L’avenir de l’allogreffe en hématologie

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L'avenir de l'allogreffe en hématologie

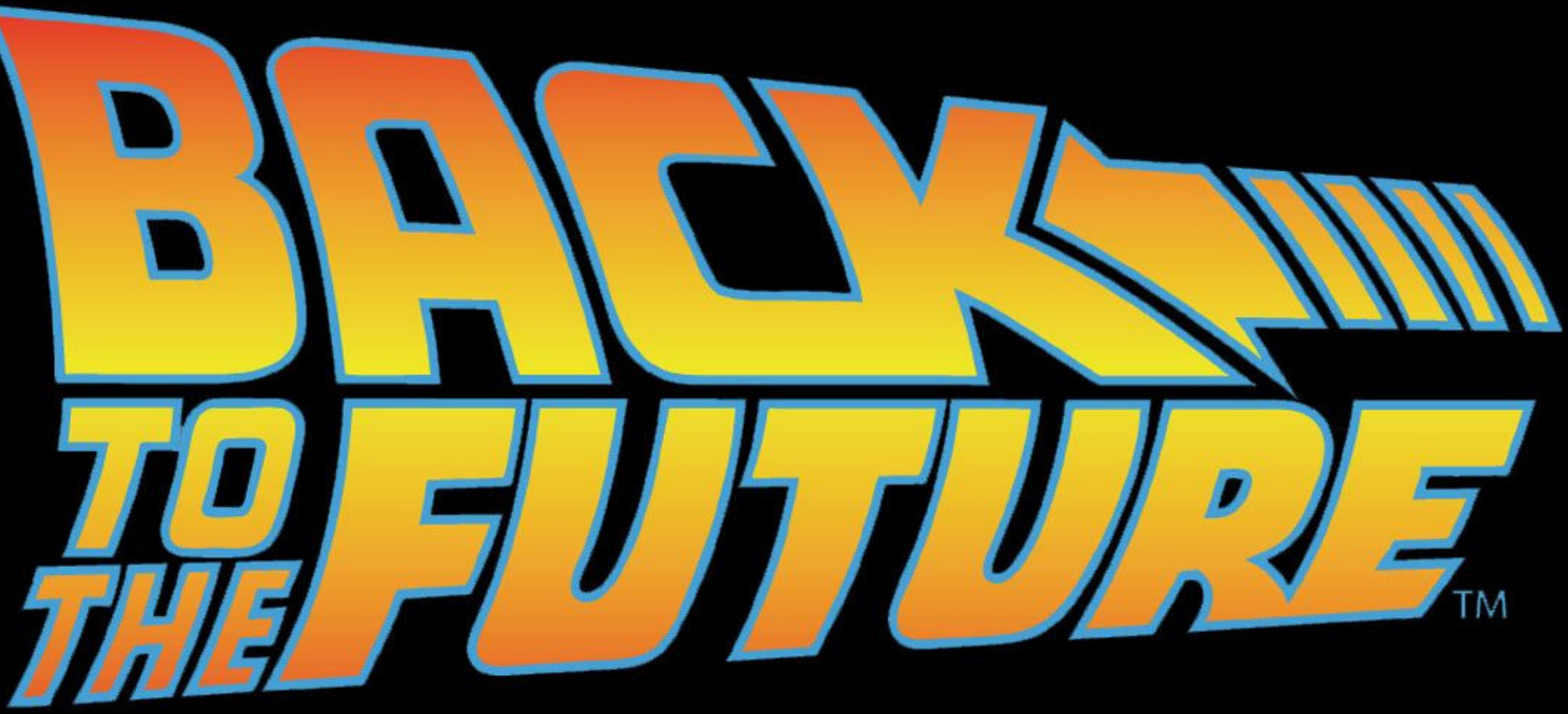
Disclosures:

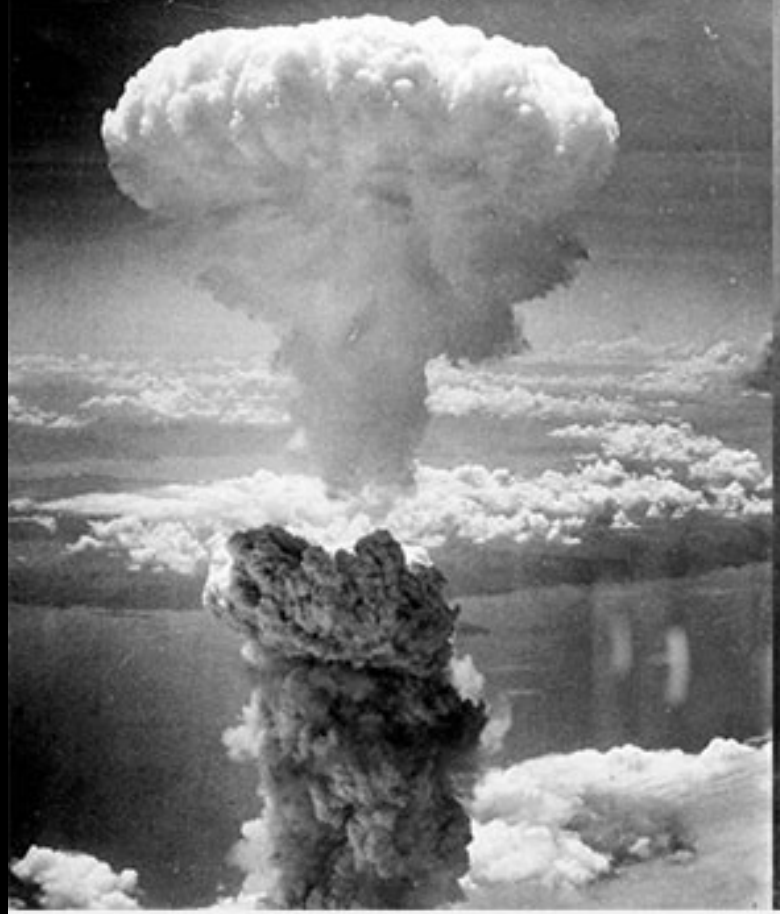
Honoraria from Novartis, Takeda and Biotest

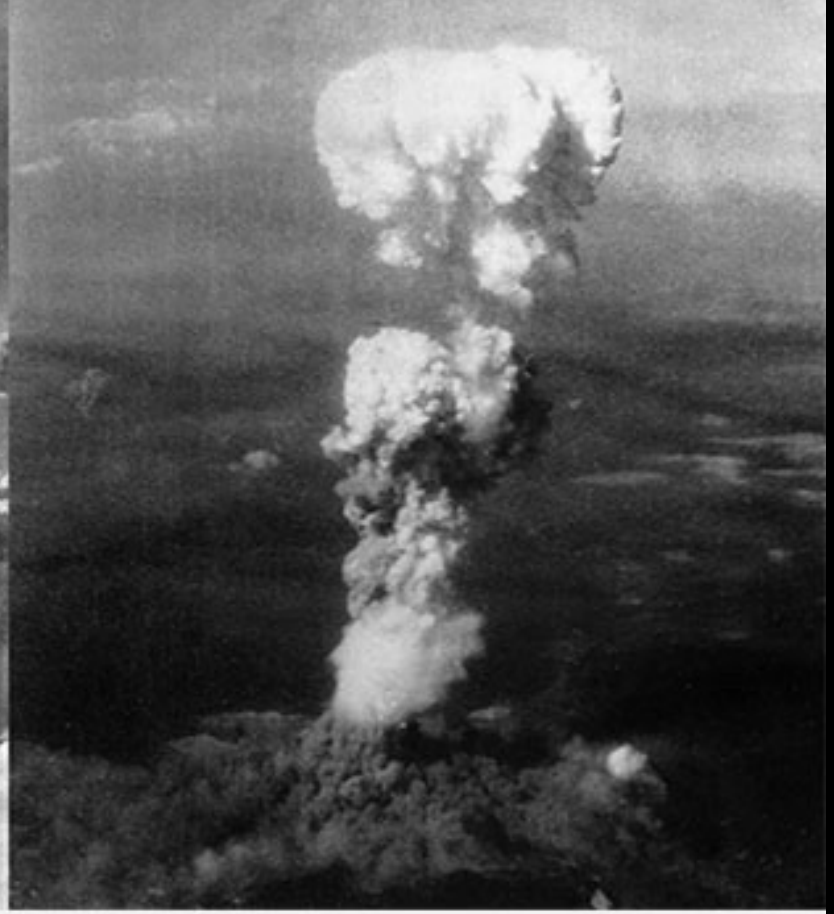
Meeting subscription fees from Kite Gilead and Novartis

Some Historical Landmarks

Allogeneic hematopoietic cell transplantation


BACK
TO THE FUTURE
TM





Nagasaki

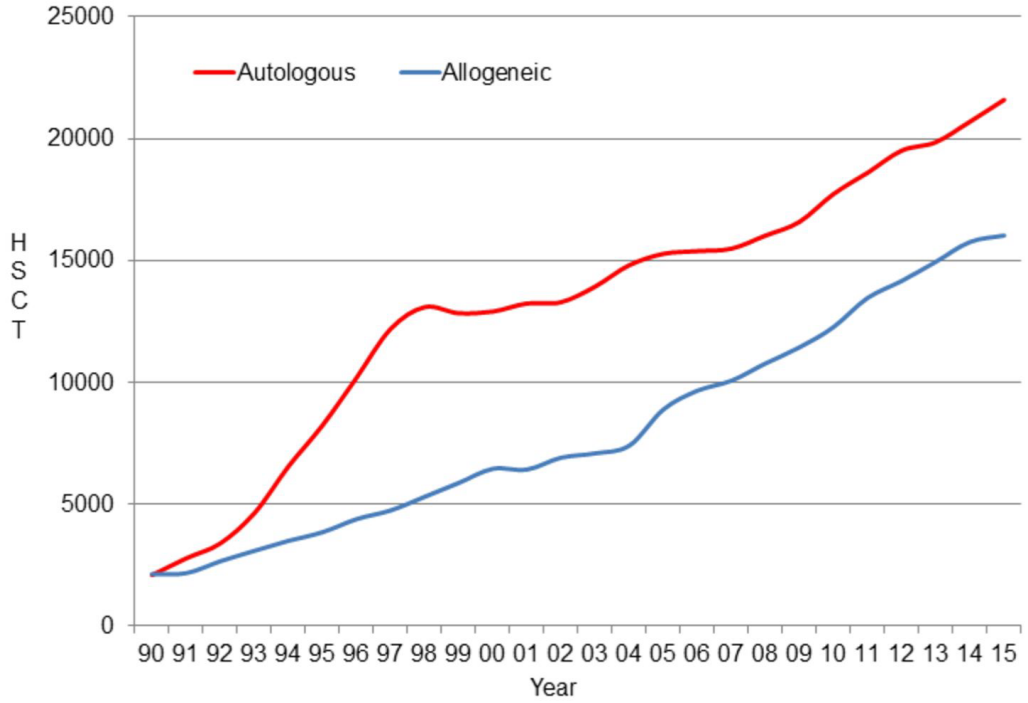
Hiroshima

Human Marrow Grafts 1958-68

Diseases	# Patients			
	Total	Graft Failure	GVHD	Alive
Aplastic anemia	73	66	5	0
Hematologic malignancies	115	56	33	0
Immunodeficiencies	15	3	9	3
Total	203	125	47	3

Bortin, Transpl 9: 571, 1970

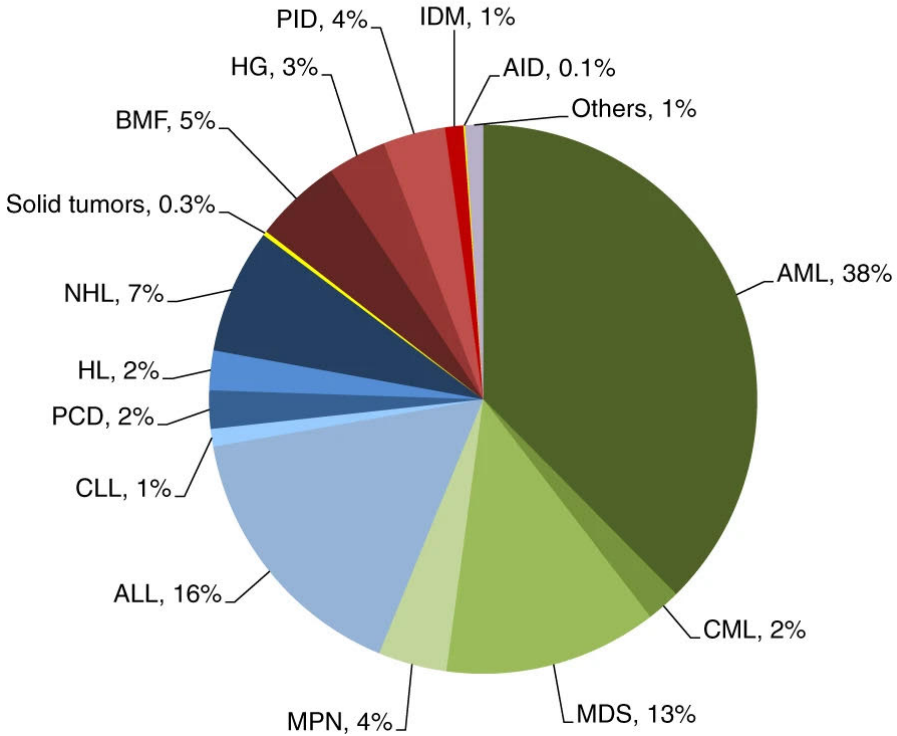
HCT Activity in Europe since 1990



Helen Baldomero
2013 Activity Survey

Allogeneic HCT Activity in Europe

Main indications



Passweg et al. *BMT* 2020

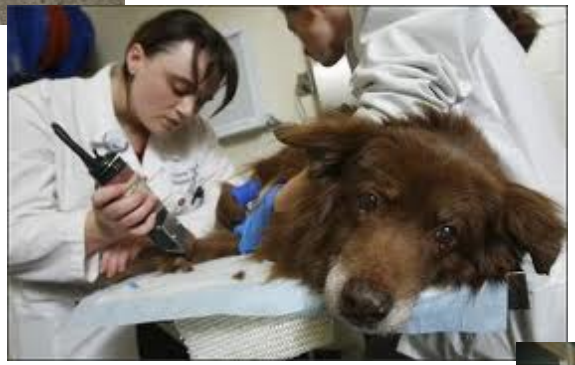
Allogeneic hematopoietic cell transplantation

Hematological diseases

- Immunotherapy: recognition of tumor cells by allogeneic immune cells
- Diseased bone marrow replaced by healthy bone marrow
- After conditioning regimen (chemotherapy, irradiation, immunosuppressive therapies)
- Only curative treatment for:
  - many hematological malignancies (refractory, relapse)
  - Bone marrow or immune system deficient diseases

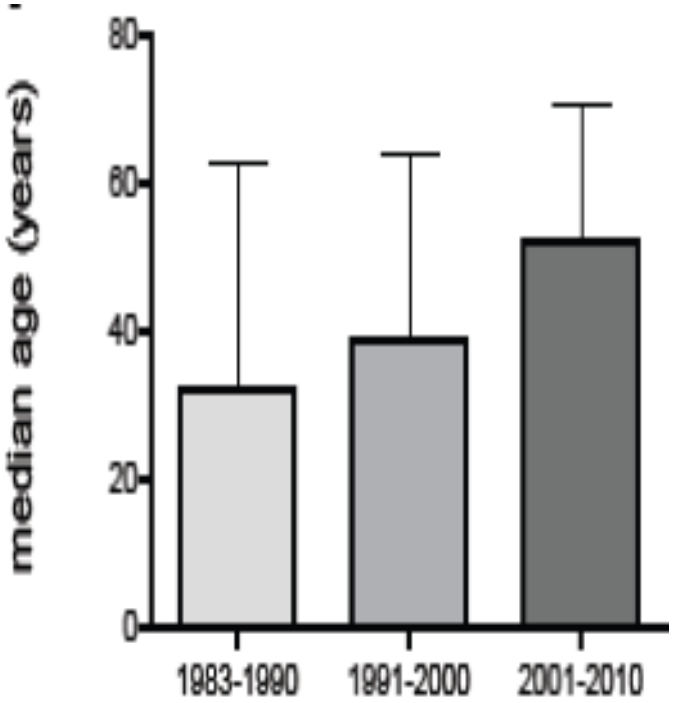
Why is transplant activity increasing?

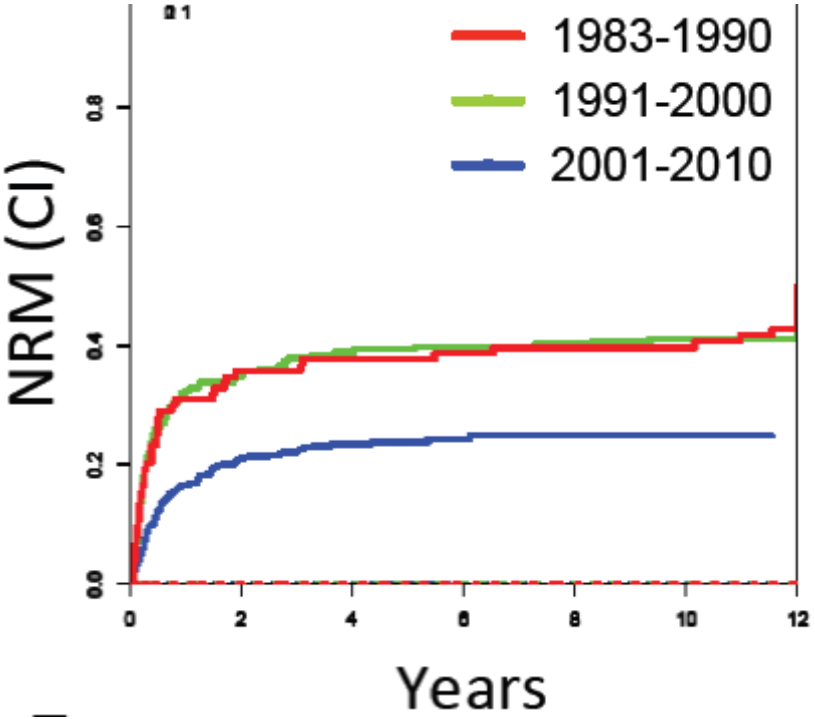
Some Historical Landmarks



Seattle – Fred Hutch BMT center

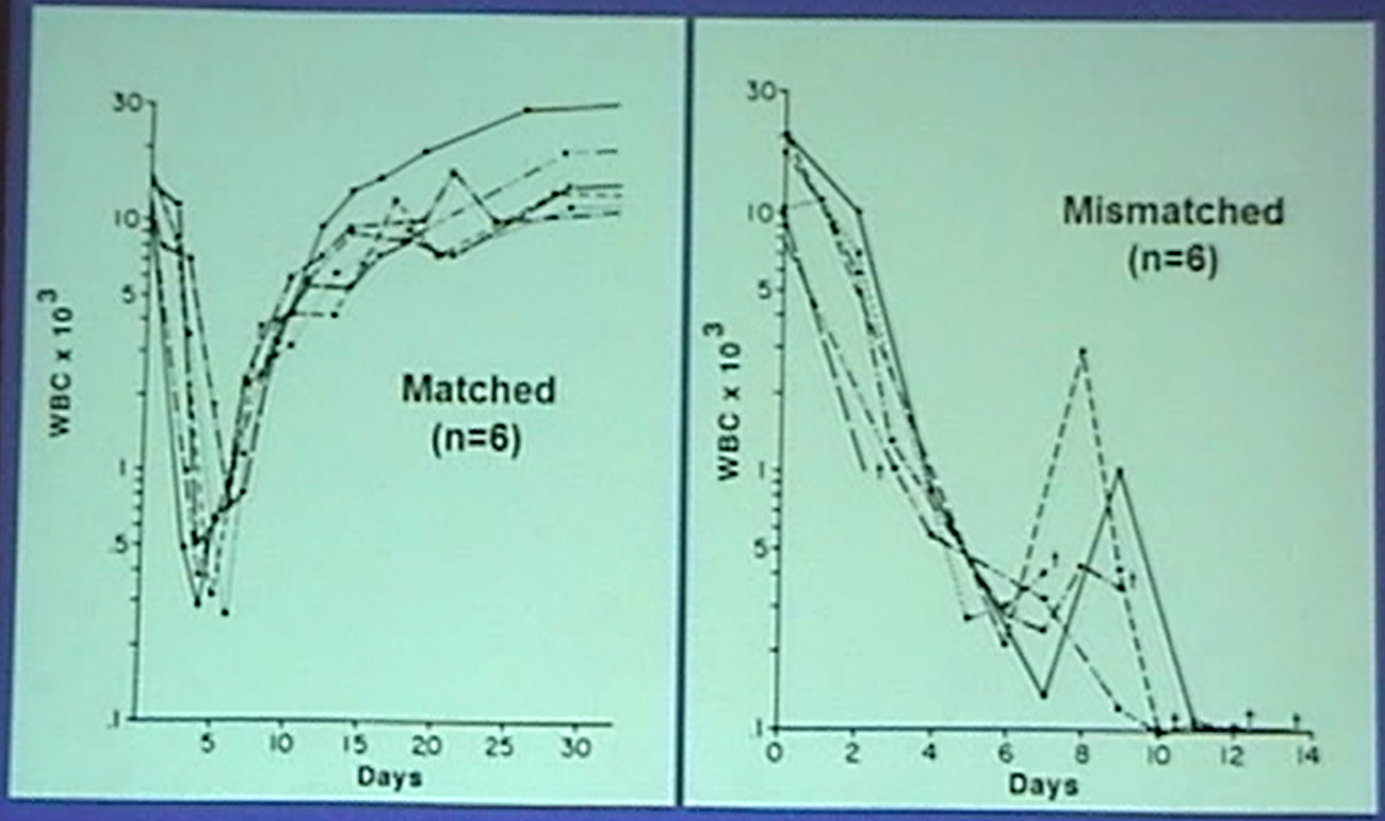
Reduced NRM after allogeneic HCT over the past decades





Malard et al. *BBMT 2014*

1140 cGy TBI + Littermate Marrow



Engraftment according to HLA-match

Epstein, et al. Transpl 6: 45, 1968

The New England
Journal of Medicine

Volume 313 SEPTEMBER 26, 1985 Number 13

MARROW TRANSPLANTATION FROM RELATED DONORS OTHER THAN HLA-IDENTICAL SIBLINGS

PATRICK G. BEATTY, M.D., PH.D., REGINALD A. CLIFT, F.I.M.L.S., ERIC M. MICKELSON, BRENDA B. NISPEROS, NANCY FLOURNOY, PH.D., PAUL J. MARTIN, M.D., JEAN E. SANDERS, M.D., PATRICIA STEWART, M.D., C. DEAN BUCKNER, M.D., RAINER STORB, M.D., E. DONNALL THOMAS, M.D., AND JOHN A. HANSEN, M.D.

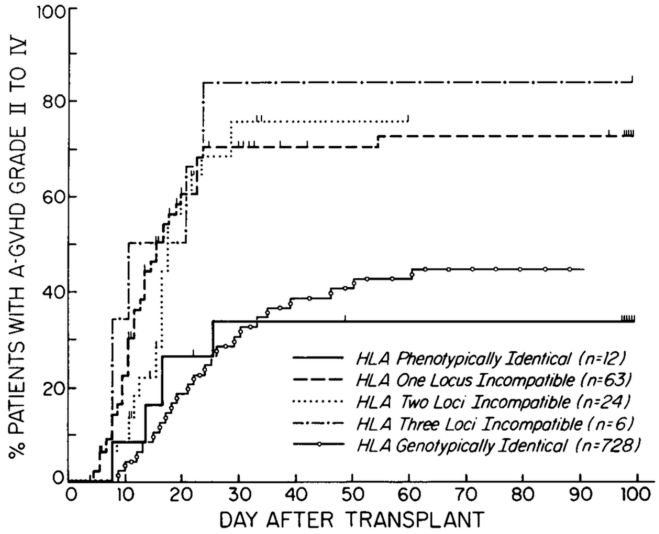


Figure 2. Risk of Acute Graft versus Host Disease (A-GVHD) in Relation to the Number of Disparate Loci.

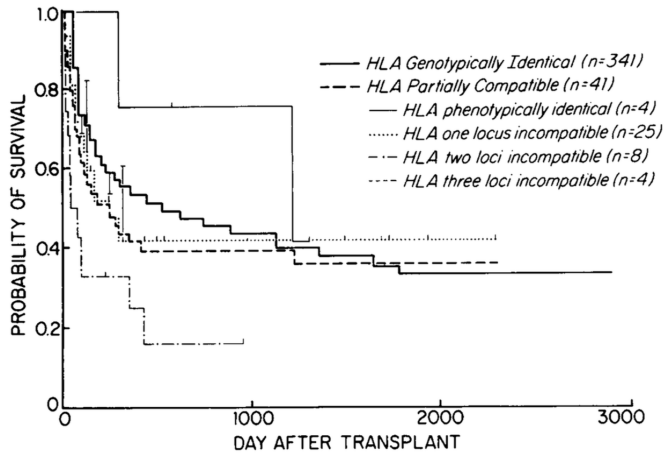
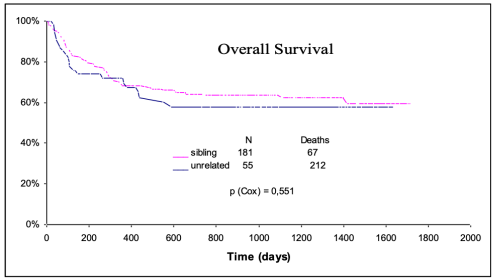
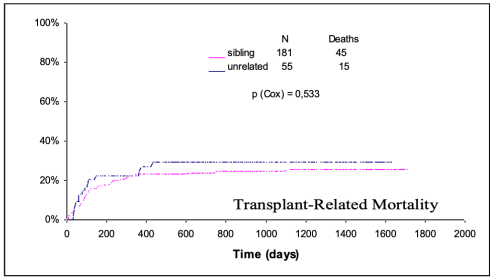
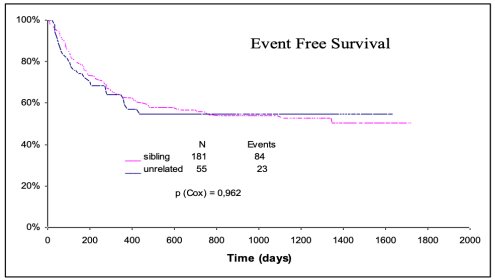


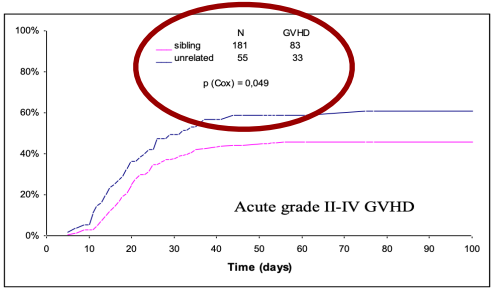
Figure 4. Probability of Survival in Patients with Acute Leukemia Undergoing Transplantation during Remission.

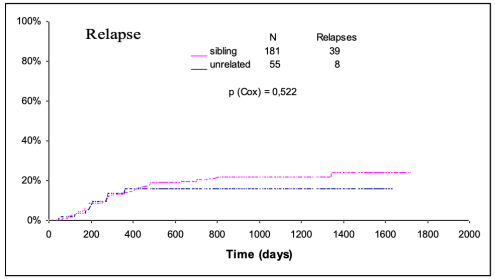
HLA-identical sibling vs 10/10 HLA-matched unrelated

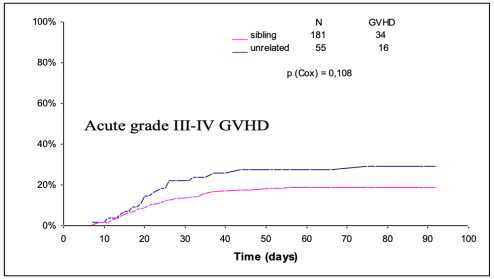












Yakoub-Agha et al. JCO 2006

Greffe de CSH : quel donneur ?

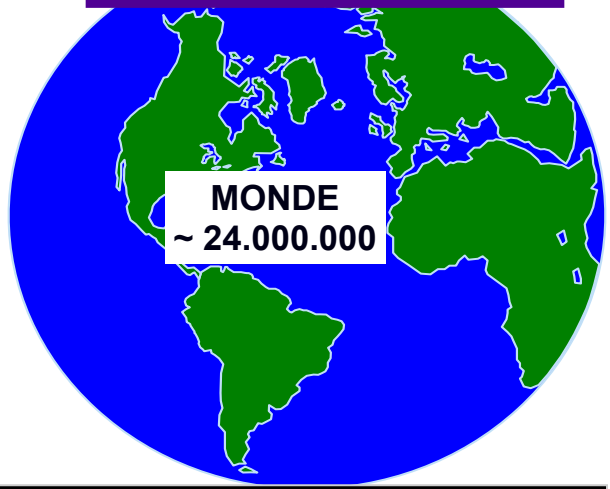
L'allogreffe familiale :

Donneur de fratrie HLA identique = meilleurs résultats

Disponibilité = **30%** des cas

30% des patients nécessitant une allogreffe n'ont pas de donneurs !!

Donneurs volontaires non apparentés dans 40 registres



40% = probabilité de trouver un donneur HLA 10/10 (A, B, Cw, DR, DQ identique)

Agence de la Biomédecine (DIU 2013)
Bone Marrow Donnors Worldwide (2015)

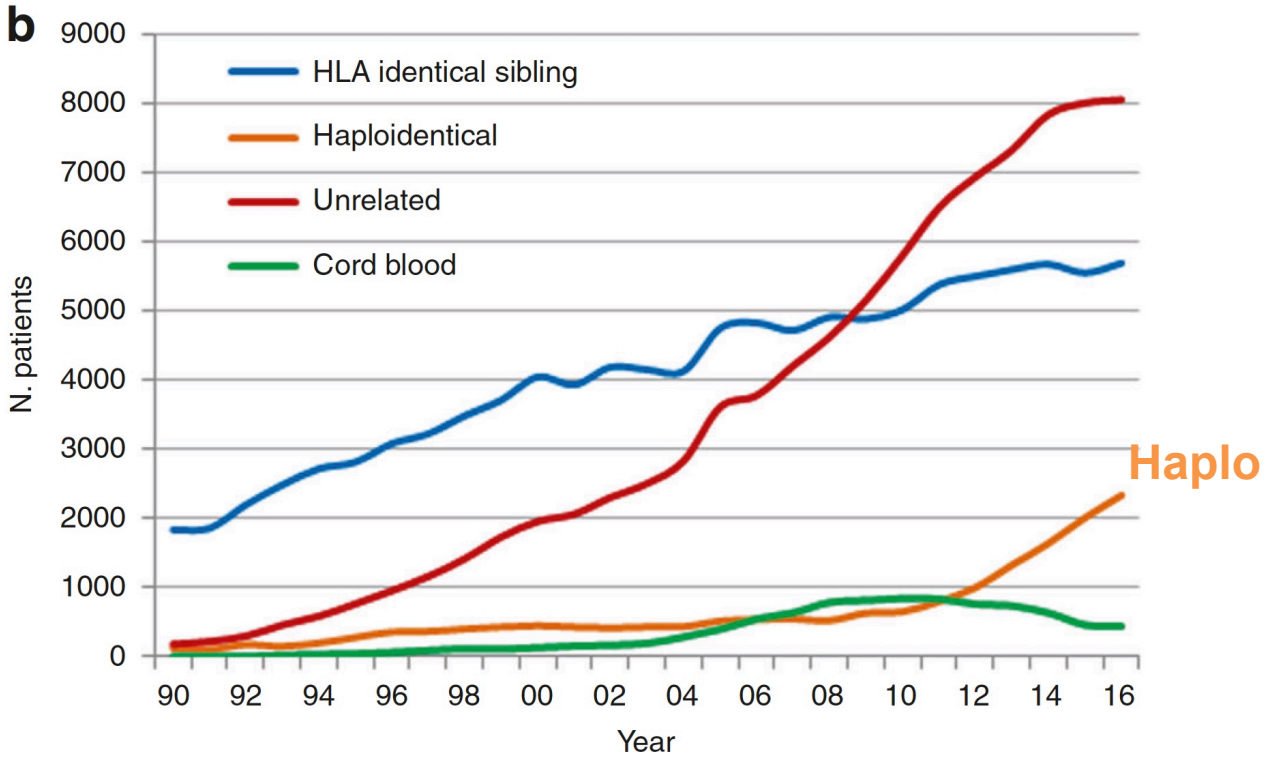
Haploidentical Transplants: Ablative Conditioning

Allograft	Center	Reference	% Rejection	% III/IV GvHD	NRM (1 yr)
T-replete	Royal Marsden	Powles, 1983	**29**	**80**	**54**
	Seattle	Beatty, 1985	**21**	**63**	
T-depleted *Ex vivo*	Perugia	Aversa, 2005	**9**	2	**37**
	Tubingen St. Judes	Lang, 2004	**17**	2	**29**

So in the late 90's…

- Reduced overall mortality and toxicity (RIC and RTC)
  - expanded the transplant option to those patients who are ineligible for MAC.
- Reduced/abrogated GVHD
- A donor for all patients is needed

Allogeneic HCT Activity in Europe since 1990



Passweg JR et al. *Bone Marrow Transplant 2017*

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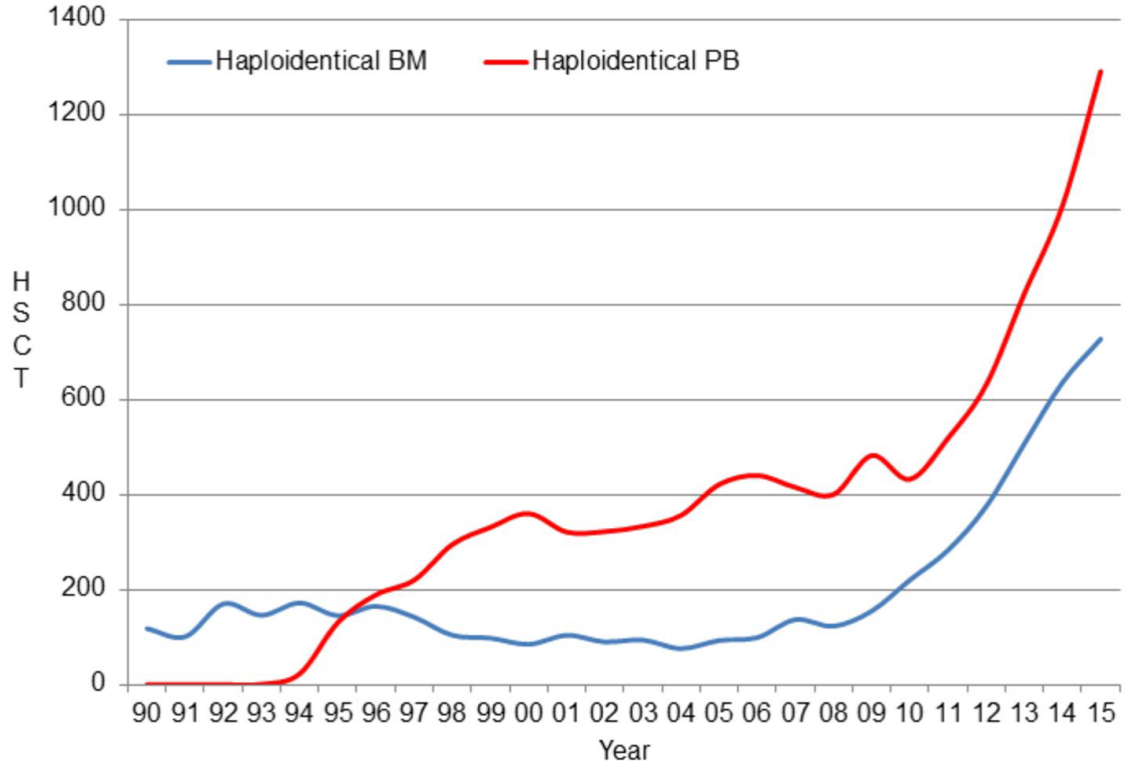

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Haploidentical HCT – Baltimore NMAC
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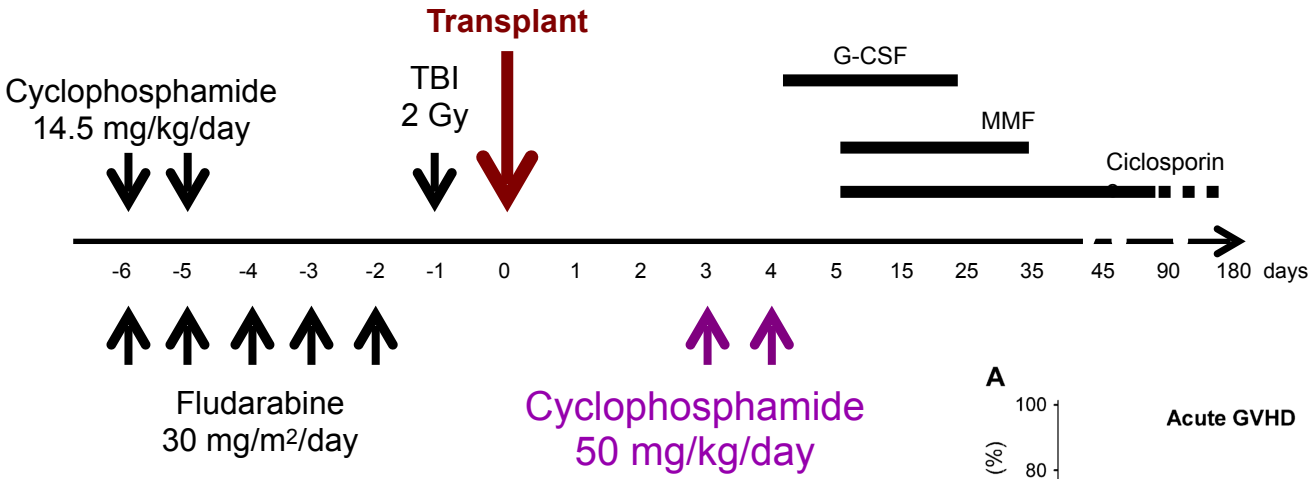
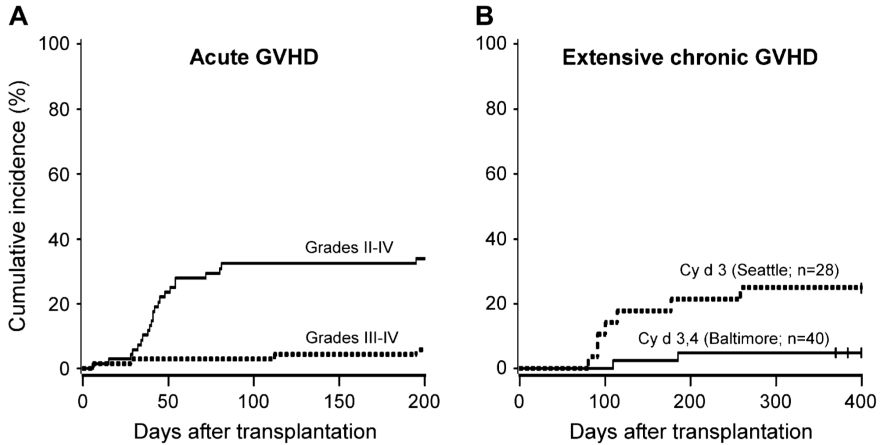
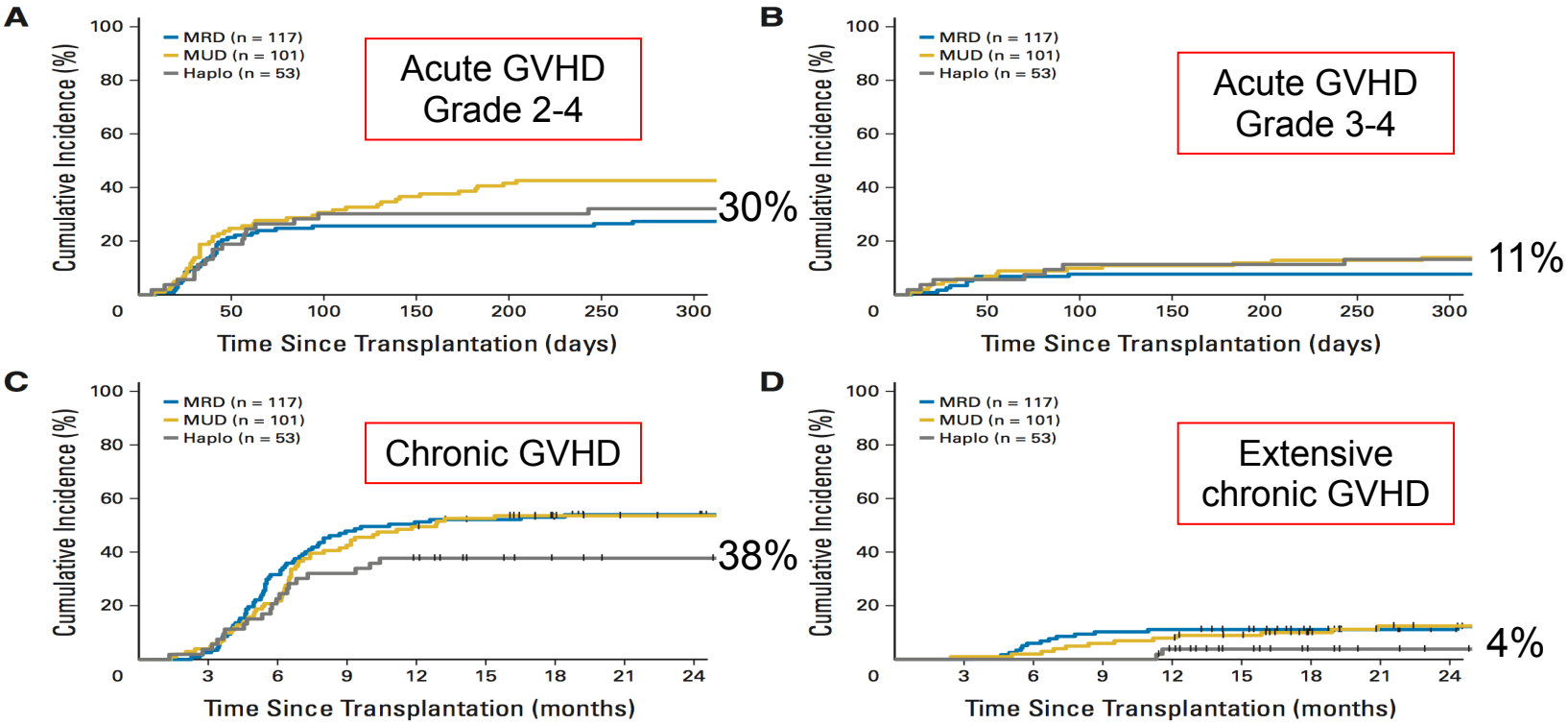




Luznik et al. BBMT 2008; 14:641-650

Haplo with PT-Cy vs. HLA-identical HSCT



Bashey et al. JCO 2013; 31:1310-1316

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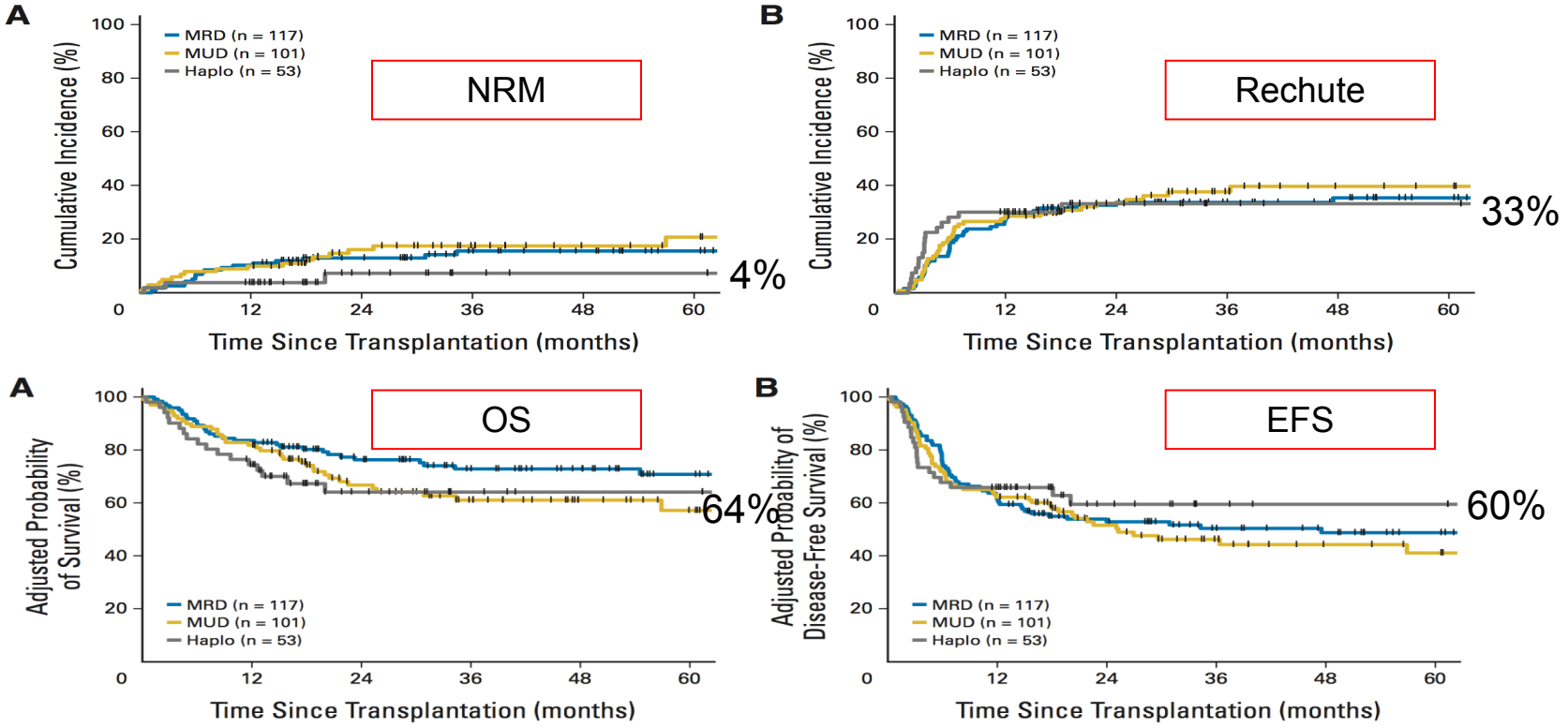

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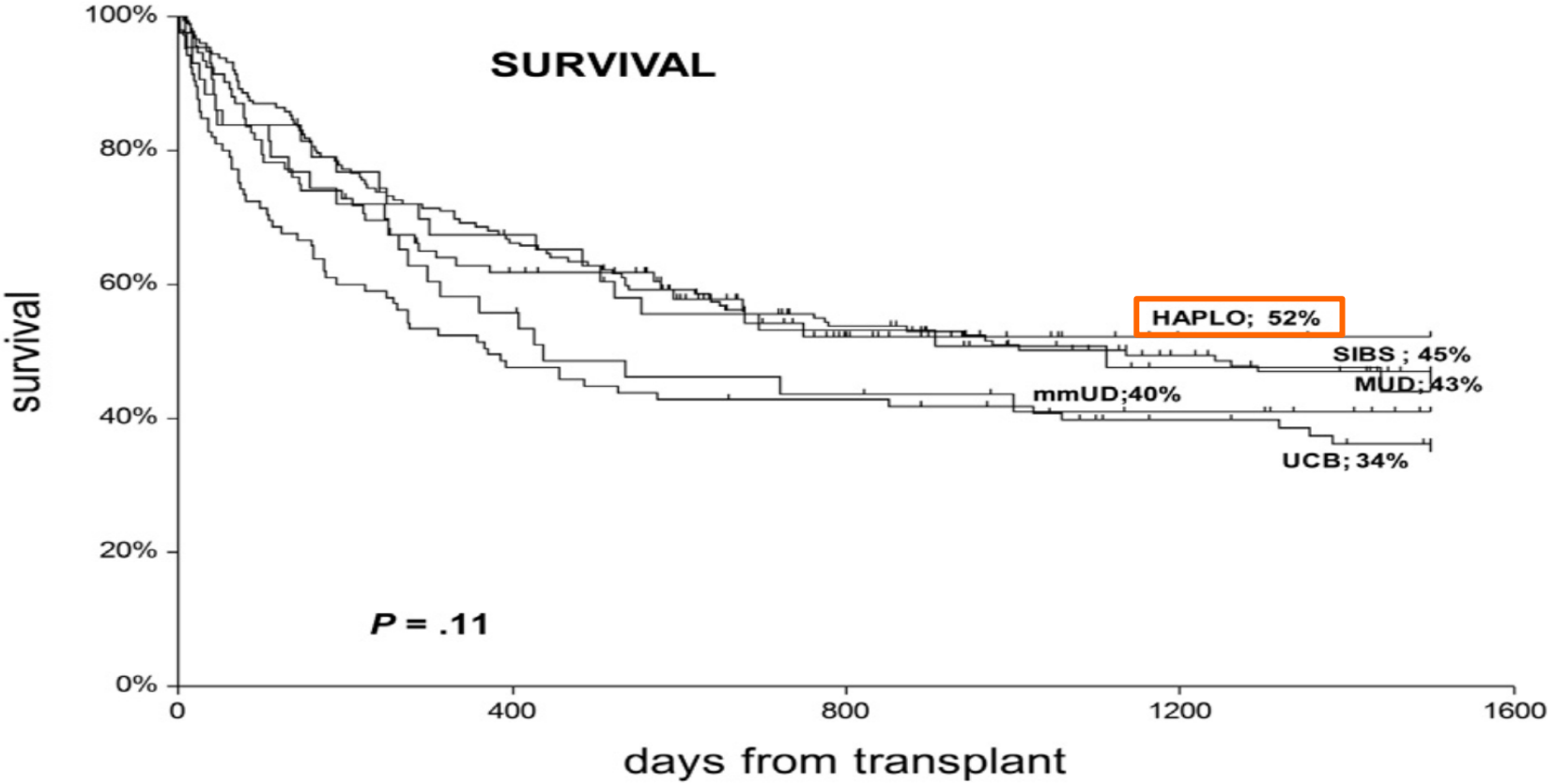
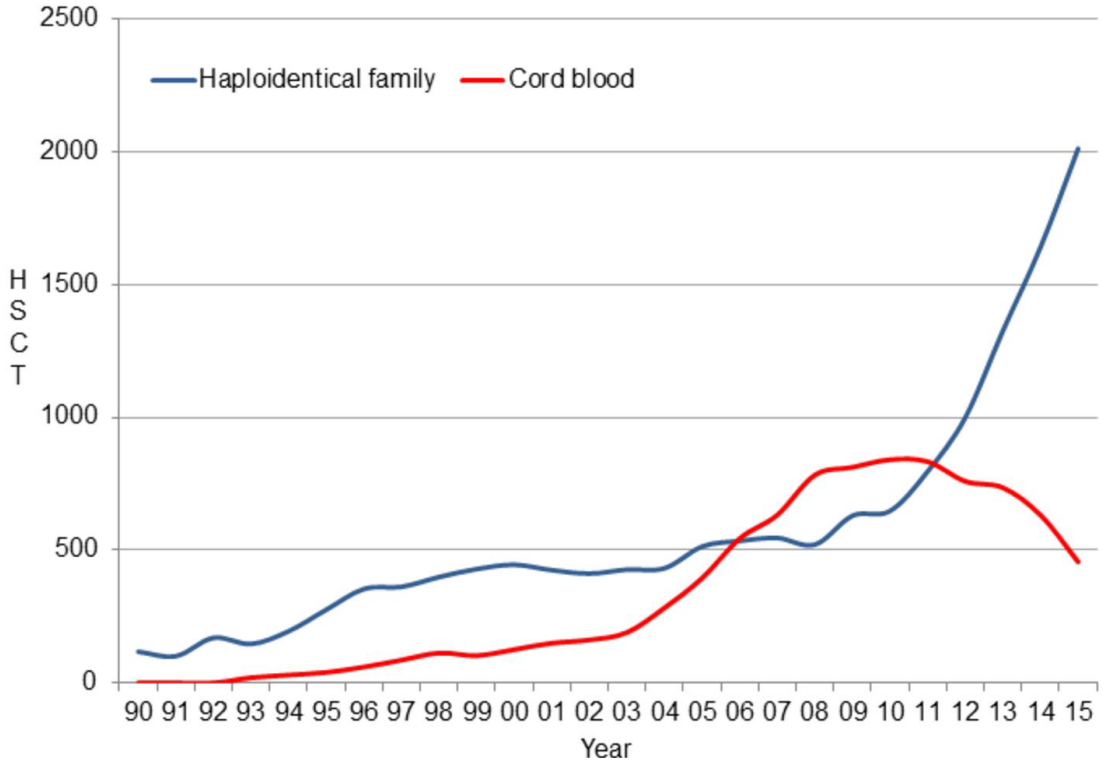


Raiola AM et al. BBMT 2014; 20:1573-79

Haploidentical HCT

A donor for all patients
deemed fit and eligible for HSCT

Allogeneic HCT Activity in Europe since 1990



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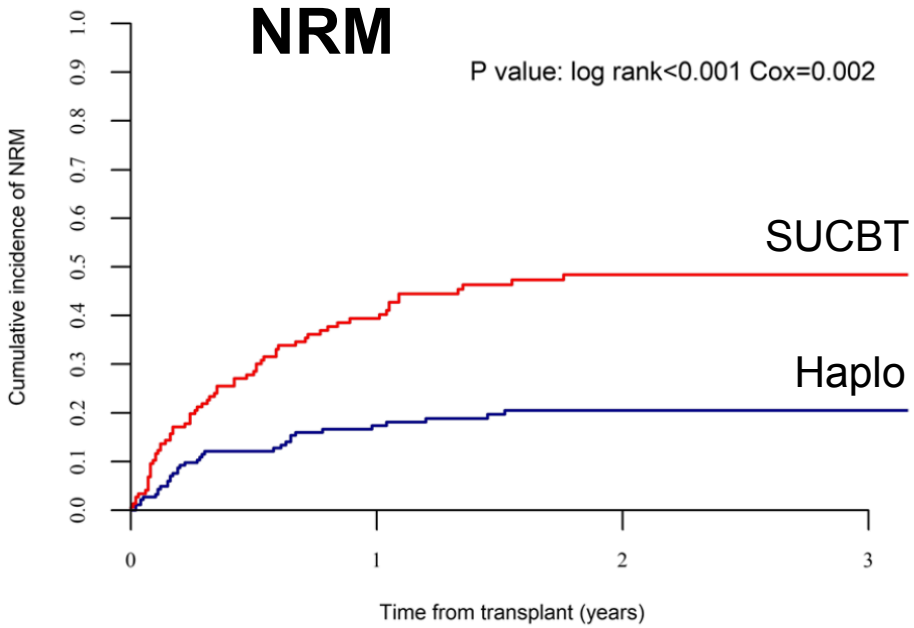
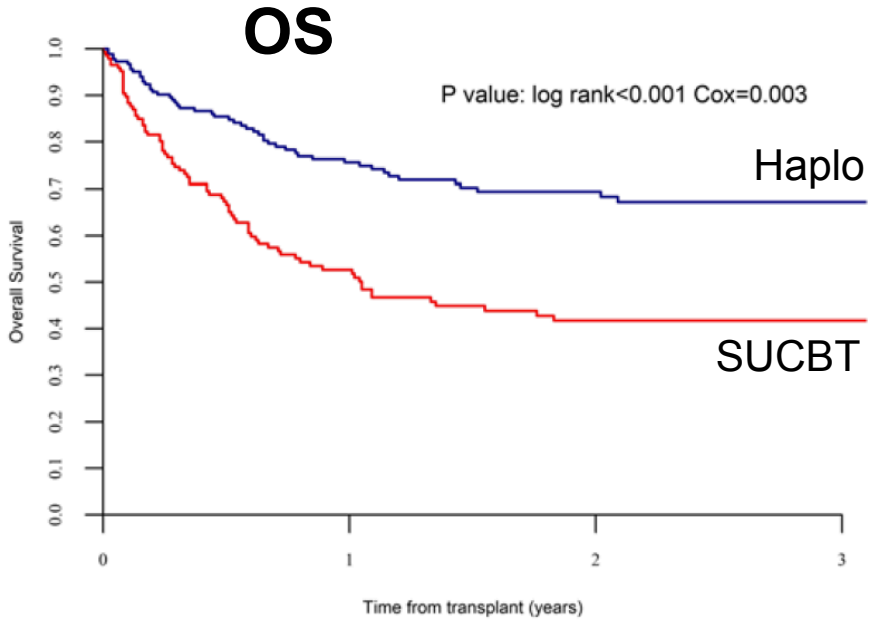
2013 Activity Survey

Haplo vs. single cord blood for AML

Thiotepa – Busulfan – Fludarabine conditioning regimen (TBF)





Haplo = 186 patients

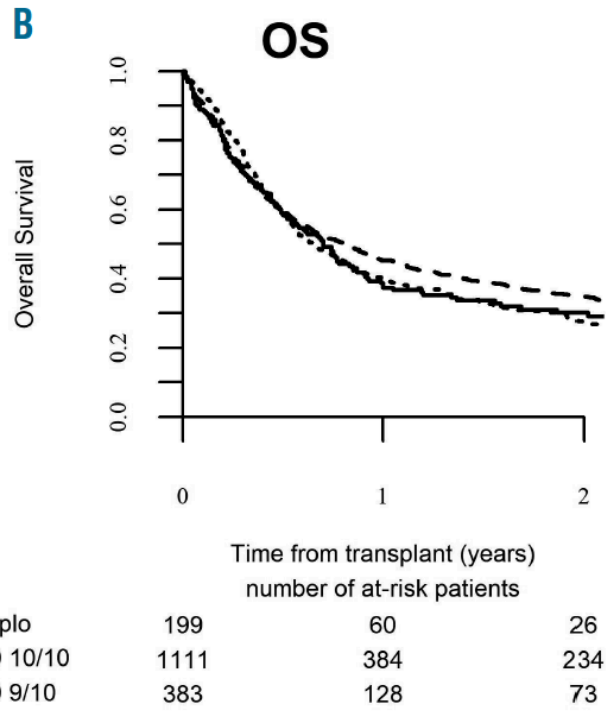
SUCBT = 147 patients

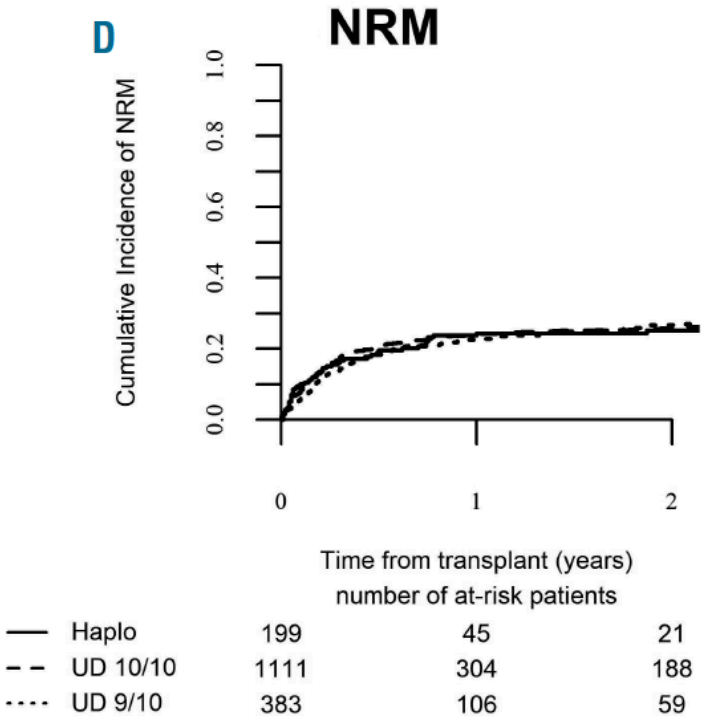
Giannotti F et al. Journal of Hematology & Oncology 2018

Haplo vs. unrelated donor HSCT

relapsed/refractory AML

N= 1578 patients





Brissot E *et al. Haematologica* 2019

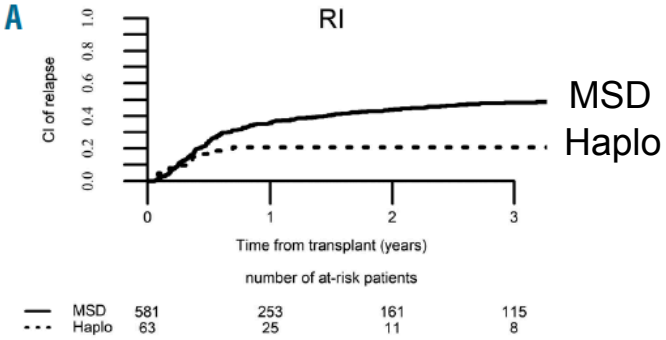
Haplo vs. HLA-matched siblings HSCT

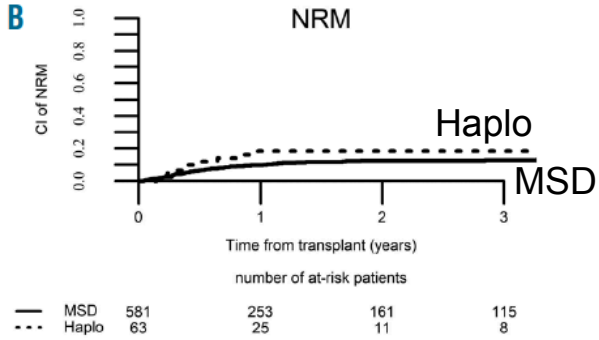
high-risk AML in CR1

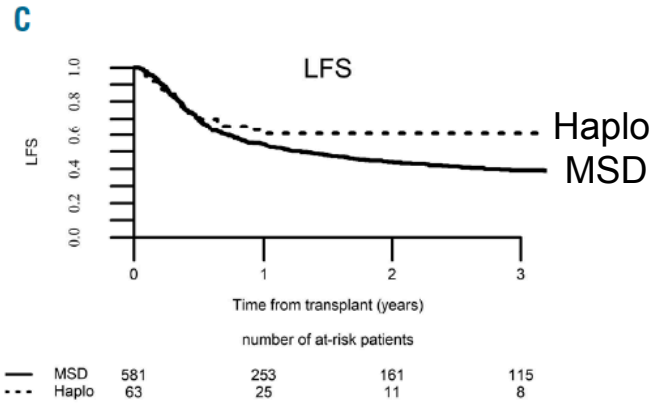
N= 644 patients

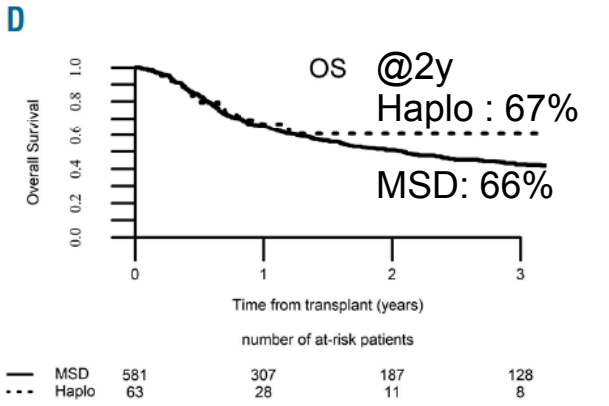
- Haplo = 63
- MSD = 581

PT-Cy = 74% haplo patients





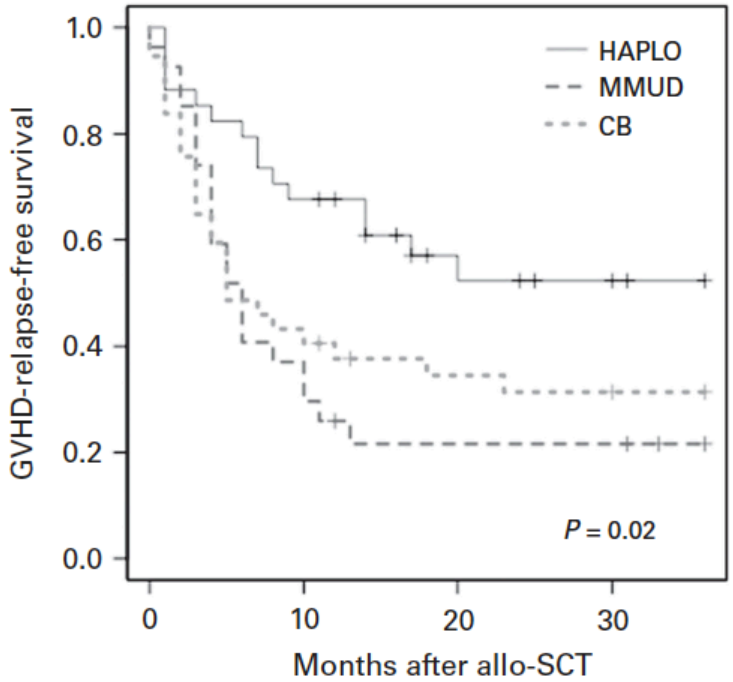




Salvatore D *et al. Haematologica* 2018

Haplo HSCT with PT-Cy – SFGM-TC study

Relapsed and refractory Hodgkin lymphoma



Gauthier J et al. *BMT* 2017

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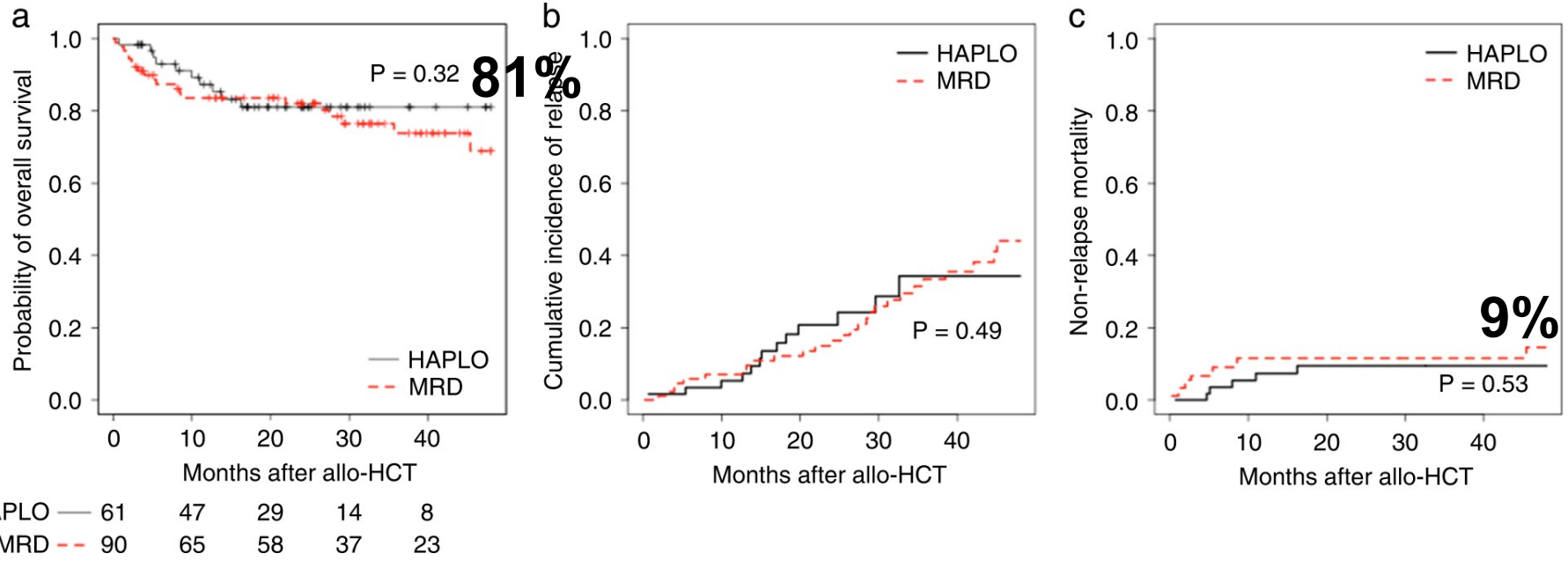
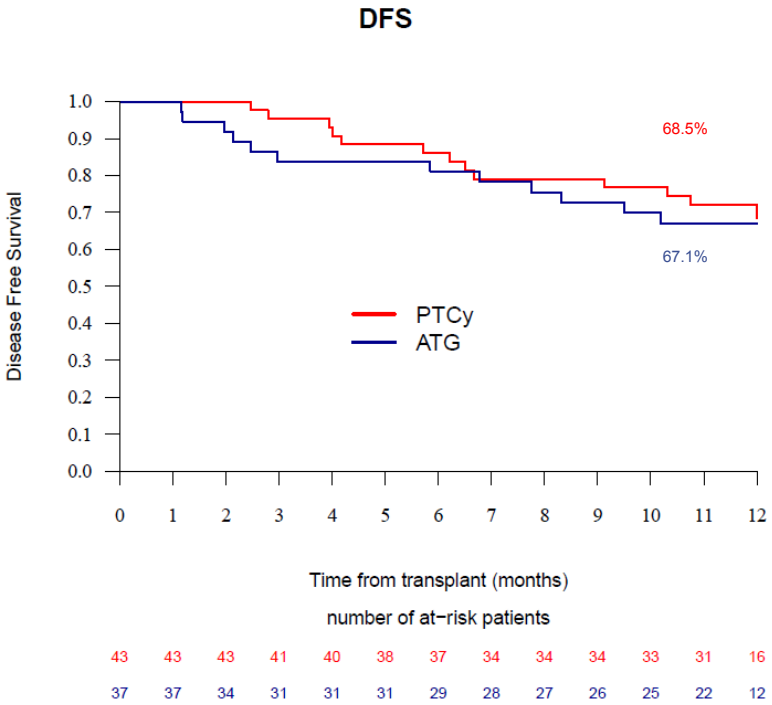
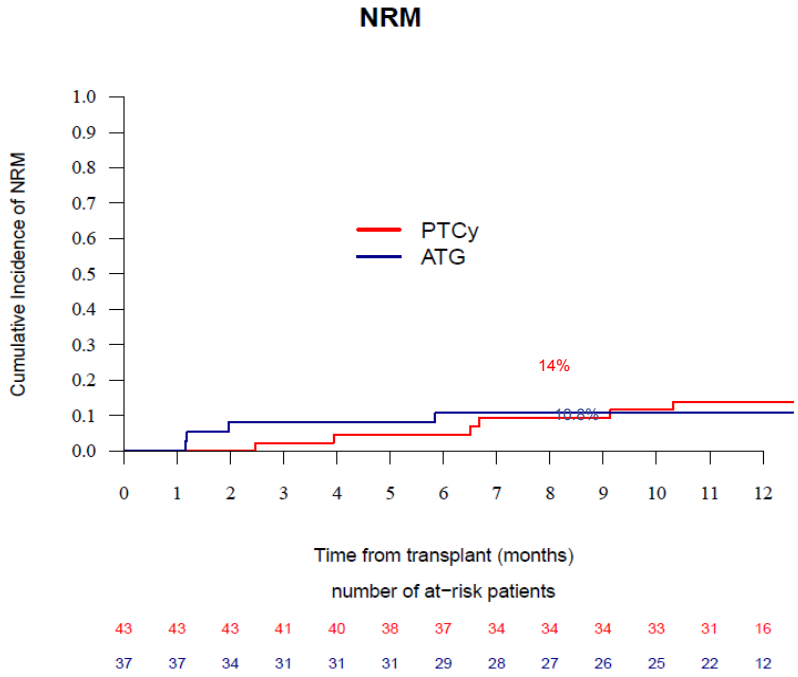


Gauthier J et al. *BMT* 2018

PT-Cy versus ATG

RIC – identical siblings or 10/10 unrelated donor





2021 Van Bekkum Award

Brissot E. et al. Abstract GS2-2, EBMT 2021

How can we improve the outcomes of patients undergoing allogeneic HSCT ?

- Negative MRD before transplant
- Donor selection
- Stem cells source
- Conditioning regimen
- GVHD prophylaxis
- Post-transplant immuno-modulation
- Maintenance strategies
- Supportive care, QoL and monitoring of complications
- JACIE

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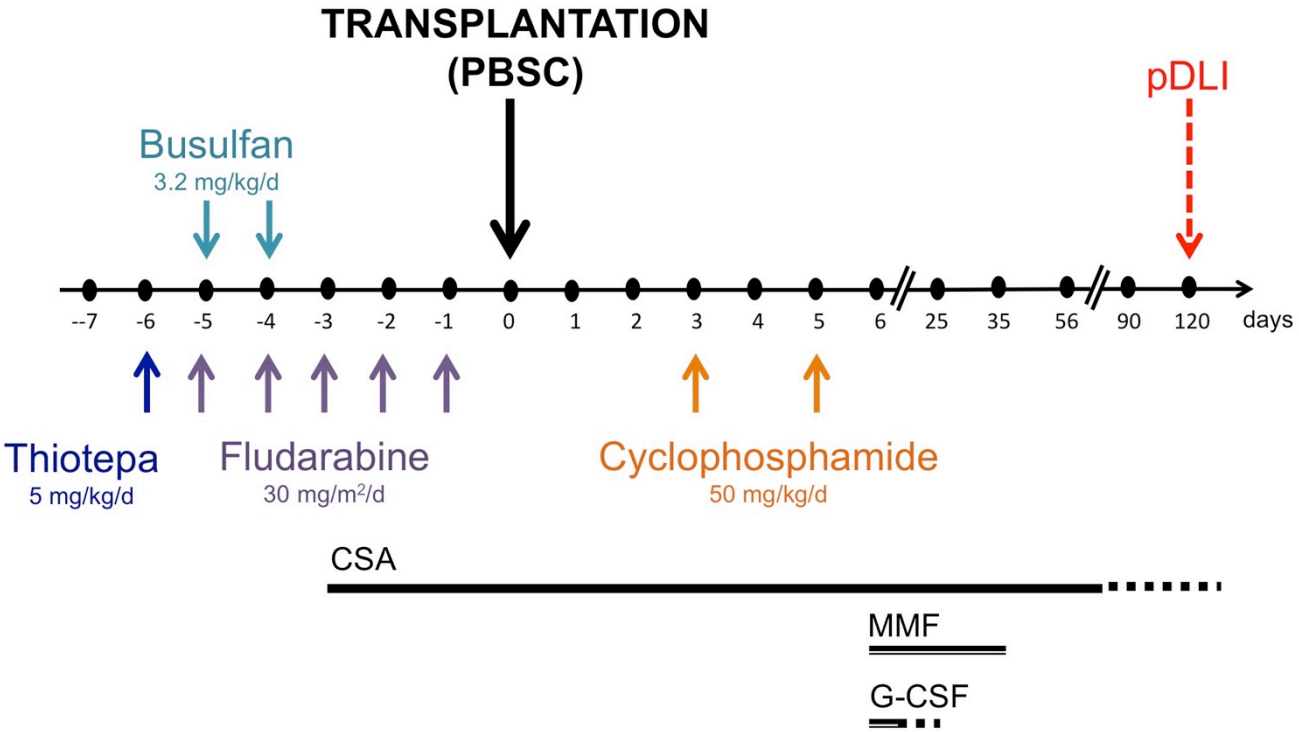
TBF conditioning regimen in Haplo HSCT

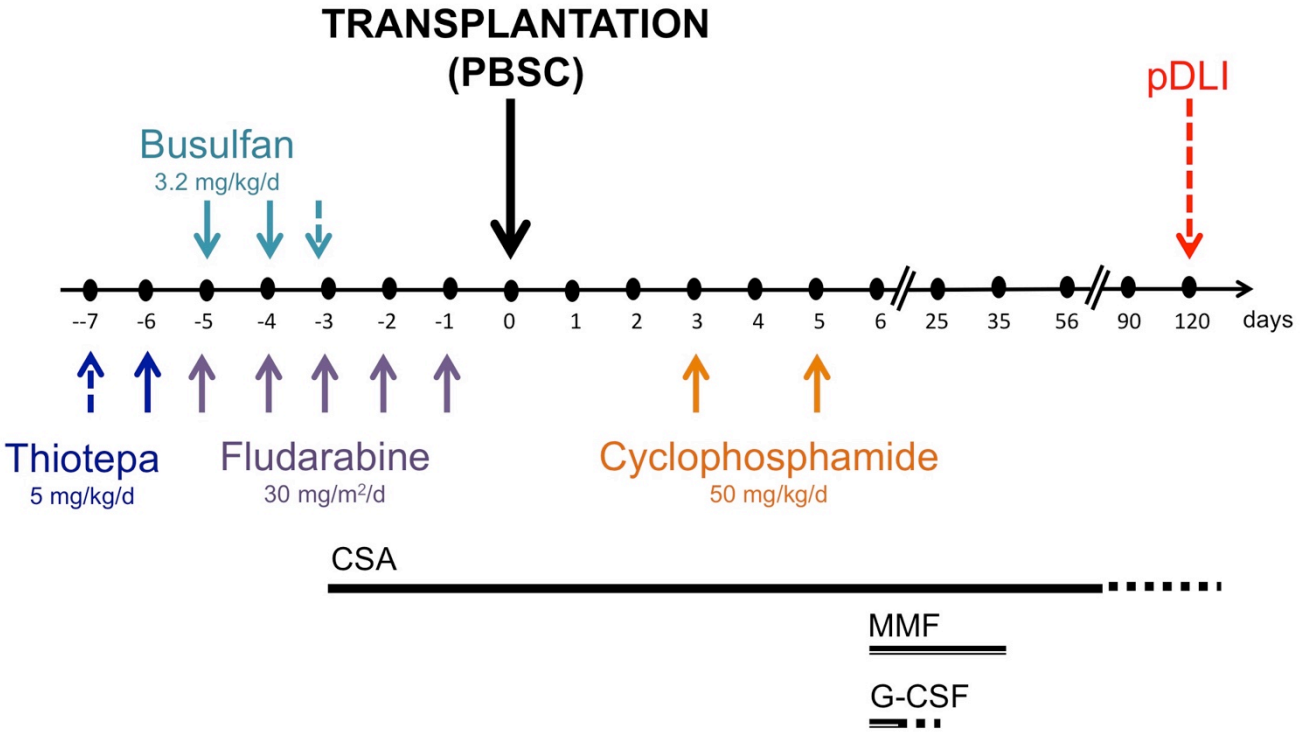
RIC



Duléry R et al. *BBMT* 2019

TBF conditioning regimen in Haplo HSCT

MAC



Duléry R et al. *BBMT* 2019

Haploidentical HCT – Baltimore NMAC
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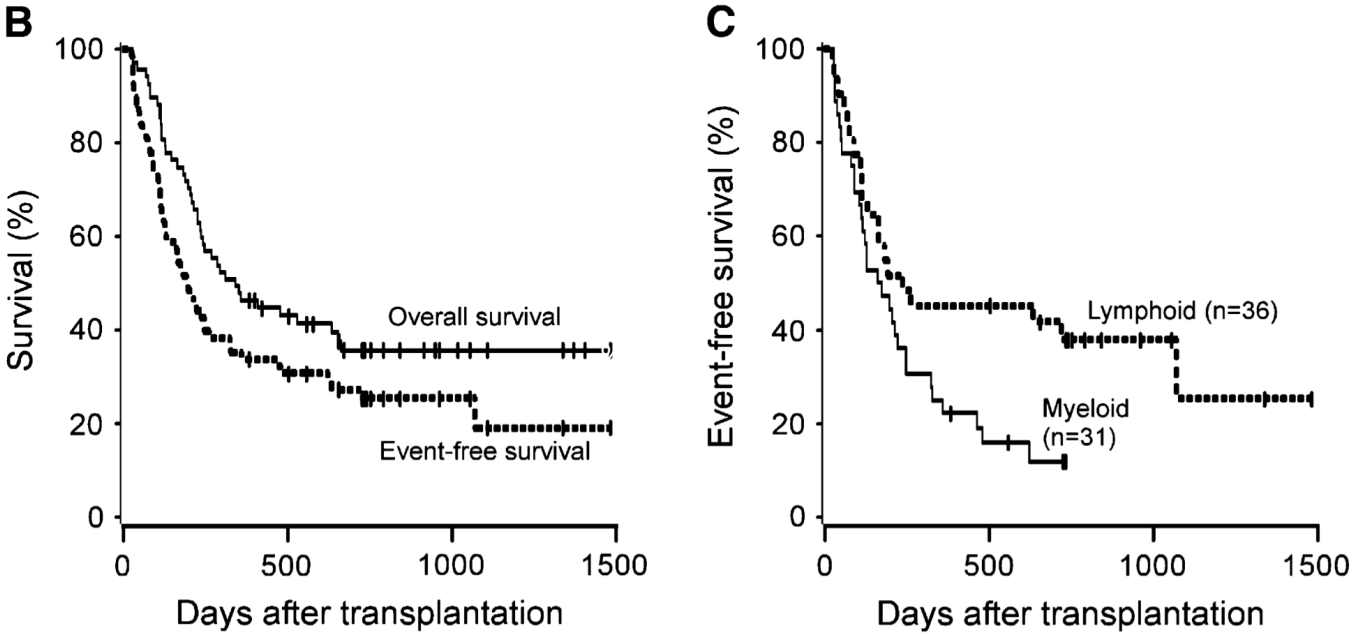


Luznik et al. BBMT 2008; 14:641-650

TBF conditioning regimen in Haplo HSCT

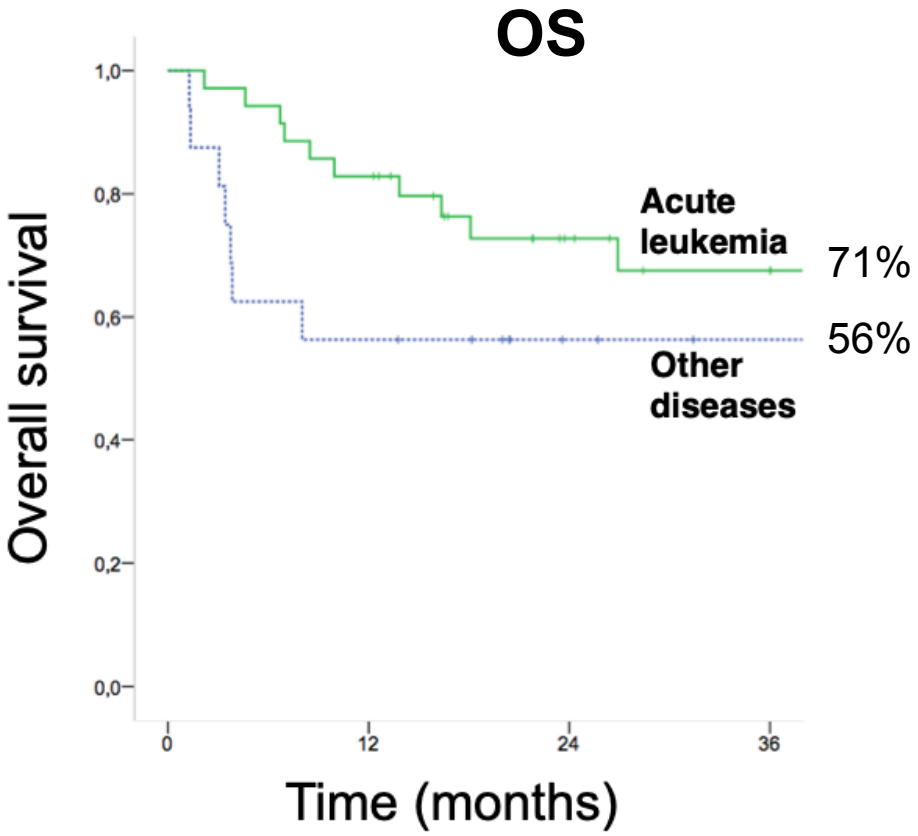
PBSC

N= 51 patients

Median FU: 25 months (12-62)

In acute leukemia patients

- Acute GVHD II-IV: 27%
- 2-y Chronic GVHD: 27%
- 2-y NRM: 15%
- 2-y LFS: 63%



Duléry R et al. *BBMT* 2019

How to move forward?

Haplo technique-related issues:

- 1 or 2 days of Cy? Reduced doses?
- BM vs. PBSC?

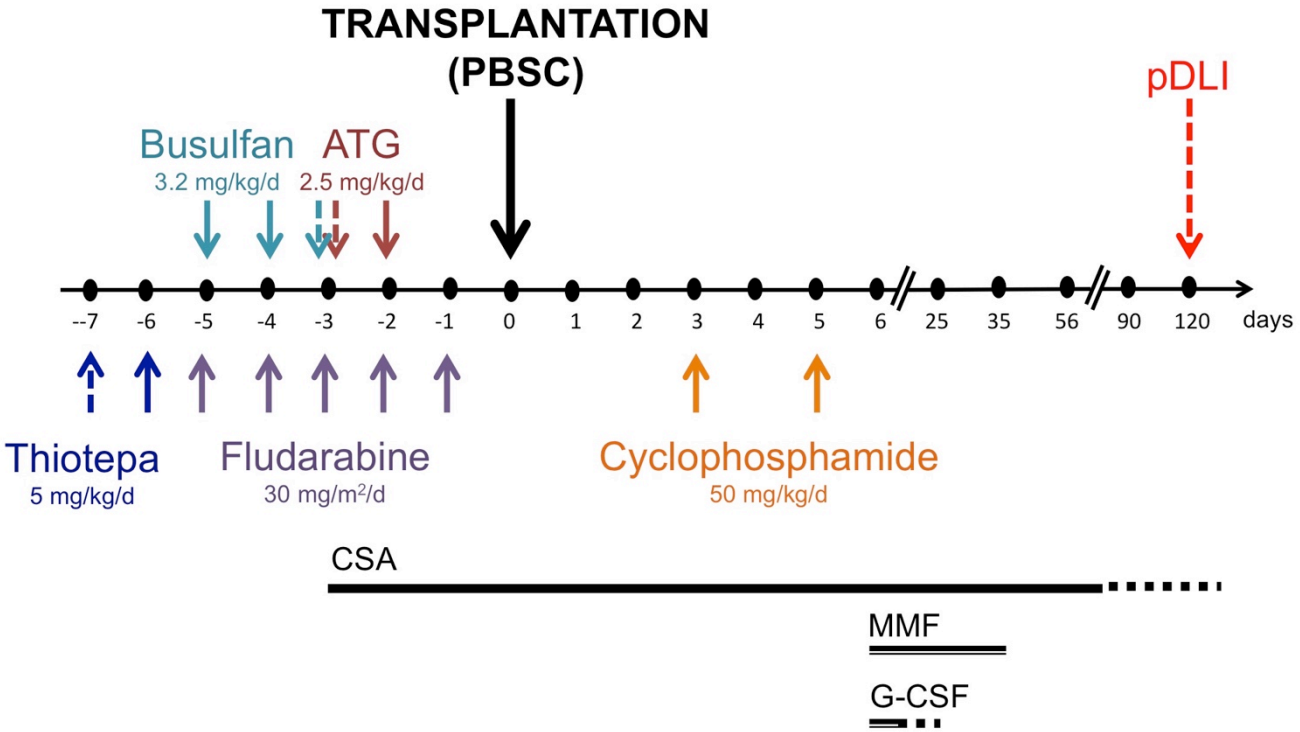
How to move forward?

Haplo technique-related issues:

- 1 or 2 days of Cy? Reduced doses?
- BM vs. PBSC?

Add ATG to Cy…

TBF conditioning regimen in Haplo HSCT
with ATG

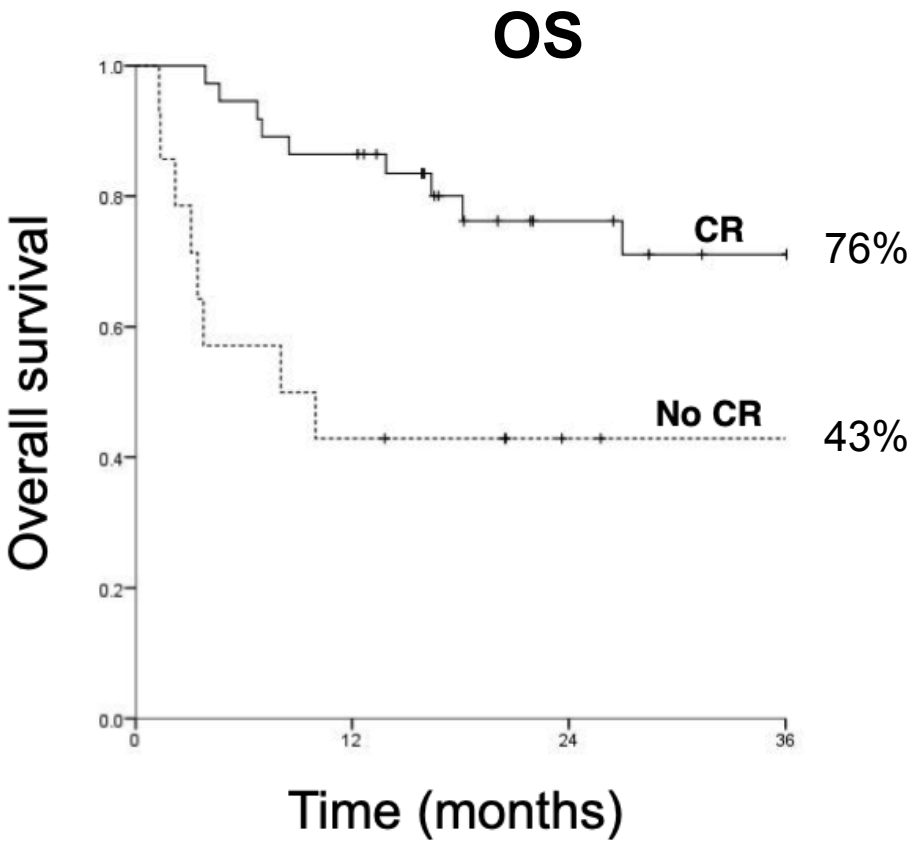


Duléry R et al. *BBMT* 2019

TBF conditioning regimen in Haplo HSCT

PBSC

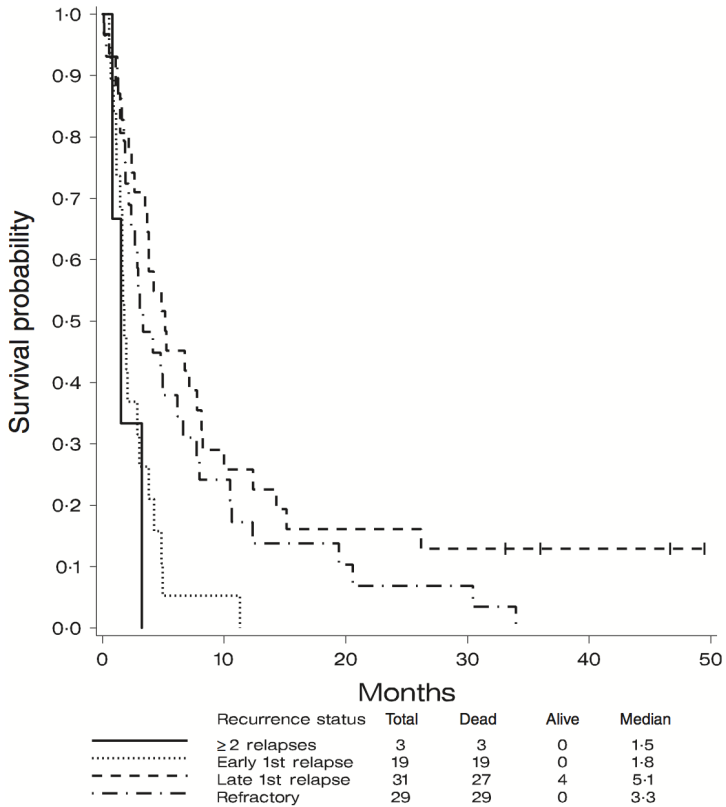
- ATG seems effective for reducing the incidence of acute grade II-IV GVHD (p=0.03)
- The addition of ATG did not increase the risk of infection or NRM
- **Using PBSC and ATG prophylaxis**
  - **Acute GVHD II-IV: 16%**
  - **Acute GVHD III-IV: 10%**



Duléry R et al. *BBMT* 2019

Conventional chemotherapy

AML in primary treatment failure



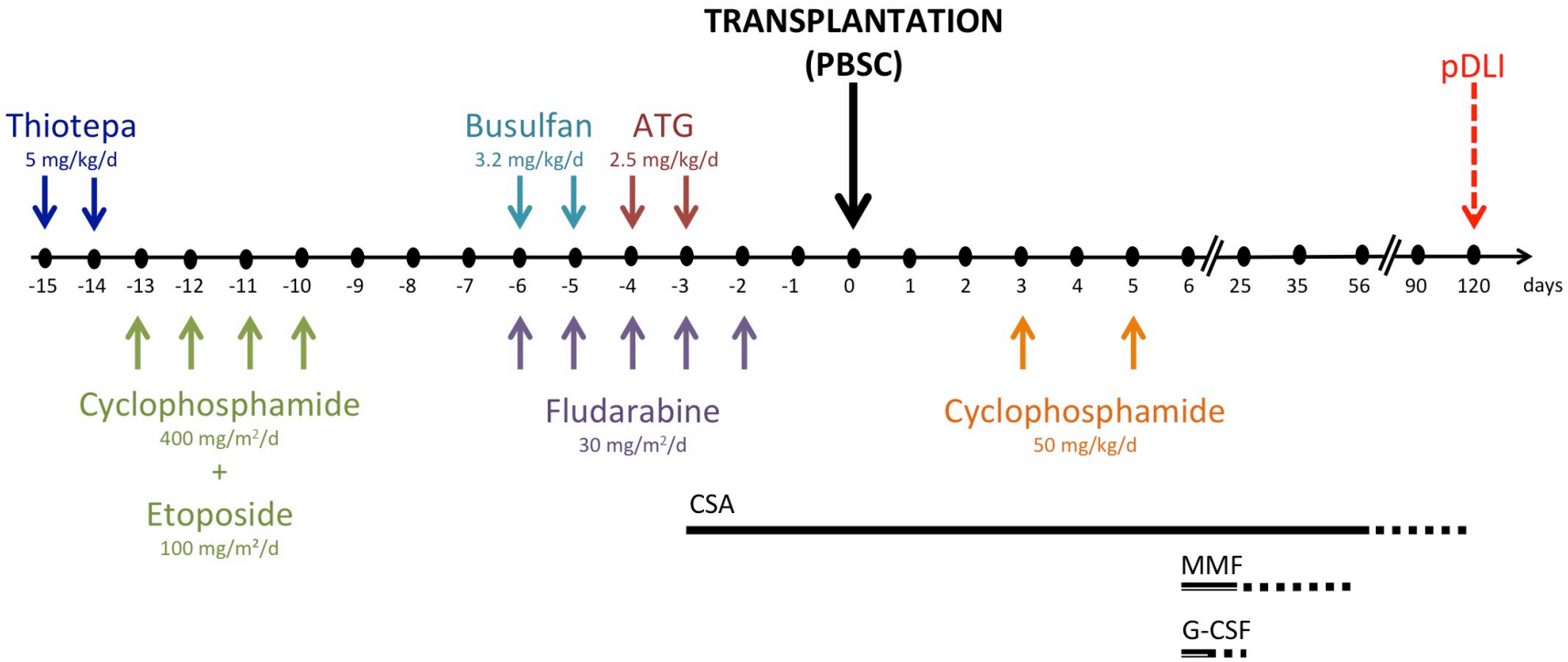
- Chemotherapy alone:
  - AraC
  - Anthracycline
  - Fludarabine
  - Gemtuzumab-ozogamicin

- CR: 10-20%
- 1-year OS: 10%
- Median OS: 4 months

Litzow M et al. *BJH* 2010
Estey EH. et al. *Leukemia* 2000

TEC RIC sequential conditioning regimen

Refractory hematologic malignancies

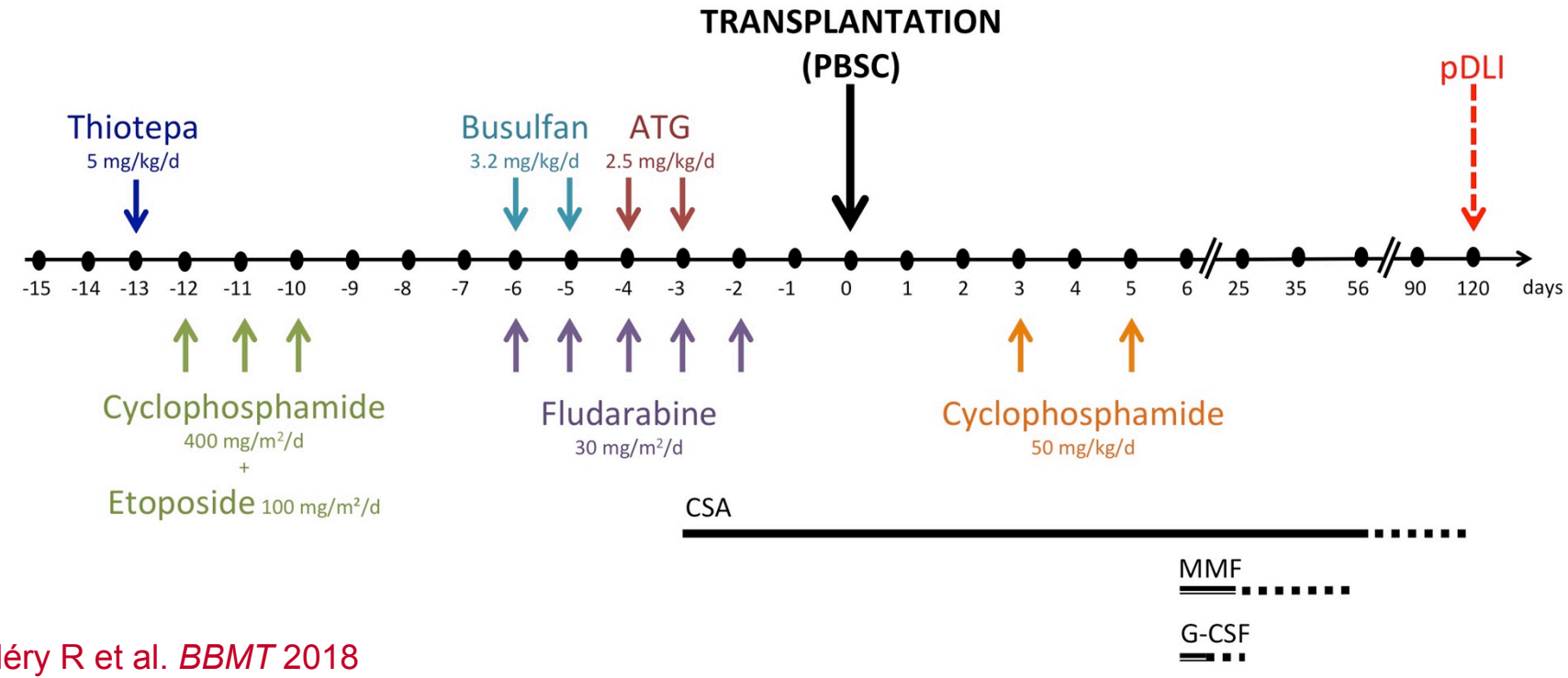


Duléry R et al. *BBMT* 2018

TEC RIC sequential conditioning regimen

Refractory hematologic malignancies

Dose reduction was allowed for patients > 60 years and/or with comorbidities



Duléry R et al. *BBMT* 2018

TEC RIC sequential conditioning regimen

Refractory hematologic malignancies – initial characteristics

	Total (n=72) n (%)	Haplo (n=27) n (%)	MRD (n=16) n (%)	UD (n=25) n (%)	p
AML	44 (61)	17 (63)	9 (56)	18 (62)	NS
ALL	7 (10)	3 (11)	2 (13)	2 (7)	NS
MDS/MPN/CMML	15 (21)	4 (15)	4 (26)	7 (24)	NS
Lymphoma	6 (8)	3 (11)	1 (6)	2 (7)	NS

Among leukemia patients

36 patients had persistent excess of blast

14 patients had positive minimal residual disease

1 patient was in CR after 1st remission < 6 months

Median age 54 years (16-72)

TEC RIC sequential conditioning regimen

Refractory hematologic malignancies – post-transplant events

	Total (n=72) n (%)	Haplo (n=27) n (%)	MRD (n=16) n (%)	UD (n=29) n (%)
Relapse incidence	38.4	35.9	31.2	43.1
NRM	23.7	14.8	25	31
Acute GVHD II-IV	23.6	11.1	12.5	41.4
Chronic GVHD	32.1	30	37.5	31

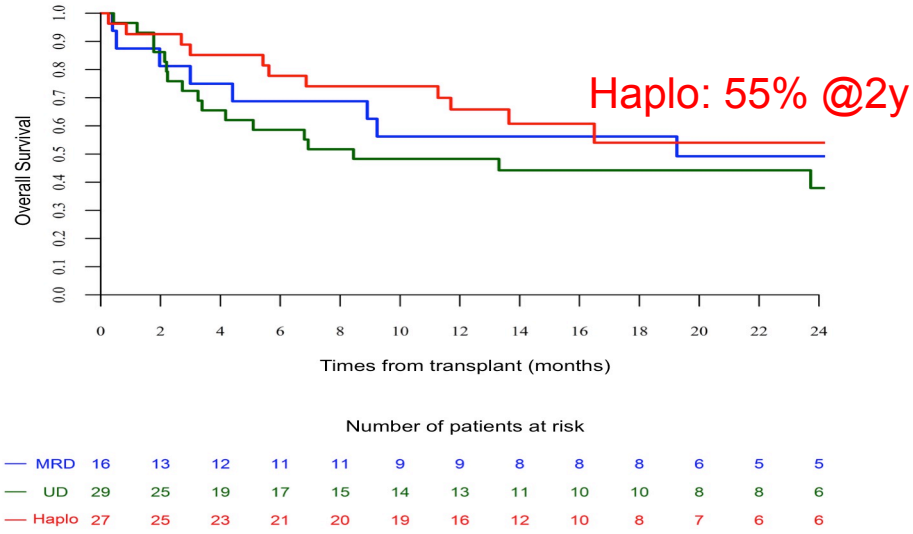
Duléry R et al. *BBMT* 2018

TEC RIC sequential conditioning regimen

Refractory hematologic malignancies

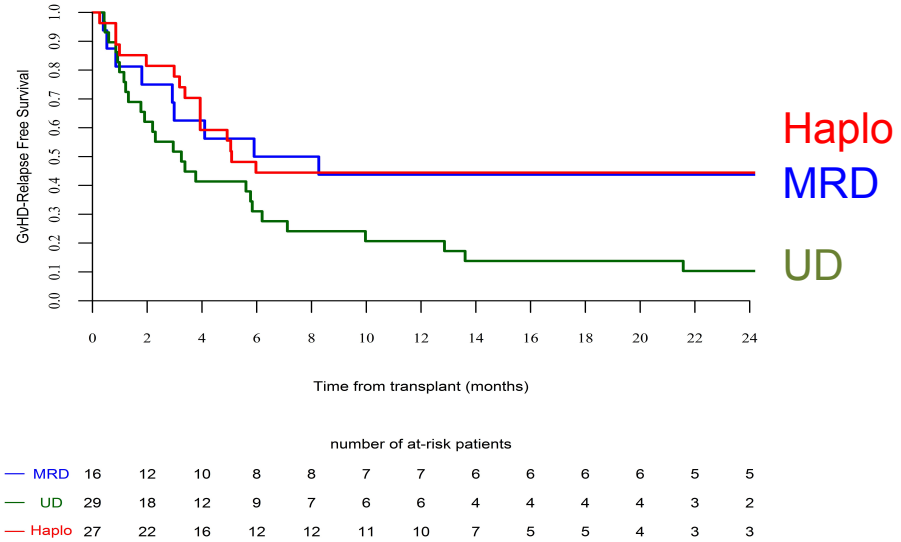
N= 72 patients

OS



Haplo: 55% @2y

GRFS



Haplo
MRD
UD

100 days NRM: 16.7% (haplo = 11.1%)
2-y NRM: 23.7% (haplo = 14.8%)

Duléry R et al. *BBMT* 2018

TEC RIC sequential conditioning regimen

Refractory AML and MDS – Saint Antoine Hospital

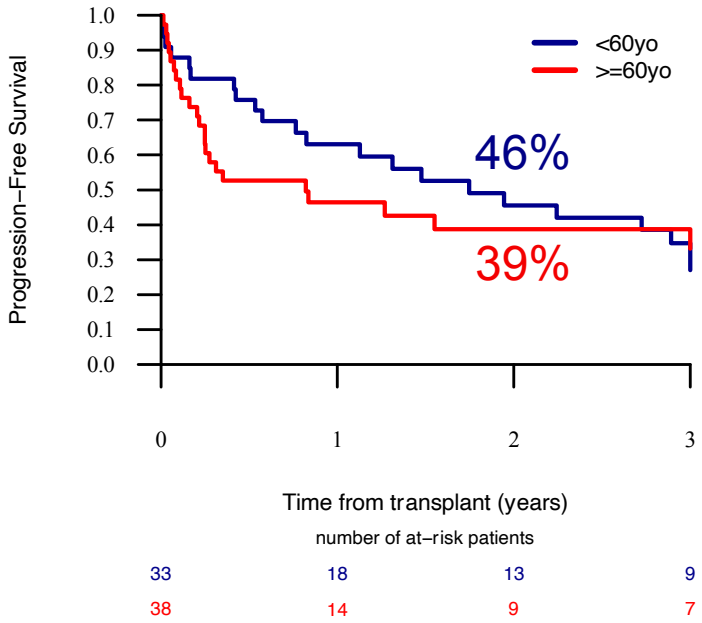
		Number of patients	%
Age (years)	Median (range)		60.9 (15-76)
	< 60	33	47%
	60-64	17	24%
	≥ 65	21	29%
Sexe	Male	44	62%
	Female	27	38%
Disease	AML	65	92%
	MDS/CMML	6	8%

Unpublished data

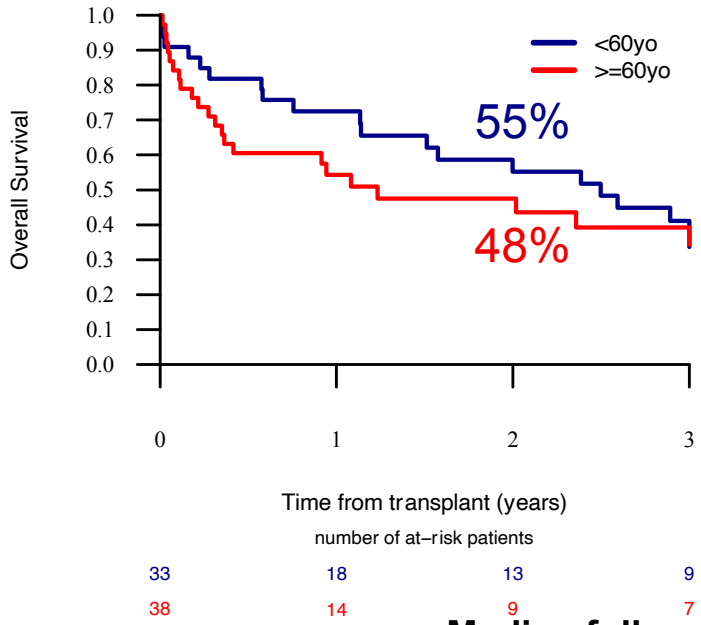
TEC RIC sequential conditioning regimen

Refractory AML and MDS – impact of age

PFS



OS



Unpublished data

Median follow-up:
45 months [37-64]

TEC RIC sequential conditioning regimen

Refractory AML and MDS

	Acute GVHD II-IV	Acute GVHD III-IV	Chronic GVHD
< 60 years old	21%	9%	35%
60-64 years old	24%	12%	19%
≥ 65 years old	14%	0%	6%
Reduced TEC-RIC	14%	0%	19%
Other doses	29%	18%	29%

Unpublished data

How to further improve results of allogeneic HCT?


Best
Possible
Quality of Life
Worst
Imaginable
0
1
2
3
4
5
6 years
ILLUSTRATION: FRED VAN DEELEN, WWW.ORGANISART.CO.UK

Quality of life

Allogeneic HCT

How can we improve quality of life ?

- Emphasis on health related QoL following therapy may inform initial treatment decisions and long-term survivorship goals.
- Future research should include prospective, longitudinal randomized designs across both treatment and time.
- It is of great importance to gain further insight into the course of recovery after cure, considering all aspects of life.
- Work as a team.
- To develop more effective and less toxic new therapies.

Enhancing the GVL effect

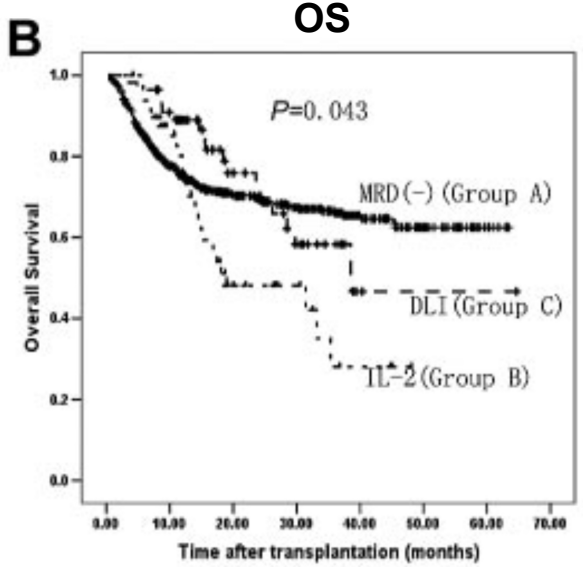
Sequential transplantation

Pre-emptive DLI

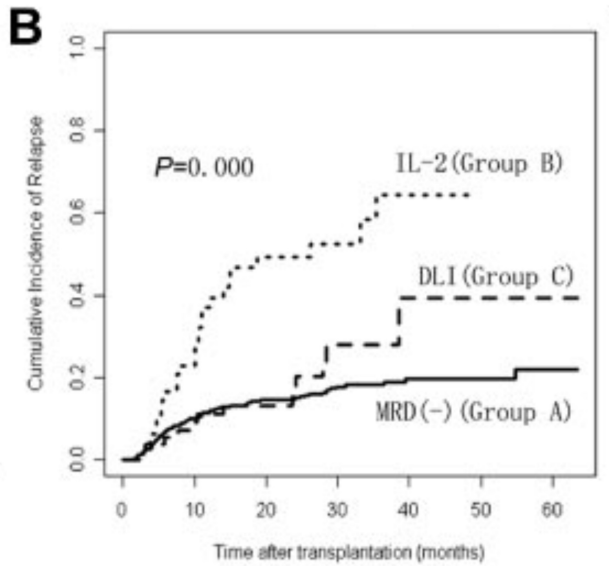
MRD triggered

- Standard risk AML
- MRD monitoring
- If **MRD +** : **DLI** (+/- chemotherapy) (n=56) or IL 2 (n=49)

OS



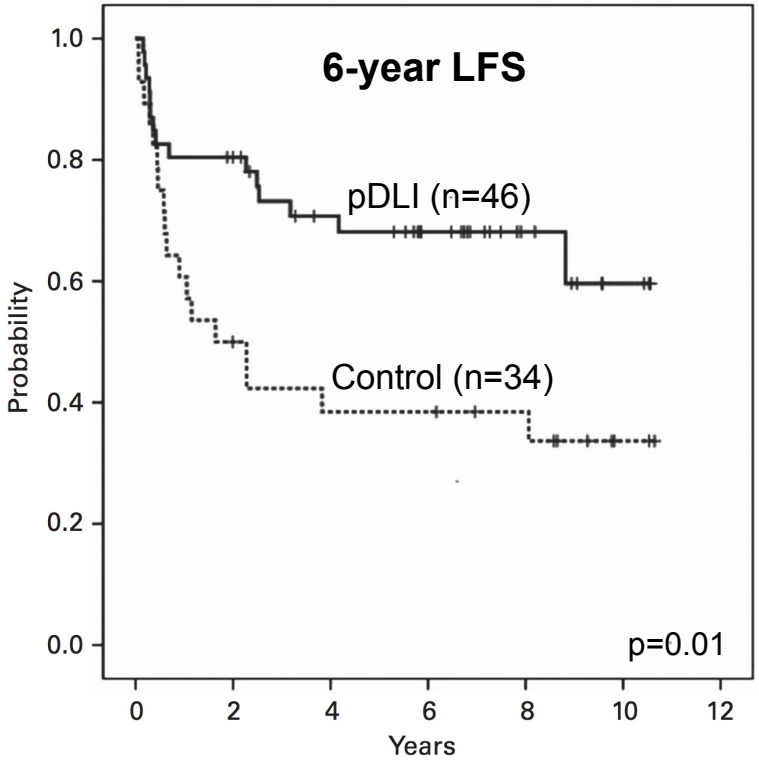
Relapse incidence



Yan CH et al. *Blood*. 2012

Prophylactic DLI

AML patients – MRD or MUD – Sequential FLAMSA conditioning



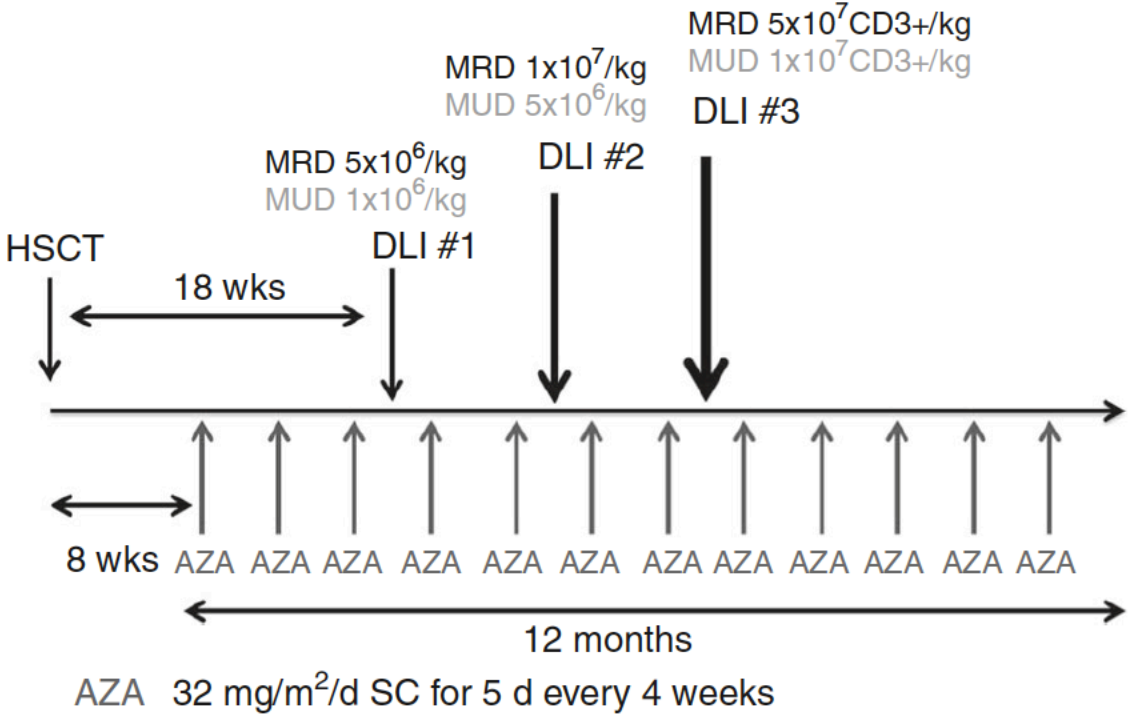
63%

38%

Jedlickova Z et al. *BMT* 2016

Enhancing GVL effect

Prophylactic low-dose azacytidine + DLI

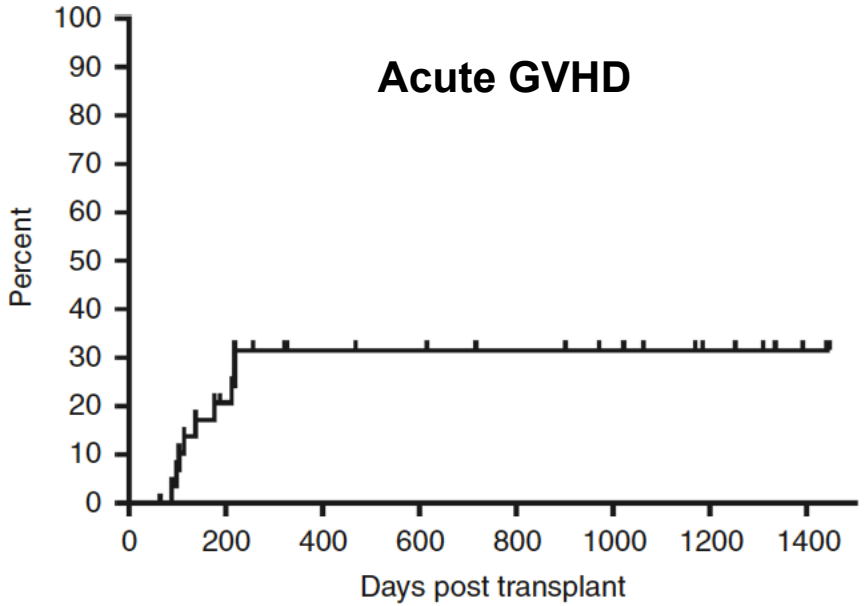


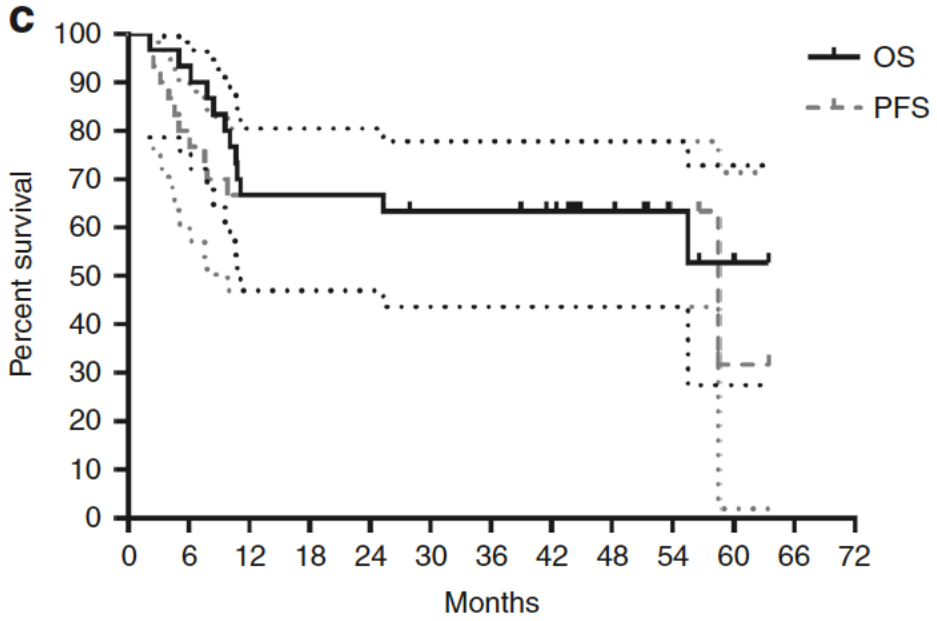
Guillaume T et al. *BMT* 2019

Enhancing GVL effect

Prophylactic low-dose azacytidine + DLI

N= 20 high-risk AML and 10 MDS

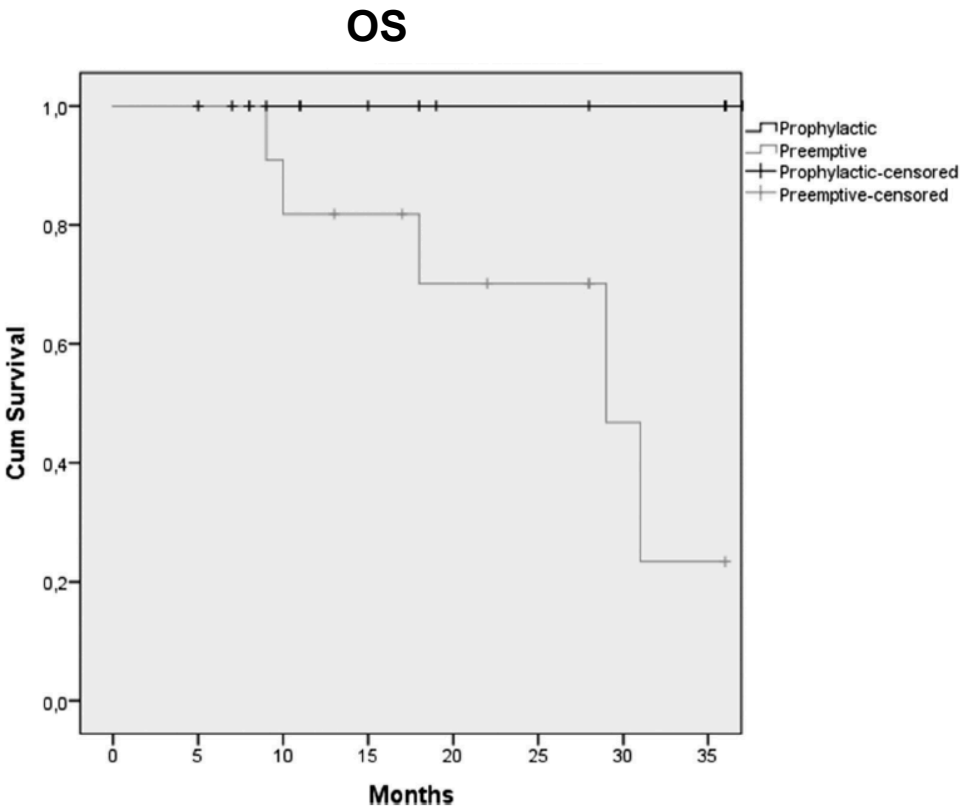




Guillaume T et al. *BMT* 2019

Enhancing GVL effect

Prophylactic low-dose azacytidine + DLI – real life data

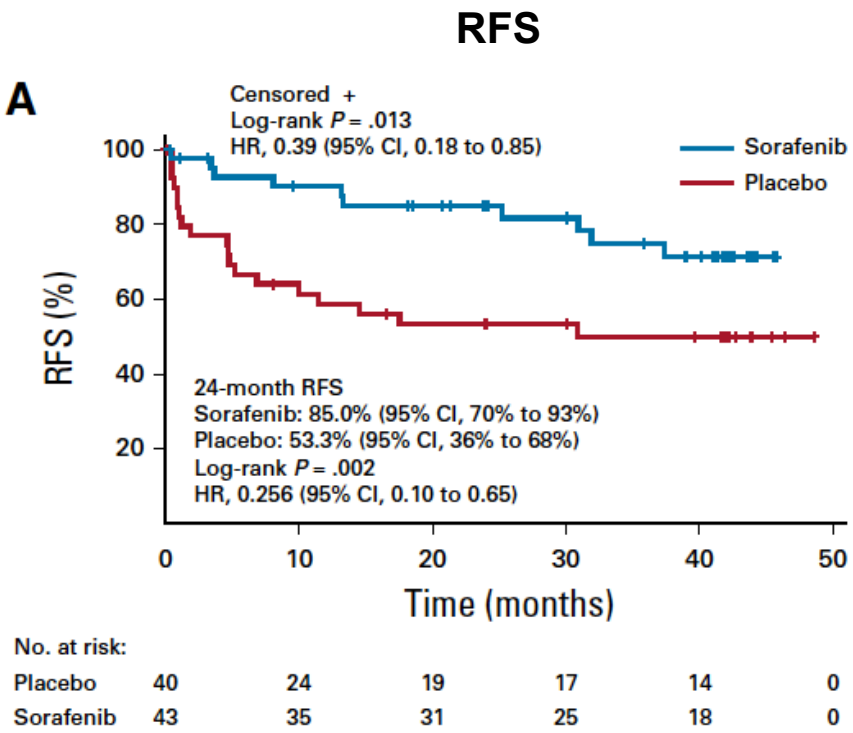


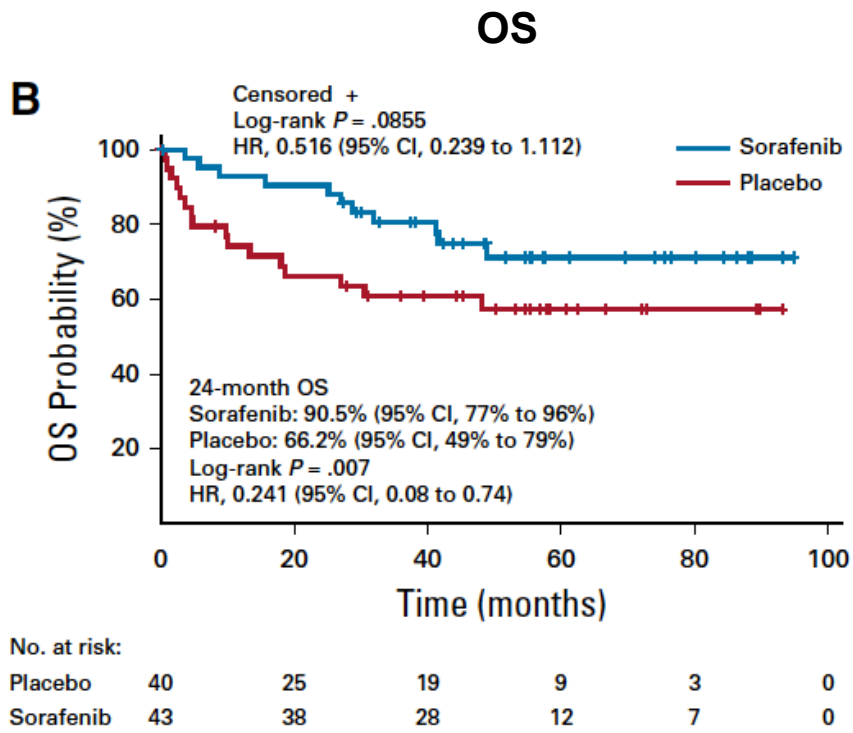
- 32 patients
  - 21 prophylactic
  - 10 pre-emptive
- DLI in 10 patients
- GVHD: 40% of patients
  - No GVHD-related death

Marini C et al. *Clinical Lymphoma, Myeloma & Leukemia* 2019

Enhancing GVL effect

Prophylactic sorafenib in FLT3-ITD patients (SORMAIN study)





Burchert A et al. *J Clin Oncol.* 2020

Maintenance therapy: Candidate agents

- FLT3 inhibitors
- Hypomethylating agents
- Histone deacethylase inhibitors
- Monoclonal or bi-specific antibodies
- Immunostimulatory agents: anti-CTLA-4, anti-PD1, anti-PDL1 (antagonistic), anti-4-1BB, anti-OX40 (agonistic)
- Cells – educated or not (eg. CAR T cells)
- Tumor vaccines etc. etc.

What will happen to allogeneic HCT in the next 10 years?

What will happen to allogeneic HCT in the next 10 years?

A few (personal) speculative Scenarios…

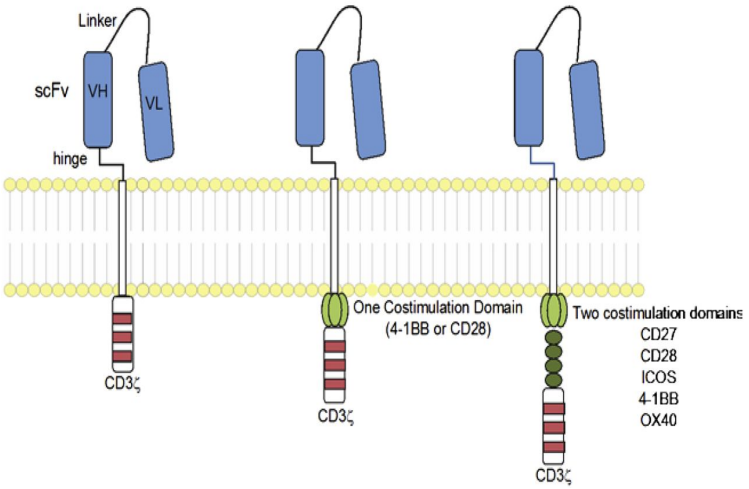

Tu m’injectes quoi avec ton hypospray ?
Des nano-CAR NK allogéniques.
J’espère que le donneur n’est pas Klingon...

Autologous CAR T-cells

- Recognize single or dual target(s)

- Recognize surface proteins
(<10% of tumor specific targets)

- Artificial continuous signaling from inserted domains cause either extreme inflammatory responses or exhaustion



CAR T cells in 10 years will be optimized for selective memory cytotoxicity and given early to avoid toxicity

Revival of autologous approaches: antigen specific autologous anti-tumor T-Cells

- Can recognize multiple targets

- Recognize intracellular proteins (majority of tumor specific targets)

- Immune regulatory mechanisms normal (less toxicity)

Adoptive therapy with T-cells expanded in presence of peptides (PRAME1 Wt1 and Survivin) have achieved CR in relapsed AML.

Peptide stimulated adoptive immunotherapy combined with vaccination (with or without allo-HCT)

- Patients are vaccinated with peptide based to generate autologous memory cytotoxic T cell anti-tumor response

- T cells are then harvested by aphaeresis and expanded ex vivo in the presence of these specific peptides to increase memory cytotoxic T cells

- T cells are then re-infused as adoptive immunotherapy without adverse side effects

- Vaccinations can then be given subsequently to maintain memory anti-tumor specific responses.

Off the shelf allogeneic donor CAR T cells

- Donor T cells will undergo CRISPR/Cas9 editing to remove native TCR (no GVHD), and transfected to target a specific tumor antigen

- After “induction” therapy to reduce tumor burden, allogeneic specific CAR T cells are thawed from off the shelf and infused as therapy

- Vaccination post allogeneic CAR T cell treatment as needed with specific peptides to maintain allogeneic memory anti-tumor responses

Conclusions and perspectives

The future of autologous and allogeneic cells transplantation

Take home messages… and hope for the future

- Allo- and auto-HCT still have future! Still the only curative therapies for many malignant and non-malignant diseases…
- A « family donor » platform is likely to fulfill most needs
- Patients older than 70 years may now be eligible for HCT
- Emerging concept of a comprehensive treatment package incorporating new drugs and novel cellular and immune therapies before and after auto- or allo-HCT

Take home messages… and hope for the future

- Once tumor burden is reduced, adoptive auto- or allo- cellular immunotherapy will achieve negative MRD, while restoring host anti-tumor immunity
- Serial gene/epigenetic profiling will allow for earlier diagnosis of relapses and selected/targeted treatment
- **BUT** immediate survival should not be the sole concern after HCT!
- We should aim to cure from the primary disease, while allowing for complete recovery of patient health status, normal physical and psychological functioning, normal family and social integration, and good subjective well being

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Thank you !

Any questions?

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