PLENARY SESSION IX.
Role of Transplantation in Acute Promyelocytic Leukemia

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Disclosures of Jaime Sanz

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Nothing to disclose							

HSCT in APL
Outline

- Introduction
- Role of HSCT in front-line therapy
- Role of HSCT in salvage therapy for relapsed APL
  - HSCT vs non-transplant strategies
  - Impact of pre-transplant molecular status
  - Autologous or allogeneic HSCT
- Conclusions

Introduction

- Marginal interest of hematopoietic stem cell transplantation (HSCT) in modern APL.
- However, around 5–15% of APL patients will eventually relapse → HSCT recommended.
- Limited information, specially in modern eras.
- Most recent studies analyze the impact of salvage strategies using ATO. There is no information on those patients failing ATO when used as front-line therapy.
- Well-designed studies are unlikely since the expected population that could potentially benefit from a transplant modality is small and diverse.

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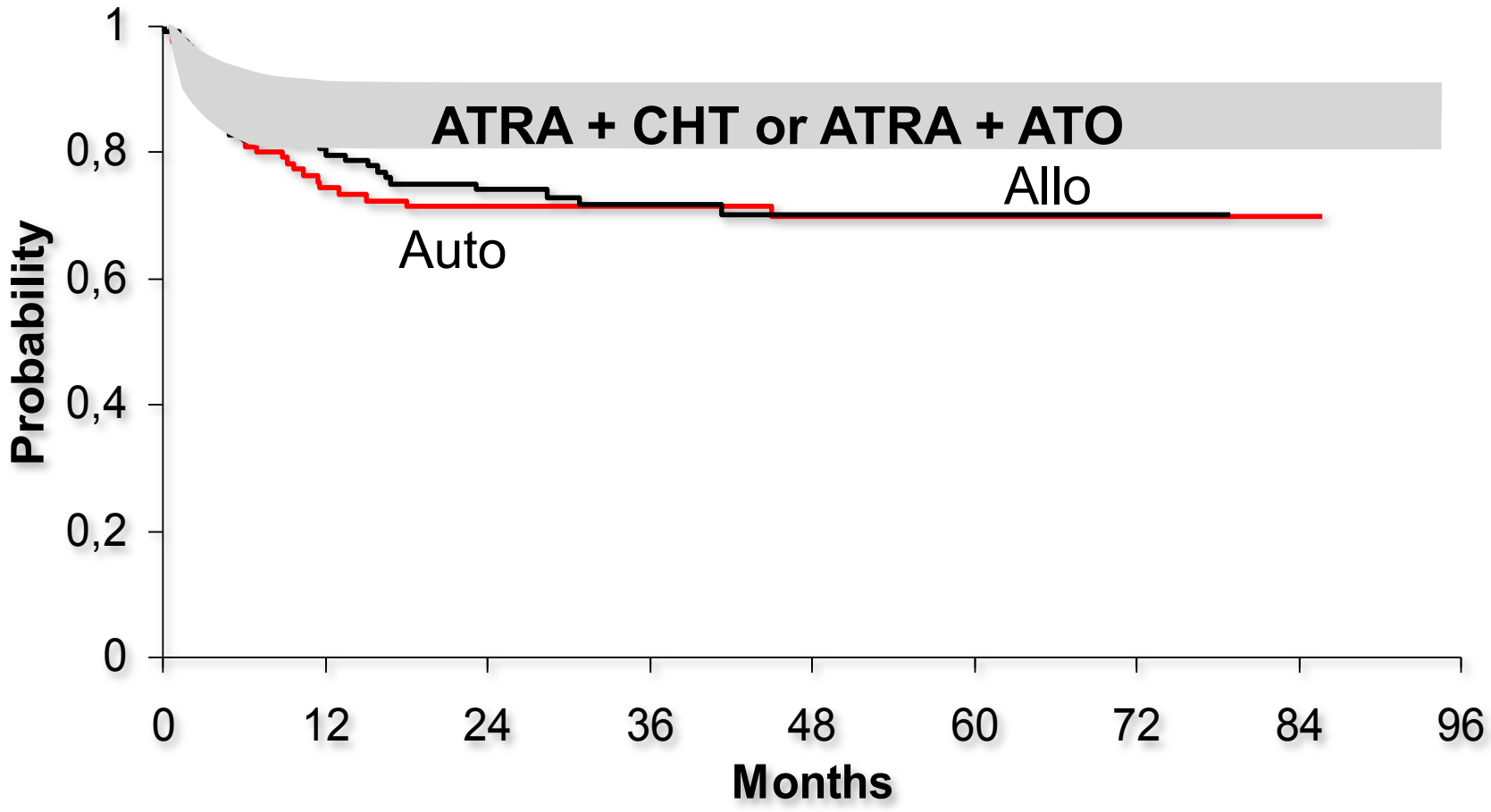
HSCT in front-line therapy

Is there room for HSCT in CR1?

Studies	No. pts.	Auto-SCT LFS	Auto-SCT TRM	No. pts.	Allo-SCT LFS	Allo-SCT TRM
EBMT survey Mandelli, 1994	187	48	19	175	42	42
EBMT survey Sanz, 2003	163	**72**	8	150	**70**	17
IBMTR survey Nabhan, 2001	123	**70**	N/A	341	**70**	N/A

HSCT in front-line therapy

Is there room for HSCT in CR1?



HSCT in front-line therapy
Risk features at presentation

- Elevated WBC
- CD56 expression
- Additional chromosome aberrations
- BCR isoform type
- FLT3 mutations

None justifies SCT (any type) in CR1!

HSCT in front-line therapy
Molecular persistance

Only indication of HSCT in front-line APL

- Molecular resistance after standard front-line therapy occurs in a tiny fraction of cases (<1%)
- Always confirm a PCR +ve result in a second sample and using reference laboratories adopting low-sensitivity ($\leq 10^{-4}$) technique
- Patients should be re-induced into PCR -ve status prior to proceed to SCT

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HSCT in salvage therapy
Drawbacks

- Retrospective analysis from registries. Several reasons for selection bias.
- Selection of studies including patients treated with ATRA in frontline therapy.
- Different salvage strategies.
- Molecular data (PCR status pre SCT) not always available.
- No data on patients treated with frontline ATO.

HSCT in salvage therapy

HSCT *vs* non-transplant strategies

Studies	Salvage therapy	HSCT strategies			Non-HSCT strategies	
		N	Type of HSCT	OS (%)	N	OS (%)
Lengfelder et al.[1]	ATO based	93	Auto Allo	73 79	55	59
De Botton et al.[2]	CHT	73	Auto Allo	60 52	49	39
Ganzel et al.[3]	ATO	140	Auto	78	67	42
Thirugnanam et al.[4]	ATO	14	Auto	100	19	38

1. Lengfelder E. *Leukemia*. 2015;29:1084–91.
2. de Botton S. *J. Clin. Oncol.* 2005;23:120–126.
3. Ganzel C. *BMT*. 2016;51:1180–83.
4. Thirugnanam R. *BBMT.* 2009;15:1479–84.

HSCT in salvage therapy
HSCT *vs* non-transplant strategies

- Limited comparability of the different cohorts: the non-HSCT group included an older and heterogeneously treated population of patients who probably did not qualify for HSCT in the majority of cases.
- A proportion of patients can maintain long-term remissions without HSCT.
- Outcomes seem much better for those who receive autologous or allogeneic HSCT.
- Available data supports the use of a HSCT modality for all transplant candidates.

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HSCT in salvage therapy
Impact of molecular status: **Autologous SCT**

Table 2. Correlation Analysis Between Pretransplant PCR of PML/RARα and Occurrence of APL Relapse

	Relapsed <14 mo	CCR* >14 mo	
Pre-ABMT PCR +ve	7	0	$P < .001$†
Pre-ABMT PCR −ve	1	7	

- MRD positivity in the bone marrow at the time of autologous HSCT was highly predictive of relapse in most but not all reports.
- Most recent series receiving ATO --> autologous HSCT are MRD negative and impact of molecular status cannot be evaluated

Meloni et al, Blood. 1997;90:1321–5.

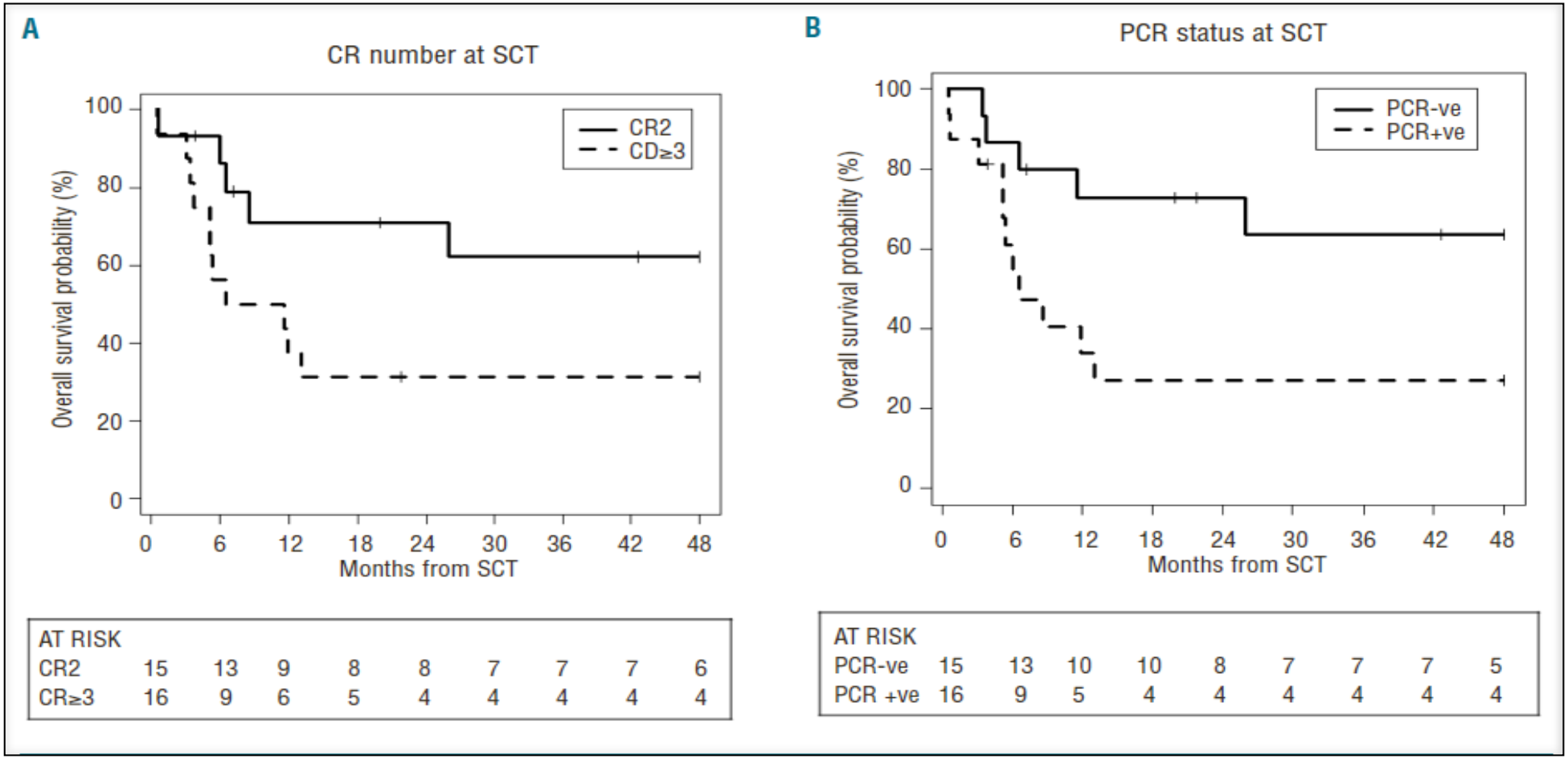
HSCT in salvage therapy
Impact of molecular status: **Autologous SCT**

Leukemic contamination of stem cell grafts, while bone marrow is in molecular remission, does not necessarily lead to leukemic relapse.

- Unclear mechanisms of surveillance and the control of low numbers of leukemic cells
- Non-clonogenic nature of the PML/RARA-positive cells present in the graft.
- Long-term hematopoiesis after autologous HSCT would be sustained by the subset of CD34+/CD38− progenitor cells administered, and these immature progenitors have been shown to lack the PML/RAR rearrangement in APL patients.

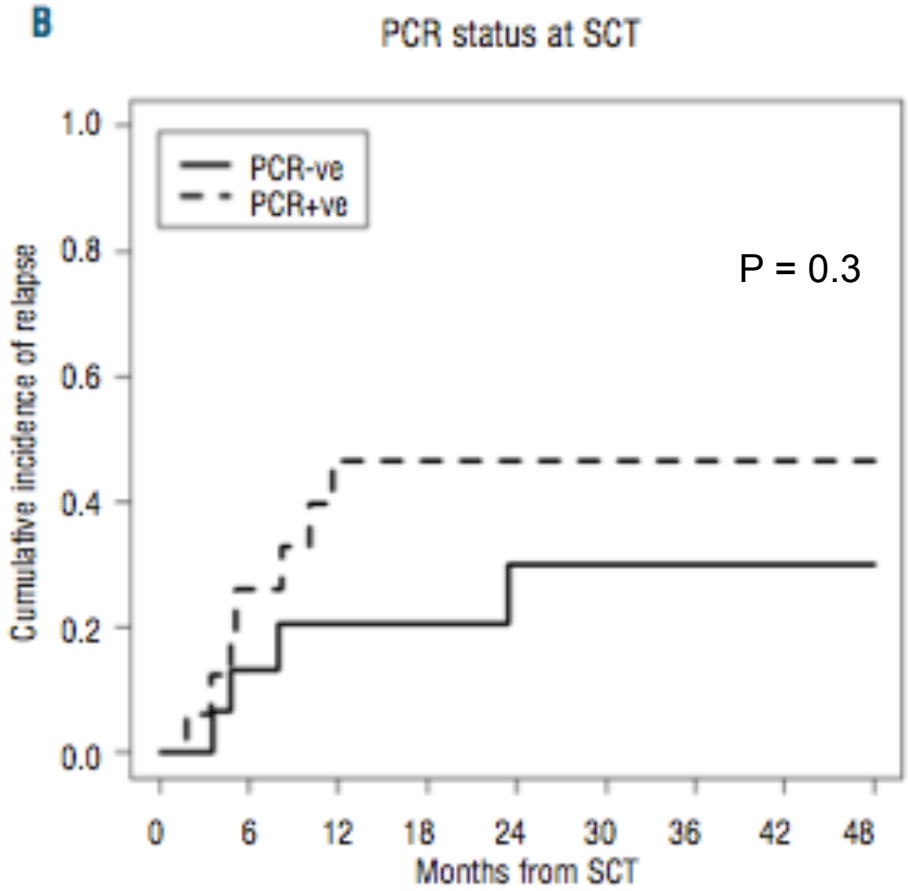
HSCT in salvage therapy

Impact of molecular status: **Allogeneic SCT**



Ramadan et al, Haematologica 2012;97:1731–35.

HSCT in salvage therapy
Impact of molecular status: **Allogeneic SCT**



The impact of MRD positivity may be counterbalanced by the graft-versus-leukemia (GVL) effect.

Ramadan et al, Haematologica 2012;97:1731–35.

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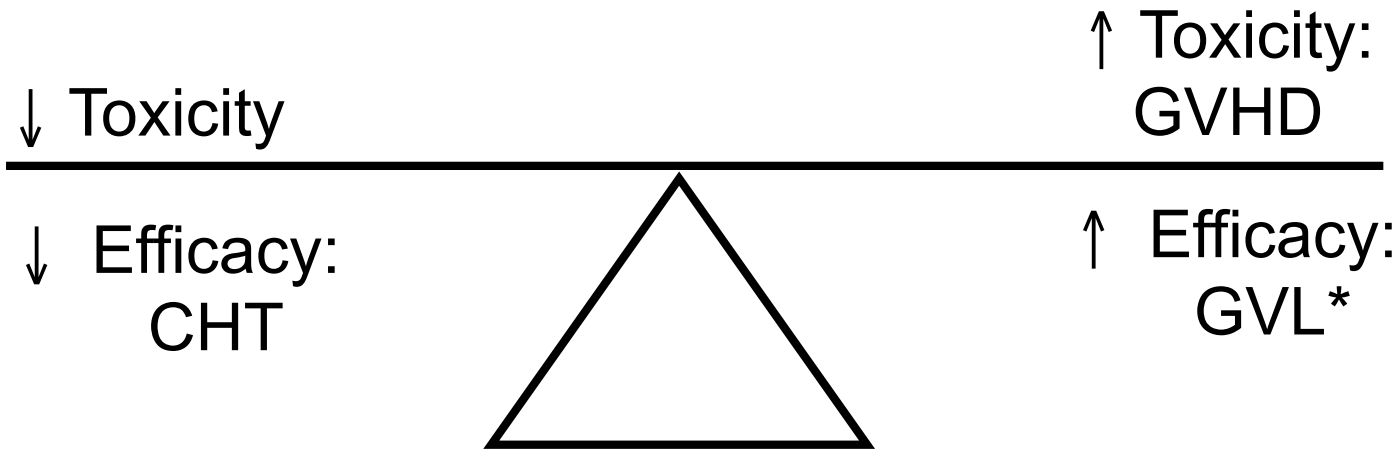
HSCT in salvage therapy
Autologous or allogeneic HSCT

Autologous SCT

Allogeneic SCT



*Lo-Coco et al. *Leukemia*. 2003;17:1930–33

HSCT in salvage therapy
Autologous or allogeneic HSCT

Studies	Salvage therapy	Autologous HSCT			Allogeneic HSCT		
		N	MRD - (%)	OS (%)	N	MRD - (%)	OS (%)
Lengfelder et al.[1]	ATO based	60	98	73	33	48	79
De Botton et al.[2]	CHT	50	93	60	23	33	52
Sanz et al.[3]	CHT	195	-	51	137	-	59
Holter Chakrabarty et al.[4]	CHT	62	86	75	232	85	54

1. Lengfelder E. *Leukemia*. 2015;29:1084–91.
2. de Botton S. *J. Clin. Oncol.* 2005;23:120–126.
3. Sanz MA. *BMT*. 2007;39:461–469
4. Holter-Chakrabarty. *BBMT.* 2014;20:1021–25 .

HSCT in salvage therapy
Autologous in the ATO era

Retrospective comparison of autologous HSCT results in the pre-ATO and ATO eras

RFS OS CIR

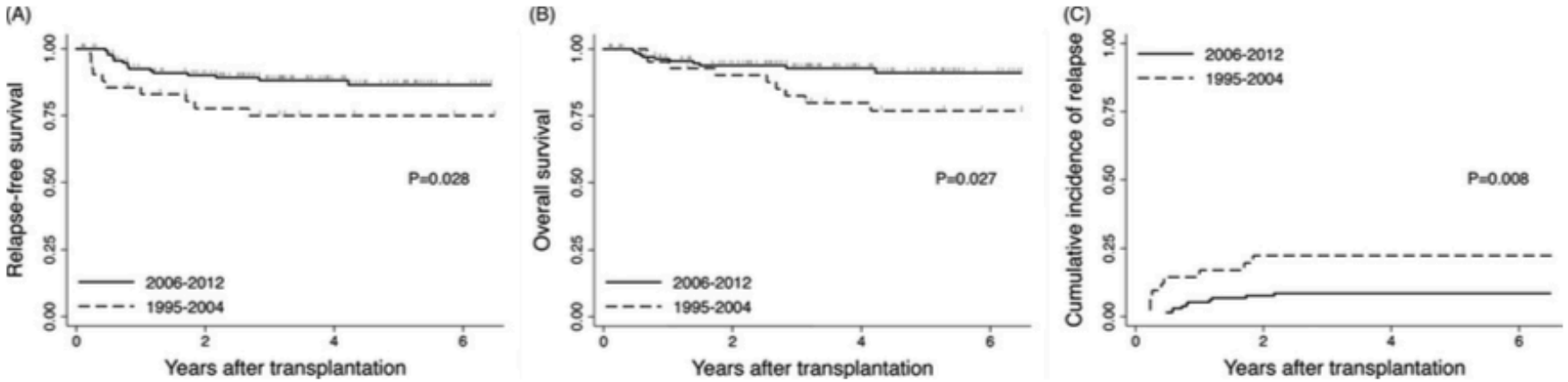


Figure 2. Relapse-free survival (A), overall survival (B), and cumulative incidence of relapse (C) according to the year of transplantation. Patients transplanted during 1995–2004 (Cohort A, $n = 43$) and those transplanted during 2006–2012 (Cohort B, $n = 141$) are compared.

95% MRD neg

Yanada et al. *Leuk. Lymphoma*. 2017;58:1061–1067

HSCT in salvage therapy
Relevant considerations

Age and performance score

Previous therapy

Duration of 1st CR

Molecular status

Donor availability

Conclusions

- SCT in CR1 only to be considered for patients with molecular resistance after consolidation.
- All transplant candidates in CR2 should probably receive a HSCT modality.
- RT-PCR before HSCT has a major impact on outcome and should guide the choice of HSCT modality.

  → If molecular remission: Auto SCT preferable

  → If PCR+ve persistence: Allo SCT preferable (try to achieve molecular negativity)

- Unknown clinical behavior of patients relapsing after frontline ATO.

Thank you