E’ ancora proponibile il Trapianto di Cellule Staminali Allogeniche?

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Clin Adv Hematol Oncol. 2015 Sep;13(9):586-94.
New insights into hematopoietic stem cell transplantation for chronic lymphocytic leukemia: a 2015 perspective.
McClanahan F, Gribben J

- HSCT→ the only potentially curative treatment option for patients with CLL.
- HSCT→ should be considered in physically *fit CLL patients who carry poor-risk features*, such as TP53 abnormalities, or who had a short response to previous immuno-chemotherapy.
- HSCT→ significant treatment-related mortality and morbidity.

- New agents and alternative treatment strategies are available that demonstrate impressive and durable responses, even in CLL patients who previously might have been candidates for transplant.
- Until data on the long-term efficacy of novel treatment approaches mature, the choice of HSCT vs alternative strategies must be assessed on a patient-by-patient basis, and treatment in the setting of randomized clinical trials should be pursued whenever possible.

Where Does Allogeneic Stem Cell Transplantation Fit in the Treatment of Chronic Lymphocytic Leukemia?

Table 2 Conditions affecting the balance between immediate versus delayed alloHSCT in patients with HR-CLL responding to signal transduction inhibitor

Conditions in favor of immediate alloHSCT
Coincidence of R/R HR-CLL with *TP53* alterations and/or 11q- (high disease risk)
Hints for incipient t-MDS, such as MDS-specific genetic aberrations and unexplained cytopenias along with significant exposure to chemotherapy (high disease risk)
Young age, no significant comorbidity (low transplant risk)
Availability of a well-matched donor (low transplant risk)
Conditions in favor of delaying alloHSCT:
Absence of an R/R situation
R/R situation in the absence of *TP53* alterations and/or 11q-
Age >70 years, significant comorbidity
Only partially matched or mismatched donor available

Peter Dreger · Emili Montserrat ·

Curr Hematol Malig Rep (2015) 10:59–64

Managing high-risk CLL during transition to a new treatment era: stem cell transplantation or novel agents?

Peter Dreger,[1] Johannes Schetelig,[2,3] Niels Andersen,[4] Paolo Corradini,[5] Michel van Gelder,[6] John Gribben,[7] Eva Kimby,[8] Mauricette Michallet,[9] Carol Moreno,[10] Stephan Stilgenbauer,[11] and Emili Montserrat,[12] on behalf of the European Research Initiative on CLL (ERIC) and the European Society for Blood and Marrow Transplantation (EBMT)

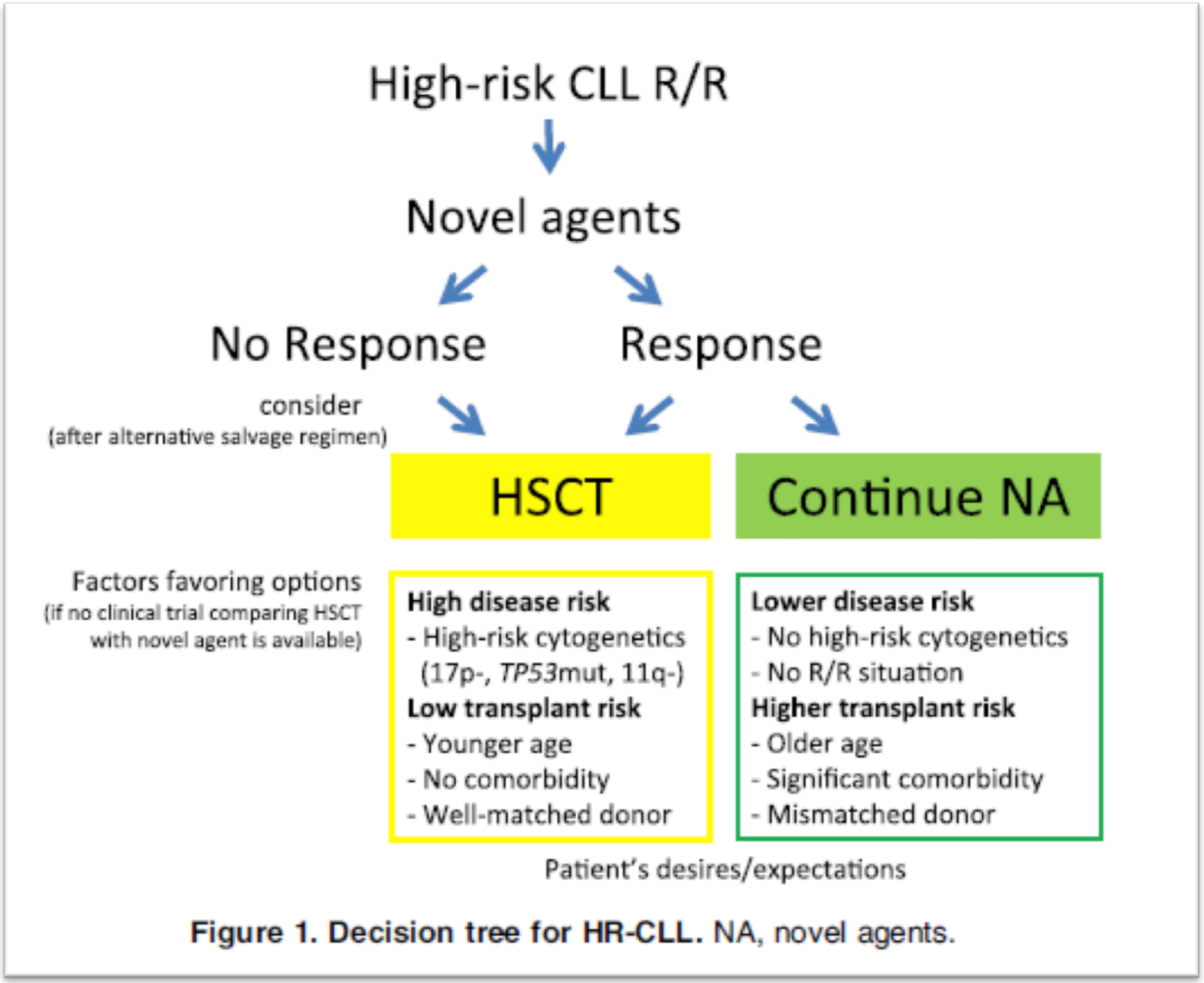
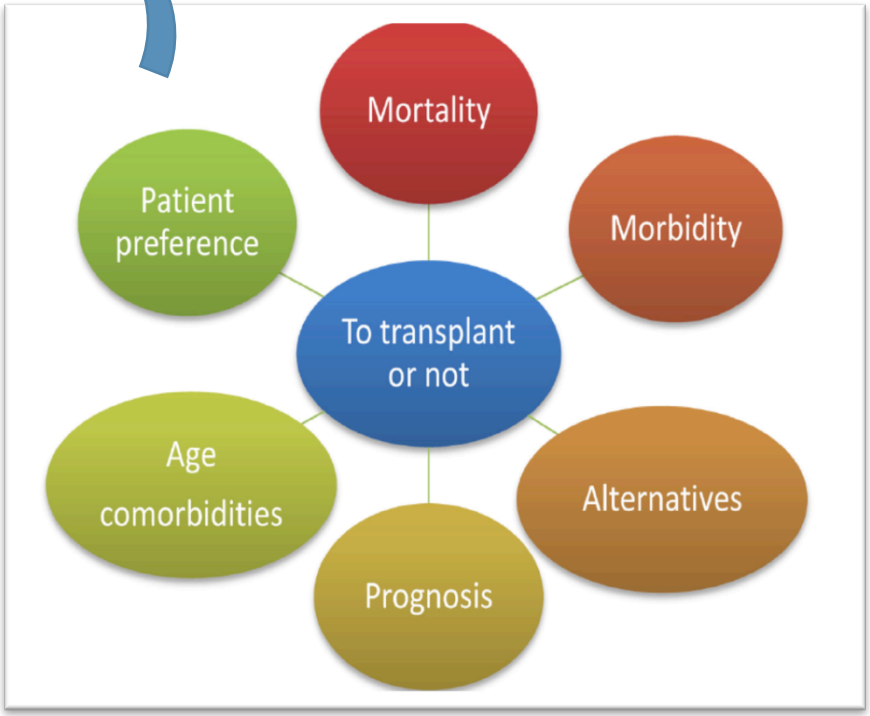


Figure 1. Decision tree for HR-CLL. NA, novel agents.

Blood. 2014;124(26):3841-3849

Factor to consider in making decisions about alloHSCT

‘SICK ENOUGH
TO NEED IT,
BUT WELL ENOUGH
TO TOLERATE IT’



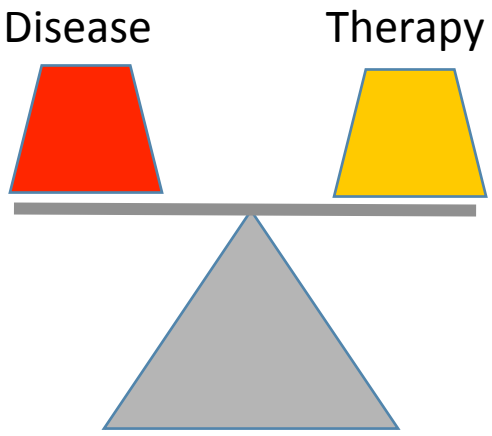
Clinical Lymphoma, Myeloma & Leukemia June 2015

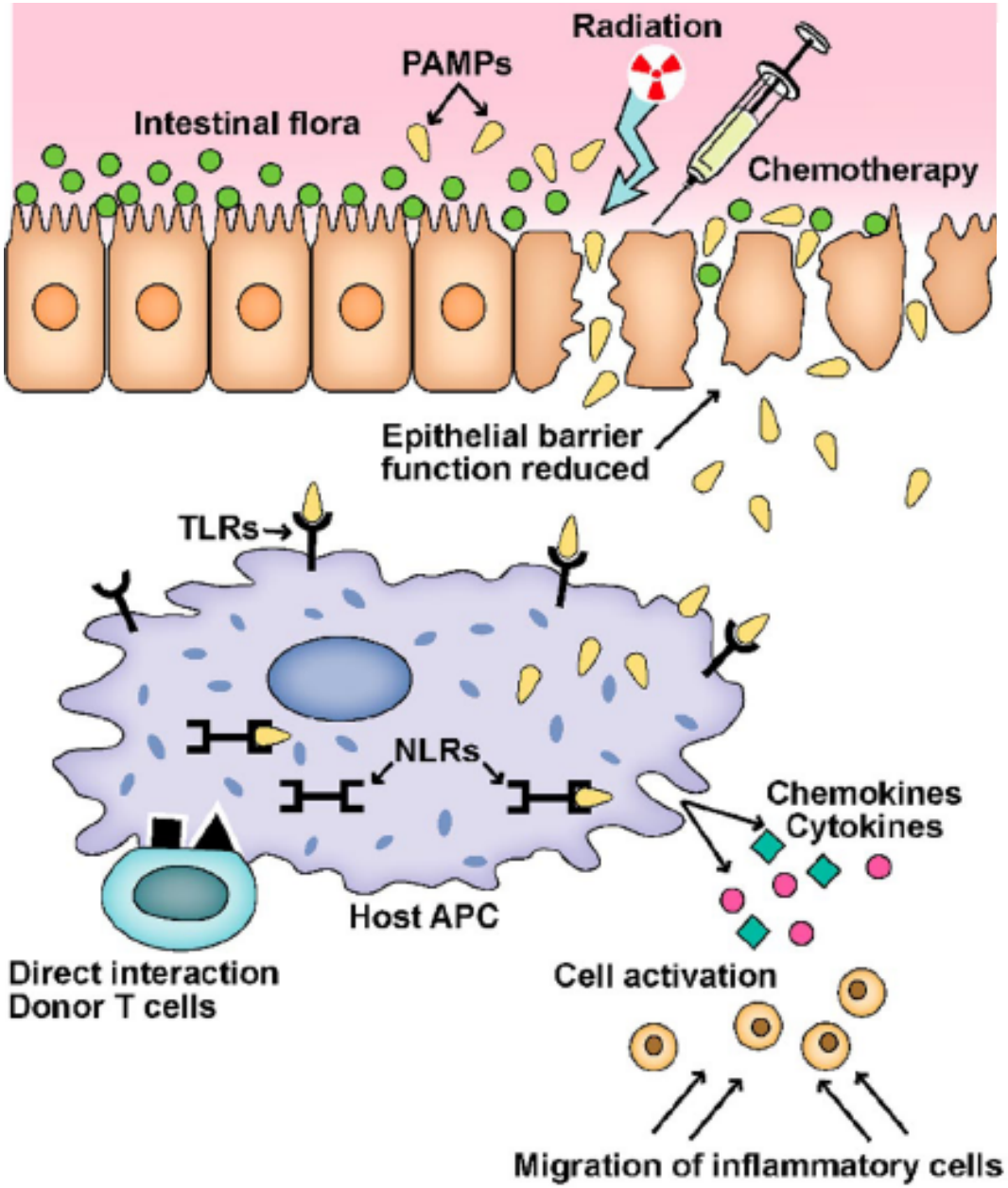
Challenges associated with AlloHSCT for patients with CLL

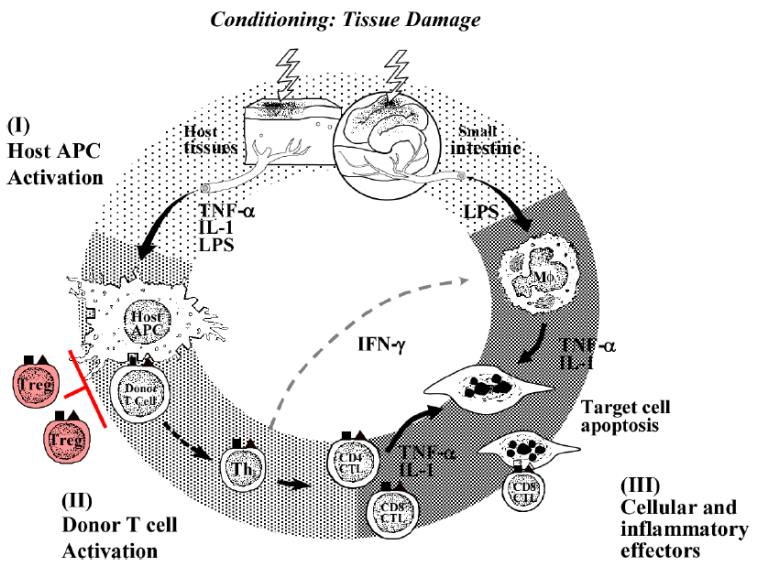
- **Effective debulking of CLL prior to alloHSCT**
- **Majority of pts aged over 70 yrs**
  - Concomitant comorbidities
  - Poor related donor availability
- **Immunosuppression and GVHD**
  - Morbidity
  - Mortality
  - QoL

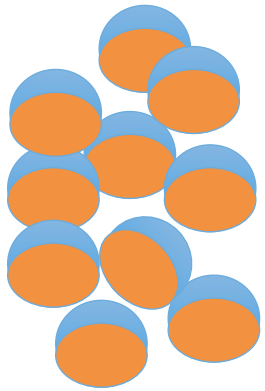
Risk factors for HSCT failure

- **Host related**
  - Age
  - Comorbidities
- **Disease related**
  - Genetics
  - Status at transplant
  - MRD (pre- and post-Tx)
- **Procedure related**
  - Conditioning regimen
  - Quality of the graft
  - GvHD prophylaxis









Donor
T
Lymphocytes

Reducing NRM in AlloHSCT

- **RIC**

- **T-Cell Depletion**
  - *In vivo* (ATG)
  - *Ex vivo* (graft processing)

Toxicity of RIC alloSCT for CLL

Study	GCLLSG	Seattle	Boston	FCGCLL	Houston	Heidelb.
n	90	82	76	40	86	66
Mucositis 3-4	6%	12%	na	<5%	na	na
Infection 3-4	55%	60%	na	48%	na	na
Early death (< d +100)	<3%	<10%	<3%	0%	3%	3%
NRM	**23% (6y)**	**23% (5y)**	**16% (5y)**	**27% (3y)**	**17% (1y)**	**24% (3y)**
Ext. cGVHD	55%	49-53%	48%	42%	56%	53%

Dreger Blood 2013; Sorror JCO 2008; Brown Leukemia 2013; Michallet Exp Hematol 2013; Khouri Cancer 2011; Hahn iwCLL 2013

Reduced-intensity conditioning lowers treatment-related mortality of allogeneic stem cell transplantation for chronic lymphocytic leukemia: a population-matched analysis

Dreger Leukemia 2005

Table 3 Prognostic factors for outcome (Cox's multivariate; $n=155$)

End point variable	*Relapse*		*TRM*		*Overall survival*	
	HR (95% CI)	*P-value*	*HR*	*P-value*	*HR*	*P-value*
RIC	2.65 (0.98–7.12)	0.054	**0.4 (0.18–0.9)**	**0.03**	0.65 (0.33–1.28)	0.21
Age (years)[a]	1.38 (0.94–2.01)	0.1	**1.63 (1.18–1.75)**	**0.003**	**1.44 (1.09–1.9)**	**0.01**
Donor not identical sibling	**2.92 (1.33–6.45)**	**0.008**	1.42 (0.66–3.06)	0.38	1.55 (0.81–2.97)	0.18
Status at SCT <PR	**3.14 (1.45–6.82)**	**0.004**	1.38 (0.7–2.71)	0.36	**1.9 (1.06–3.42)**	**0.03**
Year of SCT[b]	**1.71 (1.06–2.79)**	**0.03**		NR[c]		NR
Sex female	0.71 (0.26–1.96)	0.51	0.83 (0.33–2.06)	0.67	0.87 (0.41–1.83)	0.7

Additional variables not remaining in the models: Time from diagnosis to SCT, stem cell source.
[a]HR by percentile as linear effect (⩽45; 45⩽50; 50⩽55; >55). Reference is age ⩽45 years.
[b]HR by calendar year (1998; 1999; 2000; 2001). Reference is year=1998.
[c]NR=not remaining in the final model.
Bold indicates variables with $P<0.05$.

RIC :

- ⇩ NRM (HR 0.4; p 0.03)
- ⇧ Relapse (HR 2.7; p 0.054);
- ⇨ EFS and OS

BFR (bendamustine, fludarabine, and rituximab) allogeneic conditioning for chronic lymphocytic leukemia/lymphoma: reduced myelosuppression and GVHD

Issa F. Khouri,[1] Wei Wei,[2] Martin Korbling,[1] Francesco Turturro,[3] Sairah Ahmed,[1] Amin Alousi,[1] Paolo Anderlini,[1] Stefan Ciurea,[1] Elias Jabbour,[4] Betul Oran,[1] Uday R. Popat,[1] Gabriela Rondon,[1] Roland L. Bassett Jr,[2] and Alison Gulbis[5]

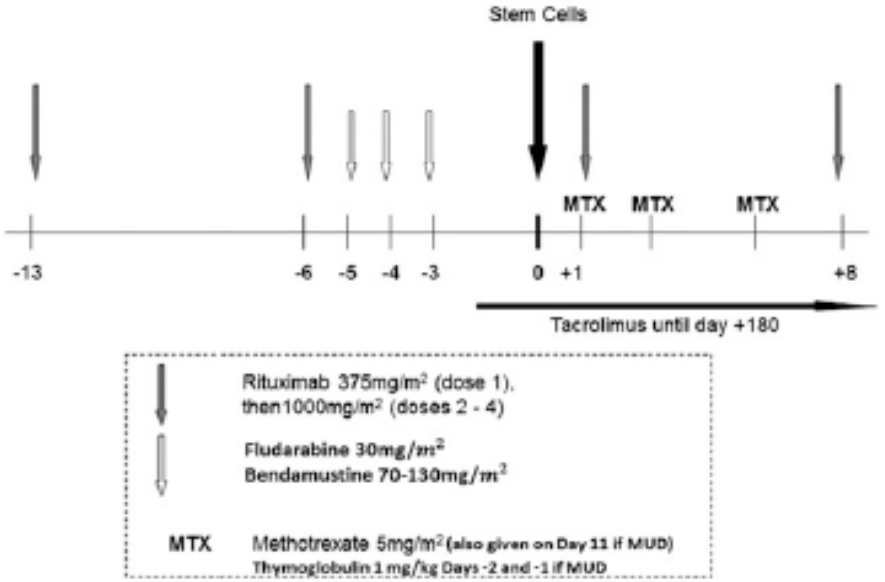
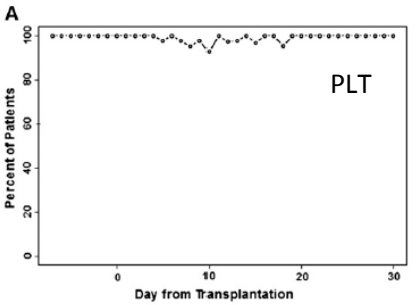
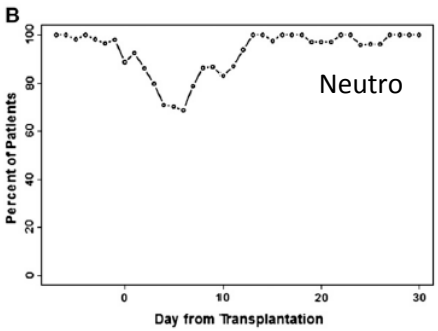


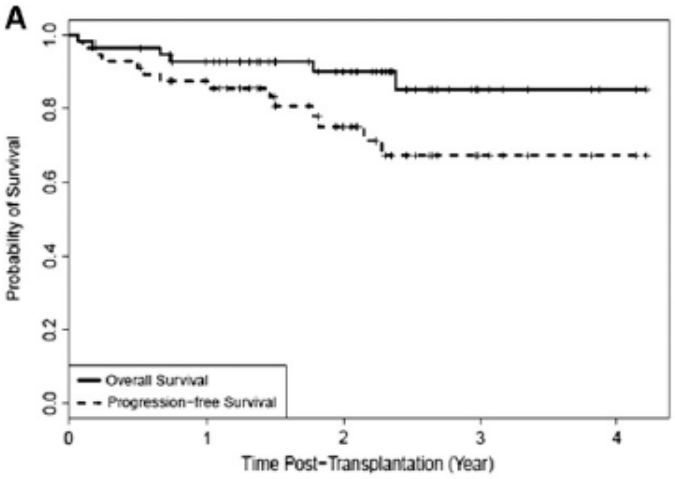
Figure 1. Treatment schema of bendamustine, fludarabine, and rituximab (rituximab was omitted in patients with T-cell lymphoma).

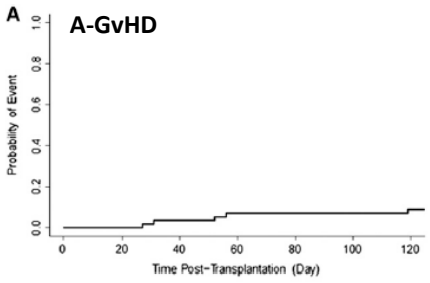
Pts	56
Age (y) Median (range)	59 (30-70)
NHL / CLL	41/15
CR/PR/REL	25/25/6
SIB/MUD	30/26
PB/BM	52/4
Median interval Dx-Tx, y (range)	4,3 (0,4-19,2)

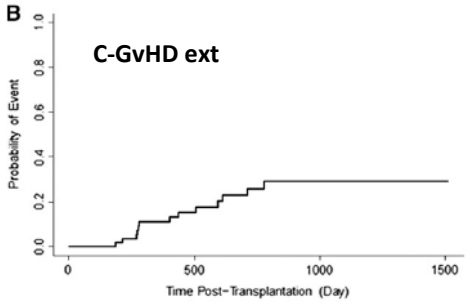
BFR protocol. Results

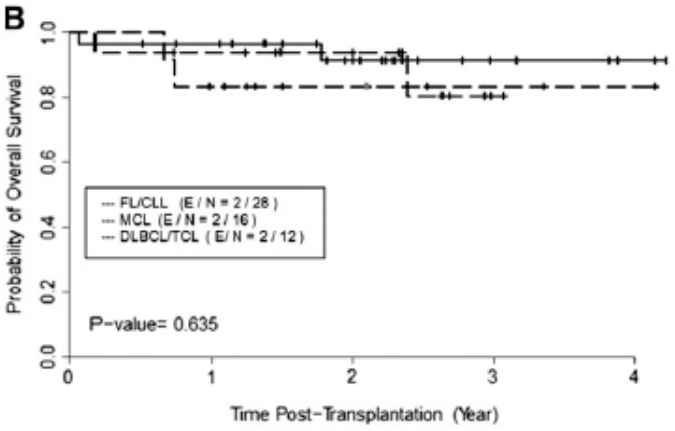


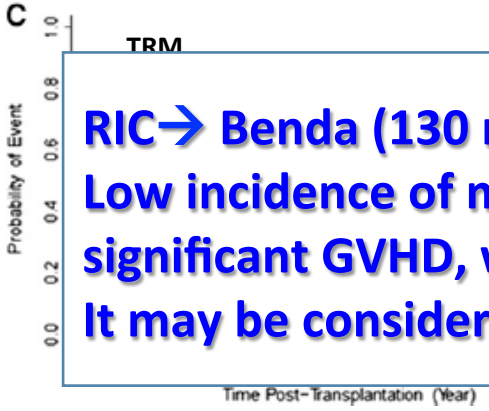


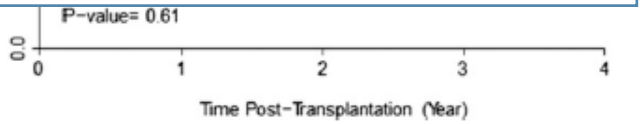












RIC→ Benda (130 mg/m^2/day x 3 days) + FR is safe.
Low incidence of myelosuppression and a low incidence of clinically significant GVHD, with no major adverse events.
It may be considered as a platform for outpatient alloHSCT.

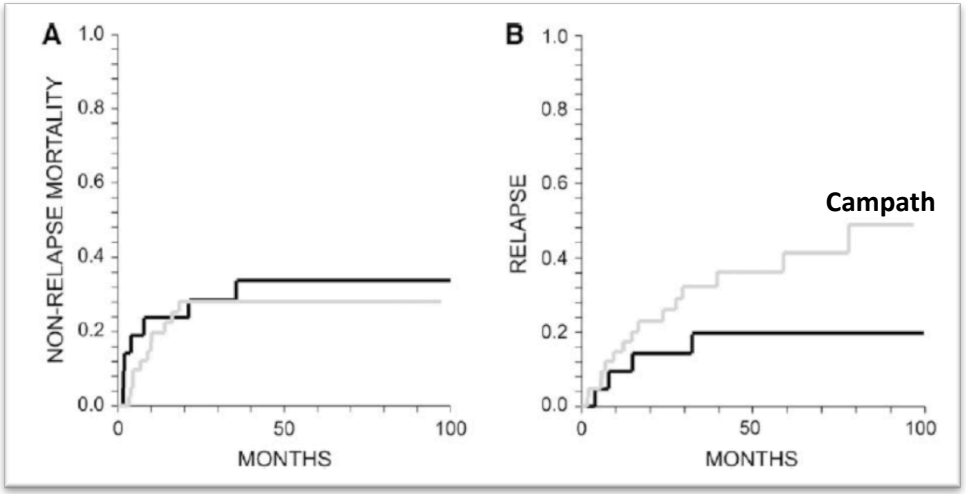
BLOOD, 2 OCTOBER 2014 • VOLUME 124, NUMBER 14

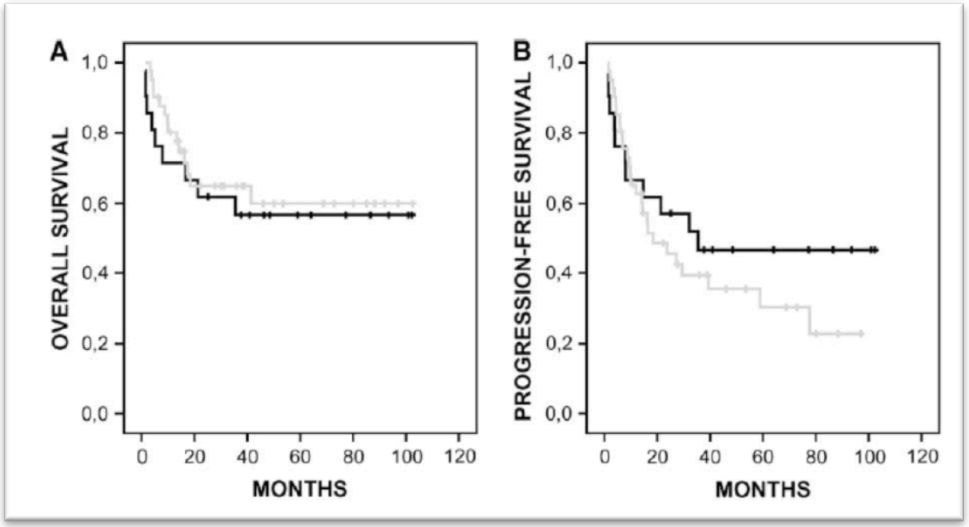
RIC and TCD?

The Effect of In Vivo T Cell Depletion with Alemtuzumab on Reduced-Intensity Allogeneic Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia

J. Delgado et al.

Conditioning: Flu+ Mel 140
GVHD prophylaxis:
alemtuzumab and CSA (cohort 1);
CSA+MTX/MMF (cohort 2).





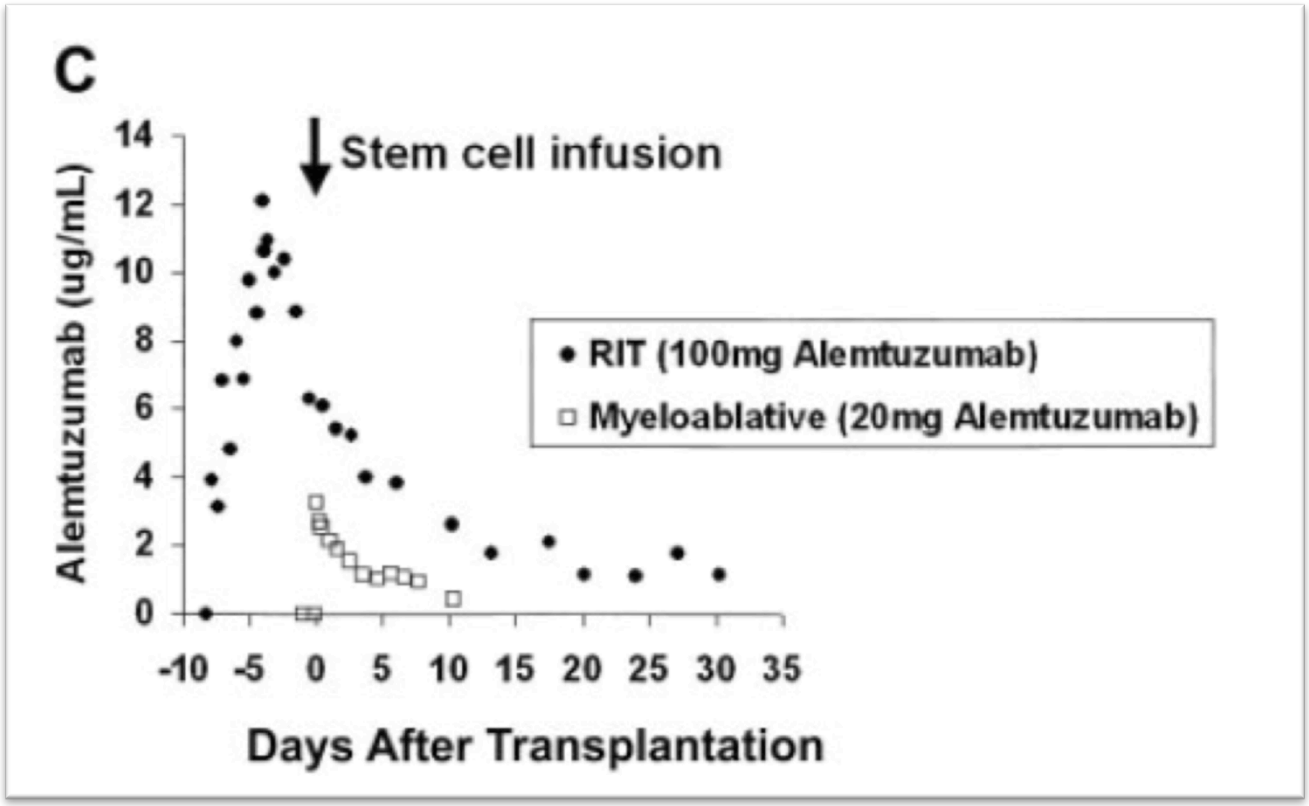
- Both conditioning regimens provided similar NRM, PFS, and OS.
- The alemtuzumab-based regimen was effective in reducing the Chronic GVHD rate but was associated with a trend toward an increased relapsed rate.
- Infection rates were similarly high for both cohorts and contributed to a significant proportion of morbidity and mortality.

Biol Blood Marrow Transplant 14:1288-1297, 2008

Pharmacokinetics of alemtuzumab used for in vivo and in vitro T-cell depletion in allogeneic transplantations: relevance for early adoptive immunotherapy and infectious complications

Emma C. Morris, Peppy Rebello, Kirsty J. Thomson, Karl S. Peggs, Charalampia Kyriakou, Anthony H. Goldstone, Stephen Mackinnon, and Geoff Hale

Median serum alemtuzumab levels.



Blood. 2003;102:404-406

…..Learning from T cell depleted BMT. The past

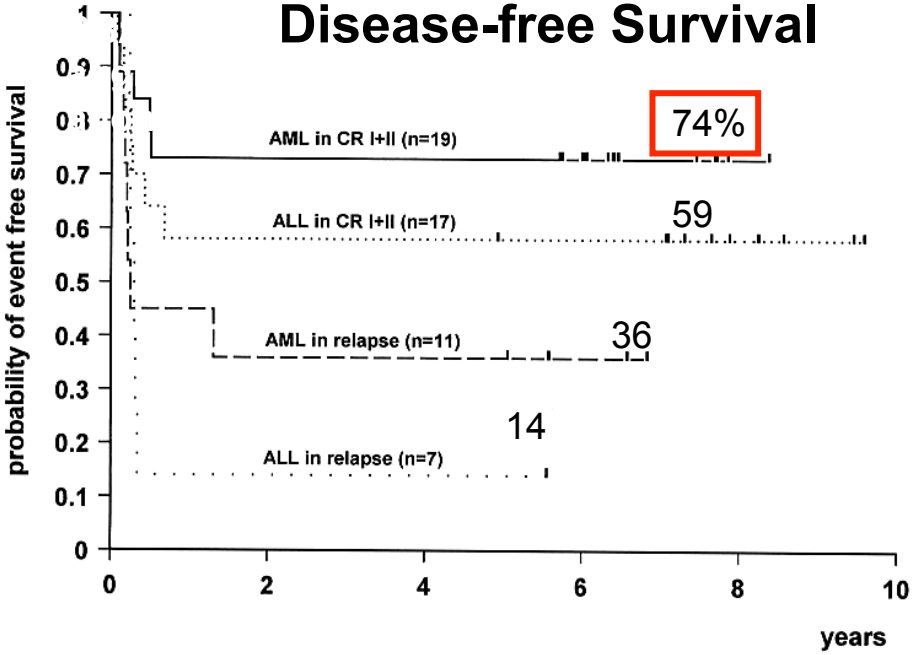
Adverse Events	Work hypothesis	CounterMeasures
↑ Rejection	↑ Myeloablation Immunosuppression	HFTBI 14,4 Gy Thiotepa ATG
↑ Leukemia Relapse	↑ Myeloablation No post-transplant immunosuppression	HFTBI 14,4 Gy Thiotepa

T-Cell-Depleted HLA-Matched Bone Marrow Transplantation in Acute Leukemia Adult Patients

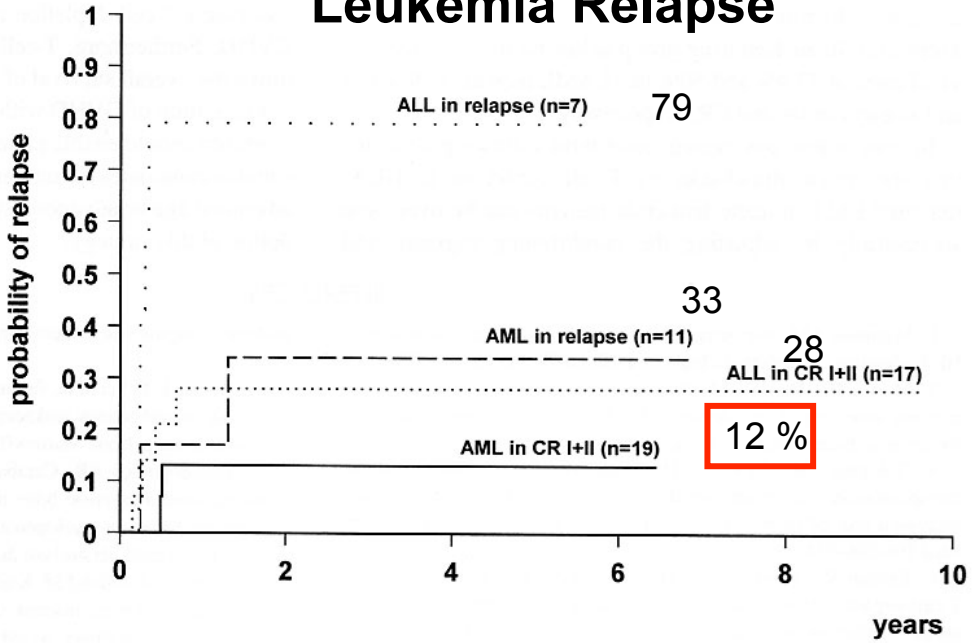
Conditioning: 14.4 HFTBI, CY, ATG, TT
Inoculum: SBA^-/E_N^- bone marrow cells
No Post-transplant immunosuppression

Graft rejection 0%; GvHD 0%

Disease-free Survival



Leukemia Relapse

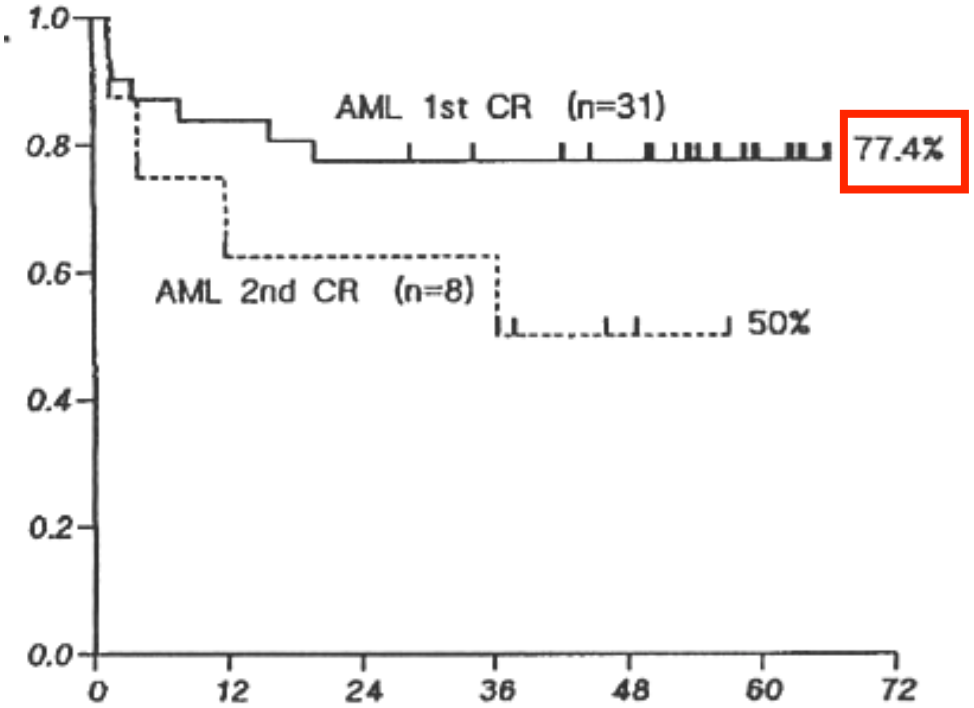


Aversa F. et al. JCO 1999;17:1545

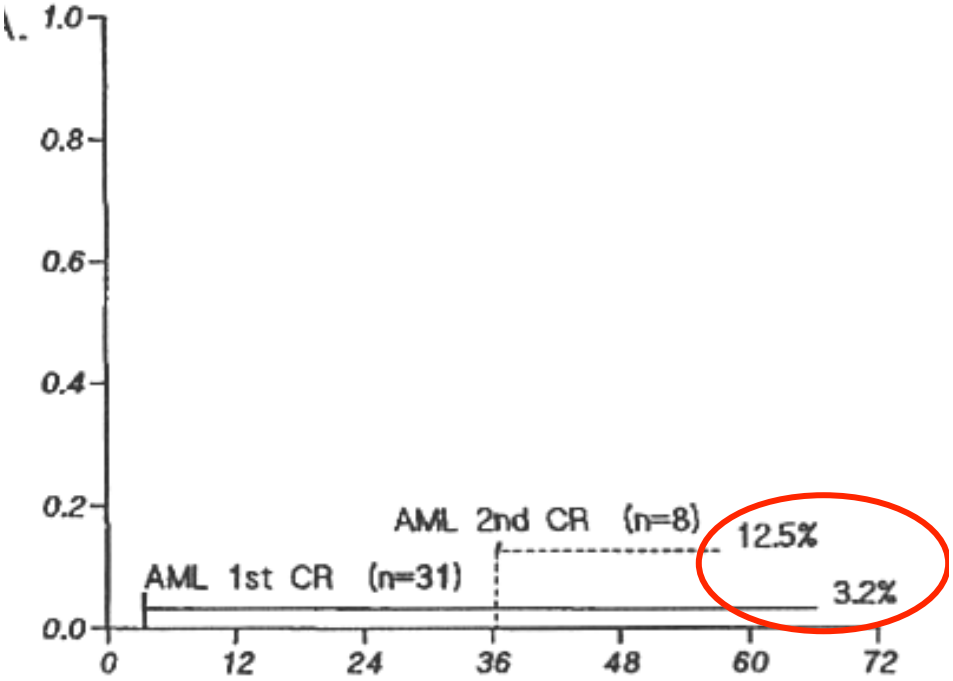
Memorial Sloan Kettering
Cancer Centre, NY

T-cell-depleted HLA-matched Bone Marrow Transplantation in acute myeloid leukemia adult patients

Disease-free Survival

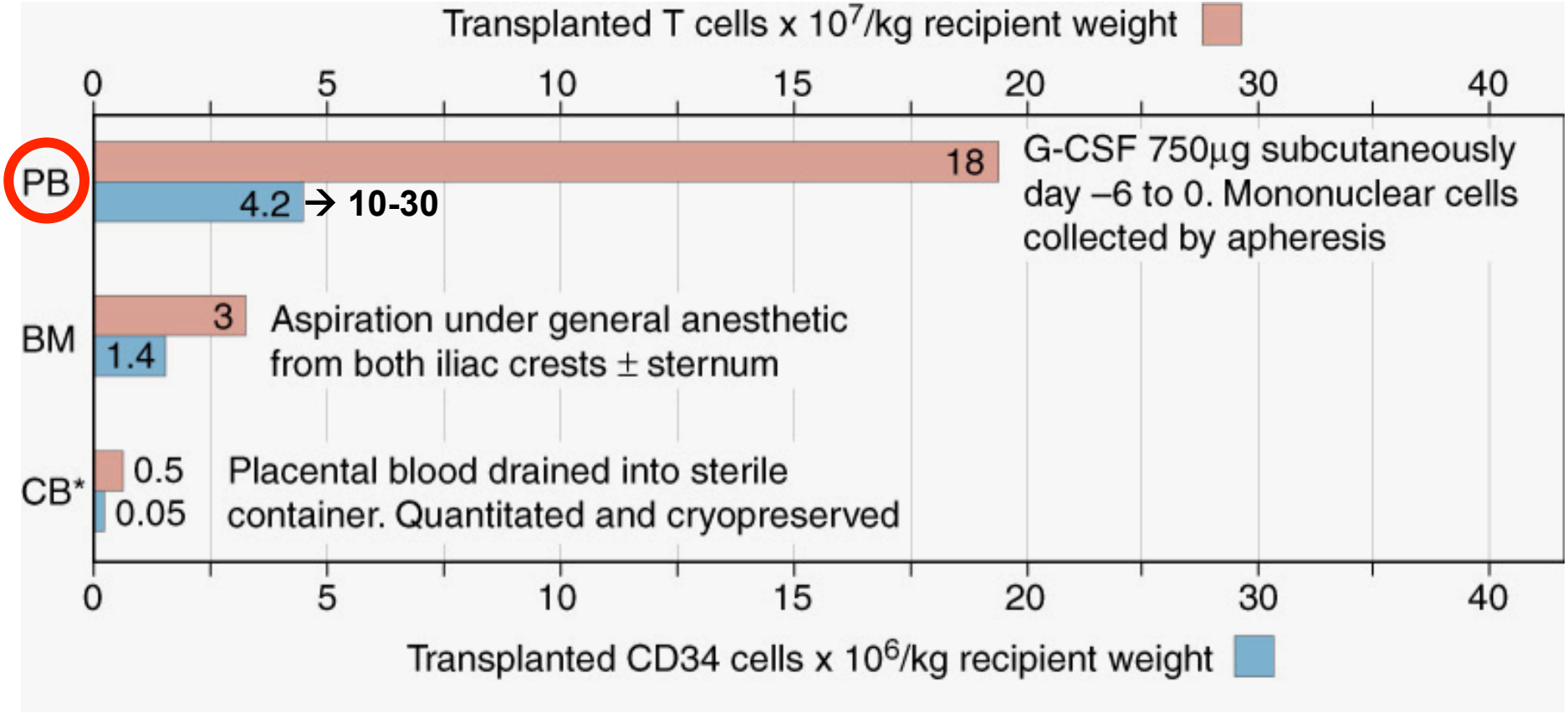


Relapse



Papadopoulos et al. Blood 1998;91:1083

From BM cells to PB cells



Y. Reisner and Coll, Ann. N.Y. Acad. Sci. 1044: 70–83 (2005).

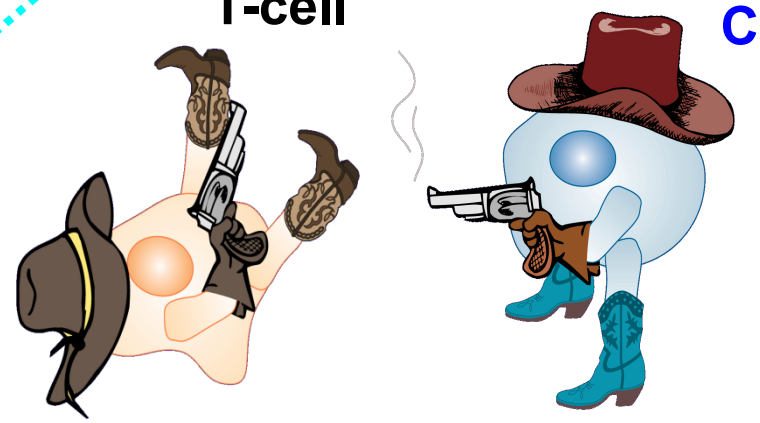
Immune Regulatory Activity of CD34⁺ Progenitor Cells

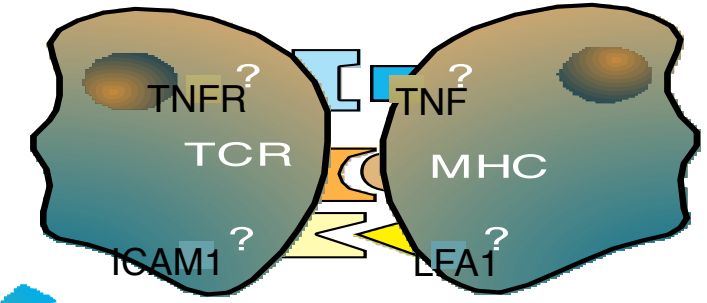
When added to bulk MLRs, they suppress CTLs against donor's stimulators but not against stimulators from a third party.

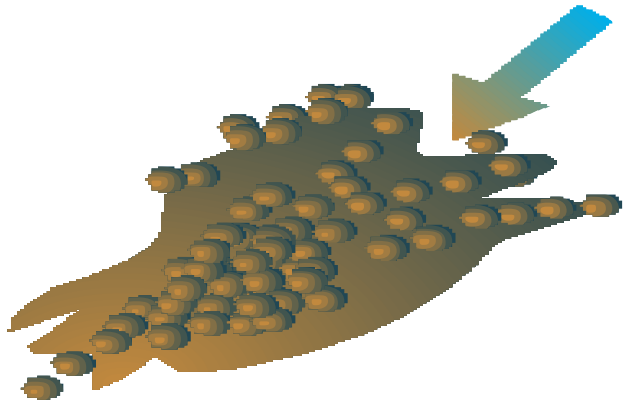
The «veto» effect

Recipient Effector T-cell

Donor Stem Cell







apoptosis

Fas-FasL apoptosis is associated with deletion of effectors by veto CTL, Regulatory activity of CD34⁺ cells is likely mediated by TNF-α

Courtesy of Yair Reisner

Haplo HSCT: MAC, immunoselected CD34⁺ cells, no post-Tx immune suppression.
(first pilot study launched in March 1993)

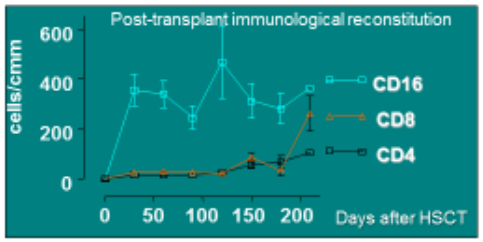
Myeloablative conditioning regimen

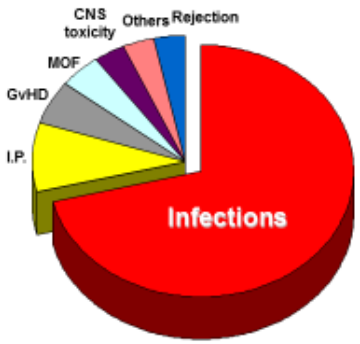
Megadose CD34⁺ (≥10 x 10⁶/kg)

Ex vivo T-cell depletion (CD3 ≤1 x 10⁴/kg)

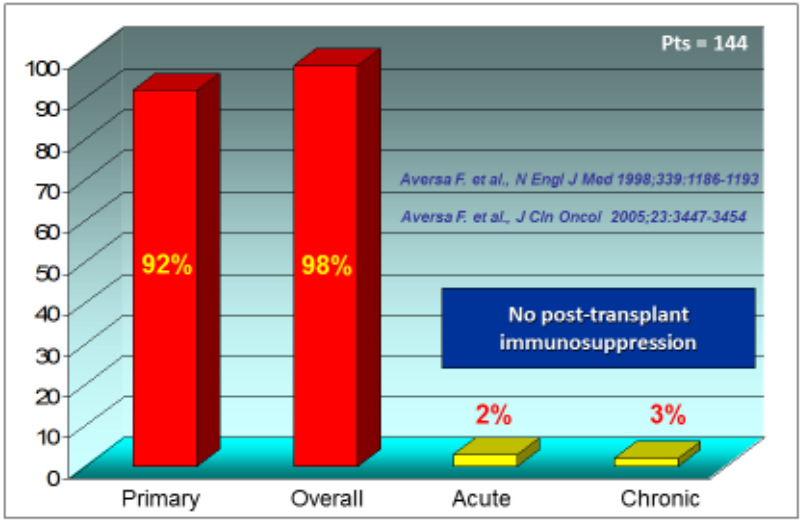
No post-Tx immune suppression

Aversa et al
Blood 1994; NEJM 1998, JCO, 2005





Engraftment GvHD



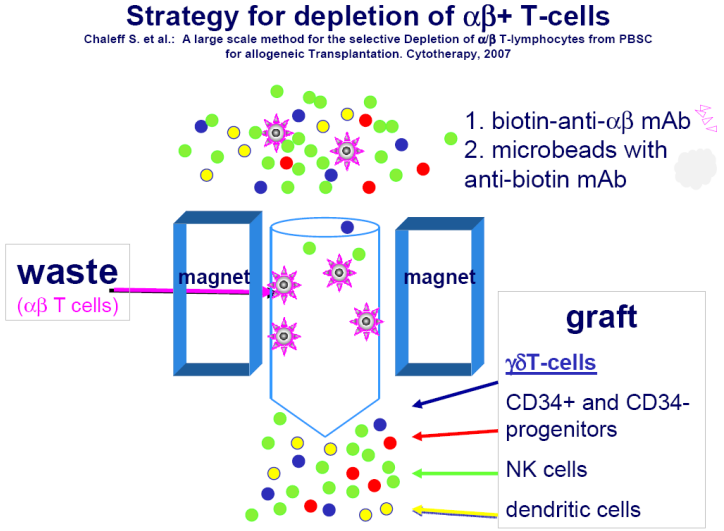
Revised T cell Depletion in HaploHSCT

T-cell depletion technique

1993 • SBA/E-rosetting
1995 • **CD34⁺ positive immunoselection**
2008 • CD34⁺/Treg/Tcon
2012 • **αβ TCR/CD19⁺ depletion**

Efficient TCRα/β+ cell depletion
→ Potentially reducing the risk of GvHD

Maintenance of stem cells and facilitating cells (TCRγδ T cells, NK cells)
→ might facilitate engraftment,
→ exerts a GvL effect and reduces the risk for infections.

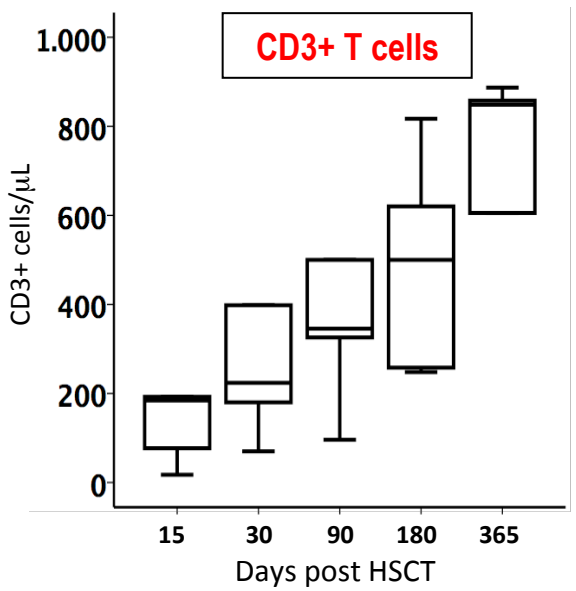


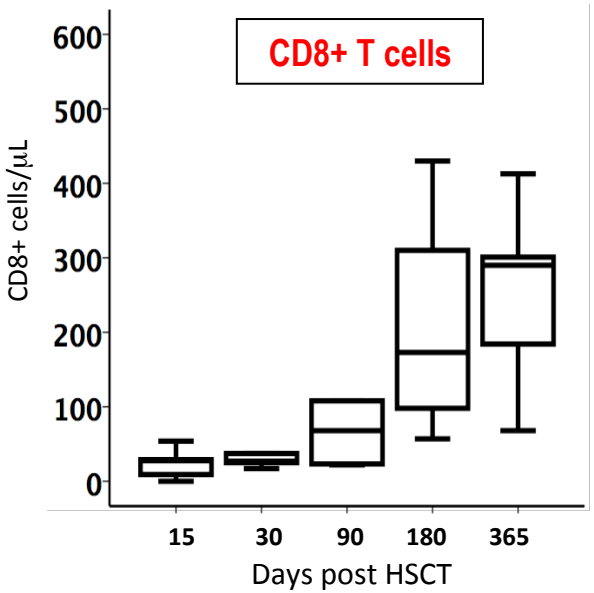
GRAFT COMPOSITION

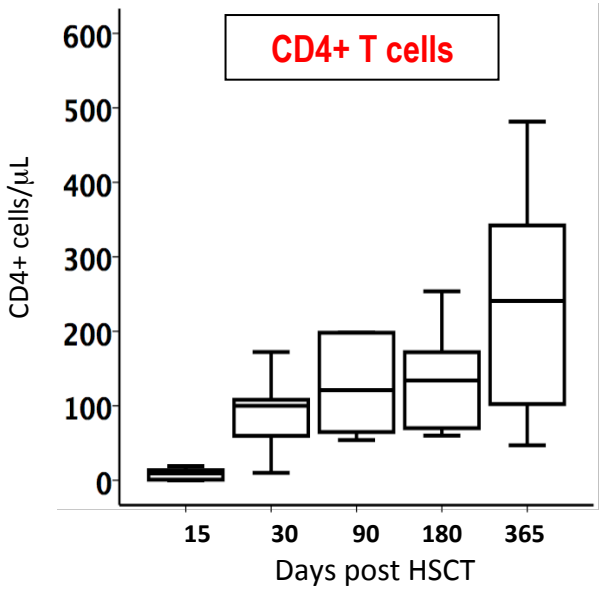
(median of the first 25 procedures)

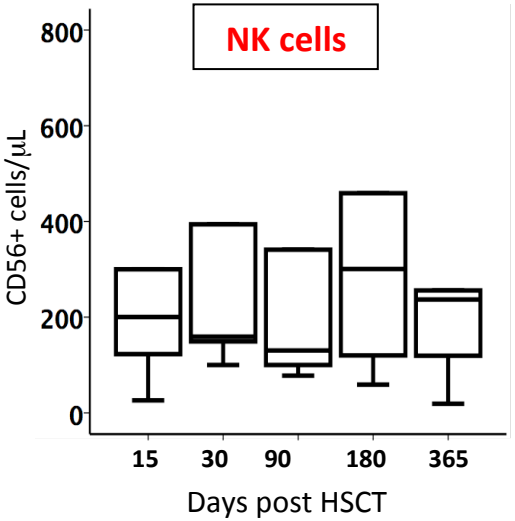
	CD34	CD3			CD20	NK
		Total CD3	γδ	αβ		
cells/kg Median	11×10^6	4.3×10^6	4×10^6	$4{,}8 \times 10^4$	4.8×10^4	30×10^6
(Range)	(5-19)	(1-35.7)	(1-34)	(0,4-37)	(1.8-32)	(8-91)

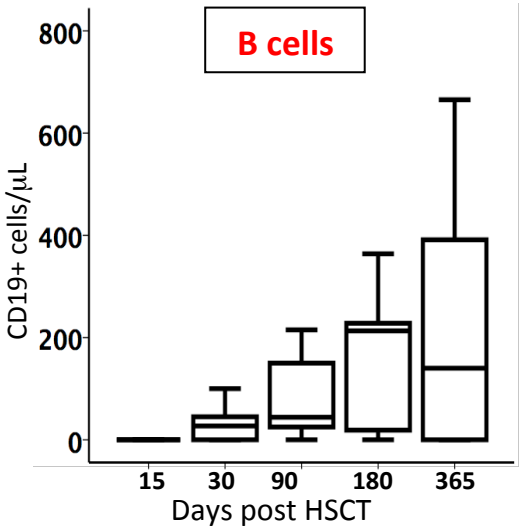
Posttransplant Immunological Reconstitution (n=32)

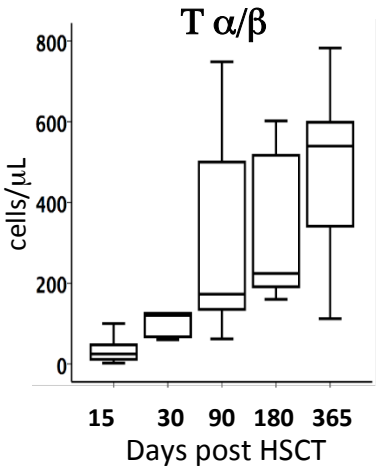


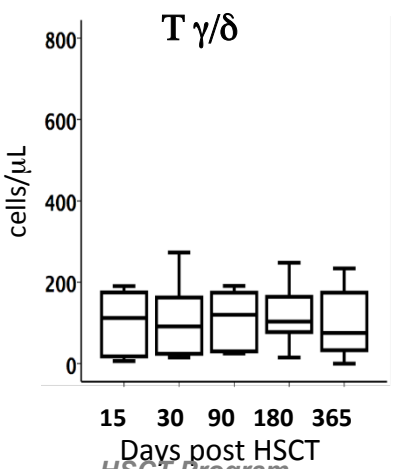






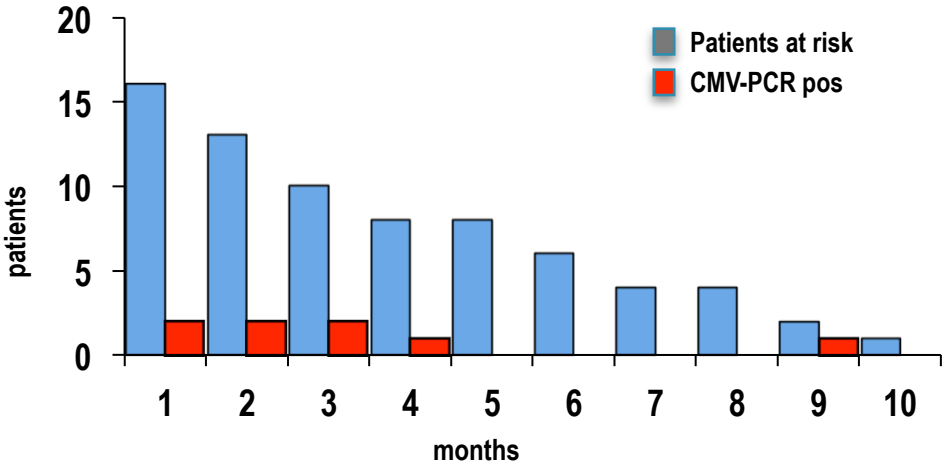






HSCT Program
University of Parma

CMV Reactivaction

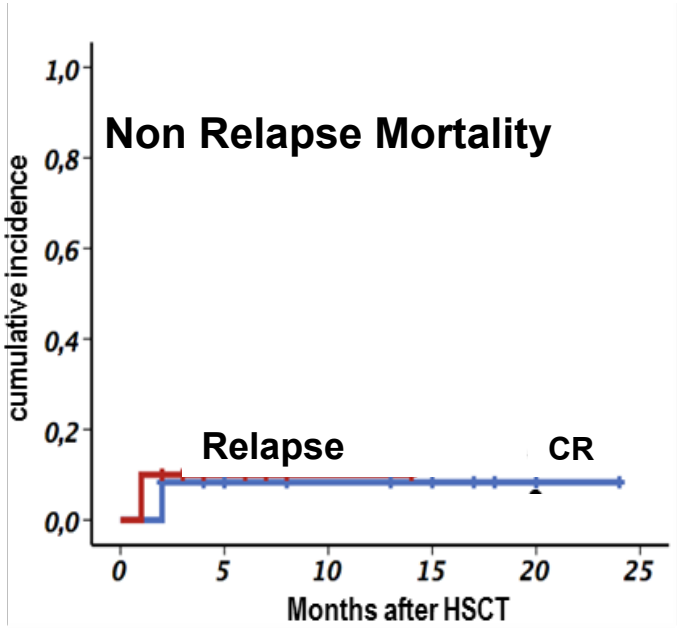


CMV infection:
Pre-emptive approach

IFD prevention:
L-AmB 3 mg/kg x 3/wk

FUNGAL INFECTION

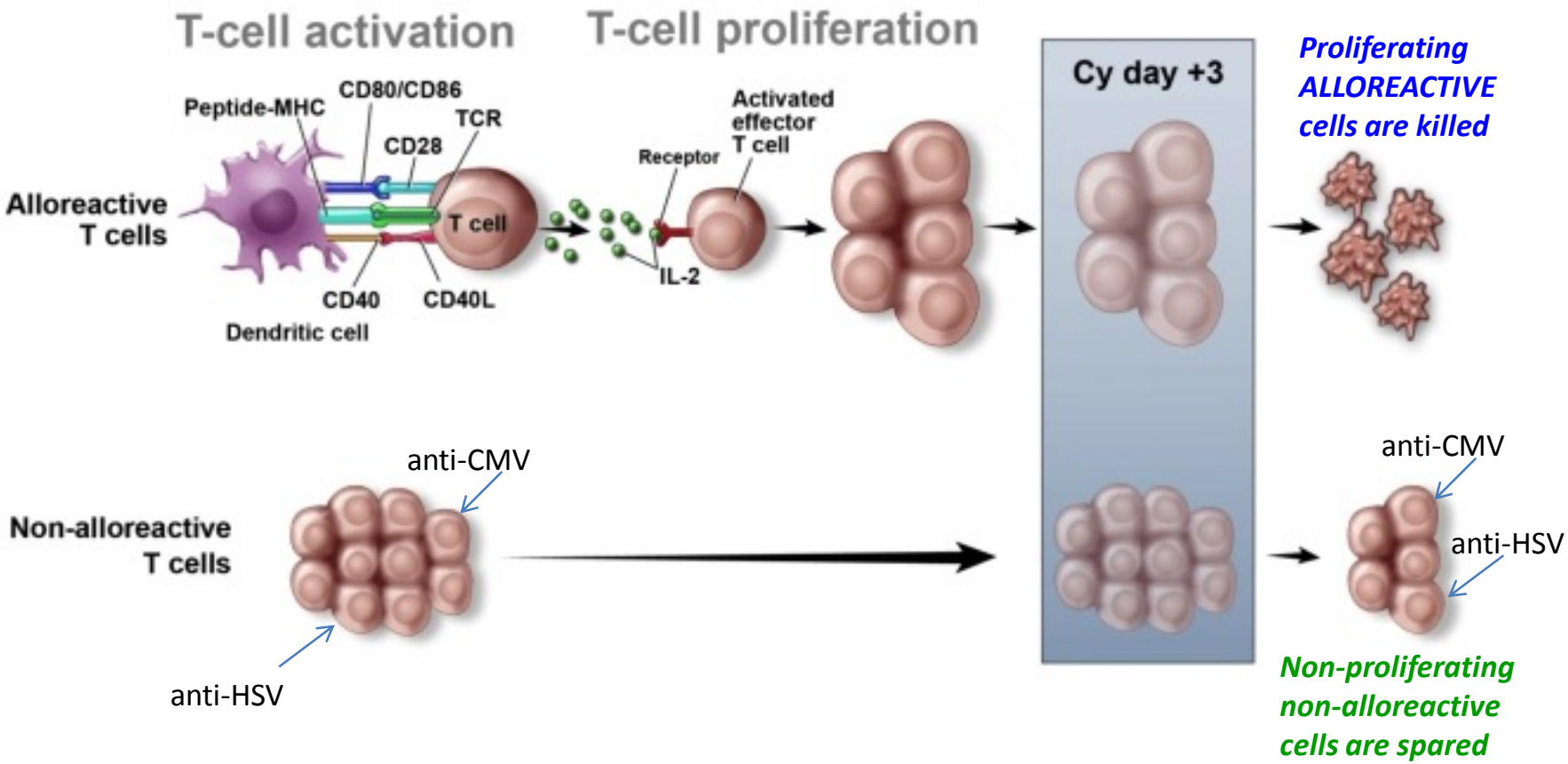
Tx phase	NEUTROPENIA (day-3 to +15)	GVHD YES	GVHD NO
anti-mold prophylaxis	L-AmB	Posaconazole	Itraconazole (if required)
IFI	#	#	#
proven	0	0	0
probable	0	0	0
possible	1	0	0



Second Generation
T cell depleted Haplo HSCT

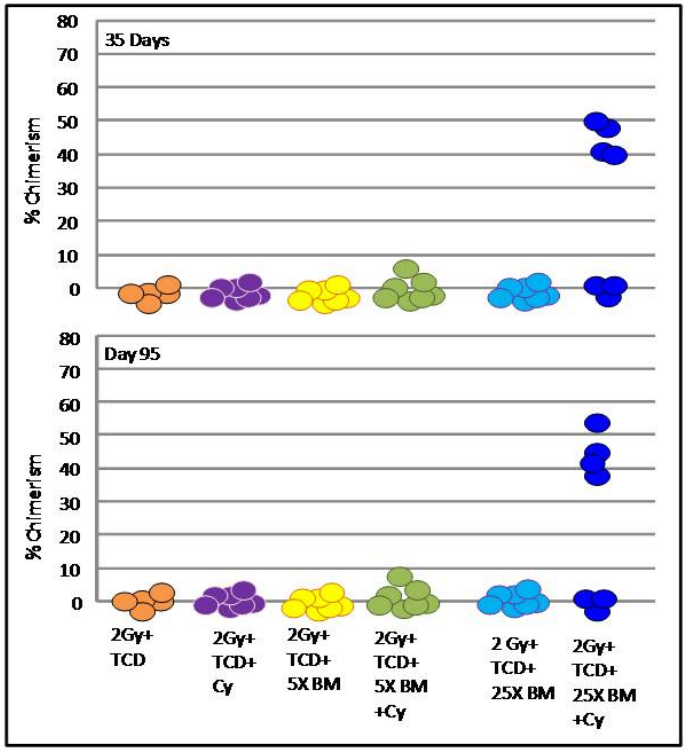
Current T cell-depleted HSCT strategies offer the unique opportunity to harness both natural and adaptive immunity to control infections in the absence of GvHD.

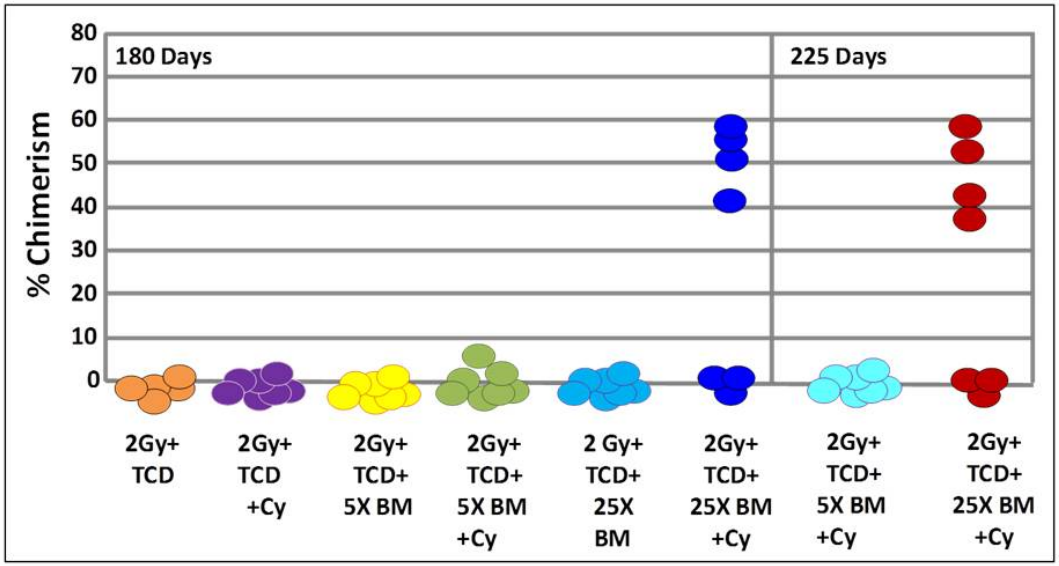
Selective allodepletion with high dose, post-transplantation cyclophosphamide (PT/Cy)



Combining the benefit of 'Megadose'
T depleted HTSC, RIC pre- and CY post transplant.

Mouse model





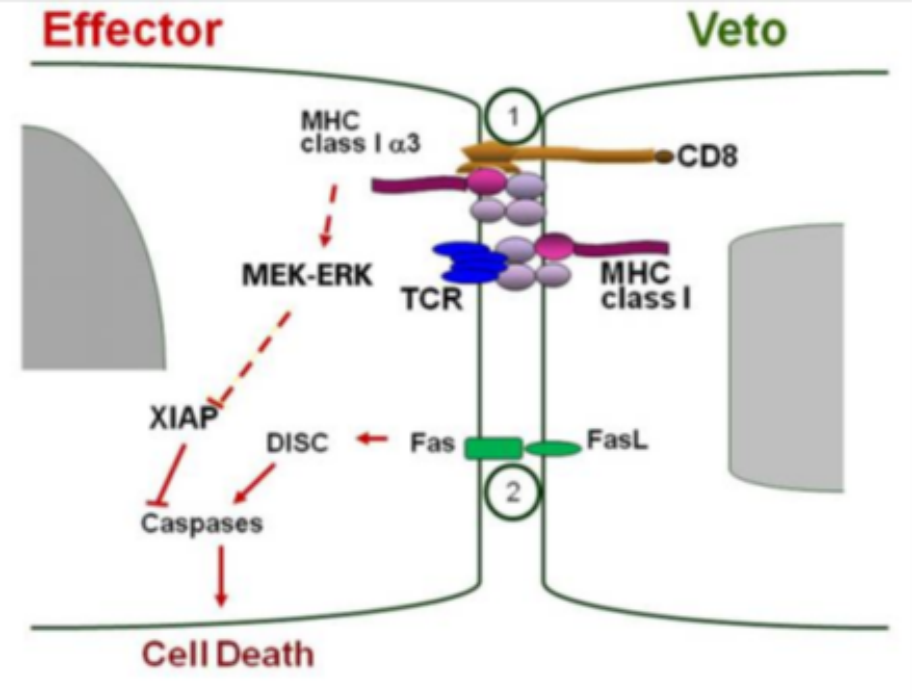
Reisner et al. Unpublished data 2016

TRANSPLANTATION

Murine anti–third-party central-memory CD8$^+$ T cells promote hematopoietic chimerism under mild conditioning: lymph-node sequestration and deletion of anti-donor T cells

*Eran Ophir,[1] *Noga Or-Geva,[1] Irina Gurevich,[1] Orna Tal,[1] Yaki Eidelstein,[1] Elias Shezen,[1] Raanan Margalit,[1] Assaf Lask,[1] Guy Shakhar,[1] David Hagin,[1] Esther Bachar-Lustig,[1] Shlomit Reich-Zeliger,[1] Andreas Beilhack,[2] Robert Negrin,[3] and Yair Reisner[1]

Blood 2013



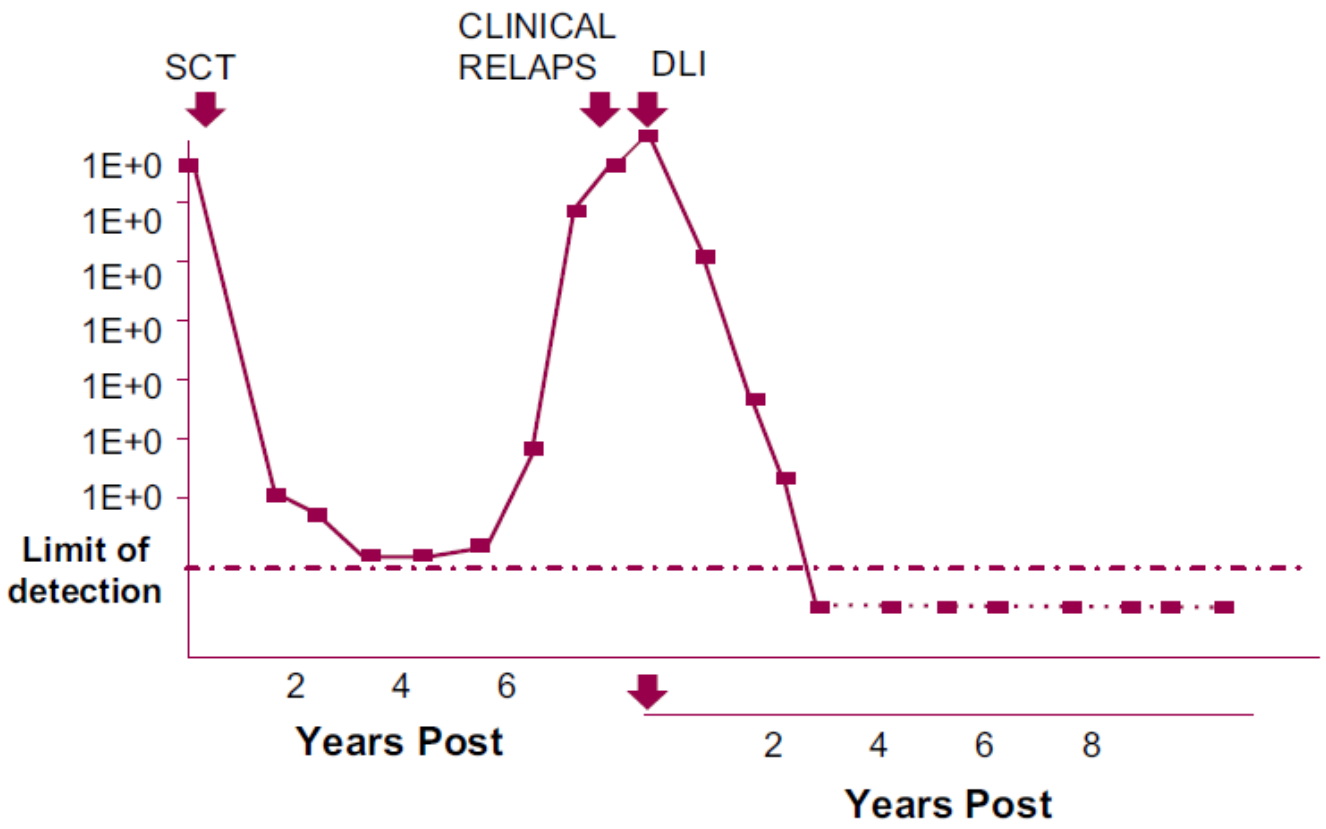
Key Points

- A new approach to achieving immune tolerance and mixed chimerism with relevance for hematopoietic stem cell and organ transplantation.
- Anti–third-party central memory T cells support engraftment with nonablative conditioning by sequestering and deleting anti-donor T cells.

Conclusioni (1)

- Benefici da nuovi farmaci pre-trapianto??
  - forse SI
- RIC/NMA + *ex vivo* TCD
  - minore GvHD e TRM, migliore QoL
- AlloSCT come piattaforma per successiva terapia cellulare adottiva.
    - Attecchimento (anche con chimerismo misto) in assenza di GVHD (con minima o nessuna profilassi immunosoppressiva)
    - DLI +/- nuovi farmaci

Response to donor lymphocyte infusion (DLI) in CLL



J. G. Gribben

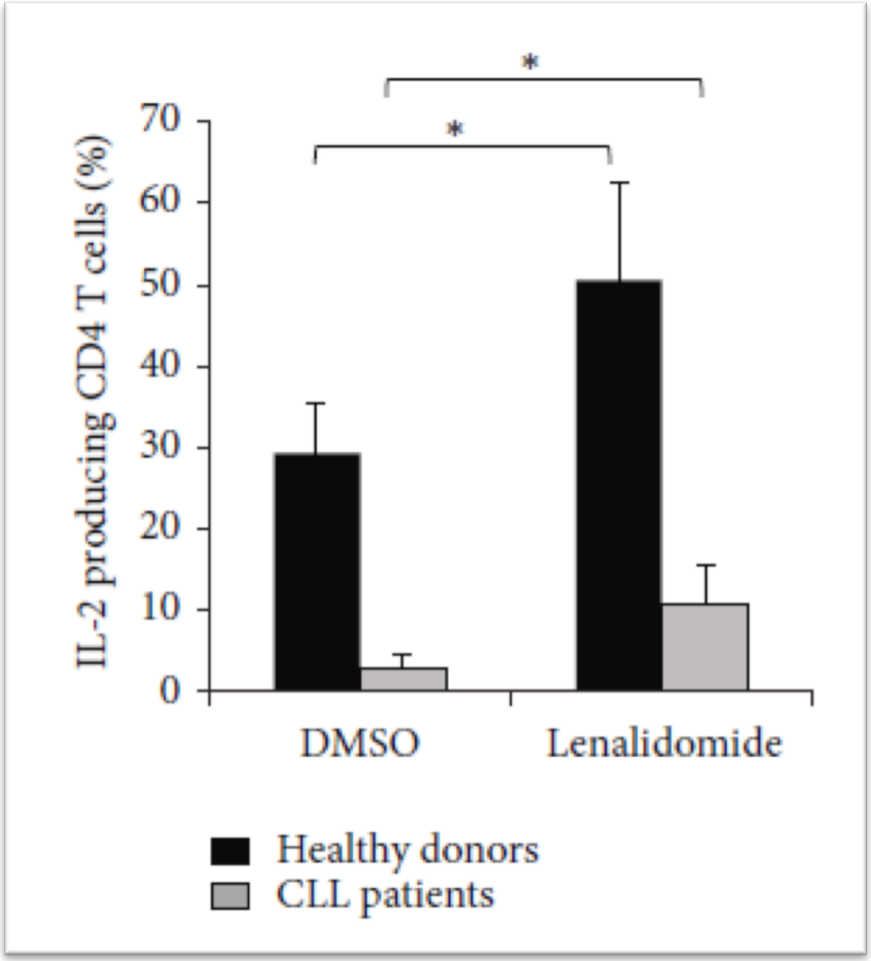
Best Practice & Research Clinical Haematology
Vol. 20, No. 3, pp. 513–527, 2007

Research Article

Lenalidomide Induces Immunomodulation in Chronic Lymphocytic Leukemia and Enhances Antitumor Immune Responses Mediated by NK and CD4 T Cells

Andrea Acebes-Huerta, et al

BioMed Research International
Volume 2014, Article ID 265840, 11 pages

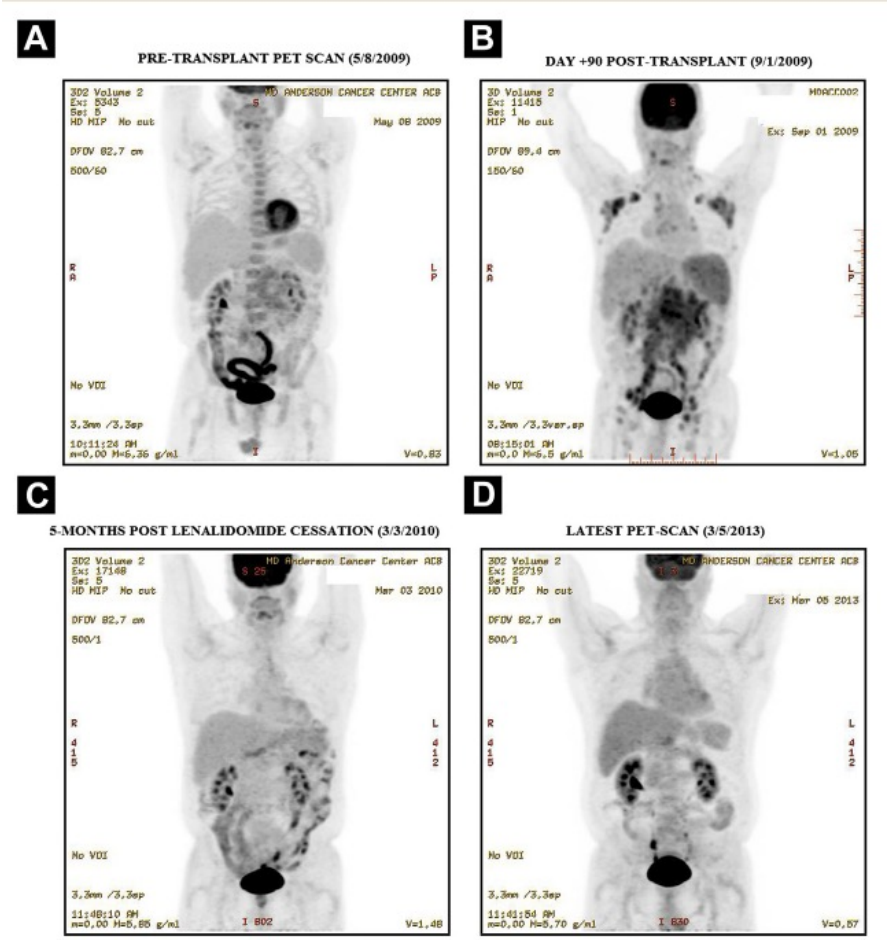


Lenalidomide did not exert a direct effect on the apoptosis of leukemia cells obtained from CLL patients, although it indirectly induced their apoptosis through the activation of non malignant immune cells.

Lenalidomide markedly increased the proliferation of NK and CD4 T cells.

The effect of lenalidomide on NK cells was secondary to the induction of IL-2 production by CD4 T cells.

Lenalidomide-Induced Graft-Vs.-Leukemia Effect in a Patient With Chronic Lymphocytic Leukemia Who Relapsed After Allogeneic Stem Cell Transplant



Day + 84: Relapse
Day +96 : IS stop, Lena 10 mg/d. → CR

He has been monitored every 3 to 6 months and continues to remain in complete remission for over 4 years without additional therapy.

The patient's PB chimerism assay has persistently shown 100% donor engraftment in the total and T-cell fraction.

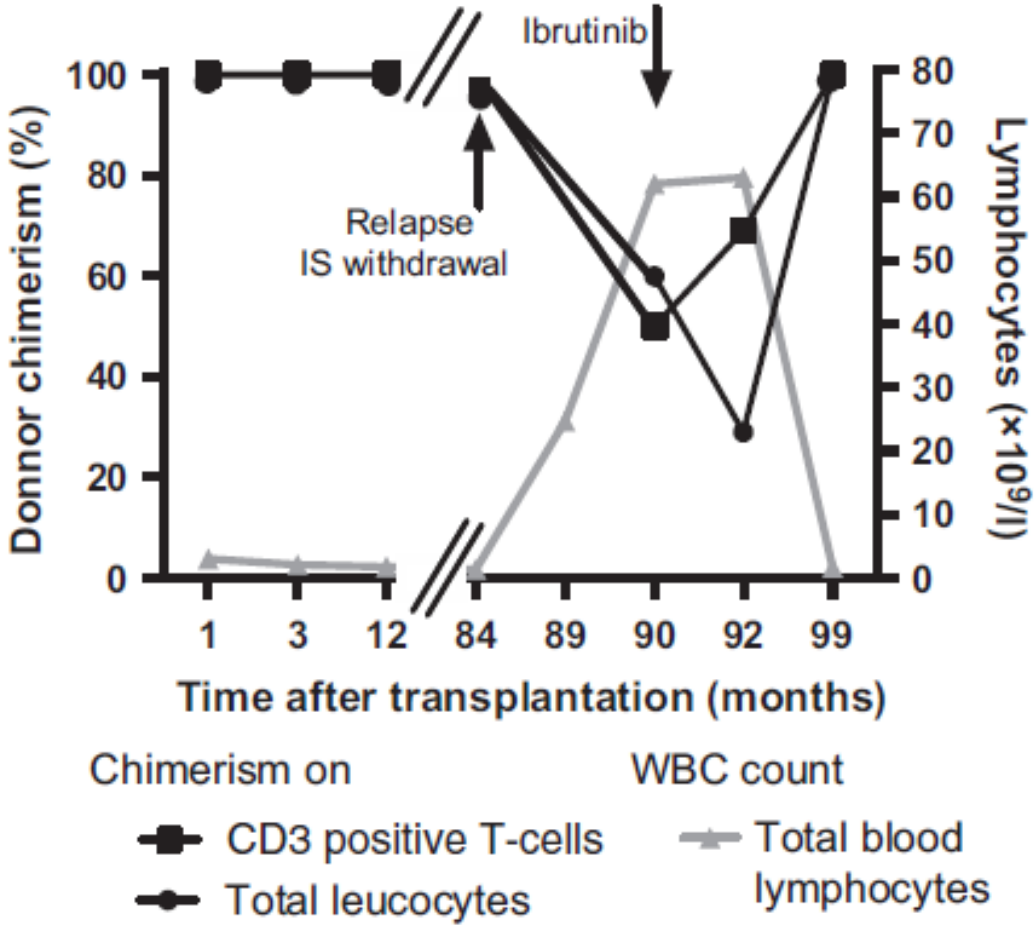
Rohtesh S. Mehta et al

Clinical Lymphoma, Myeloma & Leukemia June 2014

bjh correspondence 2016

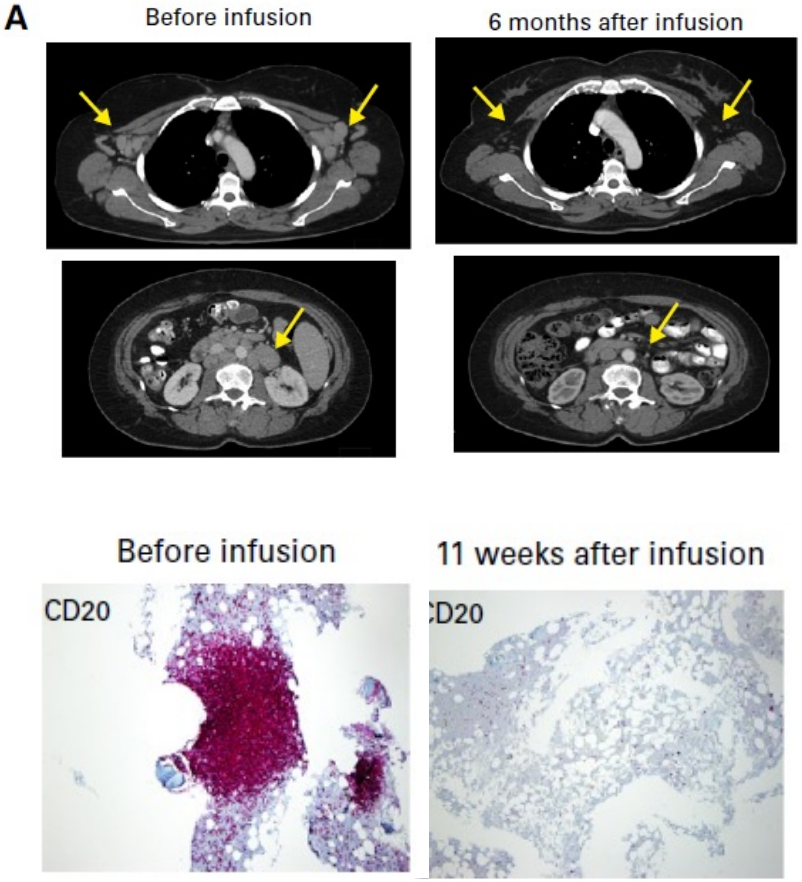
Recovery of full donor chimerism with ibrutinib therapy in relapsed CLL after allogeneic stem cell transplantation

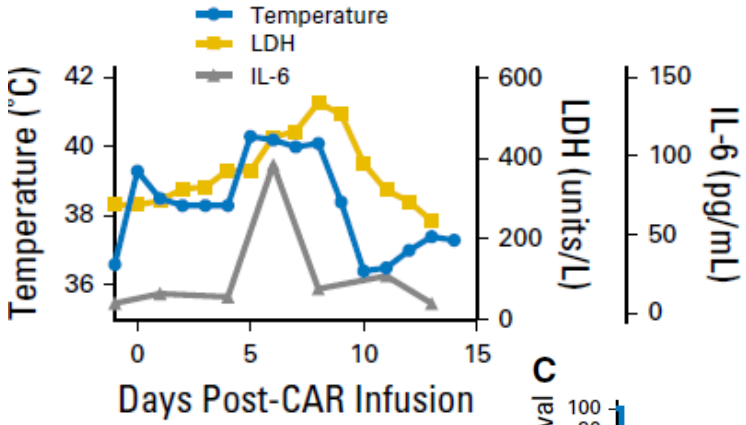
Anne Quinquenel[1]

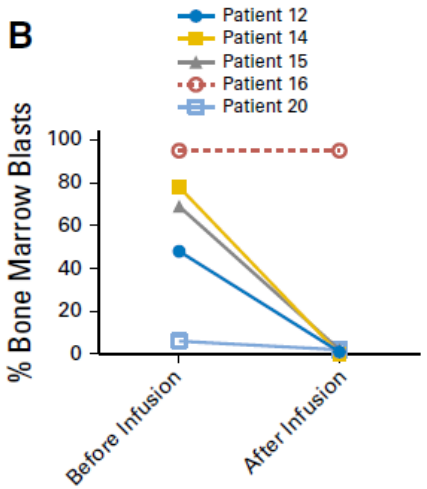


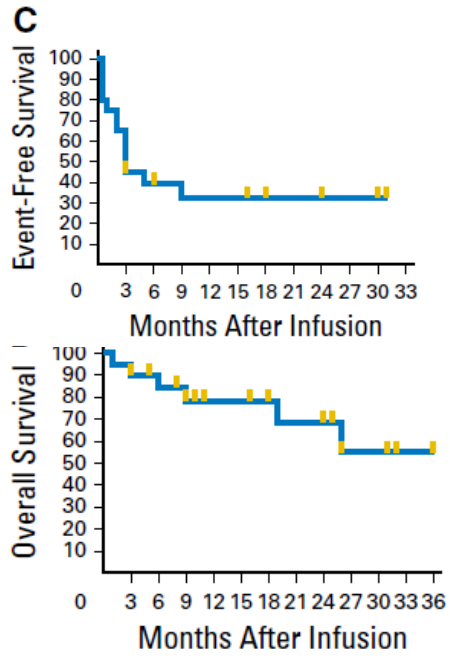
Allogeneic T Cells That Express an Anti-CD19 Chimeric Antigen Receptor Induce Remissions of B-Cell Malignancies That Progress After Allogeneic Hematopoietic Stem-Cell Transplantation Without Causing Graft-Versus-Host Disease

Jennifer N. Brudno,









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JOURNAL OF CLINICAL ONCOLOGY

Conclusions (2)

- The traditional HR-CLL criteria that define HSCT indication may no longer be valid in the upcoming new treatment landscape.
- Meanwhile, the HSCT option should not be discarded but *should be included in the treatment decision process*, considering what is known and what is still uncertain regarding different treatment possibilities.

- Aspects to be considered:
  - access to new agents,
  - prior treatment,
  - disease risk (R/R situation, genetics),
  - HSCT risk (eg, donor match, frailty, and comorbidity),
  - HSCT procedure (RIC, TCD, tolerance induction)
  - the patient's desires and expectations.