Disclosures of Massimo Breccia

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis			x				
BMS			x				
Pfizer			x				
Incyte			x				

Arsenic trioxide for the management of relapsed APL patients

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Current therapy for relapsed APL patients

- About 20% of pts have been reported to relapse after risk-adapted ATRA+CHT regimens
- Clinical benefit has been reported for early identification of disease recurrence and pre-emptive therapy at the time of molecular relapse
- Treatment of molecular relapse is associated to better tolerability, decreased need of hospitalization, decreased rate of early death and differentiation syndrome
- Current literature on the treatment of relapsed APL is only available for patients relapsing after ATRA and CHT

ELN recommendations on management of APL relapse

Table 4. Management of relapse

Recommendation	Level of evidence	Grade of recommendation
4.1. For patients with confirmed molecular relapse (defined as 2 successive PCR-positive assays, with stable or rising *PML-RARA* transcript levels detected in independent samples analyzed in 2 laboratories) preemptive therapy has to be started promptly to prevent frank relapse.	IIa	B
4.2. Although ATRA in combination with chemotherapy can be used as salvage therapy, ATO-based regimens are presently regarded the first option for treatment of relapsed APL.	IV	C
4.3. Patients achieving second CR should receive intensification with SCT or chemotherapy, if possible.	IV	C
4.4. Allogeneic HSCT is recommended for patients failing to achieve a second molecular remission.	IV	C
4.5. Autologous HSCT is a valid option for patients without detectable MRD in the marrow and with an adequate PCR negative harvest.	IIa	B
4.6. For patients in whom HSCT is not feasible, the available options include repeated cycles of ATO with or without ATRA with or without chemotherapy.	IV	C
4.7. For patients with CNS relapse, induction treatment consists of weekly triple intrathecal therapy (ITT) with methotrexate, hydrocortisone, and cytarabine until complete clearance of blasts in the cerebrospinal fluid, followed by 6 to 10 more spaced out ITT treatments as consolidation. Systemic treatment should also be given.	IV	C

Sanz et al, Blood 2009

NCCN guidelines for relapsed APL

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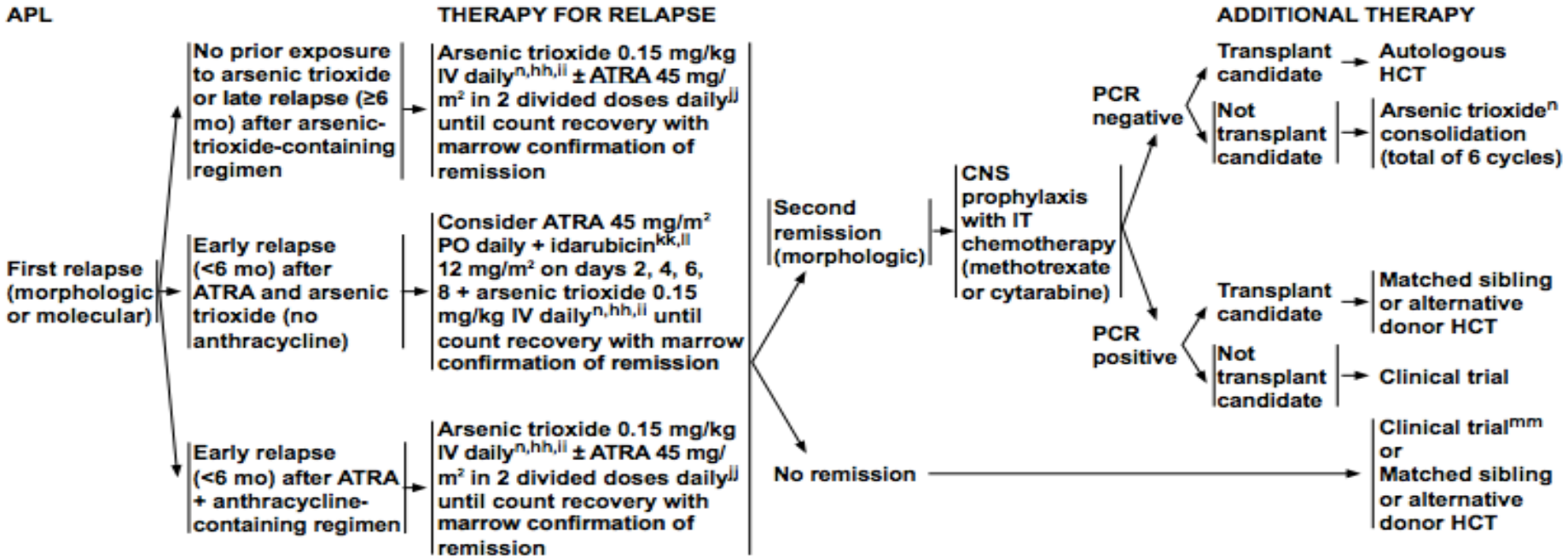
NCCN Guidelines Version 3.2017
Acute Promyelocytic Leukemia

NCCN Guidelines Index
Table of Contents
Discussion



[n]See Arsenic trioxide monitoring, Supportive Care (AML-C 2 of 2).
[hh]Following the first cycle of consolidation, if the patient is not in molecular remission (by quantitative PCR on marrow sample), consider matched sibling or alternative donor (haploidentical, unrelated donor or cord blood) HCT or clinical trial. Testing is recommended at least 2–3 weeks after the completion of arsenic to avoid false positives.
[ii]Outcomes are uncertain in patients who received arsenic trioxide during initial induction/consolidation therapy.
[jj]There is a small randomized trial that suggests that the addition of ATRA does not confer any benefit over arsenic alone. Raffoux E, et al. Combined treatment with arsenic trioxide and all-trans-retinoic-acid in patients with relapsed acute promyelocytic leukemia. J Clin Oncol 2003;21:2326-2334.
[kk]Dose adjustment for patients >60 years: 9 mg/m²/d IV (ages 61–70) or 6 mg/m²/d IV (ages >70). Iland HJ, et al. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). Blood 2012;120:1570-1580.
[ll]If patient cannot tolerate anthracycline, may use ATRA + arsenic trioxide.
[mm]Consider gemtuzumab on a compassionate use basis.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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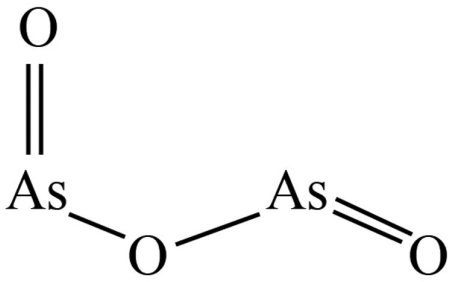
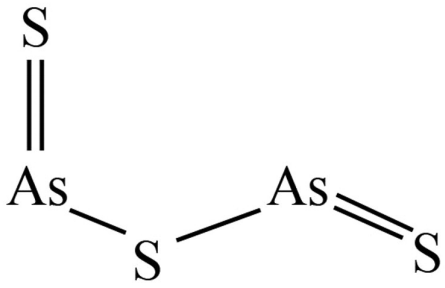
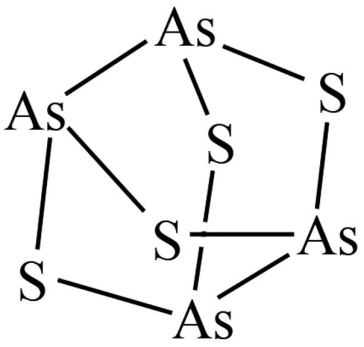
ATO different compounds



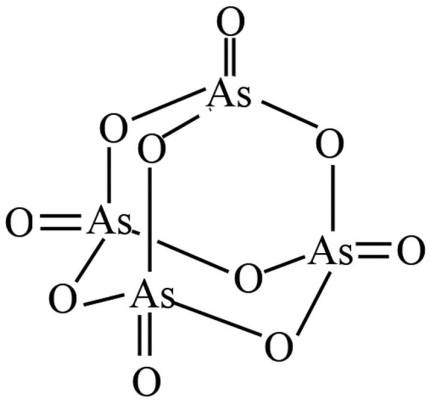
Arsenic trioxide
(white arsenic)



Arsenic trisulfide
(orpiment, yellow arsenic)



tetra-arsenic tetra-sulfide
(realgar, red arsenic)

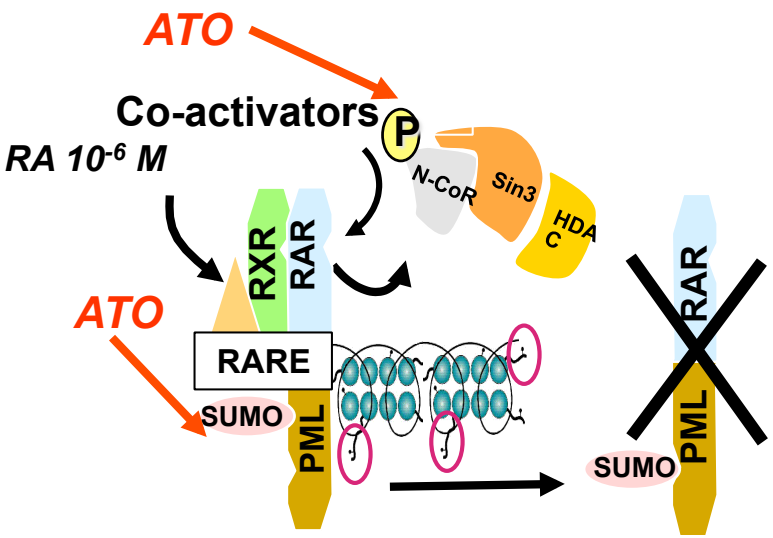


Arsenic pentoxide

Wang Z , Chen Z Blood 2008

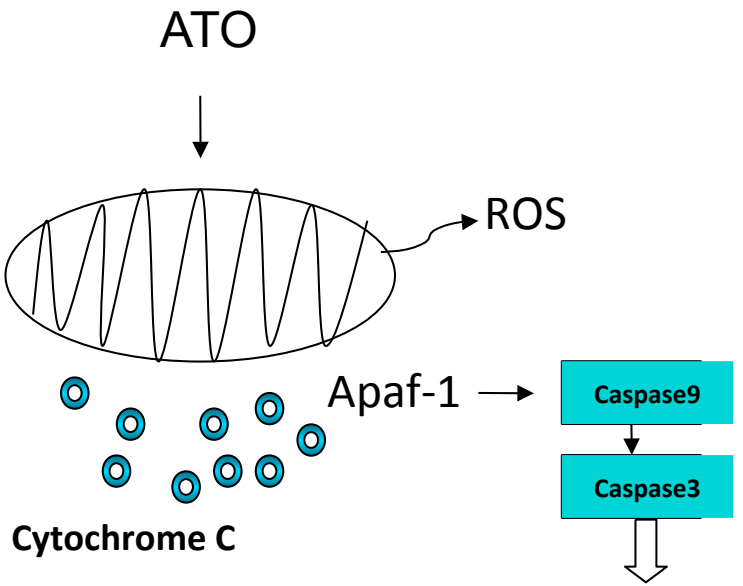
Different mechanisms of action

- Low concentration: degradation of PML-RARα (via sumoilation of PML); fosforilation of NCoR and transcriptional activation



Differentiation

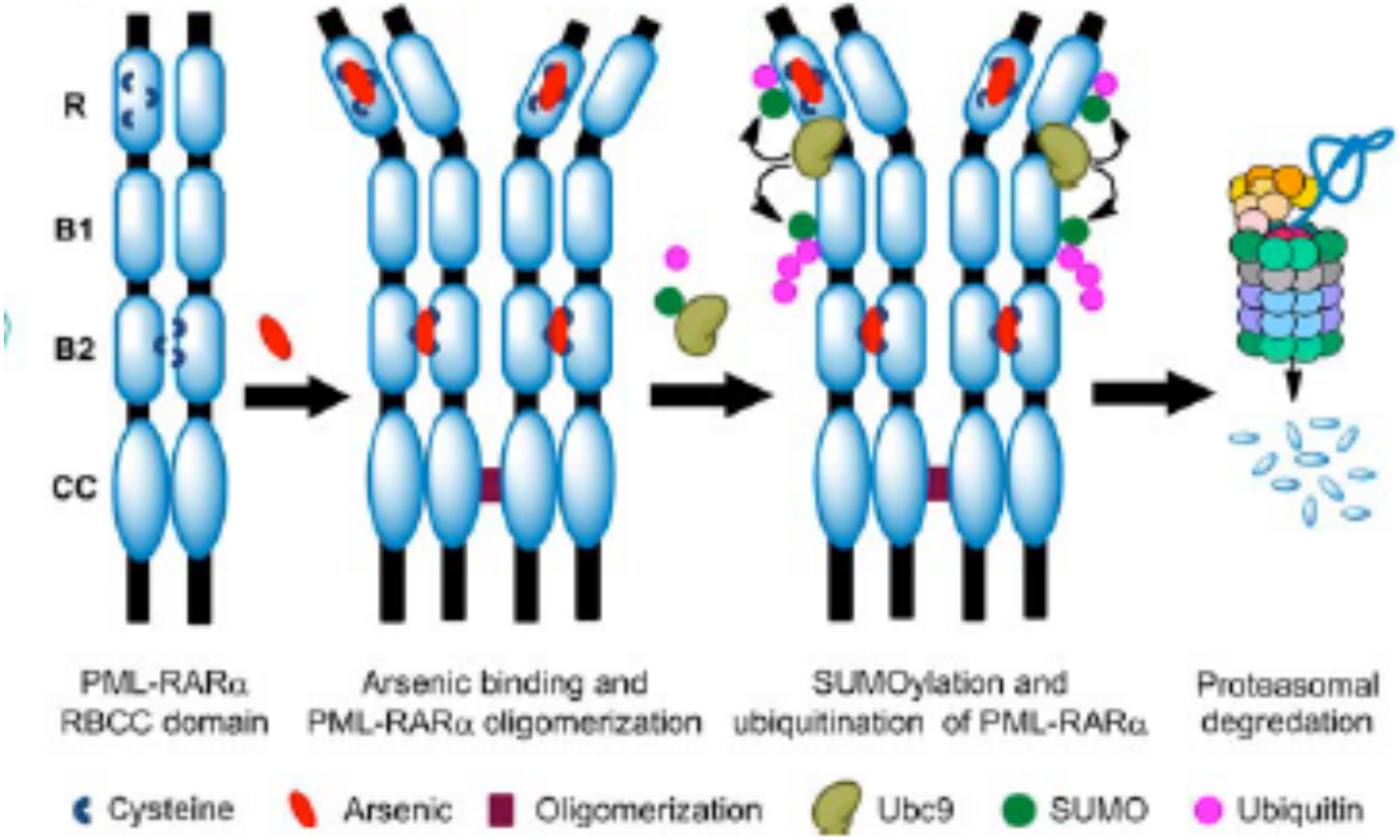
- High concentration: increased production of reactive oxygen species (ROS); induction of caspasis



Apoptosis

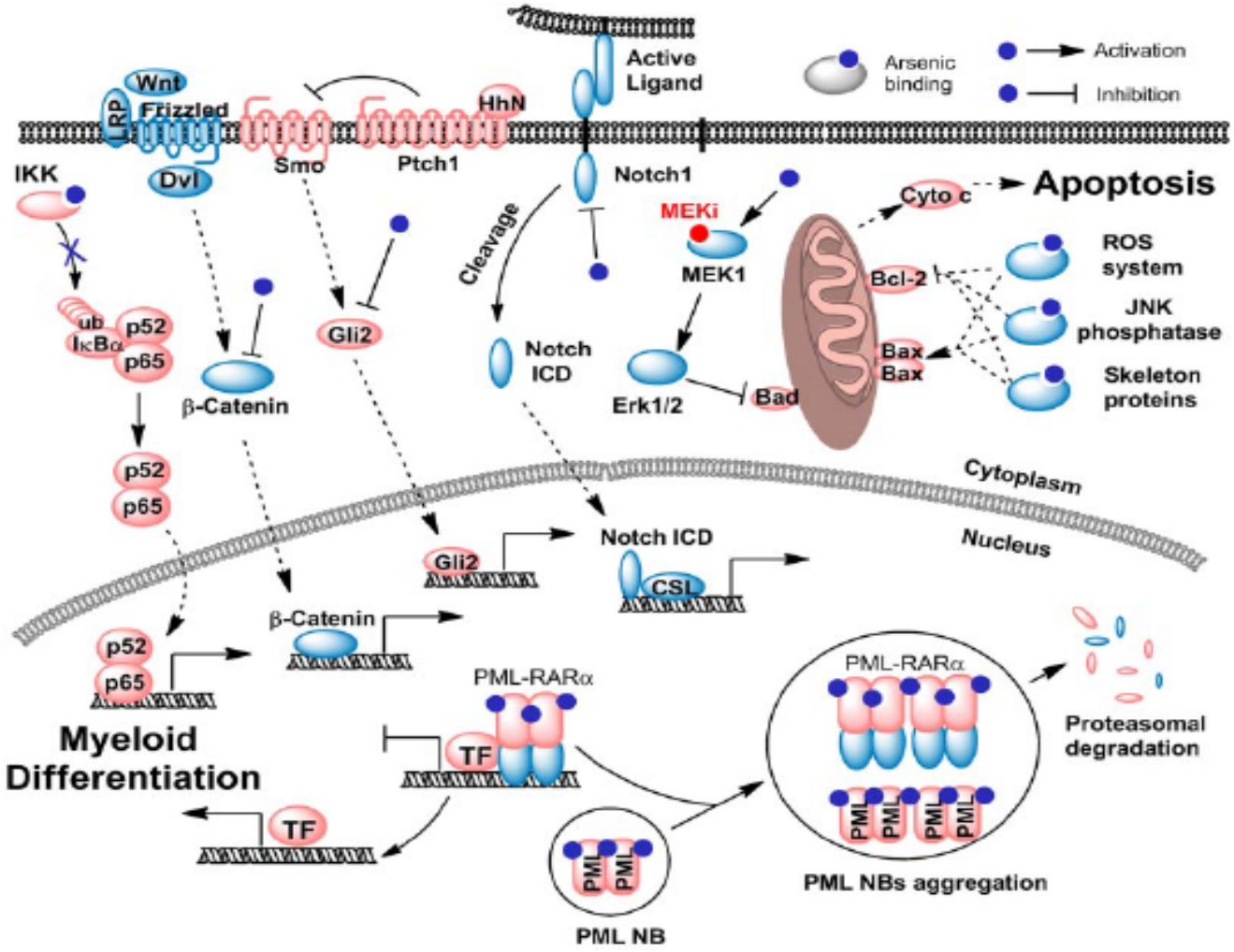
Miller *et al*. Cancer Res 2002

The real target of ATO is PML



Chen *et al*. Blood 2011

ATO can eradicate leukemia-initiating cells (LIC)



- Inhibition of Notch1, Gli2 and Beta-catenin or activation of pathways such as MEK/ERK with stimulation of autophagy and final degradation of PML.

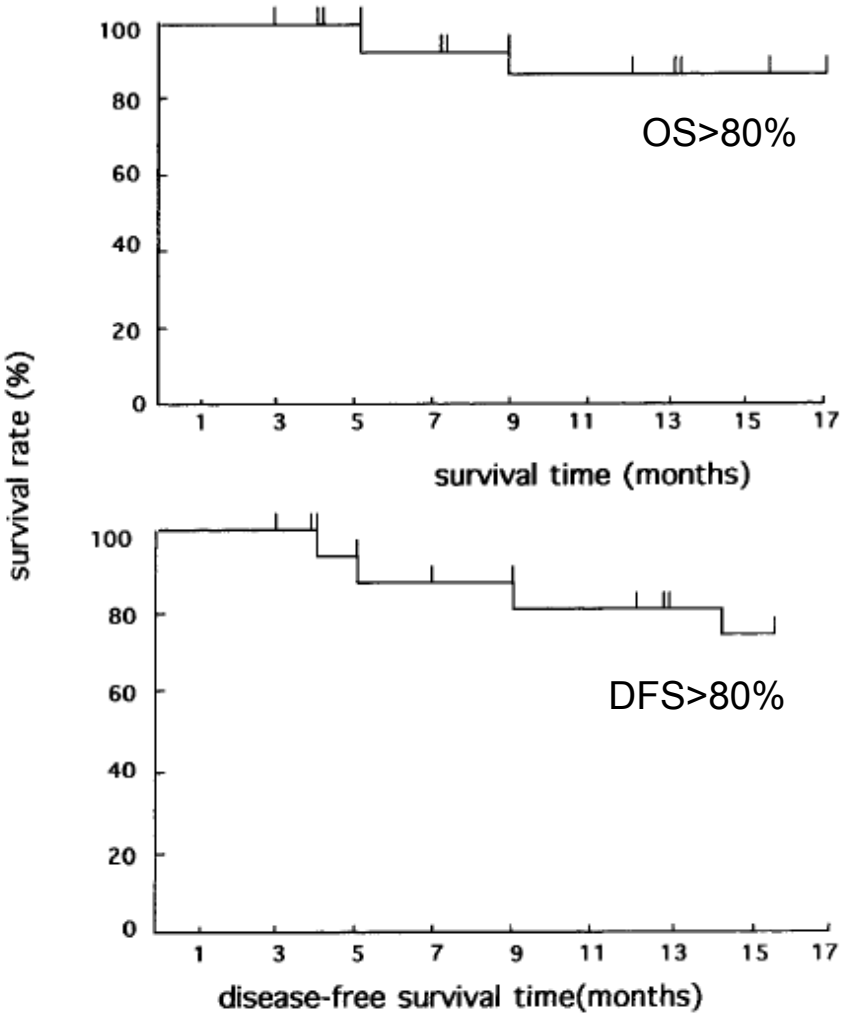
Chen *et al*. Blood 2011

….taming an evil with a toxic agent…

Wang Z , Chen Z Blood 2008

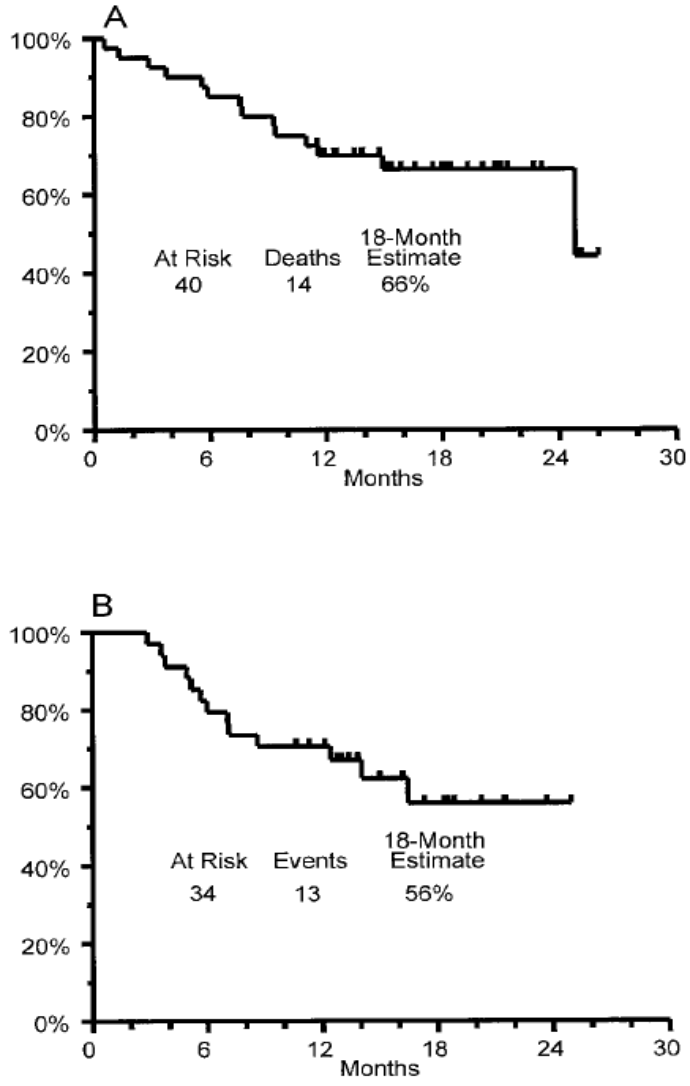
First experiences in APL relapses

15 pts; CR=90%



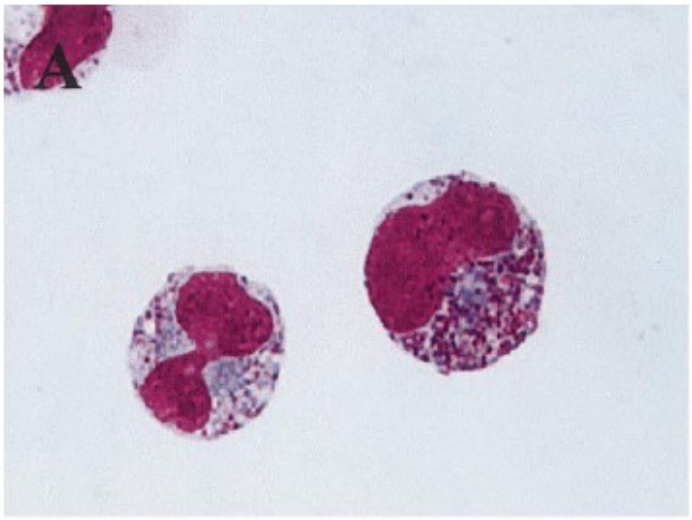
Shen *et al*. Blood 1997

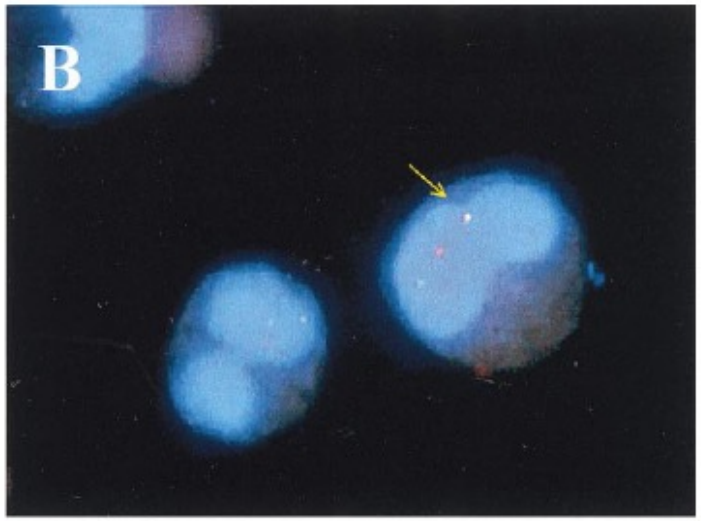
40 pts; CR=85%

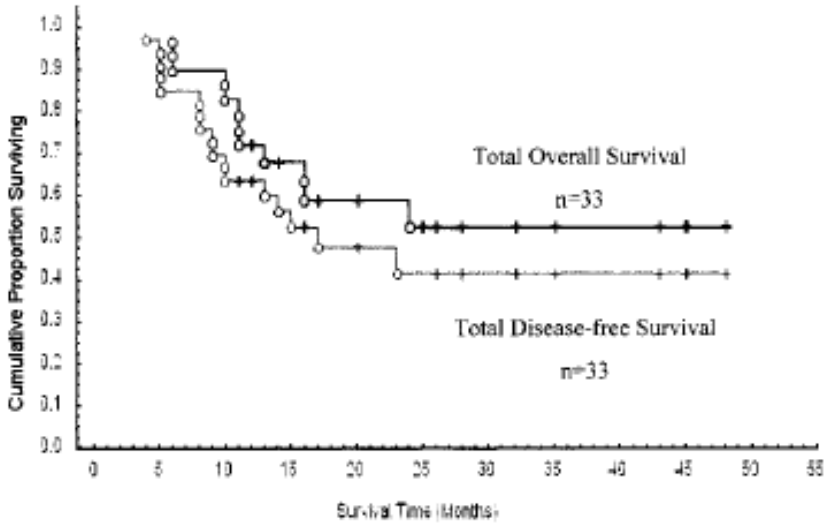


Soignet *et al*. N Engl J Med 1998-2001

Chinese experience in relapsed pts







47 pts; OS 50%
2-y DFS 41.6%

Niu *et al*. Blood 1999

Literature review of more than 300 pts

Author[ref.]	Patients n	Age (years) range (median)	ATO daily dose	Induction with ATO (days)	Post-induction therapy	Stem cell transplantation n
Shen[24]	15	14–53	10 mg	28–54	1 course ATO	
Soignet[20,44]	52	9–75	0.15 mg/kg	maximum 60	maximum 5 courses ATO	auto. 3, allo. 14
Niu[45]	47	7–55 (35)	10 mg	42[a]	ATO ± chemotherapy or chemotherapy alone	
Shen[46]	20	6–55	0.08 mg/kg	28[a]	daunorubicin	
Kwong[47]	8	22–45	10 mg	28–51	idarubicin	
Leoni[48]	7	21–71 (55)	10 mg	28–40	high-dose Ara-C, mitoxantron	auto. 2, allo. 2
Ohnishi[49]	14	23–65	0.15 mg/kg	maximum 60	1 course ATO, various chemotherapy ± ATRA	allo. 2
Lazo[50]	12	26–72 (44)	0.15 mg/kg	maximum 60	up to 4 courses ATO ± various therapy	allo. 1
Raffoux[51]	20	NR	0.15 mg/kg	maximum 56[b]	1 to 2 courses ATO ± ATRA	auto. 1, allo. 7
Carmosino[52]	11	5–53	0.15 mg/kg	maximum 60	1 course ATO, ± ATRA+idarubicin	auto. 2, allo. 2
Shigeno[53]	34	17–82 (47)	0.15 mg/kg	maximum 60	1 course ATO ± chemotherapy+ATRA ± ATO	auto. 1, allo. 9
Thomas[54]	25	21–80 (53)	0.15 mg/kg	maximum 60	1 course ATO, ± various therapy ± ATO; MT	auto. 9, allo. 3
Aribi[55]	8	18–68	0.15 mg/kg	maximum 60	5 courses ATO+ATRA+GO; MT	allo. 1
Alimoghaddam[56]	31	10–79 (27)	0.15 mg/kg	maximum 60	1 course ATO, since the year 2006: 4 courses ATO	
Total	304	5–82 years		up to 60	ATO consolidation ± variable chemotherapy ± ATRA	$n = 59$

Lengfelder E, Leukemia 2012

Results of ATO treatment in relapsed APL

Author[ref.]	*Patients* n	*CR* n *(%)*	*Doc. mCR* n *(%)*	*Resistance* n *(%)*	*ED* n *(%)*	*Days to CR median (range)*	*Estimated survival (%)*
Shen[24]	15	14 (93)	1/10 (10)[a]	1 (7)	0	38 (28–54)	>80 after 17 months
Soignet[20]	12	11 (92)	8/11 (73)[b]	0	1 (8)	47 (24–83)	
Niu[45]	47	40 (85)	1/15 (7)[a]	3 (6)	4 (8.5)	31	50 after 24 months
Soignet[44]	40	34 (85)	25/29 (86)[b]	6 (15)	0	59 (28–85)	66 after 18 months
Shen[46]	20	16 (80)	0/6[a]	2 (10)	2 (10)		62 after 24 months
Kwong[47]	8	8 (100)	0/8[a]	0	0	45	
Leoni[48]	7	6 (86)	NR	0	1 (14)	20–40	>80 after 24 months
Ohnishi[49]	14	11 (79)	6/10 (60)[a]	2 (14)	1 (7)	43 (27–60)	
Lazo[50]	12	12 (100)	7/10 (70)[a]	0	0	52 (27–75)	
Raffoux[51]	20	16 (80)	3/16 (19)[a]	2 (10)	2 (10)	42 (14–86)	59 after 24 months
Carmosino[52]	11	8 (73)	8/11 (73)[b]	0	3 (27)	37.5 (28–50)	
Shigeno[53]	34	31 (91)	18/25 (72)[b]	2 (6)	1 (3)	46 (26–60)	56 after 24 months
Thomas[54]	25	21 (84)	8/21 (38)[a]	2 (8)	2 (8)	49	77 after 24 months
Aribi[55]	8	8 (100)	8/8 (100)[b]	0	0	39 (21–56)	75% after 36 months
Alimoghaddam[56]	31	27 (77)	NR	3 (10)	4 (13)	30	81% after 24 months
Total	304	263 (86)	93/180 (52)	23 (7)	21 (7)	30–59 (range of study medians)	50–81% after 24 months

Lengfelder E, Leukemia 2012

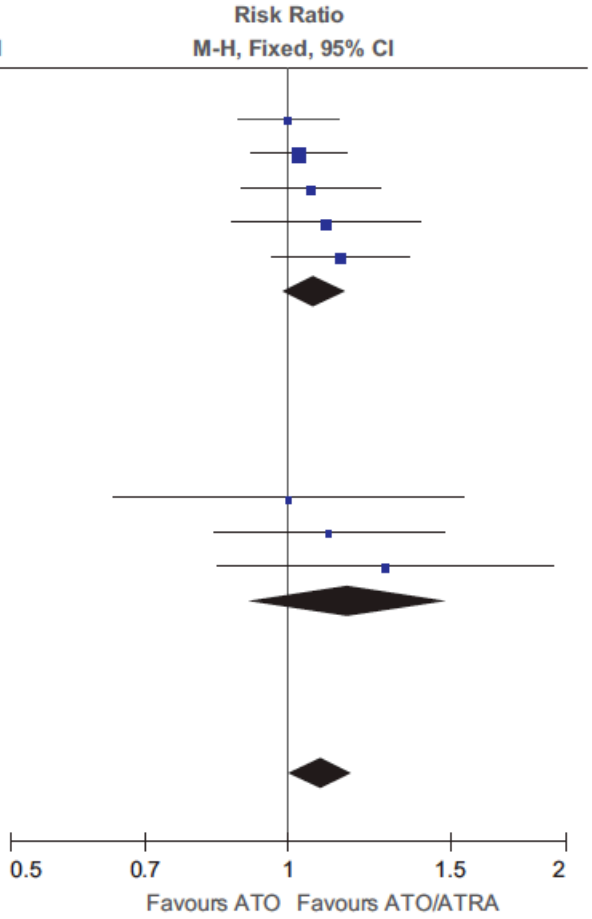
Meta-analysis of ATRA+ATO for relapsed pts

	ATO+ATRA (255 pts)	ATO (202 pts)	Significance
CR	89.8%	81.7%	ns
Time to CR	Heterogenous data		nr
ED	6%	11%	ns
mCR post 1° cycle	25%	22.7%	ns
mCR post consolidation	70%	39%	0.01
DFS 2-year	84.6%	63.6%	0.07

Wang et al, Leuk Res 2011

Synergism ATRA+ATO: impact on CR

Study or Subgroup	ATO/ATRA Events	ATO/ATRA Total	ATO Events	ATO Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 New diagnosed APL						
Bai 2007	16	16	14	14	9.0%	1.00 [0.88, 1.13]
Wang 2004N	74	80	36	40	28.0%	1.03 [0.91, 1.16]
Shen 2004	20	21	18	20	10.8%	1.06 [0.89, 1.26]
Su 2006	33	40	27	36	16.6%	1.10 [0.87, 1.39]
Li 2008	53	55	22	26	17.4%	1.14 [0.96, 1.35]
Subtotal (95% CI)		212		136	81.8%	1.07 [0.99, 1.15]
Total events	196		117			
Heterogeneity: Chi² = 2.03, df = 4 (P = 0.73); I² = 0%						
Test for overall effect: Z = 1.62 (P = 0.10)						
1.1.2 Relapsed APL						
Raffoux 2003	8	10	8	10	4.7%	1.00 [0.65, 1.55]
Niu 1999	5	5	26	31	4.9%	1.11 [0.83, 1.48]
Wang 2004R	20	28	14	25	8.6%	1.28 [0.84, 1.94]
Subtotal (95% CI)		43		66	18.2%	1.16 [0.91, 1.48]
Total events	33		48			
Heterogeneity: Chi² = 0.74, df = 2 (P = 0.69); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
Total (95% CI)		255		202	100.0%	1.08 [1.00, 1.17]
Total events	229		165			
Heterogeneity: Chi² = 3.47, df = 7 (P = 0.84); I² = 0%						
Test for overall effect: Z = 2.01 (P = 0.04)						

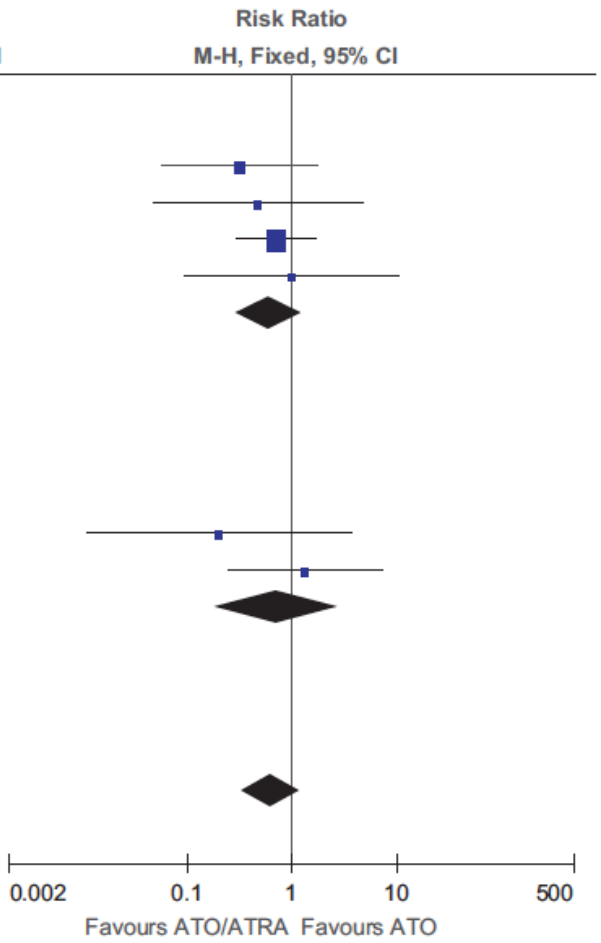


Meta-analysis results reported a significant increase of CR both in relapsed and newly diagnosed pts with ATO+ATRA association

Wang et al, Leuk Res 2011

Synergism ATRA+ATO: impact on early death

Study or Subgroup	ATO/ATRA Events	ATO/ATRA Total	ATO Events	ATO Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 New diagnosed APL						
Bai 2007	0	16	0	14		Not estimable
Li 2008	2	55	3	26	18.9%	0.32 [0.06, 1.77]
Shen 2004	1	21	2	20	9.5%	0.48 [0.05, 4.85]
Su 2006	7	40	9	36	44.0%	0.70 [0.29, 1.69]
Wang 2004N	2	80	1	40	6.2%	1.00 [0.09, 10.70]
Subtotal (95% CI)		212		136	78.6%	0.60 [0.30, 1.22]
Total events	12		15			
Heterogeneity: Chi² = 0.87, df = 3 (P = 0.83); I² = 0%						
Test for overall effect: Z = 1.41 (P = 0.16)						
1.2.2 Relapsed APL						
Raffoux 2003	0	10	2	10	11.6%	0.20 [0.01, 3.70]
Wang 2004R	3	28	2	25	9.8%	1.34 [0.24, 7.38]
Subtotal (95% CI)		38		35	21.4%	0.72 [0.19, 2.79]
Total events	3		4			
Heterogeneity: Chi² = 1.25, df = 1 (P = 0.26); I² = 20%						
Test for overall effect: Z = 0.47 (P = 0.64)						
Total (95% CI)		250		171	100.0%	0.63 [0.34, 1.17]
Total events	15		19			
Heterogeneity: Chi² = 2.22, df = 5 (P = 0.82); I² = 0%						
Test for overall effect: Z = 1.46 (P = 0.14)						
Test for subgroup differences: Not applicable						

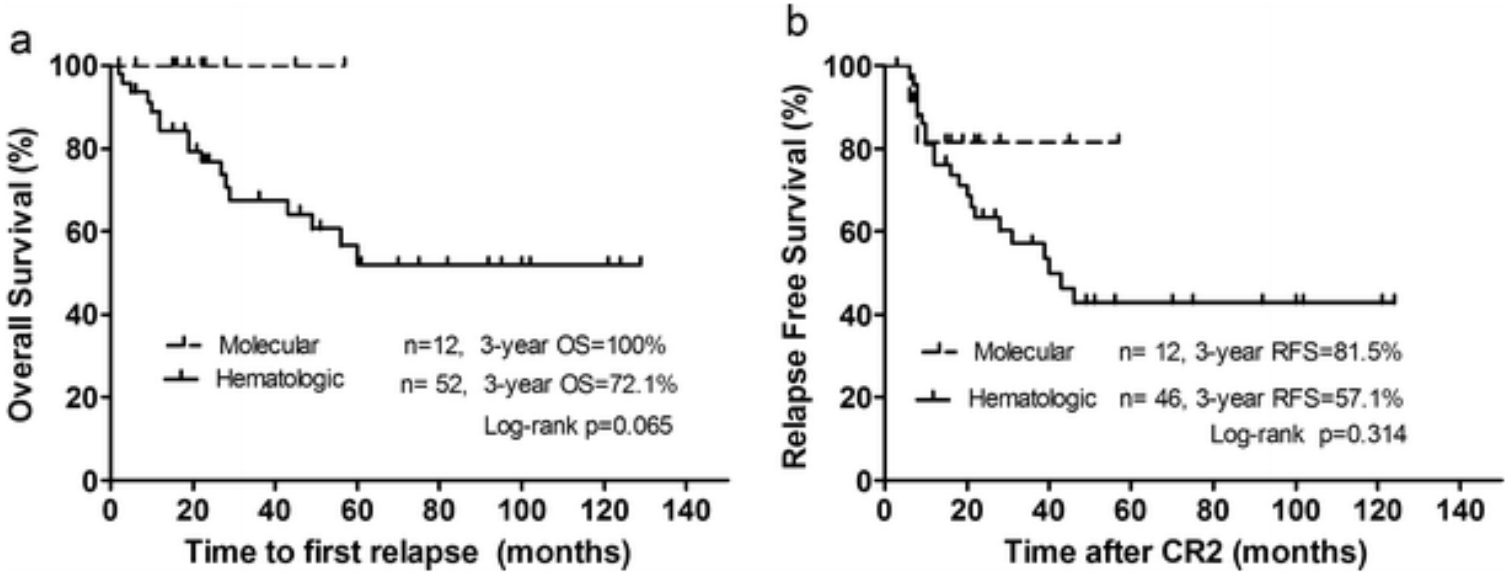


Meta-analysis results did not report and increase of ED with ATO +ATRA association

Wang et al, Leuk Res 2011

Shanghai experience

- 64 relapsed pts treated in first relapse with ATO (12 pts with molecular and 52 with hematologic relapse)
- With a median follow-up of 27 months (range, 6–57) in the molecular relapsed subgroup, the 3-year relapse-free survival (RFS) and overall survival (OS) rates were 81.5 % and 100 %, respectively. With a median follow-up of 38 months (range, 0–129) in the hematologic relapse group, the 3-year RFS and OS rates were 57.1 % and 72.1 %, respectively.
- Increased relapse rate in pts who received ATO after previous induction with the same drug



Lou et al, Ann Hematol 2014

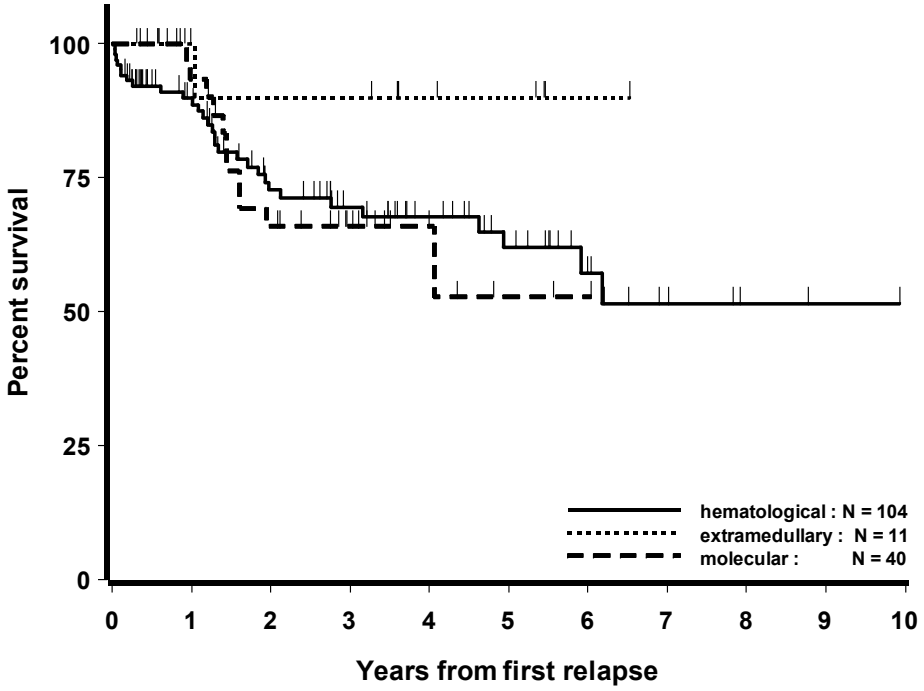
ELN registry: update

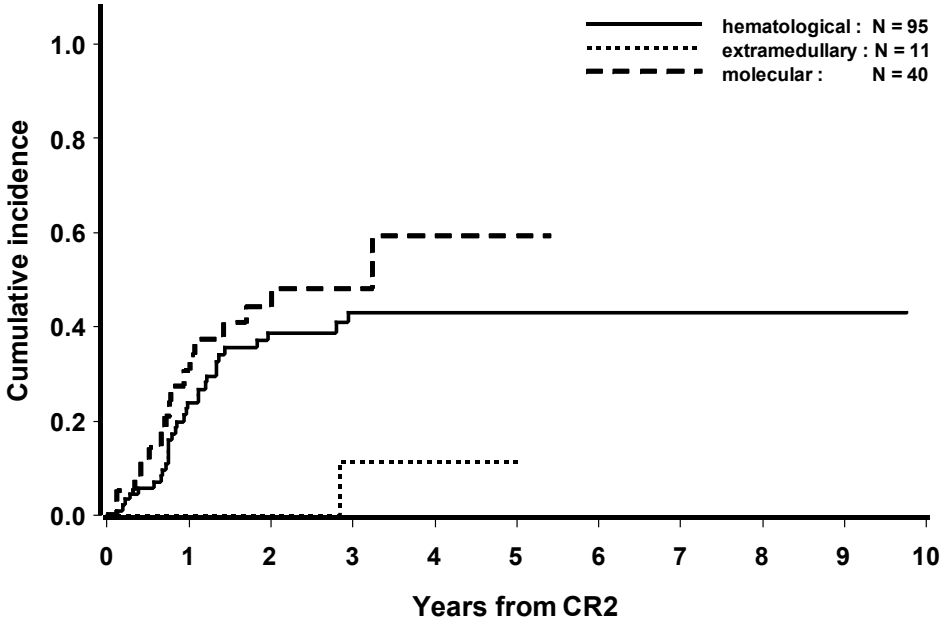
- 155 relapsed pts treated in first relapse with ATO

	Hematological relapse			Molecular relapse			*P* value*	Extramedullary relapse		
No of patients N=155		**104**			**40**				**11**	
		N	**%**		**N**	**%**			**N**	**%**
Results after induction										
CR (hematological)		92/104	88		-				11/11	100
Resistance (hematological)*		5/104	5		-				0	0
Death		7/104	7		0/40	0	0.19		0/11	0
Side effects of ATO during induction										
APL diff. syndome		22/83	27		0/40	0	<0.001		0/11	0
Leukocytosis•		36/92	39		0/40	0	<0.001		0/11	0
Infection /FUO		27/63	43		3/29	10	0.002		4/11	36
Hepatotoxicity·		11/56	20		3/28	11	0.37		2/8	25
Rate of molecular remission										
After induction		40/76	53		21/39	54	1.0		9/9	100
After consolidation		39/53	74		18/29	62	0.32		11/11	100
Outcome	**% [95% CI]**			% **[95% CI]**				**% [95% CI]**		
OS							0.85			
at 3 years	68 [58;78]			66 [57;75]				90 [82;100]		
No of patients N=146		**95**			**40**				**11**	
CIR							0.3			
at 3 years	41 [29;52)			48 [29;64]				11 [0;42]		

Lengfelder et al, Leukemia 2015

ELN registry: OS and CIR according to type of relapse





Lengfelder et al, Leukemia 2015

ATO as maintenance in relapsed patients

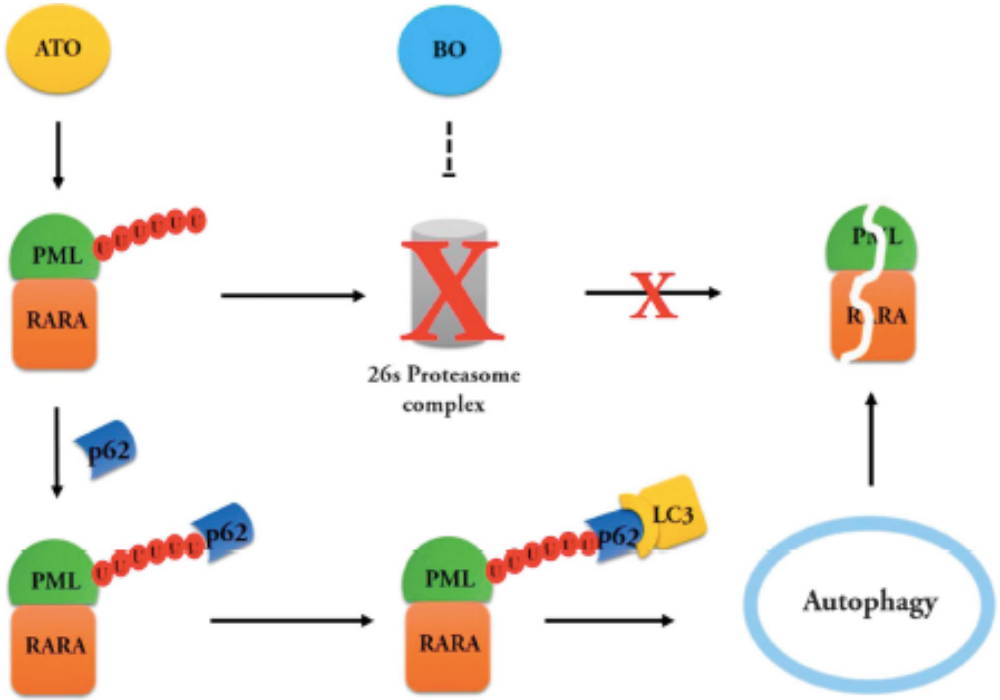
9 relapsed pts

- 7 pts in 1^ molecular relapse + 2 pts in 2^ relapse (median time from first CR 1.9 years)
- Treatment with ATRA+ATO according to Estey schedule
- 2 pts in mCR after 1 cycle and 7 pts after 2 cycles (only 2pts were hospitalized for the treatment of hematologic relapse)
- 8 pts in long-term remission (88%) without transplant for a median of 25 months (range 11-75). Only 1 pt in relapse treated with BMT.
- Update (+47 months): all pts in long-term remission after this treatment

Breccia et al, Haematologica 2011 and update

ATO + bortezomib: a potential combination

- Significant micro-environment-mediated drug resistance to ATO in APL demonstrated by Indian group
- Synergistic effect of combination of ATO+bortezomib in ATO-sensitive and ATO-resistant APL cells in vitro
- The mechanisms involved downregulation of NFkB pathway, increase in unfolded protein response, increase in ROS generation by blast cells, apoptosis
- PML-RARa is cleared by this combination through p62-dependent autophagy pathway



- Two patients in second relapse successfully treated with this combination
- A phase II trial is still ongoing

Ganesan et al, Leukemia 2016

Realgar: oral ATO for relapsed patients

- 8 pts in first relapse, 4 pts in second relapse
- All pts achieved morphologic CR after first cycle (+/- ATRA or CHT) , but none mCR
- In second CR, 5 pts were treated with oral ATO as consolidation
- 11/12 pts reached long-lasting mCR

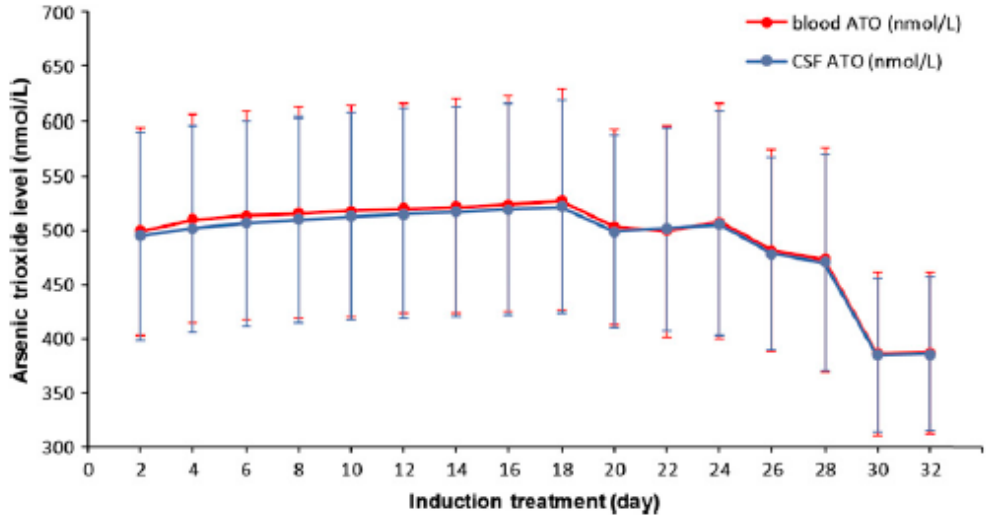
Table 1. Clinicopathologic features and outcome of 12 consecutive patients with relapsed-acute promyelocytic leukemia treated with oral As_2O_3

Patient no.	Sex/ age, y	Status	Previous induction treatment	Time from last CR, mo	Relapse			Oral As_2O_3 therapy			Consolidation	Latest PCR† (mo)	DFS, mo	Remarks
					Hb, g/L	WBC, $\times 10^9$/L	Plat, $\times 10^9$/L	Duration, d	Additional Rx	Result				
1*	M/23	R1	ATRA + Dauno	11	156	2.1	87	59	Ida	CR	Ida		13	—
		R2	IV As_2O_3 + Ida	10	140	2.5	25	76	ATRA	NR	—	+ (dead)		—
2*	M/33	R2	Dauno/IV As_2O_3 + Ida	25	134	2.1	20	32	ATRA	CR	As_2O_3 + ATRA	− (18)	19+	—
3*	F/13	R2	ATRA + IV As_2O_3	12	86	1.2	15	30	ATRA	CR	As_2O_3 + ATRA	− (18)	19+	—
4	M/54	R1	ATRA + Dauno	100	85	34.8	81	40	Ida	CR	Ida	− (18)	18+	Mother: AML
5*	M/32	R1	ATRA + Dauno + MP	22	145	2.4	177	33	NA	CR	Ida	− (18)	18+	—
6	F/32	R1	ATRA + Dauno	12	122	0.8	84	51	NA	CR	Ida	− (12)	18+	—
7*	F/45	R2	ATRA + Dauno/IV As_2O_3 + Ida	17	112	1.9	50	37	ATRA	CR	As_2O_3 + ATRA	− (14)	17+	—
8	F/65	R1	ATRA	16	72	2.8	141	28	NA	CR	As_2O_3 + ATRA	− (12)	15+	CRF due to DM on CAPD, Ida consolidation omitted due to CRF
9	F/18	R2	ATRA + Dauno/IV As_2O_3 + Ida	12	101	1.9	180	28	ATRA	CR	As_2O_3 + ATRA	− (12)	14+	—
10*	F/18	R1	ATRA + Dauno	12	82	12.6	54	44	Ida	CR	Ida	− (6)	9+	—
11*	M/45	R1	ATRA + Dauno	240	42	0.6	9	22	NA	CR	As_2O_3	− (3)	7+	Ida consolidation omitted due to high cumulative doses of anthracycline
12	F/40	R1	ATRA + Ara-c	23	85	6.5	39	28	Ida	CR	Ida	− (3)	6+	CRHD, double valve rep

Au et al, Blood 2003

ATO for CNS relapsed patients

- 17 pts in CNS relapse
- Treatment 125 mL of 20% mannitol followed by the same therapy + 7 mg/mq ATO. Pts remained in bed for the entire procedure
- After induction, 3 cycles of consolidation for 14 days and then long-term maintenance
- No particular toxicity observed. No differences observed between CSF and blood levels
- 16/17 pts achieved CR after 1st cycle and 9 pts maintained mCR in the long-term



Wang et al, Blood 2014

Conclusions

❖ ATO is the most effective drug for relapsed pts (synergism with ATRA)

❖ ATO is the first choice considered by ELN recommendations and NCCN guidelines

❖ATO as long-term maintenance warranted confirmation in large series of patients

Management of ATO complications

Complication	Management
Differentiation syndrome	• Temporary discontinuation only in case of severe APL differentiation syndrome • Dexamethasone 10 mg BID until resolution of signs and symptoms
QTc prolongation	• In case of QTc prolongation above 500 ms, ATO discontinuation and daily monitoring • Electrolytes correction (K+, Mg) • Discontinuation of other concomitant medication that may prolong QTc
Leukocytosis	• Cytoreductive agent suggested if WBC increase up to 10 x 10^9/l
Hepatic toxicity	• Liver enzymes should be monitored during therapy • If grade > 2, ATO should be temporarily discontinued until normalization

Wang et al, Blood 2014