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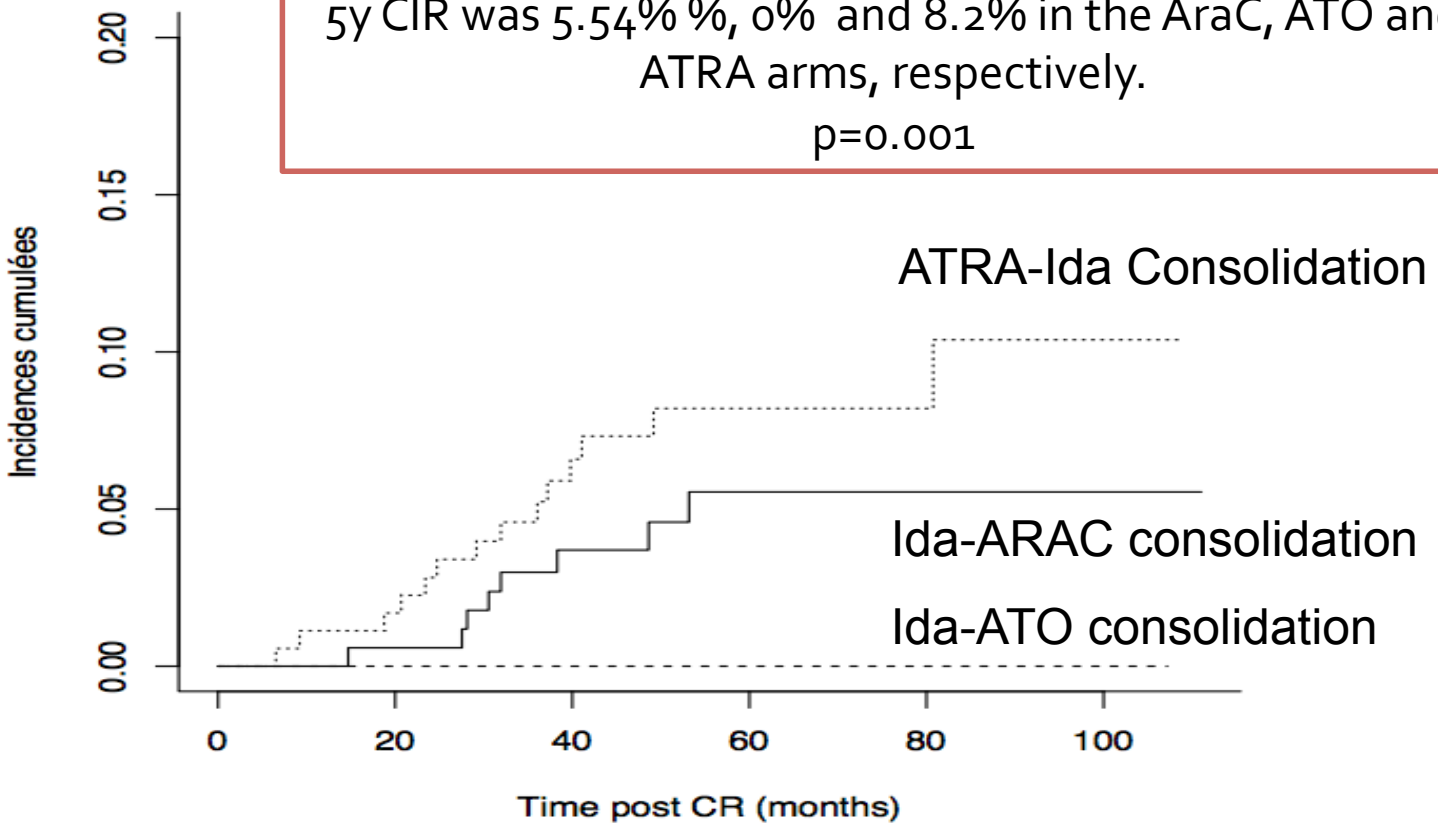
Acute Promyelocytic Leukemia
Therapy of relapse

Lionel Adès, MD PhD
Hopital Saint Louis , Paris Diderot University

Frequency of relapse in APL

- In the APL2006 trial (Std Risk APL, n=584)

5y CIR was 5.54% %, 0% and 8.2% in the AraC, ATO and ATRA arms, respectively.
p=0.001

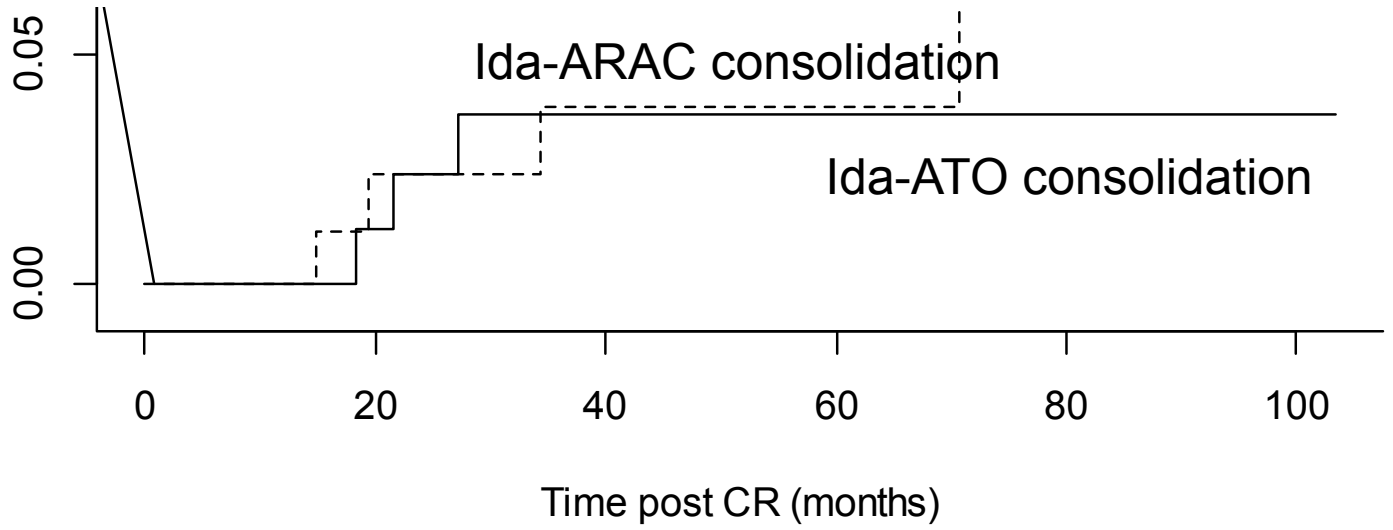


Ades, ASH 2016

Frequency of relapse in APL

- In the APL2006 trial (Higher Risk APL, n=584)

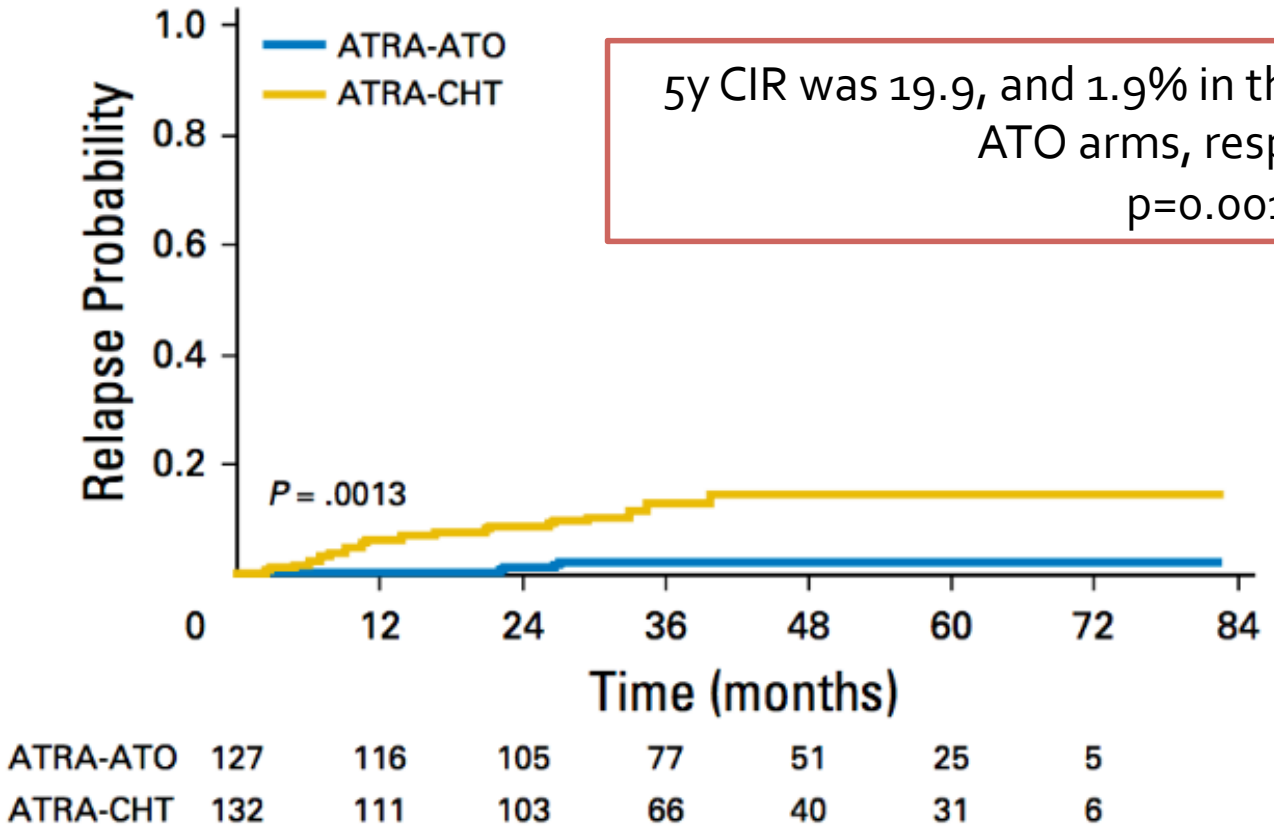
5y CIR was 3.7, and 3.2% in the AraC and ATO arms, respectively.
p=NS



Ades, ASH 2015

Frequency of relapse in APL

- In the ATO-ATRA Era (low risk APL)



5y CIR was 19.9, and 1.9% in the ATRA-CHT and ATRA-ATO arms, respectively.

p=0.0013

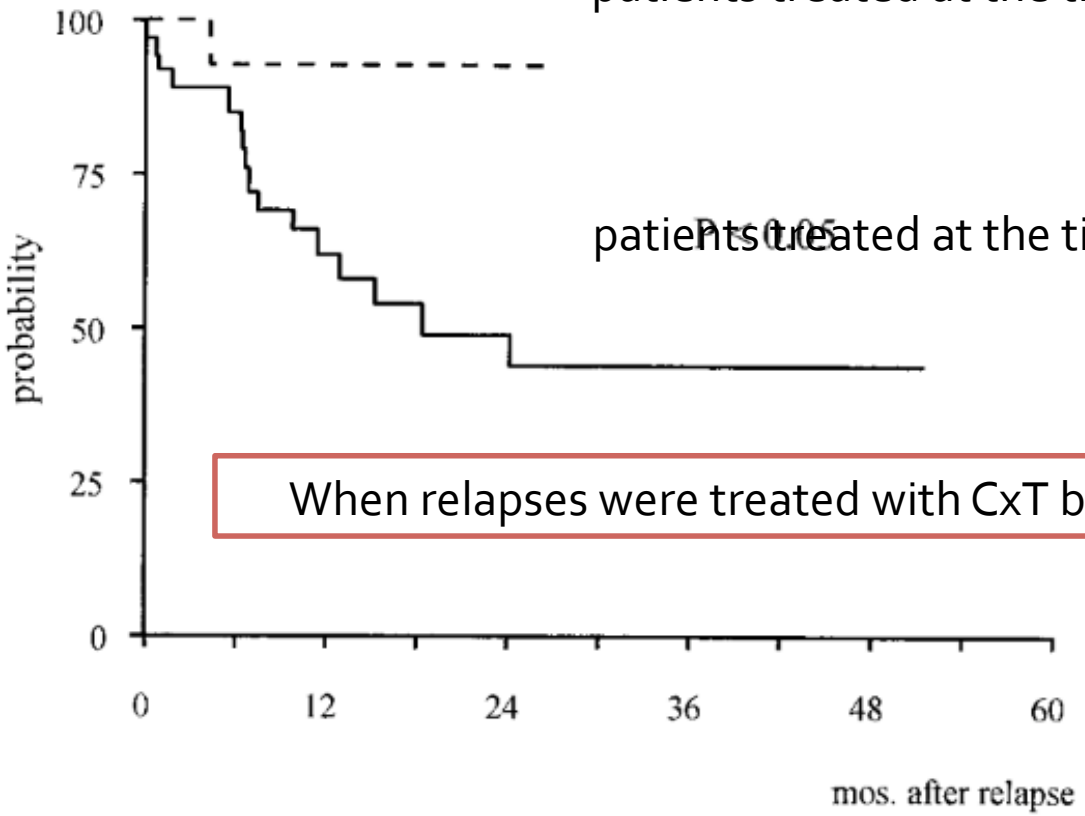
Platzbecker, J Clin Oncol 2016

How to indentify patients who are more likely to relapse ?

- Current literature on the relapsed APL is only available for patients relapsing after ATRA and chemotherapy.
- In the context of ATRA-CxT:
  - WBC
  - Flt3 ITD
  - CD56
- Early identification by RT-PCR/RQ-PCR of disease recurrence is of importance

Early identification of Relapse

- Identification of molecular relapse and anticipation of treatment at the time of molecular relapse is a key point !



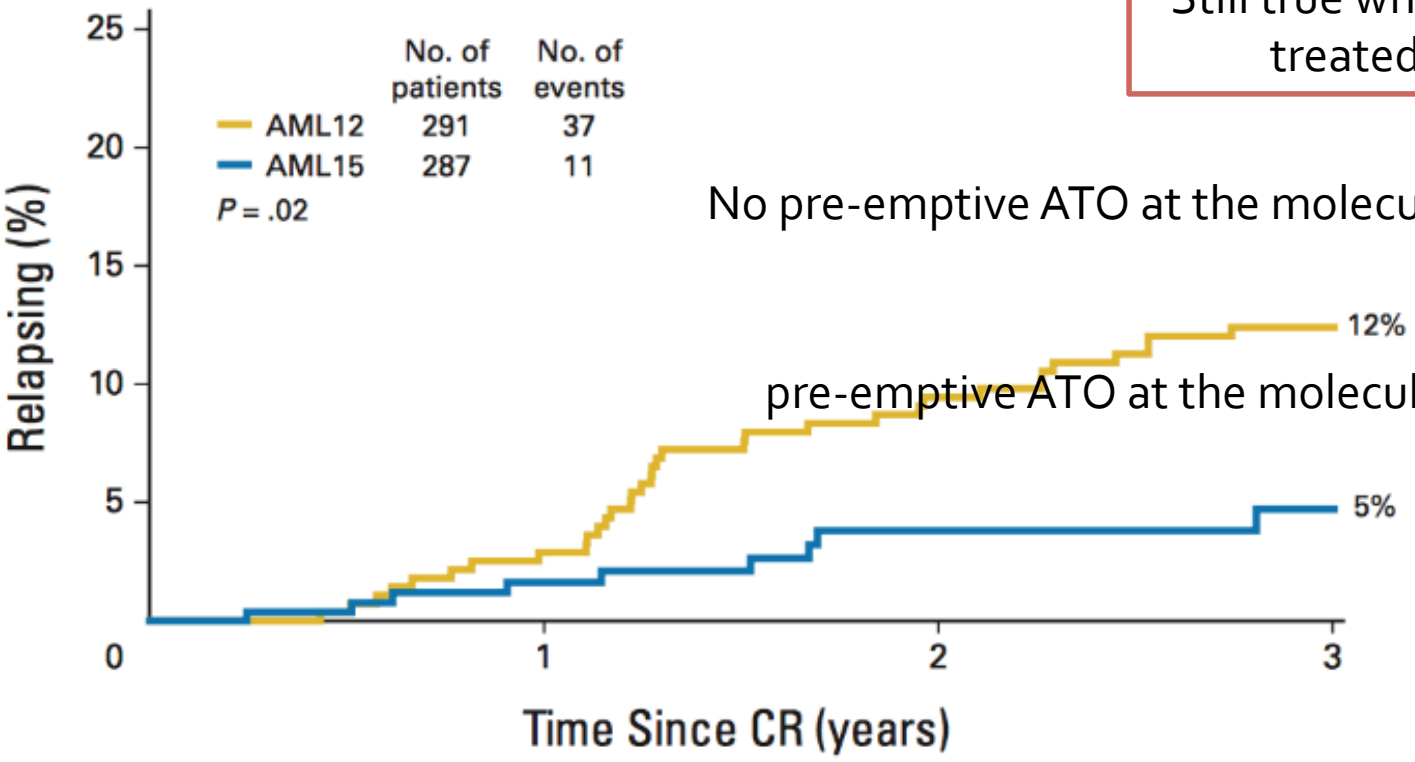
When relapses were treated with CxT based regimen

Lo Coco, Blood 1999

Early identification of Relapse

- Identification of molecular relapse and anticipation of treatment at the time of molecular relapse is a key point !

Still true when relapses are treated with ATO



Grimwade, J Clin Oncol 2009

Extra Medullary relapse

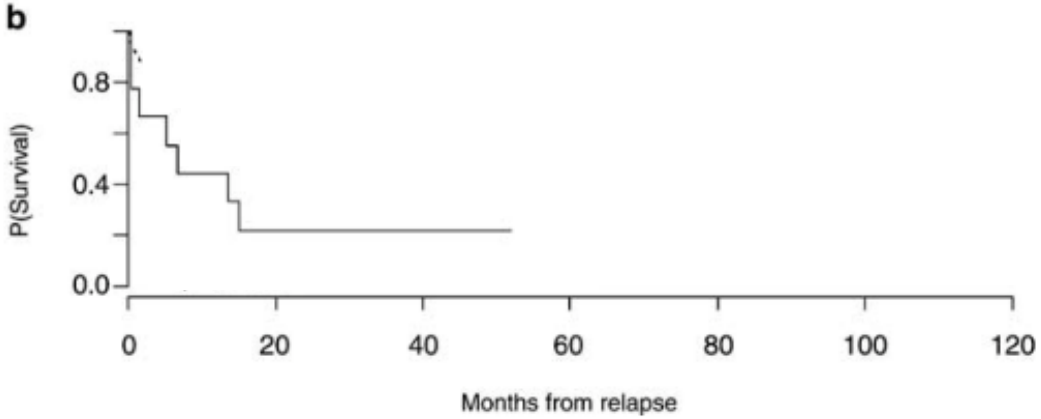
Predictive Factors

- age < 45
- WBC >10 G/L
- bcr 3
- CNS bleeding during induction
- In the context of CxT based therapy, Role of High dose AraC and/or intrathecal MTX+ AraC to prevent CNS relapse in patients with WBC > 10G/L

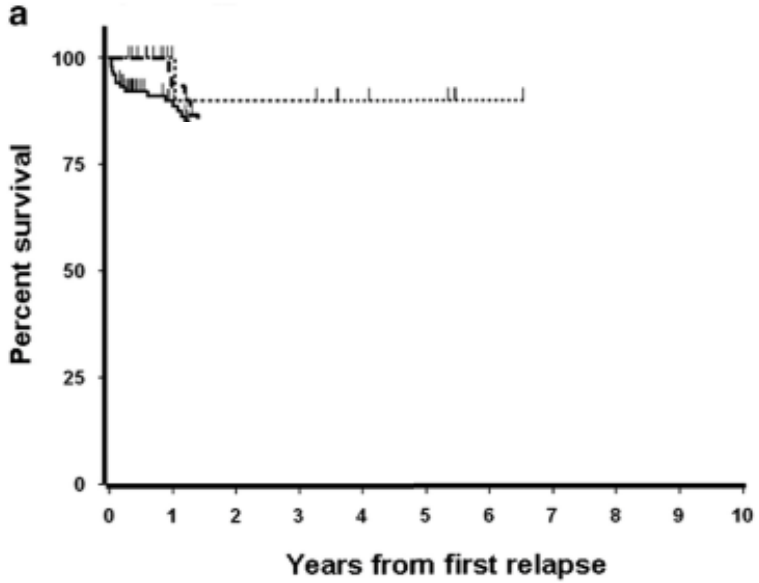
De Botton, Leukemia 2006
Montesinos, Haemtologica 2009

Outcome

- Poor in the 90's



- Better nowadays



de Botton, Leukemia 2006
Lengfelder, Leukemia 2015

EM Relapse in the ATO era

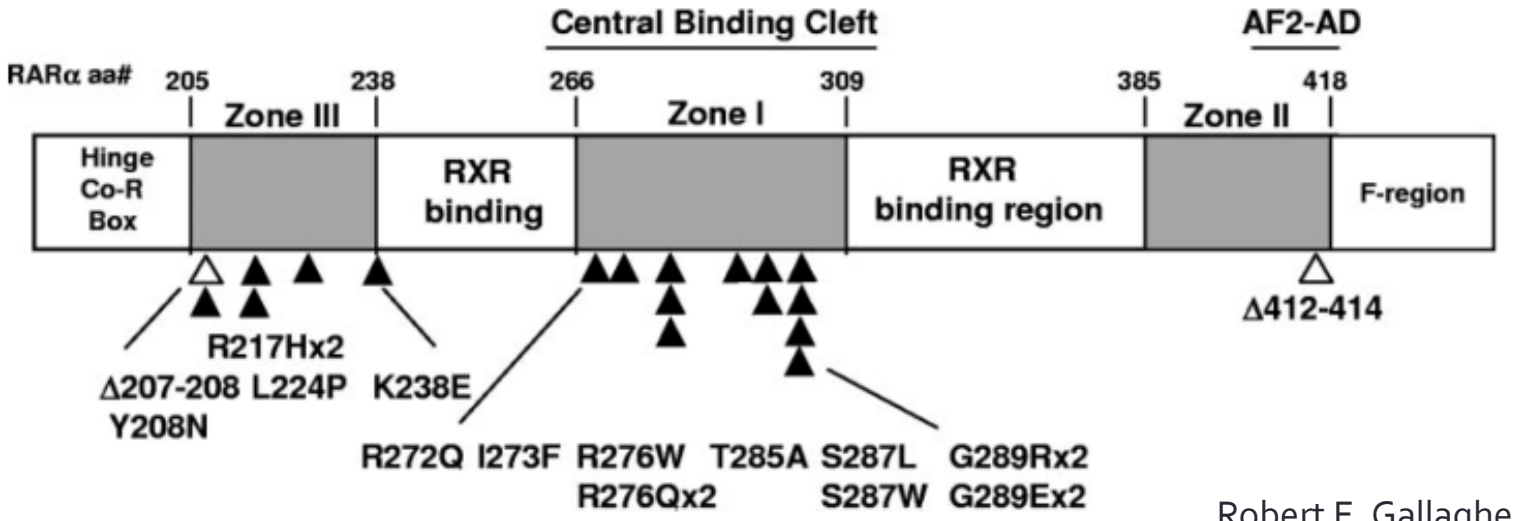
- Little is known
- Number of patients are limited
- No EMD relapse in the Italian/German experience
- 1 CNS relapse in the MRC trial

Platzbecker, J Clin Oncol 2016
Burnett, Lancet Oncol 2016

Why few patients still relapse?

Why few patients still relapse?

- Resistance to the RA/chemotherapy regimen remains imperfectly understood
- In some situations RA-resistance may be caused by mutations in the RARA moiety of PML/RARA



Robert E. Gallagher, Blood 2012

Other genetic events?

- we performed WES of diagnosis/relapse pairs from 23 patients
- most relapsing APLs are associated with the presence at diagnosis of mutations in:
  - activators of MAP kinases (NRAS, KRAS, BRAF)
  - and/or epigenetic regulators (primarily WT1, but also TET2 or ASXL1)

This study will be presented by C. Bally on Monday 11:30

How to treat relapse?

ELN 2009 recommendation

- Two cycles of ATO-ATRA
- In patients achieving a second mCR, the suggested options were
  - intensification with autologous SCT
  - or, alternatively, prolonged ATRA-ATO.
- Allogeneic SCT was recommended for patients who fail to achieve a second mCR after two ATO cycles or in those who relapse after a short-lived (<1 year) first CR

M. Sanz, Blood 2009

ELN 2009 recommendation

- Two cycles of ATO-ATRA
-
-

Published in 2009
For patients treated with
ATRA-CxT in 1st Line

Is it still a Valid option in 2017?

ATO cycles or in those who relapse after a short-lived (<1 year) first CR

M. Sanz, Blood 2009

The role of ATO in relapsing APL

	n	CR rate	Post induction	outcome
Shen et al.	20	80%	variable	2y OS 61%
Niu et al.	47	85%	ATO	-
Soignet et al.	40	85%	Allo or Auto	2y OS 66%
Kwong et al.	8	100%	Ida	7/8 still in CR
Ohnishi et al.	14	78%	ATO	-
Raffoux et al.	20	80%	ATO	2y OS 70%
Thomas et al.	25	84%	Allo or Auto	2y OS 88%

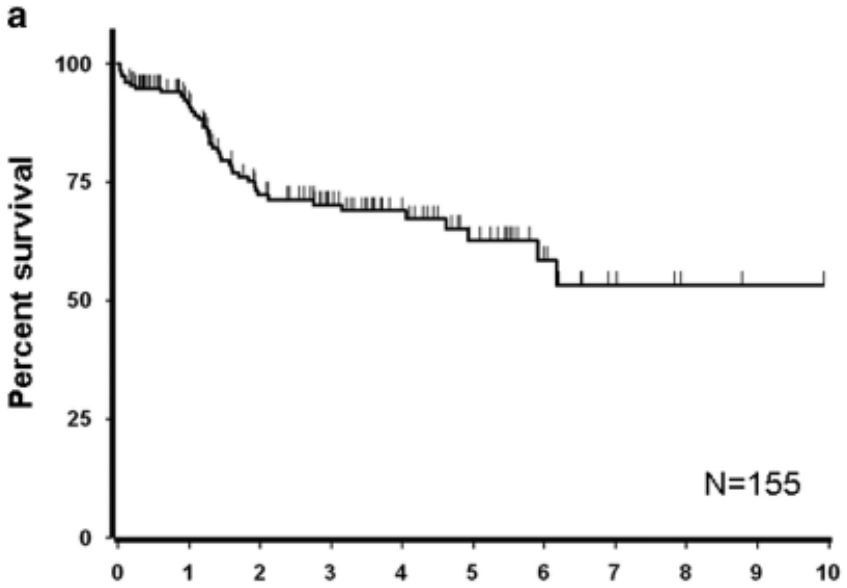
Lenglfelder	**304**	**86%**	**Variable**	**2y OS 50–81%**

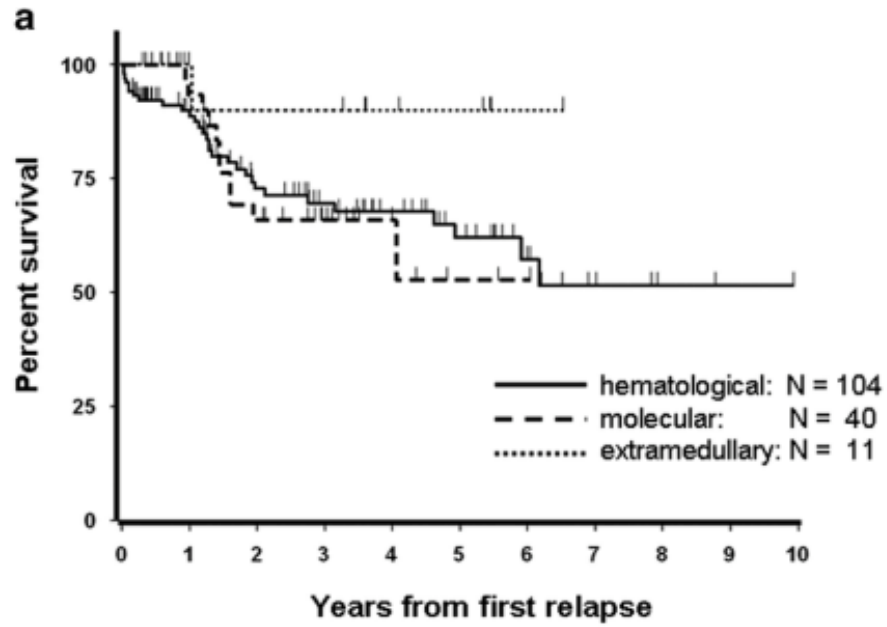
The European LeukemiaNet Experience with ATO

- 155 patients treated with arsenic trioxide in first relapse
  - 91% achieved CR
  - 7% had induction death
  - 2% resistance
- All patients with extramedullary relapse (n = 11) achieved mCR.
- Post induction treatement :
  - Autologous SCT (n=60)
  - Allogeneic SCT (n=33)
  - No Transplant (n=55)

Lengfelder, Leukemia 2015

The European LeukemiaNet Experience with ATO





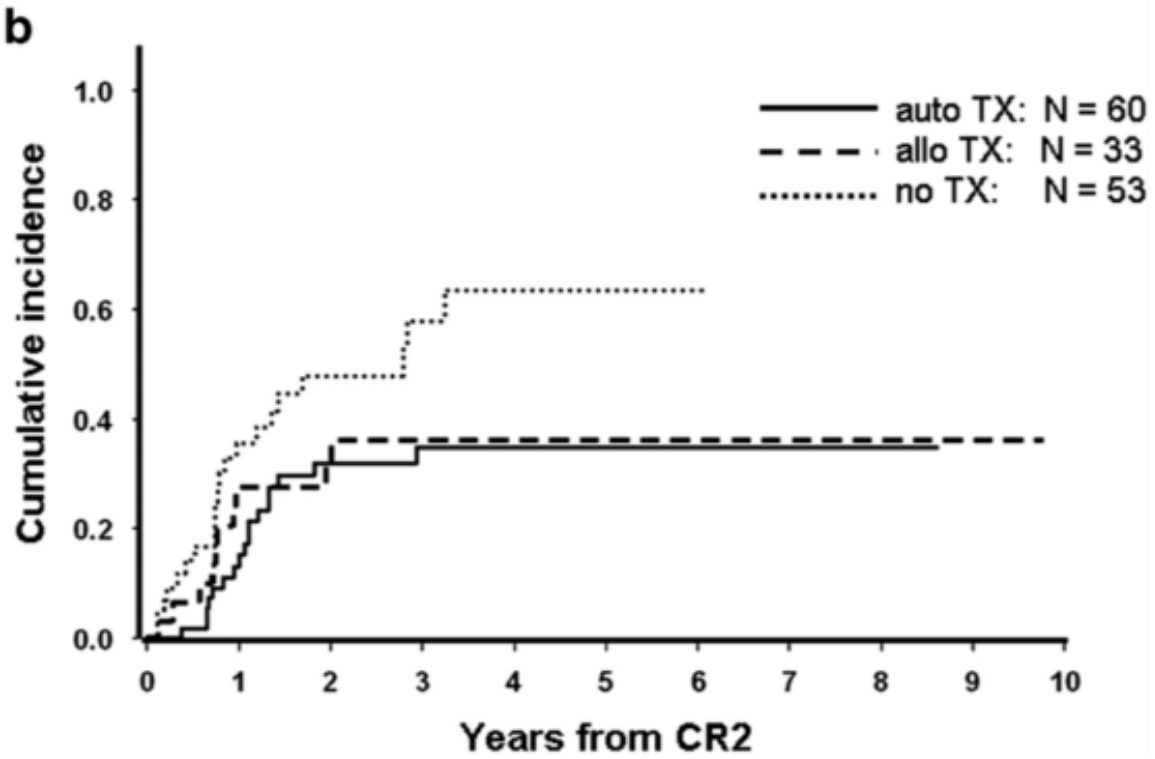
3-year overall survival 68%

3-year overall survival
68% in hematological relapse
66% in molecular relapse
90% in extramedullary relapse

A higher rate of APL DS (27% vs. 0%) and infections (43% vs. 10%) was recorded in patients treated in haematological relapse as compared with molecular relapse.

Lengfelder, Leukemia 2015

The European LeukemiaNet Experience with ATO

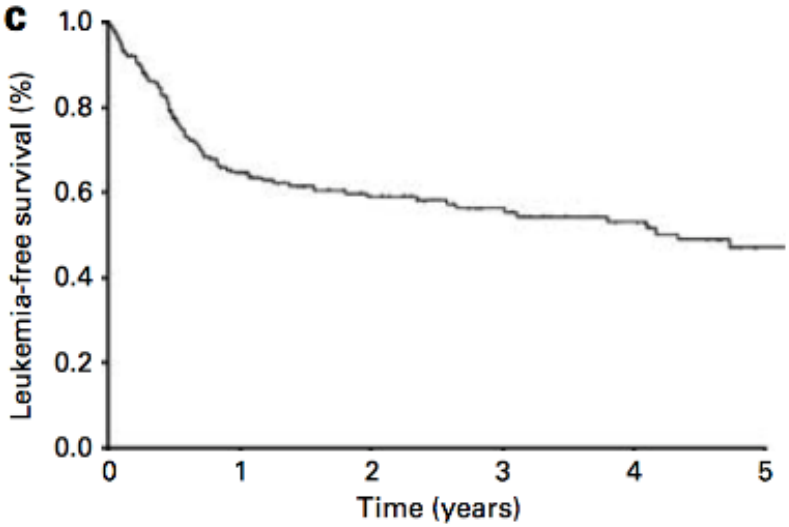


Significant lower relapse rate in patients who received Autologous or Allogeneic SCT

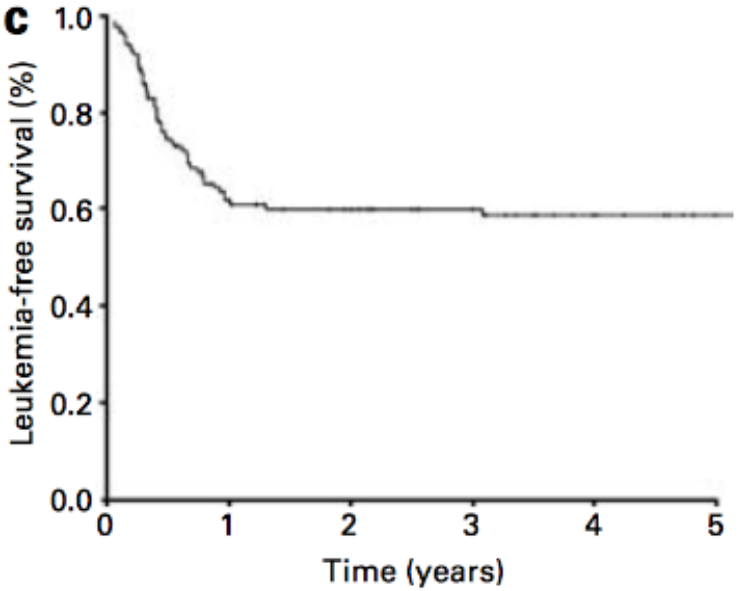
Lengfelder, Leukemia 2015

Auto or Allo SCT ?

LFS after Autologous SCT



LFS after Allogeneic SCT



Rather similar results with 51% 5-year EFS and 16% treatment-related mortality

Sanz, BMT 2007

Impact of MRD (−) before ASCT

Pt. No.	Age/Sex	PML/RARα Junction Type	Initial Therapy/Consolid.	CR1 Length (mo)	Therapy of Relapse/ Consolid.	Time to ABMT (mo from CR2)	Pre-ABMT PCR*	CR2 Length (mo post-ABMT)	Outcome
1	50/F	bcr3	IDA/yes	12	ATRA/no	2	Positive	2	Relapsed/dead
2	38/M	bcr1	DNR/yes	16	ATRA/no	2	Positive	5	Relapsed/dead
3	17/F	bcr3	IDA/yes	10	ATRA/no	2	Positive	7	Relapsed/dead
4	43/M	bcr1	IDA + AraC/ATRA/yes	20	ATRA/yes	2	Positive	3	Relapsed/dead
5	40/M	bcr2	IDA/yes	40	ATRA/yes	3	Positive	9	Relapsed/dead
6	39/F	bcr1	IDA/yes	6	ATRA/yes	6	Positive	4	Relapsed/dead
7	10/M	bcr3	LAM 8704	6	ATRA/yes	7	Positive	7	Relapsed/dead
8	46/F	bcr1	IDA + AraC/yes	18	ATRA/yes	2	Negative	60+	A & W†
9	23/F	bcr3	IDA + AraC/yes	12	ATRA/yes	2	Negative	44+	A & W
10	27/M	bcr1	IDA/yes	12	ATRA/yes	2	Negative	27+	A & W
11	45/F	bcr1	IDA + AraC/yes	22	ATRA/yes	3	Negative	10	Relapsed/dead
12	31/M	bcr1	IDA + AraC/yes	13	ATRA/Mitox + AraC/yes	4	Negative	36	Dead‡
13	35/F	bcr3	AIDA/yes	13	ATRA/yes	2	Negative	15+	A & W
14	53/F	bcr1	AIDA/yes	11	ATRA/yes	3	Negative	20+	A & W
15	32/M	bcr1	IDA + AraC/yes	11	ATRA/yes	5	Negative	30+	A & W

Meloni, Blood 1997

A non-transplant strategy is feasible

UPN	Sex/age*	FAB	WBC ($x10^9$/L)	Relapse risk	Previous treatments	Duration of previous CR(s)	Disease status at time of ATO+ATRA initiation	Toxicity during ATO + ATRA	Outcome
1	M/51	M3	2.5	Low	AIDA§	15 months	1st molecular relapse	no	relapsed at 10 mos
2	M/54	M3	3.5	Interm	AIDA	12 months	1st molecular relapse	QTc prolongation	CRm^ (22+ mos)
3	F/46	M3	4.2	Interm	AIDA	32 months	1st molecular relapse	no	CRm (28+ mos)
4	F/70	M3	5.1	Interm	AIDA	28 months	1st molecular relapse	no	CRm (18+ mos)
5	M/38	M3	1.0	Interm	AIDA	84 months	1st EM° and molecular relapse	no	CRm (39+ mos)
6	F/32	M3	4.2	Interm	AIDA	48 months	1st molecular relapse	no	CRm (50+ mos)
7	M/61	M3v	9.5	Interm	AIDA	17 months	1st molecular relapse	electrolyte abnormalities	CRm (14+ mos)
8	M/69	M3	1.8	Low°°	AIDA/GO' + ATRA	22 months/ 12 months	2nd hematologic relapse	no	CRm (31+ mos)
9	M/52	M3	11	High	AIDA/ARA-C + MTZ@	17 months/ 13 months	2nd molecular relapse	neutropenia (grade 2)	CRm (11+ mos)

this might be an option for patients relapsing after prolonged first CR (>2 years) in which continued ATRA and ATO (for up to 5–6 cycles) without SCT might be curative

Breccia, Haematologica 2011

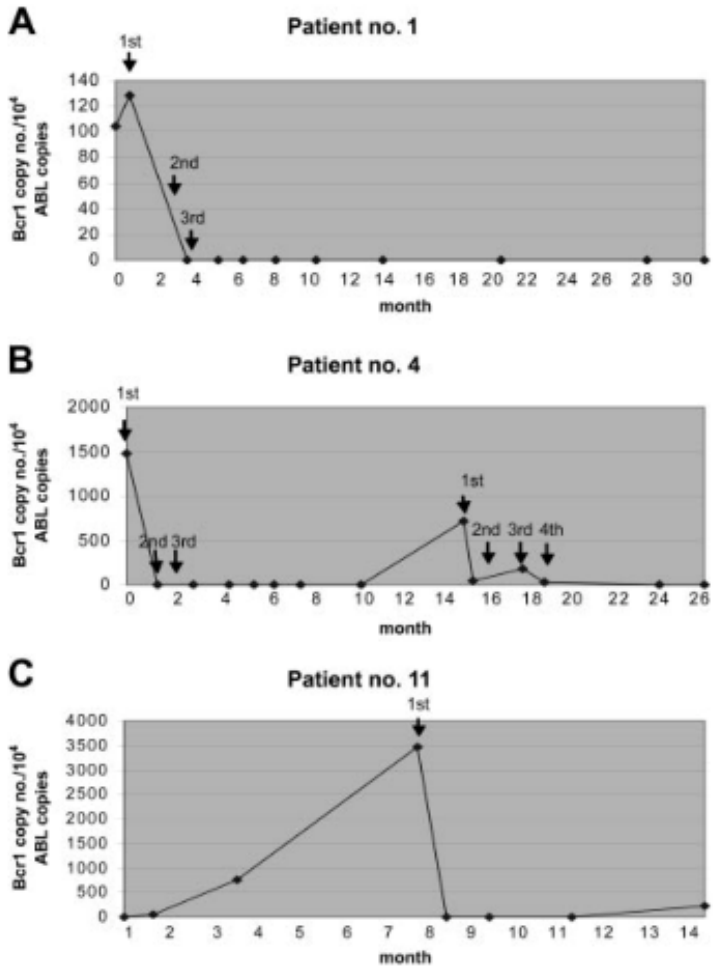
Post induction strategy

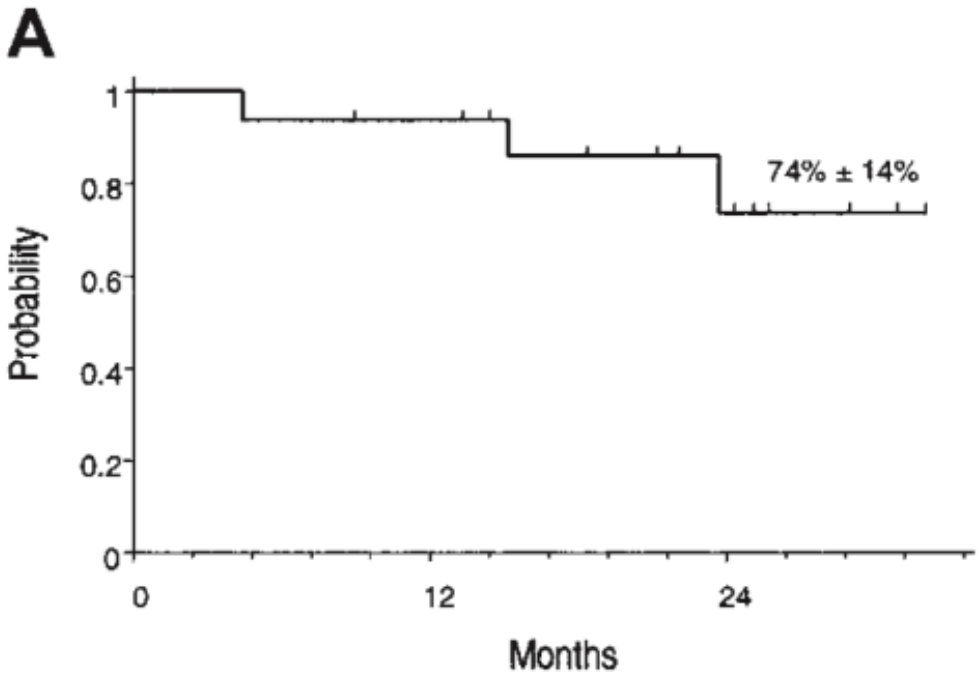
- autologous SCT appears to be a suitable option for younger patients (able to receive intensive chemotherapy) in second mCR
- Allogeneic SCT should be restricted to patients not achieving mCR after two cycles of therapy.
- A non-transplant strategy with 5-6 cycles of ATRA-ATO is feasible in selected patients

Other therapeutic Option

Gemtuzumab Ozogamycin

16 pts with molecular relapse
GO 6mg/m2 x 2
14 molecular CR achieved





LoCoco, Blood 2004

Tamibarotene for Relapsing APL

	n	CR rate	Post induction	outcome
Tobita et al.	24	58%	-	-
Takeuchi et al.	23	78%	-	-
Di Veroli et al.	1	100%		CNS relapse
Takeuchi et al.	7	100%	Various	Prolonged OS
Kimatura et al.	19	58%		

Tamibarotene after treatment with ATRA and arsenic trioxide

- phase II study of tamibarotene in adult patients with relapsed or refractory APL after treatment with ATRA and ATO (n = 14)
- tamibarotene (6 mg/m2/d) during induction and for up to six cycles of consolidation.
- overall response rate was 64% (n = 9)
- median overall survival was 9·5 months

Sanford, Br J Haematol, 2015

Conclusion

- Relapse in APL is a rare event :
  - With risk adapted strategies using ATRA-CxT
  - Even more With ATO-ATRA regimen
- Identification of the events leading to relapse is of importance to understand the mechanism of ATRA/ ATO resistance.
- Early identification by RQ-PCR of disease recurrence is of importance
- Therapy should be driven by the previous therapy received by the patient
- SCT remain of importance in younger fit patients