fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

8th SYMPOSIUM ON

Acute Promyelocytic Leukemia

Dedicated to ***Prof. Francesco Lo Coco***

Featuring an AML meeting coordinated by ***EHA*** *SWG AML*

10-11 Aprile 2024

ROMA • Hotel NH Collection Roma Centro

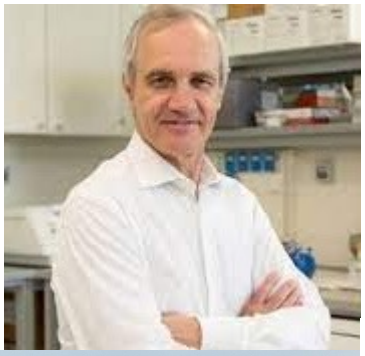
Richard Dillon, Guy's Hospital / King's College London

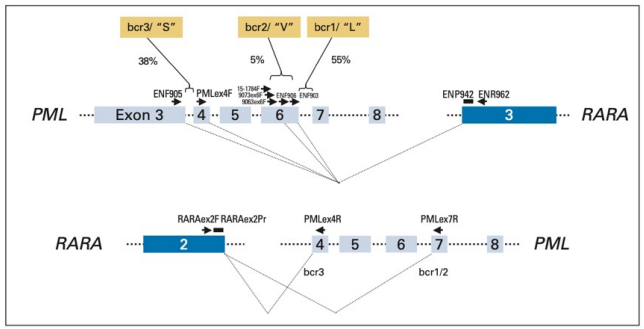
Is Disease Monitoring Still Necessary ?

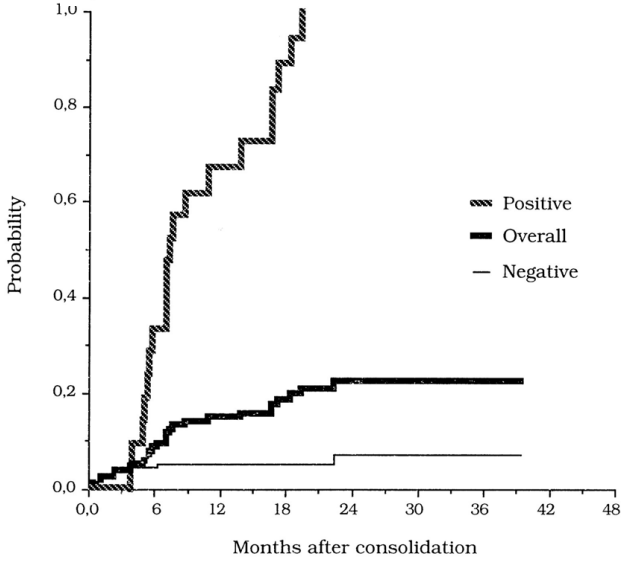
Disclosures of Richard Dillon

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	X		X			X	
Amgen	X						
Astellas			X			X	
Jazz	X		X				
Pfizer	X						
Servier			X				

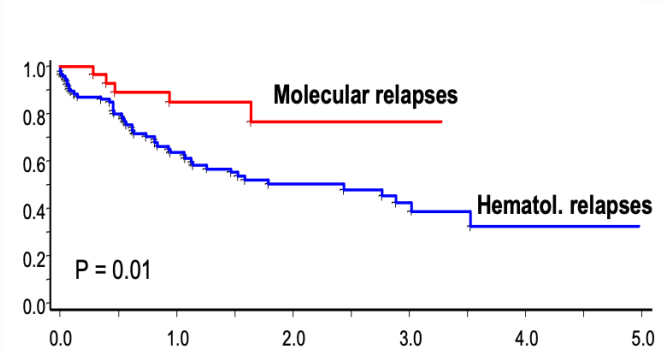
The pioneers of molecularly guided therapy in APL



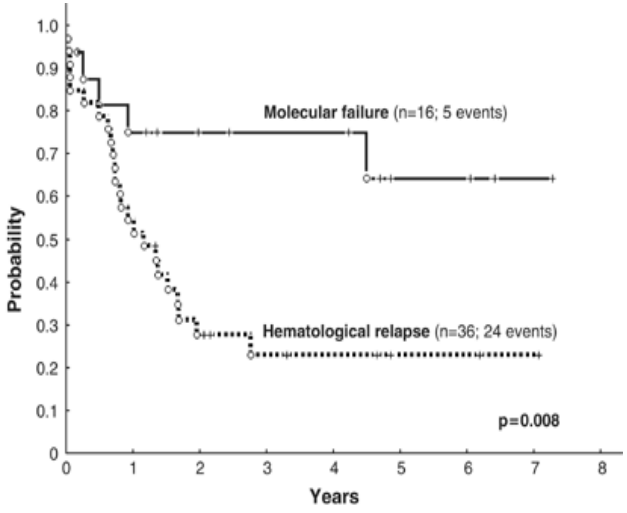




Diviero, D. et al, Blood, 1998

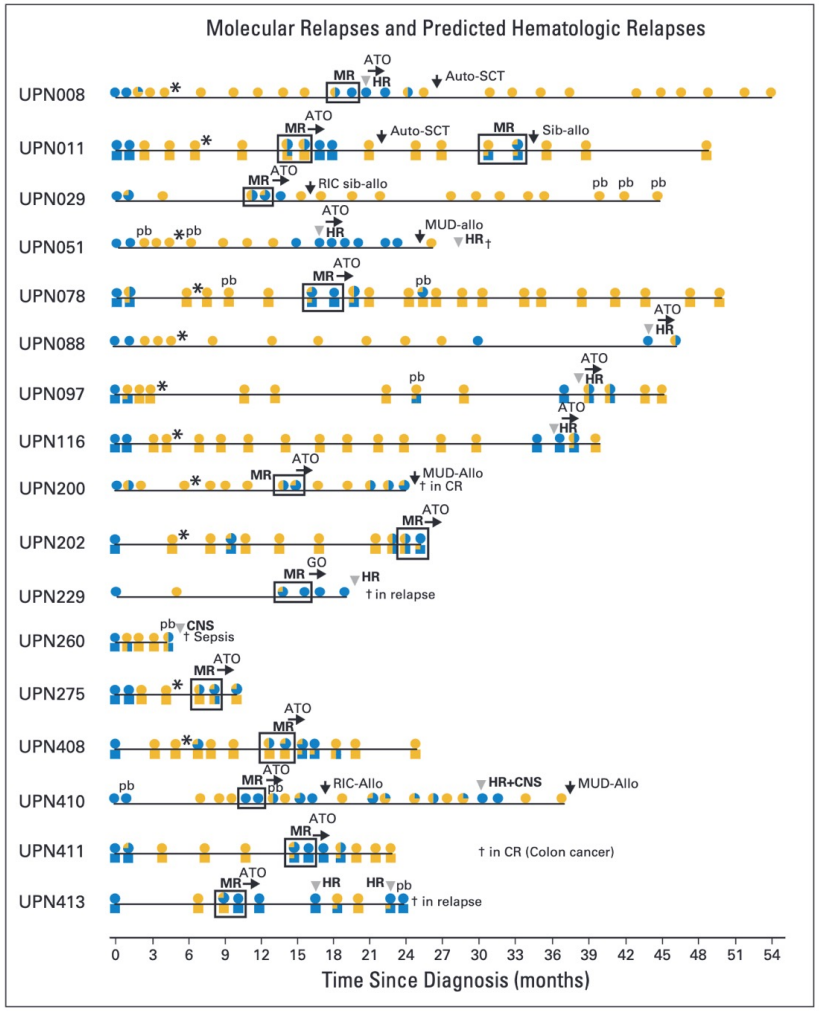


Lo Coco F. et al, Semin Haematol, 2002



Esteve, J. et al, Leukaemia, 2007

The pioneers of molecularly guided therapy in APL



1) Almost eliminated frank relapse

2) Made frontline ATO trials possible

3) Demonstrated the effectiveness of using targeted therapies at MRD relapse

> a therapeutic revolution

> now used in other types of AML

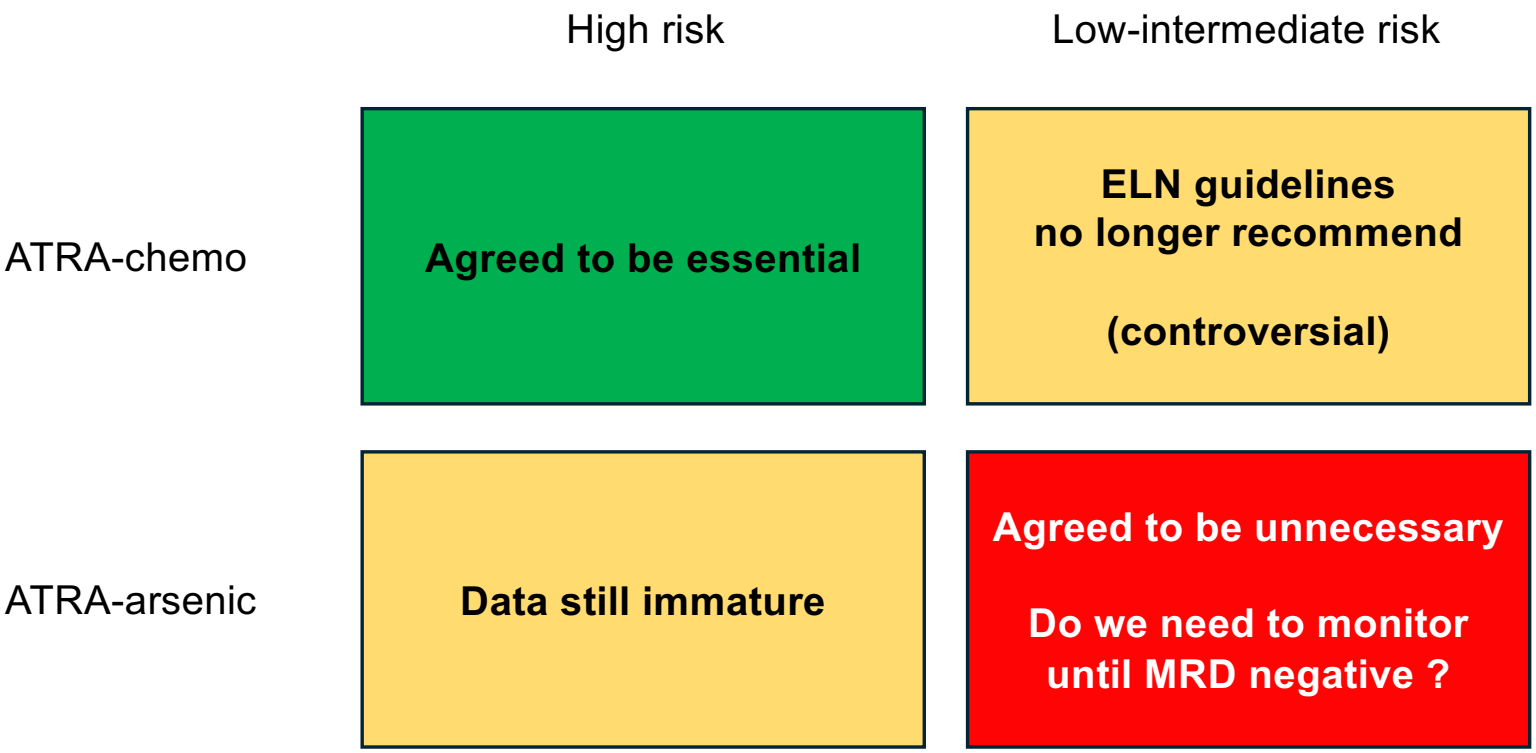
Grimwade, D. et al, JCO, 2009

Current ELN Guidelines

2.12. Because early treatment intervention in patients with evidence of MRD affords a better outcome than treatment in hematologic relapse, MRD monitoring of BM every 3 mo should be offered to high-risk patients (WBC count >10 × 10^9/L) for up to 3 y after completion of consolidation therapy; given the very low probability of relapse for non–high-risk patients (WBC count ≤10 × 10^9/L), prolonged MRD monitoring could be avoided in this setting or carried out using PB	IIb–B	Slightly modified

Because early treatment intervention in patients with evidence of MRD affords a better outcome than treatment in full-blown relapse, MRD monitoring of BM has been used in routine clinical practice for all patients. However, the striking outcome improvements obtained with modern treatments call into question the benefit of stringent and prolonged monitoring of MRD, at least in non–high-risk patients (WBC count ≤10 × 10^9/L) where the risk of relapse is extremely low. Given uncertain cost-effectiveness, postconsolidation MRD monitoring can be avoided in this setting and performed only in high-risk patients (WBC count >10 × 10^9/L) in routine clinical practice. This is in contrast to recently reported recommendations from the ELN MRD Working Party.[42] Although the NCRI group suggested that longitudinal monitoring postconsolidation at the 3-month interval could be carried out in patients receiving ATRA and chemotherapy, with the intent to administer ATO-based salvage early at the time of molecular relapse,[43] we reiterate that MRD monitoring can be avoided in non–high-risk patients who achieve CR_{MRD-} status after consolidation, not only in patients treated with ATRA plus ATO, but also in those with ATRA plus chemotherapy. We also do not recommend MRD evaluation after induction outside of clinical trials, and emphasize again that MRD evaluation postinduction should definitely not influence therapeutic decisions.

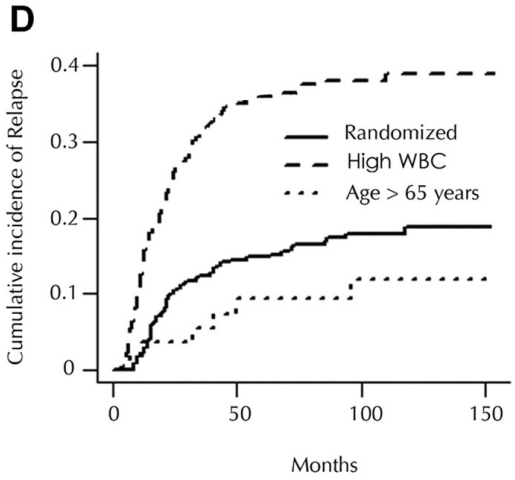
Is Disease Monitoring Still Necessary ?



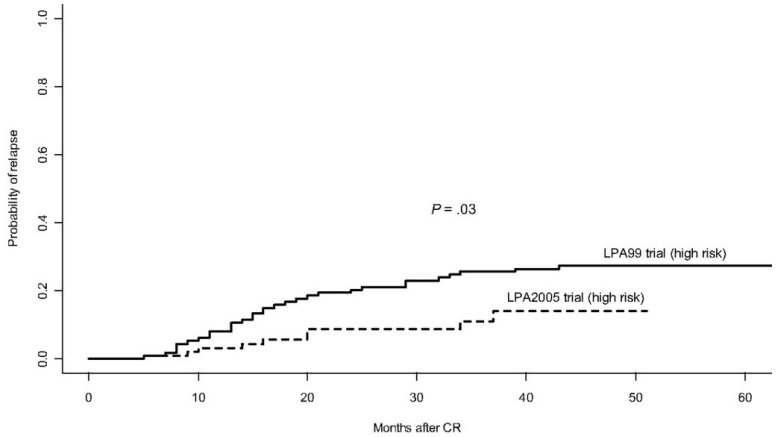
Is Disease Monitoring Still Necessary ?

	High risk	Low-intermediate risk
ATRA-chemo	**Agreed to be essential**	
ATRA-arsenic		

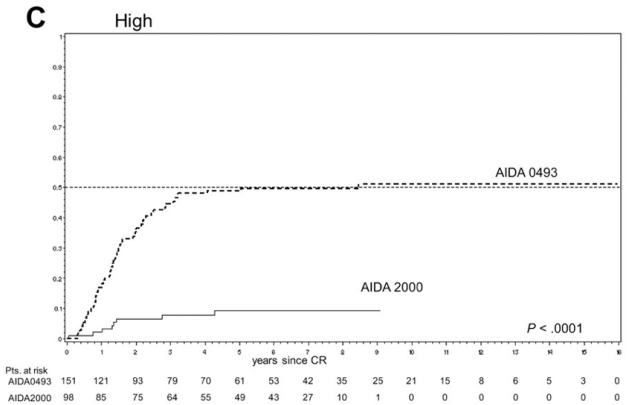
Relapse in high-risk patients receiving chemotherapy



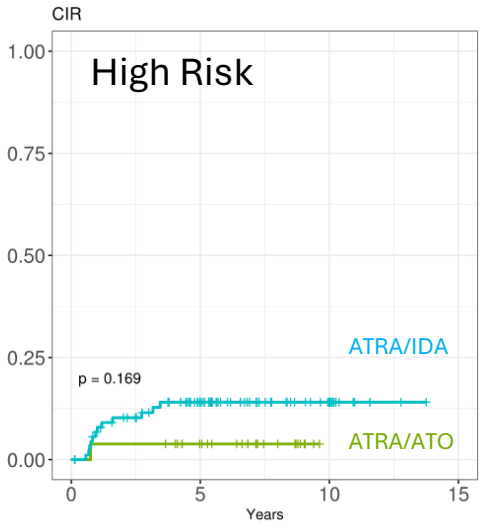
Adés L. et al, Blood 2010



Sanz M. et al, Blood 2010

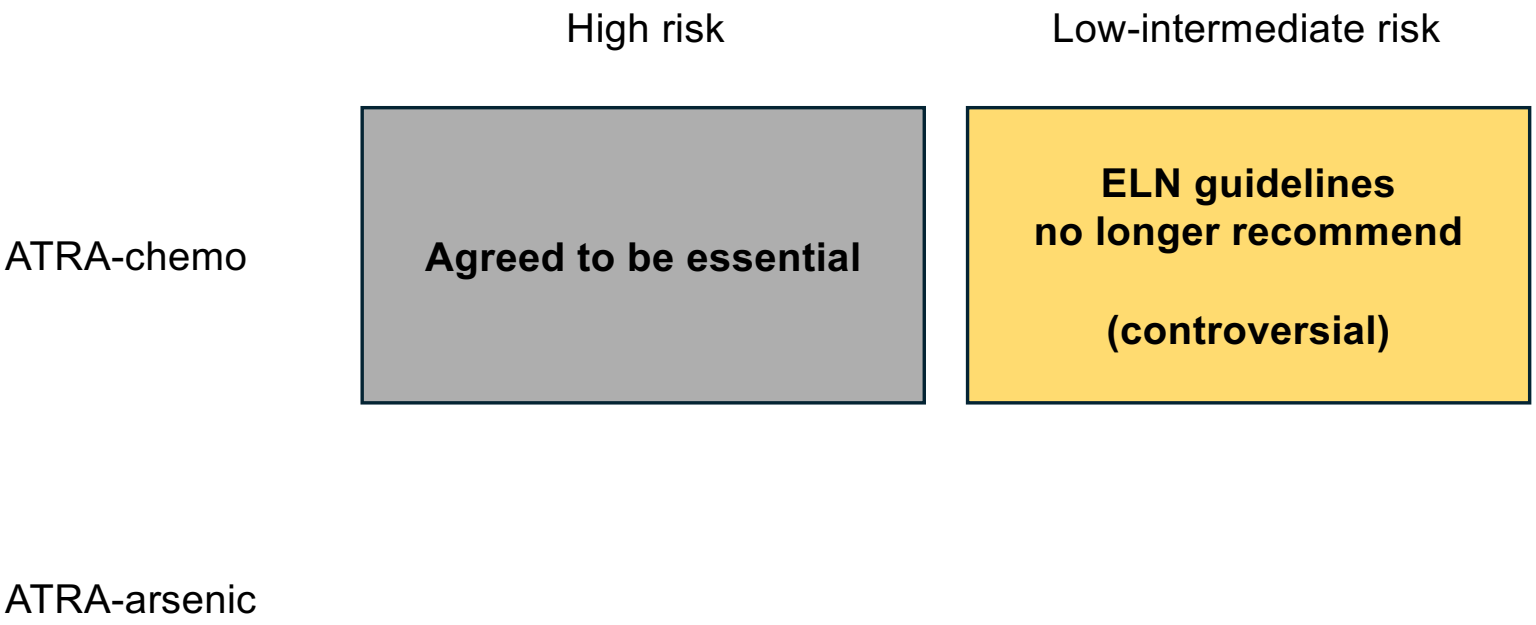


Lo Coco F. et al, Blood 2010

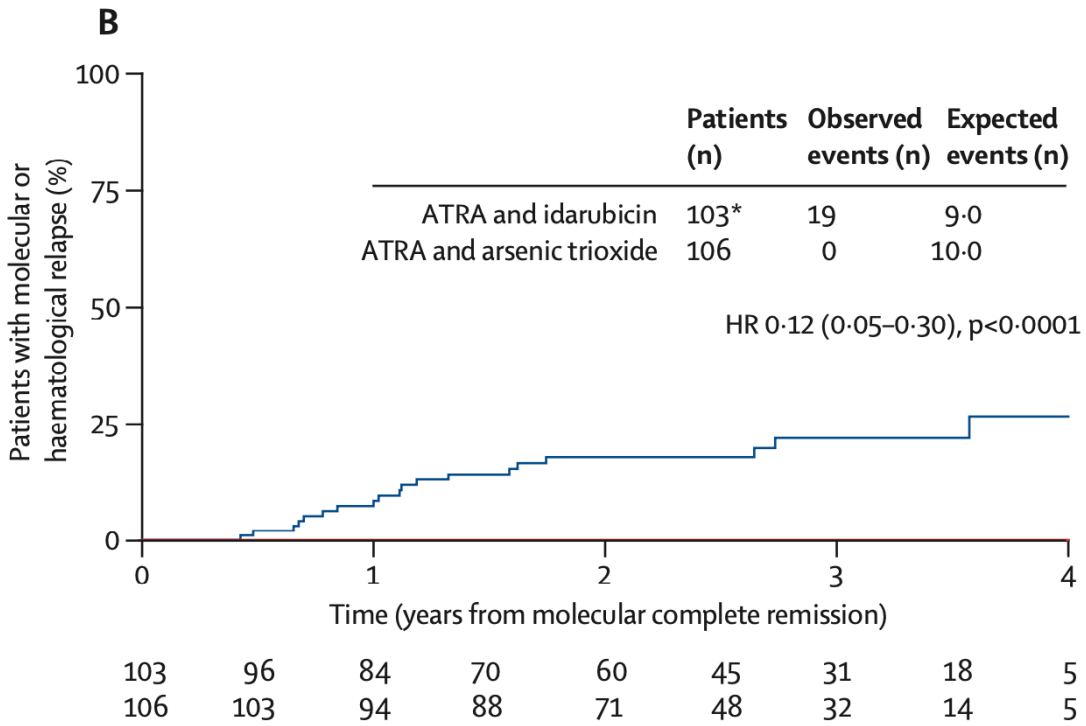


Guarnera L. et al EHA 2023

Is Disease Monitoring Still Necessary ?



Non-high risk patients have a non-trivial relapse risk



Molecular or haematological relapse from MRD- after AIDA

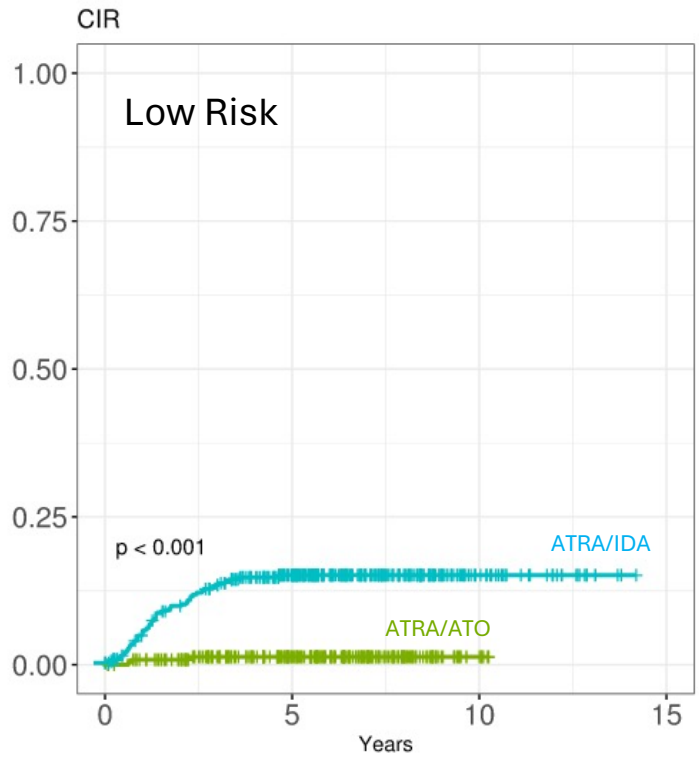
Overall = 18%

HR = 36% (8/22)

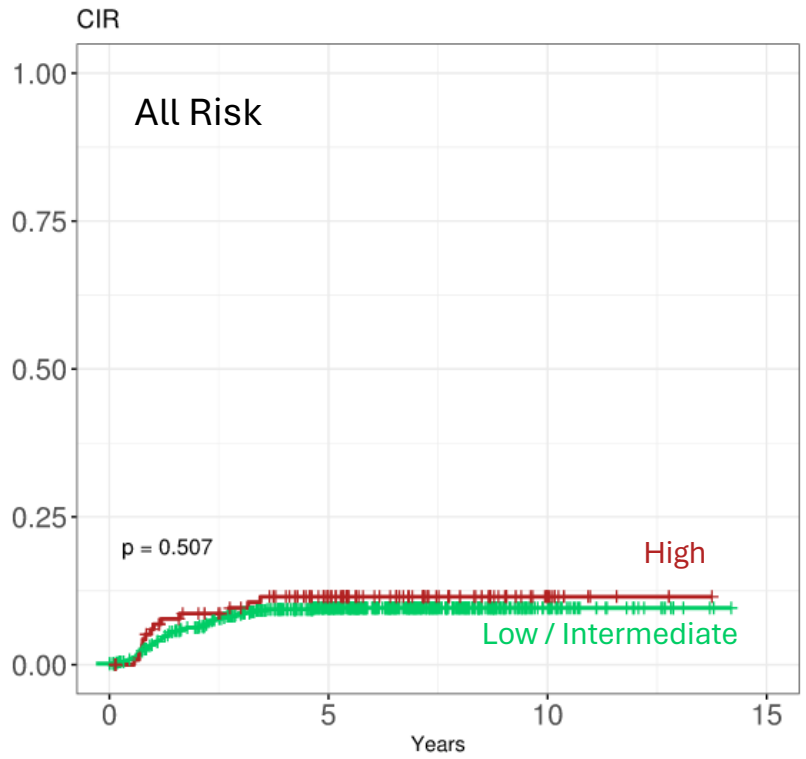
SR = 14% (11/79)

Burnett, A.K. et al, Lancet Oncol 2015

Non-high risk patients have a non-trivial relapse risk



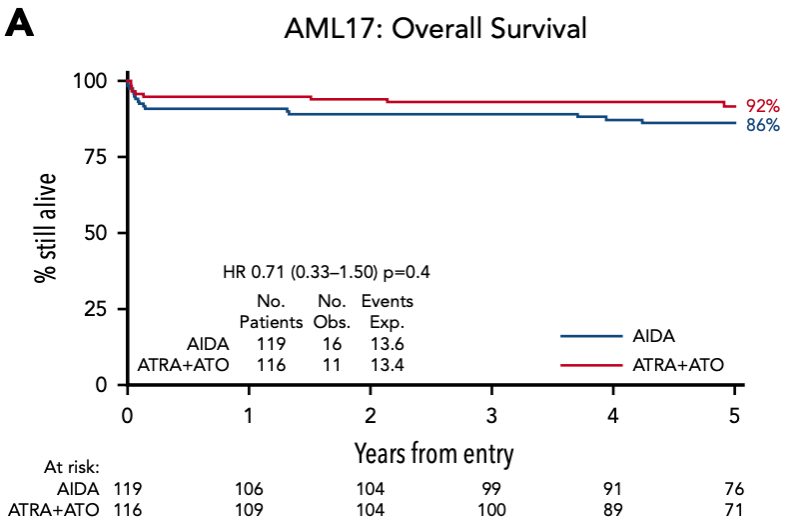
Arsenic_trioxide_and_ATRA	239	145	6	0
ATRA_and_Idarubicin	333	215	29	0

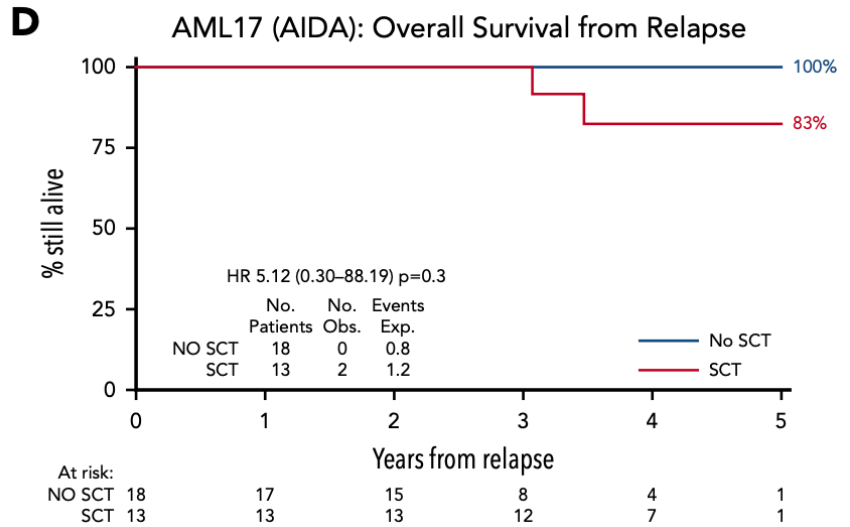


Low_Intermediate	576	361	35	0
High	119	73	12	0

Guarnera L. et al ASH/EHA 2023

Survival after MRD relapse is excellent

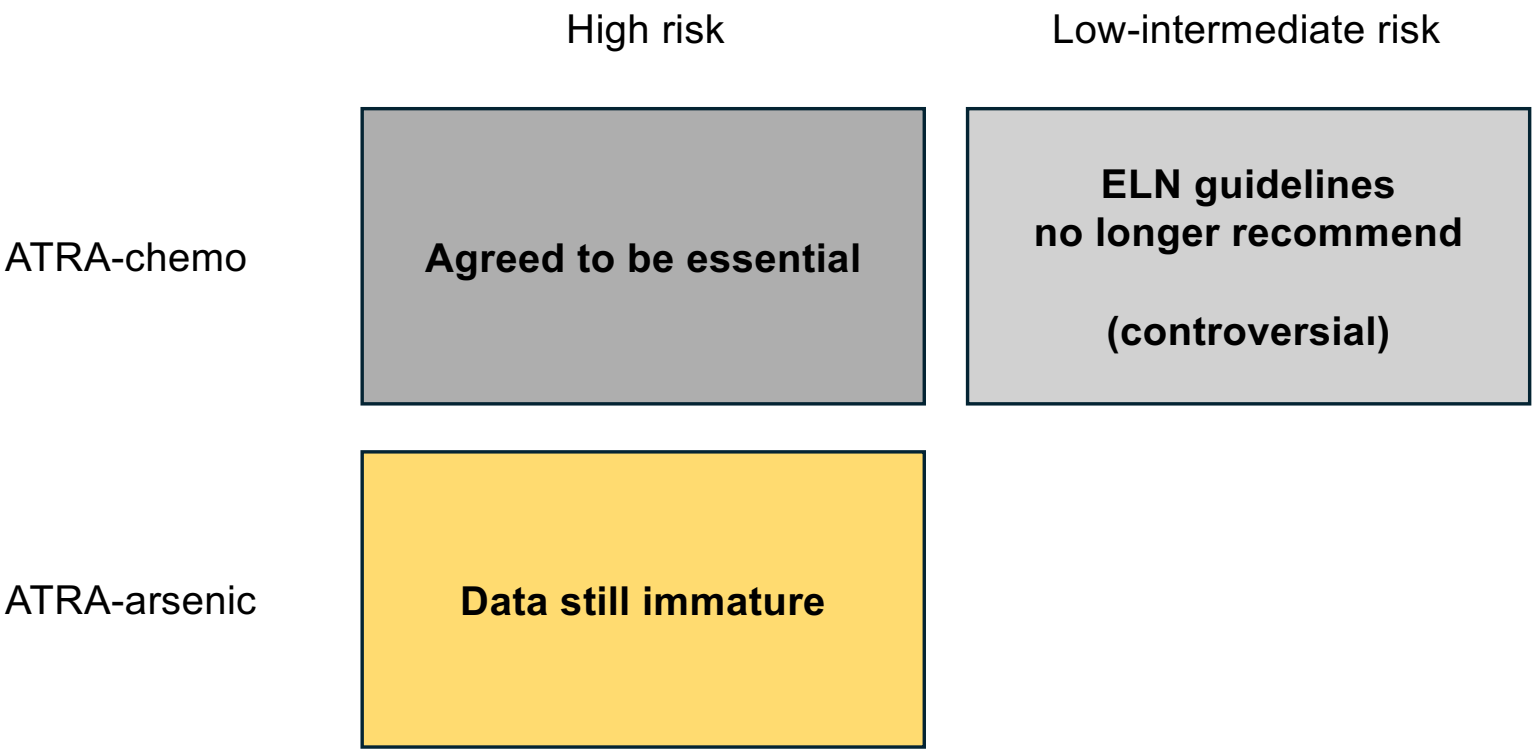




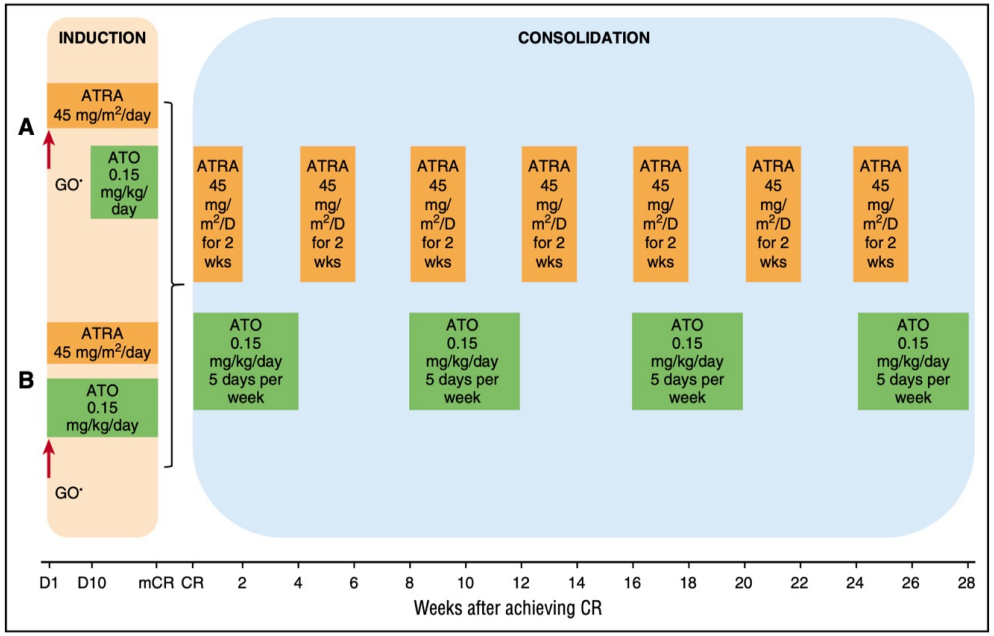
Russell, N.H. et al, Blood 2018

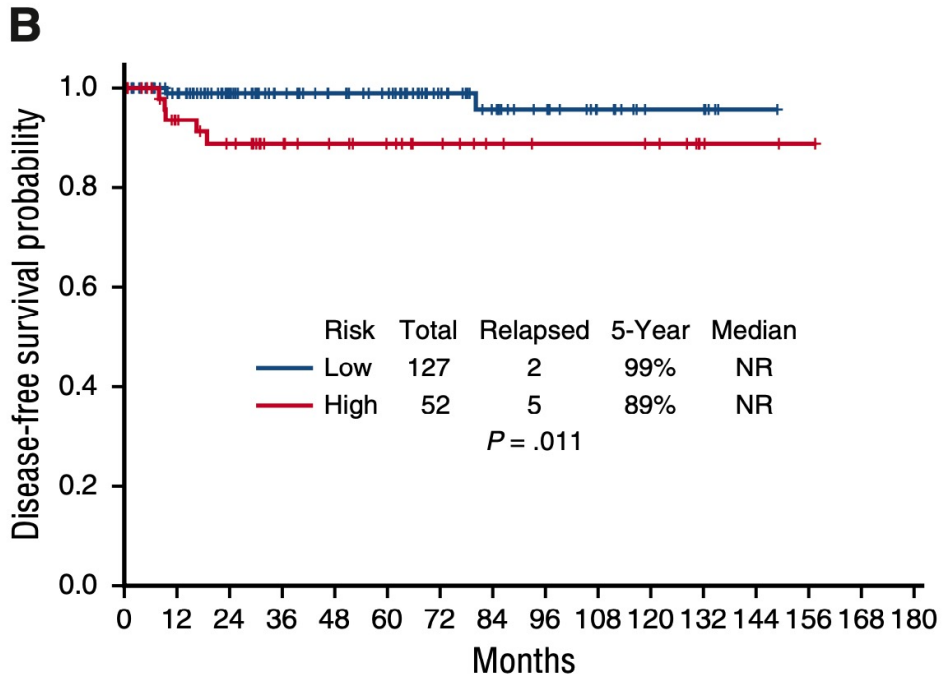
32 molecular / haematological relapses in AIDA
(17/32 MRD relapse = 53%)
1 patient died before treatment
31 became MRD negative with ATO-ATRA salvage

Is Disease Monitoring Still Necessary ?



MD Anderson ATO-ATRA series





HR 5/52 = 9.6%
LR 2/127 = 1.6%

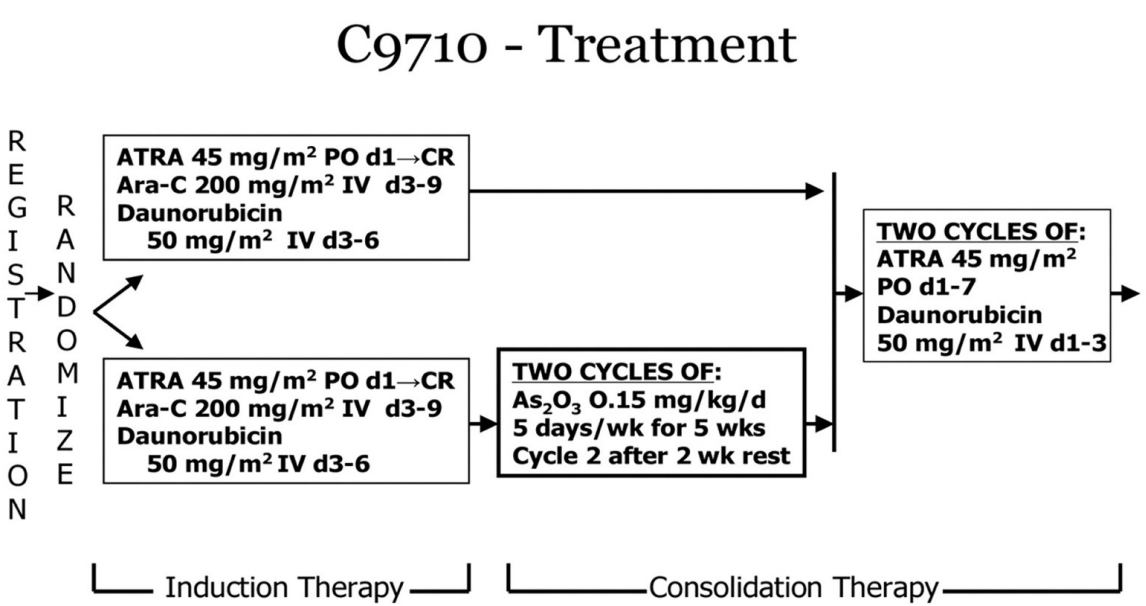
> All had achieved MRD-

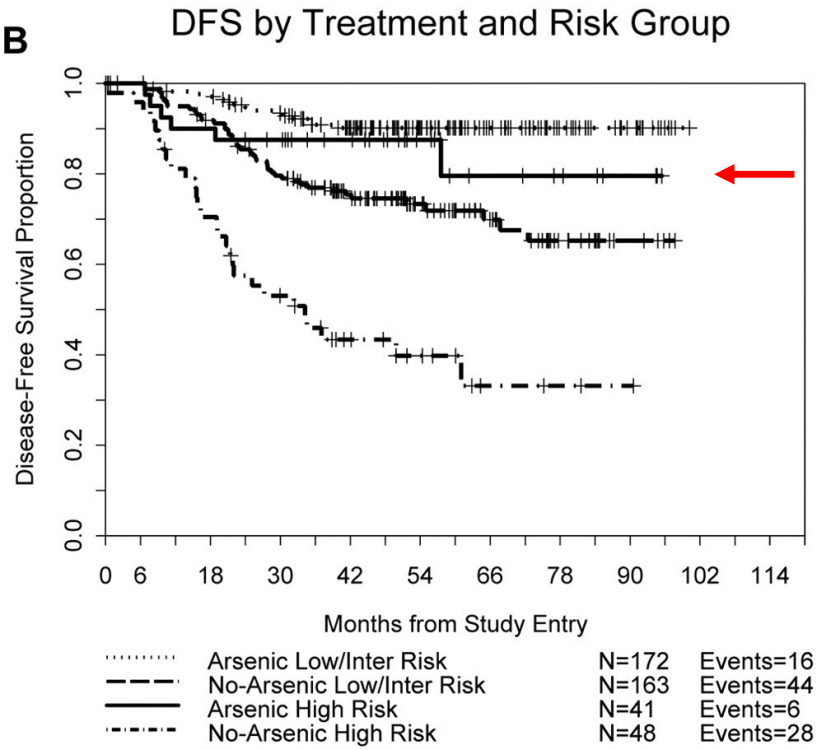
Table 2. Characteristics of relapsed acute promyelocytic leukemia patients

Patient no.	Risk category	Age (y)	Sex	Cytogenetics	FLT3 status	Time to first relapse (mo)	Type of first relapse
1	High	52	F	Diploid	ND	9.2	Molecular*
2	Low	42	M	46XY t(15;17) [20]	ND	79.5	Hematological/molecular
3	High	38	M	46XY t(15;17) [19]	ND	9	Hematological/molecular
4	High	79	M	46XY t(15;17), der (17) i (17) (q10) [18]; 46 XY [2]	Neg	12.4	Molecular*
5	High	18	M	46XY t(15;17) [19]	ND	9.4	Molecular*
6	Low	19	F	Diploid	Neg	9.5	Hematological
7	High	35	M	46XY t(15;17) [16]; 46 idem, del 7 [1]; 46 XY [3]	Neg	7.9	Hematological

Abaza Y. et al, Blood 2017

US Intergroup C9710 Study

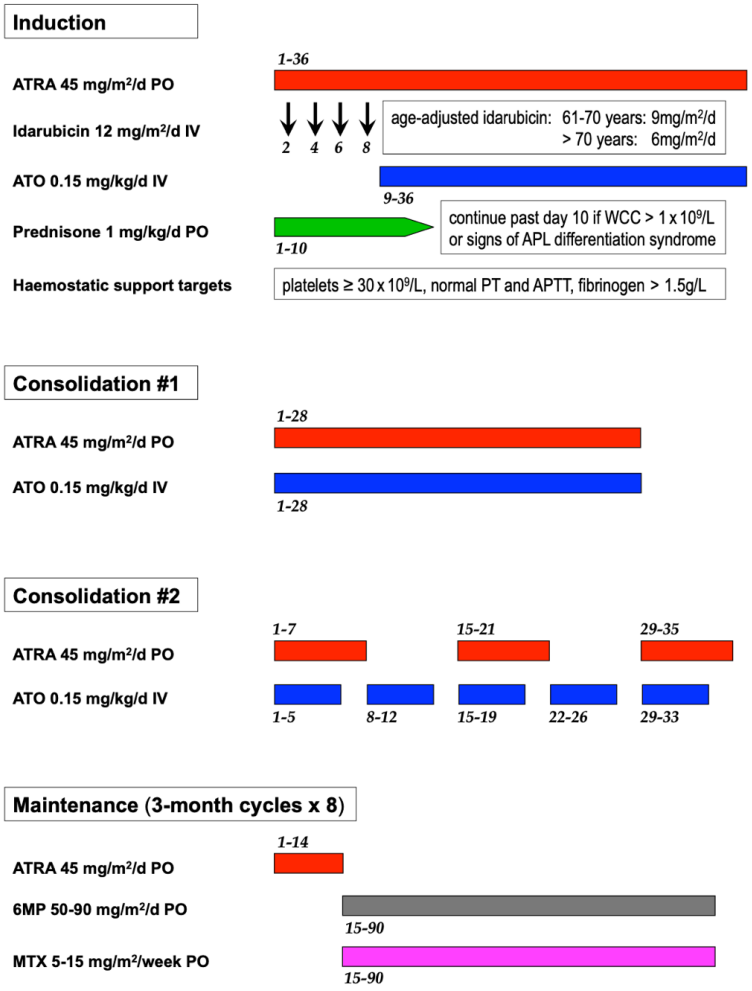


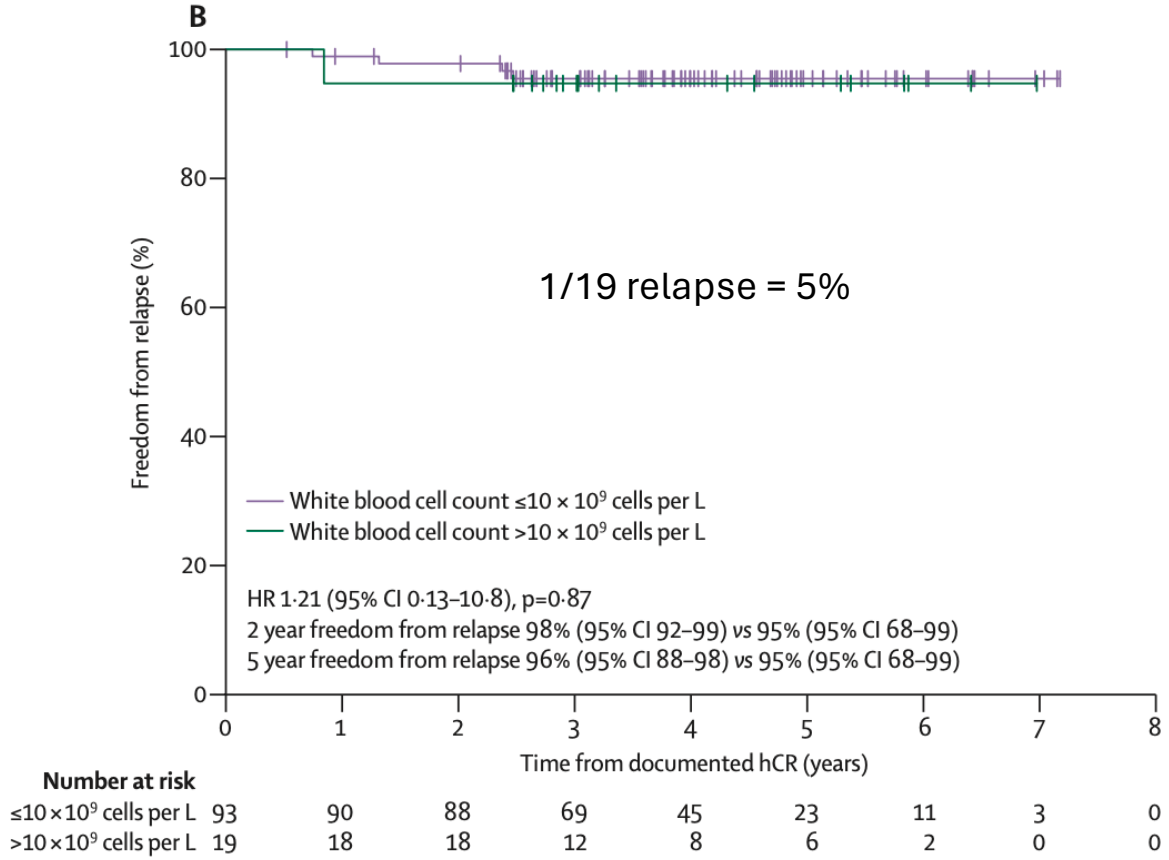


Powell B.L. et al, Blood 2010

Relapse or death after CR in high risk patients
ATO+ATRA+Chemo 10% at 2y, 14% overall

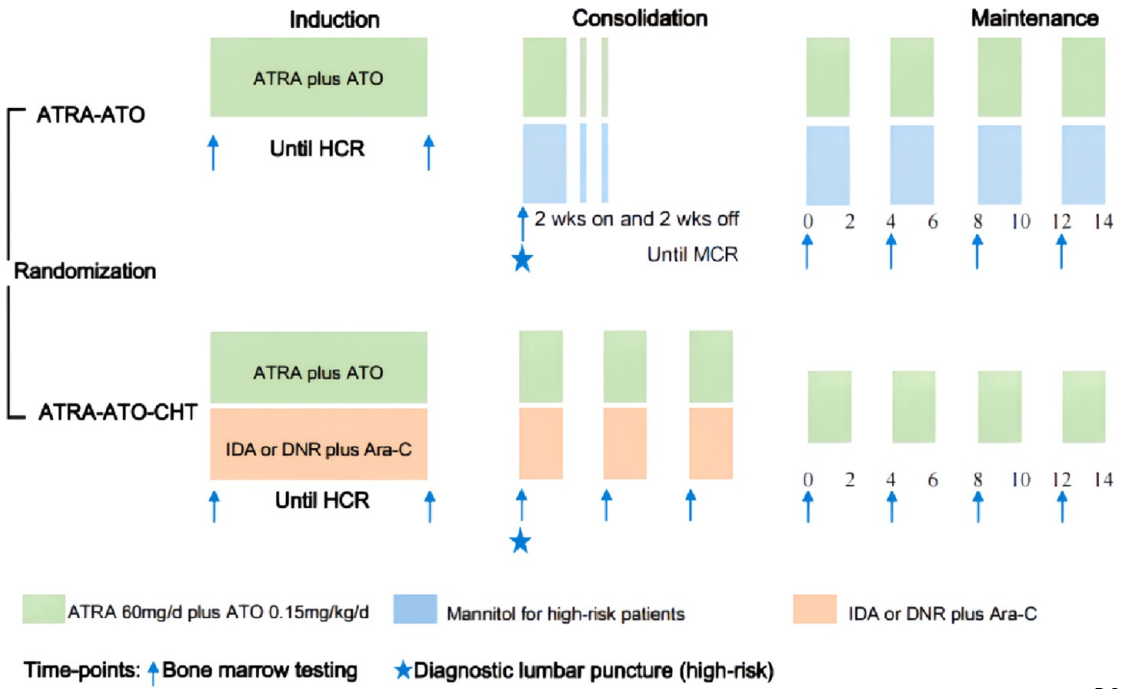
ALLG APML4 Study

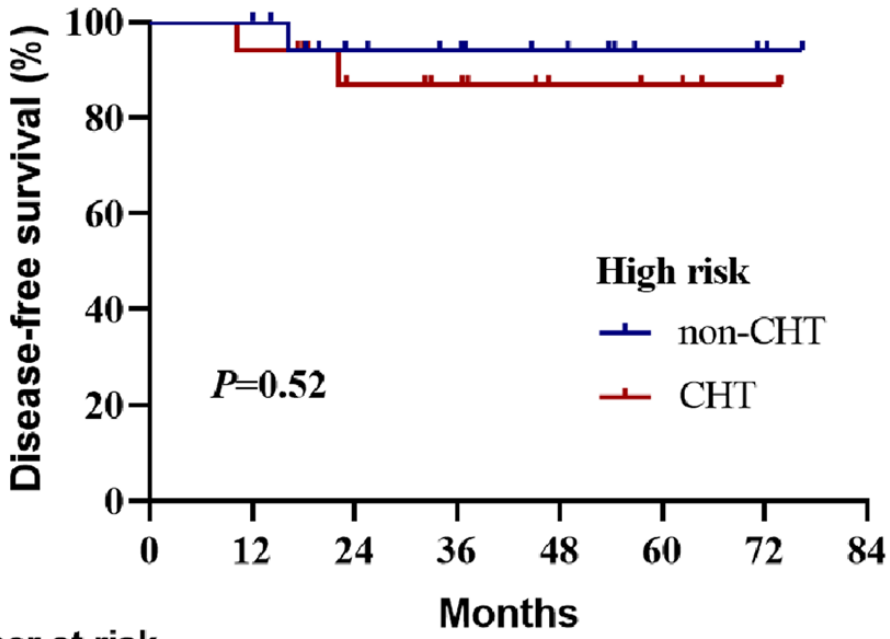




Iland, H. Lancet Haematology 2015

Xi’an APML15 Study





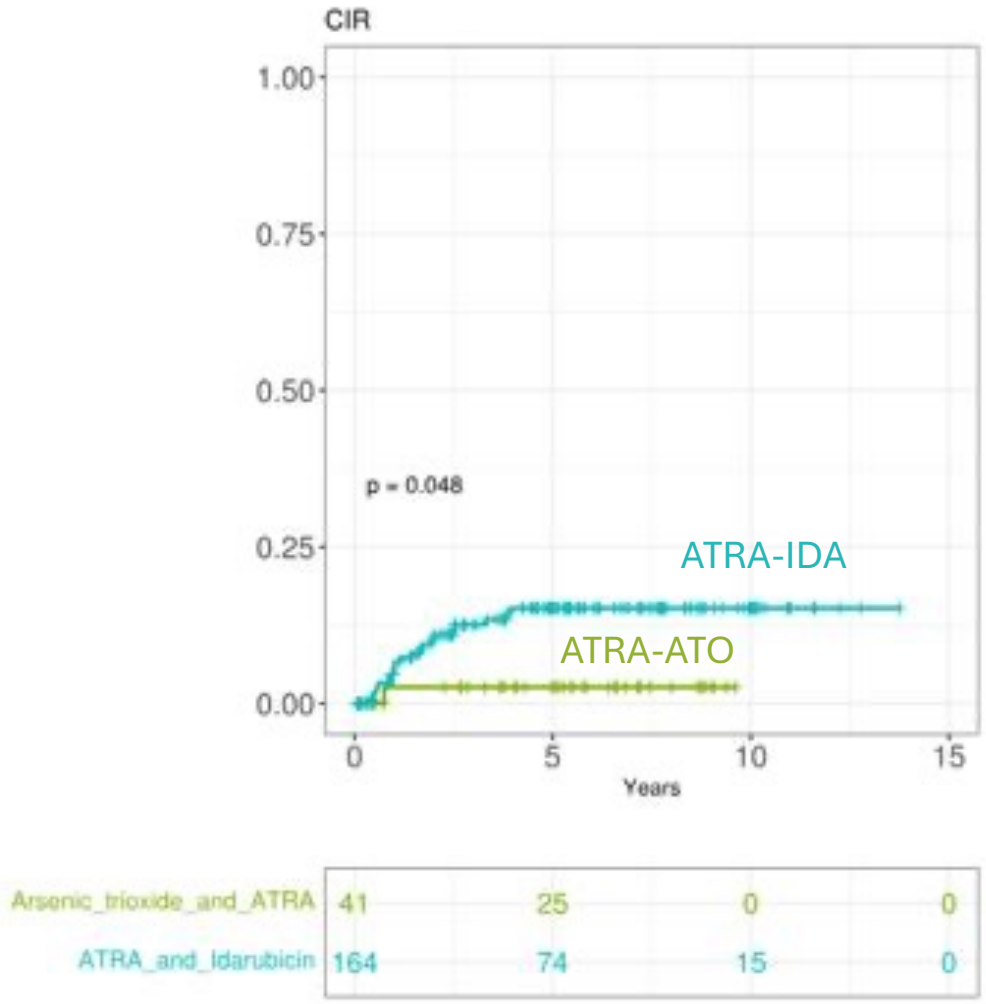
Number at risk

non-CHT	19	13	11	8	4	3	1
CHT	17	12	10	6	5	3	1

Overall 3 / 36 = 8% relapsed

Wang, H-Y. Blood Cancer Journal 2022

HARMONY APL Cohort



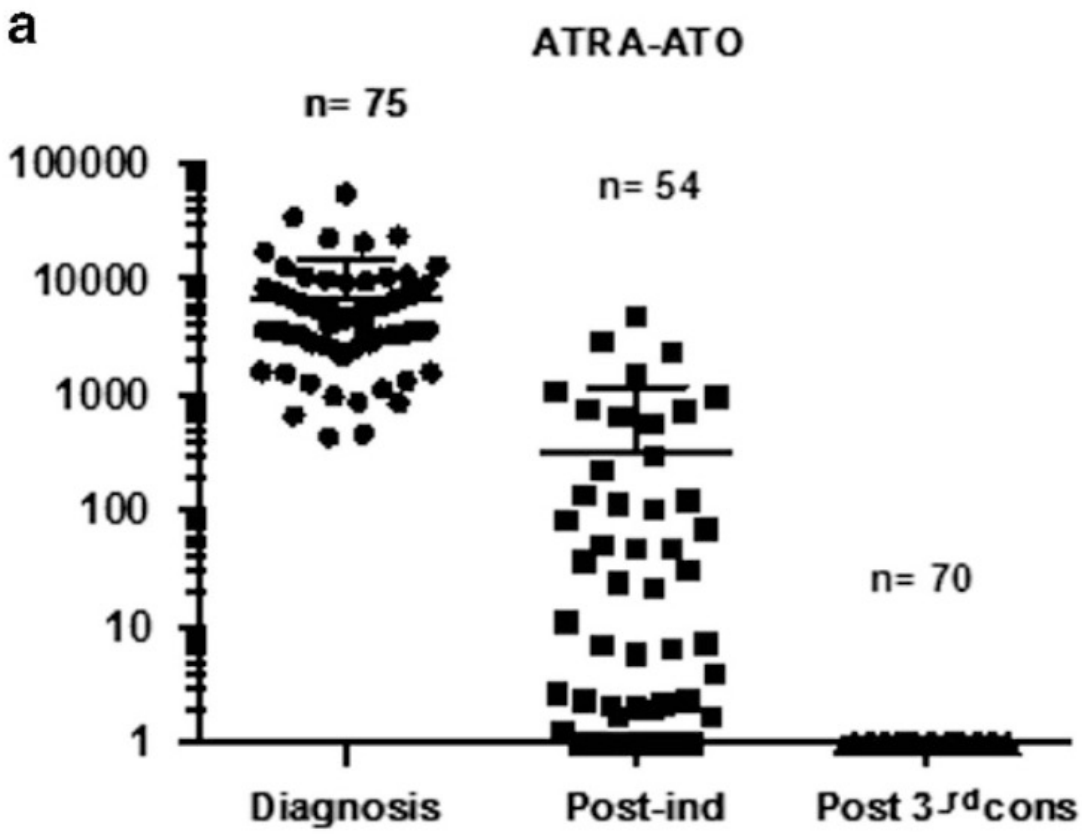
1/41 = 2.4%

Guarnera, L. et al ASH 2023

Is Disease Monitoring Still Necessary ?

	High risk	Low-intermediate risk
ATRA-chemo	**Agreed to be essential**	**ELN guidelines no longer recommend** **(controversial)**
ATRA-arsenic	**Data still immature** **Relapse 0-14%** **Protocol dependent**	**Agreed to be unnecessary** **Do we need to monitor until MRD negative ?**

MRD Clearance after Front Line ATO-ATRA



Cicconi L. et al, Leukaemia 2016

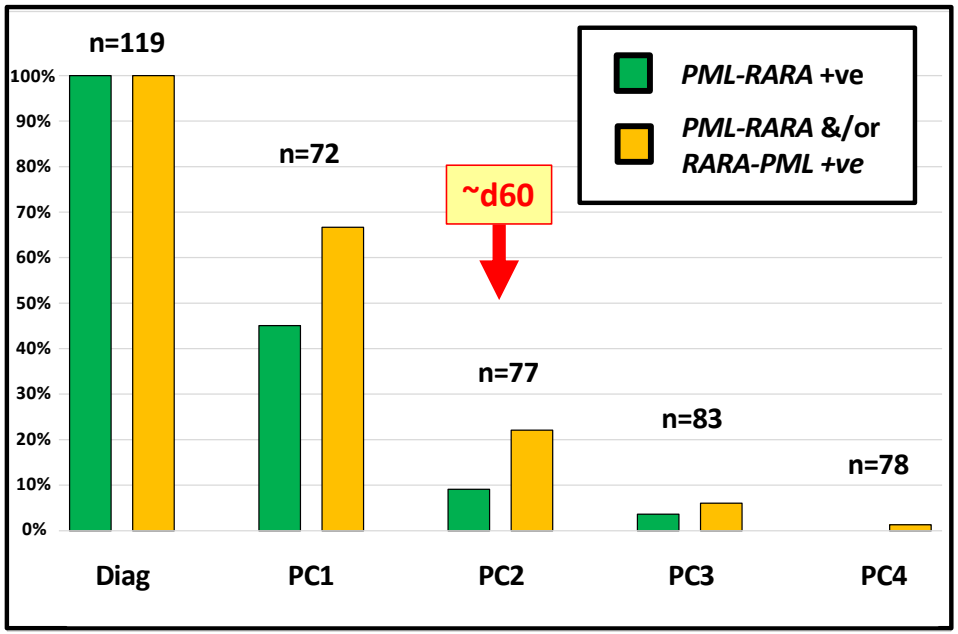
ALLG APML4

105/105 patients MRD negative
After second consolidation

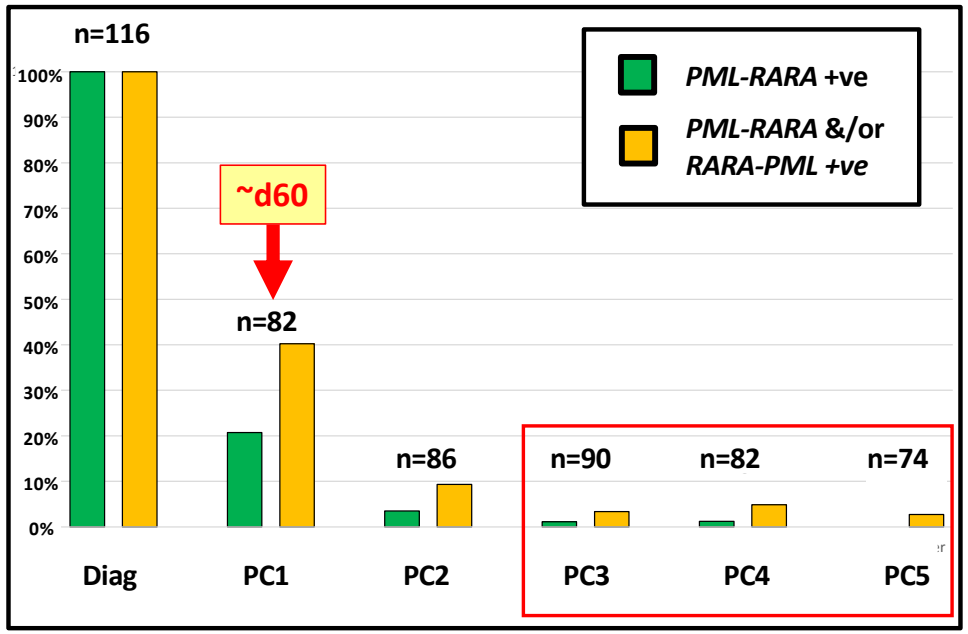
Iland, H. Lancet Haematology 2015

MRD Clearance after Front Line ATO-ATRA

AIDA

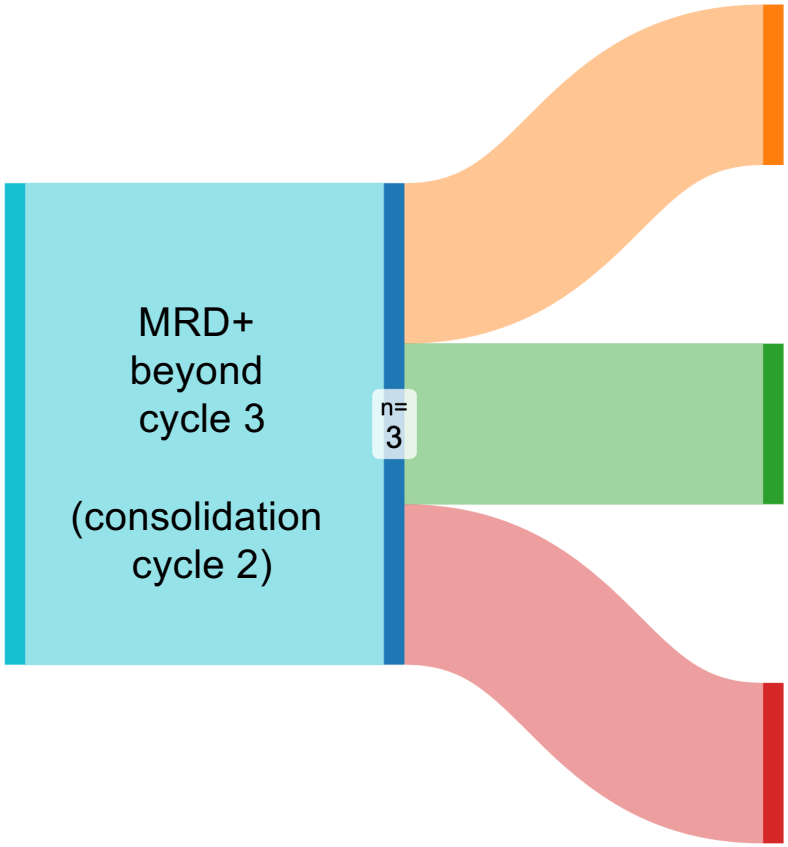


ATRA + ATO



Burnett AK *et al*, *Lancet Oncol.* 2015;16(13):1295-305

Outcomes for Patients with MRD persistence after ATO



CNS relapse after cycle 5
Died post-allograft due to infection

Received GO and became MRD-
Alive and well

Received maintenance and became MRD-
Alive and well

All three were low risk

Is Disease Monitoring Still Necessary ?

	High risk	Low-intermediate risk
ATRA-chemo	**Agreed to be essential**	**ELN guidelines no longer recommend** **But, significant relapse risk remains (~15%)**
ATRA-arsenic	**Data still immature** **Relapse 0-14%** **Protocol dependent**	**Agreed to be unnecessary** **Occasional MRD failures** **Monitor until MRD-**

Many thanks for your attention. We gratefully acknowledge all trial participants and their families.

Blood cancer UK

CANCER RESEARCH UK

NIHR | National Institute for Health Research

ELN-DAVID