Thérapeutiques pré-transplantation

Modulation de la dose-intensité / modulation de l'immunossuppression

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AIH, Marseille, September, 28th , 2013

Donor
- Match sibling or UD
  - 6/6 vs 8/8 vs 10/10
- Mismatched RD or UD

Stem Cell Source
- Bone Marrow
- primed BM
- PBSC
- Cord Blood

Dis. Status
- CR1
- CRn
- advanced

Patient
- **Age**
- Comorbidities

Allo SCT

Disease
- Cytology
- Gen Abnormality
- Response to Trt

Conditioning preparation
- Standard Myeloablative
  - TBI or No TBI
- Reinforced Myeloablative
- **NMAC or RIC or RTC**

GVHD prophylaxis
- CSA /CSA + MTX
- Tacrolimus
- Ex vivo T Cell depletion
- **ATG**
- HD CY post HSCT

Biology of Blood and Marrow Transplantation 5:341–346 (1999)

Historical markers in the development of allogeneic hematopoietic cell transplantation

E. Donnall Thomas,[1] Karl G. Blume[2]

1949–1951: THE HUMORAL HYPOTHESIS

1954–1956: THE CELLULAR HYPOTHESIS

1956–1959: ADVANCES IN MARROW GRAFTING TECHNOLOGY THROUGH ANIMAL STUDIES

1956–1959: RECOGNITION OF THE POTENTIAL OF MARROW GRAFTING IN THE TREATMENT OF HUMAN DISEASE

1960–1967: PESSIMISM ABOUT ALLOGENEIC MARROW GRAFTING IN HUMAN PATIENTS BUT PROGRESS IN ANIMAL MODELS OF ALLOGENEIC MARROW GRAFTING

1968–1975: THE BEGINNING OF THE MODERN ERA OF HUMAN MARROW TRANSPLANTATION

1976–1986: WIDENING APPLICATION OF ALLOGENEIC MARROW GRAFTING FOR HUMAN PATIENTS

1986–PRESENT: HEMATOPOIETIC CELL TRANSPLANTATION AS STANDARD THERAPY

TBI / BM / Sibling

1999- now

- **No TBI**
- **PBSC**
- **UD/CB**

- **RIC**
- **Haplo**

Malignancies After Marrow Transplantation for Aplastic Anemia and Fanconi Anemia: A Joint Seattle and Paris Analysis of Results in 700 Patients

By H.J. Deeg, G. Socié, G. Schoch, M. Henry-Amar, R.P. Witherspoon, A. Devergie, K.M. Sullivan, E. Gluckman, and R. Storb

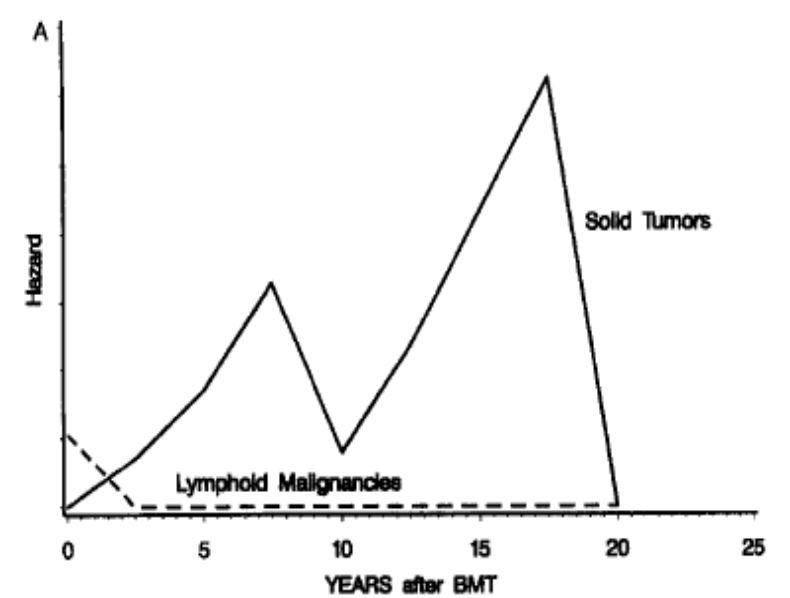


Table 4. Predictors of Postransplant Solid Tumors by Multivariable, Stepwise Proportional Hazards Model

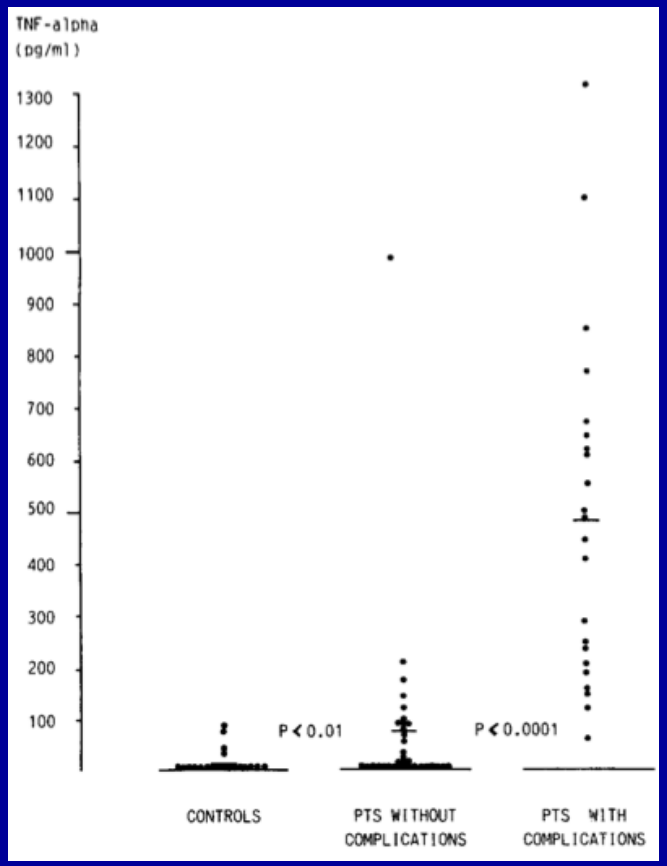
Patient Population	Step Entered in Model	Univariable *P*	Multivariable *P*	RR (95% CI)
All patients				
Azathioprine/chronic GHVD*	1	.0001	.0005	11.7 (3.9-34.6)
Fanconi anemia	2	.0002	.0001	11.2 (3.9-34.6)
Non-Fanconi patients				
Azathioprine/chronic GVHD*	1	.0001	.0043	7.5 (1.8-30.2)
Irradiation	2	.0024	.0424	3.9 (1.0-15.0)
Age	3	.0525	.0252	1.1 (1.0-1.12)

* Azathioprine modeled as a time-dependent variable and assumed to be started at diagnosis of chronic GVHD (see Materials and Methods).

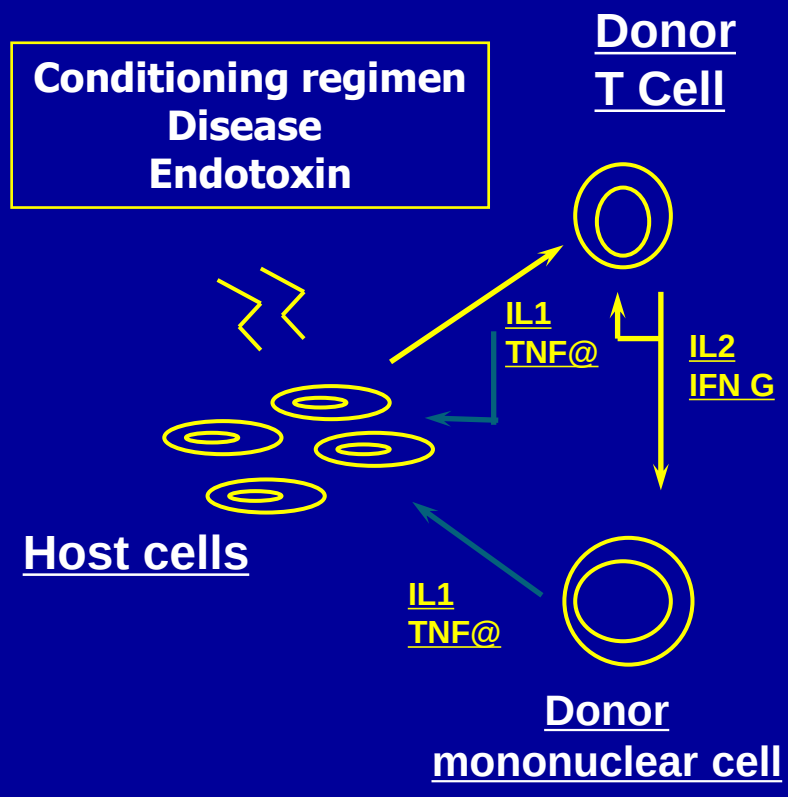
Post transplant malignancies

Blood, Vol 87, No 1 (January 1), 1996: pp 386-392

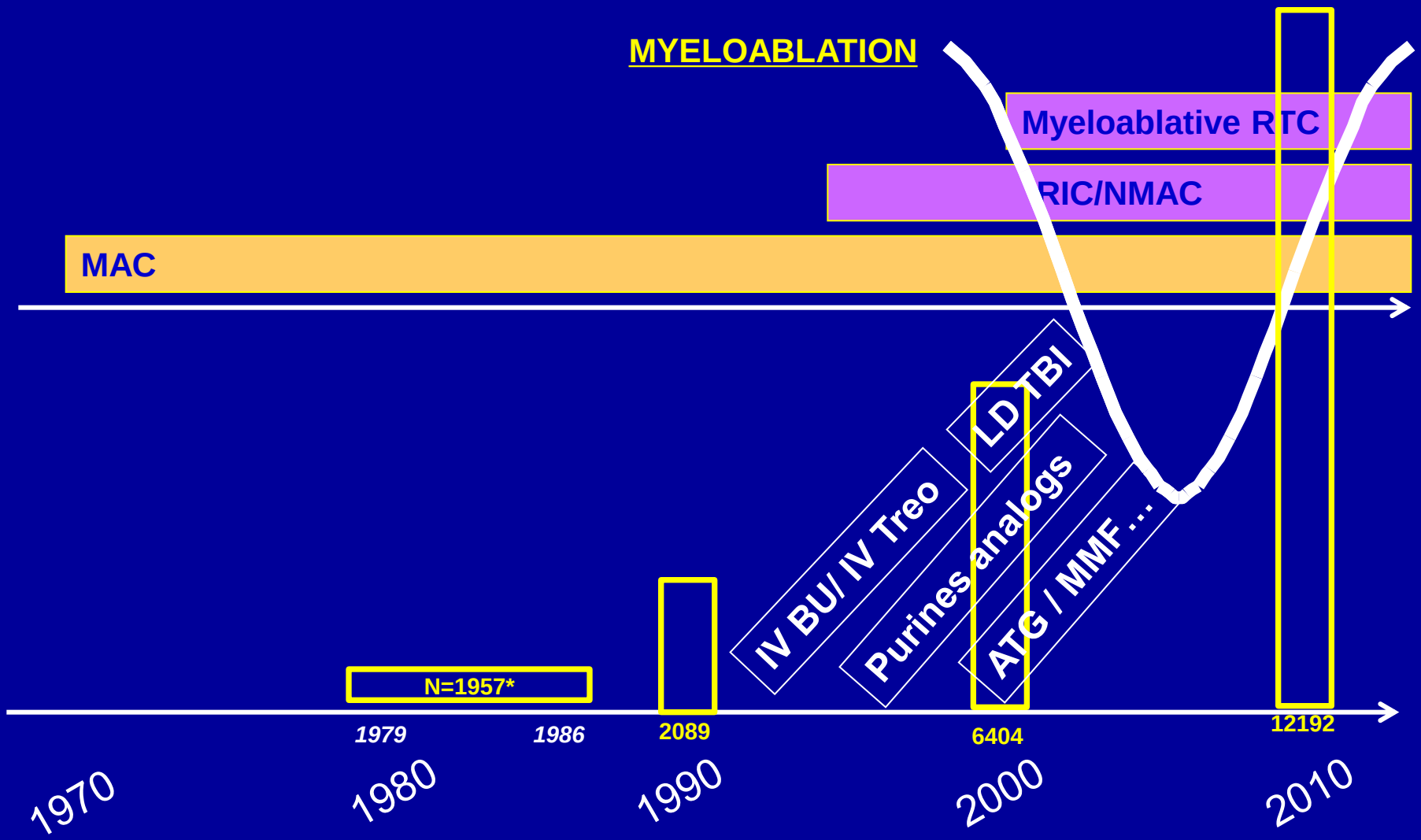
Historical Myeloablative Conditionings
Cytotoxicity and Procedure Toxicity



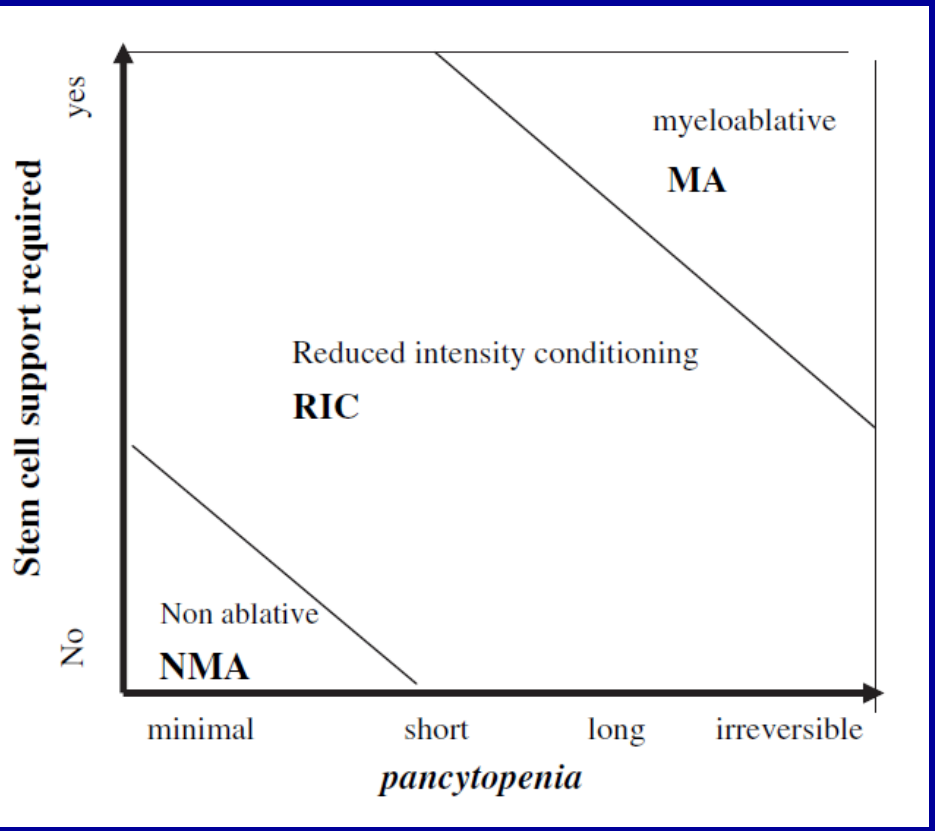
Holler, E, Blood 1990



Conditioning Regimens History



Conditioning intensity definition



Myeloablative (MA)*
TBI ≥5 Gy single dose or ≥8 Gy fractionated
Bu >8 mg/kg orally or intravenous equivalent
Nonmyeloablative (NMA)†
TBI ≤2 Gy± purine analog
Flu + Cy ± ATG
Flu +AraC + Ida
Cladribine + AraC
Total Lymphoid Irradiation + ATG

Bacigalupo, A, BBMT 2009

What was/is (were/are) the goal(s)?

- Absence of induced deaths?
  - First step
- Disease control?
  - Of course
- Higher survival and higher cure?
  - Not bad

Survival + Cure + Quality of Survival !

Reduced procedure related toxicity?

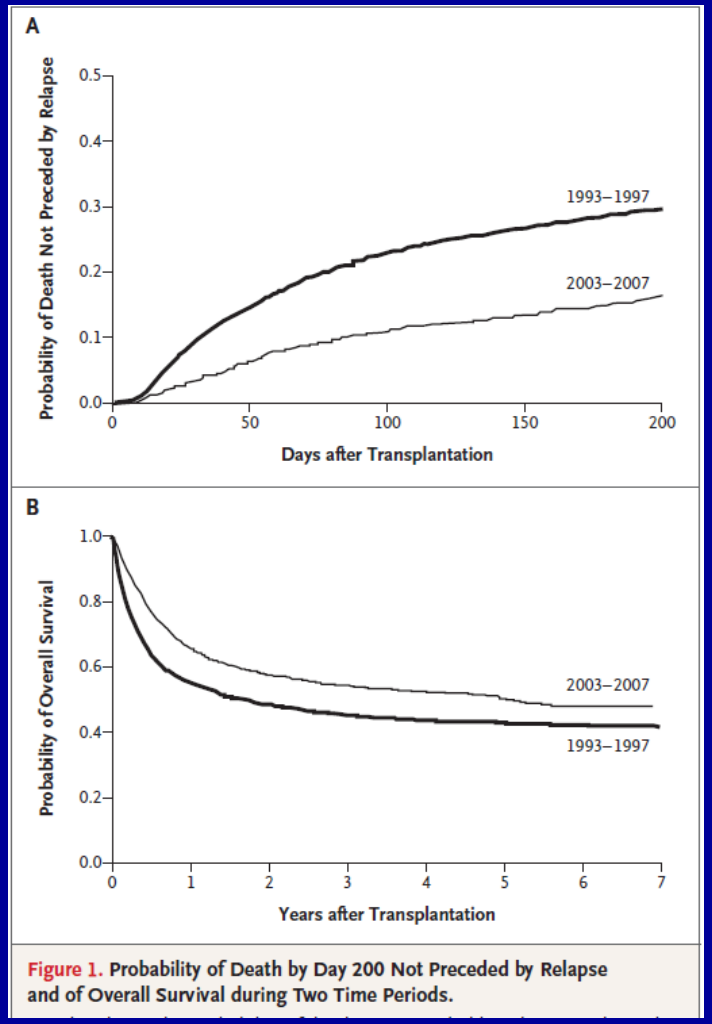
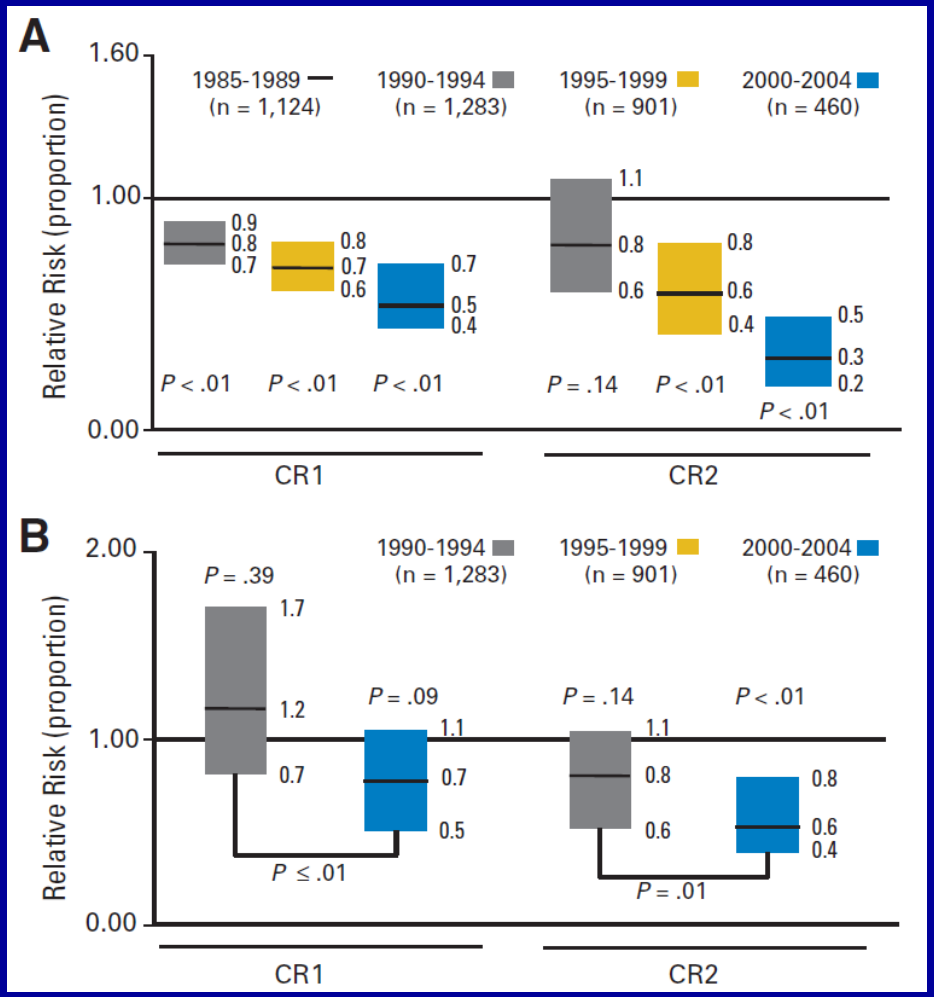


Figure 1. Probability of Death by Day 200 Not Preceded by Relapse and of Overall Survival during Two Time Periods.

Gooley, T, NEJM 2010

MRD



UD

Horan, J, J Clin Onco 2011

Reasons for an overall reduced NRM

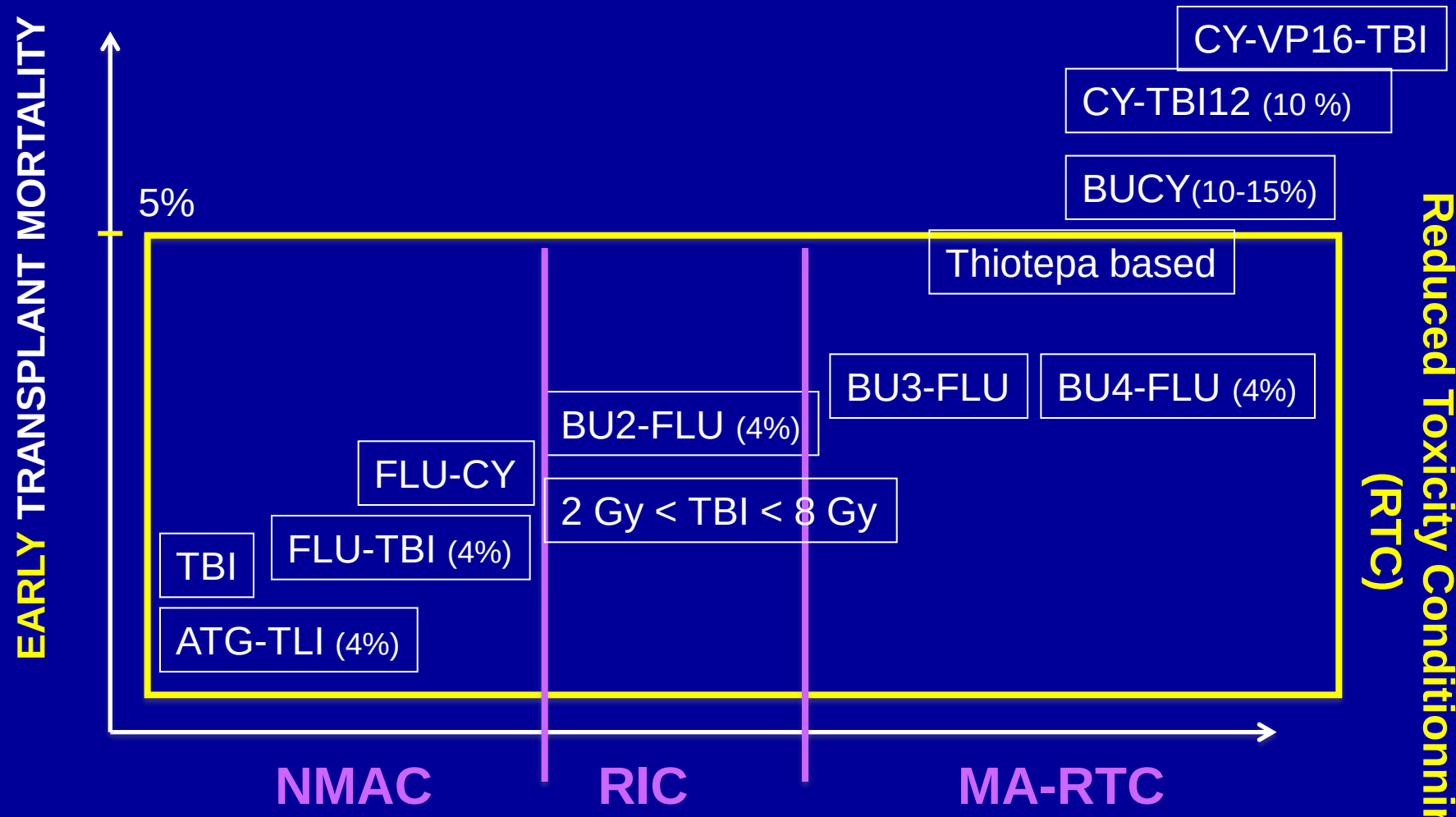
- Implementation of standard operating procedures
- Improved transplant management
  - Shorter initial neutropenia
  - Effective drug PK
- Improved complication management
  - More effective approaches for GVHD prevention
  - More effective approaches for fungal infections and CMV disease
  - Advances in nephrology, critical care and transfusion medicines
- Better donor selection
  - Improvement in HLA typing and matching
- Better disease monitoring
  - MRD monitoring
- Better patient selection
  - Comorbidities score
- Reduced intensity conditioning?

Further Reduced NRM after RIC?

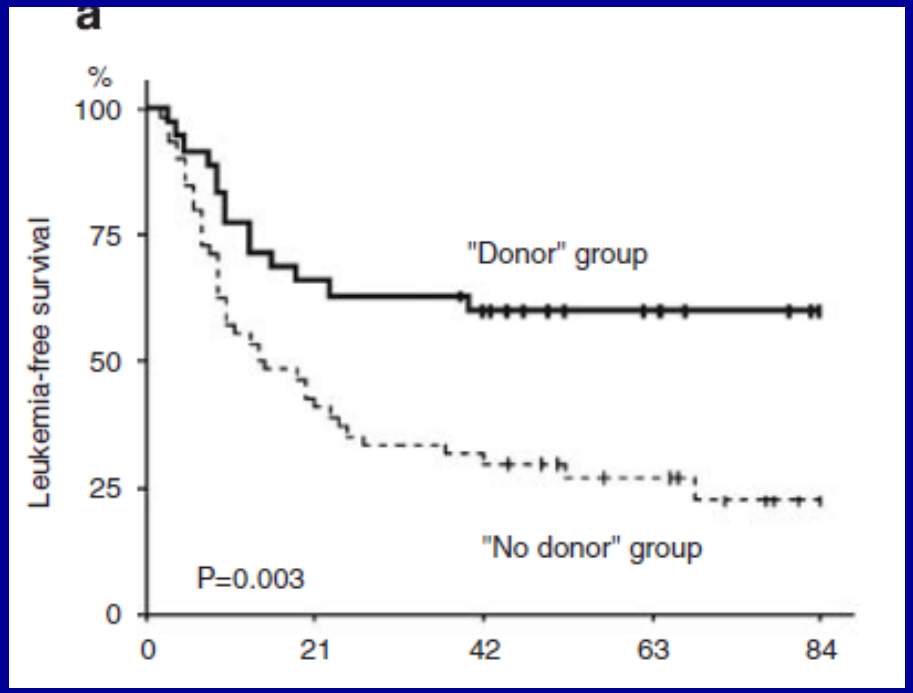
Study	Dg/ Age	CDT	N	NRM
Luger, BMT 2011,**CIBMTR**	AML/MDS 1-82	MAC 37 (1-82)	3731	1
		RIC BM 35 (16-69)	273	0,96 (0,77-1.19)
		RIC PBSC 41 (1-78)	768	0,90 (0,77-1,05
		NMA 41 (19-75)	407	1,05 (0,87-1,28)
Cornelissen, ASH 2011, Hovon	CR1 AML 45 (40-60)	MAC	237	**24% +/- 3**
		RIC	144	**9% +/- 3**
Lioure, Blood 2012, Goelams	CR1 AML 44 (17-60)	CY-TBI < 50y	117	15.8% (9.8-23)
		F-B-ATG> 50y	47	6.5% (0.2-16)

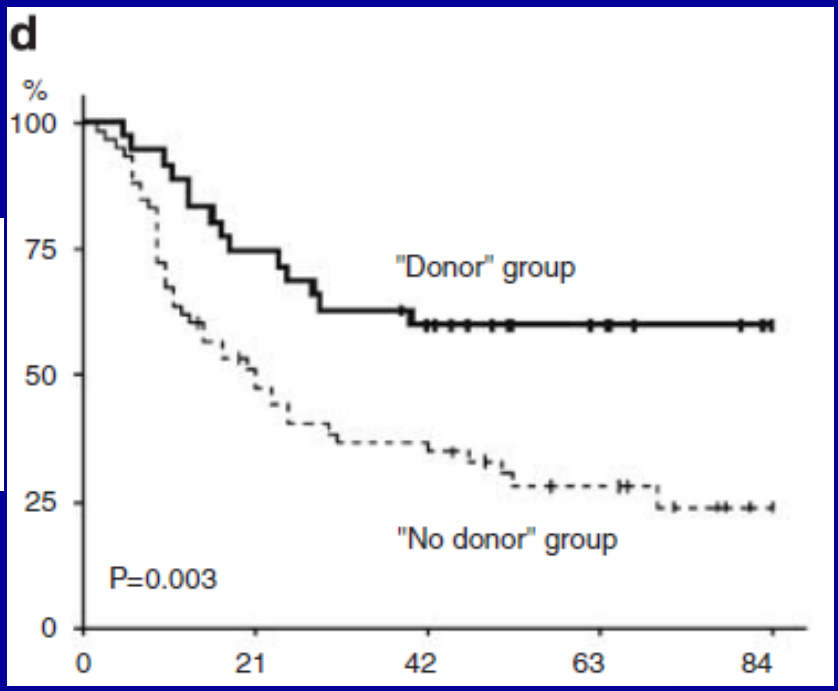
Reduced early mortality is a mandatory goal

When a patient is gone, he cannot be cured!



RIC allo SCT for patients with AML
Long term results of a "donor" vs. "no donor" comparison





Mohty , M, Leukemia 2009

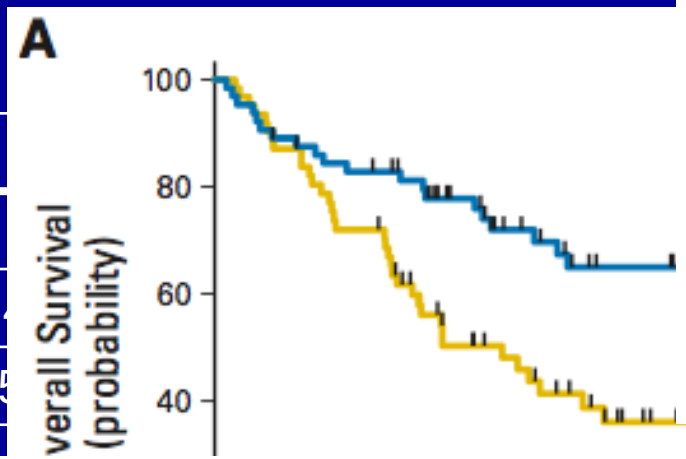
RIC vs. Standard CDT before allo HSCT in patients with AML in CR1: a prospective, open-label randomised phase 3 trial

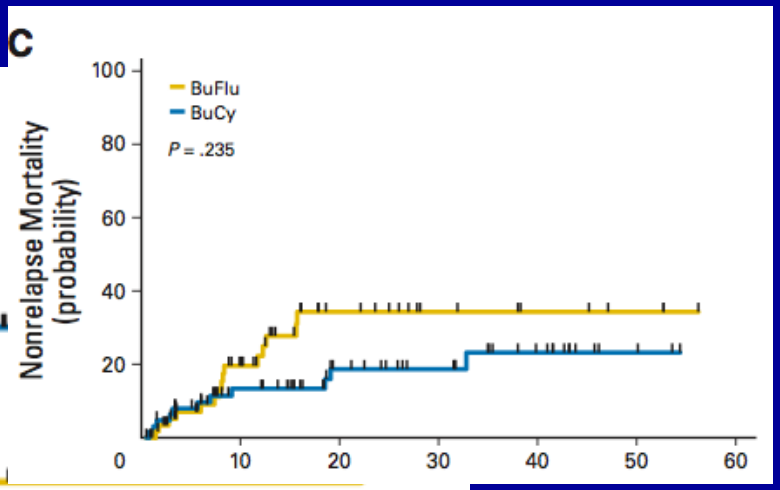
	RIC	Standard	HR (95% CI)
N	99	96	
CDT	**Flu-TBI (2gy x 4)**	**Cy-TBI (2gy x 6)**	
Age	45 (18-60)	44 (18-60)	
NRM	13%	18%	0.62 (0.30-1.31)
Relapse	28%	26%	1.10 (0.63-1.90)
Survival	61%	58%	0.77 (0.48-1.25)
DFS	58%	56%	0.85 (0.55-1.32)

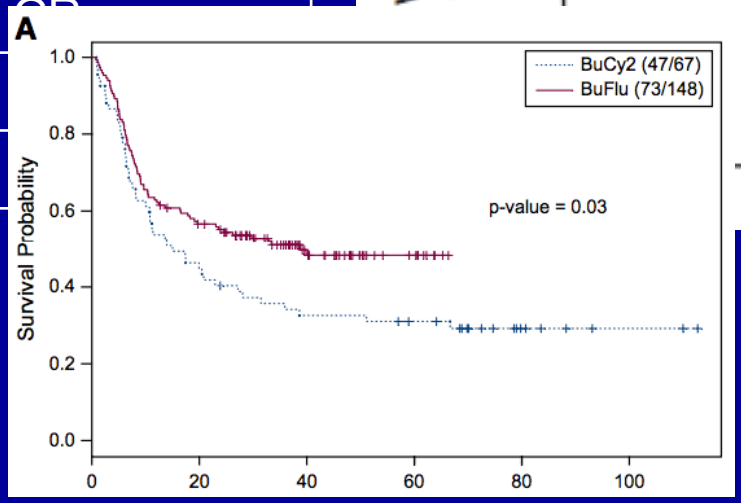
Bornhauser, Lancet Oncology, 2012

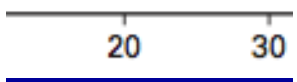
Randomized trial of MAC regimens BUCY vs. BUFLU

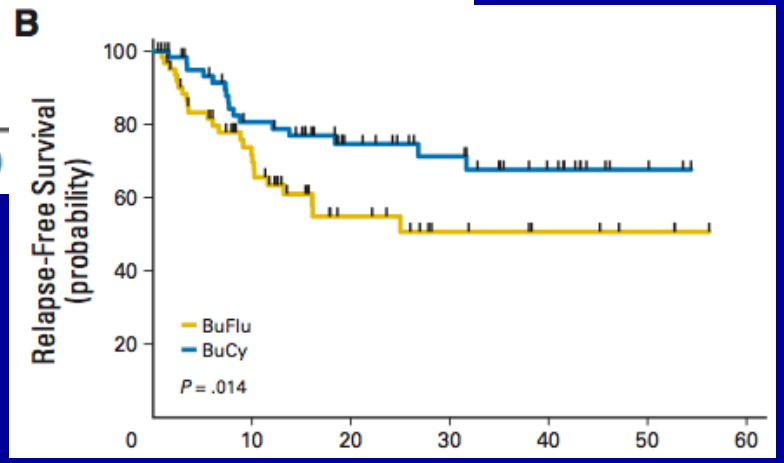
N	
Age	
AML/ALL	
CR	







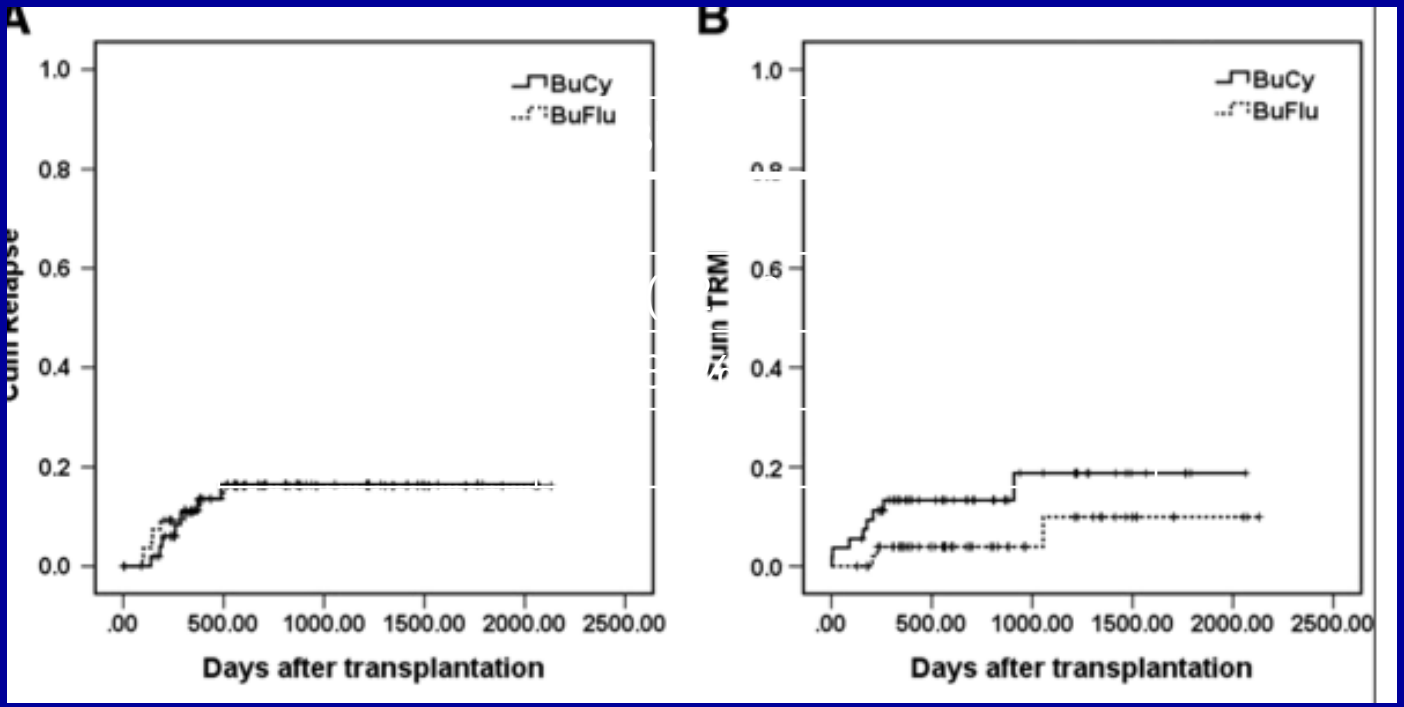




Andersson, B, BBMT 2008

Lee, JH, J Clin Oncol, 2012

Bu + FLU as a myeloablative CDT compared with BU + CY for AML in CR1 undergoing allo HSCT: a prospective and multicenter study



Liu, H, J of Hematology & Oncology, 2013

Randomized Study of 2 RIC Strategies for HLA-Matched, Related Allo PBSCT

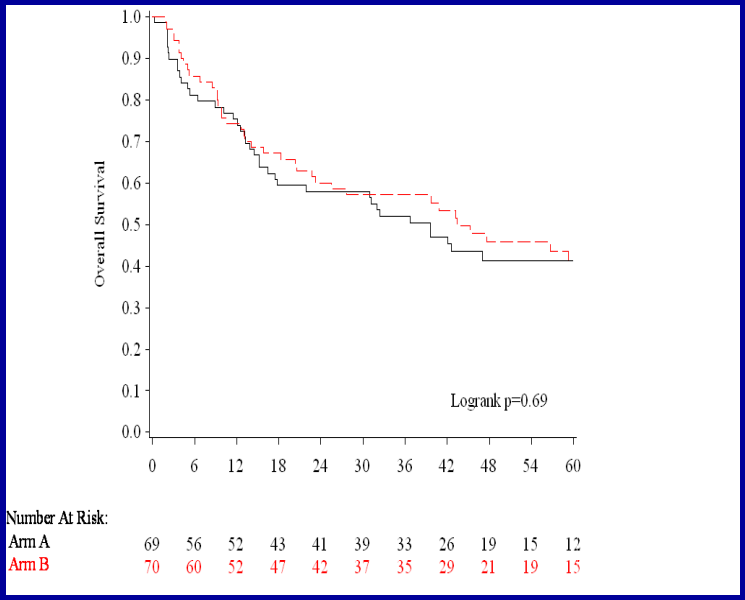
R

Fluda-BU-ATG	D-5	D-4	D-3	D-2	D-1	D0	D+1
Fludarabin: 30 mg/m²	X	X	X	X	X		
Po Busulfan: 4 mg/kg		X	X				
Thymoglobulin: 2.5 mg/kg			X				
PBSC Transplant						X	
CSA: 3 mg/kg				X	X	X	X→

Fluda-TBI	D-5	D-4	D-3	D-2	D-1	D0	D+1
Fludarabin: 30 mg/m²		X	X	X			
TBI: 2 gy						X	
PBSC Transplant						X	
CSA: 3 mg/kg				X	X	X	X→
MMF: 2g/day (d1→d+28)							X→

	Flu-Bu-ATG	Flu-TBI
2-4 aGVHD	**47%**	28%
Ext cGVHD	61%	46%
NRM	**38%**	22%
Relapse	27%	**54%**

	Flu-Bu-ATG N=69	Flu-TBI N=70
Age	54 (21-65)	52 (34-65)
- AML/HMY	37%	27%
- HLY	63%	73%
- Advanced	63%	65%

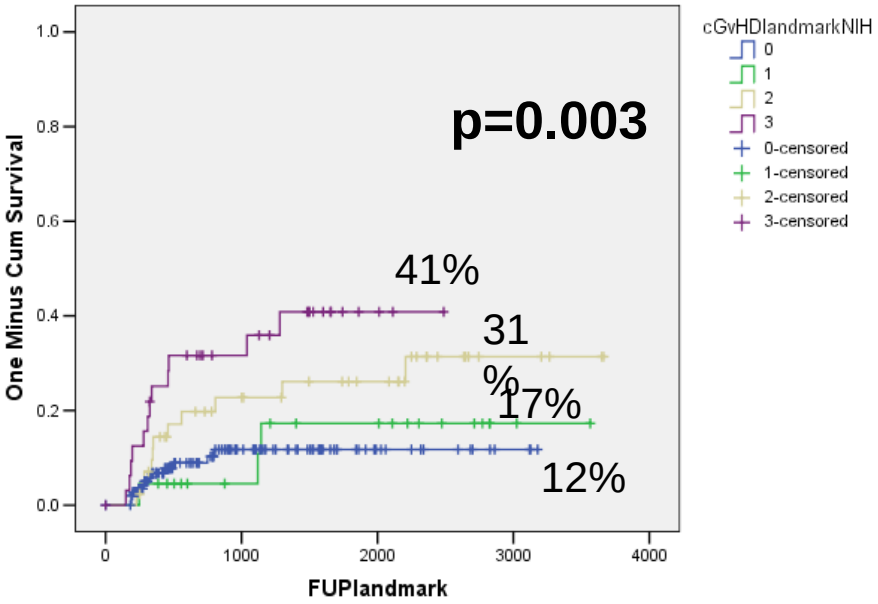


Blaise, D , cancer 2012

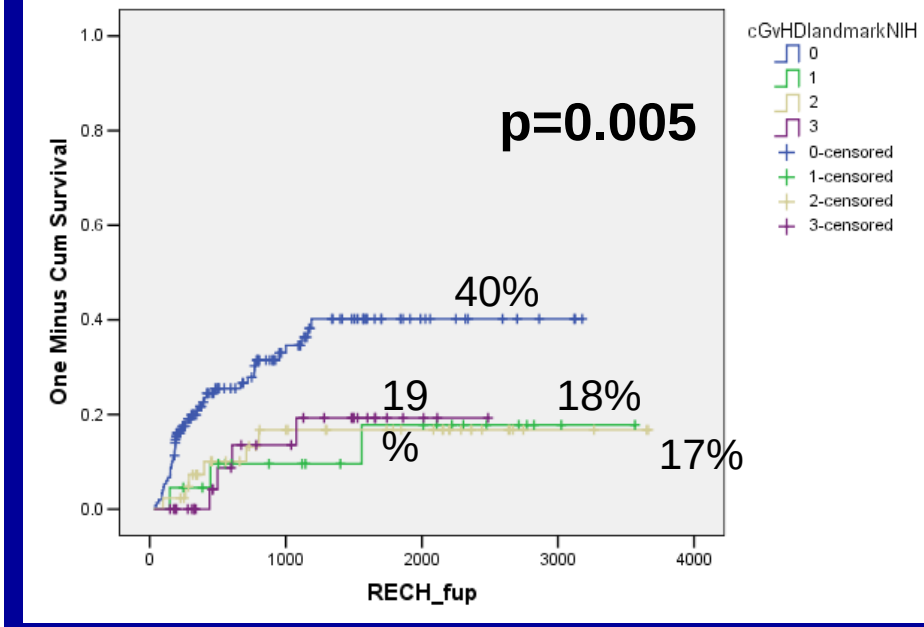
Reduced toxicity approach

Does GVHD remain the same old challenge?

Non Relapse Mortality



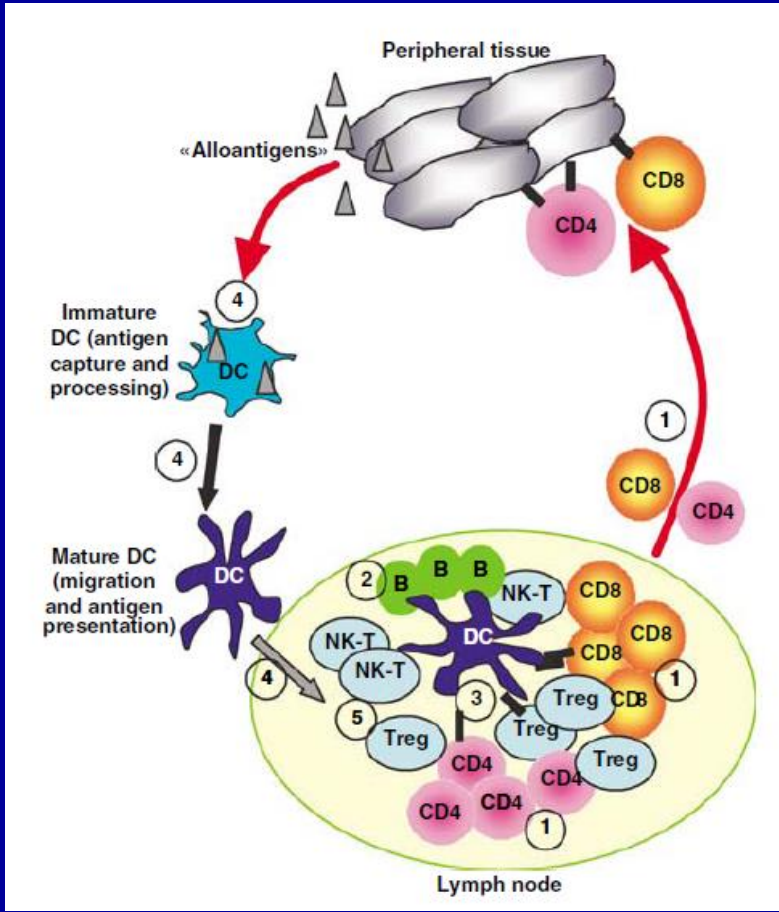
Relapse



0: No GVHD; 1: Mild; 2: Moderate: 3: Severe

Saillard, C , Submitted

Mechanisms of action of antithymocyte globulin: T-cell depletion and beyond



- *The polyclonal nature of Thymoglobuline is reflected in its diverse effects on the immune system:*
  - *T-cell depletion in blood and peripheral lymphoid tissues*
  - *Interference with leukocyte/endothelium interactions*
  - *Apoptosis in all B-cell lineages*
  - *Induction of Tregs / NKT cells*
- *Thymoglobuline provides multifaceted immunomodulation*

Leukemia (2007) 21, 1387–1394

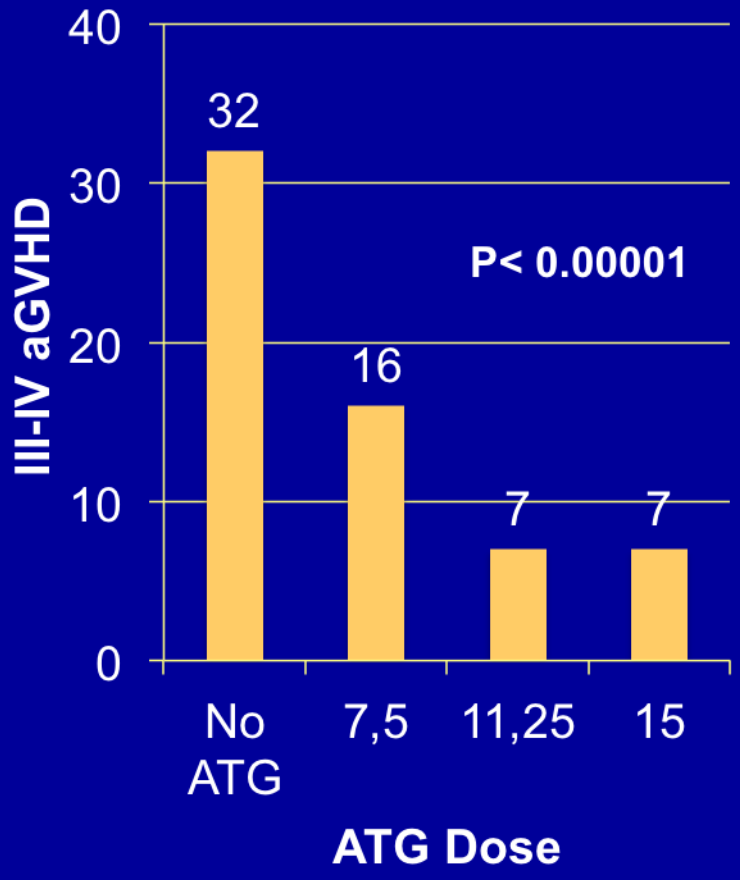
GVHD prophylaxis with ATG: Which is more important, dose or timing?

- 257 adults with MUD or Haplo HSCT
- Age: 32 (15-64)
- CR1 + CR2: 66%
- CY-TBI: 56%

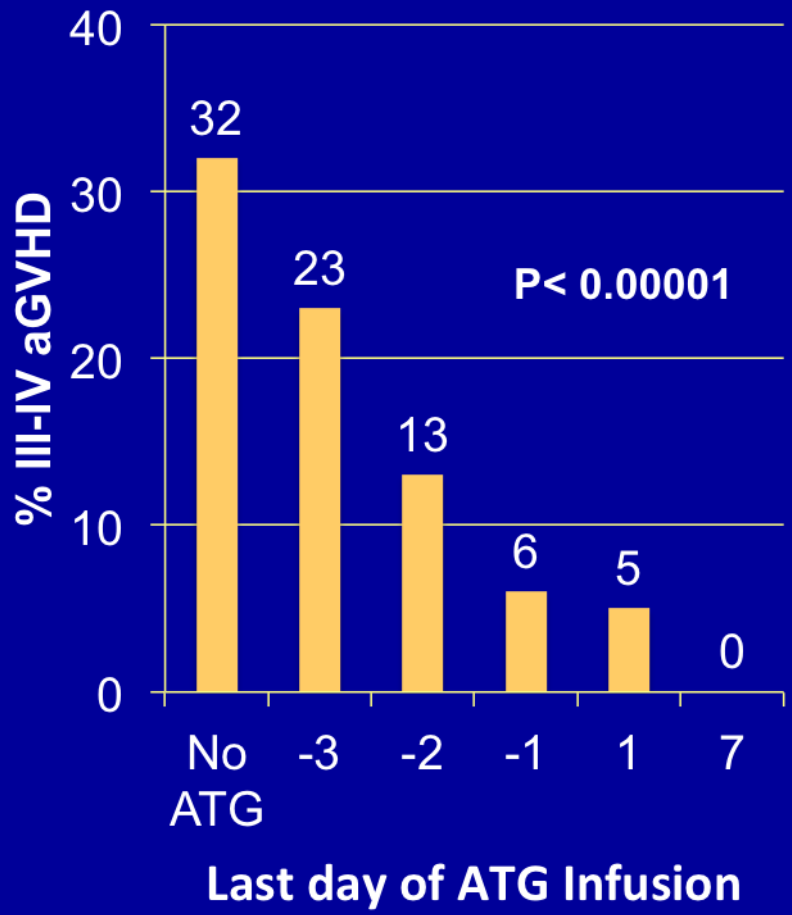
DOSE mg/kg	TIMING
0	day -3
7,5	day -2
11,25	day –1
15	day +1
	day +7

Sormani, EBMT, 2007
Courtesy from A Bacigalupo

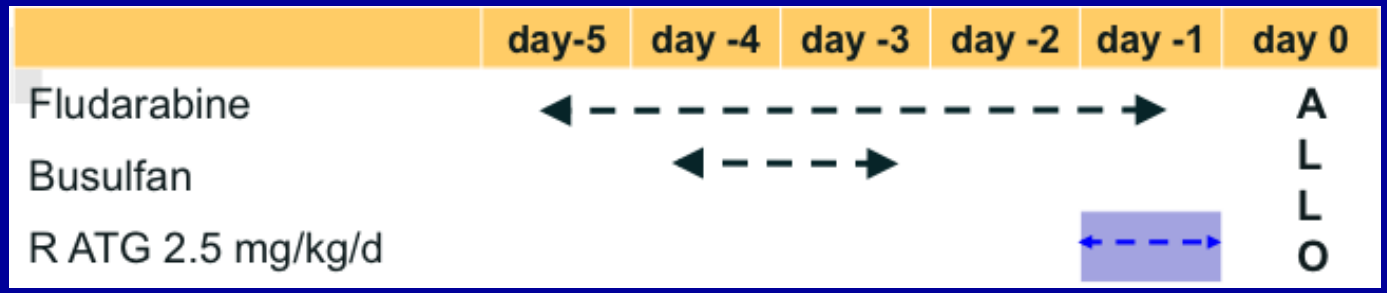
GVHD prophylaxis with ATG: which is more important, dose or timing?



MV analysis: Timing



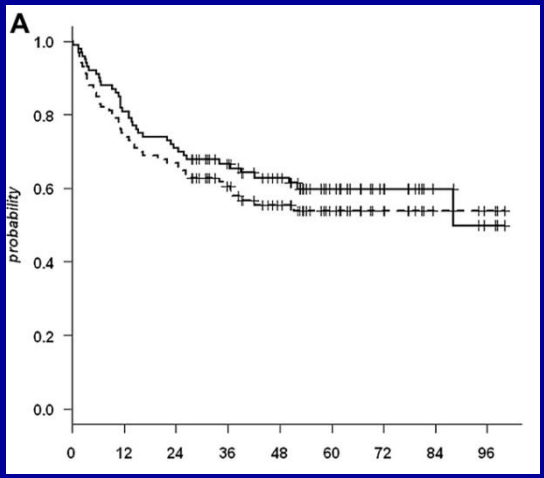
Sormani, EBMT, 2007
Courtesy from A Bacigalupo

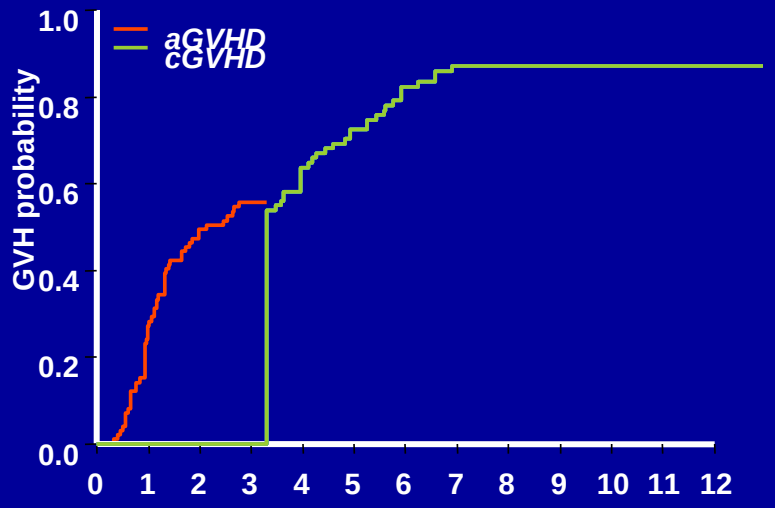


	N=100
Patient Age – Age ≥ 55	50 (18-64) 23
Comorbidity Score >2	21

DIAGNOSIS	N=100
• Acute Leukemia • Myeloid Malignancies • Lymphoid Malignancies	• 39 • 16 • 45

DISEASE STATUS	N=100
• CR1/CP1 • CR>1 or RP/Stable • Refractory	• 45 • 39 • 14





Blaise, D, Exp Hematol, 2010

rATG: 2.5 vs. 5 mg/kg

Retrospective study on 229 patients

	day-5	day -4	day -3	day -2	day -1	day 0
Fludarabine	← – – – –	– – – –	– – – –	– – – –	– – – –	– – – – ►
Busulfan		← – –	– – ►			
R ATG 2.5 mg/kg/d					← – – –	– – – ►

ALLO

	day-5	day -4	day -3	day -2	day -1	day 0
Fludarabine	← – – – –	– – – –	– – – –	– – – –	– – – –	– – – – ►
Busulfan		← – –	– – ►			
r ATG 2.5 mg/kg/d				← – –	– – – –	– – – ►

ALLO

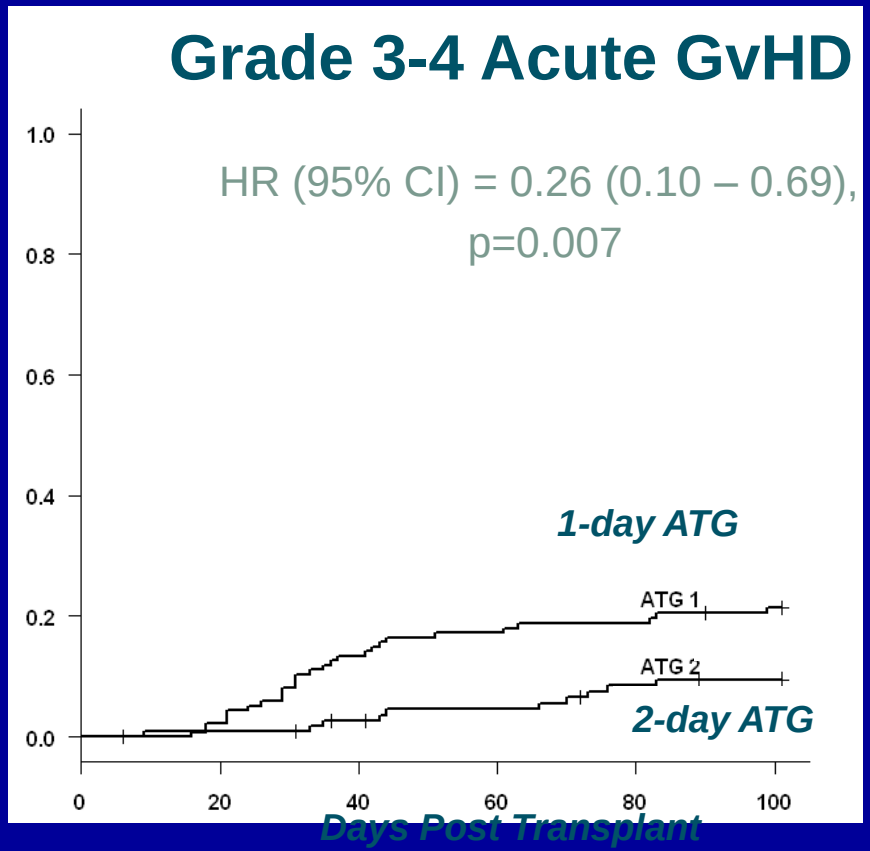
Crocchiolo, R, Cancer, 2013

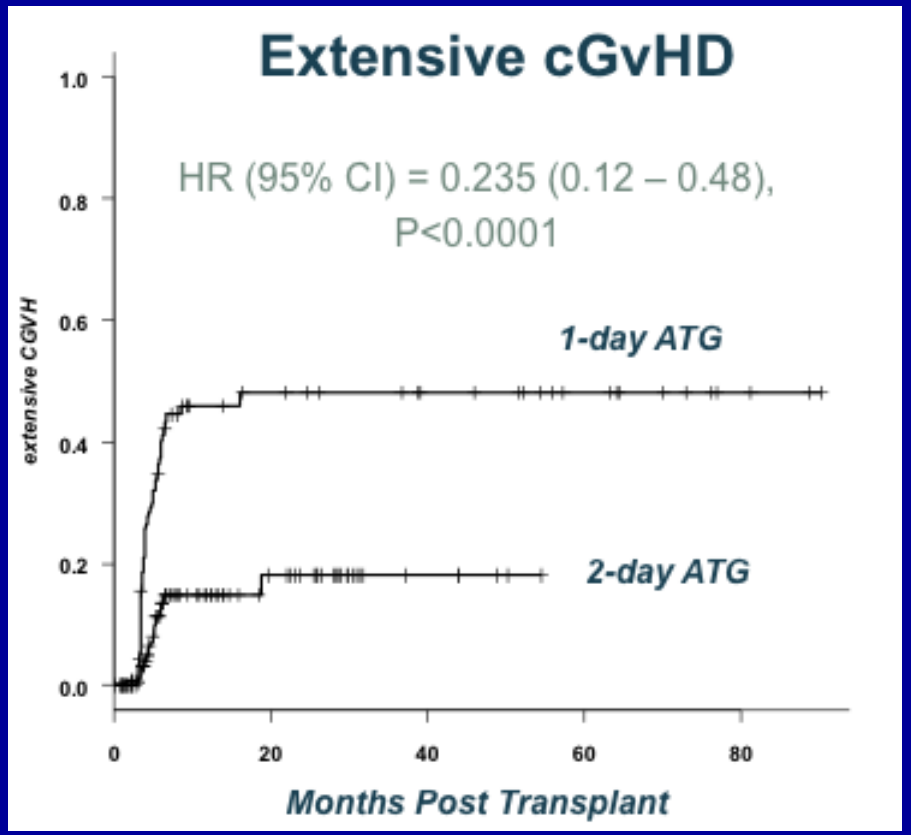
Patient characteristics

	1-day ATG: 2.5 mg/kg (N=124)	*2-day ATG 5 mg/kg (N=105)*	*p-value*
Follow-up	62 [10-108]	16 [2.5-55]	<0.0001
Age	**51 [18-70]**	**58 [24-68]**	**<0.0001**
Myeloid Malignancies	56%	49%	0.3497
Kahl classification Low Standard high	19% 57% 24%	23% 51% 26%	0.6309
IV Busulfan	5%	98%	<0.0001
Unrelated Donor	**2%**	**38%**	**<0.0001**

Crocchiolo, R, Cancer, 2013

Graft vs. Host Disease





Crocchiolo, R, Cancer, 2013

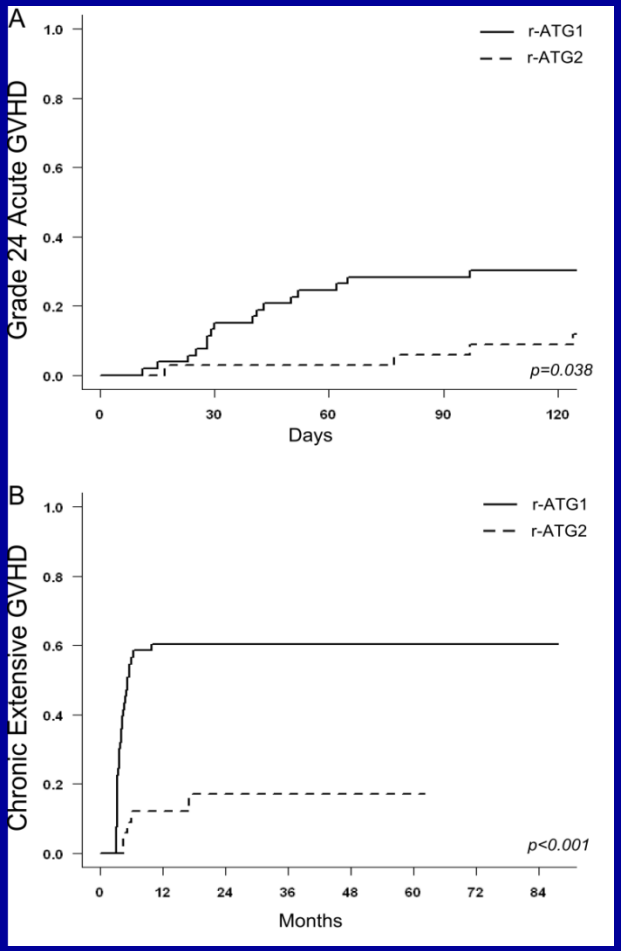
AML/MDS patients after MRD HSCT

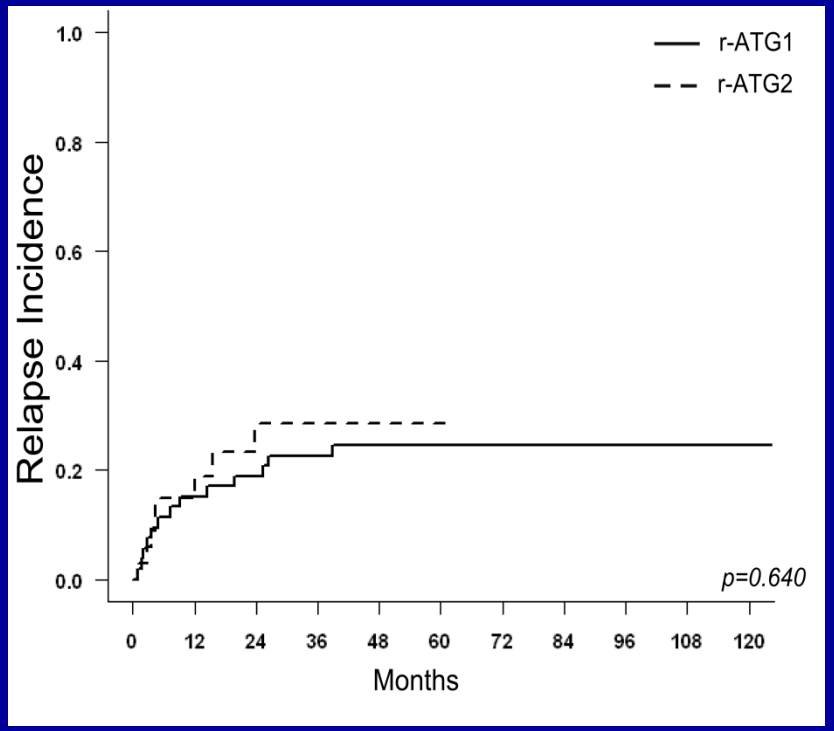
Variable	*1-day ATG (N=53)*	*2-day ATG (N=22)*	*p-value*
Transplantation year	2004 [2000-2009]	2008 [2003-2010]	<0.0001
Age	**49 [18-70]**	**60 [31-68]**	**0.032**
AML/MDS	89% / 11%	82% / 18%	0.325
High Risk Disease*	40%	45%	0.415
CsA/CsA+MMF	**81% / 19%**	**100% / 0**	**0,024**

- *High risk AML: secondary AML, Adverse caryotype, no CR at the time of transplantation
- *High risk MDS: high risk IPSS, therapy related MDS

Devillier, R , BMT 2012

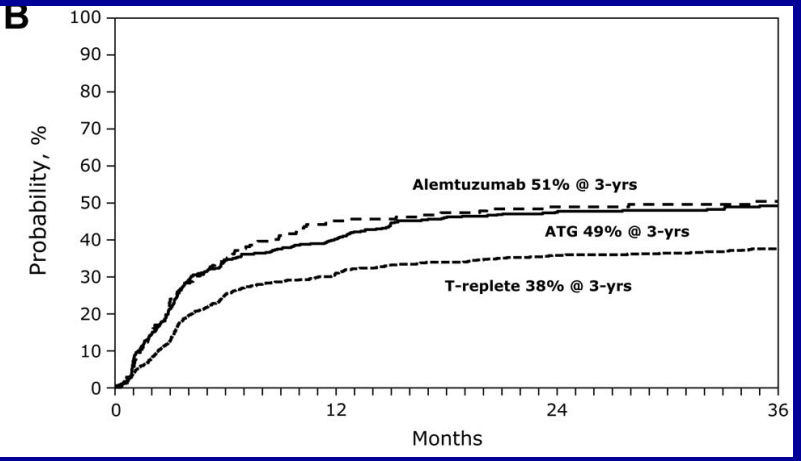
The increase from 2.5 to 5 mg/kg of r-ATG dose in RIC ***reduces acute and chronic GVHD*** *after allo MRD HSCT*

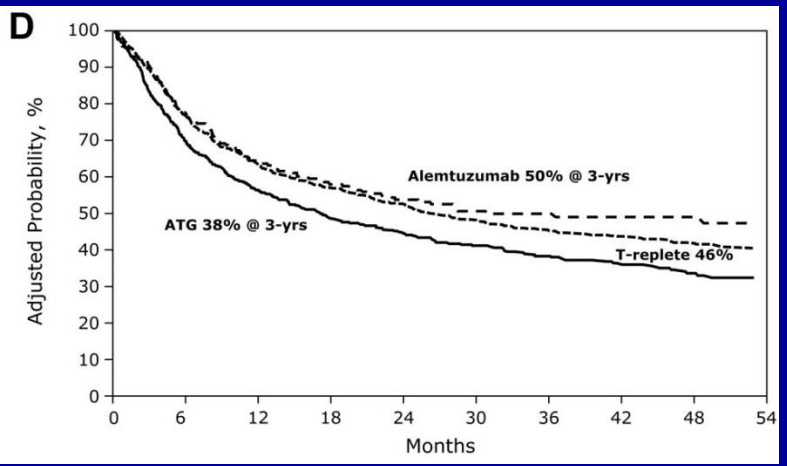




Devillier, R , BMT 2012

Impact of immune modulation with anti−T-cell antibodies on the outcome of reduced-intensity allogeneic hematopoietic stem cell transplantation for hematologic malignancies





The median total dose of alemtuzumab was 60 mg. Among patients who received ATG, approximately 70% of recipients received rabbit ATG (median dose, 7 mg/kg) and 27%, horse ATG (median dose, 40 mg/kg). The type of ATG administered was not reported for 3% of patients.

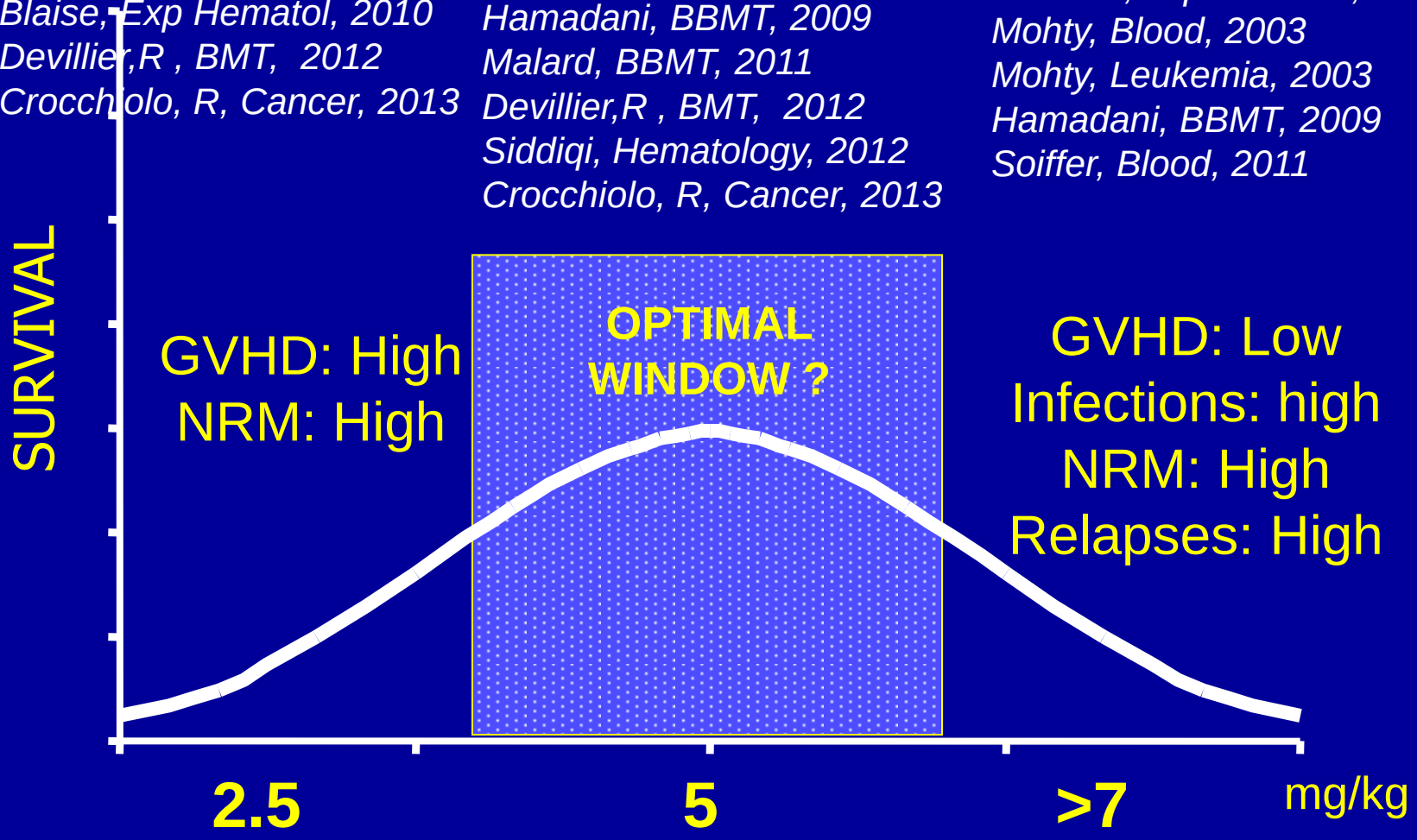
Soiffer, Blood, 2011

Importance of Dose ?

Blaise, Exp Hematol, 2010
Devillier,R , BMT, 2012
Crocchiolo, R, Cancer, 2013

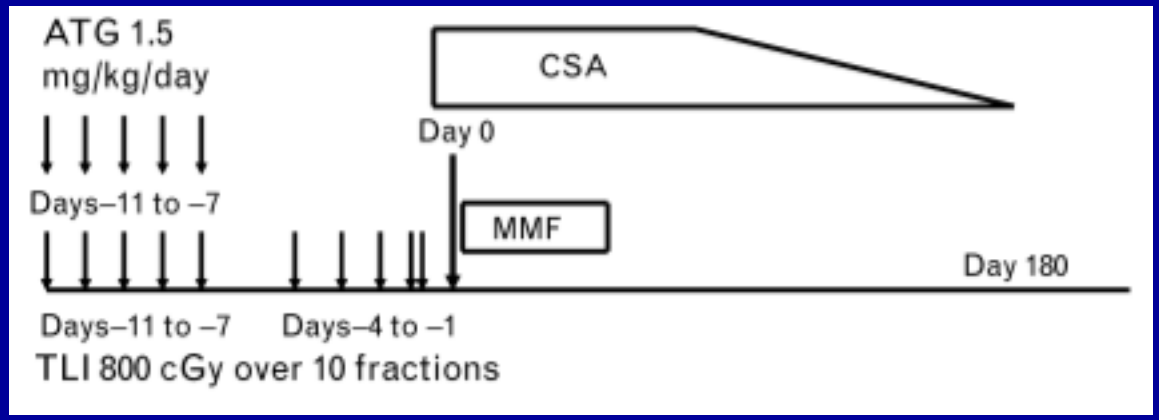
Duggan, P, BMT, 2002
Hamadani, BBMT, 2009
Malard, BBMT, 2011
Devillier,R , BMT, 2012
Siddiqi, Hematology, 2012
Crocchiolo, R, Cancer, 2013

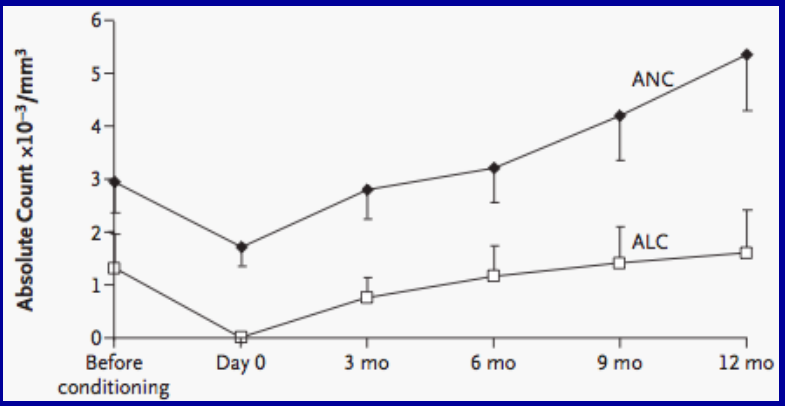
Faucher, exp Hematol, 2003
Mohty, Blood, 2003
Mohty, Leukemia, 2003
Hamadani, BBMT, 2009
Soiffer, Blood, 2011

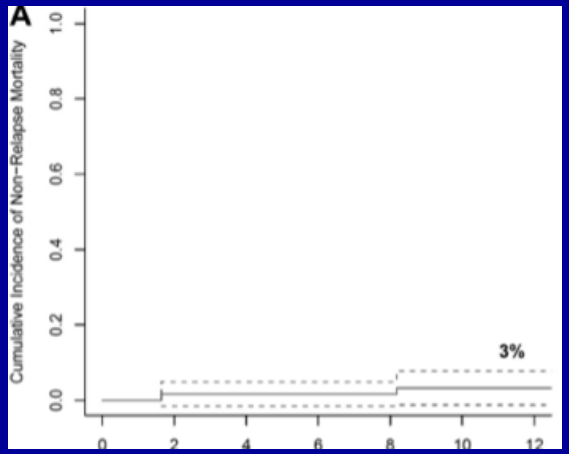


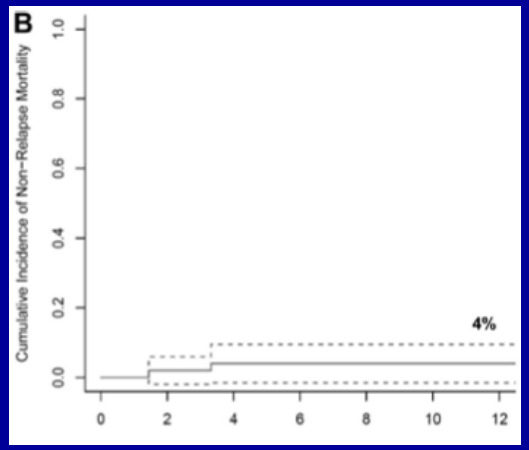
What about timing?

Protective Conditioning for AGVHD



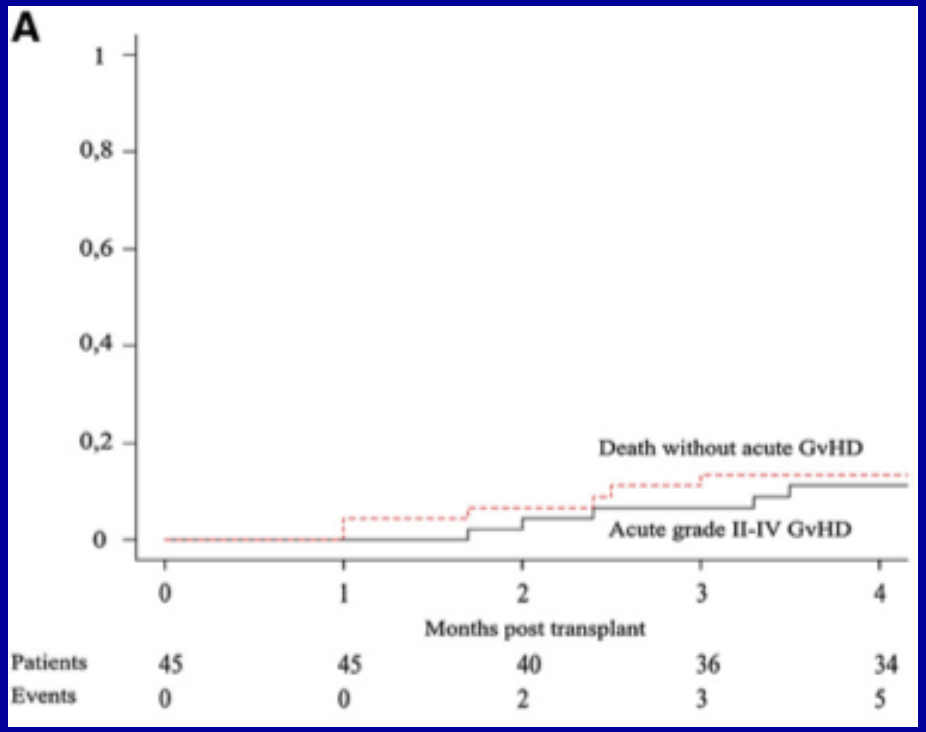


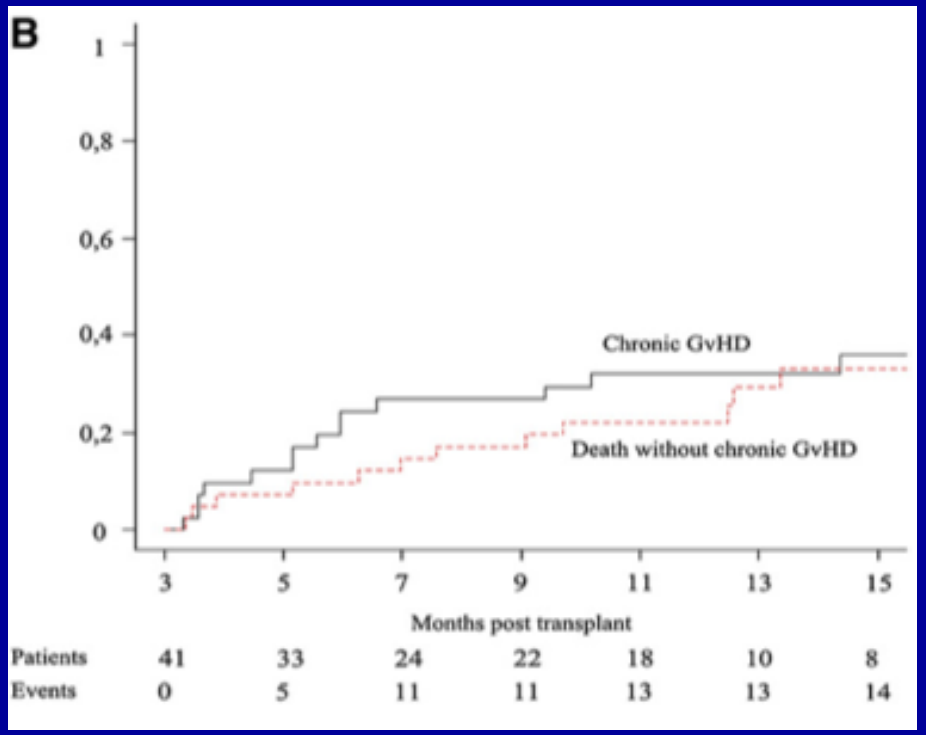




Lowsky, NEJM, 2005
Kohrt , Blood, 2009

Multicenter Experience using TLI and ATG as conditioning for allografting in hematological malignancies





Biol Blood Marrow Transplant 18:1600-1613, 2012

THE ADDITION OF ONE-DAY REST BETWEEN LAST ATG INFUSION AND STEM CELL INFUSION DID NOT AFFECT GVHD OCCURRENCE AFTER ALLOGENEIC TRANSPLANTATION WITH FLUDARABINE-BUSULFAN-ATG CONDITIONING

	No rest	1-day ATG rest	p
N. patients	57	51	
Age	57 (21-68)	58 (20-71)	0.27
Donor : sibling/MUD/MMUD	36/14/7	23/19/9	0.17
Disease risk* : low/interm/high/very high	3/41/10/2 **	3/34/13/1	0.77

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Incidence at 2-y=			
Grade 2-4 aGvHD	23% (12-34)	24% (12-36)	0.73
Grade 3-4 aGvHD	11% (3-19)	4% (0-9)	0.23
cGvHD overall	35% (22-48)	39% (24-54)	0.52
cGvHD extensive	26% (14-38)	20% (8-32)	0.74

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OS (95%CI)	64% (53-75)	73% (61-85)	0.87
PFS (95%CI)	49% (36-62)	69% (56-82)	0.14
NRM	18% (7-29)	17% (6-28)	0.75

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PFS (95%CI)	49% (36-62)	69% (56-82)	0.14
NRM	18% (7-29)	17% (6-28)	0.75
Relapse/progression	**39% (26-52)**	**27% (17-37)**	**0.04**

Conclusions

- rATG is efficient preventing severe forms of GVHD
- In the setting of minimal conditioning it prompts
  - Myeloid and lymphoid engraftment
  - GVHD prevention
- In the setting of RIC or MA-RTC
  - An intermediate dose
    - Triggers engraftment
    - Prevents GVHD
    - Is not associated with increased disease relapse
    - Is not associated with increased infection rates
  - Optimal timing ? Yet to be determined
    - Caution if few hours before graft infusion
    - Allow tuning of Immunosuppression / T-cell depletion effects
    - Probable balance dose / timing

Reduced Toxicity Conditionings in older pts NMAC vs. RIC vs. MA-RTC

Study	**NMAC Seattle Cons**
N	274
Age	60 (5-74)
AML	100%
CR1 / CR>1 /adv	58% / 36% / 6%
CDT TBI2 BU2 BU4	100%
Thymoglobulin	0%
MRD / UD	43% / 57%

Reduced Toxicity Conditionings in older pts NMAC vs. RIC vs. MA-RTC

Study	**NMAC Seattle Cons**	**RIC IPC, Marseille H Dieu, Nantes**
N	274	102
Age	60 (5-74)	58 (20-70)
AML	100%	100%
CR1 / CR>1 /adv	58% / 36% / 6%	76% /20% / 4%
CDT TBI2 BU2 BU4	100%	100%
Rabbit ATG	0%	100%
MRD / UD	43% / 57%	56% / 44%

Reduced Toxicity Conditionings in older pts NMAC vs. RIC vs. MA-RTC

Study	**NMAC Seattle Cons**	**RIC IPC, Marseille H Dieu, Nantes**	**MA-RTC MD Anderson**
N	274	102	79
Age	60 (5-74)	58 (20-70)	58 (55-76)
AML	100%	100%	80%
CR1 / CR>1 /adv	58% / 36% / 6%	76% /20% / 4%	32% / 23% / 47%
CDT TBI2 BU2 BU4	100%	100%	100%
Thymoglobulin	0%	100%	1 AG mm / UD
MRD / UD	43% / 57%	56% / 44%	52% / 48%

Reduced Toxicity Conditionings in older pts NMAC vs. RIC vs. MA-RTC

Study	**NMAC Seattle Cons**	**RIC IPC, Marseille H Dieu, Nantes**	**MA-RTC MD Anderson**
N	274	102	79
Graft Failure	12	0	0
G 2-4 aGVHD	52%	23%	41%
cGVHD	43%	32%	43%
NRM	16%-26%	24%	26%

Reduced Toxicity Conditionings in older pts NMAC vs. RIC vs. MA-RTC

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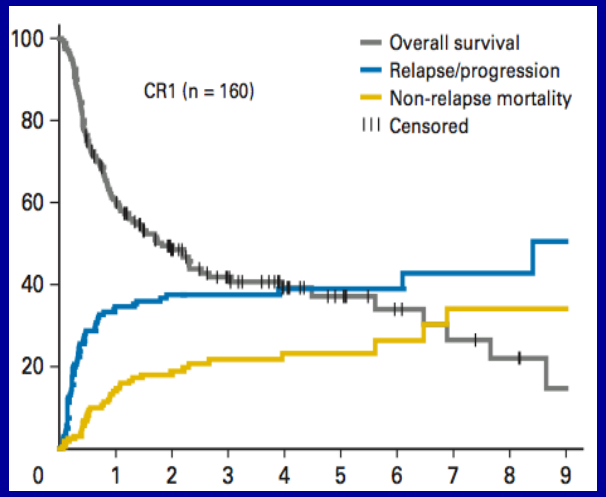
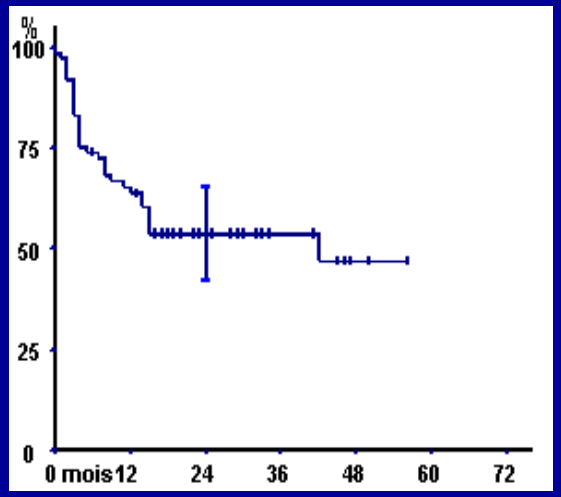
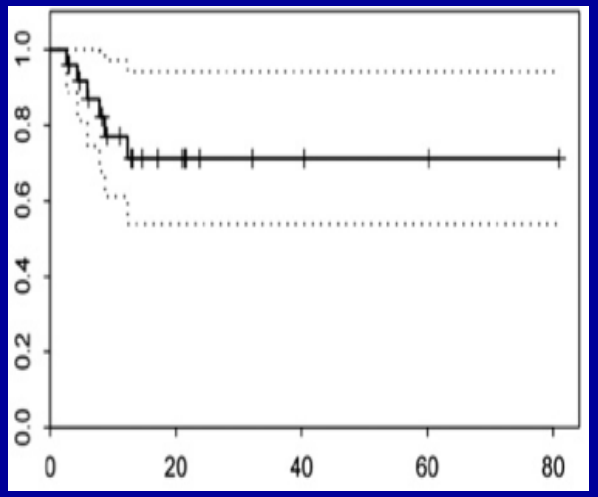
Reduced Toxicity Conditionings in older pts NMAC vs. RIC vs. MA-RTC

CR1 AML







NMAC
N=160

RIC
N=78

MA-RTC
N= 25

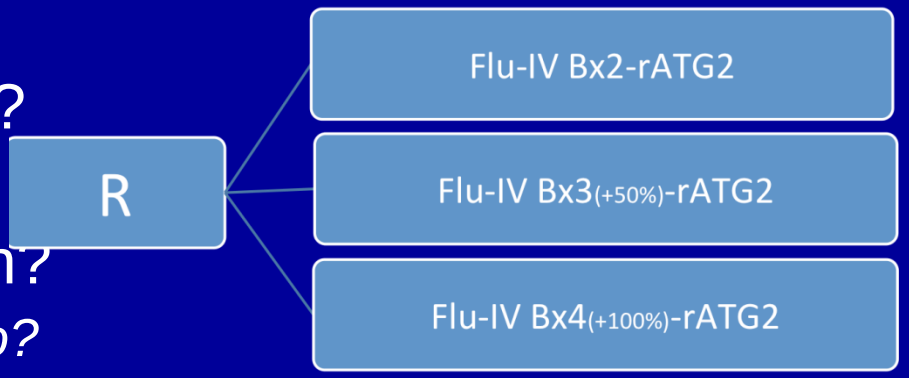
Fifteen years of RTC…So?

- Achievements in transplantation
  - Stable engraftment
  - Decreased NRM
  - There is an efficient allogeneic antitumor effect
- Achievements in therapy
  - Older and/or unfit patients
  - Different diagnoses
  - Alternative donors: Haploidentical Donor

Thus…RTC (RIC/MA-RTC) have changed the stage!

What's next?
Remaining major issues

- Tumor control
  - Are MA-RTC a step forward?
    - *Dose Intensity studies*
  - Optimal Immunosuppression?
    - *Ex vivo T Cell depletion vs. No?*
  - Post Transplant intervention?
    - Cellular immunotherapy
    - Tumor antigen vaccination
    - Targeted therapy



- Quality of life
  - Efficiency must be evaluated on composite events:

    Tumor control + survival + quality of survival

Acknowledgments

- Institut Paoli Calmettes
  - **Transplant Program**
    - S Furst
    - J El Cheikh
    - L Castagna
    - A Granata
    - S Harbi
    - R Crocchiolo
    - R Devillier
    - C Oudin
    - C Saillard
    - I Rahal
  - **Nursing Staff**
    - L Caymaris
  - **Cellular Therapy Unit**
    - C Chabannon
  - **Hematology department**
    - N Vey
    - R Bouabdallah
  - M Mothy (Nantes, Paris)
  - FB Petersen (SLC)
  - B Andersson (Houston)

R. Devillier

R. Crocchiolo

C Saillard

I Rahal


That's all Folks!