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

Treatment approaches at relapse

Conventional and new drugs

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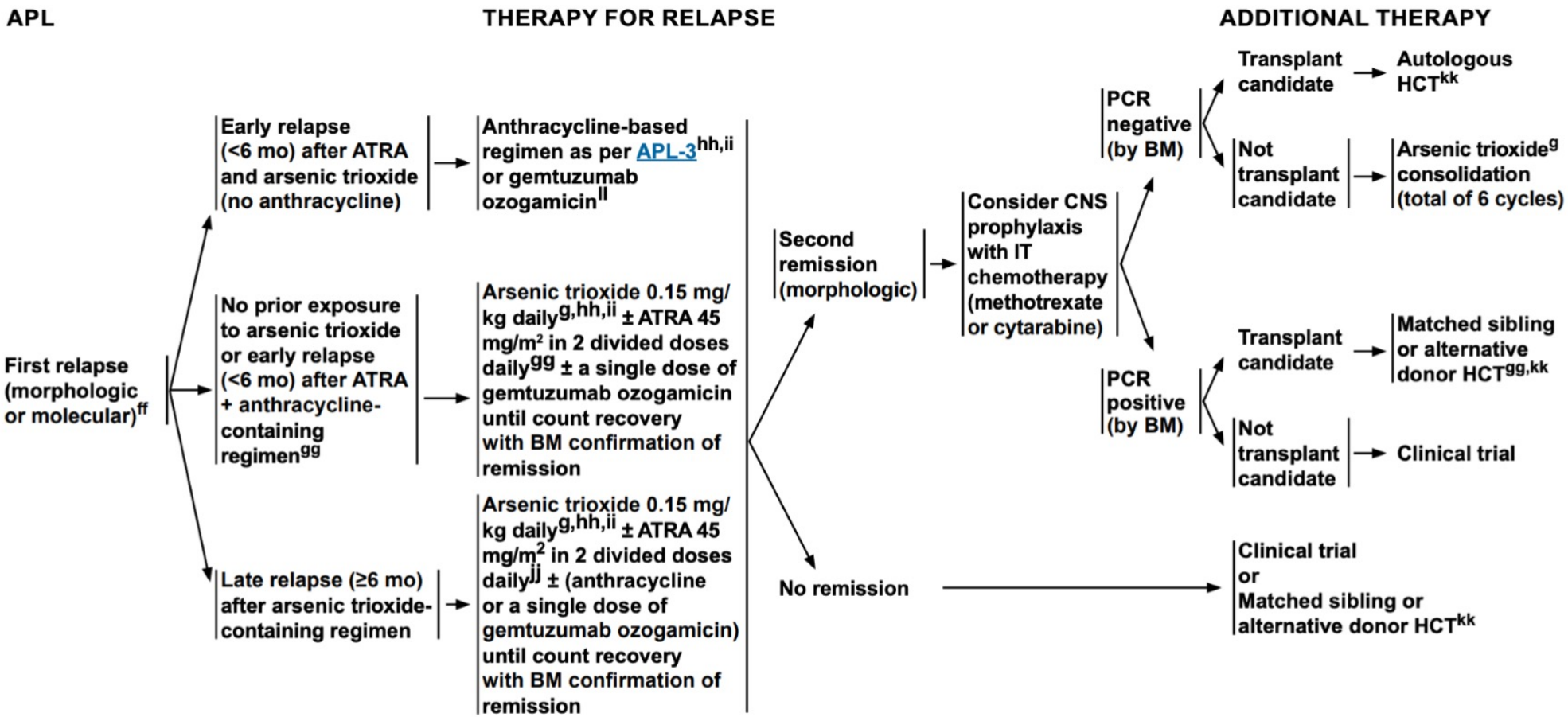
Disclosures of Name Surname

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

2024 NCCN guidelines for relapsed APL



Outcome of APL relapsed patients in the pre-ATO era

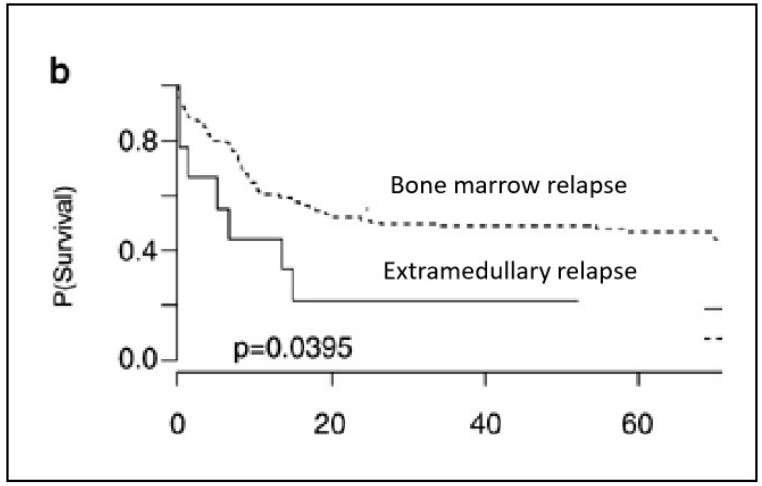
Results with chemotherapy:

Complete remission: 90% (85 - 95)

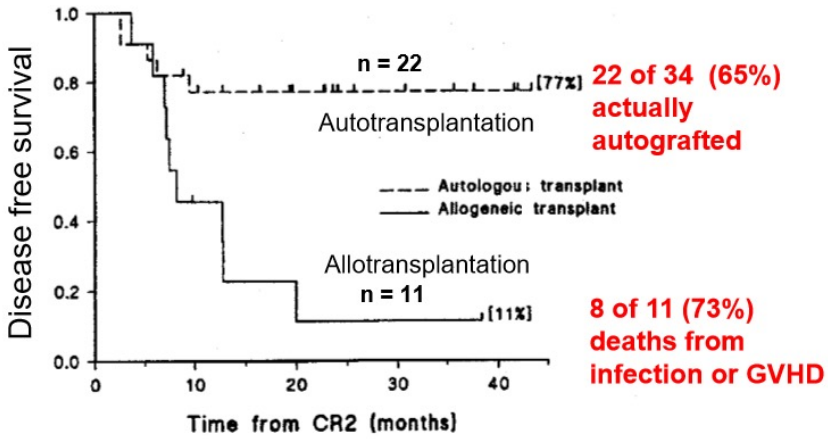
Failure (death, refractory): approx. 10%

Survival after 2 to 3 years: 40 - 50%

Castagnola, Haematologica 1998; Fenaux, Leukemia 2000; Thomas, Leukemia 2000;
Estey, Best Pract Res Clin Haematol 2003.

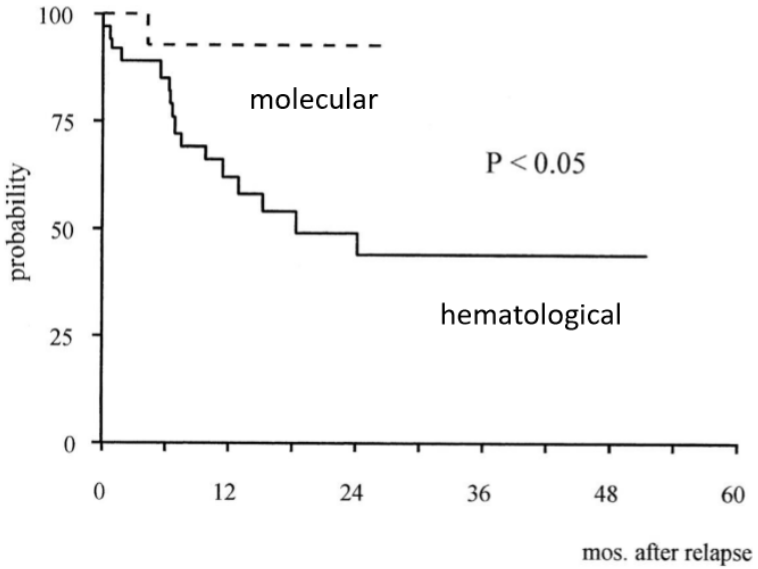


De Botton S et al., Leukemia 2006;20:35-41.

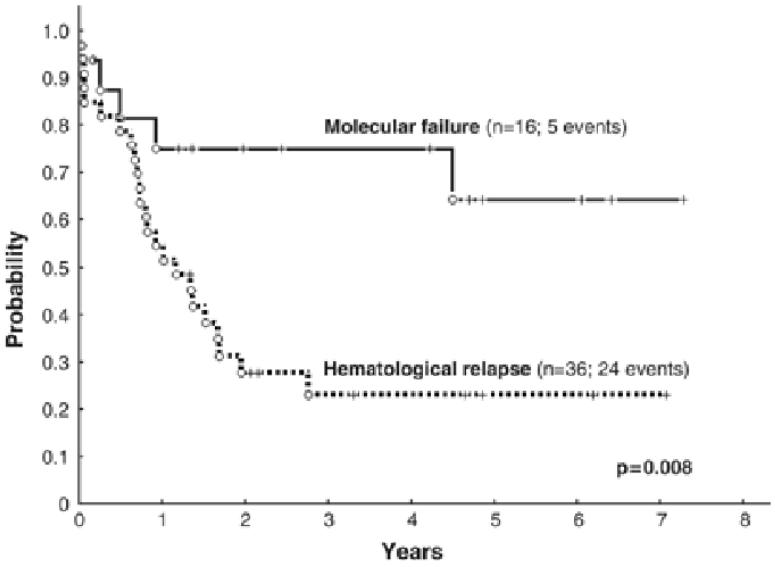


Thomas X et al, Leukemia 2000;14:1006-1013

Outcome of patients in molecular vs hematological relapse



Lo Coco et al, Blood 1999;94:2225-2229



Esteve et al, Leukemia 2007;21:446-452

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 et al, 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

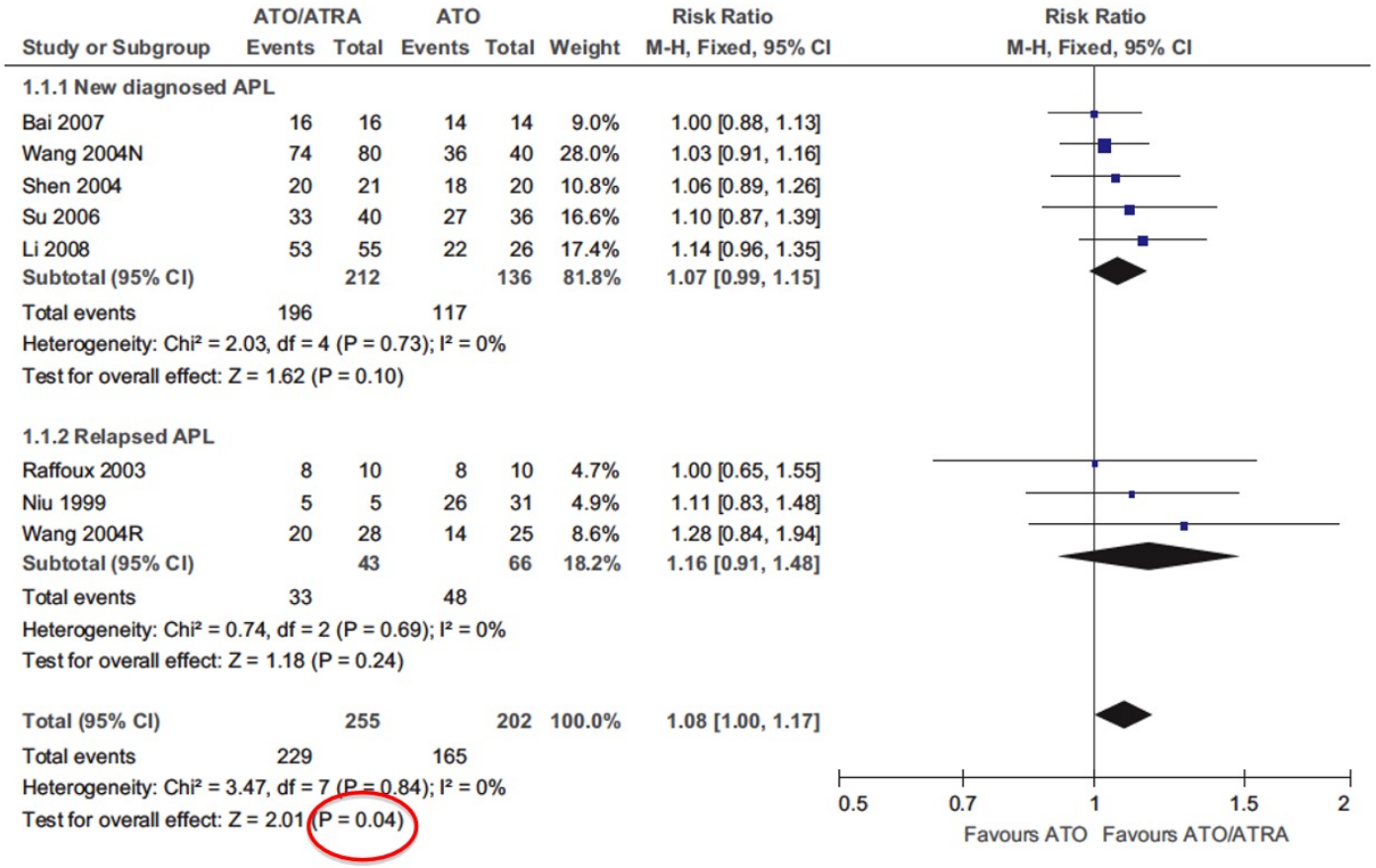
Lengfelder E et al, Leukemia 2012

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

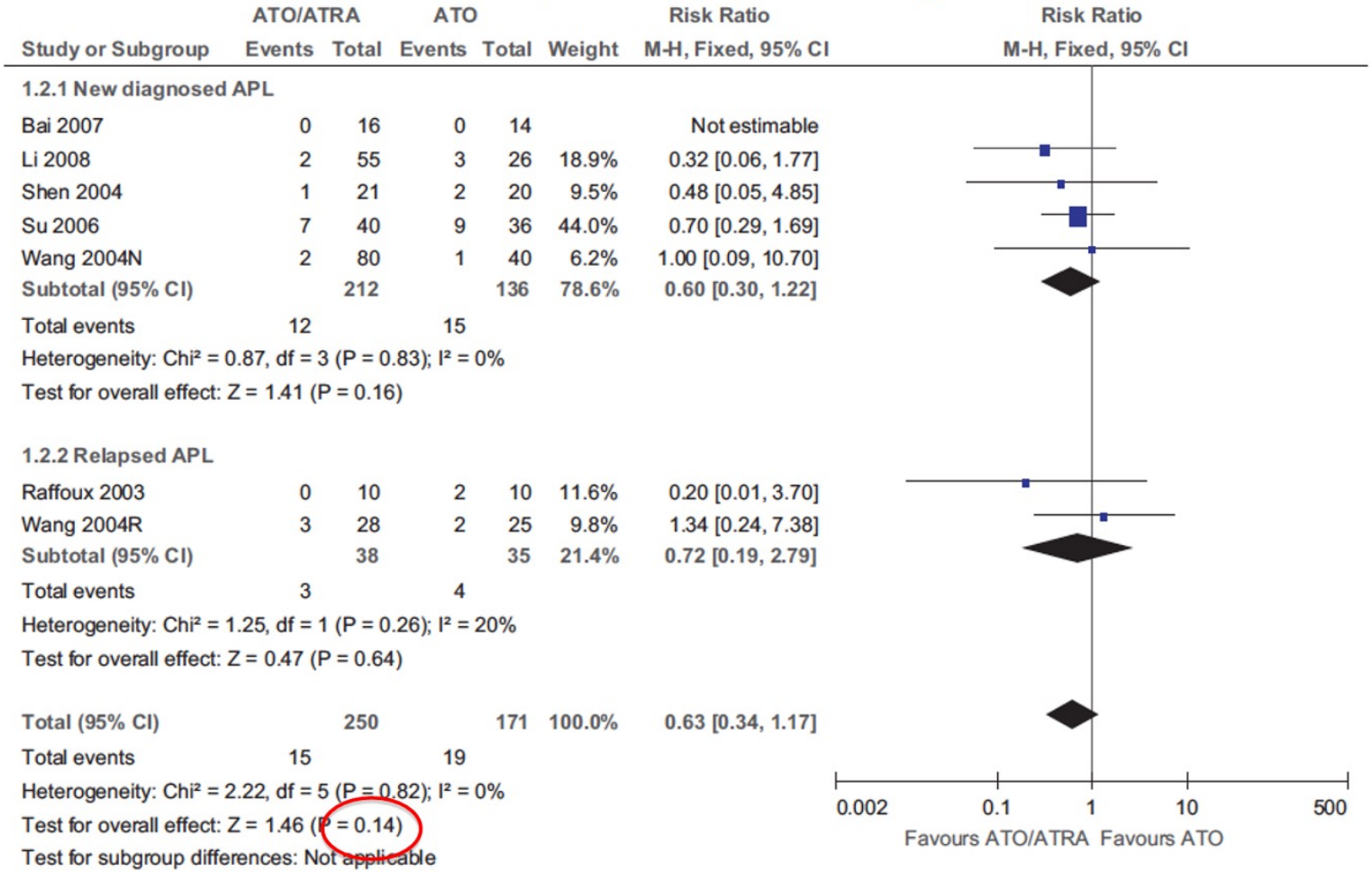


Study or Subgroup	ATO/ATRA Events	Total	ATO Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 New diagnosed APL						
Bai 2007	16	16	14	14	9.0%	1.00 [0.88, 1.13]
Wang 2004N	74	80	36	40	28.0%	1.03 [0.91, 1.16]
Shen 2004	20	21	18	20	10.8%	1.06 [0.89, 1.26]
Su 2006	33	40	27	36	16.6%	1.10 [0.87, 1.39]
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

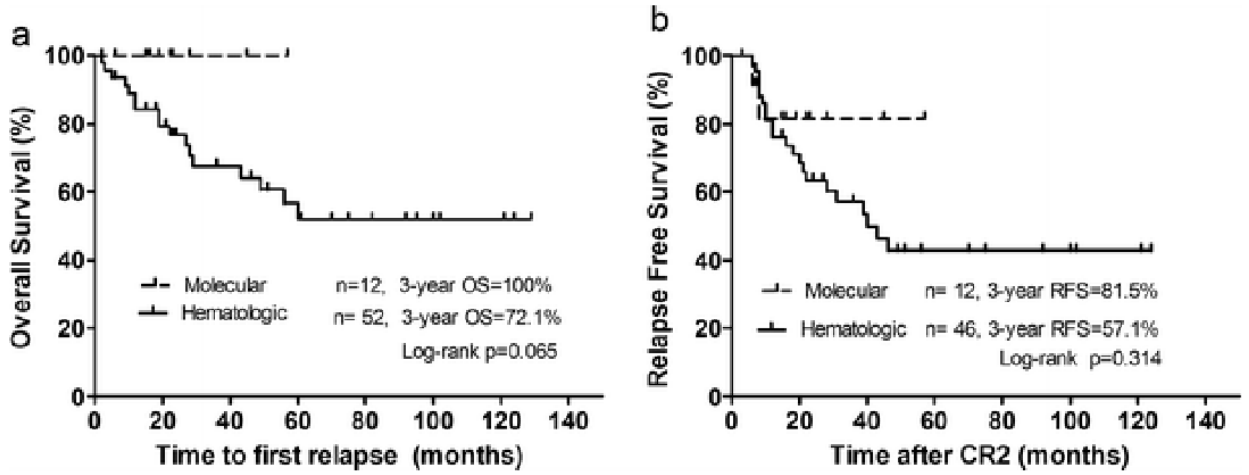


Meta-analysis results did not report an increase of ED with ATO+ATRA association

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

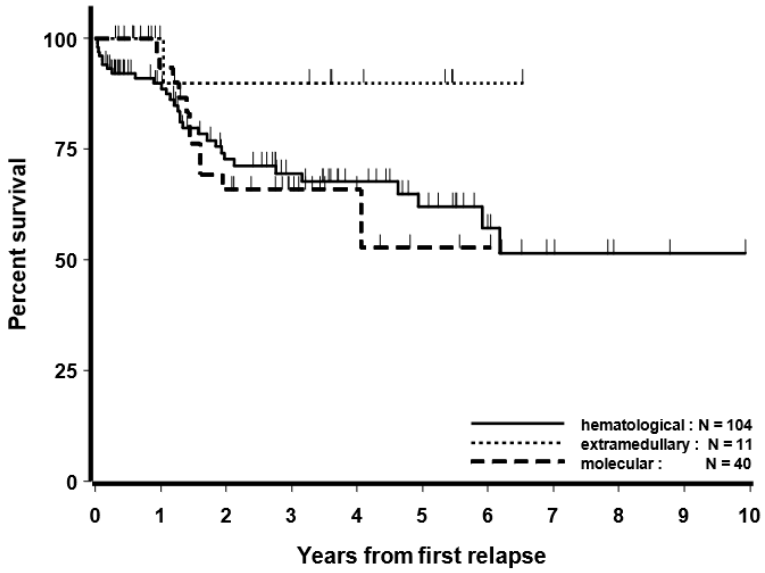
ELN registry of ATO relapsed treated pts

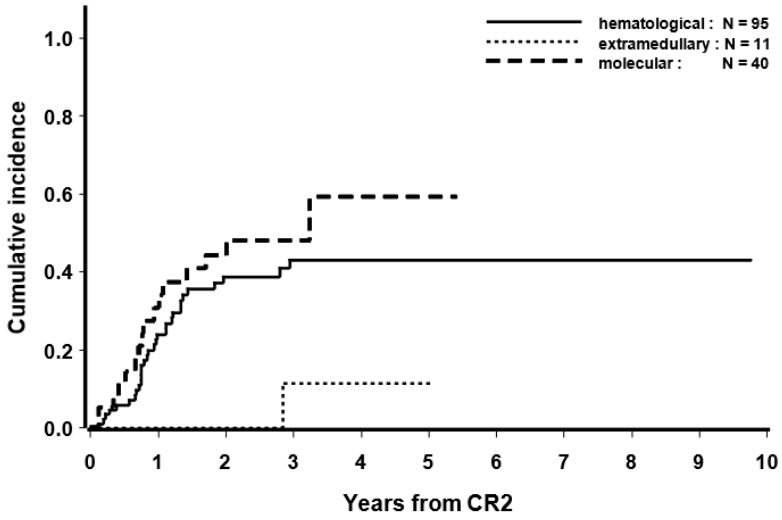
- 155 relapsed pts treated in first relapse with ATO

	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





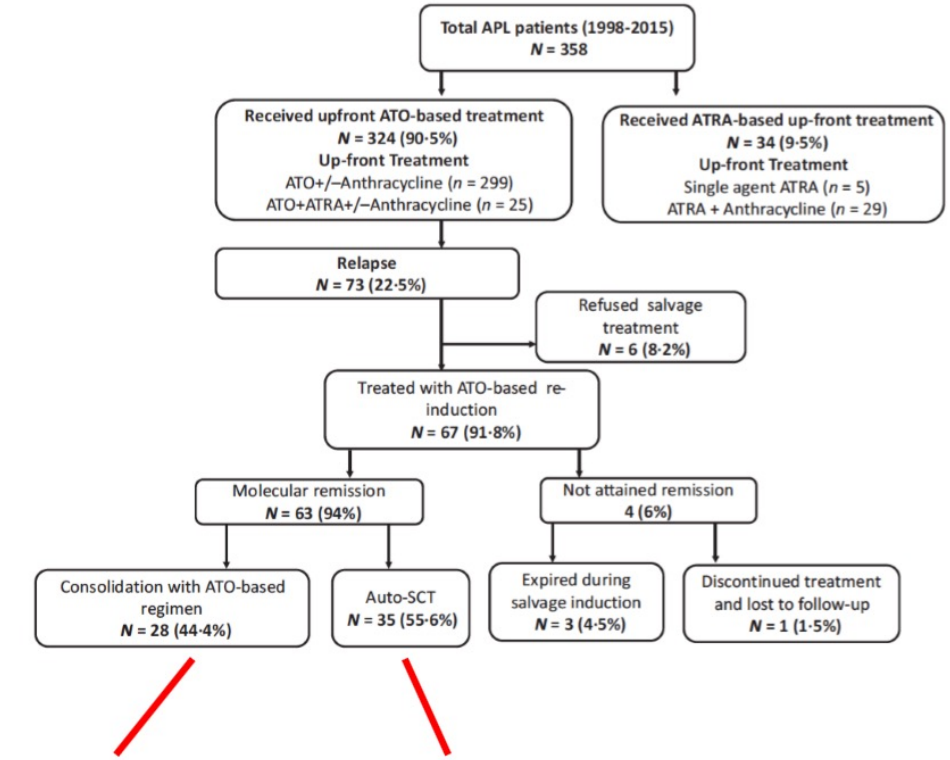
Lengfelder et al, Leukemia 2015

Summary of results of «induction» in relapsed APL

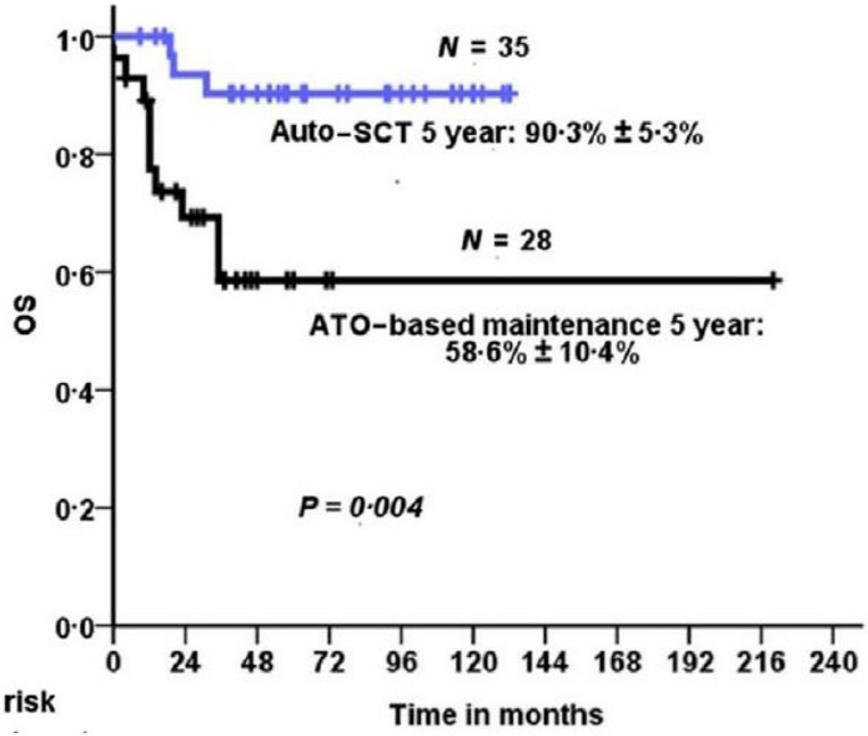
Study	*N*	*Study type*	*Previous therapy*	*Induction therapy*	*Hematological CR**	*Molecular CR*
Niu et al., 1999 [15]	47	Retrospective	ATRA + chemotherapy	ATO-based	85%	NA
Soignet et al., 2001 [16]	40	Prospective	ATRA + chemotherapy	ATO	85%	86%
Shigeno et al., 2005 [17]	34	Prospective	ATRA + chemotherapy	ATO	91%	72%
Yanada et al., 2013 [18]	35	Prospective	ATRA + chemotherapy	ATO	81%	71%
Raffoux et al., 2003 [19]	20	Prospective	ATRA + chemotherapy	ATO ± ATRA	80%	NA
Russell et al., 2018 [20]	31	Retrospective	ATRA + chemotherapy	ATRA + ATO	100%	100%
Cicconi et al., 2018 [21]	22	Retrospective	ATRA + chemotherapy	ATRA + ATO	100%	91%
Lo-Coco et al., 2004 [22]	16	Prospective	ATRA + chemotherapy	GO	-†	88%
Tobita et al., 1997 [23]	24	Prospective	ATRA + chemotherapy	Tamibarotene	58%	NA
Kulkarni et al., 2020 [24]	22	Prospective	ATO-based	ATRA + ATO + MIT + BTZ	100%	91%
Fouzia et al., 2021 [25]	67	Retrospective	ATO-based	ATO-based	94%	94%
Sanford et al., 2015 [26]	14	Prospective	ATRA + ATO-based	Tamibarotene	64%	21%

Yanada, Ann Hematol 2022

ATO-based regimens as salvage Tx after ATO 1st line



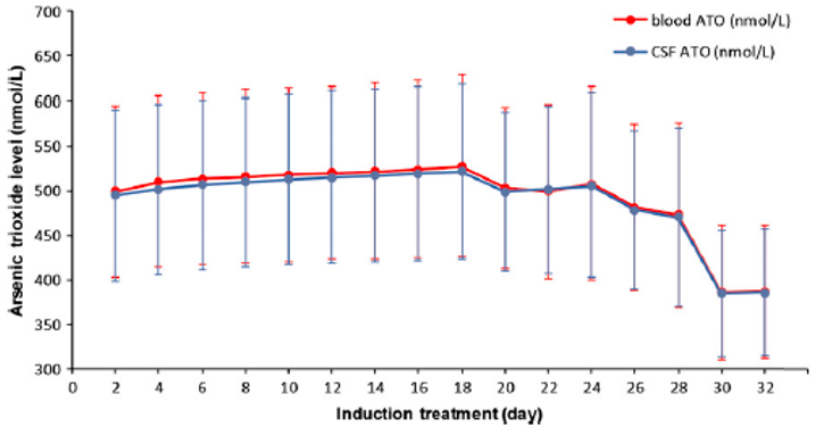
17/28 (60%) in CR **32/35 (91%) in CR**



Fouzia et al, Br J Haematol 2021

ATO for CNS relapsed patients

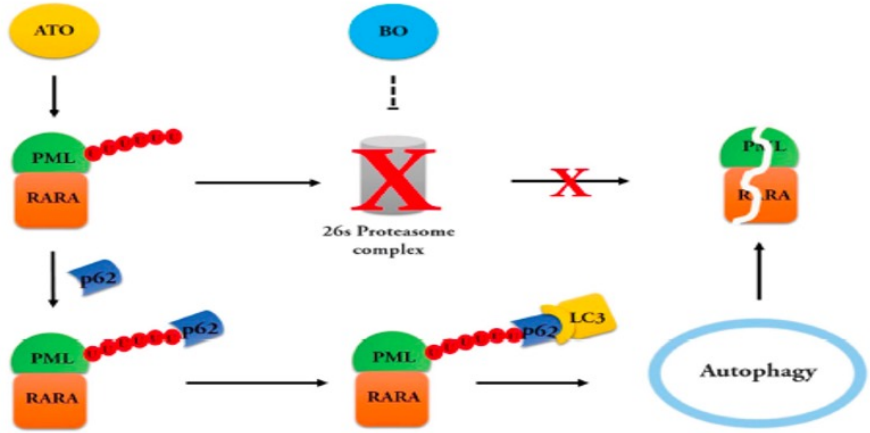
- 17 pts in CNS relapse
- Treatment 125 mL of 20% mannitol followed by the same therapy + 7 mg/mq ATO. Pts remained in bed for the entire procedure
- After induction, 3 cycles of consolidation for 14 days and then long-term maintenance
- No particular toxicity observed. No differences observed between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



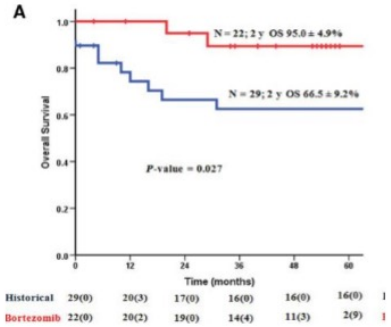
Wang et al, Blood 2014

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



- A phase II trial enrolled 22 relapsed pts
- 19/22 (86%) in mCR after induction
- 1 pt required discontinuation for neuropathy
- 12 pts performed autoSCT: 11/12 alive
- 7 pts performed maintenance and 3/7 relapsed



Kulkarni et al, Cancer Med 2019

Realgar: oral ATO for relapsed patients

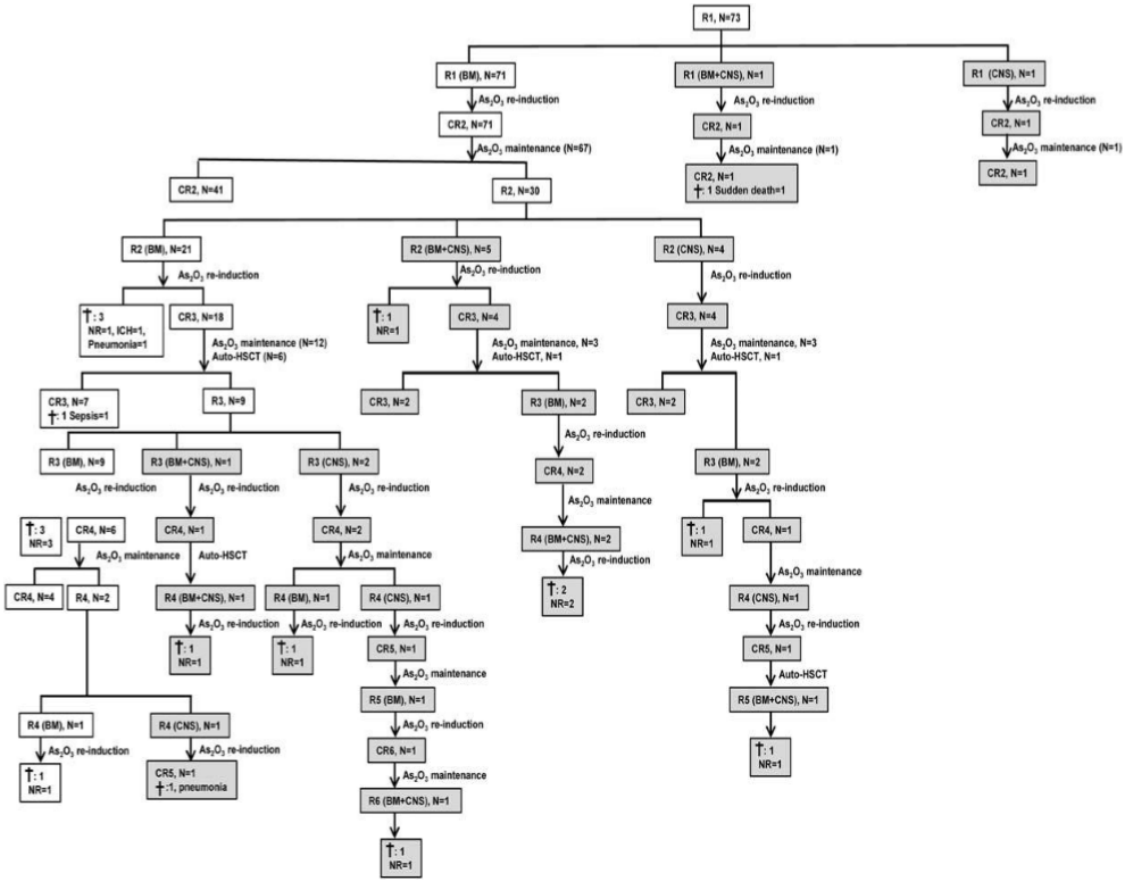
- 8 pts in first relapse, 4 pts in second relapse
- All pts achieved morphologic CR after first cycle (+/- ATRA or CHT) , but none mCR
- In second CR, 5 pts were treated with oral ATO as consolidation
- 11/12 pts reached long-lasting mCR

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: Hb, g/L	Relapse: WBC, $\times 10^9$/L	Relapse: Plat, $\times 10^9$/L	Oral As_2O_3 therapy: Duration, d	Oral As_2O_3 therapy: Additional Rx	Oral As_2O_3 therapy: Result	Consolidation	Latest PCR† (mo)	DFS, mo	Remarks
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

Oral ATO for relapsed patients after 15-year prospective study



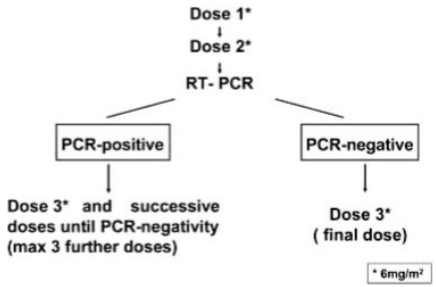
- 73 pts in first relapse
- All pts treated with oral ATO achieved a CR2
- At a median FU of 94 months, 43 pts still in CR2.
- Hepatotoxicity occurred in 47.9%
- 10-year LFS was 56.8%
- 30 pts in R2: oral ATO led to CR3 in 90% of pts
- At a FU of 30 months, 11 pts still in CR3

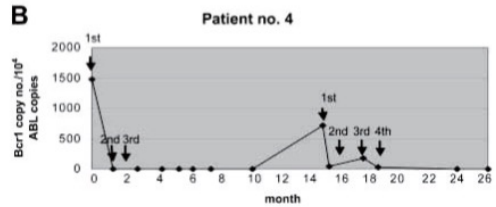
Gill et al, Cancer 2018

GO as single agent for relapsed APL

Patient no.	Results of qualitative RT-PCR for PML-RARα*			No. GO cycles received	Relapse/type	Duration of molecular remission, mos.	Successive therapies	Outcome
	1st cycle	2nd cycle	3rd cycle					
1	ND	Negative	Negative	3	No	31+	—	Alive in MR
2	Negative	Negative	Negative	3	No	14+	—	Alive in MR
3	Positive	Positive	—	2	Yes/morphologic	NE	MITOX, MITOX†	Alive in MR
4	Negative	Negative	Negative	3	Yes/molecular	13	GO†/MITOX + ARA-C	Alive in MR
5	Negative	Negative	Negative	3	Yes/morphologic	6	MITOX + ARA-C	Died of disease progression
6	ND	Negative	Negative	3	No	7+	—	Alive in MR
7	ND	ND	—	2	Yes/morphologic	NE	—	Died of disease progression
8	Negative	ND	Negative	3	Yes/molecular	7	MITOX + ARA-C	Alive in MR
9	ND	Negative	Negative	3	Yes/molecular	8	GO‡	Alive in MR
10	ND	Negative	Negative	3	No	19+	—	Alive in MR
11	Negative	—	—	1	Yes/molecular	6	DLI	Alive in MR
12	ND	ND	Negative	3	No	12+	—	Alive in MR
13	ND	ND	Negative	3	No	19+	DLI	Alive in MR
14	ND	Positive	Negative	3	No	15+	—	Alive in MR
15	ND	Negative	Negative	3	Yes/molecular	15	—	Alive in MR
16	Negative	Negative	Negative	3	Yes/morphologic	3	ATO	Died of disease progression

56% → 81%





Lo Coco et al, Blood 2004

ATO+ATRA+GO as consolidation for relapsed APL

- 7 patients in 1st relapse
- All received ATO until CR
- Once in CR, they received consolidation with ATO+ATRA+GO for 10 months
- Then, a maintenance with idarubicin, ATRA, 6-MP and oral MTX for 11 months
- At a median FU of more than 36 months, 6 remained in second CR (2 pts died for second neoplasia and one for sepsis)

Patient	Age, y	No. of days to achieve CR	No. of days to achieve negative PCR	Previous CR duration, mo	Duration of second CR, mo
1	64	21	91	17	≥55
2	43	0	165	20	≥51
3	68	28	127	28	≥48*
4	51	56	125	22	≥45
5	54	56	123	16	≥7*
6	18	28	24	7	≥27
7	22	56	177†	15	≥23
8	52	39	96	48	≥1

Aribi et al, Cancer 2006

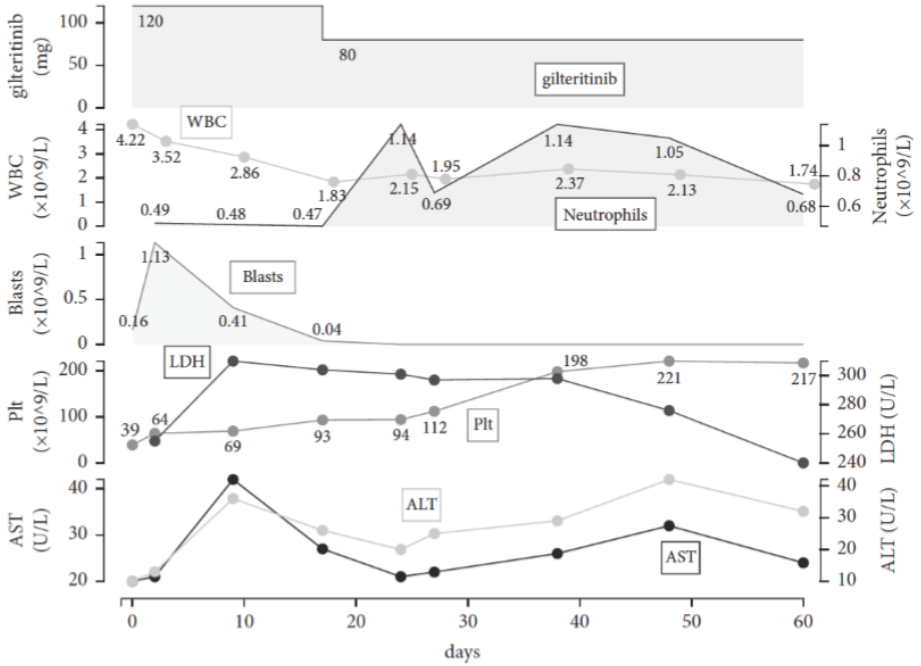
Tamibarotene for rAPL after ATRA+ATO

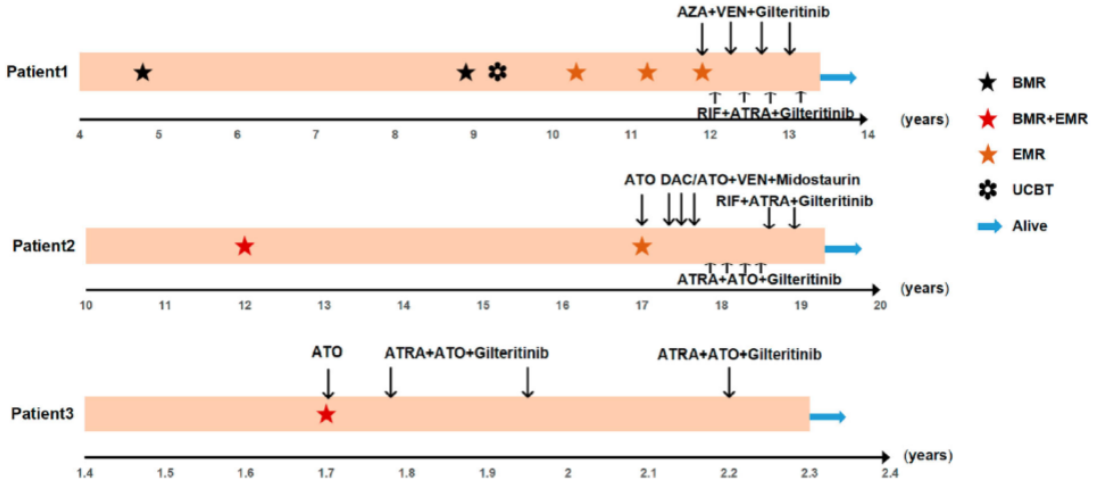
- 14 patients in 1st relapse after ATRA+ATO
- ORR 64% (CMR 21%)
- Relapses were frequent: 7/9 after a median of 4.6 mos, with median OS 9.5 mos and EFS 3.5 mos

	Disease status at enrolment									
Patient	Haematological relapse (Y/N)	Cytogenetic relapse (Y/N)	Molecular relapse (Y/N)	Haematological response	Cytogenetic response (Y/N)	Molecular response (Y/N)	Relapse (Y/N)	Time to relapse (d)	Overall survival (d)	Alive at last follow-up (Y/N)
1	Y	Y	Y	RD	N	N	–	–	289	N
2*	Y	Y	Y	CR	Y	N	N	–	257	N
3*	Y	Y	Y	CR	Y	N	N	–	526	N
4	Y	Y	Y	CRi	Y	N	Y	183	213	N
5	Y	Y	Y	RD	N	N	–	–	378	N
6†	Y	Y	N/A	CR	N	Y	Y	117	183	Y
7*	Y	Y	Y	CRi	Y	Y	Y	816	1432	N
8	Y	Y	N/A	RD	N	N	–	–	154	N
9	N	N	Y	CRi	Y	N	Y	295	320	N
10	Y	Y	Y	CR	Y	Y	Y	49	233	N
11‡	Y	Y	Y	CR	N/A	Y	Y	56	1769	Y
12	N	N	Y	CRi	N/A	N	Y	141	385	N
13	Y	Y	Y	RD	–	–	–	–	64	N
14	Y	Y	Y	RD	–	–	–	–	93	N

Sanford et al, Br J Haematol 2015

Gilteritinib for FlT3+ rAPL after ATRA+ATO



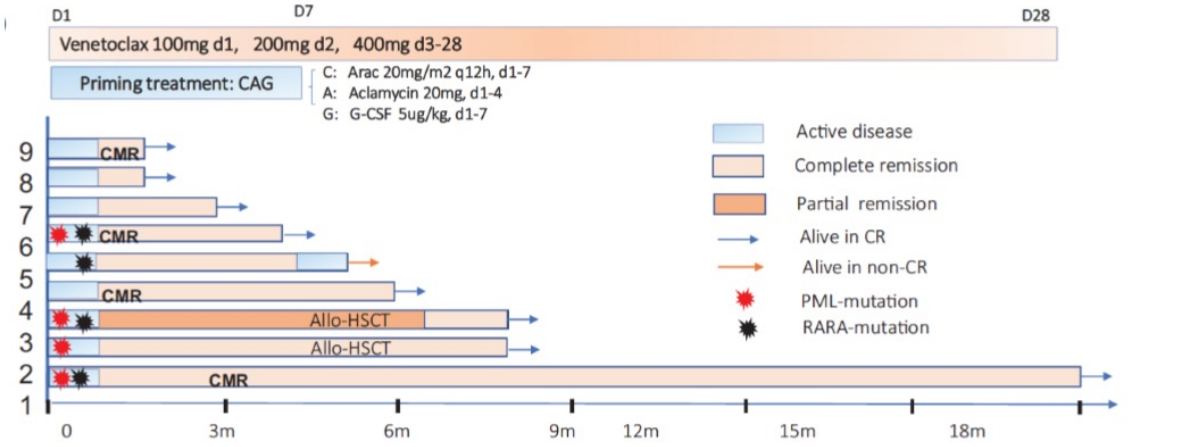


- Female pt, 52 y, treated with ATRA+CHT and IT for CNS
- Relapse after 14 mos, FLT3+ (79%). ATO for relapse but failure
- Tamibarotene yielded a CR. High dose cytarabine as consolidation
- 2 relapse: gilteritinib with 2CR after 60 days

- 3 pts treated with gilteritinib in combination
- 2 pts with isolated persistent extramedullary relapse achieved CR
- 1 pt had BM+CNS and achieved mCR

Kobayashi et al, Case Report Hematol 2023; Hou et al, Hematology 2023

Venetoclax combined with chemo for rAPL



SN	sex	age	diagnosis	risk	front-line	relapse	Arsenic	PML	RARA	Lastest	V-CAG	toxic grade of V-CAG treatment					Response of V-CAG treatment			subsequent treament	current status
		ys	time	grade	treatment	numbers	resistance	mutation	mutation	slavage	time	Neutropenia	Anaemia	Thrombocytopenia	TLS	infection		PML-RARA	FCM		(2021-7-20)
1	M	22	2009.9	intermediate	ATRA+Chemo	5	yes	A216T	R272Q	ATRA+ATO+Ida	2020/1/8	1	0	0	no	0	CR	0.06%	0	V-CAG*1cycle,Ven2cycles	alive in CR for 17months
2	M	43	2016.5	intermediate	ATRA+RIF	4	yes	A216V	no	ATRA+RIF	2020/11/28	4	3	4	no	0	CR	0.45%	0	V-CAG*1cycle,Allo-HSCT	alive in CR for 7months
3	F	43	2014.9	intermediate	ATRA+Chemo	4	yes	A216T	H298D	ATRA+ATO+Ida	2021/1/9	4	4	4	no	3	PR	7.13%	0	V-CAG*1cycle ,Allo-HSCT	alive in CR for 7months
4	M	23	2016.5	high	ATRA+ATO	3	yes	no	no	ATRA+RIF	2021/1/9	3	0	2	no	0	CR	0	0	V-CAG*2cycle,Ven2cycles	alive in CR for 5months
5	F	57	2017.4	high	ATRA+Chemo	6	yes	no	I273V	HA	2021/1/22	4	3	4	no	2	CR	0.95%	0	V-CAG*2cycle-HAG	relapse after 4 and alive
6	M	15	2019.6	low	ATRA+Chemo	2	yes	A216T	T285I	Ida	2021/3/16	1	0	1	no	0	CR	0	0	V-CAG*1cycle,Ven 2cycles	alive in CR for 3months
7	M	30	2017.5	intermediate	ATRA+ATO	3	yes	no	no	ATRA+ATO+Ida	2021/4/23	0	1	1	no	0	CR	16%	0	V-CAG 1cycle	alive in CR for 2months
8	M	32	2019.7	intermediate	ATRA+ATO	1	yes	no	no	ATRA+RIF	2021/5/2	4	1	2	no	0	CR	0	0	V-CAG 1cycle	alive in CR for 1months
9	M	60	2014.1	low	ATRA+ATO	3	yes	NA	NA	ATRA+ATO+Ida	2021/5/20	4	3	4	no	2	CR	0.24%	0	V-CAG 1cycle	alive in CR for 1months

- 9 patients
- Median age 35 years
- All pts resistant to ATO
- 8 pts achieved CR, among them 3 achieved mCR and 1 PMCR

Wang et al, Br J Hematol 2022

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 could be considered also for CNS involvement
- ATO based regimens could also be considered for pts in >2 relapses (bortezomib, GO)
- New possible drugs in multi-relapsed patients (Venetoclax) or for selected patients (Gilteritinib)