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

8th SYMPOSIUM ON

Acute Promyelocytic Leukemia

Dedicated to ***Prof. Francesco Lo Coco***

Featuring an AML meeting coordinated by ***EHA*** *SWG AML*

10-11 Aprile 2024

ROMA • Hotel NH Collection Roma Centro

The Role of Autologous and Allogeneic Transplantation in Relapsed APL

Alessandro Rambaldi

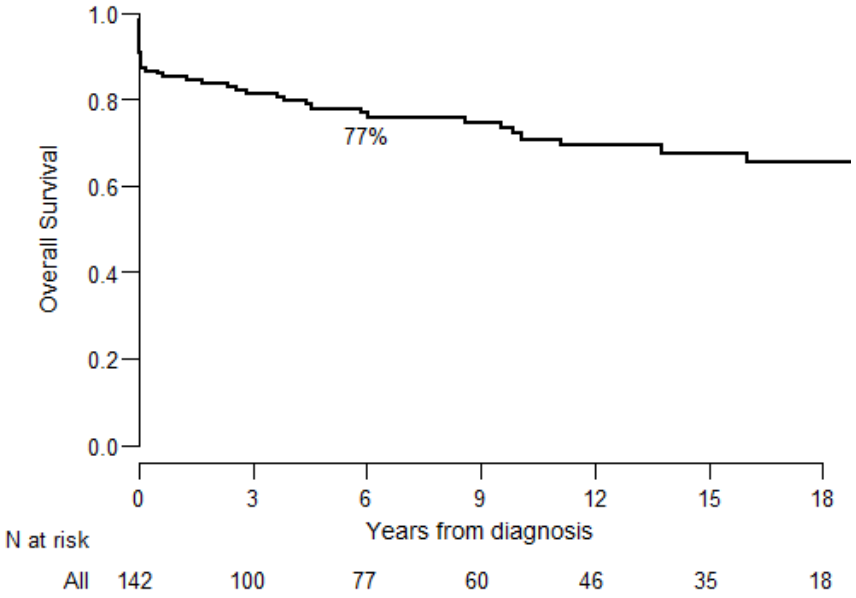
Disclosures of Alessandro Rambaldi

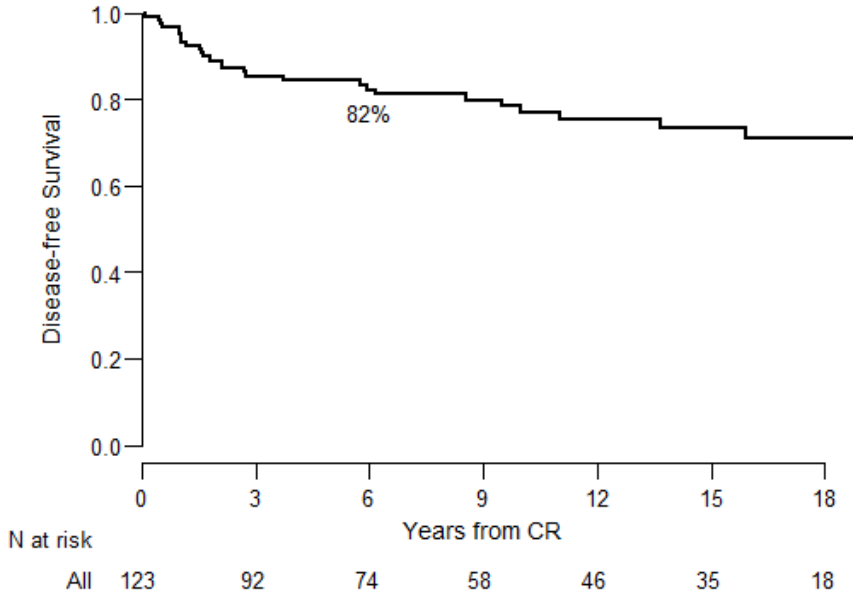
Fees for consultancies and participation into meetings, boards and symposia sponsored by

- Amgen
- Pfizer
- Novartis
- Kite-Gilead
- Jazz
- Astellas
- Abbvie
- Incyte
- Sanofi
- Omeros

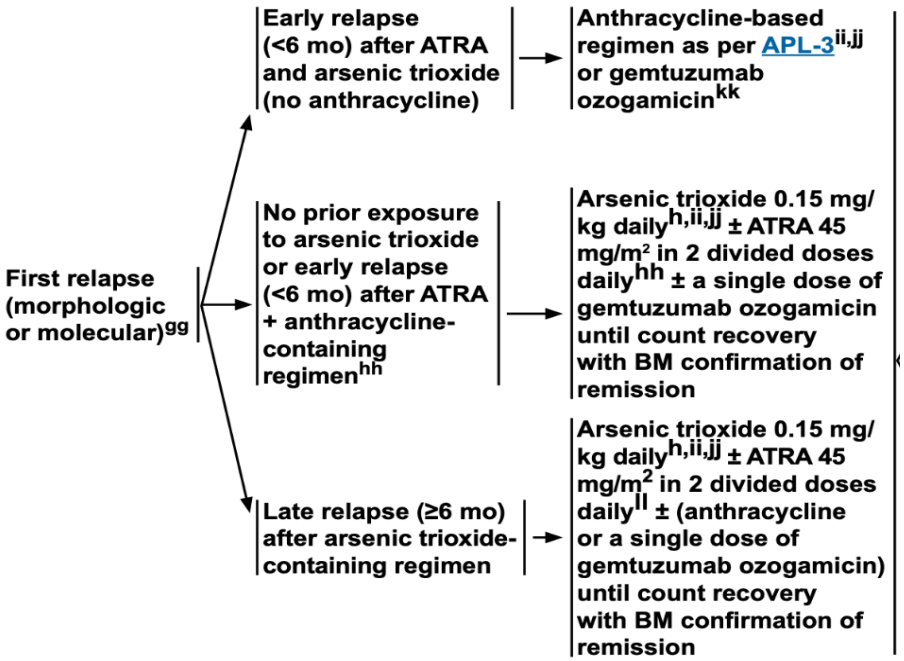
Twenty years Bergamo experience in the treatment of APL

Median Age	48 (19-85)
Deaths within 7 days	13 (9%)
Deaths within 30 days	18 (12%)
All deaths	39 (26%)
Relapse	14 (9%)

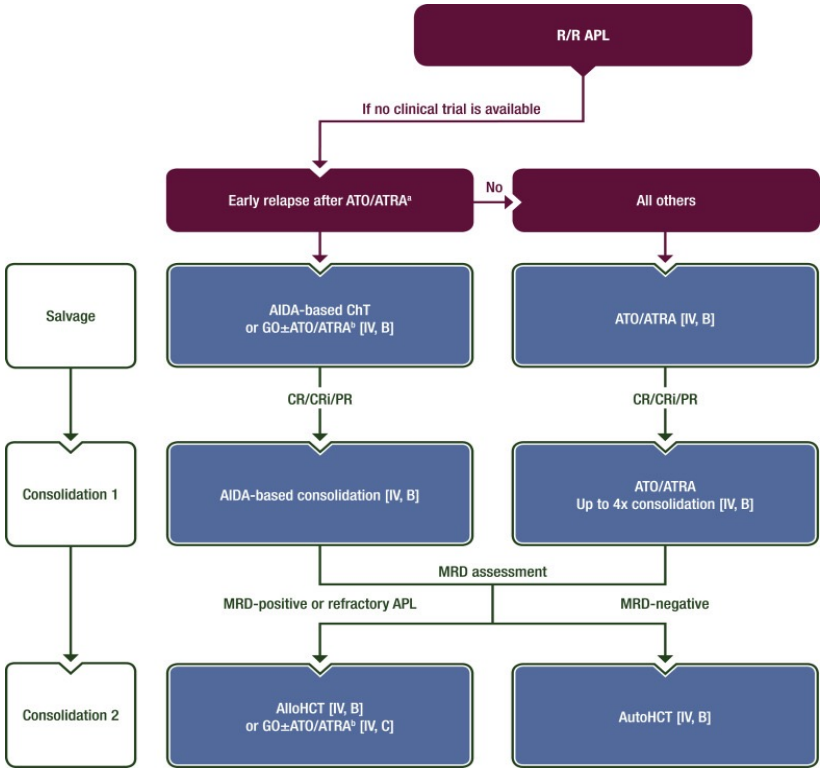




Relapsed APL: ESMO and NCCN Guidelines

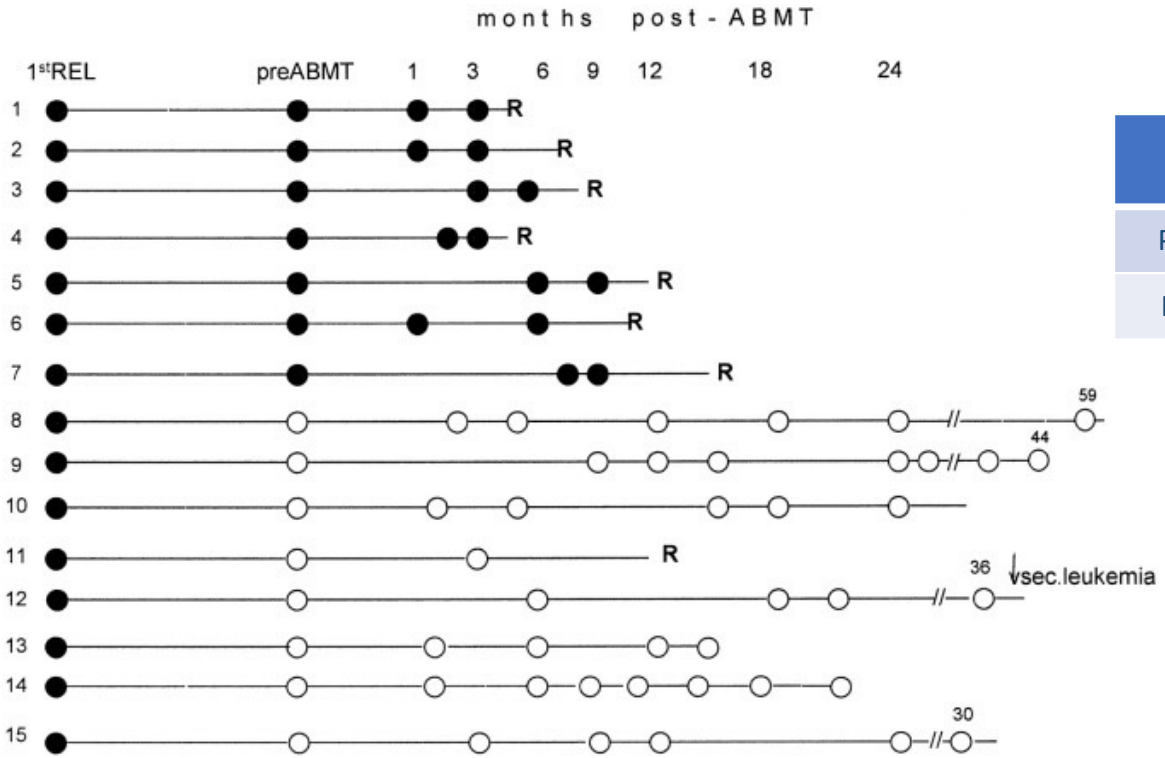


Pollyea, D. A., et al, NCCN Guidelines in Oncology.
Journal of the National Comprehensive Cancer Network, 21(5), 503-513.



Heuser M et al, *Annals of Oncology* volume 31, issue 6 p 697-712, June 2022

Autologous Bone Marrow Transplantation for Acute Promyelocytic Leukemia in Second Remission: Prognostic Relevance of Pretransplant Minimal Residual Disease Assessment by Reverse-Transcription Polymerase Chain Reaction of the PML/RARα Fusion Gene

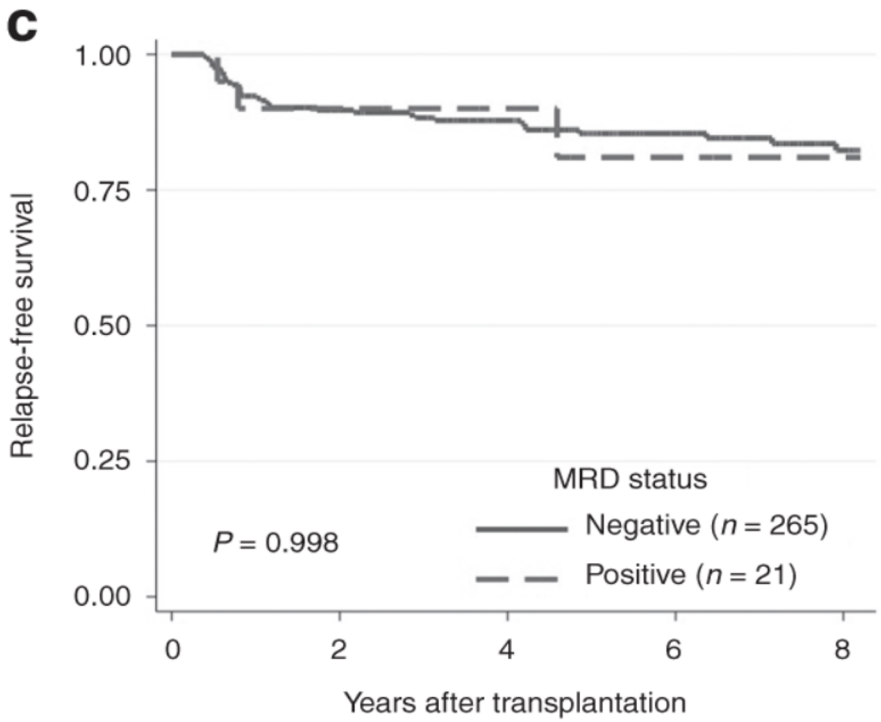


	Relapsed < 14 mo	CCR > 14 mo
Pre auto-HSCT PCR+	7	0
Pre auto-HSCT PCR-	1	7

P<.001

Meloni G….and Lo Coco F. Blood Volume 90, Issue 3, 1 August 1997, Pages 1321-1325

Is MRD negativity at the time of auto-HSCT always necessary?



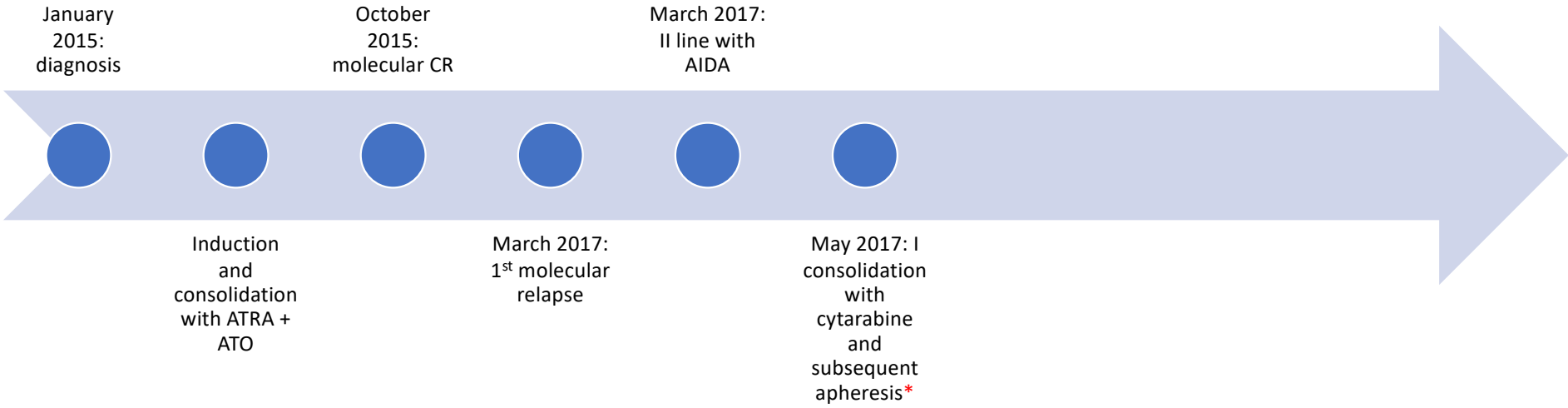
Maybe not…

- small retrospective experiences;
- PBSCs as a stem cell source in most cases;
- in the largest reported case history, on 21 patients with MRD+, only 2 relapsed

BUT…

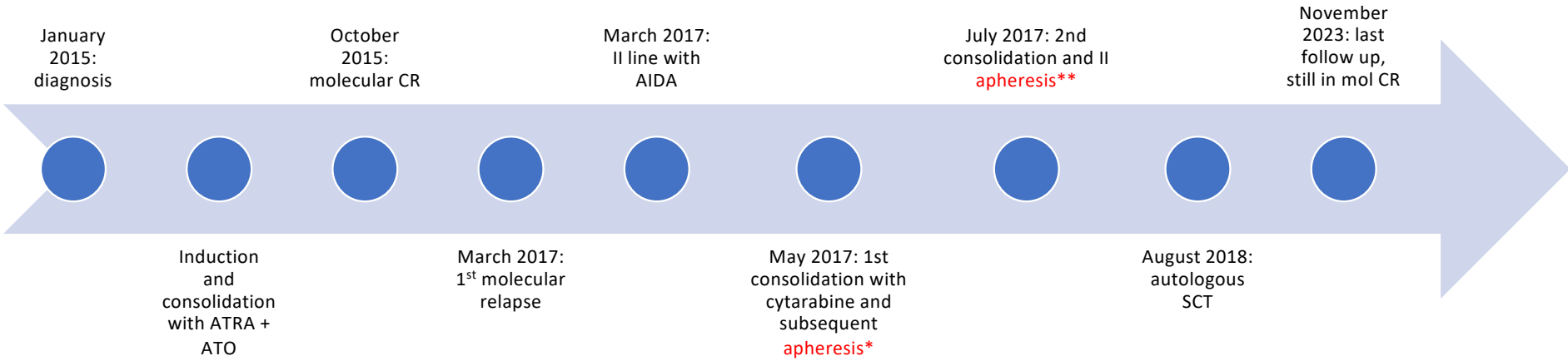
Yanada, M. et al *Bone Marrow Transplant* 57, 78–82 (2022).

Clinical case 1: allo or auto HSCT?



- Man, 55 years-old, no relevant comorbidity, diagnosis of APL intermediate risk according to Sanz, symptomatic for mild mucocutaneous bleeding.
- ATRA 45mg/sqm, ATO 0,15mg/kg induction and 4 cycles of consolidation
- AIDA: idarubicin 12mg/sqm for 4 days, I consolidation with idarubicin 5mg/sqm and cytarabine 1g/sqm for 4 days
- After I consolidation he obtained MRD negativity on bone marrow BUT the apheresis was PCR +.

Clinical case 1: allo or auto HSCT?

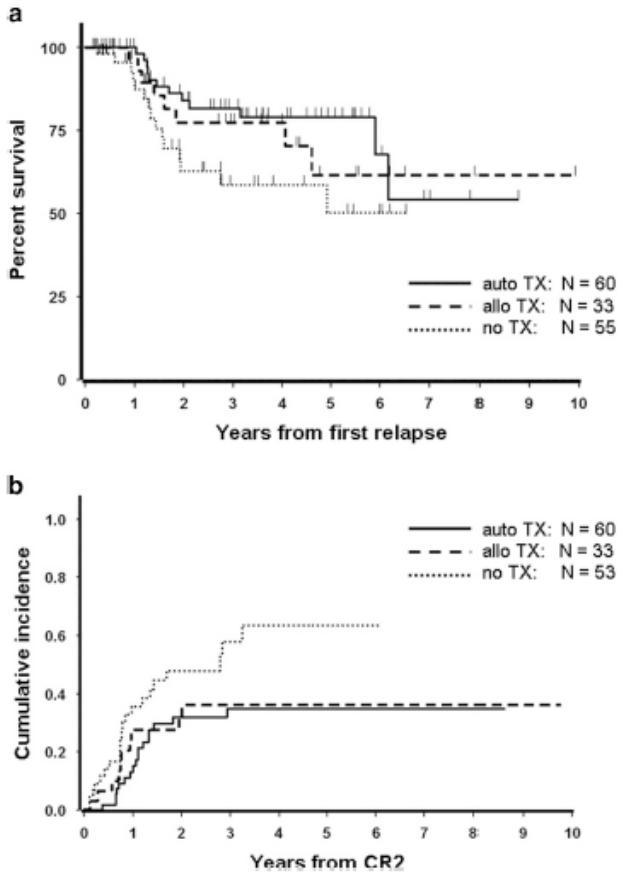


- We went on with a second Cytarabine and second apheresis (PCR-)
- Then AutoHSCT following conditioning with melphalan 200mg/sqm

Is auto or allo HSCT always necessary for relapsed APL?

Is auto or allo HSCT always necessary for relapsed APL?

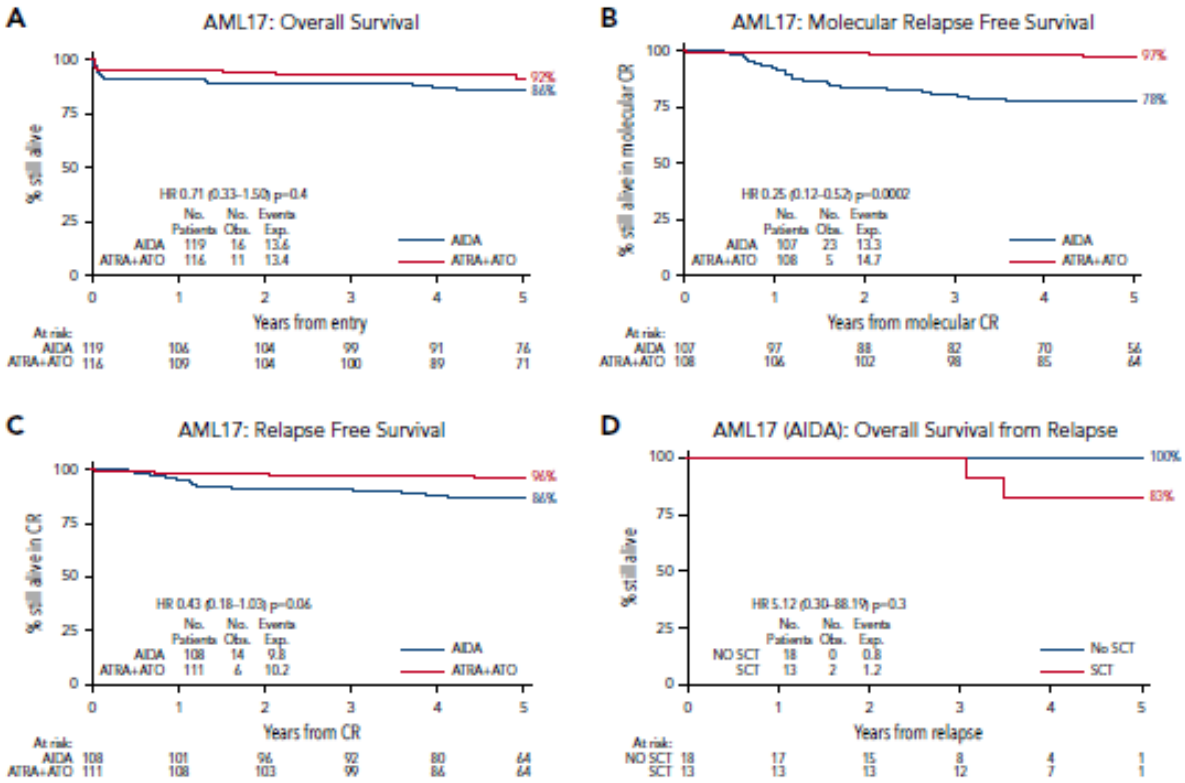
	Hematological relapse			*Molecular relapse*			*P-value*[a]	*Extramedulla relapse*
	Median (range)	N	%	*Median (range)*	N	%		*Median (rang*
No. of patients, N = 155		*104*			*40*			
Induction therapy							1.0	
ATO monotherapy		71/104	68		28/40	70		
ATO+ATRA		33/104	32		12/40	30		
Treatment duration of ATO ± ATRA (days)	31 (16–60)			29 (19–60)			0.21	27 (19–38)
No. of patients, N = 148		*97*			*40*			
Consolidation therapy							0.006	
ATO monotherapy		45/74	61		13/36	36		
ATO+ATRA		16/74	22		19/36	53		
Systemic chemotherapy		13/74	17		4/36	19		
No information		23			4			
Treatment duration of ATO ± ATRA (days)	25 (15–28)			25 (20–30)			0.9	25 (20–25)
Intrathecal methotrexate		4/104	4		2/40	5	0.67	
Postconsolidation therapy							0.34	
Autologous transplantation		42/97	43		12/40	30		
Allogeneic transplantation		22/97	23		10/40	25		
No transplantation in second CR		33/97	34		18/40	45		



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

Is auto or allo HSCT always necessary for relapsed APL?

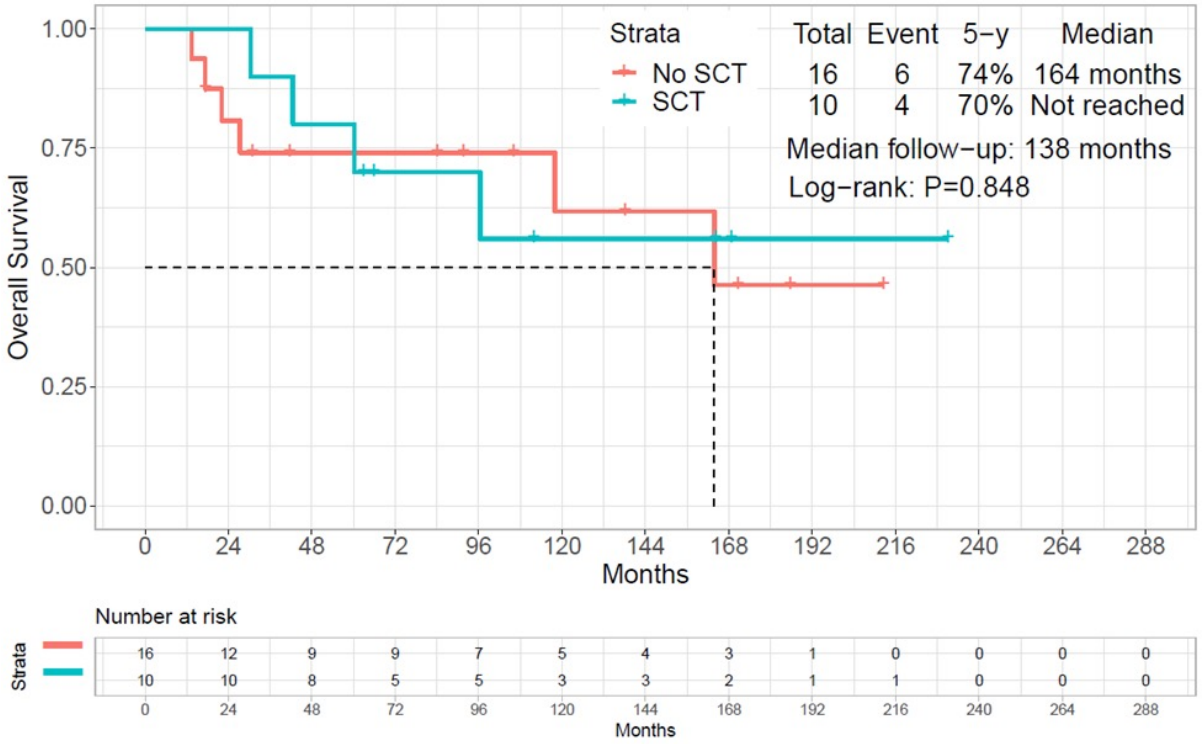
- 32 APL patients treated with ATO + ATRA (after AIDA failure)
- some patients maintained a molecular response even without transplantation
- small numbers



Russell N.: Blood 27 SEPTEMBER 2018 | VOLUME 132, NUMBER 13, 1452-1454

Is auto or allo HSCT always necessary for relapsed APL?

- 61 relapsed APL patients
- 31 patients (51%) received modern therapy (ATRA-ATO +/- GO or idarubicin), 30 patients (49%) received historical therapy
- among patients treated with **modern therapy** those in CR and MRD- who do not went to SCT had a similar outcome to those who underwent SCT.
- More data is needed to correctly identify those patients who could benefit for a non-SCT approach.



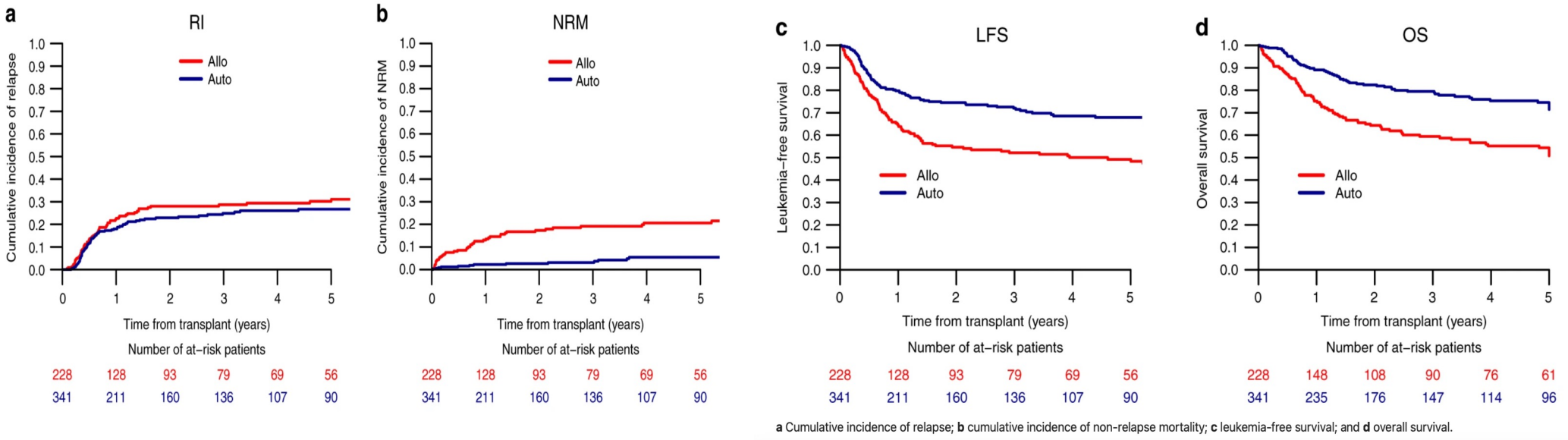
Sasaki K. et al, *Clinical Lymphoma, Myeloma & Leukemia*, in press (2024)

Allogeneic transplantation in relapsed APL: when and for whom

The preferred option for patients:

- in CR2 with positive MRD?
- with extramedullary relapse (especially CNS)?
- relapsed after auto-SCT (in CR3)
- For patients not in CR

Allogeneic or autologous SCT in CR2



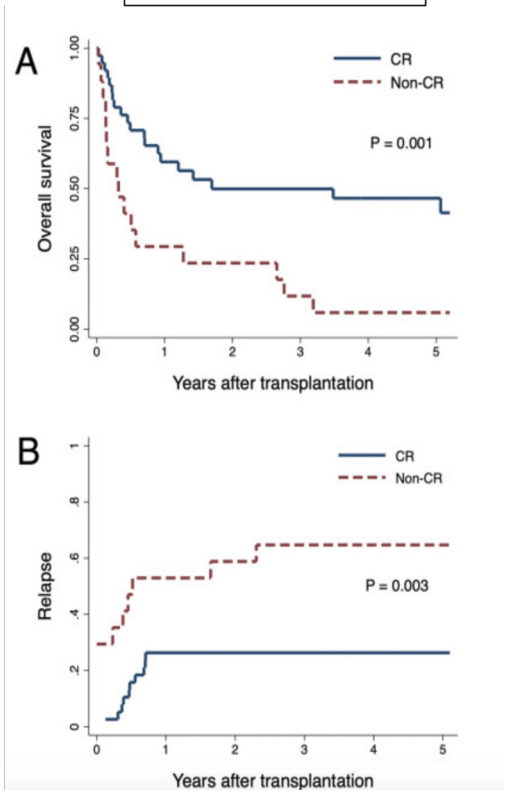
a Cumulative incidence of relapse; **b** cumulative incidence of non-relapse mortality; **c** leukemia-free survival; and **d** overall survival.

- Better OS after Auto in patients MRD negative at transplant.
- Patients selected for Allo were more frequently MRD+ at trasplant but did not show higher relapse rate.
- Among 8 patients of auto-SCT cohort with MRD+, 5 mantained molecular CR.

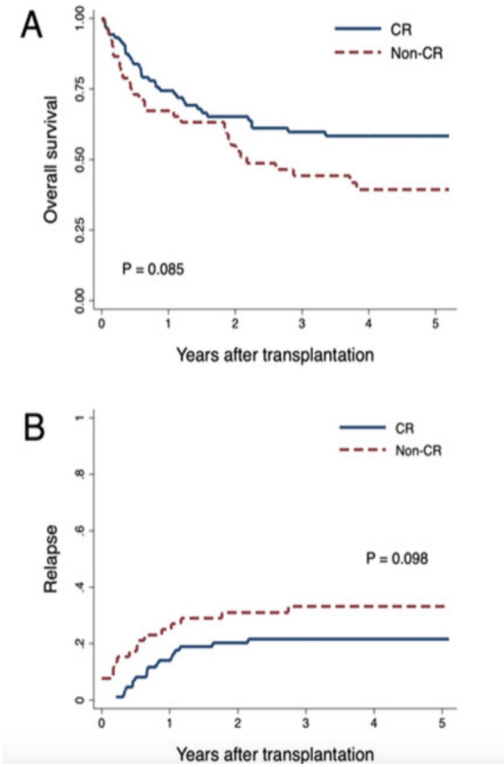
Sanz, J., et al. Bone Marrow Transplant 56, 1272–1280 (2021).

Allogeneic transplantation for relapsed APL according to previous auto-SCT

Previous autologous



NO previous autologous



Yanada M. et al. *Transplantation and Cellular Therapy*, 2022 Dec;28(12):847.e1-847.e8.

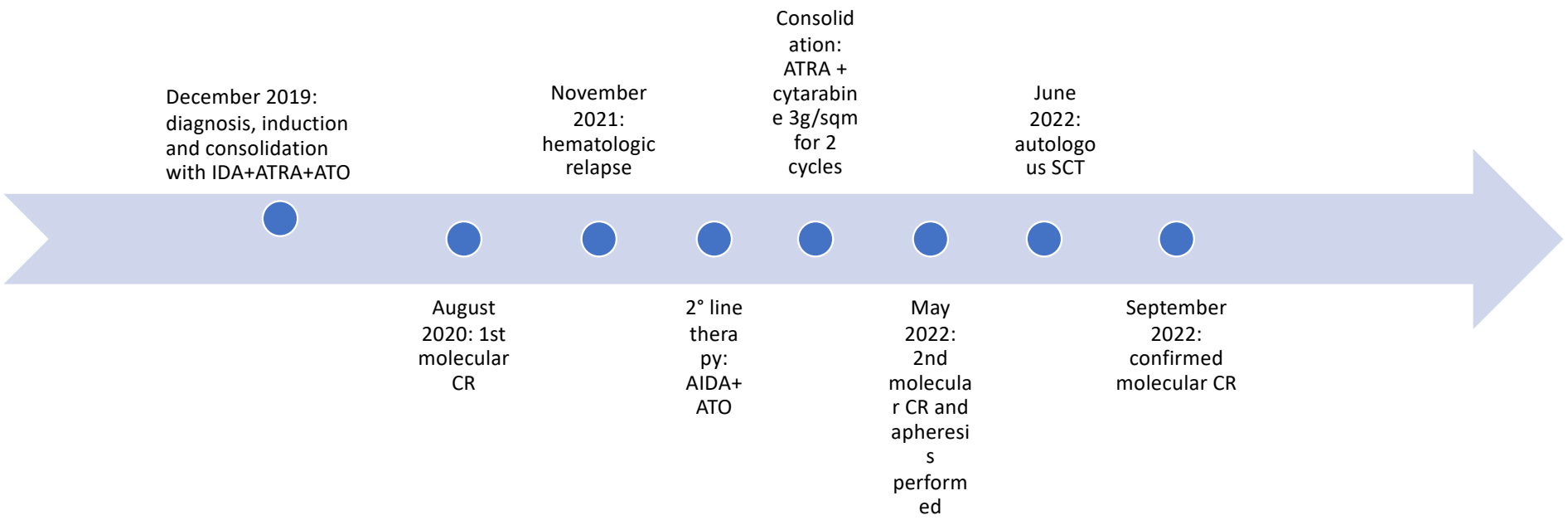
The problem of CNS relapse and other extramedullary sites involvement

- 10% of relapsed APL shows involvement of CNS
- CNS relapse is almost invariably associated with BM relapse.
- The prognosis is poor
- Treatment is often similar to those of other forms of leukemia involving CNS.

5.7. For patients with CNS relapse, induction treatment consists of weekly triple ITT with methotrexate, hydrocortisone, and cytarabine until complete clearance of blasts in the cerebrospinal fluid, followed by 6-10 more spaced out ITT treatments as consolidation; systemic treatment should also be given following recommendations 5.1 to 5.6	IV–C

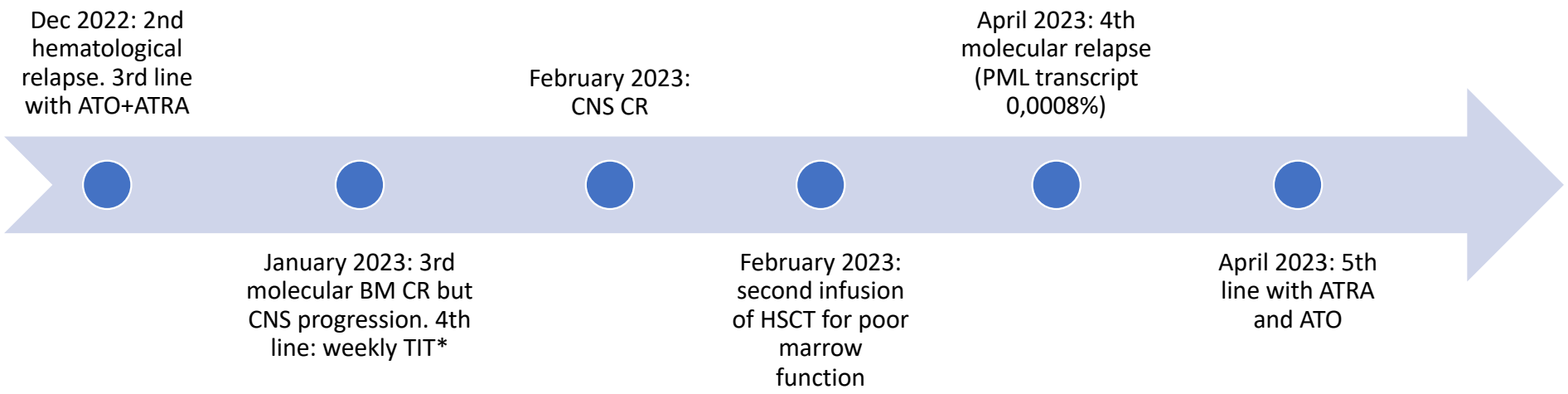
Sanz MA, *Blood*. 2019 Apr 11;133(15):1630-1643.

Clinical case 2: a long story…



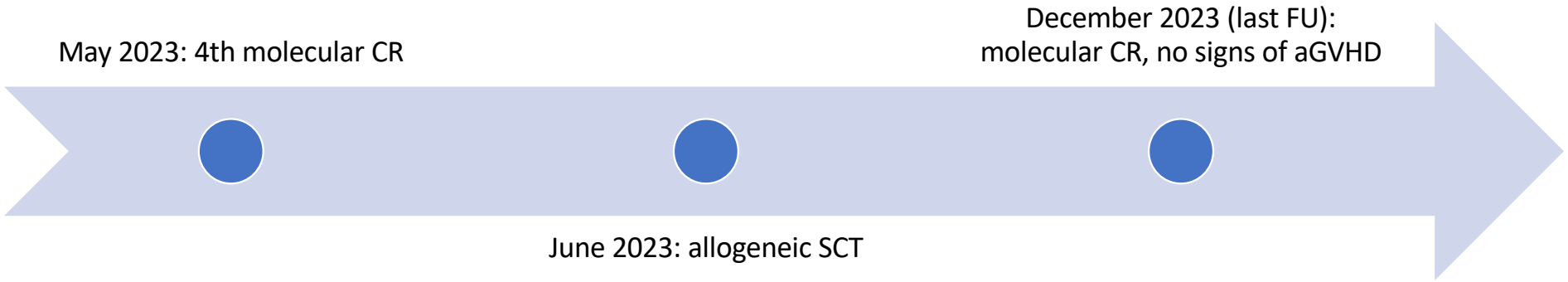
- Woman, 56 years, smoker, no comorbidities
- Characteristics of disease at diagnosis: PML-RARα bcr1, high risk according to Sanz, symptomatic for mild muco-cutaneous bleeding

Clinical case 2: a long story…



- Conditioning regimen before auto-SCT: busulfan (TD 729,6 mg) and cyclophosphamide (TD 6840 mg)
- Re-infused 5,4 x 10^6 CD34+/Kg
- At 2nd relapse a mutation of FLT3-TKD (codons 835-836) was found for the first time.
- * MTX 12,5 mg, Ara-C 50 mg, dexamethasone 4 mg

Clinical case 2: a long story…



- Re-infused 2,7 x 10^6 CD34+/Kg

- Donor: MUD 9/10, infused TNC 42013 x 10^6; CD34+ 445 x 10^6 (8.1 10^6/kg); CD3+ tot 8688 x 10^6 (158 x 10^6/Kg)
- Conditioning regimen: fludarabine 30 mg/kg and TBI 200cGy
- GVHD prophylaxis with ATG, cyclosporine, and MTX

Conclusions

- Relapse in APL is a rare event, especially in the ATRA-ATO era

- Salvage treatments (reinduction and consolidation) should consider the time from the end of front-line therapy, the type of relapse (hematologic vs molecular), the involvement of extra-hematologic sites. ATO-ATRA might be an option even after 6 months from the previous administration (NCCN guidelines)

- Autologous HSCT is a standard for patients in CR2 and MRD-, but it could be safely avoided in MRD- patients. However, it may also be effective in some MRD+ patients

- Allogeneic HSCT allows to cure a proportion of patients failing to achieve a hematologic or molecular CR, those relapsing after Auto and some patients with extra-hematologic relapse