High-Risk AML in older patients: Does Conditioning Intensity Matter? The answer is: YES!!!

Antonio Pierini, MD, PhD

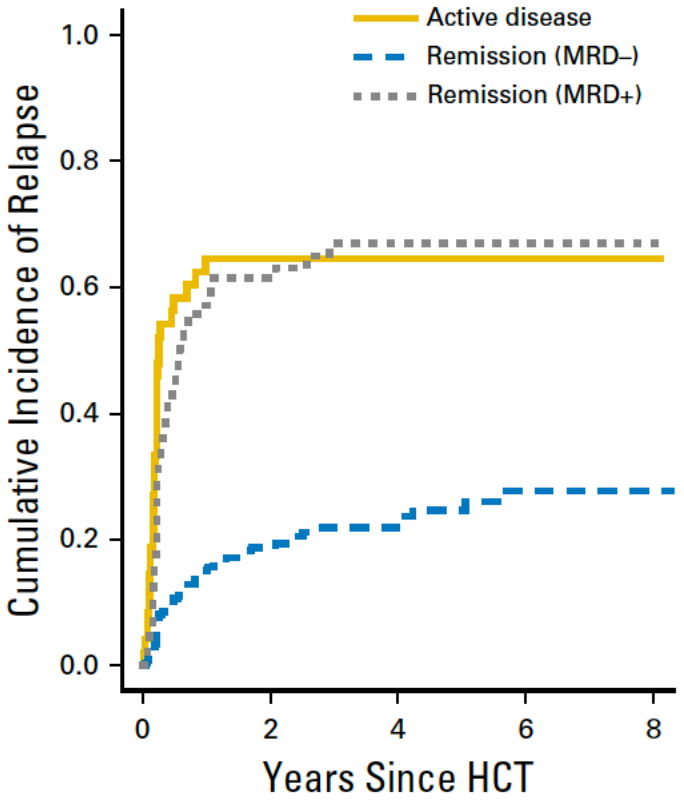
antonio.pierini@unipg.it

Azienda Ospedaliera di Perugia

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Incyte							X
Pfizer							X
MSD							X

Disease relapse is the major cause of transplant failure in acute leukemia patients

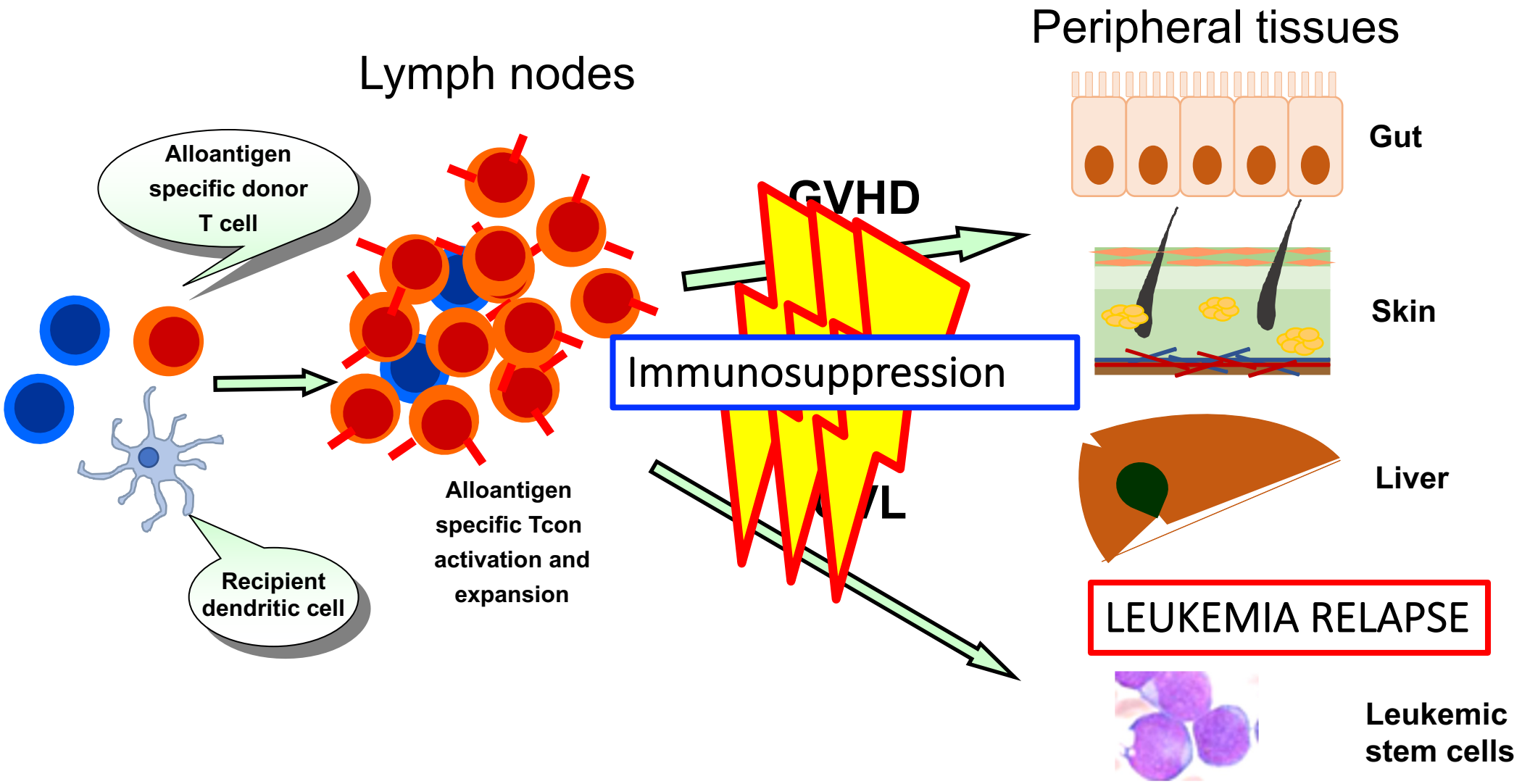


Araki et al. *JCO 2016*

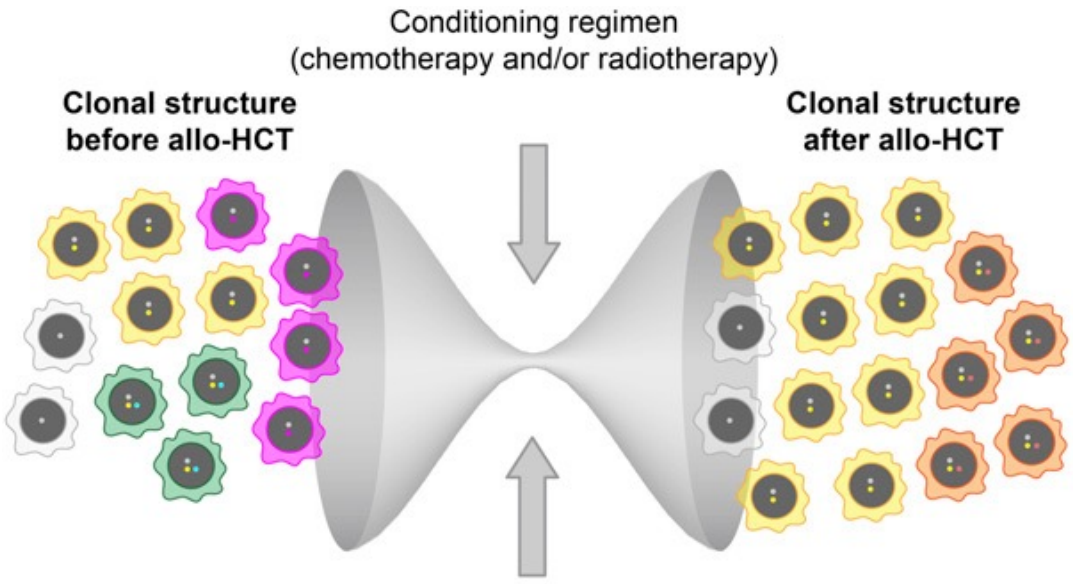
	Donor	Relapse (%)	DFS (%)
Gupta et al *Blood 2010*	MSD	37	42
CR1 AML with unfav. cytogen.	MUD	40	34
Bashey et al *J Clin Oncol 2013*	MSD	34	52
	MUD	34	53
Lorentino et al *EBMT, Leukemia 2020*	MUD **PT-Cy**	28	56
Ciurea et al. *Blood 2015*	HAPLO **After RIC**	58	46
	HAPLO **After MA condition.**	44	45
Piemontese et al. *EBMT, J Hem Onc 2019*	HAPLO **Mixed**	32	

Whatever the transplantation strategy and whoever the donor, all these diverse forms of HSCTs do not have a strong enough anti-leukemic effect.

Post-transplant pharmacologic immune suppression that is required to help prevent/treat GvHD may also reduce or abrogate the GvL effect



Clonal evolution in hematopoietic cell transplantation



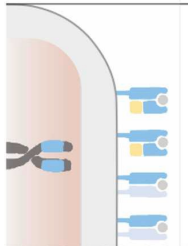
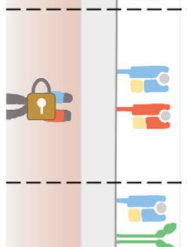
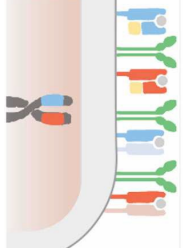
Adapted from Vago L, Blood 2019

Transplant factors that might impact on disease clonality:

- Intensity of conditioning regimen
- Donor-Patient HLA-matching
- Need of prolonged immune suppression
- Use of post-transplant antileukemic maintenance therapy

Biology of post-transplant leukemia relapse

Tumor-intrinsic mechanisms

	Alteration	Molecules involved	Frequency	Therapy
	Genomic HLA loss (CN-LOH)	Incompatible HLAs (both class I and II)	30% in haploidentical 5-10% in unrelated	Second transplantation or non-HLA-restricted immunotherapies
	Epigenetic downregulation of HLA class II	Compatible and Incompatible class II HLAs	30-40% overall	Induction of IFN-γ release (leukemia cross-recognition, inflammatory microenvironment)
	Epigenetic upregulation of inhibitory molecules	PD-L1, B7-H3, PVR, PVRL2	20%? (difficult to address due to complex pattern)	Immune checkpoint blockade

Rovatti et al. Frontiers in Immunology 2020

Transplant associated factors

- Use of conditioning regimens with limited antileukemic potential
- Early and/or prolonged immune suppression

MAC vs RIC

?

Case study: ID 005

Was the conditioning intense enough???

AML relapse

Complex Karyotype

AML therapy

Chemo-based HSCT

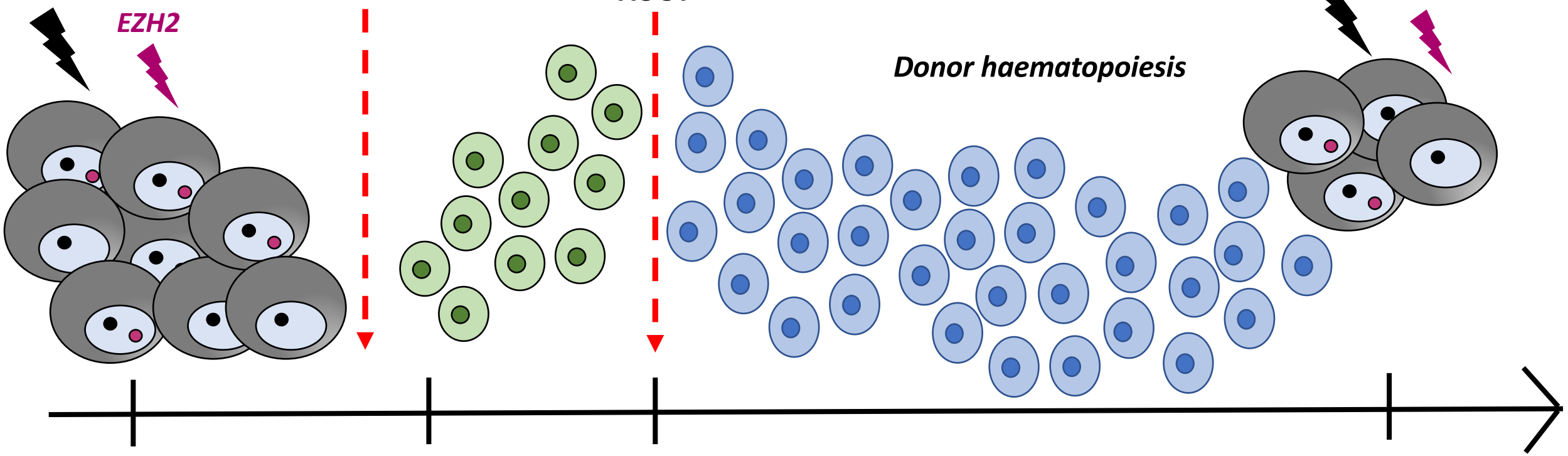
BCORL1

EZH2

Donor haematopoiesis

BCORL1

EZH2



0
AML diagnosis

4

6

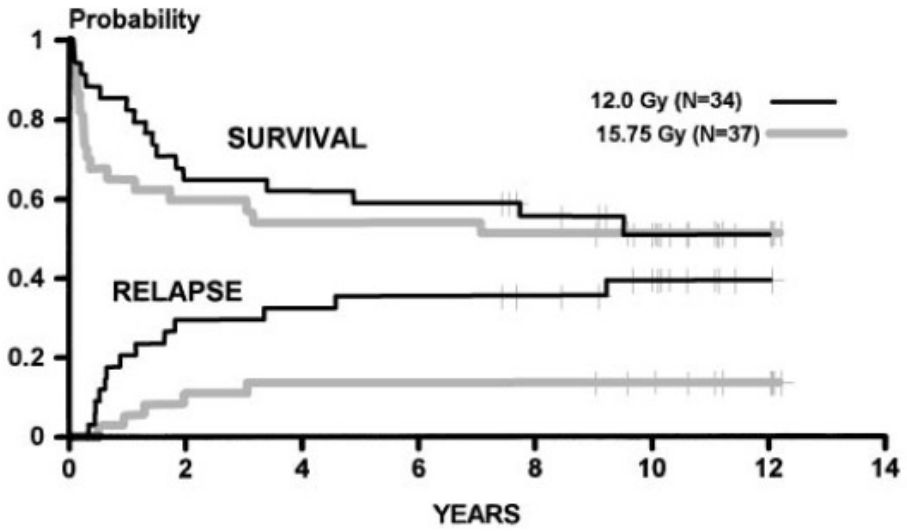
52
(+46)

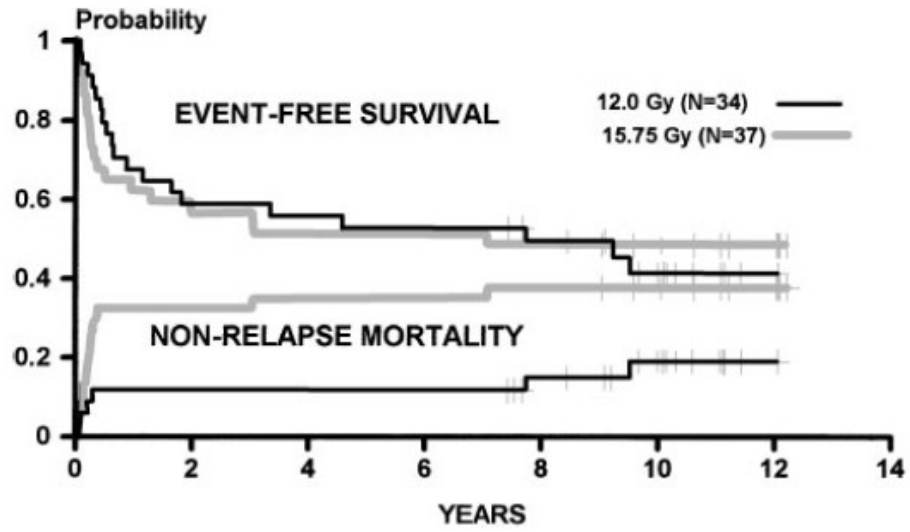
cGvHD/GvL

↓ ↓ GvL (?)

Complex Karyotype

WHAT ABOUT CONDITIONING INTENSITY?





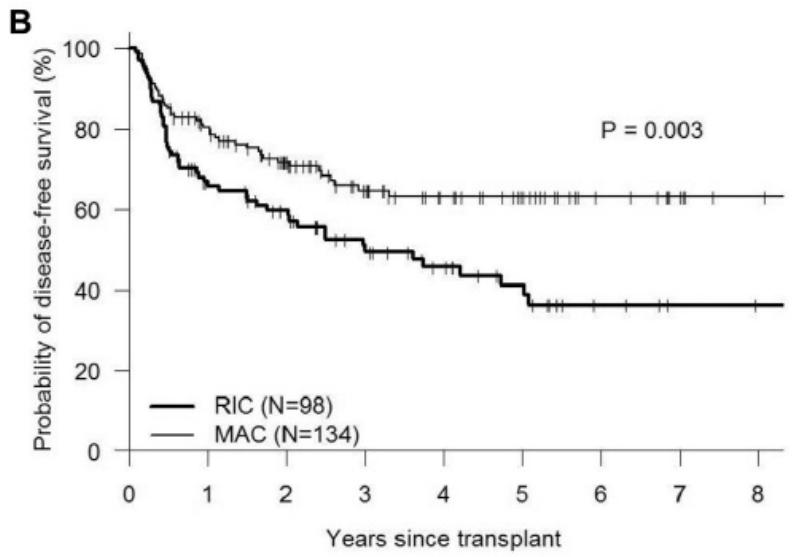
MORE IRRADIATION

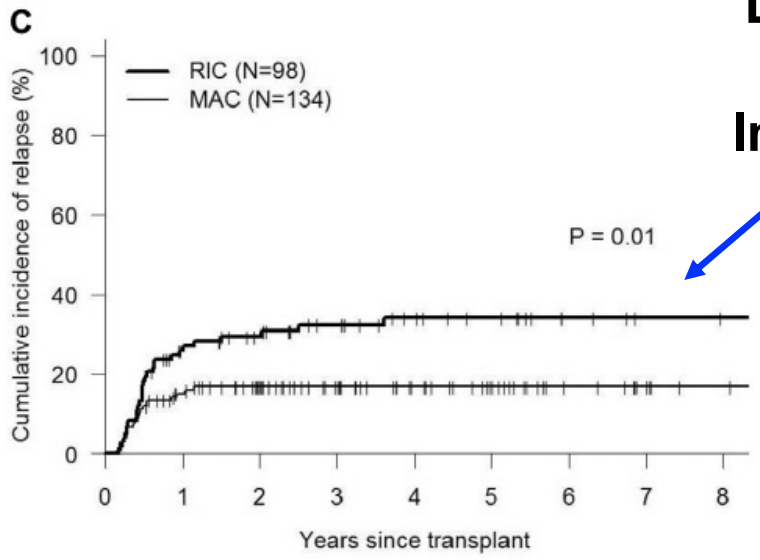
LESS RELAPSE, MORE NRM, SAME SURVIVAL

Clift et al. Blood 1998

MYELOABLATION REDUCES RELAPSE AT NRM EXPENSES…

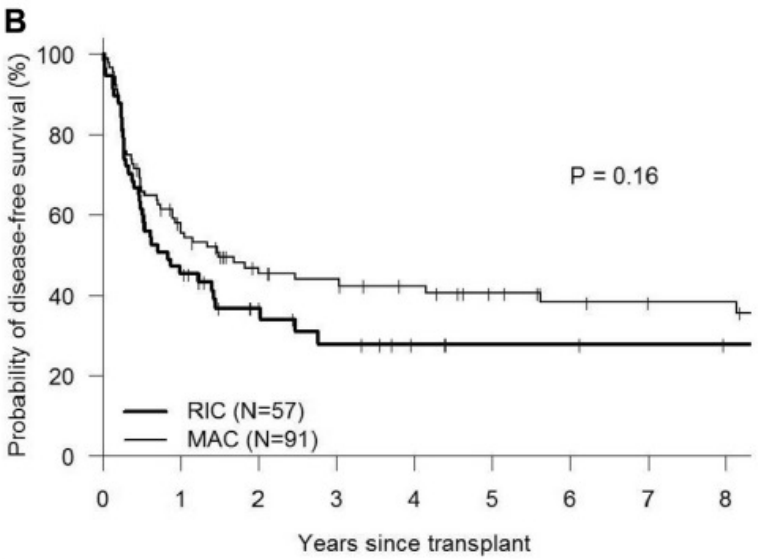
LOW/ INTERMEDIATE DRI

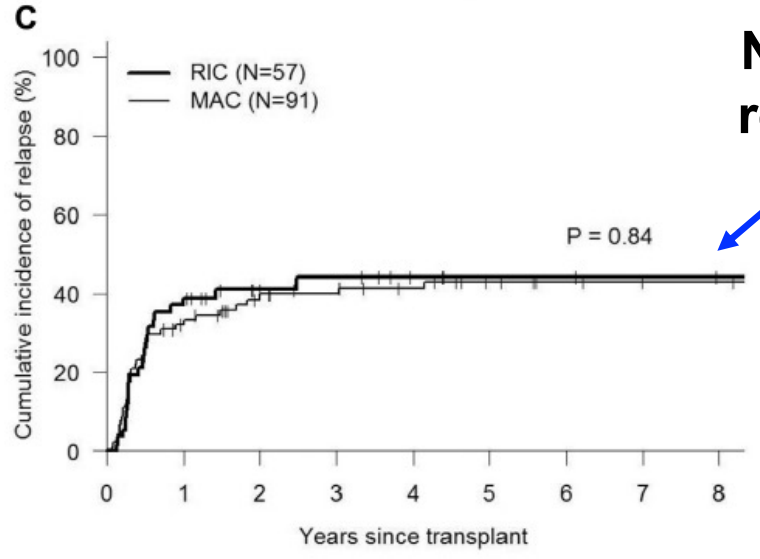




Less relapse, same NRM Improved DFS

HIGH/ VERY HIGH DRI

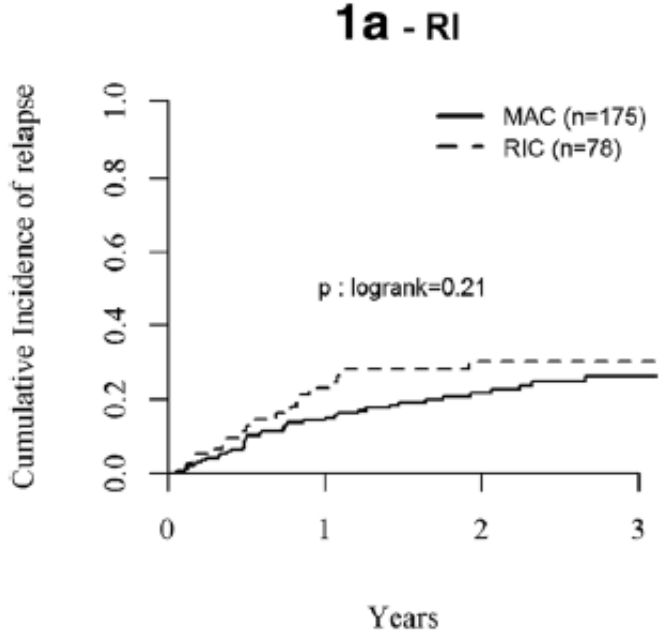


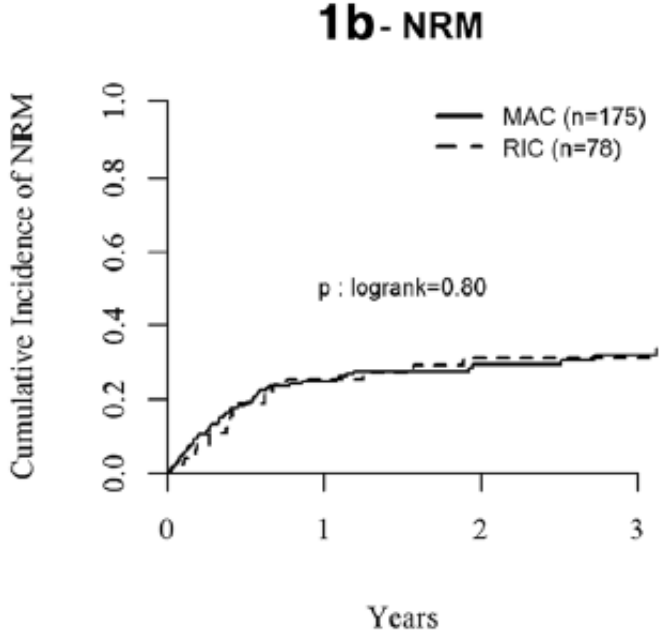


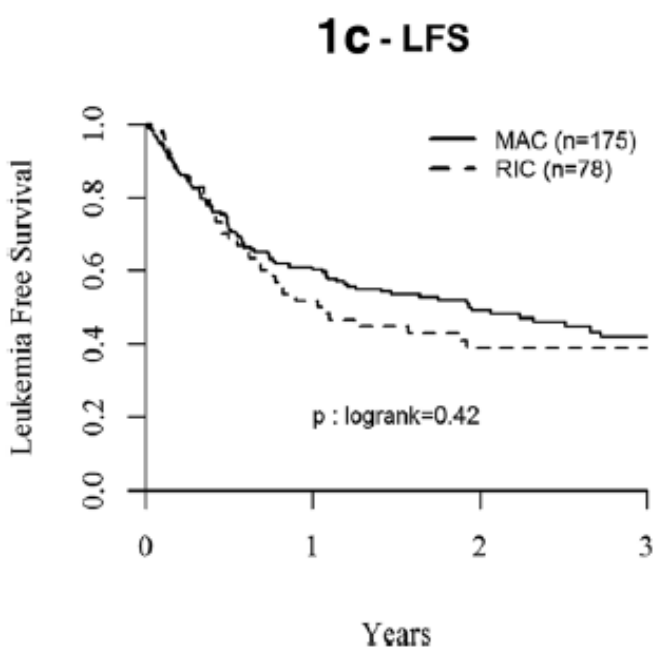
No advantage in relapse and DFS

Solh et al. bBMT 2019

…BUT DATA ARE NOT CONCLUSIVE!





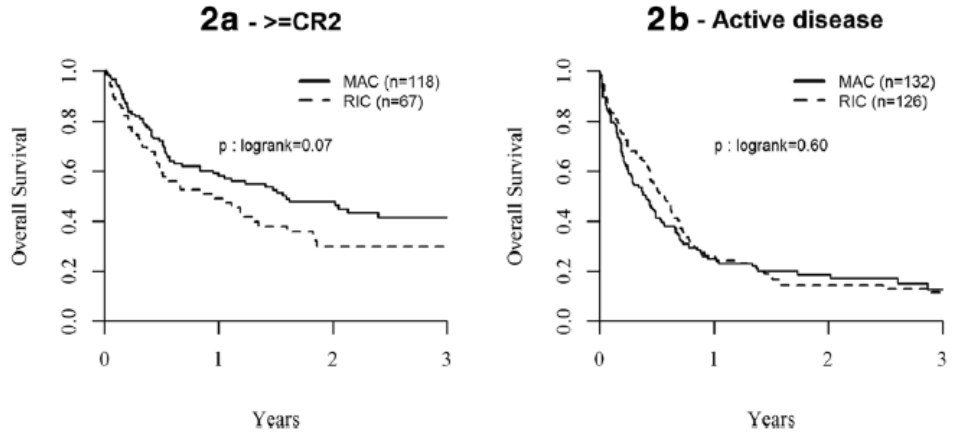


HLA-haplo RIC vs MAC, EBMT registry

Rubio et al. JHO 2016

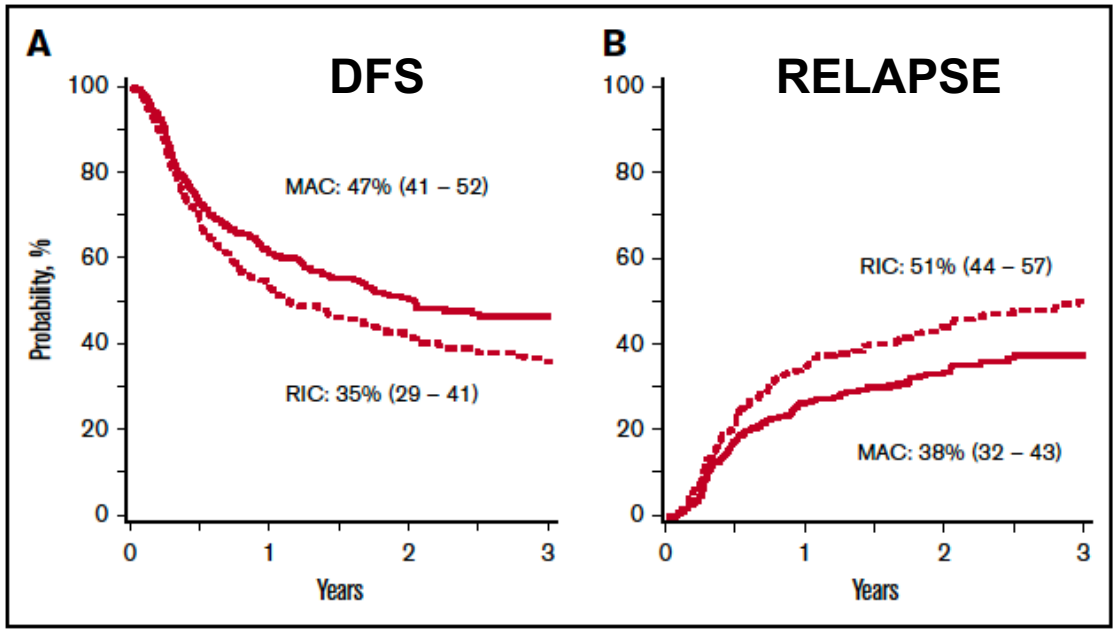
Indeed many factors impact on conditioning regimen efficacy such as:

- **Use of irradiation**
- **Type of disease**
- **Disease Burden**
- **And more…**

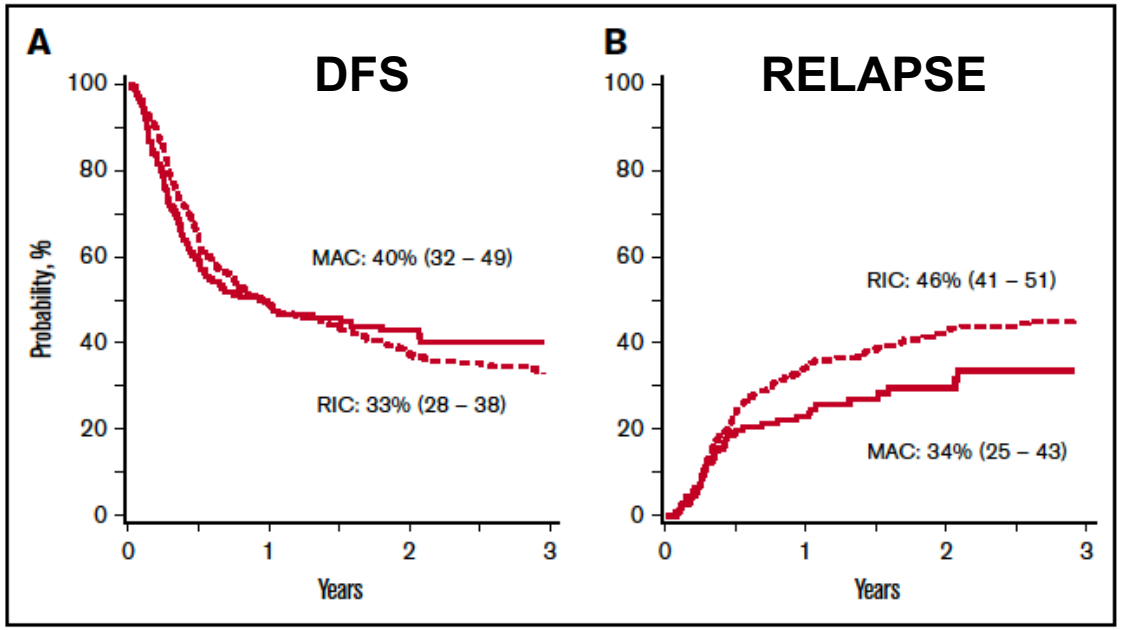


AND THE AGE?

18-54 yo



55-70 yo



No clear advantage of MAC regimens in older patients despite lower relapse rates in T repleted haplo-HSCT with PT-Cy

HLA-haplo with PT-Cy, USA CBMTR registry

Solomon et al. Blood Advances 2019

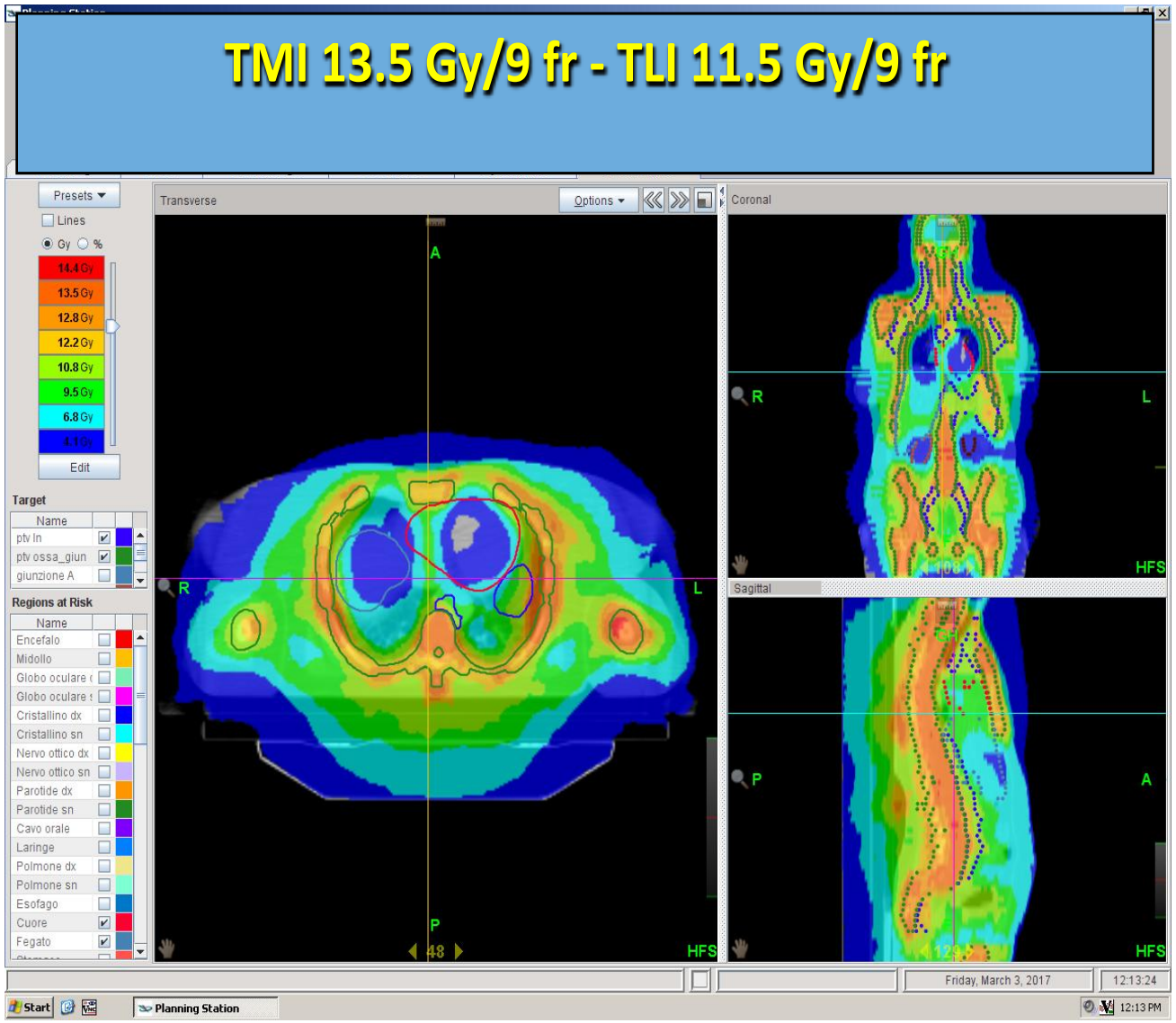
WHY ARE WE LOSING EFFICACY OF MAC REGIMENS IN OLDER PATIENTS?

- Frailty (e.g., comorbidities, poor organ function)
- Higher risk diseases
- Higher disease burden at transplant
- Use of old-style conditioning approaches

INTRODUCING NOVEL DRUGS/TECHNOLOGIES

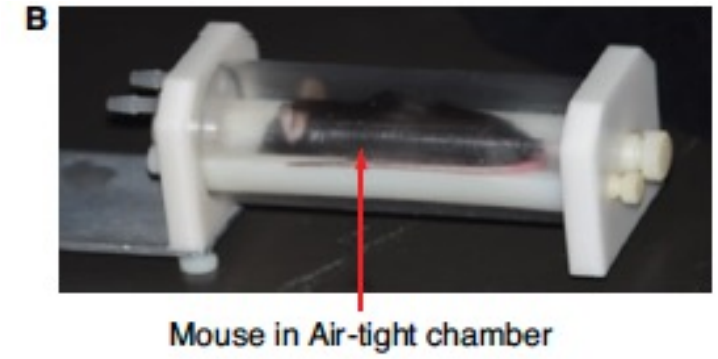
One example: Total Marrow/Lymphoid Irradiation (TMLI) technology

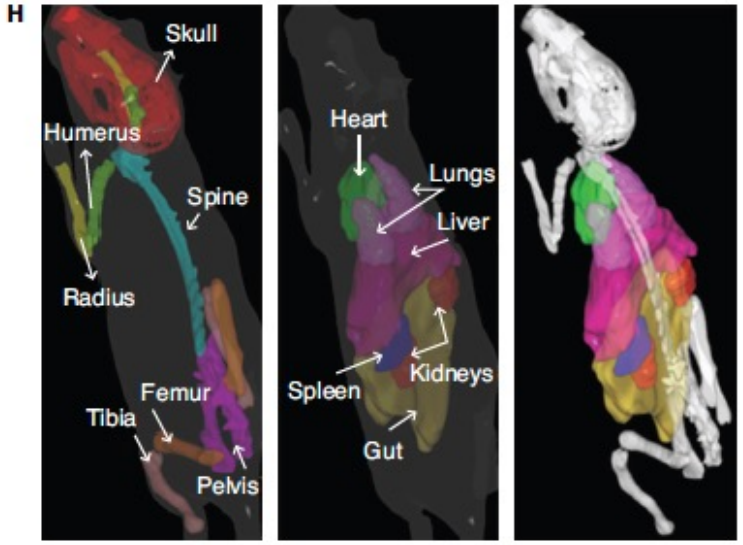
Boosting irradiation in marrow and lymph nodes while sparing vital organs!

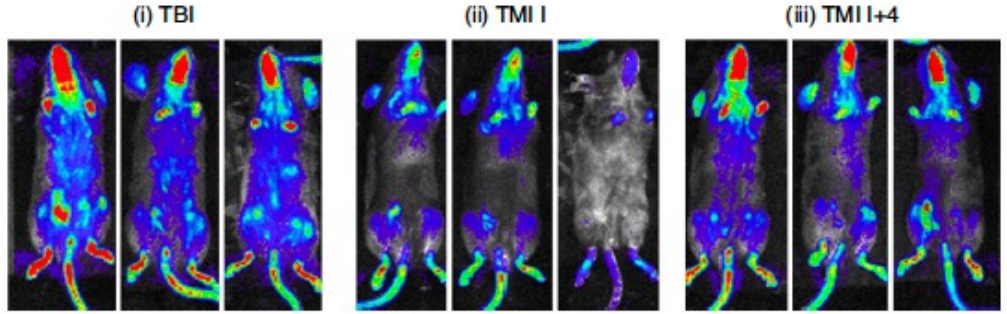


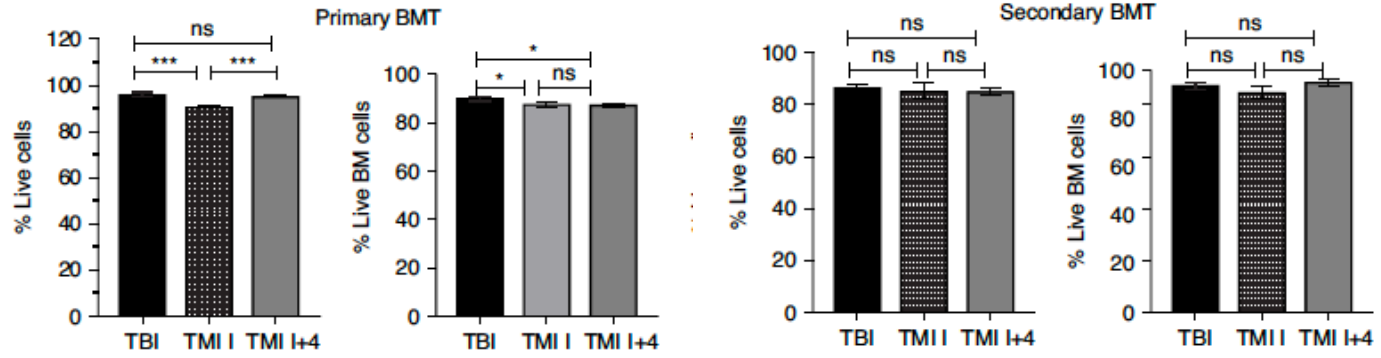
Courtesy of Prof. C. Aristei

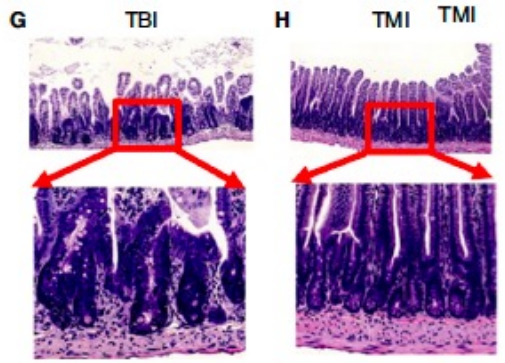
TMLI ensures engraftment and protects vital organs





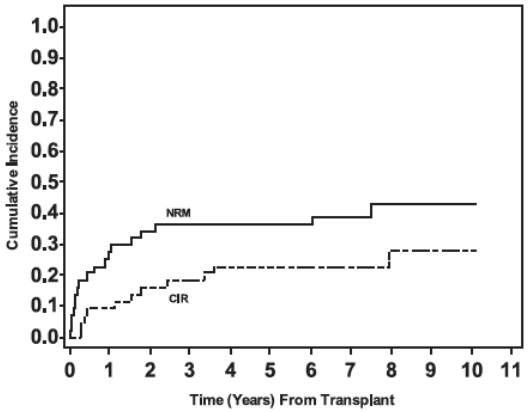


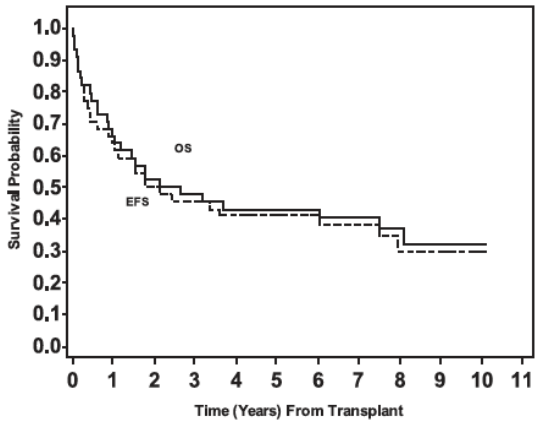




Zuro et al. Int J Rad Onc 2021

TMLI/FLU/MEL
T repleted MSD and MUD
61 pts >50 yo
Median Age: 55 yo
AML CR2 or active disease: 55%





LIMITED TOXICITY

AND

PROMISING ANTILEUKEMIC ACTIVITY

Transplantation-related Toxicity and Mortality Comparison

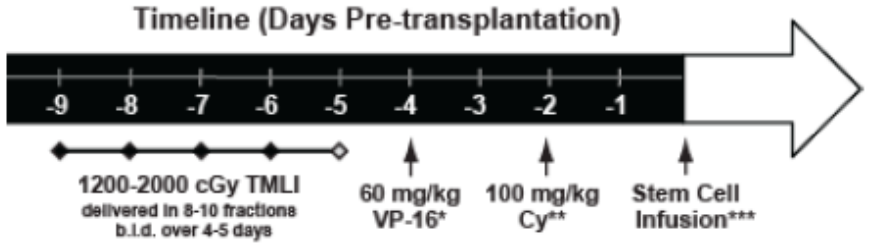
Study	No. of Patients	Deaths, n (%)	Stomatitis, n (%)	Gut, n (%)	Hepatic, n (%)	Pulmonary, n (%)	Cardiac, n (%)	Renal, n (%)	1-yr NRM, mean ± SD
Giralt et al., 2001 [15]	78	3 (4)	0	0	5 (6)	5 (6)	2 (3)	7 (9)	44.7*
Giralt et al., 2002 [43]	22	1 (5)	0	0	1 (5)	1 (5)	1 (5)	1 (5)	40 ± 10
Ritchie et al., 2003 [44]	39	4 (10)	2 (5)	0	2 (5)	4 (10)	1 (3)	3 (8)	30 ± 7
de Lima et al., 2004 [45]	62	6 (10)	1 (2)	4 (6)	1 (2)	9 (14)	4 (6)	3 (5)	30
Present study	61	2 (3)	1 (2)	3 (5)	3 (5)	7 (11)	2 (3)	6 (10)	25

All toxicities listed used the Bearman scale and show grade III and IV (lethal) toxicities before day +100. Studies listed used FLU/MEL conditioning regimens.
* NRM was not given at 1 year. At 2 years, 44.7%, at 100 days, 37.4%.

Rosenthal et al. Blood 2011
Updated, Jensen et al. bBMT 2018

PUSHING ON TMLI → UP TO 20 GY

MSD or MUD in Active AML
TMLI up to 20Gy/Cy/VP-16

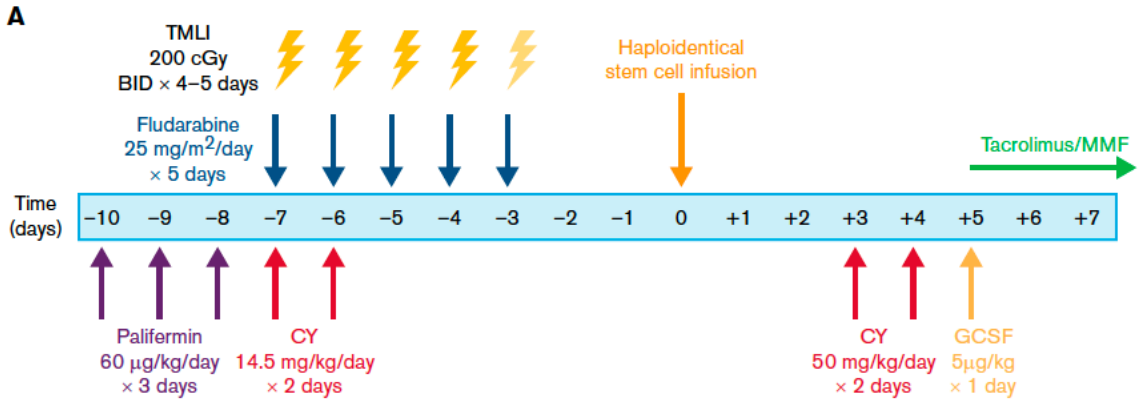


51 pts < 60 yo
Many with peripheral blasts

1-year NRM 8.1%, but Relapse 33/51

Stein et al., bBMT 2017

HLA-haplo in all AL
TMLI up to 20Gy + PT-Cy



31 pts up to 58 yo
High-risk: 55%

1-year NRM 9%, Relapse 17%, DFS 74%

Al Malki et al., Blood Advances 2022

Key Achievements of TMLI technology in HSCT

- **Reduced toxicity to organs that are not site of disease**

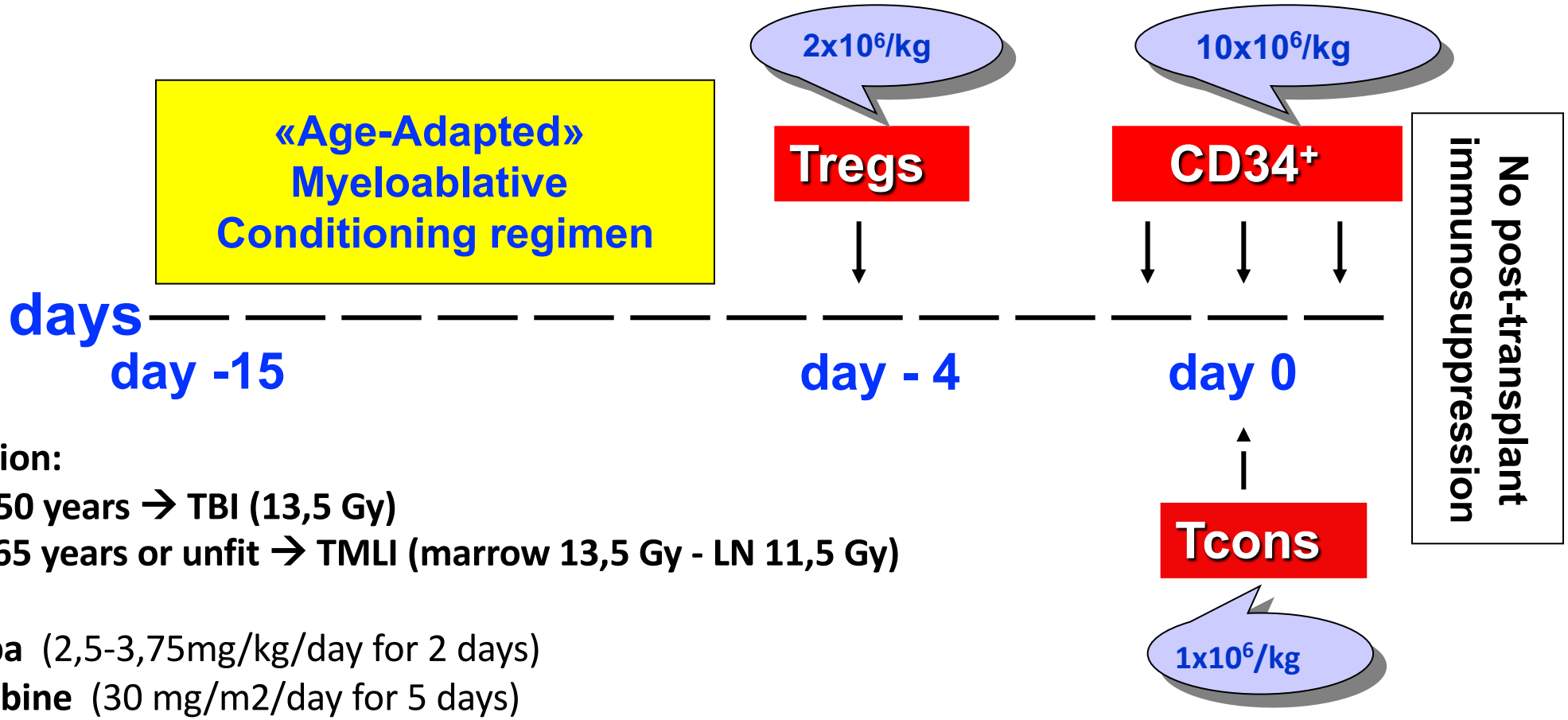
  ↳ **Unfit and Old patients can SAFELY receive myeloablative HSCT**

- **Possibility to boost areas of disease during conditioning**

  ↳ **Increase antileukemic activity of the conditioning regimen**

CAN WE DO MORE TO PREVENT RELAPSE?

LET'S PUT MYELOABLATION TOGETHER WITH IMMUNITY



Irradiation:

- up to 50 years → TBI (13,5 Gy)

- 50 to 65 years or unfit → TMLI (marrow 13,5 Gy - LN 11,5 Gy)

+

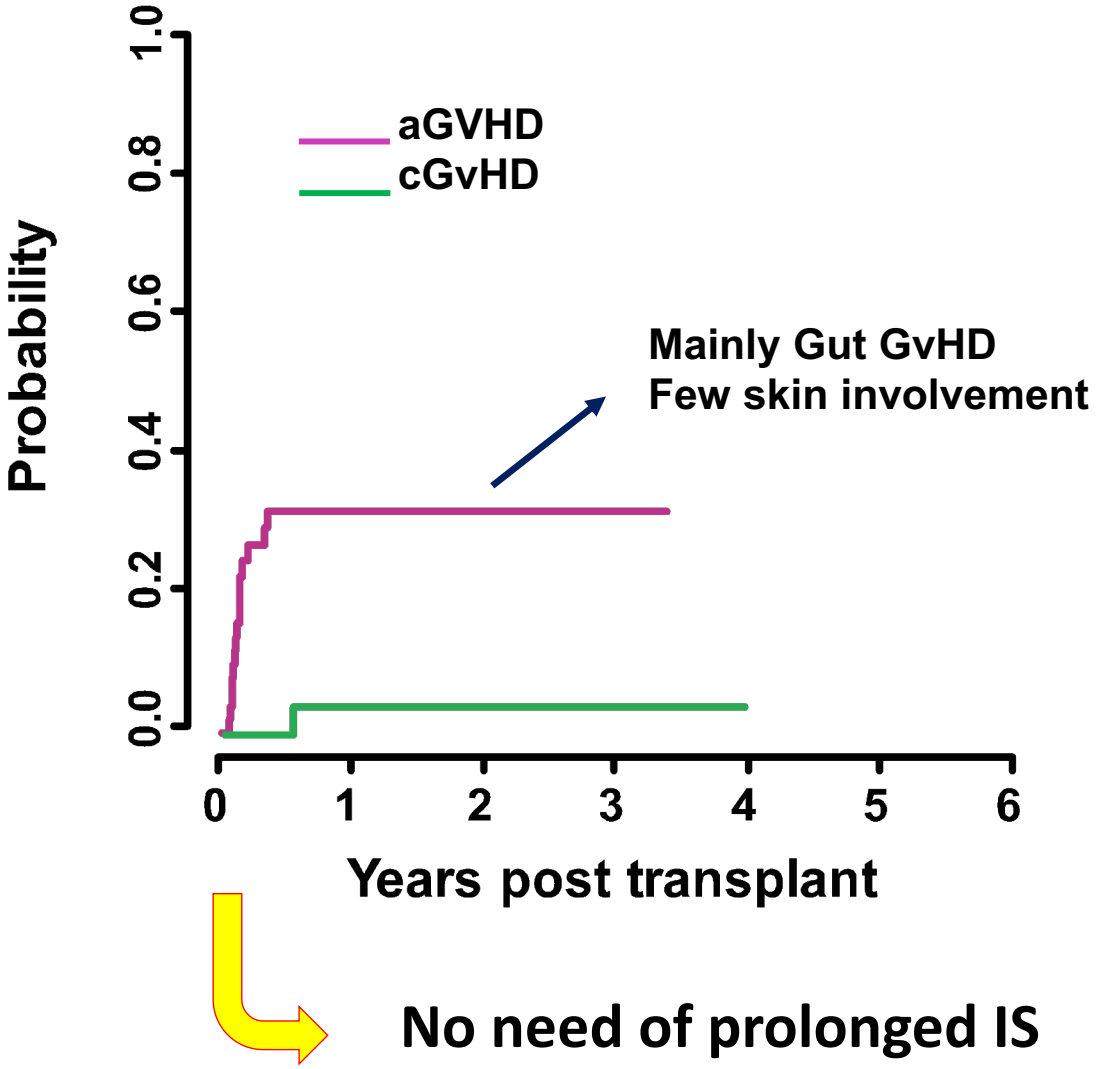
Thiotepa (2,5-3,75mg/kg/day for 2 days)

Fludarabine (30 mg/m2/day for 5 days)

Cyclophosphamide (15 mg/kg/day for 2 days)

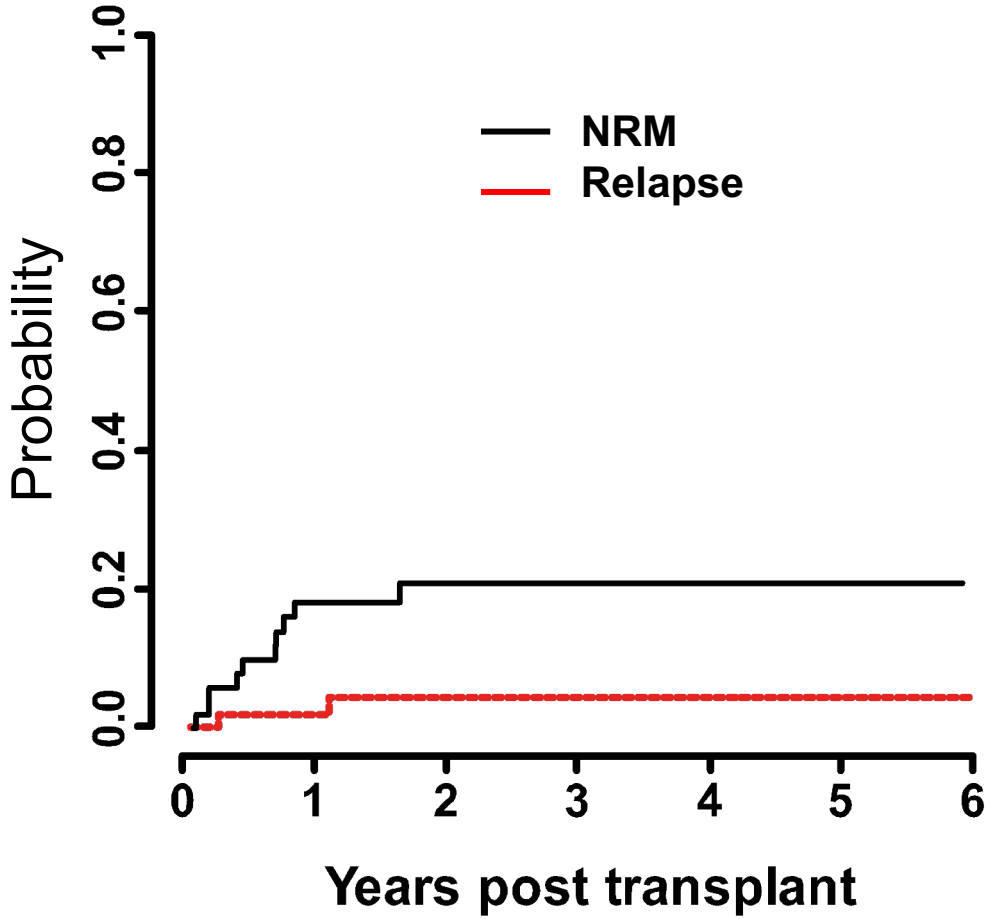
Pierini et al. Blood Advances 2021

GvHD

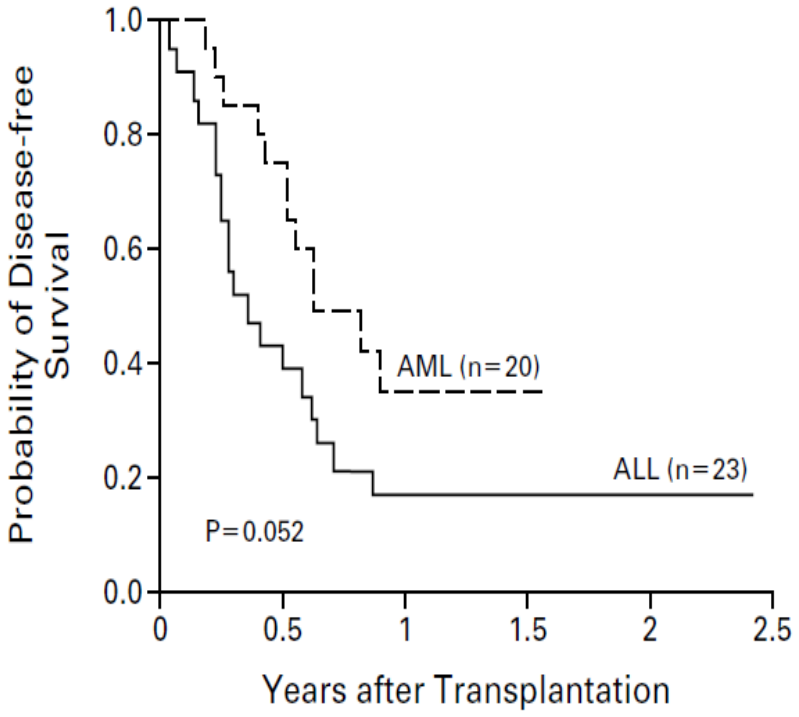


No need of prolonged IS

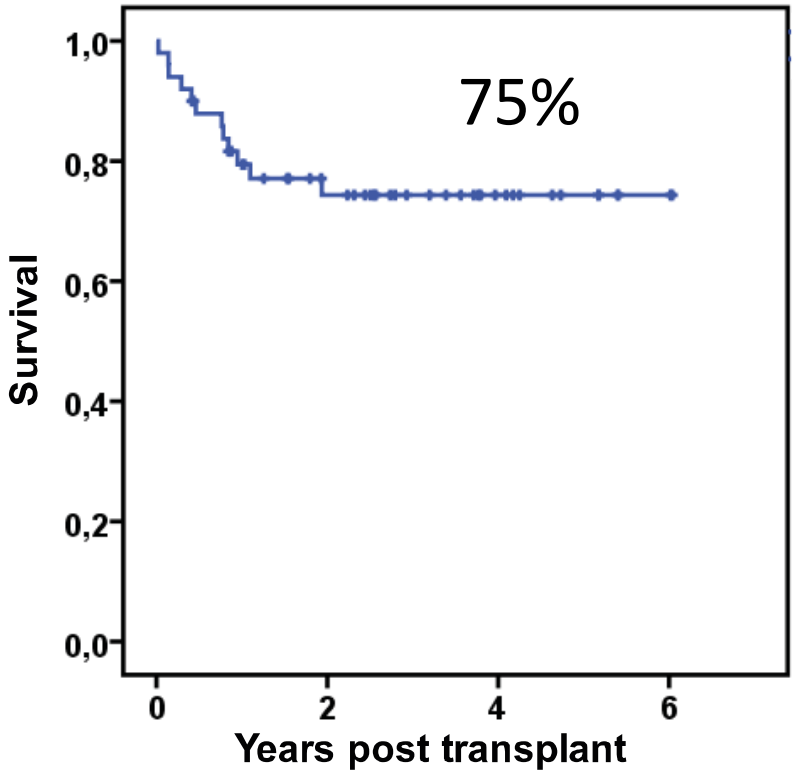
NRM and Relapse

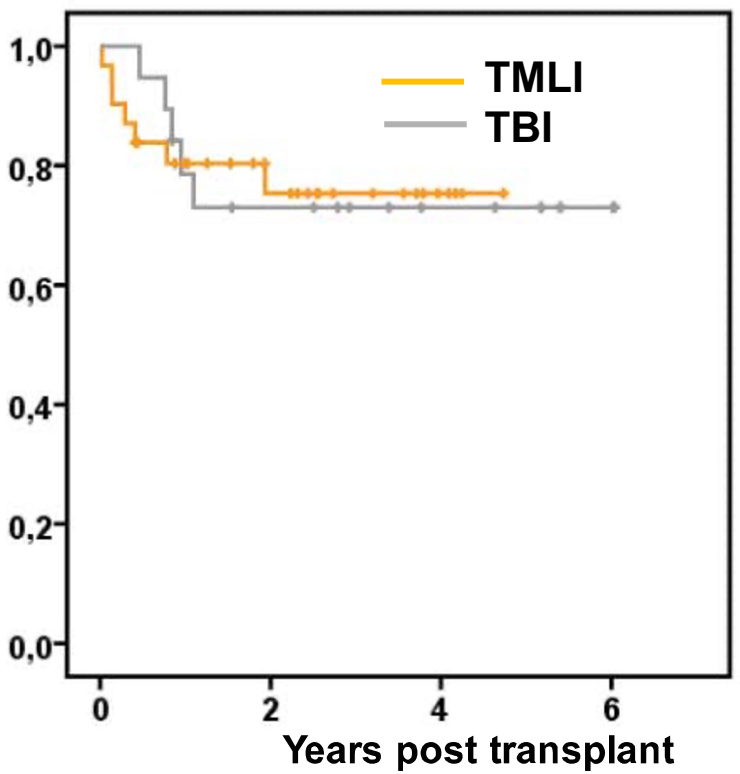


cGvHD-Relapse Free Survival



Aversa et al. NEJM 1998, updated on JCO 2005





Median Follow-up: 29 months

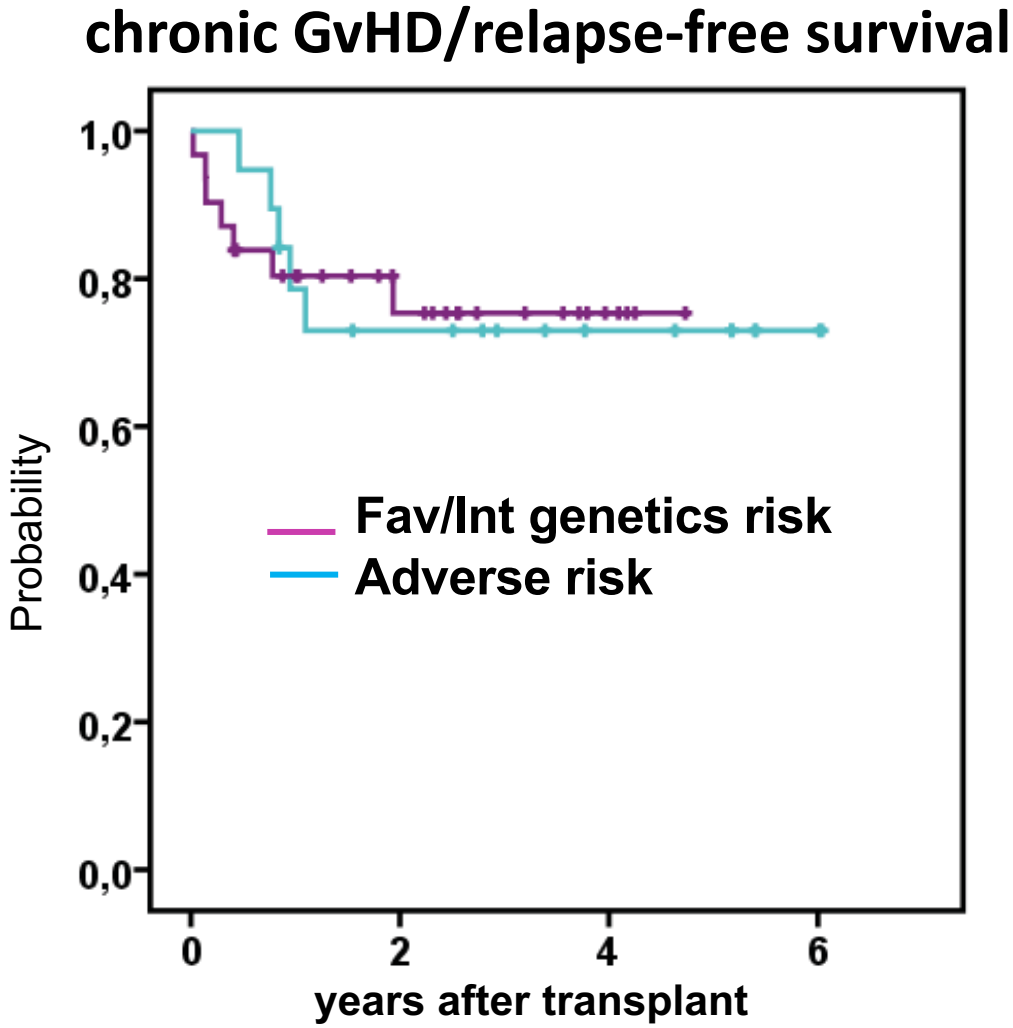
Pierini et al. Blood Advances 2021

Impact of Adverse Genetics

Adverse genetics at diagnosis (including monosomal and/or complex karyotype) had

no impact on

chronic GvHD/relapse-free survival



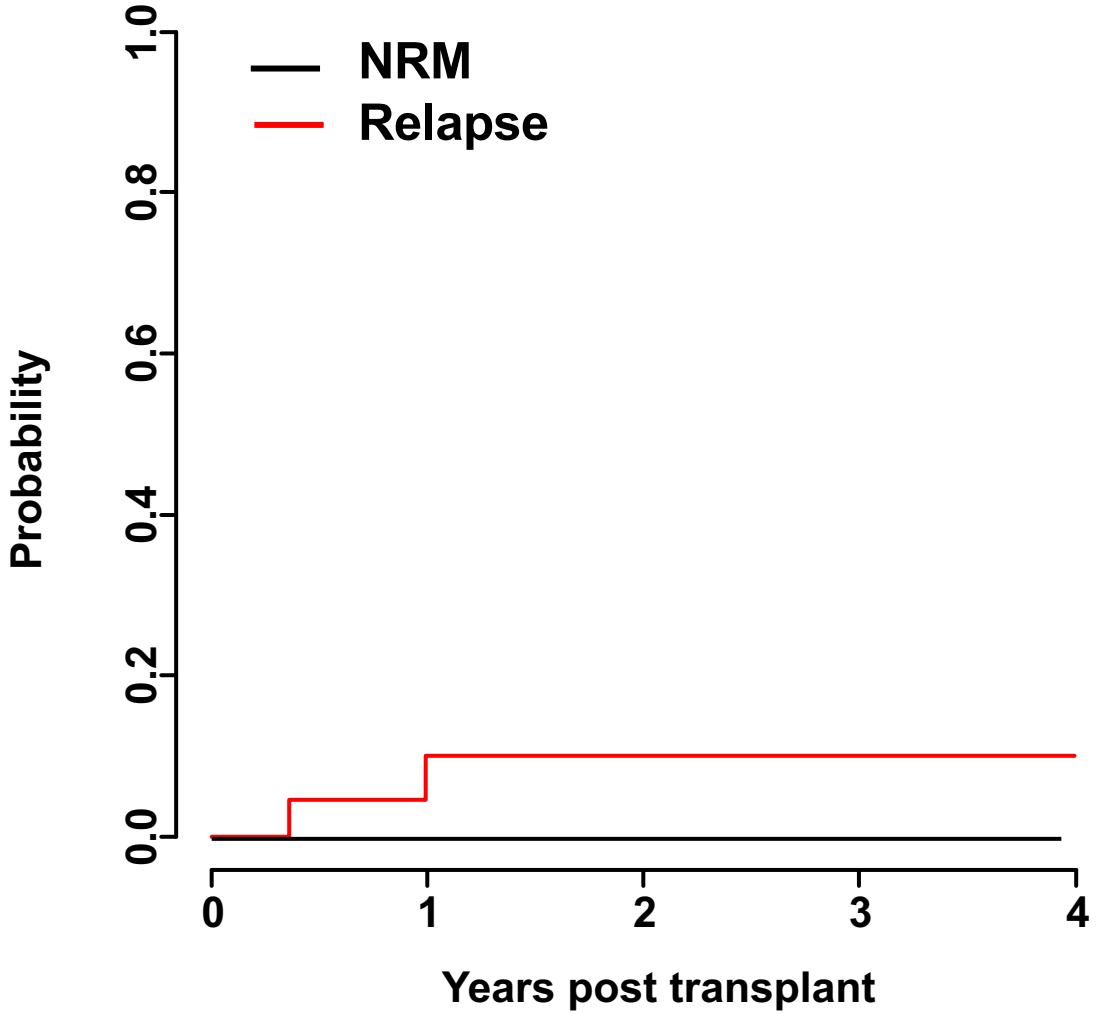
EXTENSION OF THE PROTOCOL TO HLA-MATCHED HSCT (23 PTS)

NRM and Relapse

No patient died because of Transplant related causes (**NRM=0%**)

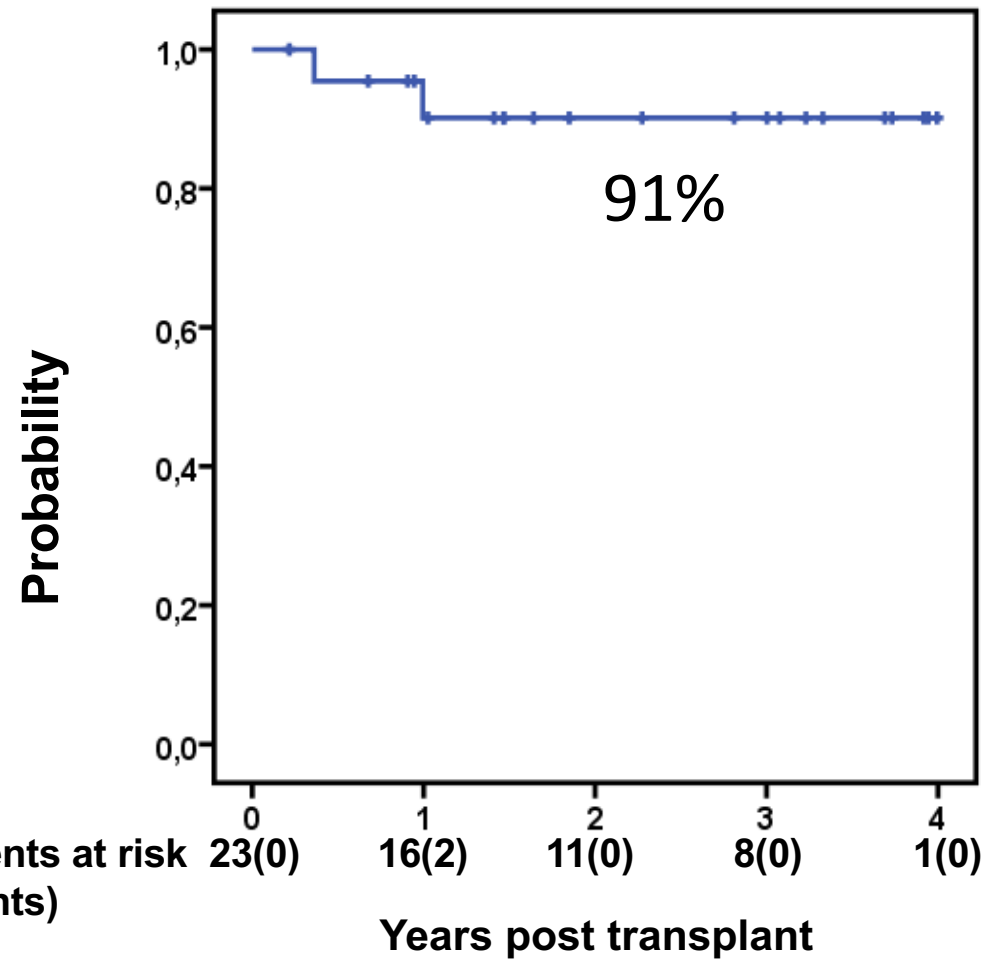
Relapse: 2 pts (CI=**9%**)

- FLT3-ITD AML, PIF, MRD^{pos} at transplant
- B-ALL, delIKZF1, rescued with CAR-T

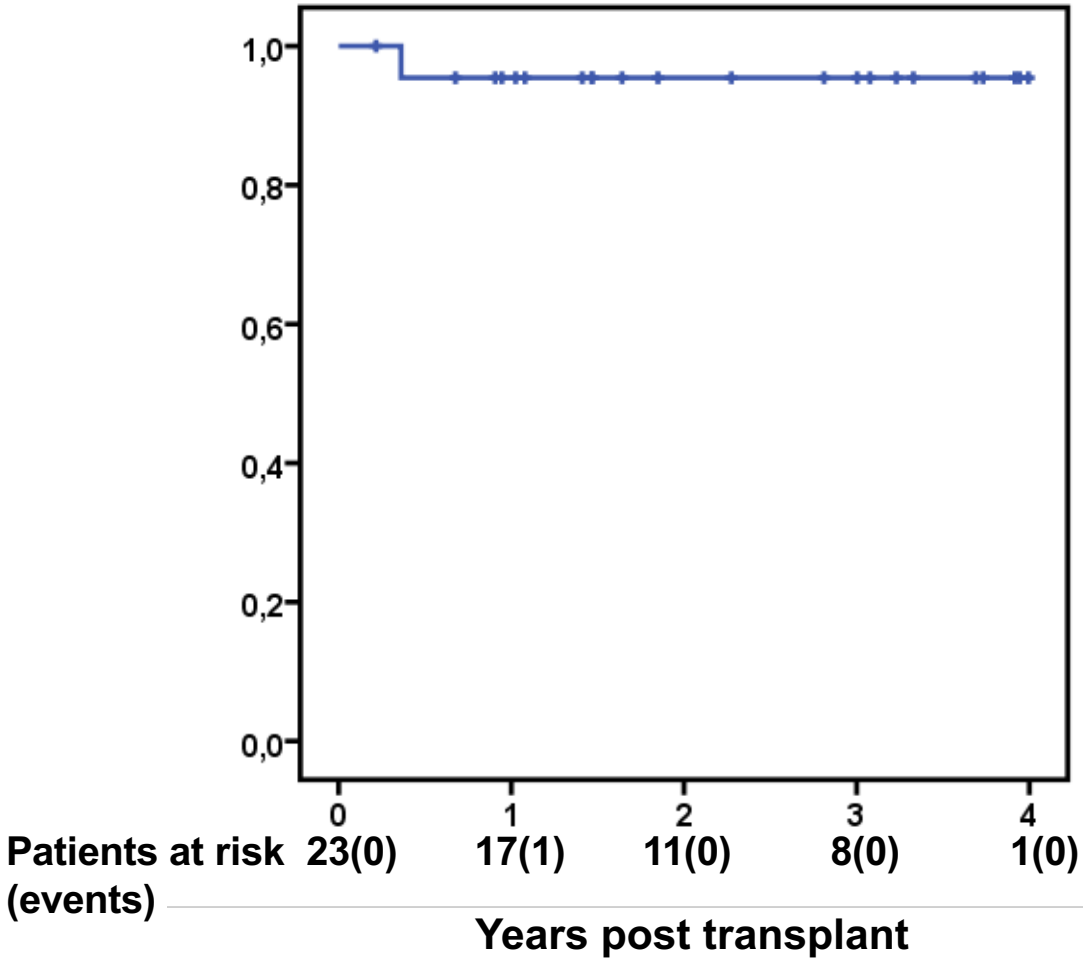


Pierini et al. ASH 2022, EBMT 2023, in preparation

Chronic GvHD/Relapse-Free Survival



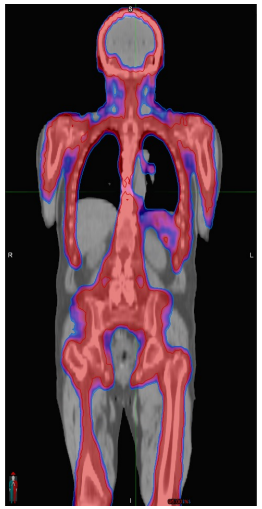
Overall Survival



Median Follow-Up: 31 months

Pierini et al. ASH 2022, EBMT 2023, in preparation

“AGE-ADAPTED” TMLI-BASED CONDITIONING



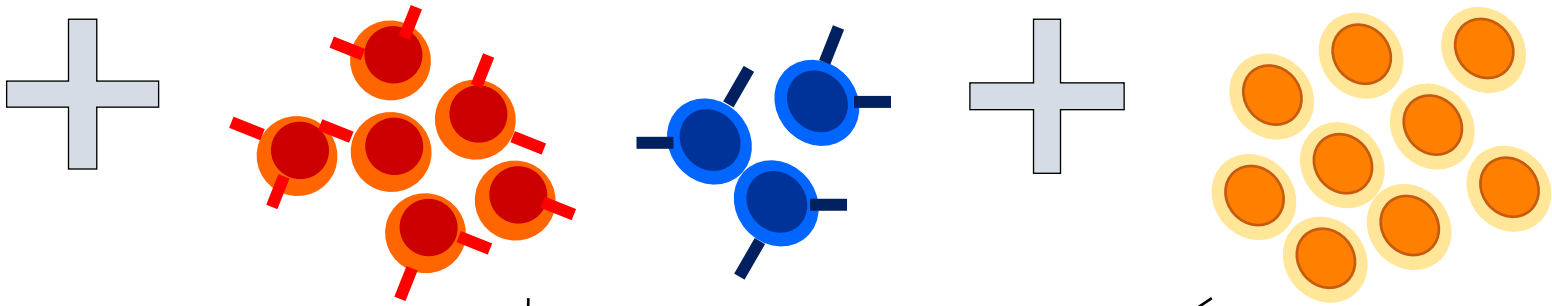
ADOPTIVE T CELL IMMUNOTHERAPY

Donor Tregs

Donor Tcons

IS-FREE DONOR GRAFT

Donor HSCs



POTENT ANTILEUKEMIC ACTIVITY ACROSS HLA DISPARITIES

IS MYELOABLATION POSSIBLE IN OLDER PATIENTS???

YES, BUT CONSIDER:

- Fitness and Comorbidities
- Disease Genetics
- Disease Status at HSCT

If possible, we should employ novel technologies to retain efficacy of myeloablation and safety of RIC protocols!

It is not just a matter of intensity...

Let's design the HSCT around the patient!

BMT PROGRAM

Director: Alessandra Carotti

BMT UNIT
Adelmo Terenzi
Sara Tricarico
Rebecca Sembenico
Valerio Viglione
Alessandra Cipiciani
Mattia Mariannelli
Francesco Zorutti

Clinical Immunology Lab
Loredana Ruggeri
Francesca Marzuttini
Sara Ciardelli
Elena Urbani

AIRC START UP
Antonella Mancusi
Eni Hoxha
Roberto Limongello

Apheresis
Mauro Marchesi
Olivia Minelli
Marina Onorato
Nicola Albi
Barbara Pasqua

Data Manager
Mara Merluzzi

Hematology Division
Maria Paola Martelli
Cristina Mecucci
Brunangelo Falini
Enrico Tiacci
Paolo Sportoletti

… nurses and patients!!!

Massimo F. Martelli
Andrea Velardi
Franco Aversa

Graft Processing
Tiziana Zei
Roberta Iacucci
Franca Falzetti
Mauro Di Ianni

Radiation Oncology
Cynthia Aristei
Simonetta Saldi
… and the physicists

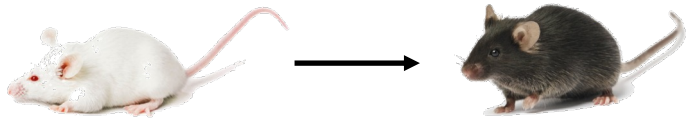
Pediatric Unit
Maurizio Caniglia
Ilaria Capolsini
…aria Speranza Massei
… and the whole Clinical Team

HLA unit
Rita Tognellini
Federica Alunni

CAN WE DO MORE TO PREVENT RELAPSE?

LET'S PUT MYELOABLATION TOGETHER WITH IMMUNITY

Strong biological studies
to be translated to robust clinical trial



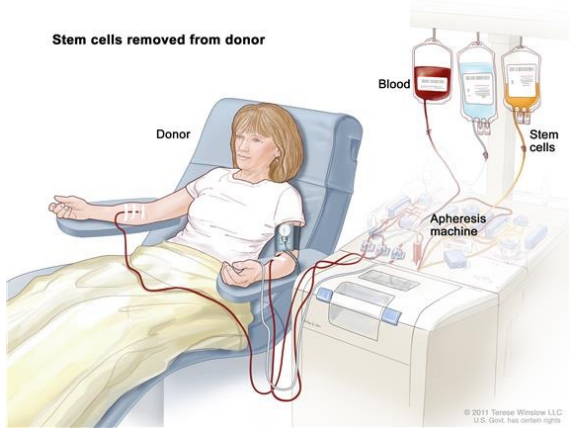
donor host

GITMO

EBMT

NIH U.S. National Library of Medicine
ClinicalTrials.gov

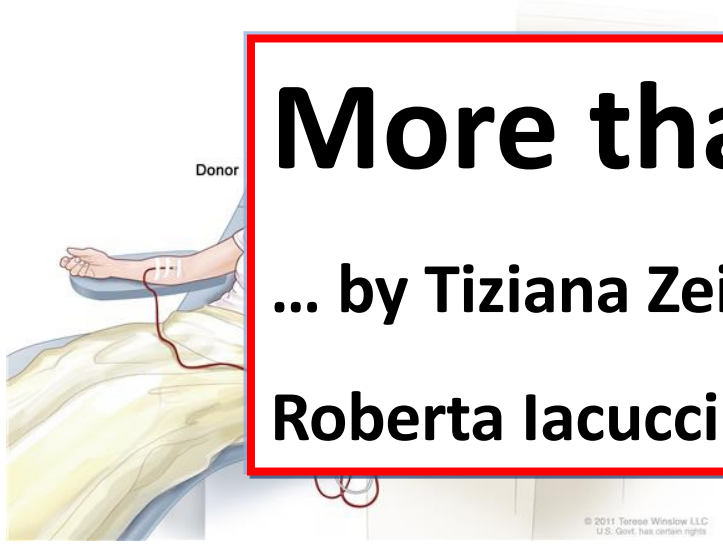
Novel technologies for graft manipulation

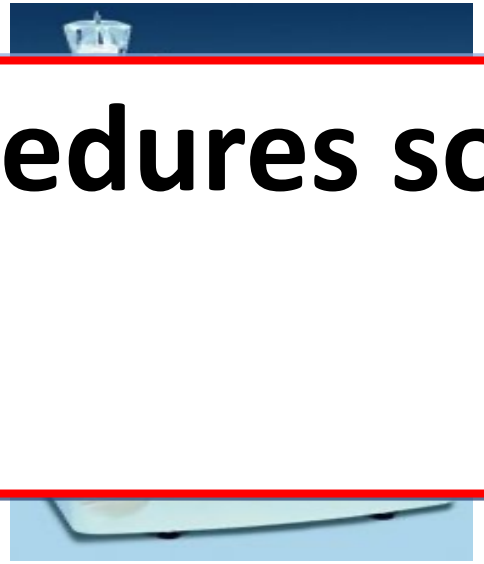


- Hematopoietic stem cells
- Immune cell subpopulations
- Engineered cells

The goal should be to safely avoid immune suppression
as much as possible and unleash strong post-transplant immunity
that eradicates residual leukemic clones

Easy clinical scale selection of CD4+/CD25+ regulatory T Cells





More than 250 Procedures so far

… by Tiziana Zei and

Roberta Iacucci Ostini

n of
19+cells

:

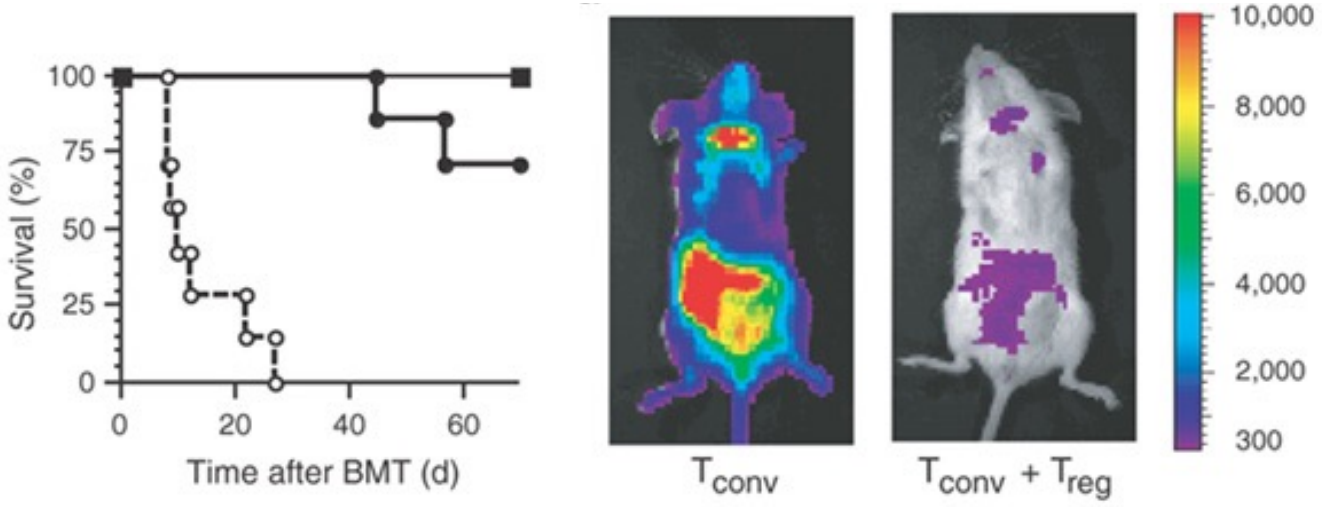
n of
cells

«Treg»	Cells (x10^9)	= 280 (202- 390)
Final product	CD4/CD25+	= 92% (90-97%)
	FOXP3+ cells	= up to 90%

Treg suppress GvHD with no loss of GvL activity

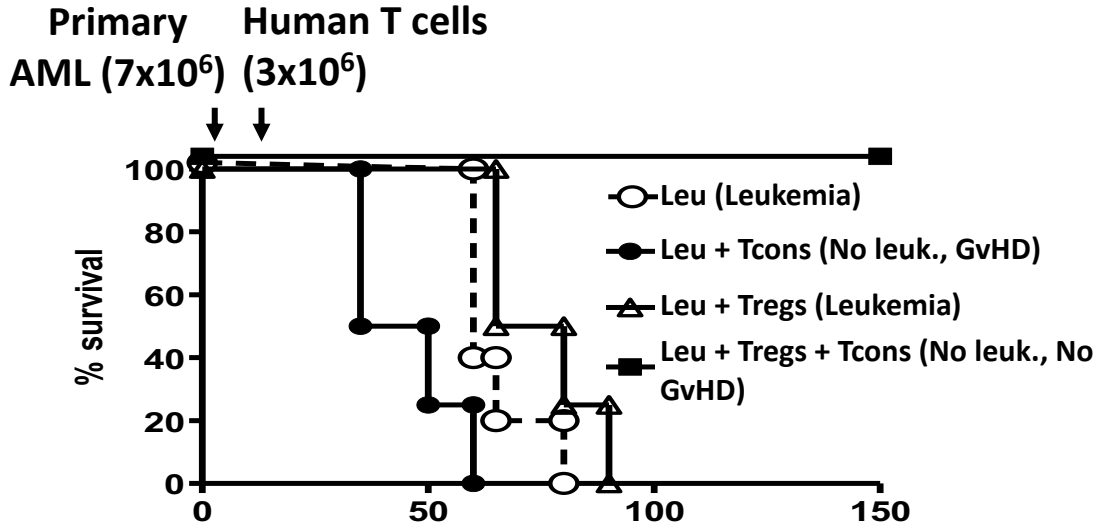
In animal models

- Tregs inhibited early expansion of alloreactive donor T cells in lymphoid organs and their capacity to induce GVHD



Edinger M et al. Nature Medicine 2003

- Tregs did not inhibit co-transplanted Tcon activation and cytotoxic functions against leukemia and lymphoma cell lines



Martelli MF et al. Blood 2014; Ruggeri et al. In preparation