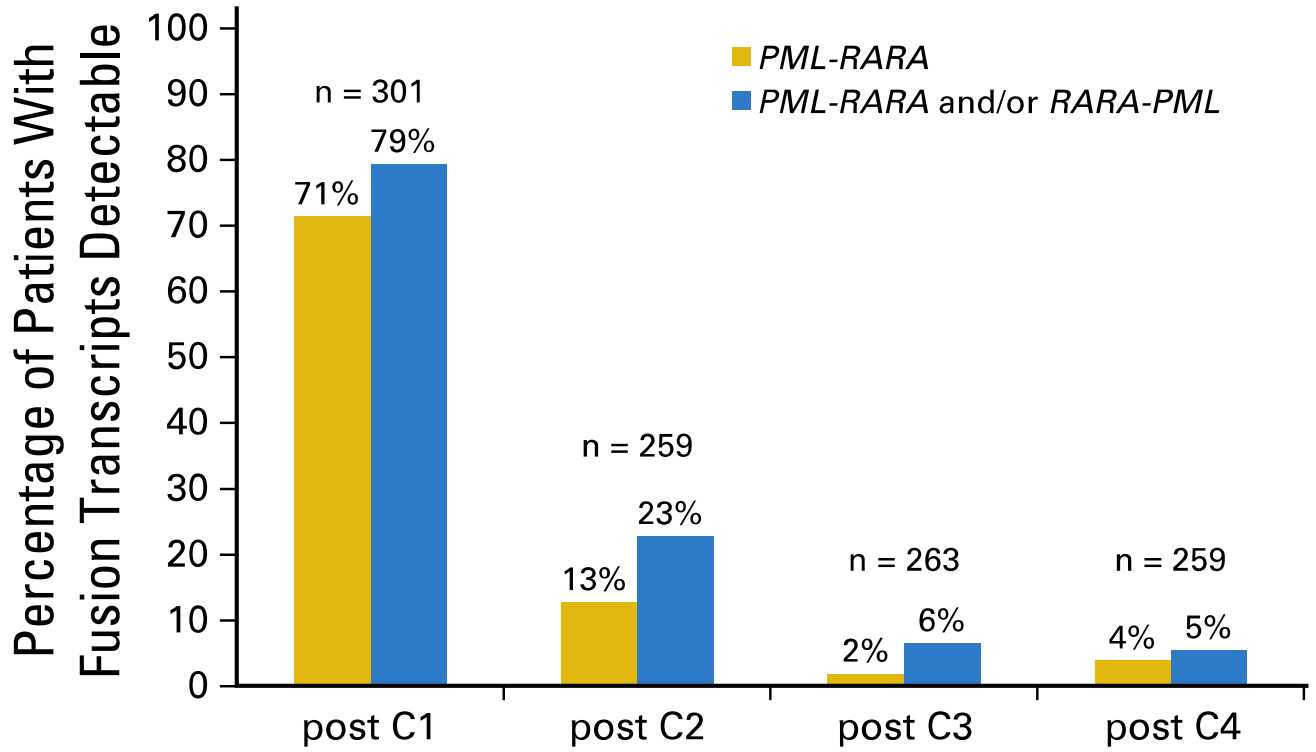
1. Still some early death
2. Limited number of relapses
3. Low rate of deaths in CR

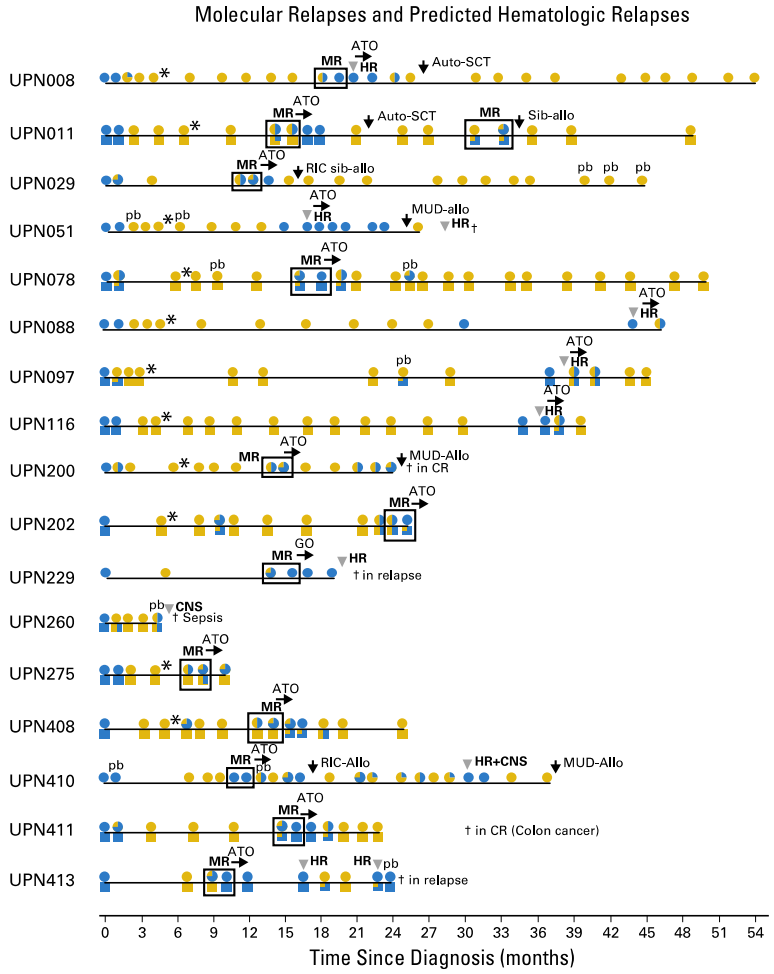
Burnett et al. , Lancet Oncol 2016

The 6th Issue in APL : MRD monitoring

MRD monitoring in standard risk: ATRA-CxT

Sequential RQ-PCR monitoring provides the strongest predictor of RFS in APL and, when coupled with pre-emptive therapy, provides a valid strategy to reduce rates of clinical relapse

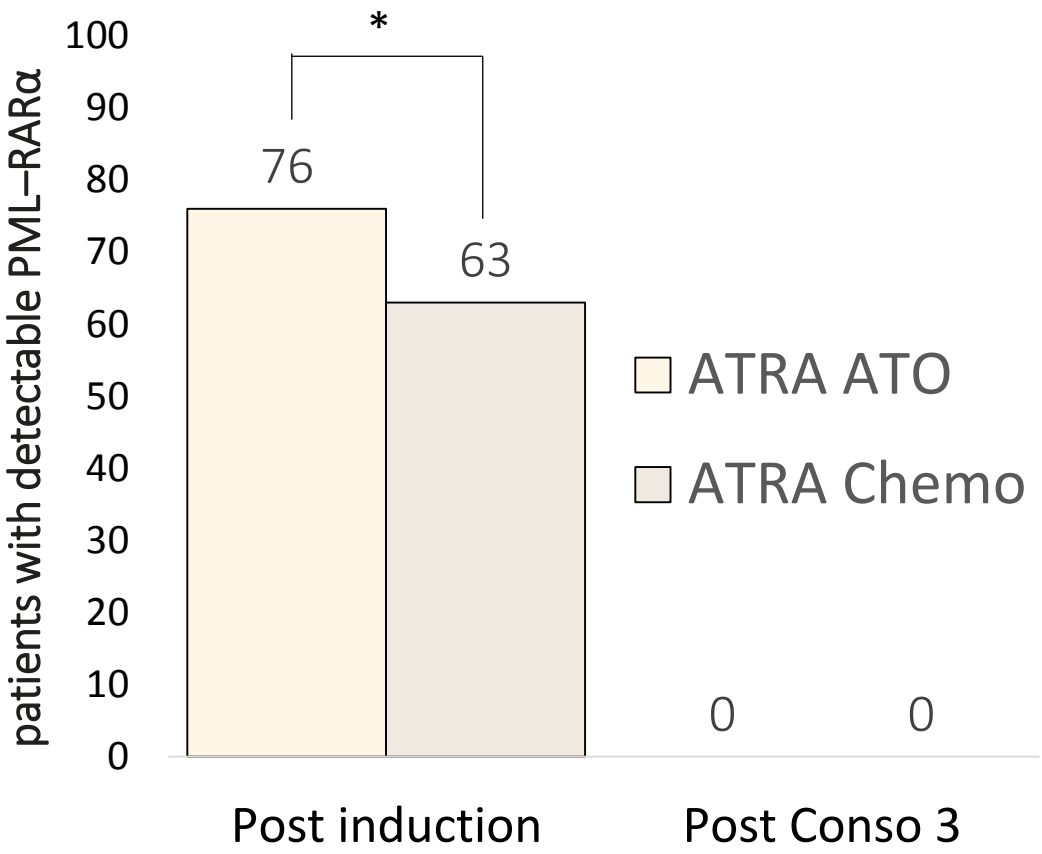




Grimwade et al. J Clin Oncol 2009

MRD evaluation after induction

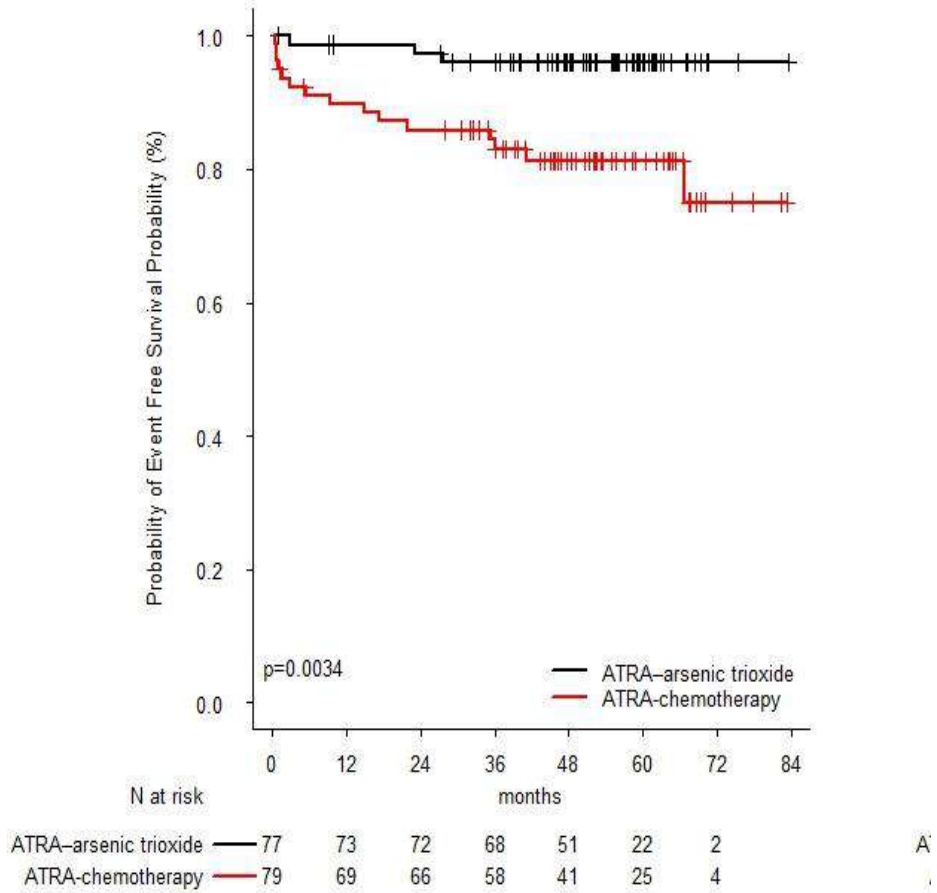
- Proportion of patients with detectable PML–RARα transcript after induction therapy was higher in the ATRA–ATO arm as compared with the ATRA–CHT arm
- The log reduction of PML–RARα transcript between diagnosis and post induction did not affect CIR in either ATRA–CHT or ATRA–ATO arms
- All patients in mCR after Consolidation courses
- No impact of Ftl3-ITD in ATRA-ATO Arm



Cicconi et al. Leukemia (2016) 30, 1987–1992

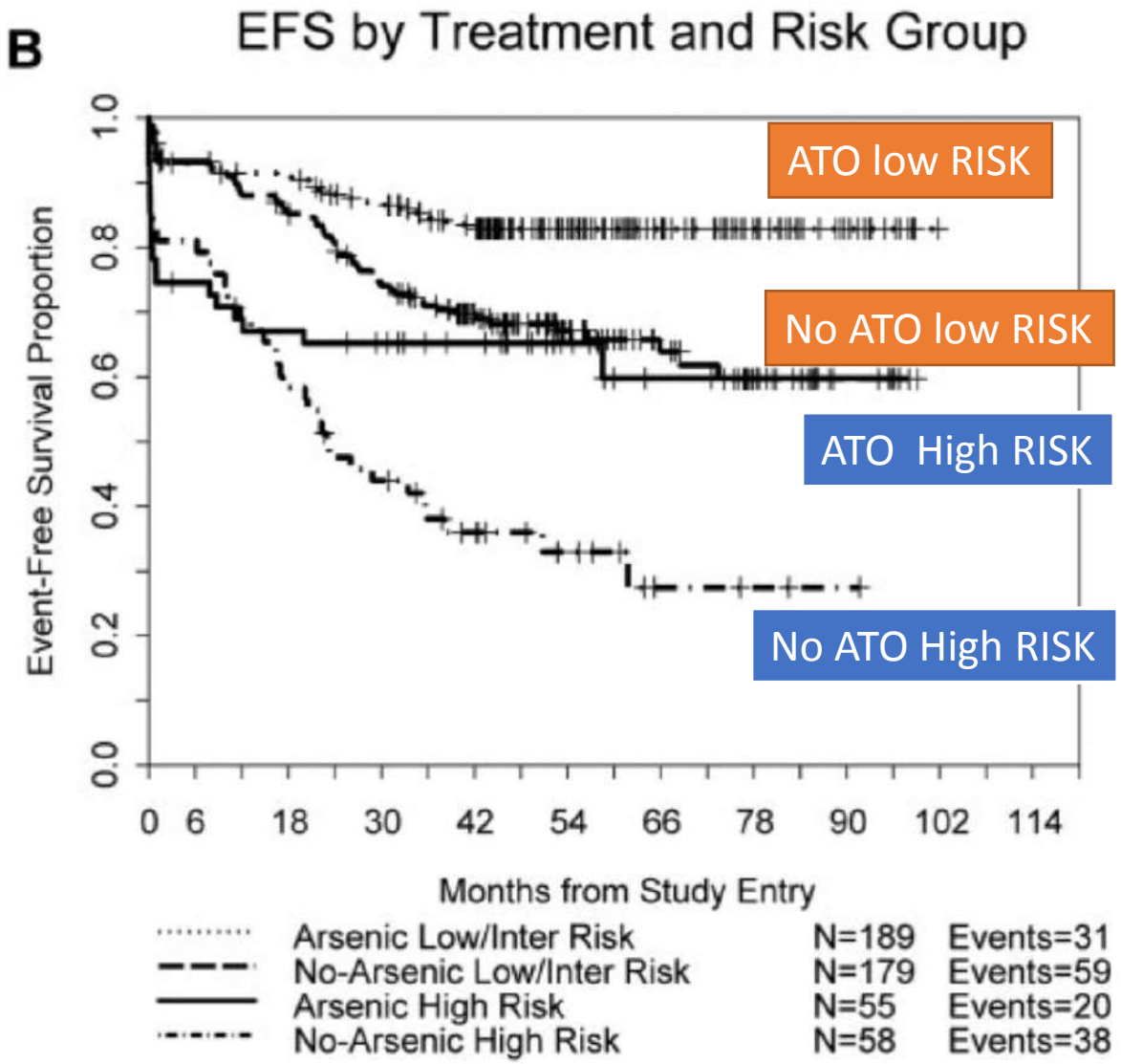
MRD monitoring in standard risk : ATO era

- Given the impact of MRD positivity detected at the end of consolidation (molecular persistence) on decision making, it is still recommended to perform, within 2 weeks of this time, a marrow for MRD determination
- Modern treatments has questioned the benefit of stringent and prolonged monitoring of MRD, at least in non high-risk patients



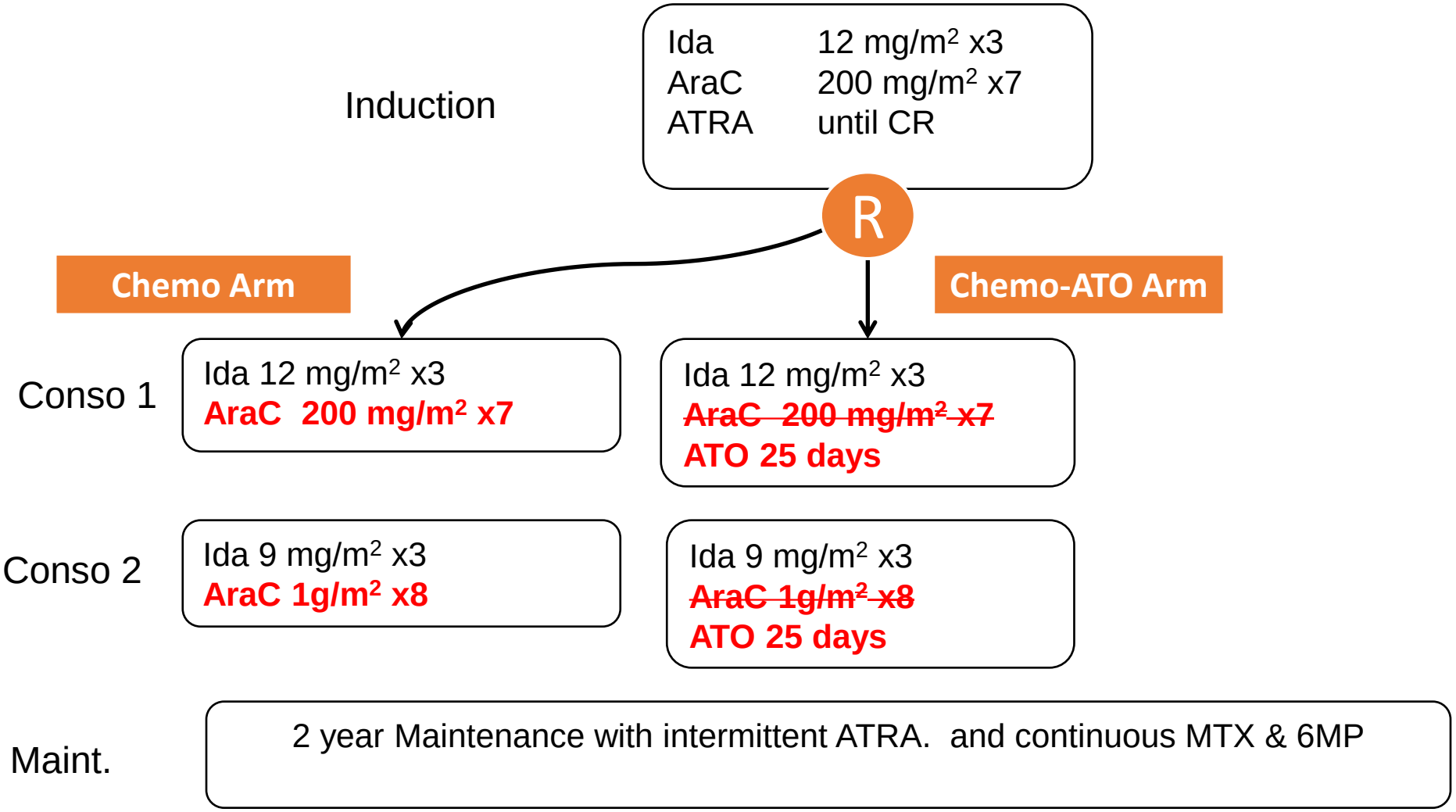
7th Issue
Patients with High risk APL

Addition of ATO to Chemo in pts with APL



Powell et al. Blood 2010

APL2006 Trial : addition of ATO in high WBC APL

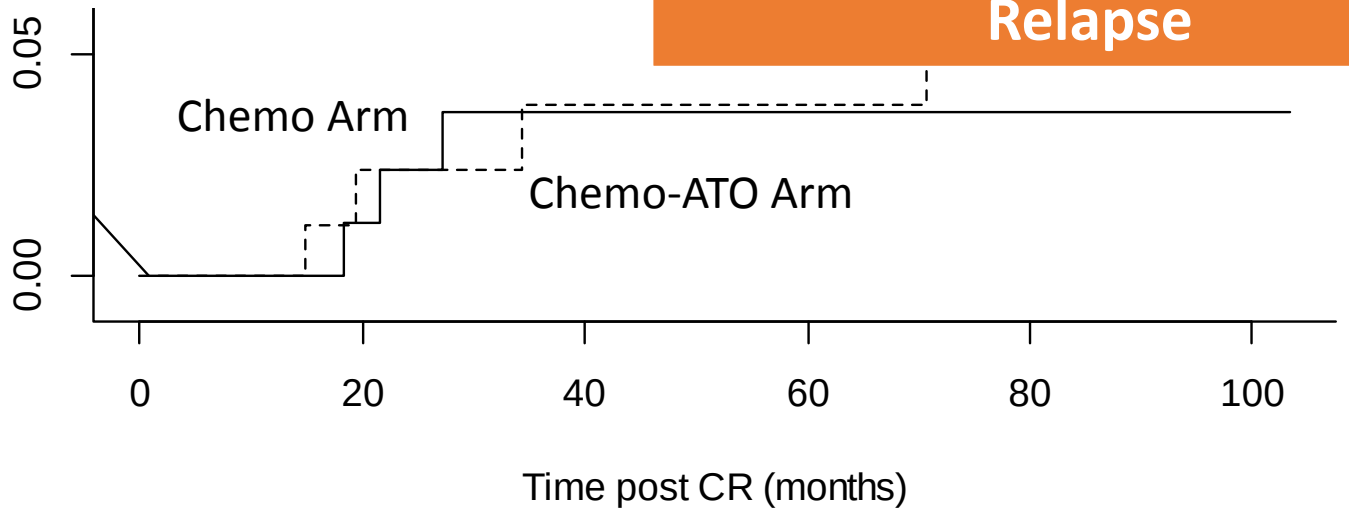


Adès, Haematologica 2018

Cumulative incidence of Relapse

	Chemo Arm	Chemo ATO Arm	P value
Nb of relapses post CR	3	4	
2 year Cumulative incidence relapse	3.7 [1.0; 9.6]	3.9 [1.0; 10.0]	0.69

No difference in terms of Relapse

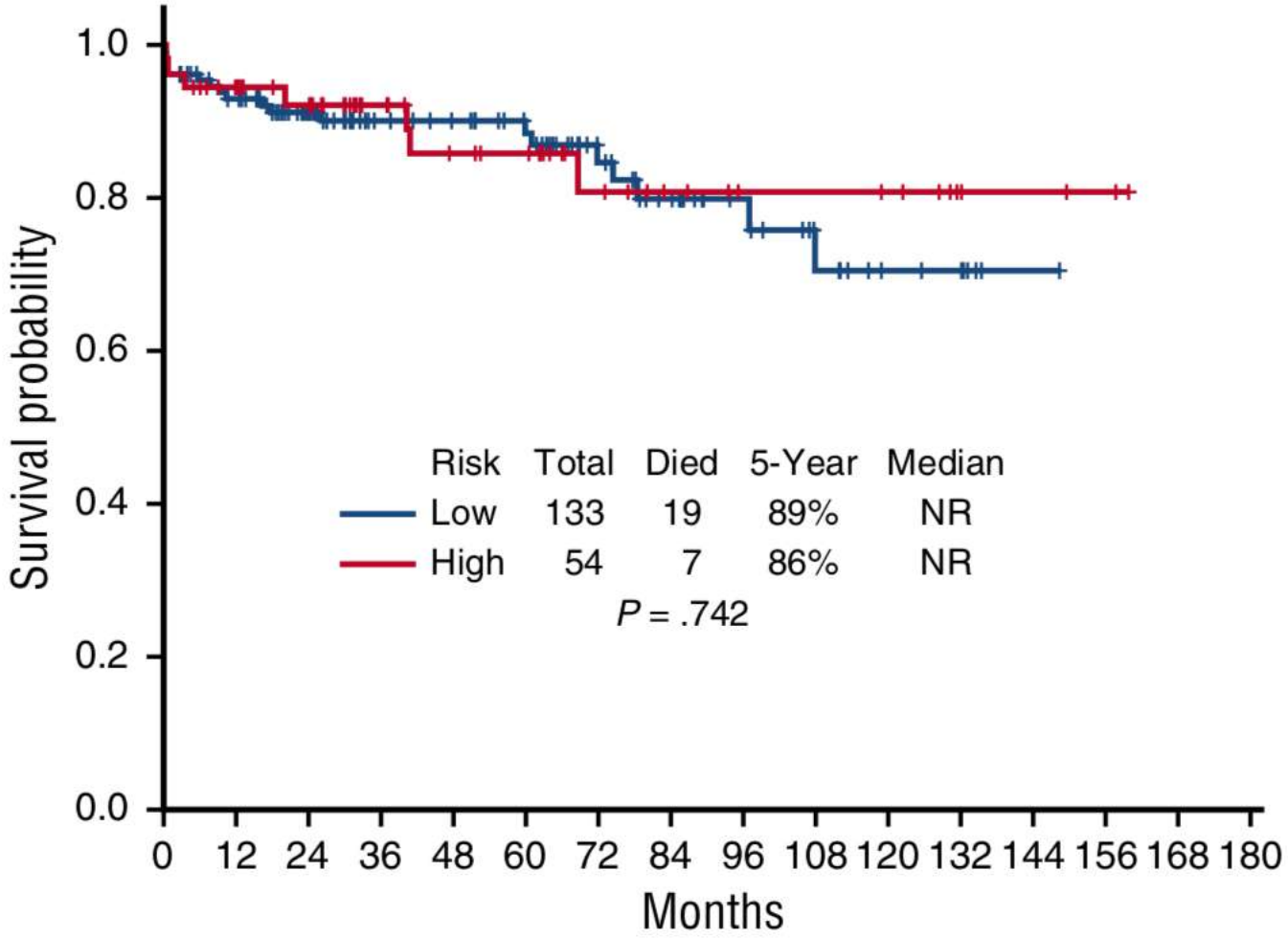


Adès, Haematologica 2018

The MDA experience

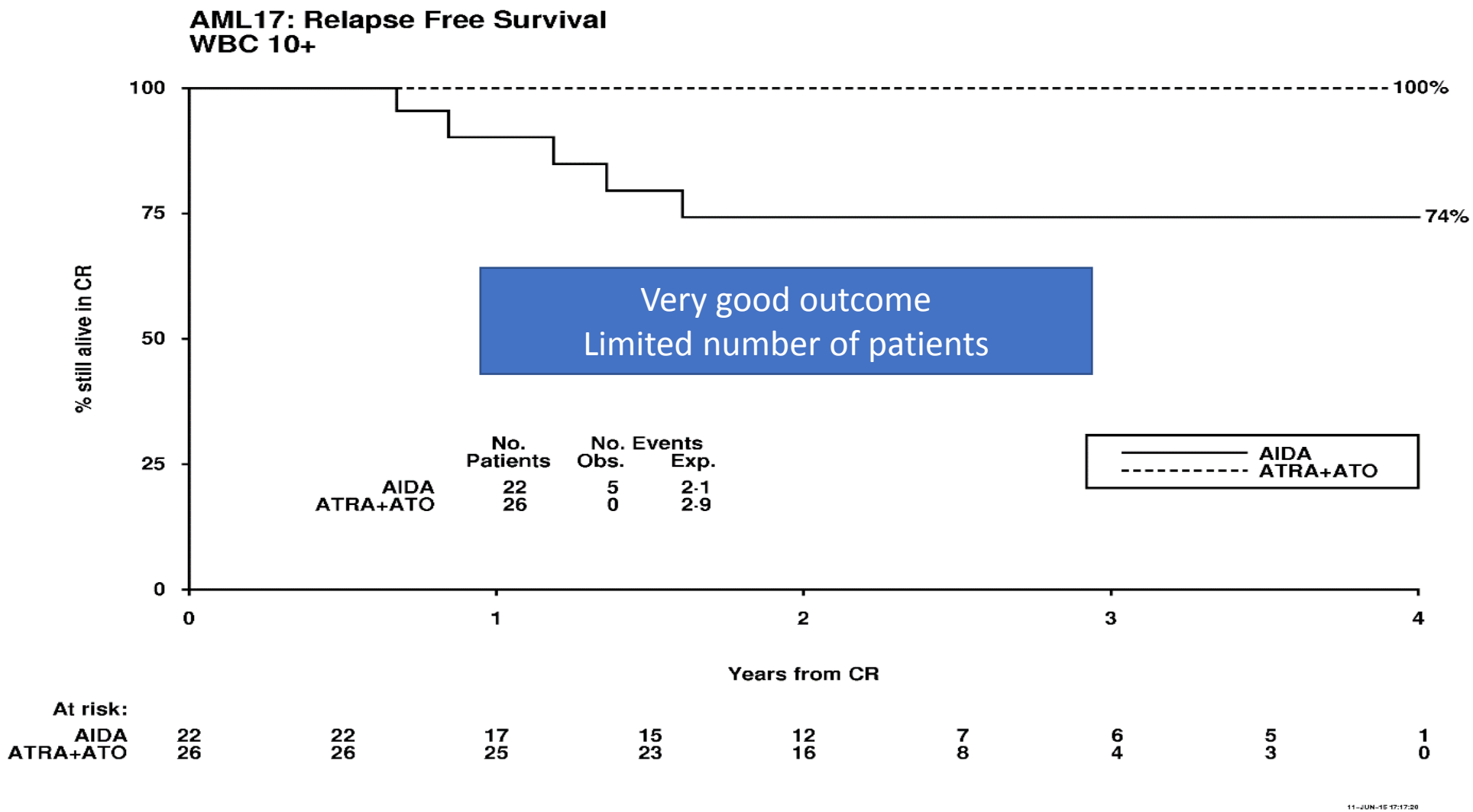
- ATO-ATRA based therapy for 239 patients with APL
- Addition of
  - 1 dose of GO 9 mg/m2
  - or Idarubicin (IDA) 12 mg/m2
  - on day 1
  - In patients with WBC > 10 G/L
  - n=54

Similar outcome
Not Randomized



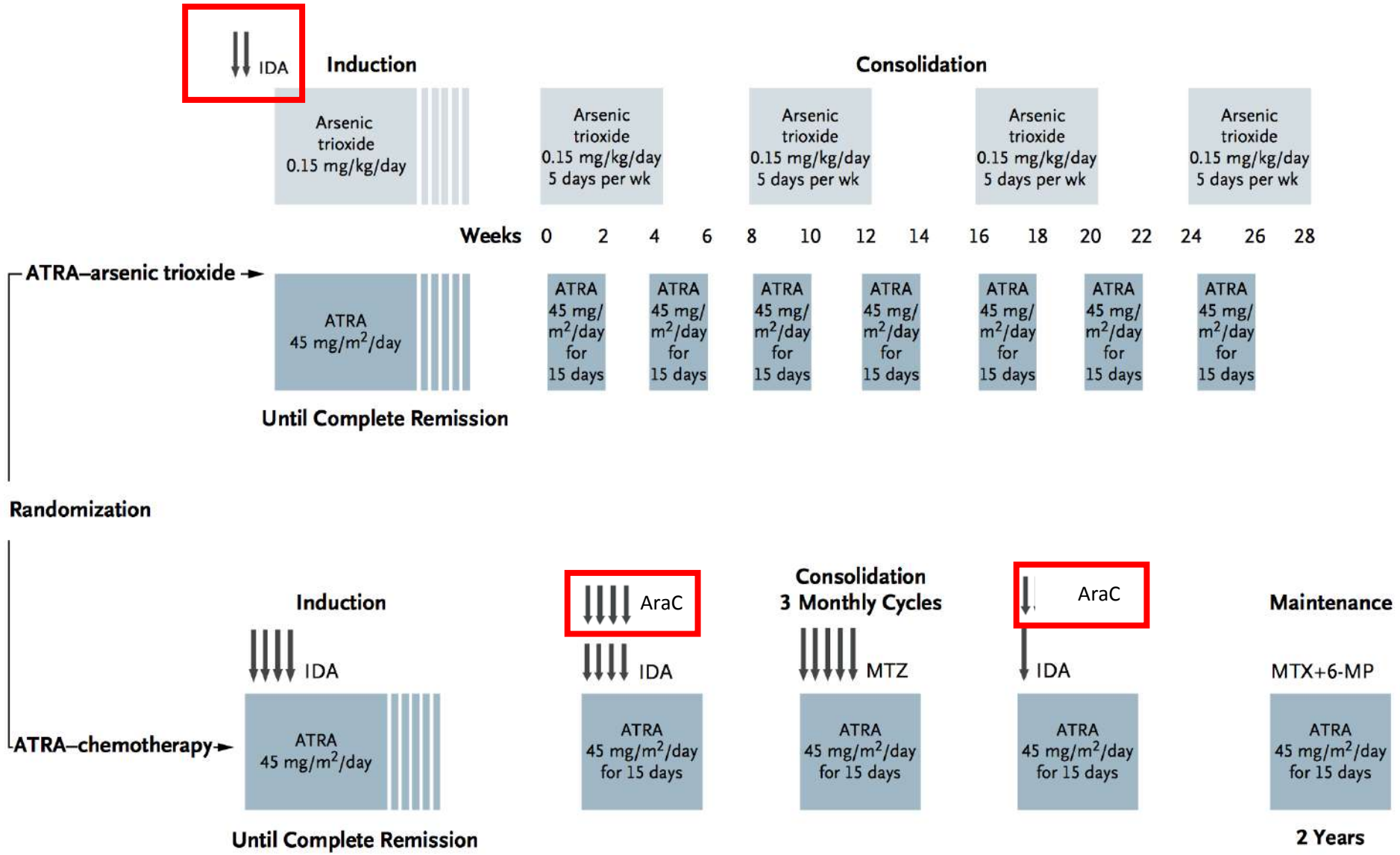
Abaza Y et al. Blood. 2017 Mar 9;129(10):1275-1283

MRC AML17 Study: ATRA + ATO



Burnett et al. Lancet Oncology 2015

The Ongoing Apollo-Trial for HR APL



Future Direction

- Novel Oral Arsenic Trioxide Formulation (ORH-2014) in Combination with ATRA, in Newly Diagnosed Patients with Low Risk Acute Promyelocytic Leukemia
- Chemo (almost) Free therapy in HR APL

- Elderly/frailed patients : Still an issue

- Early death rate : How to improve ? Education !

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