

# LEUKEMIA2022

Rome, Hotel NH Collection - Vittorio Veneto

May 5-6, 2022

AIL President: G. Toro  
Coordinators: A.M. Carella, S. Amadori



## From biology to therapy: progress in acute promyelocytic leukemia

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UNDER THE AUSPICES OF:



SIE - Società Italiana di Ematologia

## Disclosures

Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other
<b>Celgene/ BMS</b>	x				x	x	
<b>Astellas</b>					x		
<b>Jazz</b>			x		x	x	
<b>Abbvie</b>					x		
<b>Novartis</b>	x				x		

## Outline

- ❖ Biology and targeted therapy
- ❖ Long-term results of ATRA/ATO protocols
- ❖ Oral ATO
- ❖ ATO-resistance
- ❖ Therapy-related APL
- ❖ APL-like AMLs

# Milestones in APL biology



1973

Response to anthracyclines  
*J Bernard*

1977

t(15;17)  
 Identification  
*JK Rowley*

1988

Differentiation with retinoids  
*Z-Y Wang*

1990

t(15;17) cloning  
*A Dejean, F Lo-Coco, PG Pelicci*

1992

Monitoring MRD  
*WH Miller, F Lo Coco*

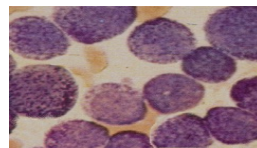
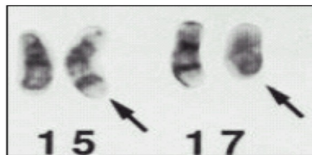
1998

Effects of PML/RAR $\alpha$  on transcription  
*PG Pelicci, F Lo Coco, PP Pandolfi*

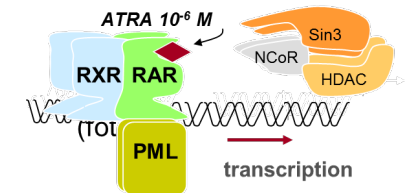
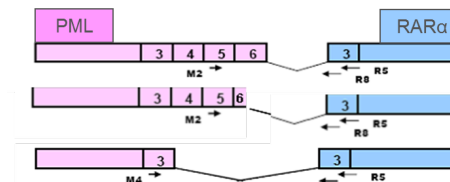
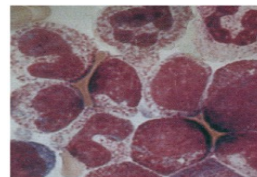
**BLOOD** *The Journal of Hematology*  
 VOL. XLII, NO. 4 APRIL 1973

Acute Promyelocytic Leukemia: Results of Treatment by Daunorubicin

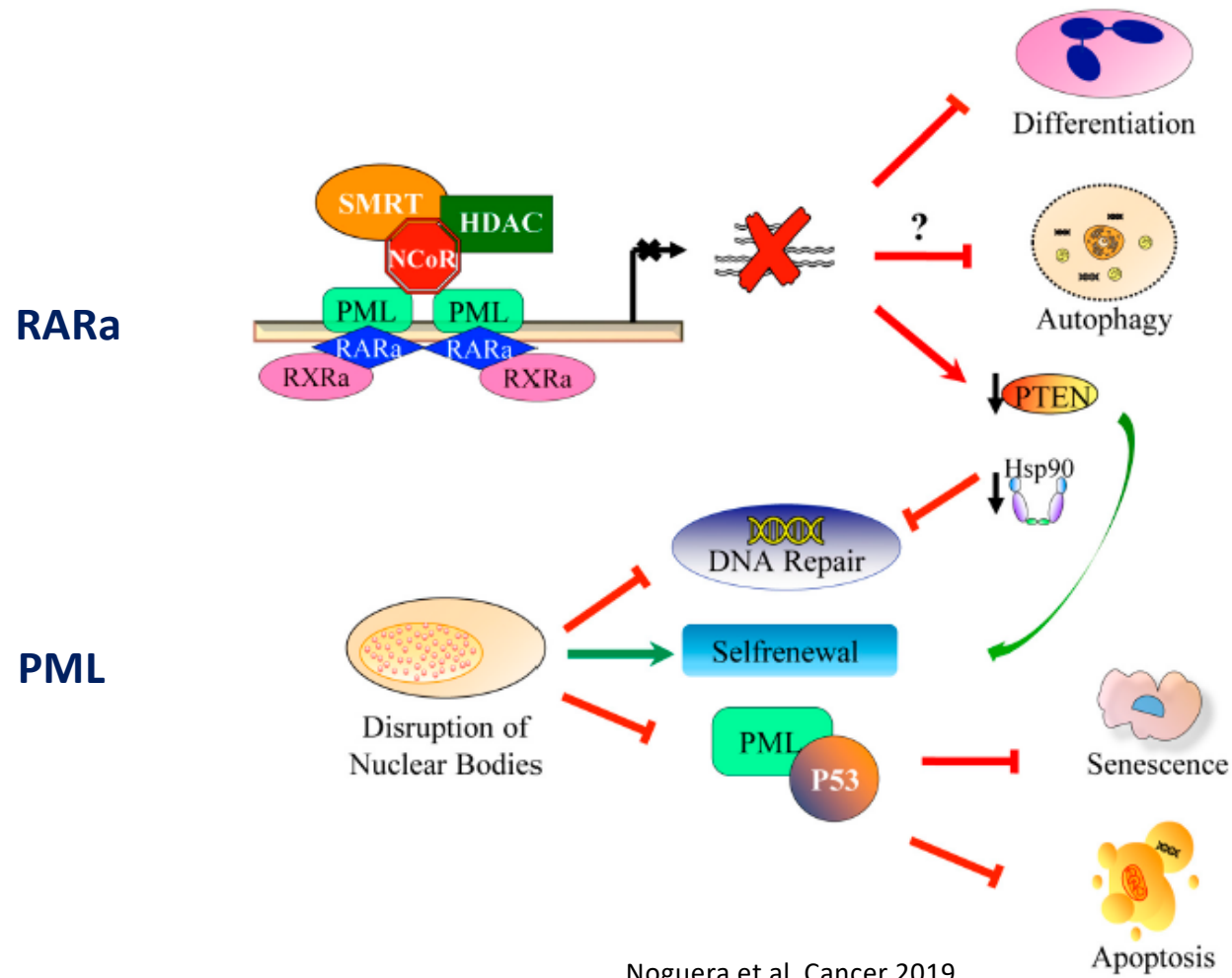
By Jean Bernard, Marise Weil, Michel Bolron, Claude Jacquillat, Georges Flandrin, and Marie-Françoise Gemon



**ATRA**



# Pathogenesis of APL

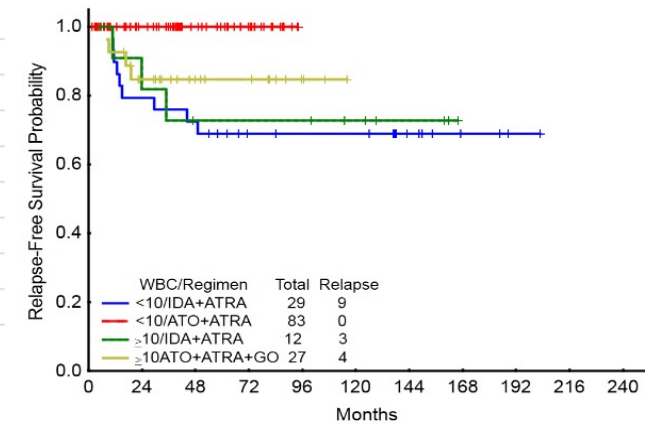
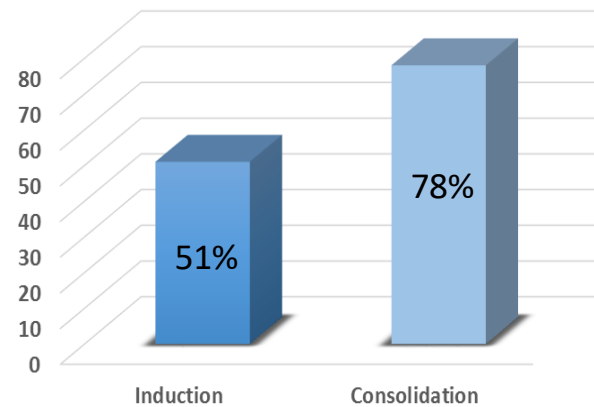
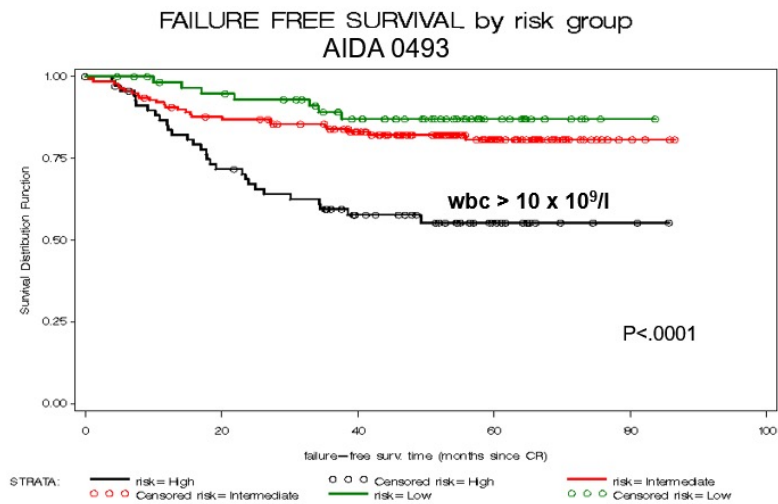


Noguera et al. Cancer 2019

## GIMEMA/PETHEMA risk categories

## ATRA/ATO at relapse: molecular responses

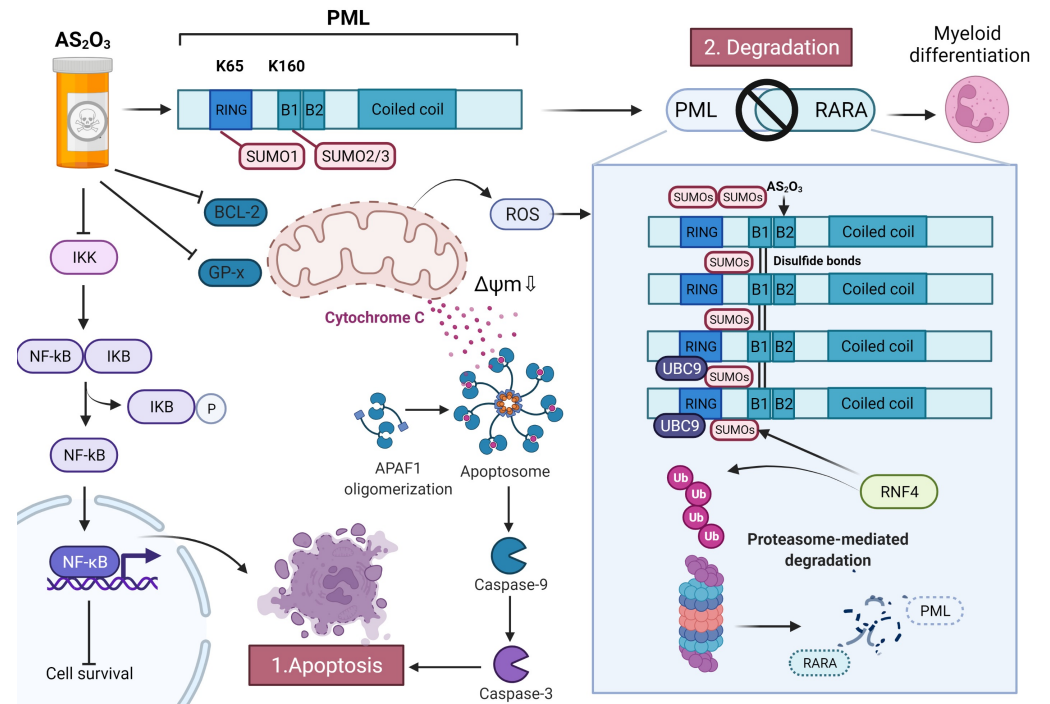
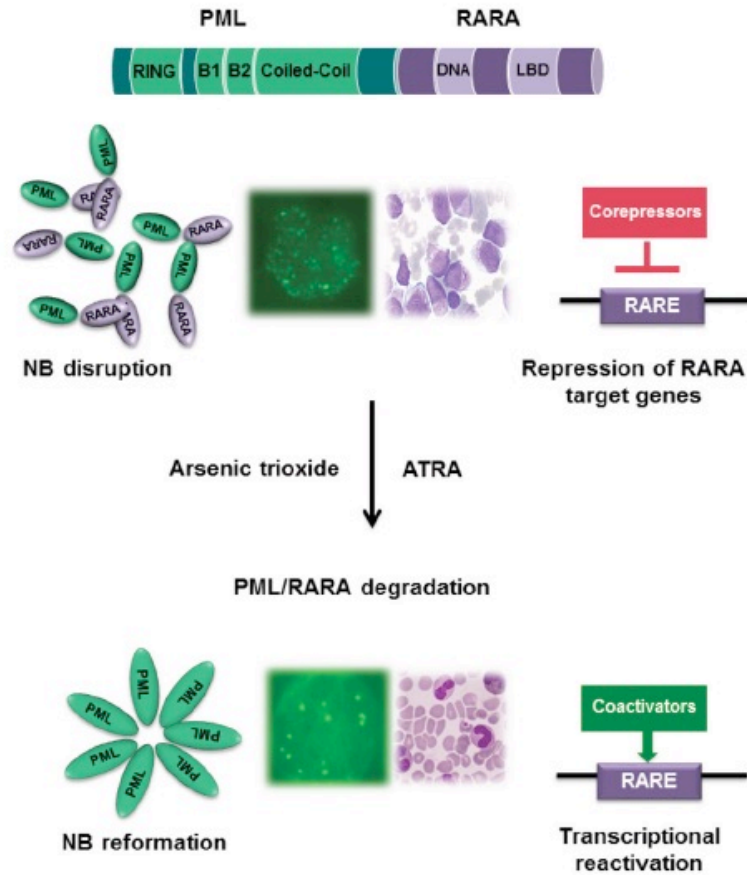
## ATRA/ATO first-line: RFS



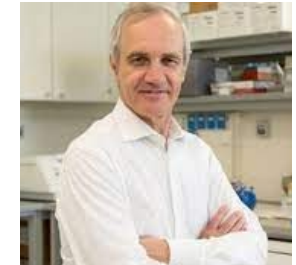
Sanz et al, Blood 2000  
 Raffoux et al, JCO 2002  
 Estey et al, Blood 2006



# Activities of ATRA/ATO in APL



Courtesy of C. Gurnari

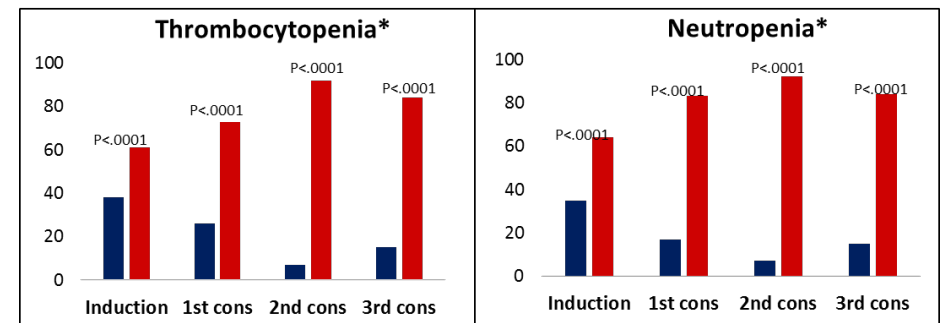
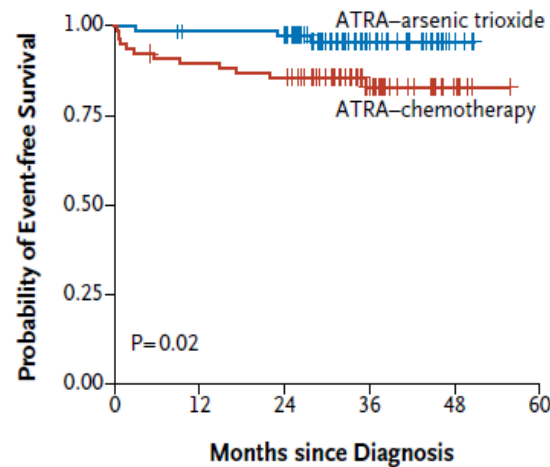
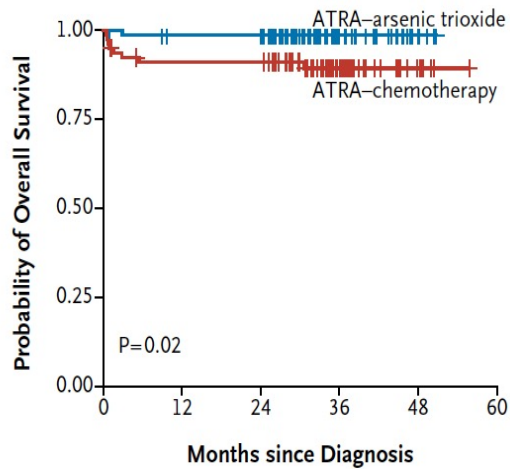


Retinoic Acid and Arsenic Trioxide  
 for Acute Promyelocytic Leukemia

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

n=156 pts, yy 2007-2012

APL0406 : prospective, randomized, multicenter, open-label, phase III, noninferiority trial.



\*grade 3/4

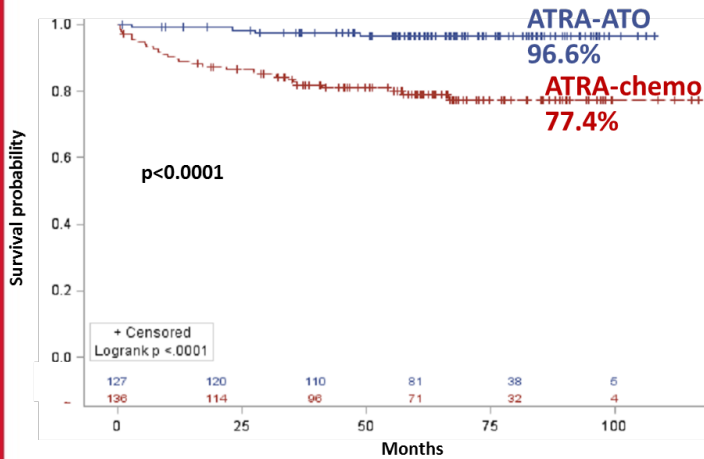
	ATRA-Chemo	ATRA-ATO
Leukocytosis	5-10%	40%
AST/ALT elevation	5%	40%
QTc prolongation	-	10%

NCCN 2015 Recommendations:  
 ATRA+ATO as first line therapy for low to intermediate risk APL

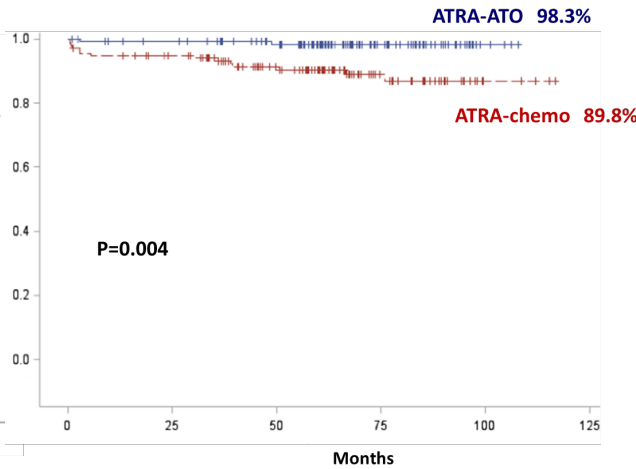


Update at 72 months

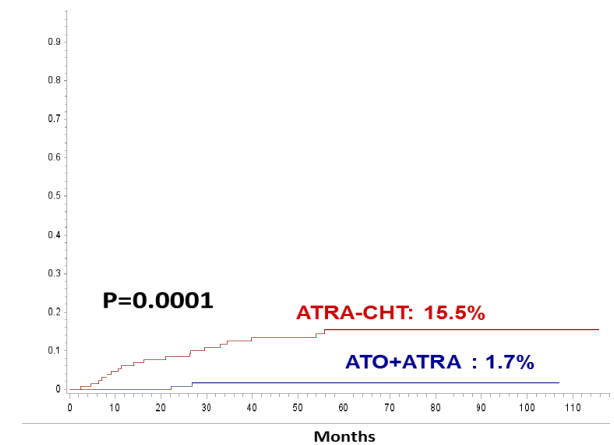
Event-free survival



Overall survival



Cumulative incidence of relapse



Fatal events

Pt	Age	Arm	Disease phase	Time to event (m)	Cause of death
1	61	ATRA-Chemo	Induction	0.5	ARDS
2	26	ATRA-Chemo	Induction	0.6	Cardiovascular accident
3	46	ATRA-Chemo	Induction	0.4	Ischemic stroke
4	51	ATRA-Chemo	Induction	0.9	Differentiation syndrome
5	55	ATRA-Chemo	CR	2.9	Hemorrhagic shock
6	67	ATRA-Chemo	CR	5.4	Pneumonia
7	69	ATRA-Chemo	CR	2.8	Pulmonary embolism
8	62	ATRA-Chemo	CR	66.6	t-AML
9	60	ATRA-Chemo	CR	36.1	t-MDS evolved in AML
10	29	ATRA-Chemo	Relapse	7.3	Progressive disease
11	43	ATRA-Chemo	Relapse	34.7	Progressive disease
12	52	ATRA-Chemo	Relapse	55.1	Transplant related death
13	49	ATRA-Chemo	Relapse	9.1	Progressive disease
14	52	ATRA-ATO	CR	2.8	Pneumonia (H1N1)
15	64	ATRA-ATO	CR	48.8	Colon cancer

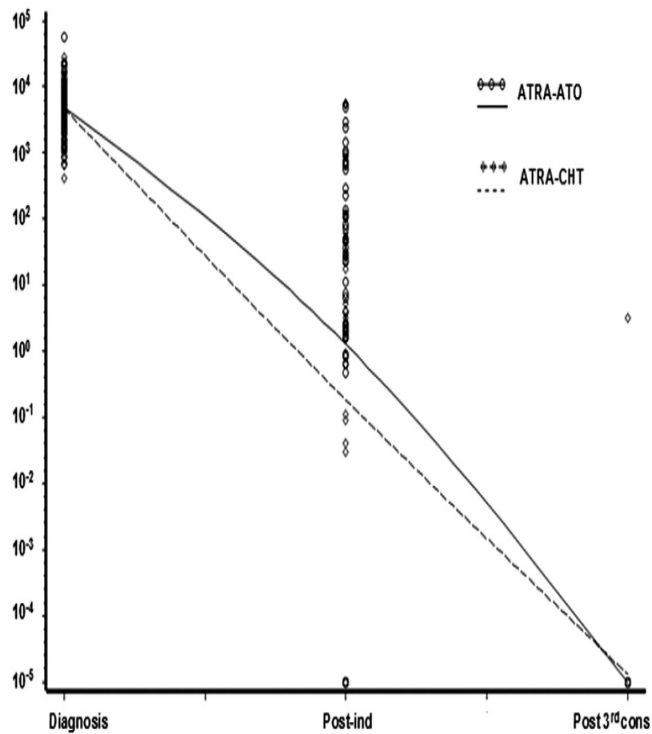
✓ Improved short and long-term **patient-reported outcomes and HR-QOL** with ATRA/ATO vs ATRA/chemotherapy

Platzbecker et al, J Clin Oncol 2017  
Cicconi *et al*, Leukemia 2019  
Efficace et al, J Clin Oncol 2014 and Blood Adv 2021

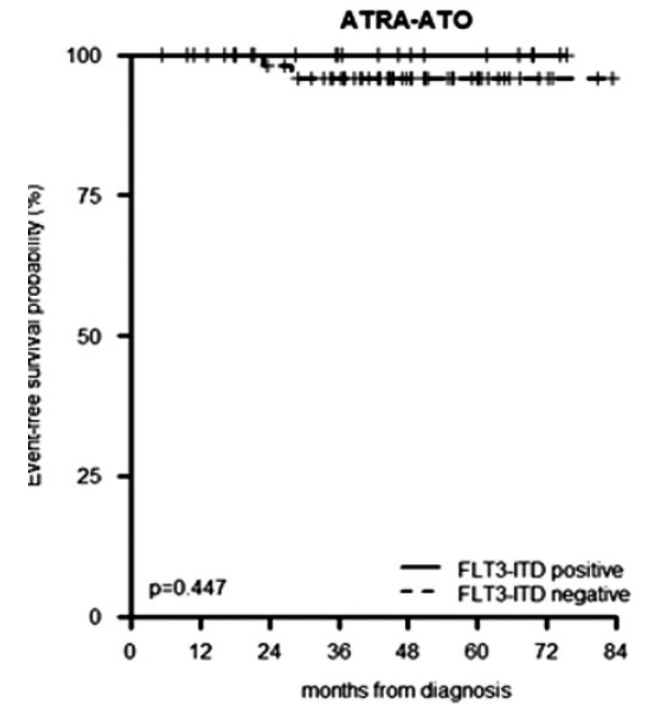
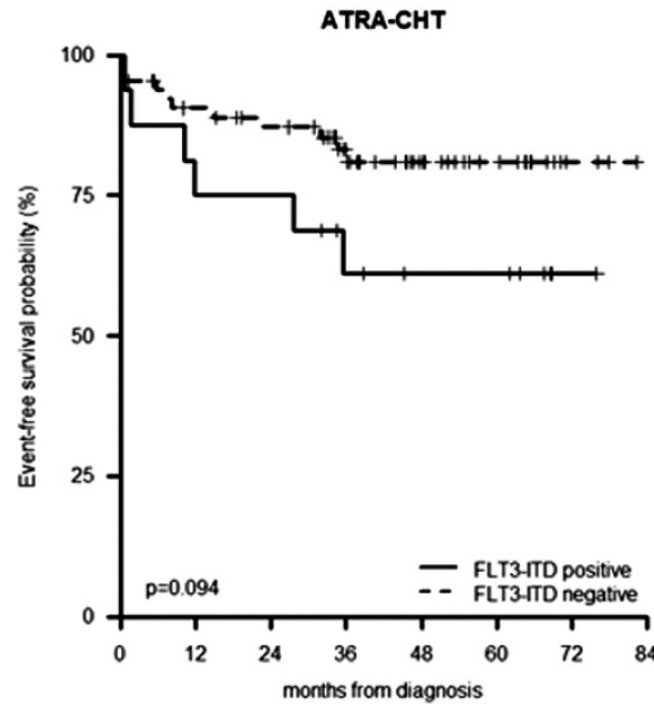
# APL0406: Molecular studies



## MRD



## Role of FLT3-ITD mutations



Cicconi L, Divona M *et al*, Leukemia 2016

# AML17 trial, AIDA vs ATRA/ATO



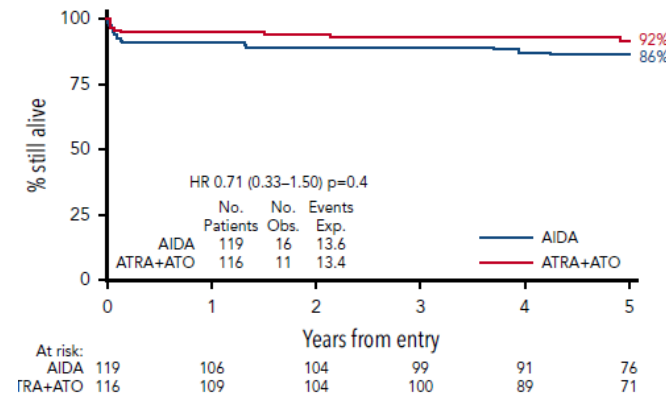
## Follow-up at 5 years

ATO 0.3 mg/kg day 1-5,  
 0.25 mg/kg 2x/w on w 2-8 of cy 1,  
 + 3 consolidations

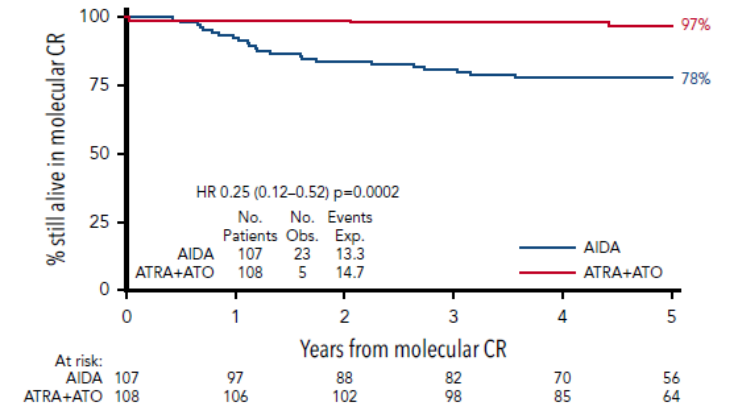
High-risk APL: GO 6 mg/sqm on d 1-4

No maintenance treatment  
 No CNS prophylaxis

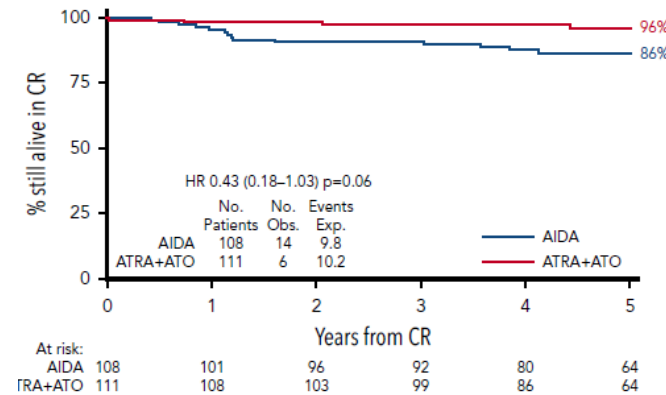
**A** AML17: Overall Survival



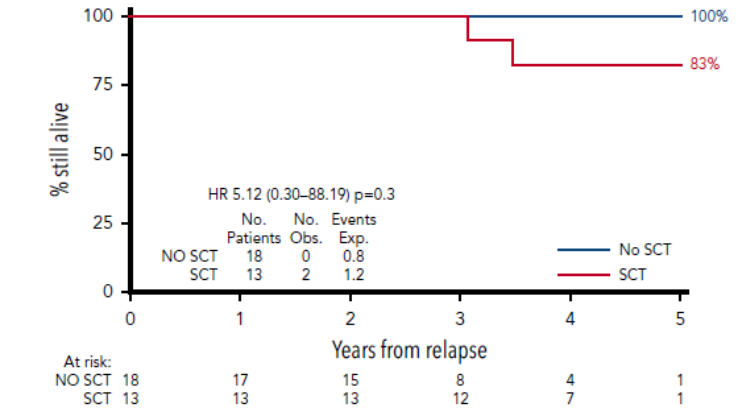
**B** AML17: Molecular Relapse Free Survival



**C** AML17: Relapse Free Survival

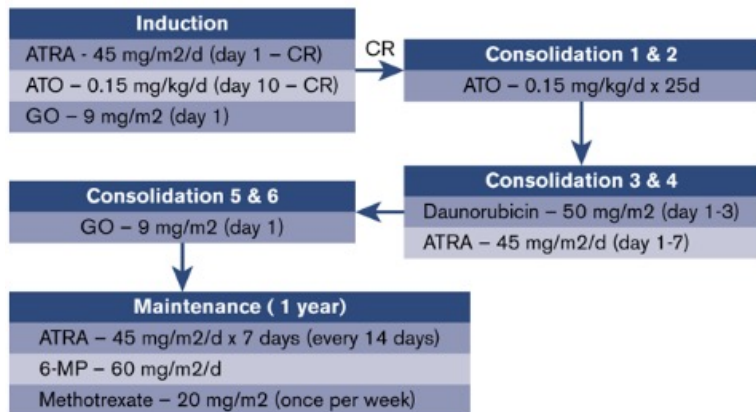


**D** AML17 (AIDA): Overall Survival from Relapse



Burnett et al, Lancet Oncol 2015  
 Russell et al, Blood 2018

## A phase 2 study of ATRA, arsenic trioxide, and gemtuzumab ozogamicin in patients with high-risk APL (SWOG 0535)



Primary end points:

- 3-year EFS
- early (6-week) death rates

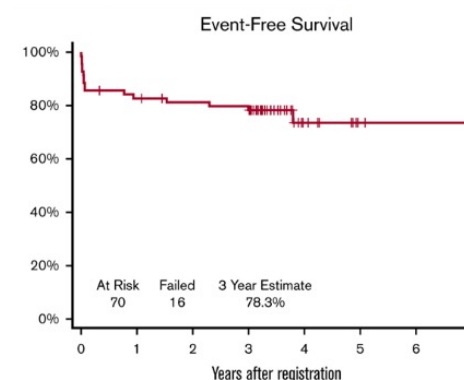
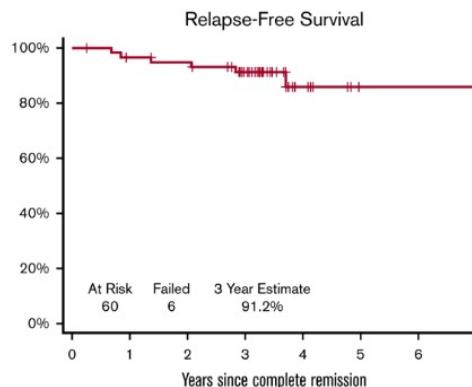
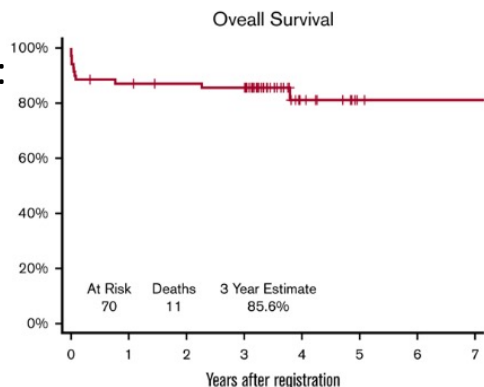
n=70 patients enrolled,  
 60 achieved CR (86%)

RA-differentiation syndrome:  
 6 pts (9%), only 1 Grade 3-4  
 All during induction phase

Of 8 deaths by 6-weeks,  
 3 were for hemorrhage,  
 2 infections, 1 hepatic failure,  
 2 unknown.

Median follow-up:  
 3.4 years

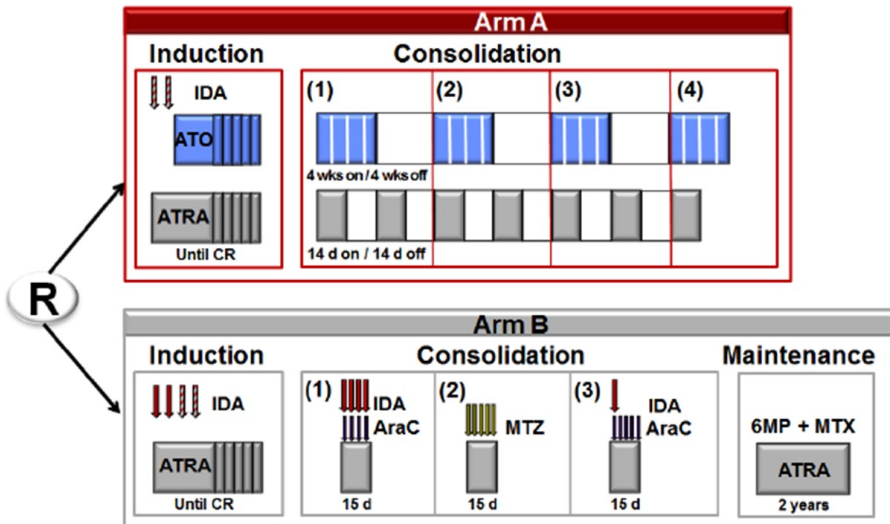
At 3 yrs:  
 OS: 86%  
 EFS: 78%



# What's next?



## High-risk APL: APOLLO Trial



Ongoing  
EoE: July 2022

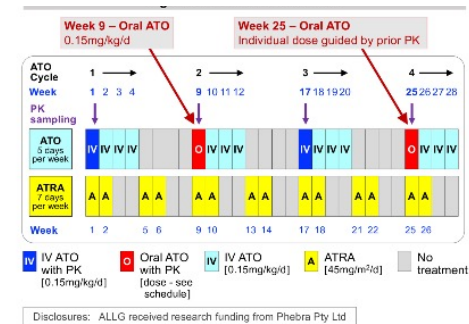
Zhu et al, J Clin Oncol 2013  
Gill et al, Cancer 2019  
Illand et al, EHA 2019

## Oral Arsenic formulations

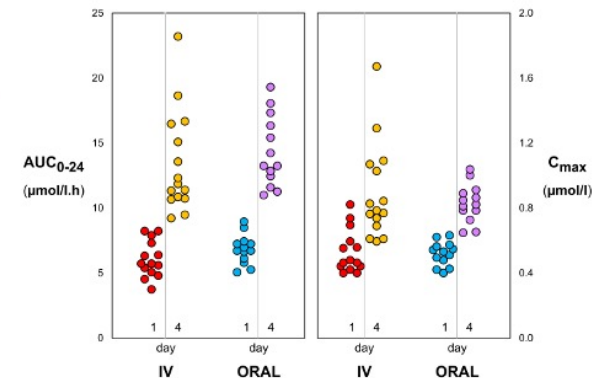
- ✓ Liquid oral As<sub>2</sub>O<sub>3</sub> (Hong-Kong, Au et al, 2003)
- ✓ RIF: Realgar natural mixture containing tetra arsenic tetra sulfide (As<sub>4</sub>S<sub>4</sub> pills, China, Zhu et al, 2013)
- ✓ ATO oral powder capsules, ORH-2014

**ALLG  
APML5**  
ACTRN12616001022459

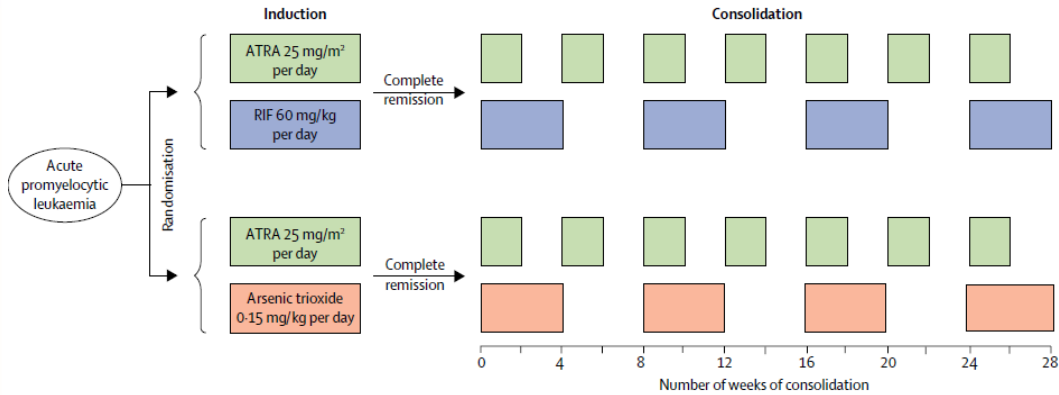
n=31 pts, ATO powder  
with APL at DG



Whole blood PK parameters: IV (cycles 1 & 3) vs ORAL (cycles 2 & 4)

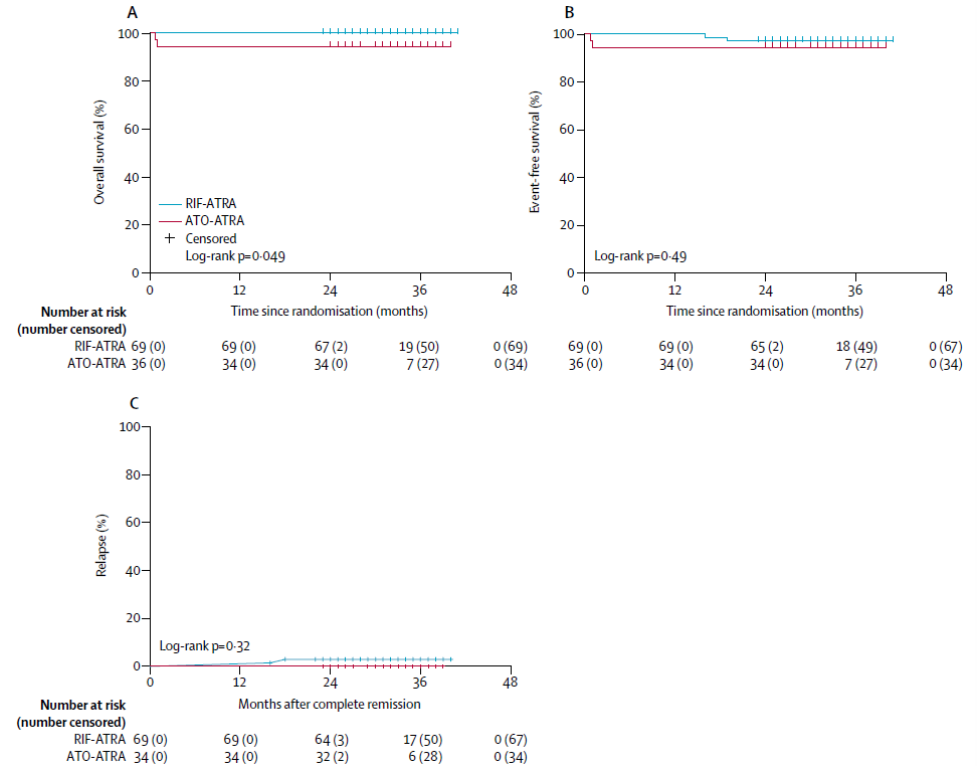


# ATRA/RIF vs ATRA/ATO in Std risk APL



	RIF-ATRA group (n=69)	Arsenic trioxide-ATRA group (n=36)	p value
Complete remission	69 (100%)	34 (94%)	0.12
Molecular remission after consolidation*	68 (100%)	34 (100%)	..
30-day mortality	0	2 (6%)	0.11
2-year event-free survival	67 (97%)	34 (94%)	0.49
2-year overall survival	69 (100%)	34 (94%)	0.049
2-year cumulative incidence of relapse	2 (3%)	0%	0.32

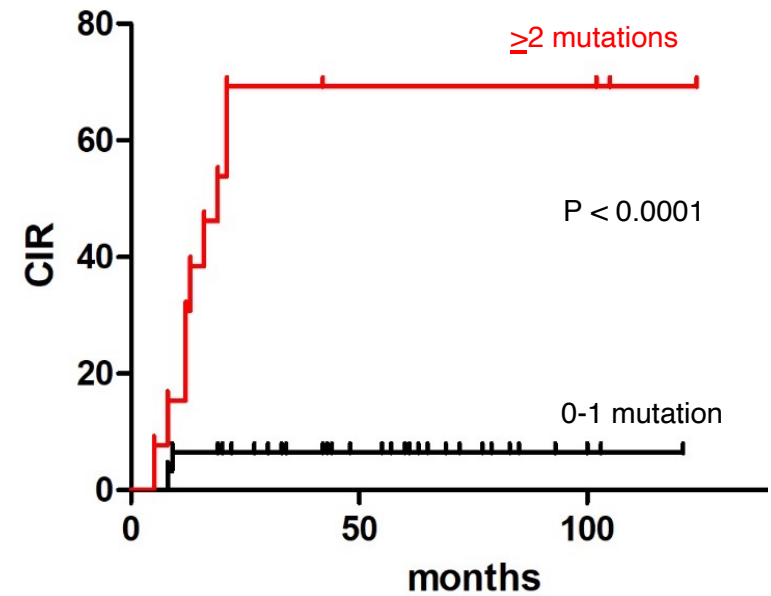
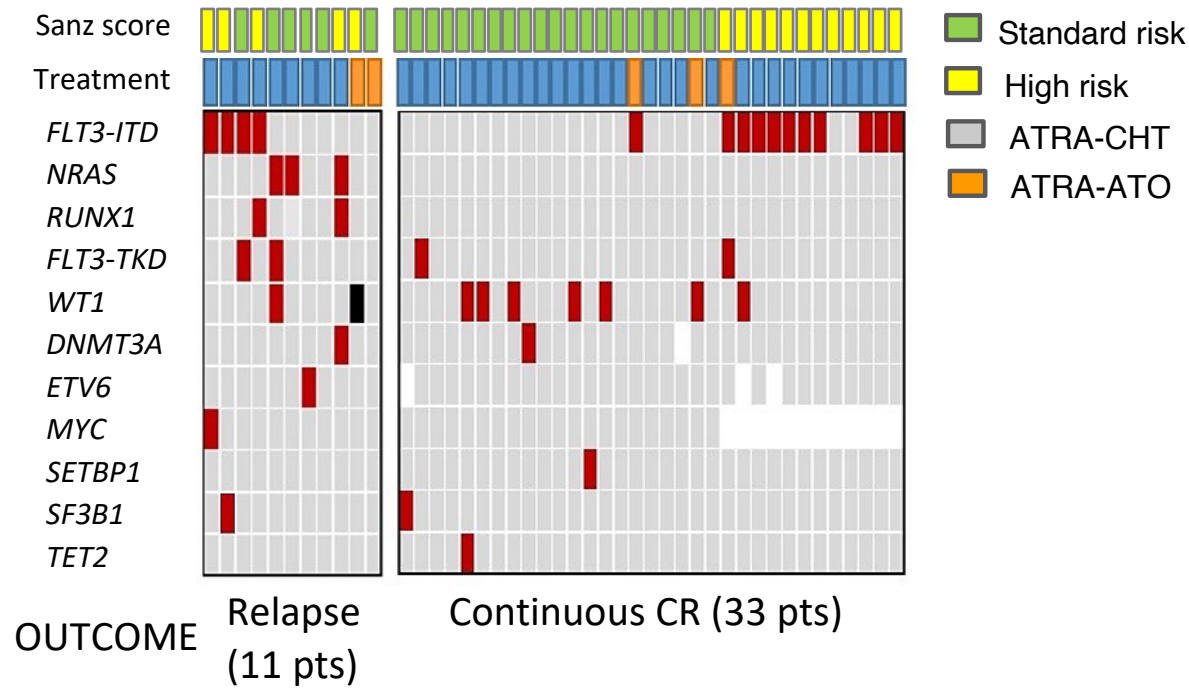
	RIF-ATRA group (n=69)			Arsenic trioxide-ATRA group (n=36)		
	Grades 1-2	Grade 3	Grade 4	Grades 1-2	Grade 3	Grade 4
Nausea	14/66 (21%)	0	0	8/36 (22%)	1/36 (3%)	0
Vomiting	8/66 (12%)	0	0	3/36 (8%)	0	0
Diarrhoea	6/66 (9%)	0	0	2/36 (6%)	0	0
Mucositis	6/66 (9%)	0	0	5/36 (14%)	1/36 (3%)	0
Thrombosis or embolism	3/66 (5%)	0	0	0	0	0
Haemorrhage	22/66 (33%)	1/66 (2%)	1/66 (2%)	9/36 (25%)	2/36 (6%)	1/36 (3%)
Cardiac	4/66 (6%)	1/66 (2%)	0	2/36 (6%)	0	1/36 (3%)
Prolonged QTc interval	8/43 (19%)	0	0	6/31 (19%)	0	0
Infection	27/64 (42%)	14/64 (22%)	1/64 (2%)	12/36 (33%)	14/36 (39%)	1/36 (3%)
Increased liver ALT or AST concentrations	34/69 (49%)	6/69 (9%)	0	23/36 (64%)	4/36 (11%)	1/36 (3%)
Hyperbilirubinaemia	17/66 (26%)	0	0	13/36 (36%)	0	0
Raised creatinine	1/63 (2%)	0	0	0	1/34 (3%)	0
Neutropenia	6/66 (9%)	12/66 (18%)	42/66 (64%)	4/36 (11%)	7/36 (19%)	22/36 (61%)
Anaemia	22/66 (33%)	38/66 (58%)	5/66 (8%)	8/36 (22%)	19/36 (53%)	8/36 (22%)
Thrombocytopenia	5/66 (8%)	10/66 (15%)	45/66 (68%)	3/36 (8%)	9/36 (25%)	23/36 (64%)



Zhu et al, Lancet Oncol 2018



# Mutation profile at APL diagnosis

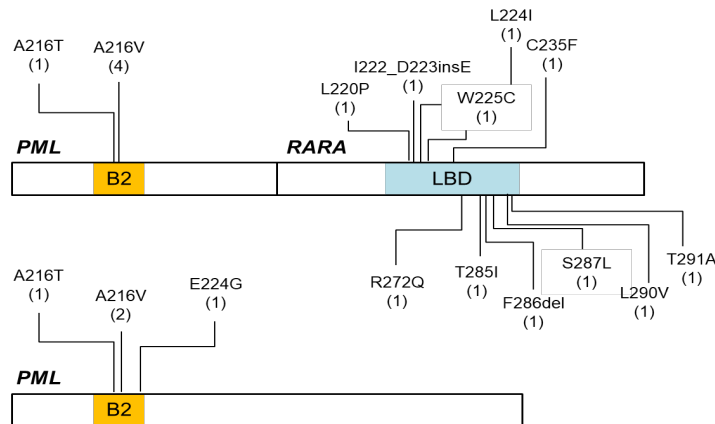
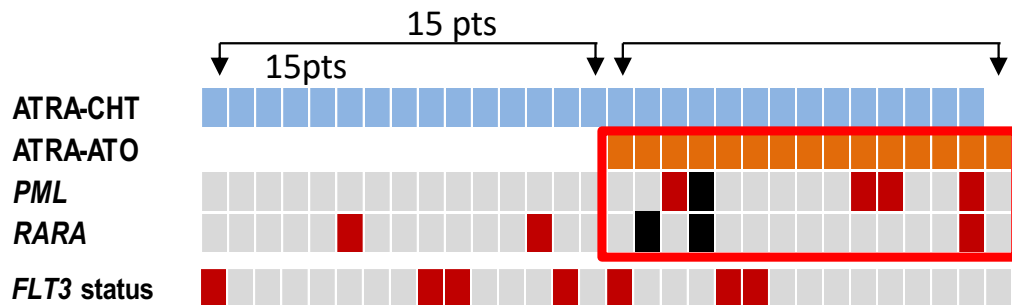


❖ A higher number of mutations at diagnosis is associated with an increased risk of relapse

# Mutations in *PML* and *RARA* genes at relapse

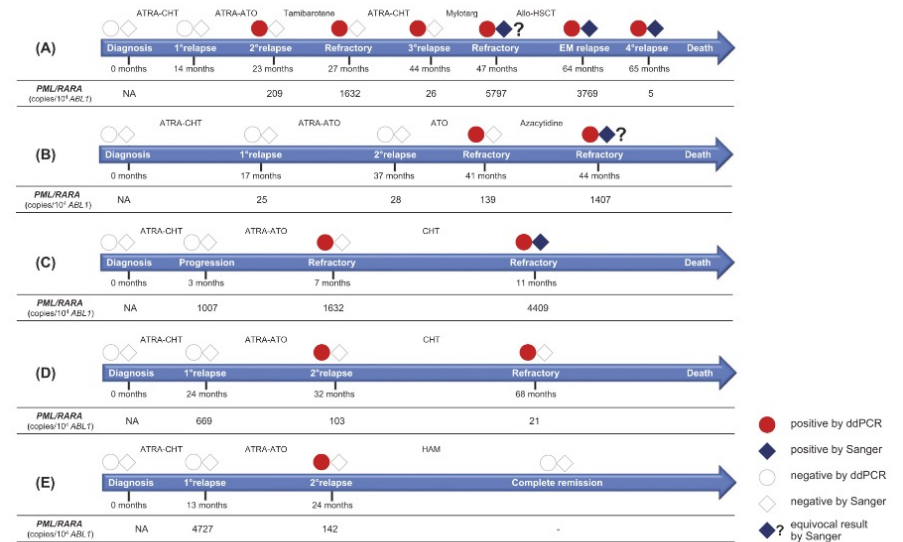
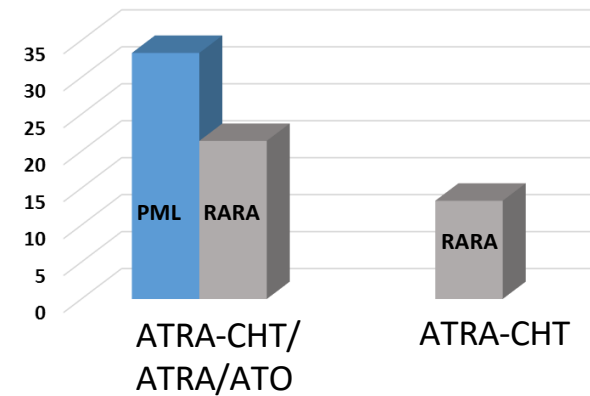


- Single mutation
- Multiple mutations

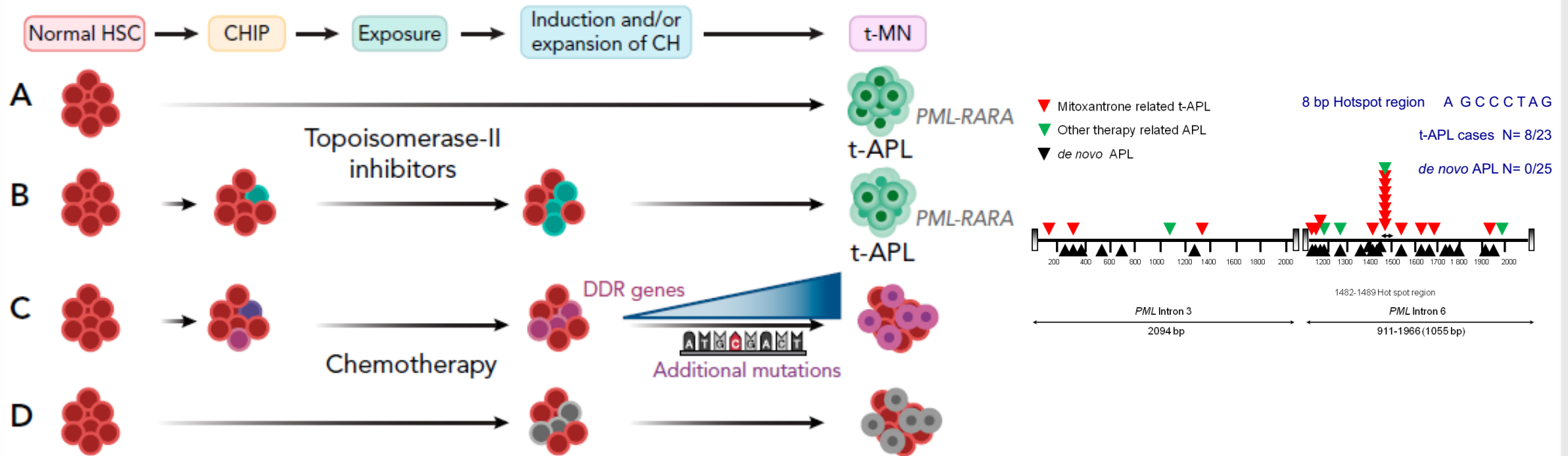


Iaccarino et al, Am J Hematol 2019  
 Alfonso et al, Leukemia 2017

% of mutated patients



# Therapy-related APL



Hasan et al, Blood 2008  
 Dillon et al, Blood 2020

Ottone et al, Am J Hematol 2014  
 Voso et al, Blood 2021

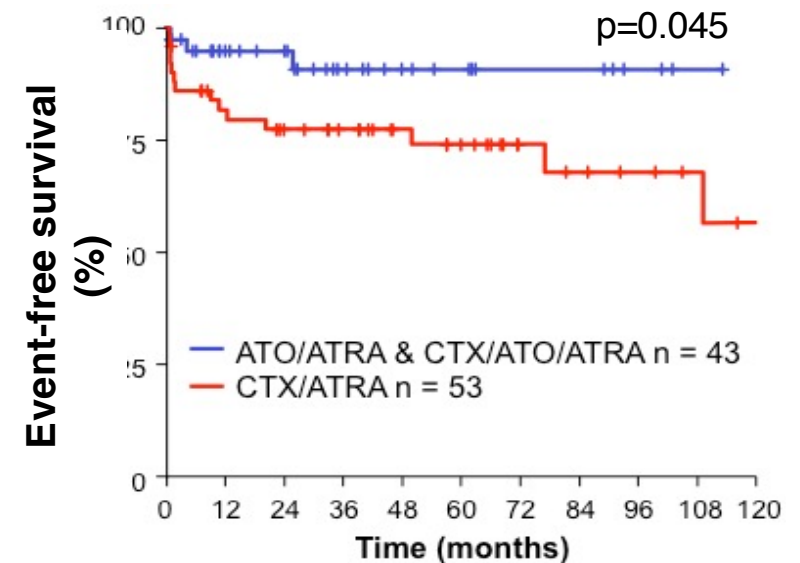
## Outcome of t-APL



### Treatment Response

% (N)	CTX/ATR A n=53	ATO/ATRA n=24	CTX/ATO ATRA n=19	ATRA only n=7
<b>CR</b>	<b>78%</b> (40)	<b>100%</b> (23)	<b>95%</b> (18)	<b>57%</b> (4)
<b>PR</b>	<b>10%</b> (5)	—	—	—
<b>ED</b>	<b>12%</b> (6)	—	<b>5%</b> (1)	<b>43%</b> (3)

### Intensively treated patients, excluding treatment with ATRA only

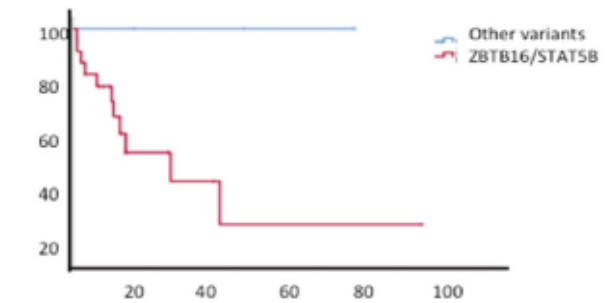
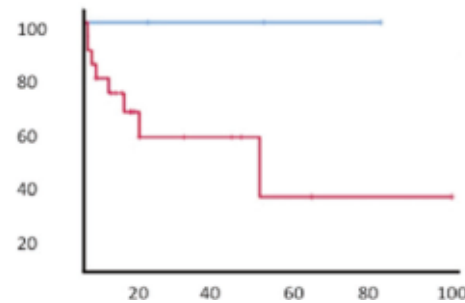
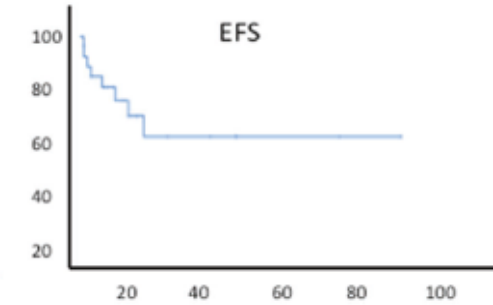
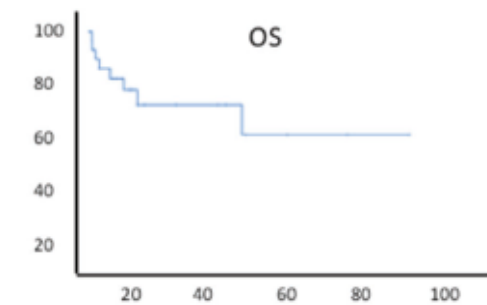


- ❖ t-APL display outcomes similar to dn-APL when standard treatment is feasible.

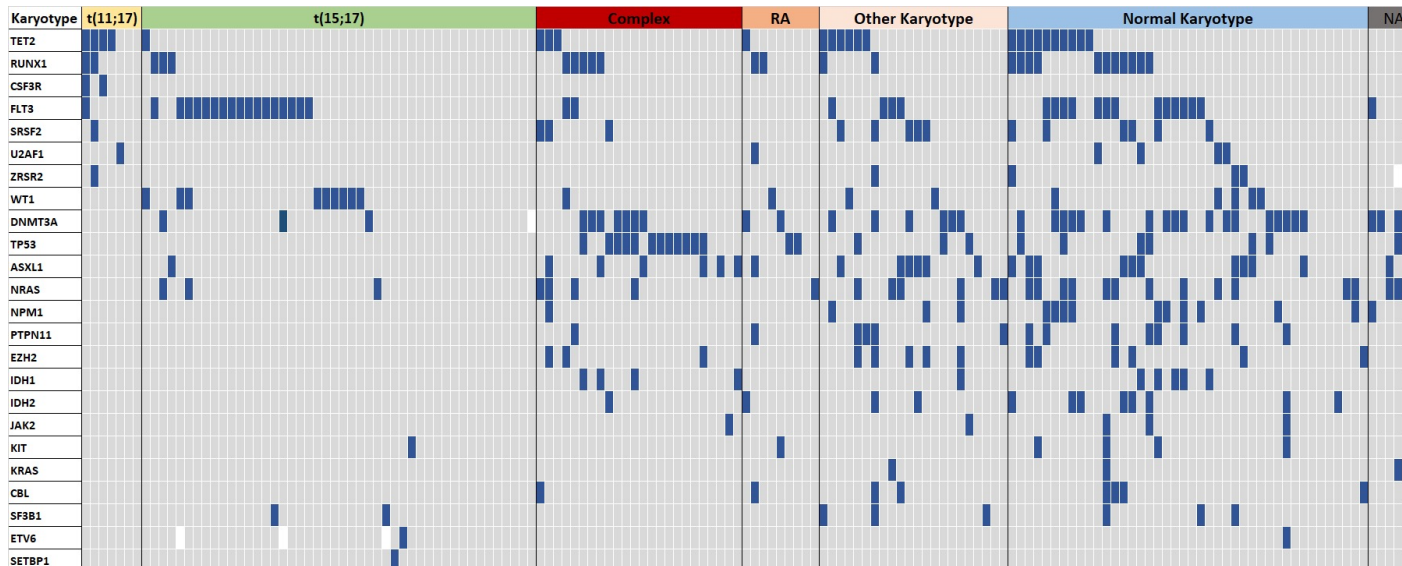
## Atypical APL

- ✓ 18 ZBTB16-RARA (RT-PCR)
- ✓ 3 STAT5B-RARA (RT-PCR)
- ✓ 1 each PRKAR1A-RARA, NuMA-RARA, FIP1L1-RARA (FISH)

	RARA variants	APL	p value
Age, years (range)	47 (2-83)	51.5 (14-82)	0.2
Sex F/M	5/19	15/23	0.1
Morphology M3/M3v	23/1	33/5	0.5
WBC, $\times 10^9/L$ (range)	$11.5 \times 10^9/L$	$1.58 \times 10^9/L$	0.04
Platelets, $\times 10^9/L$ (range)	$75.5 \times 10^9/L$	$25.5 \times 10^9/L$	0.0009
Fibrinogen, mg/dL (range)	176 (60-675)	121 (62-237)	0.007
FLT3-ITD (POS/NEG)		5/8	
Early death	2/24	5/38	0.6
Outcome of induction (CR)	16/24	33/38	0.1
EFS, 24 months/ 48 months, %	54.1/34	70.3/62.9	0.2
OS, 24 months/ 48 months, %	72/60	86.7/82.9	0.07

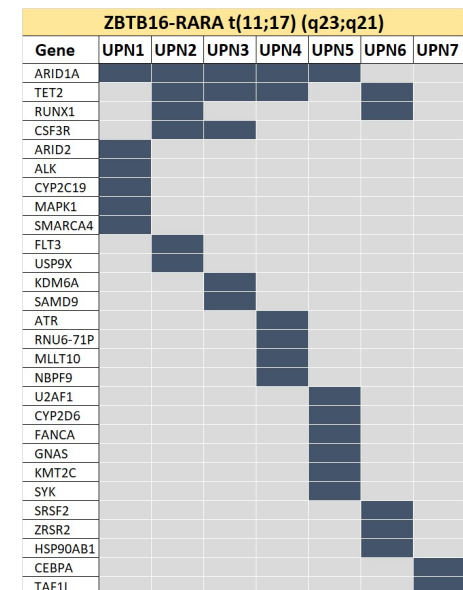


Targeted-NGS of 156 AML patients  
 (7 ZBTB16/RARA , 46 PML/RARA and 103 non RARA-rearranged AML)



	n	Mutations (≥1 gene)	Mean mut/pt	p	Most frequently <sup>mut</sup> -genes
AML	103	94.17%	2.86 ± 2.03	<0.0001	DNMT3A (35%), NRAS, ASXL1 (25% for both), TP53 (23%)
APL	46	69.6%	0.89 ± 0.77		FLT3 (37%), WT1 (20%)
ZBTB16/RARA	7	71.4%	1.71 ± 1.7		TET2 (57%), RUNX1 & CSF3R2, (28.6%)

## Chromatin remodeling complex





# LEUKEMIA2022 May 5-6, 2022

AIL President: P. Toro  
Coordinators: A.M. Carella, S. Amadori

## Acknowledgements



### UOSD Laboratorio di Diagnostica Avanzata Oncoematologica

«Francesco Lo-Coco»



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