Which is the best treatment for relapsed APL?

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Disclosures of Eva Lengfelder

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
TEVA			+		+	+	
Novartis						+	

Treatment Options for Relapsed APL

- Arsenic trioxide (ATO)
- Chemotherapy
- Autologous transplantation
- Allogeneic transplantation
- Gemtuzumab ozogamicin

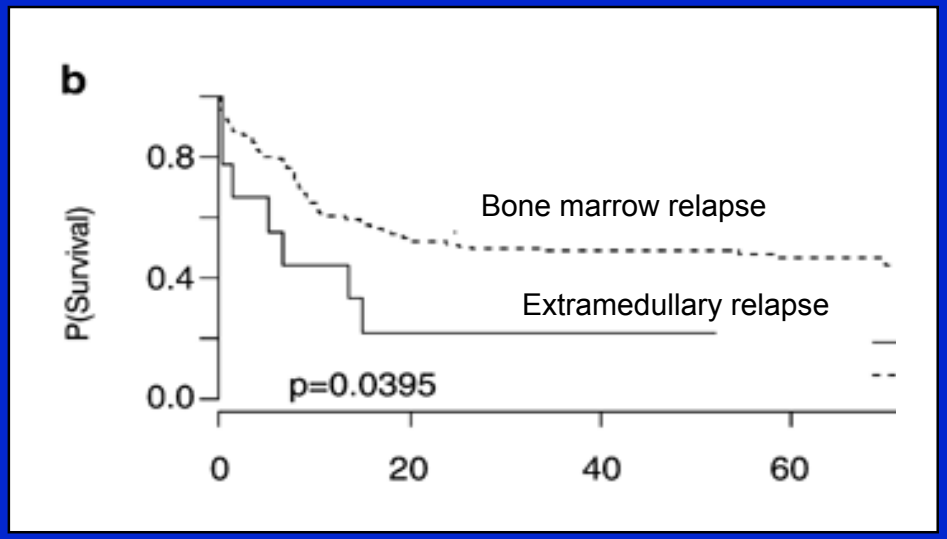
Synthetic retinoids

Outcome of APL Relapses in the Pre-ATO Era

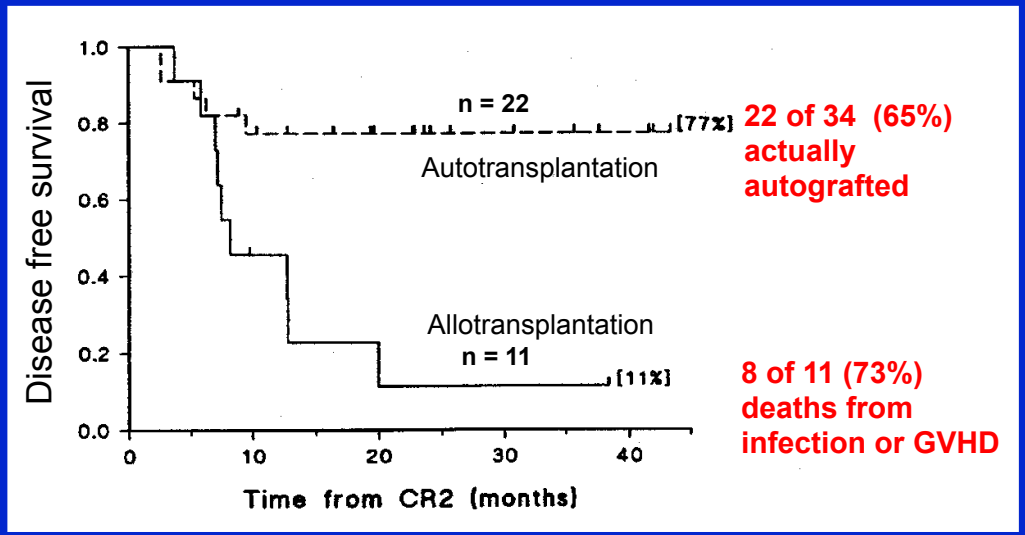
Results with chemotherapy:

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.



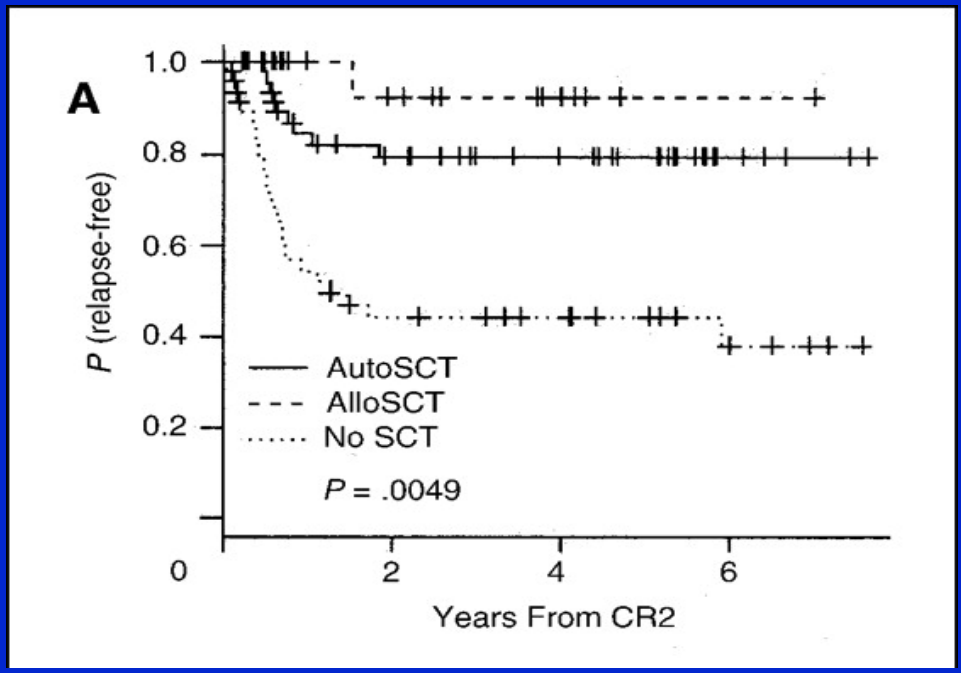
De Botton S et al., Leukemia 2006;20:35-41.



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

Outcome of the 122 APL patients in second hematological complete remission according to postremission therapy

RFS



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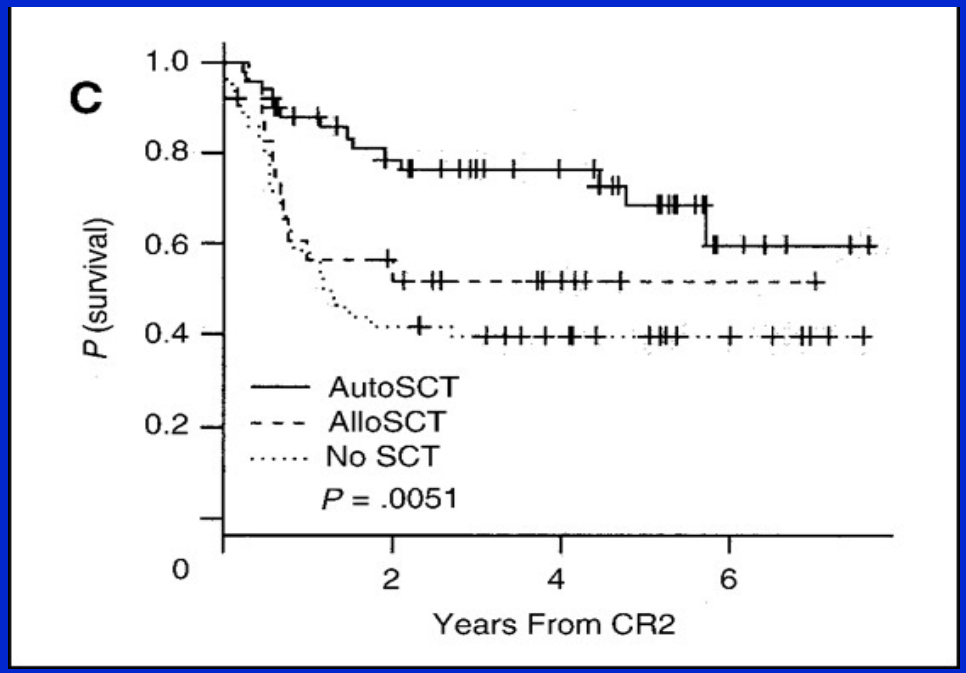


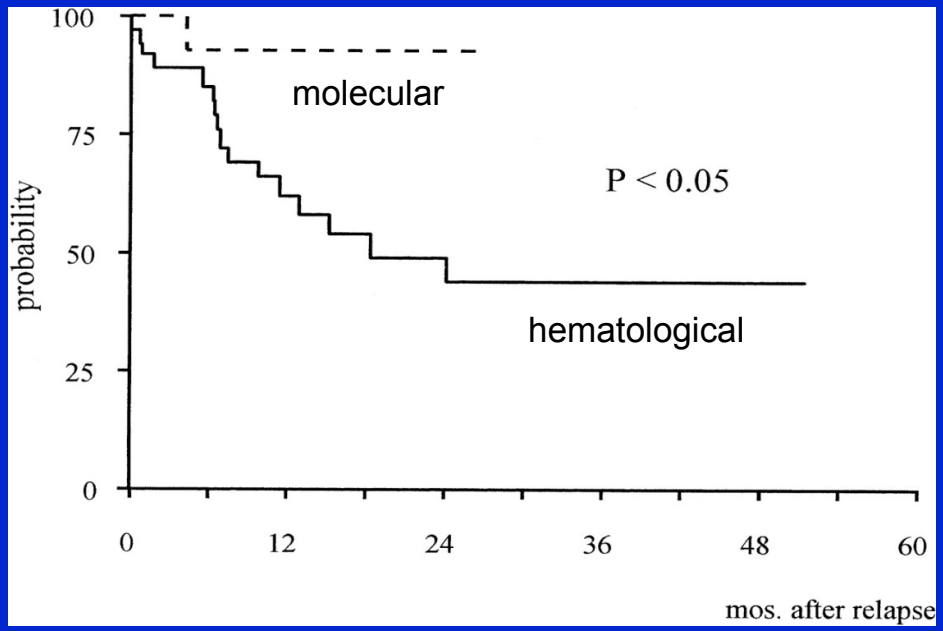
De Botton et al, JCO 2005;23:120-126

Hematopoietic stem cell transplantation for adults with acute promyelocytic leukemia in the ATRA era: EBMT Survey

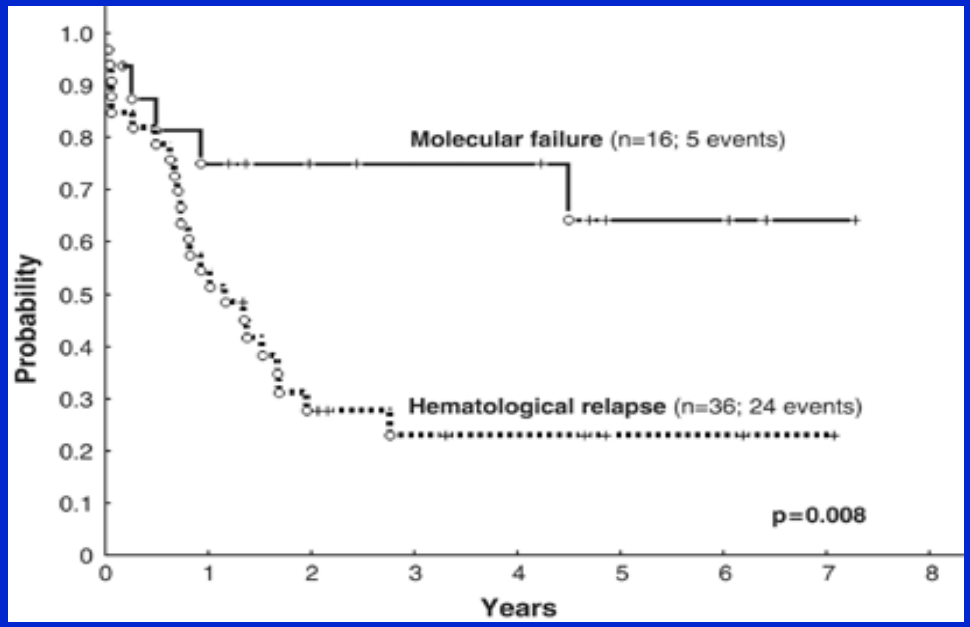
	Autologous Tx					Allogeneic Tx			
	n	LFS	TRM	RI		n	LFS	TRM	RI
		% at 5y					% at 5y		
CR1	149	69	**10**	**21**	**CR1**	144	68	**20**	**13**
CR2	195	51	**16**	**37**	**CR2**	137	59	**24**	**17**

Sanz et al, Bone Marrow Transplant 2007;39:461-469

Outcome of Patients in Molecular versus Hematological Relapse



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



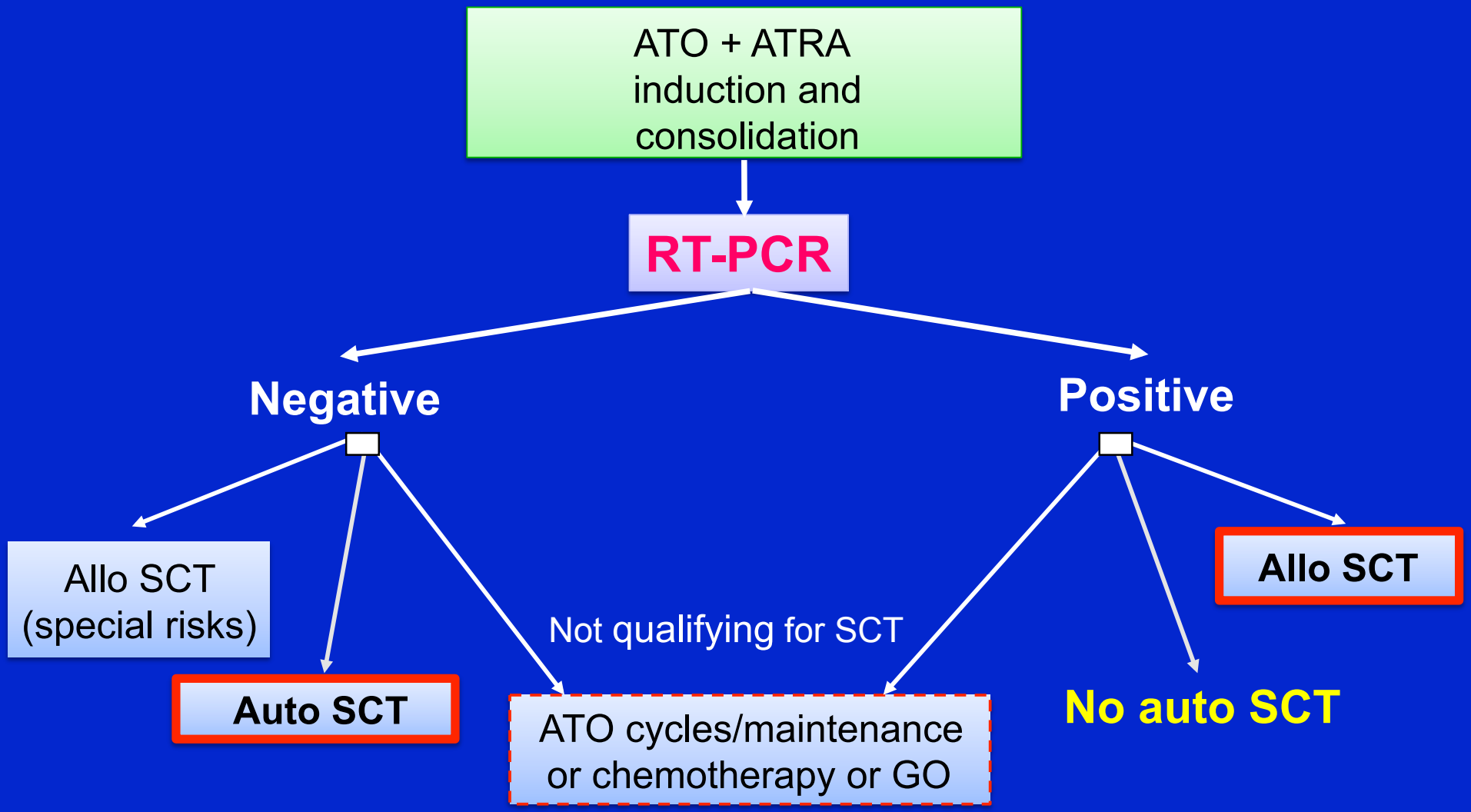
Esteve et al, Leukemia 2007;21:446-452

Cumulative Results of Studies with ATO in Relapsed APL
n = 304

	number of patients
CR	**263 (86%)**
Molecular remission	**up to 86%**
Resistance	23 (7%)
Death during induction	21 (7%)
Days to CR (range of medians)	30 - 59
Estimated survival	50 to 81% (after 24 mo.)

Shen (1997), Soignet (1998, 2001), Niu (1999), Shen (2001), Kwong (2001), Leoni (2002), Ohnishi (2002), Lazo (2003), Raffoux (2003), Carmosino (2004), Shigeno (2005), Thomas (2006), Aribi (2007, Alimoghaddam (2011) – reviewed in Lengfelder et al, Leukemia 2012;26:433-442.

Treatment Options for APL Relapses after ATRA + Chemotherapy



Sanz et al, Haematologica 2005;
ELN website. Available from: www. leukemia-net.org/content/.

Prospective / Retrospective European APL Relapse Registry (PROMYSE)

Inclusion criteria

- Patients with relapse of APL

  (first or later molecular, hematological, or extramedullary)
- Genetic confirmation of relapse
- Any treatment option for relapsed APL
- Use of uniform online CRFs mandatory

Evaluable (among 237 patients registered in 8 countries)

n=155 pts treated with ATO in 1. relapse

n= 48 pts treated with Chemotherapy in 1. relapse

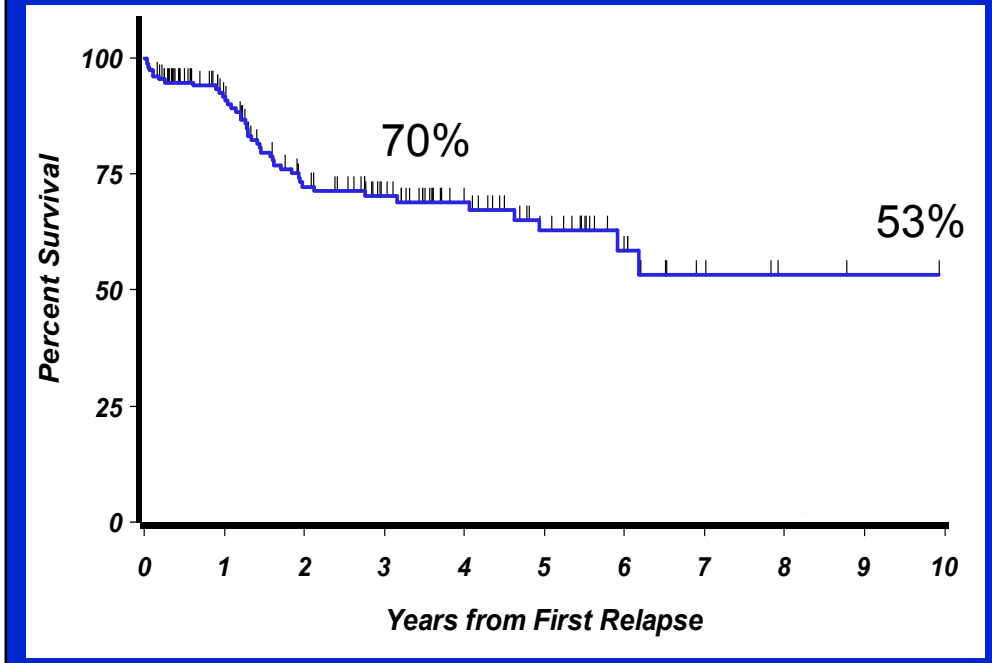
Salvage Therapy with ATO in 155 Patients with Genetically Confirmed First Relapse of APL

Type of relapse:	
Hematological	n = 104 (67%)
Molecular	n = 40 (26%)
Extramedullary	n = 11 (7%)
State-of-the-art front-line therapy:	
AIDA	60%
ATRA+anthrac±ara-C±etoposide	40%
ATO	No patients
Age at relapse	44 years (range 4–81)
Median duration of first CR	1.7 years (range 31 days–9.5 years)
Sanz relapse risk score	Low: 24%; intermediate 46%; high 29%

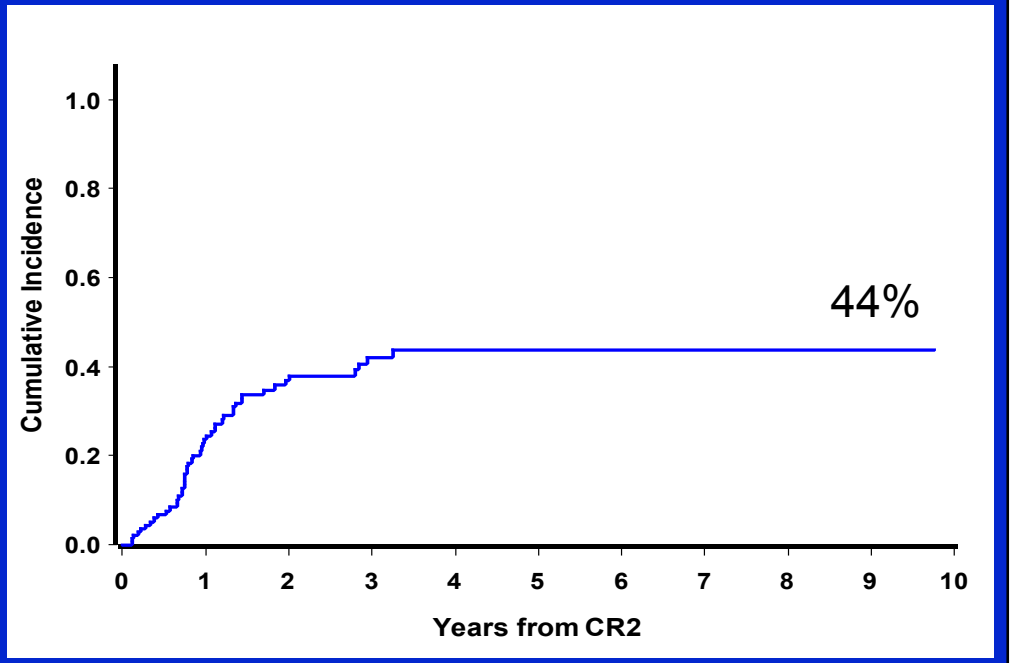
Lengfelder E, et al. Leukemia. 2015;29:1084-1091.

Outcome of Patients With First Relapse of APL after ATO-based Salvage Therapy

Overall survival after relapse (n = 155)



Cumulative incidence of 2nd relapse (n = 146)



- Median follow up 3.2 years (range 1 day to 10 years)

Lengfelder E, et al. Leukemia 2015;29:1084-1091

Comparison of Patients in Hematological Versus Molecular Relapse

Pts' characteristics at first relapse	Hematological relapse (n=40)	Molecular relapse (n=104)	P - value
	median (range)	median (range)	
WBC ($x10^9$/L)	3.2 (0.5-112)	4.4 (1.9-7.6)	**0.04**
Platelets ($x10^9$/L)	66 (8-479)	187 (40-426)	**<0.001**
Hb (g/dL)	12.5 (5.5-17.2)	13.8 (9.1-16.1)	**0.003**
Bleeding	23%	0	**0.0008**
Coagulopathy	34%	0	**0.001**
APL diff. syndrome	27%	0	**<0.001**
Leukocytosis	39 %	0	**<0.001**

Lengfelder E, et al. Leukemia 2015;29:1084-1091

Response to ATO ± ATRA (n = 155)

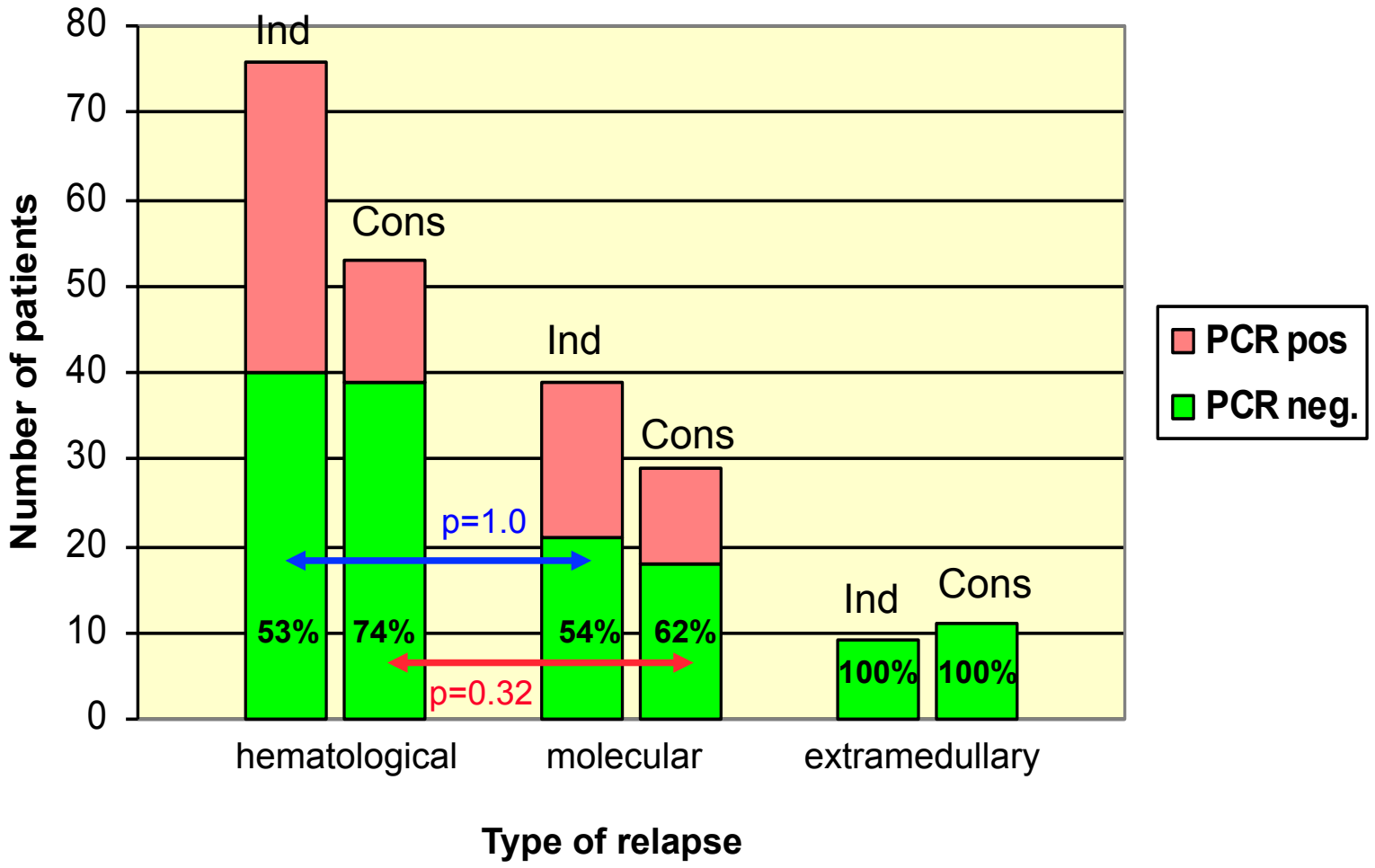
	Molecular relapse (n = 40)	Hematological relapse (n = 104)	Extramedullary relapse (n = 11)
CR (hematological)		91%	100%
Death	0	7%	
Resistance (hematological)		2%	
Molecular remission (after consolidation)	62%	74%	100%

Induction death at day: 1, 3, 11, 19 (cerebral bleeding)

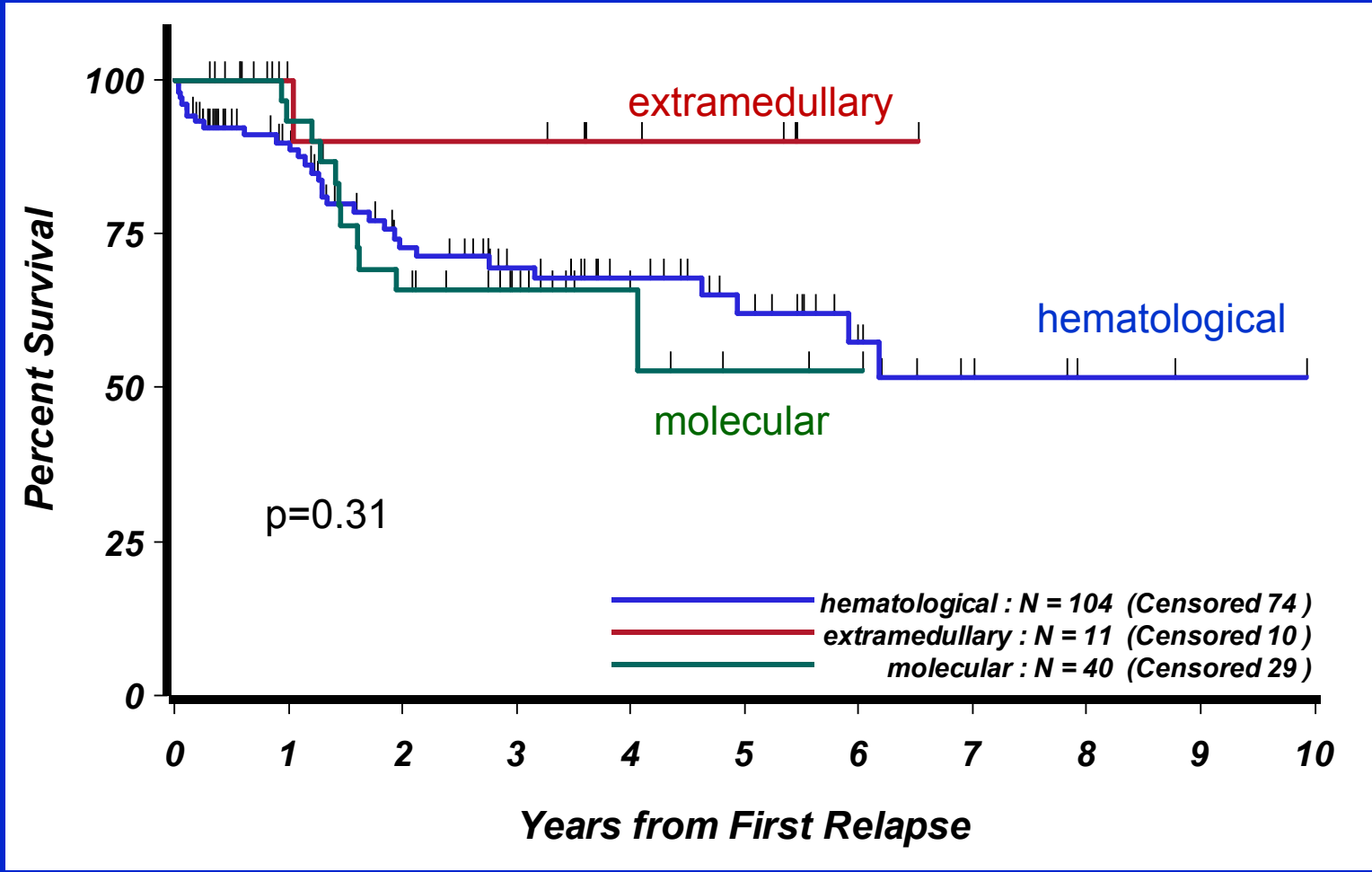
32, 33, 64 (2 infection, 1 not reported)

Lengfelder E, et al. Leukemia 2015;29:1084-1091

Rates of Molecular Remission after Induction and Consolidation with ATO (n=155)

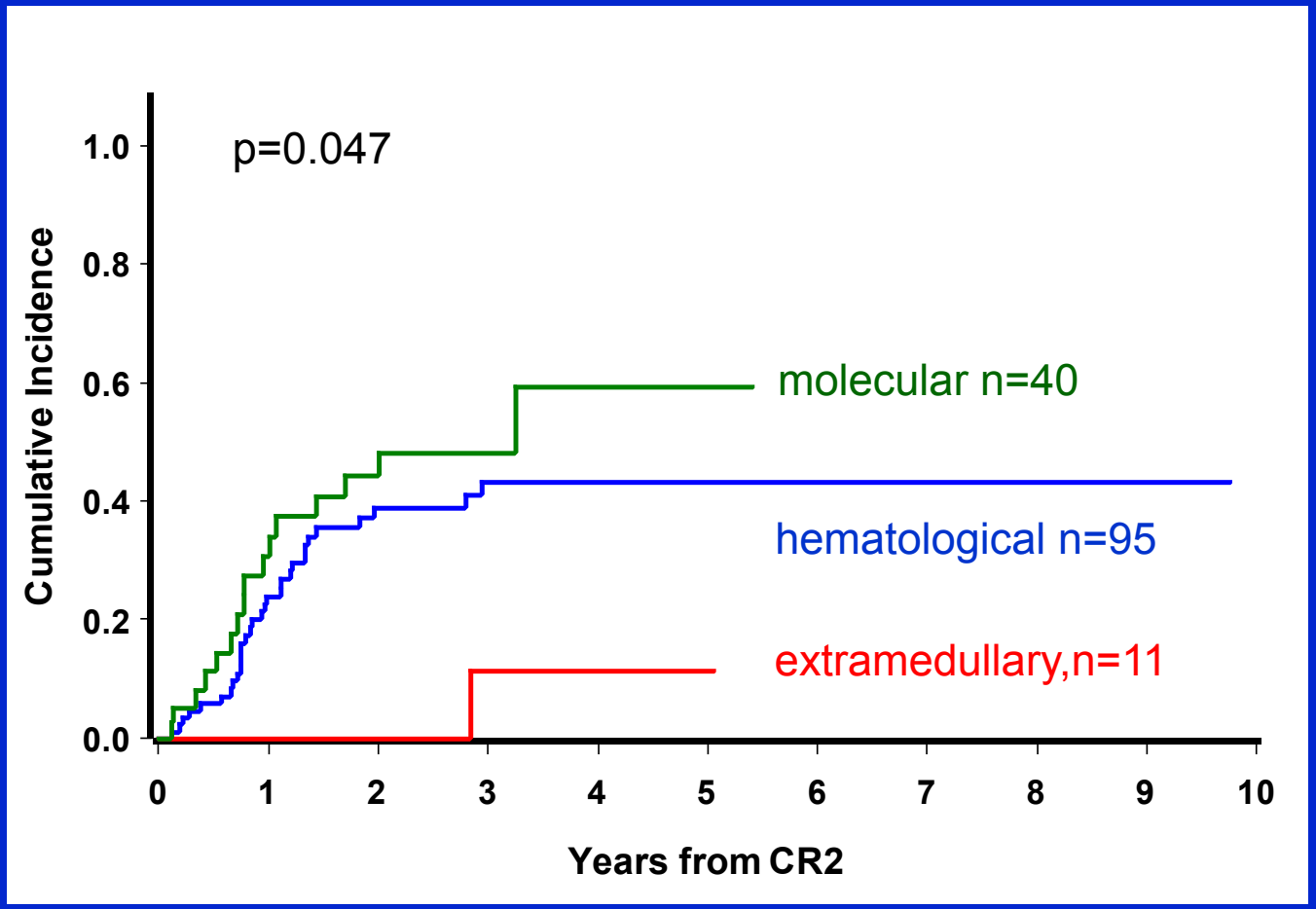


Overall Survival After First Relapse according to Type of Relapse (n = 155)



Lengfelder E et al, Leukemia 2015;29:1084-1091

Cumulative Incidence of Relapse
According to Type of Relapse



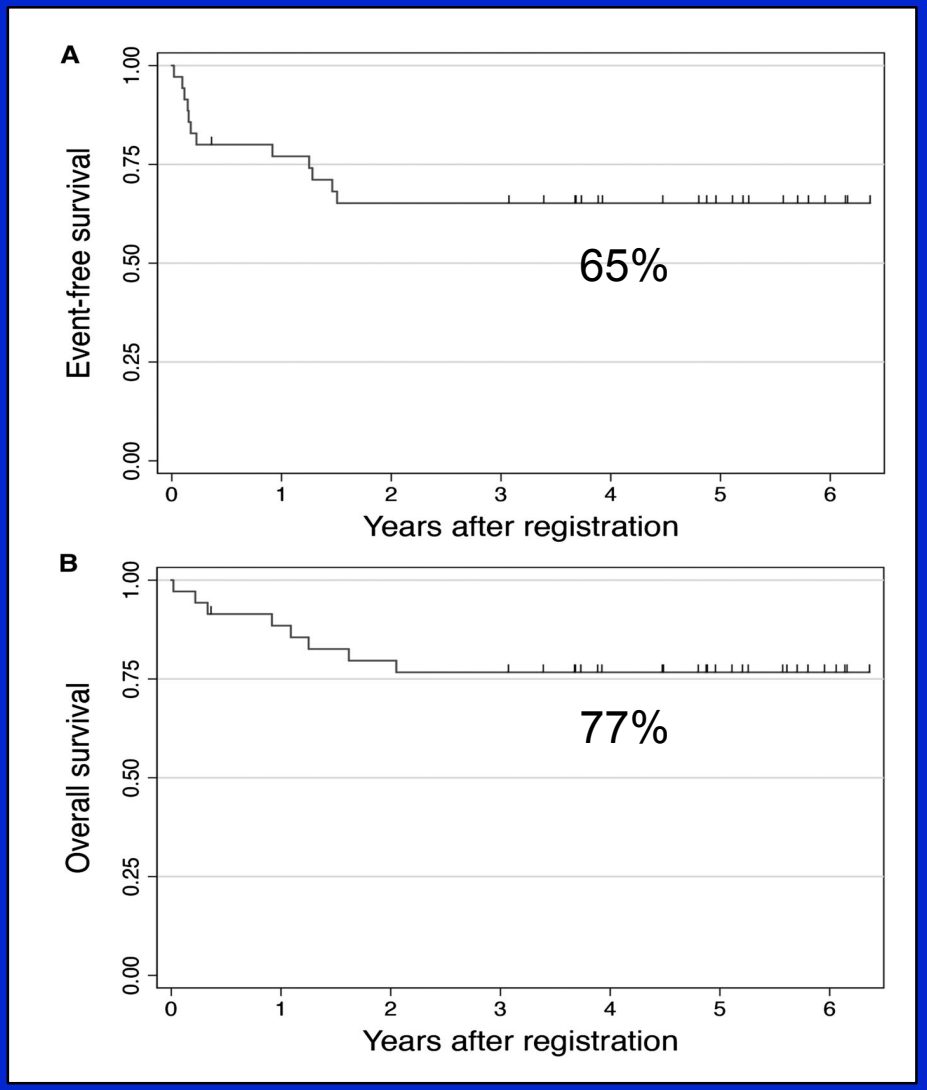
Lengfelder E et al. Leukemia 2015;29:1084-1091

Phase 2 study of ATO followed by auto-Tx for relapsed APL

n=35

EFS

OS



Yanada et al, Blood 2013;121:3095-3102

Overview on Published Results with Auto-Tx, Allo-Tx and without Tx in Relapsed APL in the ATO-Era

First author (year)	n	Percent overall survival			Time
		Auto Tx	Allo Tx	No Tx	
Kohno (2008)	28	**76**	**46**	-	at 4 y
Thirugnanam (2009)	37	**100**	-	**39 (ATO-based)**	at 5 y
Ramadan (2012)	31	-	**62**	-	at 4 y
Pemmaraju (2013)	40	**69**	**49**	**40 (Chemo)**	at 7 y
Yanada (2013) *	35	**77**	-	-	at 5 y
Fujita (2013)	57	**83**	**76**	**75 (Chemo, Retinoid)**	at 5 y
Holter-Chakrabarty (2014)	294	**75**	**54**	-	at 5 y
Lengfelder (2015)	155	**77**	**79**	**59 (ATO or Chemo)**	at 3 y
Ganzel (2016)	207	**79**	-	**42 (ATO)**	at 5 y
Yanada (2016)	141	**93**	-	-	at 4 y
Range (%)		**69 - 100**	**46 - 76**	**39 - 75**	

* prospective

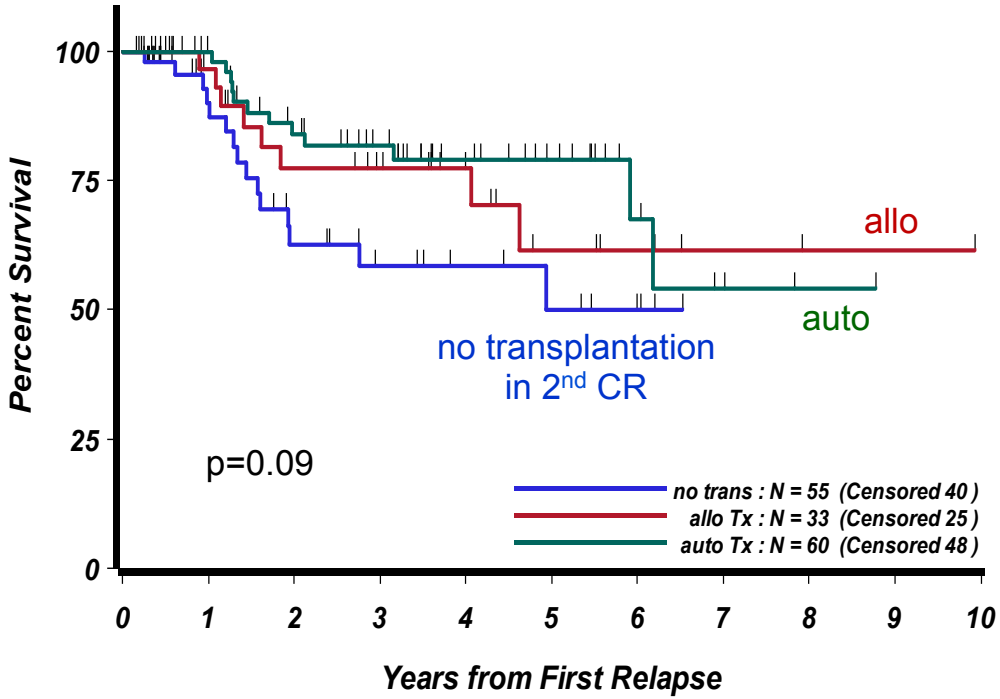
Post-Consolidation Therapy (n=148)

	Patients, n (%)	RT-PCR, %		Age ≥ 60 years, %
		Positive	Negative	
		Before transplant.		
Allogeneic transplant.	33 (22%)	52%	48%	0%
Autologous transplant.	60 (41%)	2%	98%	5%
		After consolidation		
No transplant	55 (37%)	17%	83%	46%

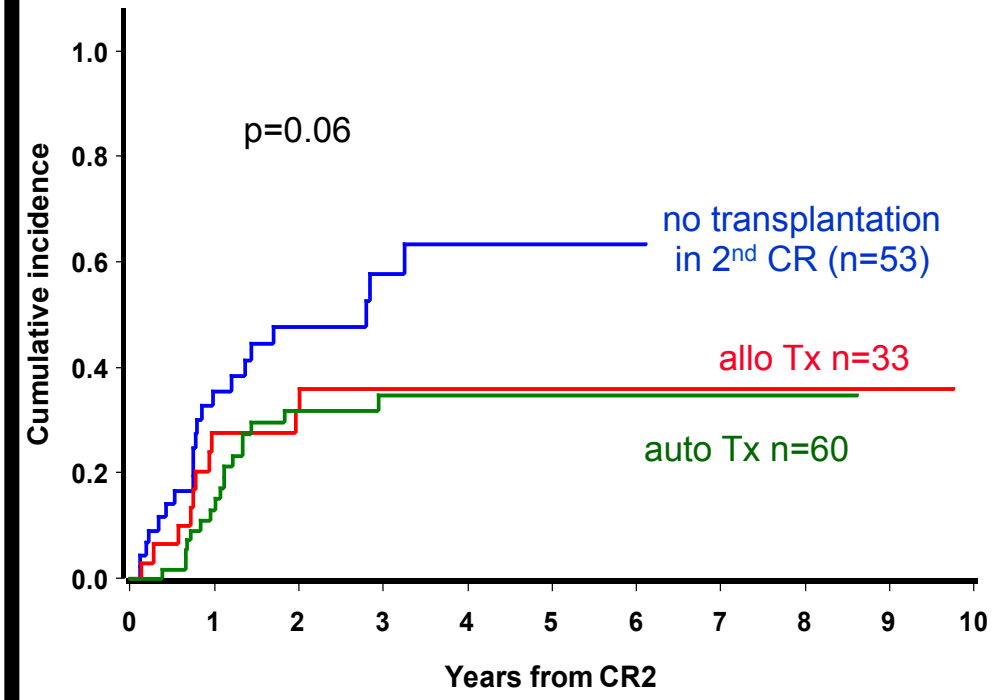
Lengfelder E et al, Leukemia 2015;29:1084-1091

Results after First Relapse According to Type of Post-Consolidation Therapy: Allogeneic or Autologous or No Transplantation

Overall survival after relapse



Cumulative incidence of 2nd relapse



Lengfelder E et al, Leukemia 2015;29:1084-1091

Results of univariable and multivariable analysis of prognostic factors

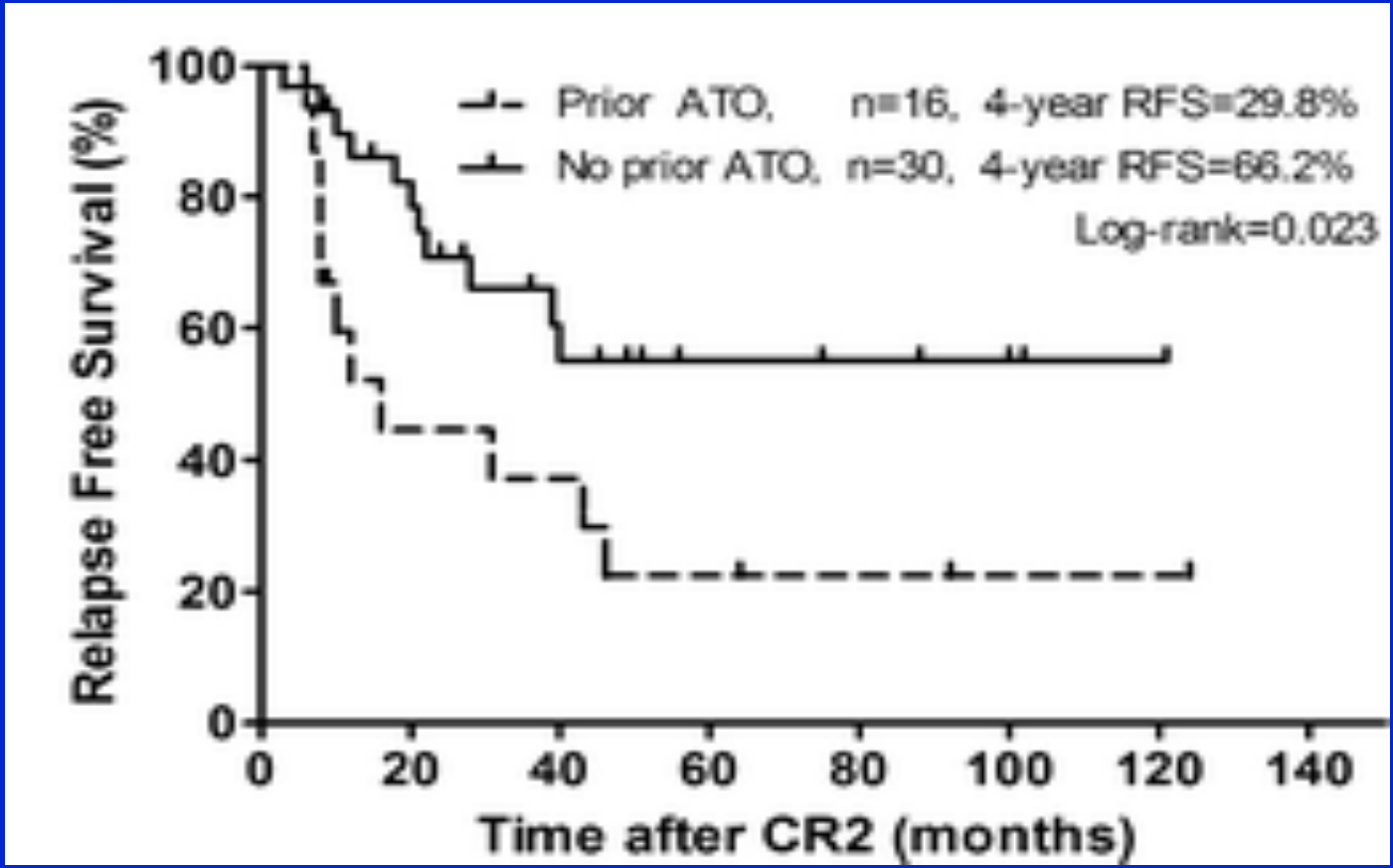
Variable	Overall survival			Leukemia-free survival		
	Univariable P-value	Multivariable HR [95% CI]	P	Univariable P-value	Multivariable HR [95% CI]	P
	N=148*			N=146		
Time in 1st CR (</≥1.5 y)	**0.046**	0.410 [0.183;0.919]	**0.03**	**0.004**	0.401 [0.210;0.764]	**0.006**
Tx vs. no Tx	**0.039**	0.326 [0.139;0.763]	**0.01**	**0.017**	0.363 [0.186;0.708]	**0.003**
Molecular CR (yes or no)	**0.019**	0.314 [0.129;0.764]	**0.01**	**<0.0001**	0.249 [0.125;0.496]	**<0.0001**

No significant prognostic impact: gender, initial WBC count ≤/>10000/µl, additional ATRA , type of relapse

*OS of patients alive after induction therapy

Lengfelder E et al.,Leukemia 2015;29:1084-1091

Relapse free survival in pts with first relapse of APL treated with ATO in dependence on frontline therapy with or without ATO



Lou et al, Ann Hematol 2014;93;941-948

Gemtuzumab Ozogamicin (GO) in Patients with Relapsed APL
Results of the Literature

Patients in first to third relapse of APL: n= 33 (of 8 publications)

Single dose of GO: 3 to 9 mg/m²/day

Repetitions variable

→ Molecular CR in 91% (30/33 pts)

Most common side effects: myelosuppression, hepatotoxicity

Petti et al, 2001; Lo Coco et al, 2004; Schwarz et al, 2004; Tsimberidou et al, 2004; Takeshita et al, 2005; Aribi et al, 2007; Breccia et al, 2007; Tageja et al, 2009.

Conclusions

- Historical comparisons show a longer survival with ATO-based therapy in first relapse compared to chemotherapy (probably due to a lower relapse rate and a higher transplantation rate).
- Patients in molecular relapse benefit in the first time after start of therapy due to less side effects of ATO compared to patients in hematological relapse.
- The summary of data indicates higher cure rates after transplantation compared to no transplantation – also in the ATO-era.
- In advanced relapses longer lasting remissions can still be induced.
  The curative potential of ATO seems to diminish with increasing number of relapses.
- The most suitable salvage therapy has to be chosen on the basis of the individual risks.