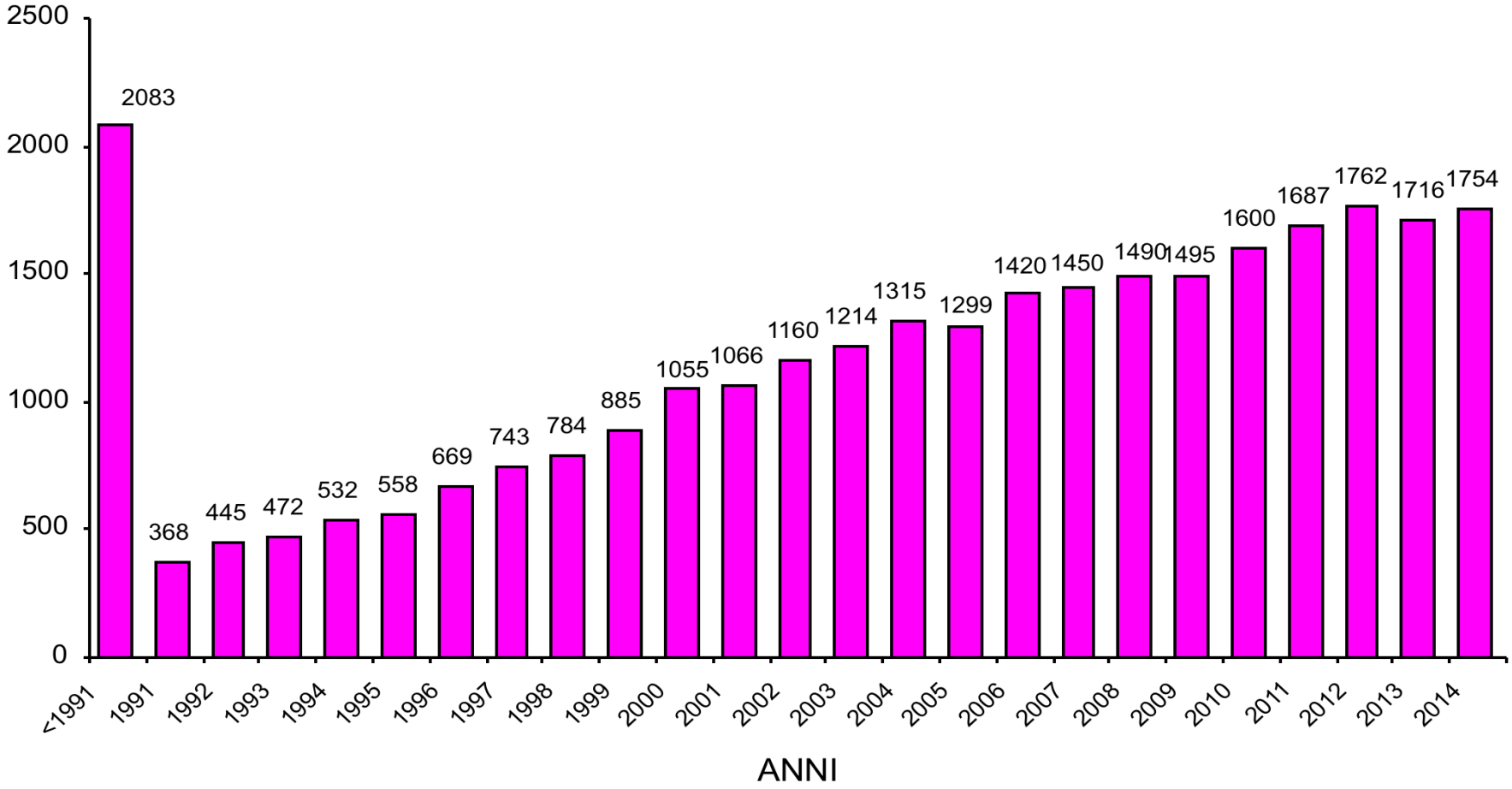
OSPEDALE
SAN RAFFAELE

# Nuovi farmaci nel condizinamento del trapianto nelle leucemie acute

*Jacopo Peccatori*

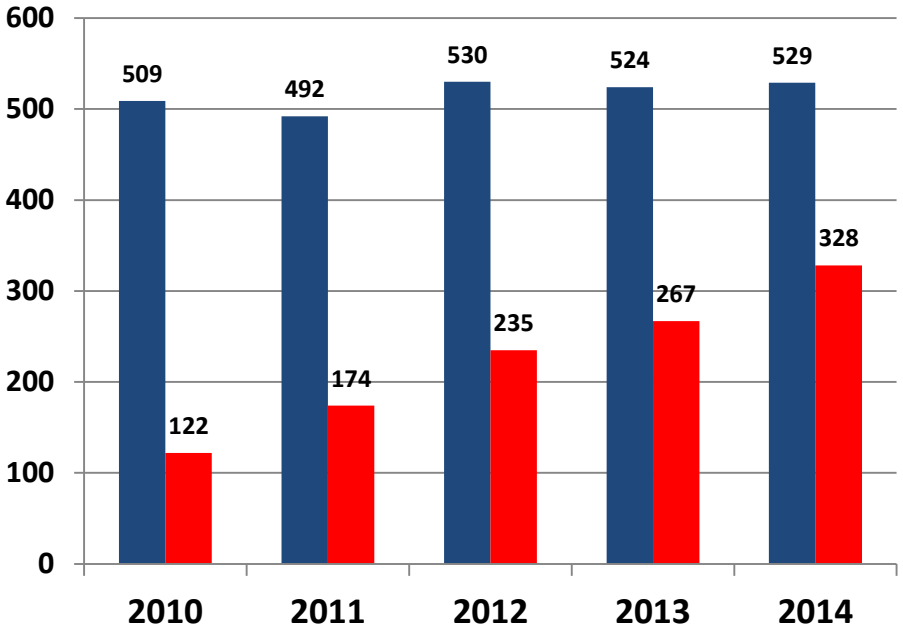
# GITMO Trapianto Allogenico

*Allotrapianti registrati*

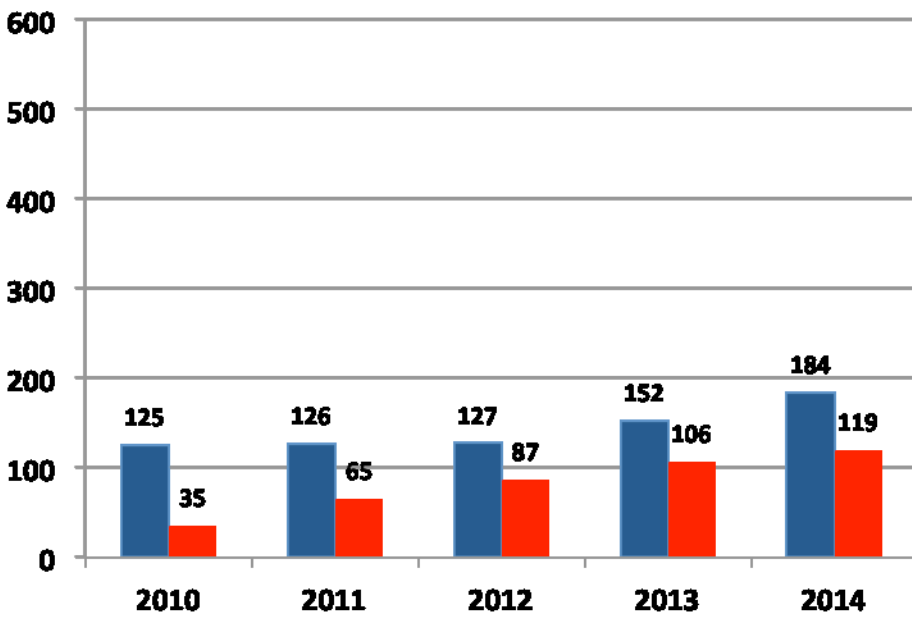


# Pazienti adulti sottoposti ad 1 solo trapianto (APLO o MUD) nel periodo 2010-2014

## Qualunque patologia




## Solo LAM



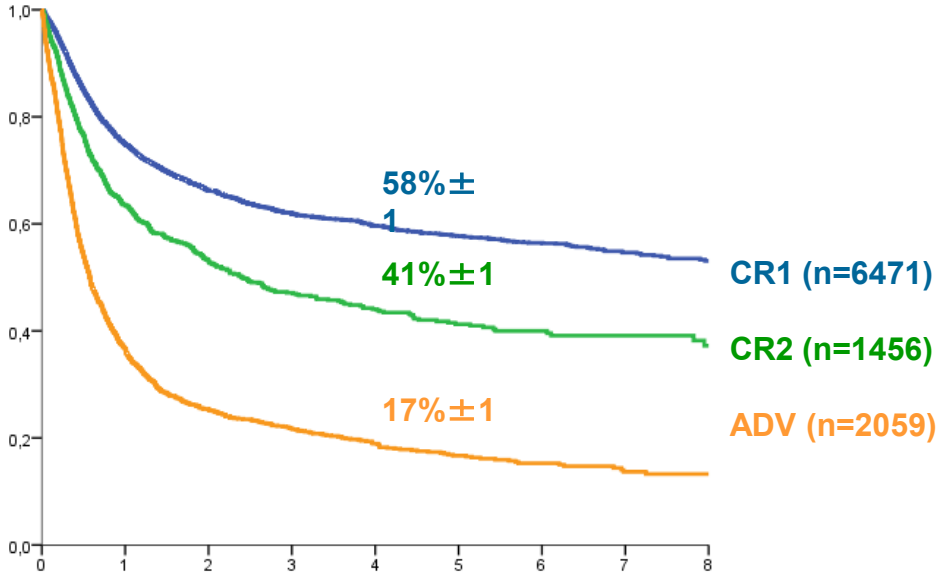

MUD Haplo

# ACUTE LEUKAEMIA REGISTRY

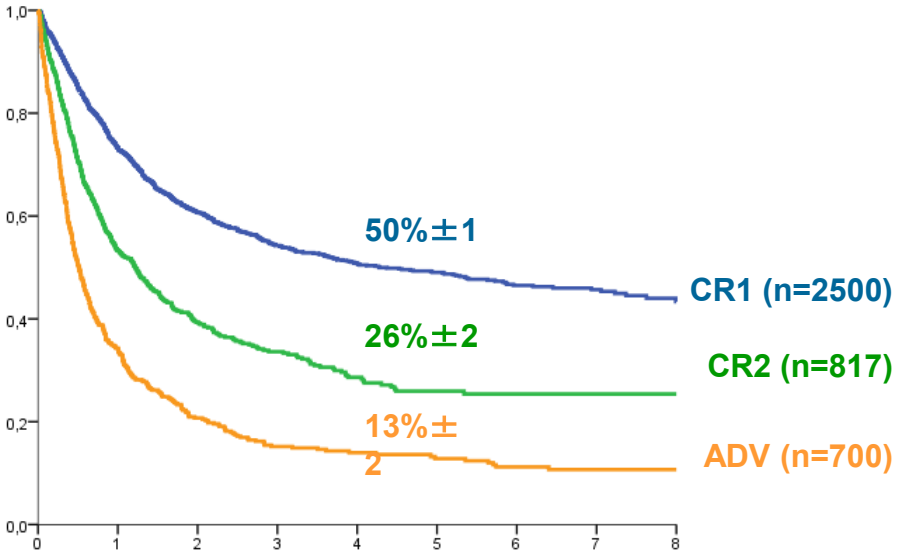
## ADULTS TRANSPLANTED FROM 2000 TO 2010

## HLA ID SIBLING ALLOGENEIC (Overall Survival)

### AML n=9986




### ALL n=4017

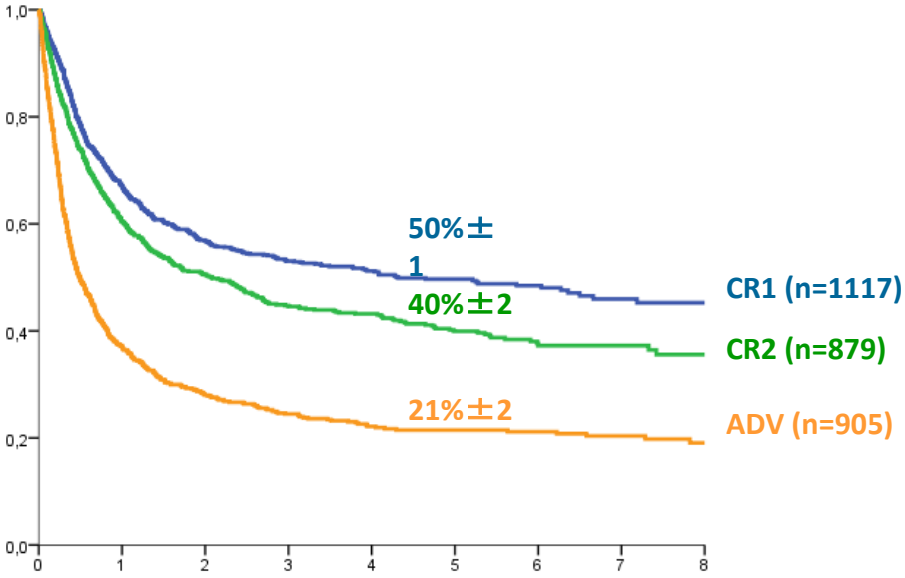


# ACUTE LEUKAEMIA REGISTRY

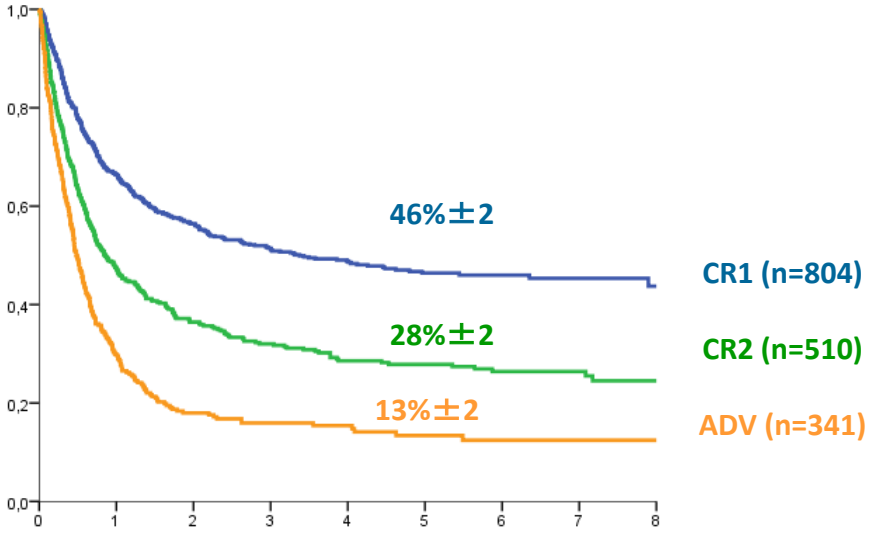
## ADULTS TRANSPLANTED FROM 2000 TO 2010

## MATCHED UNRELATED DONOR (Overall Survival)

### AML n=2901




### ALL n=1655



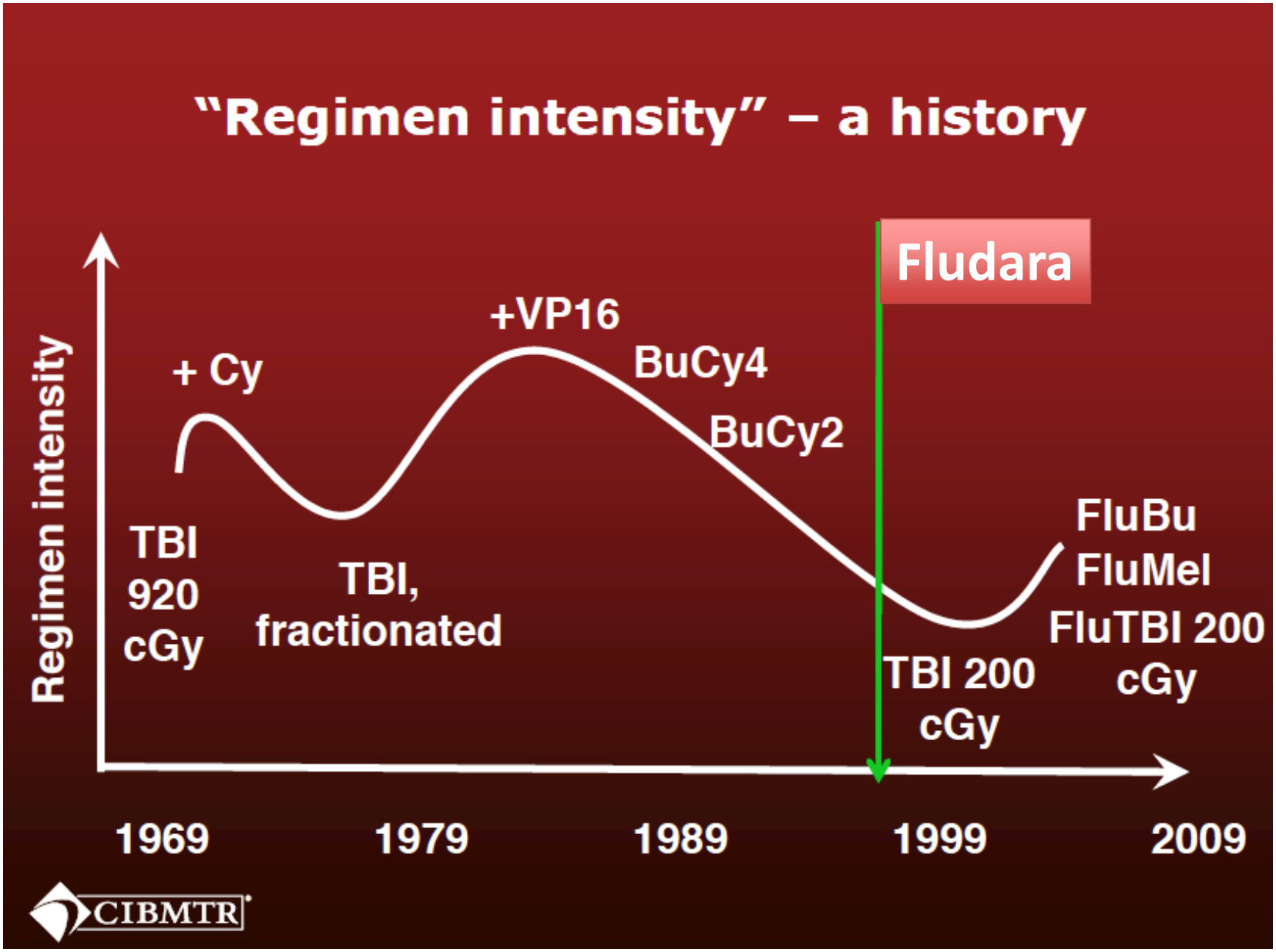
# Conditioning Paradigm Shift

**OLD**

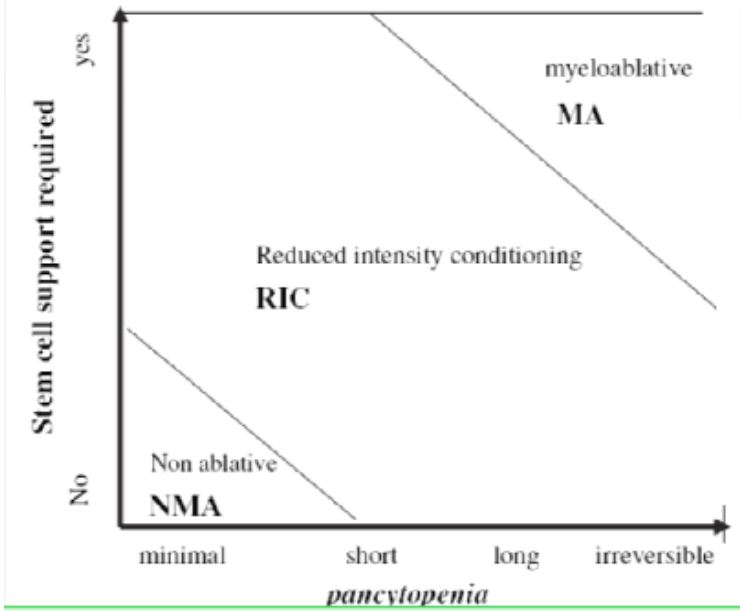
- Engraftment requires marrow ablation
- Conditioning regimen is the mainstay for tumor eradication
- Narrow Therapeutic window

**NEW**

- Host immune suppression
- Graft versus Tumor Effect is significant in many diseases
- Wider Therapeutic Index


"Regimen intensity" – a history
Regimen intensity
+ Cy
+VP16
BuCy4
BuCy2
Fludara
TBI
920
cGy
TBI,
fractionated
TBI 200
cGy
FluBu
FluMel
FluTBI 200
cGy
1969
1979
1989
1999
2009
CIBMTR

# Regimen Definitions and Abbreviations




## Consensus Examples of Common Regimen Combinations

**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 et al; BBMT 2009; 15: 1628

**Operationally Defined**
**Basis :** expected duration of cytopenia & need for HSC support for recovery
**MA:** irreversible cytopenia & manadatory HSC support

**NMA:** minimal cytopenia & do not need HSC support

**RIC :** a regimen that does not fulfill MA or NMA criteria

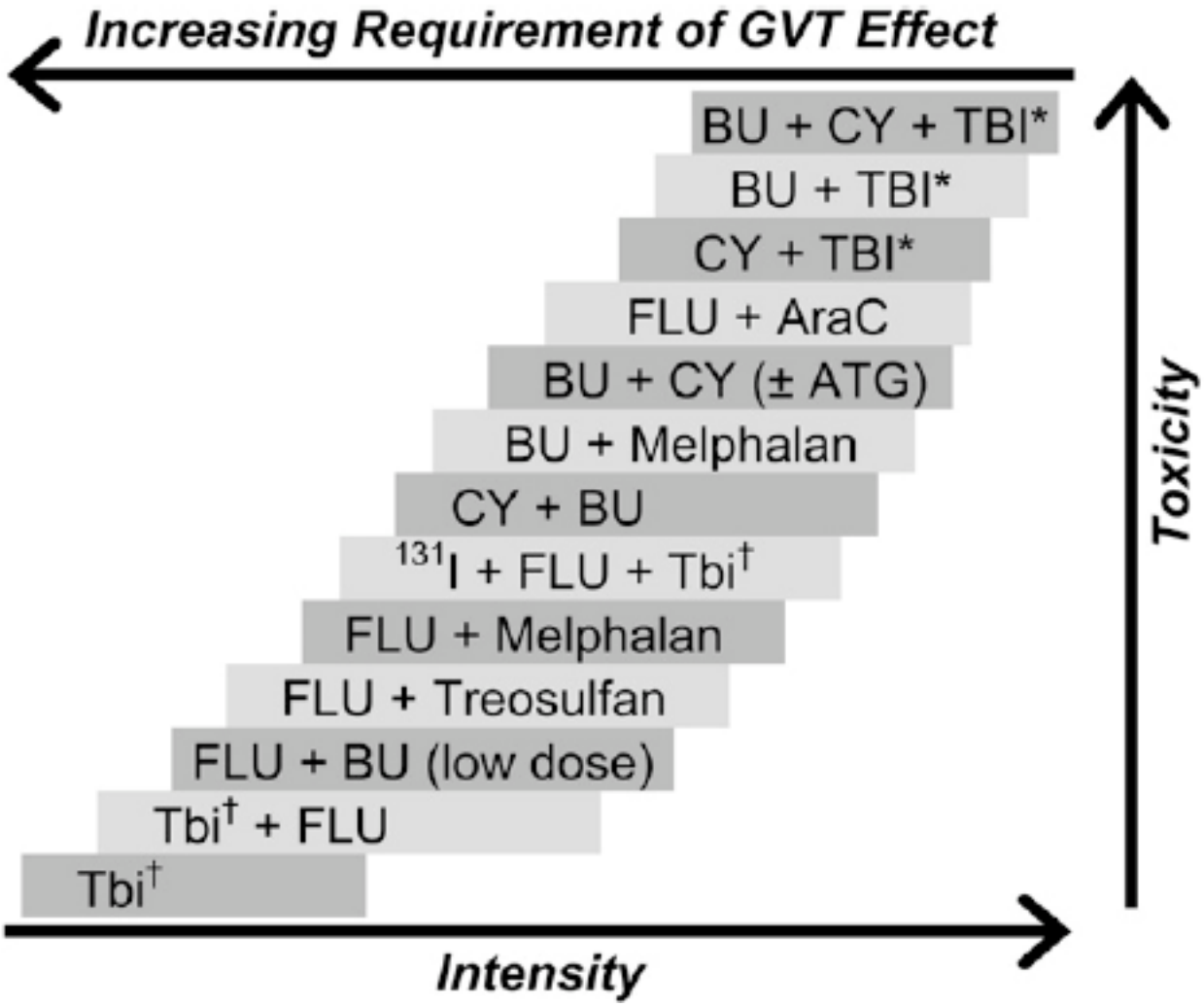
# Conditioning regimens for hematopoietic cell transplantation: one size does not fit all

Boglarka Gyurkocza[1,2] and Brenda M. Sandmaier[3,4]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Weill Cornell Medical College of Cornell University, New York, NY; [3]Fred Hutchinson Cancer Research Center, Seattle, WA; and [4]University of Washington School of Medicine, Seattle, WA

| RIC regimens | Nonmyeloblative regimens |
|---|---|
| TBI ≤500 cGy as a single fraction or ≤800 cGy if fractionated | FLU + CY + ATG |
| Total BU ≤9 mg/kg | FLU + AraC + Ida |
| Total MEL <140 mg/m$^2$ | Cladribine + AraC |
| Thiotepa <10 mg/kg | Total lymphoid irradiation + ATG |
| | TBI ≤2 Gy ± purine analog |

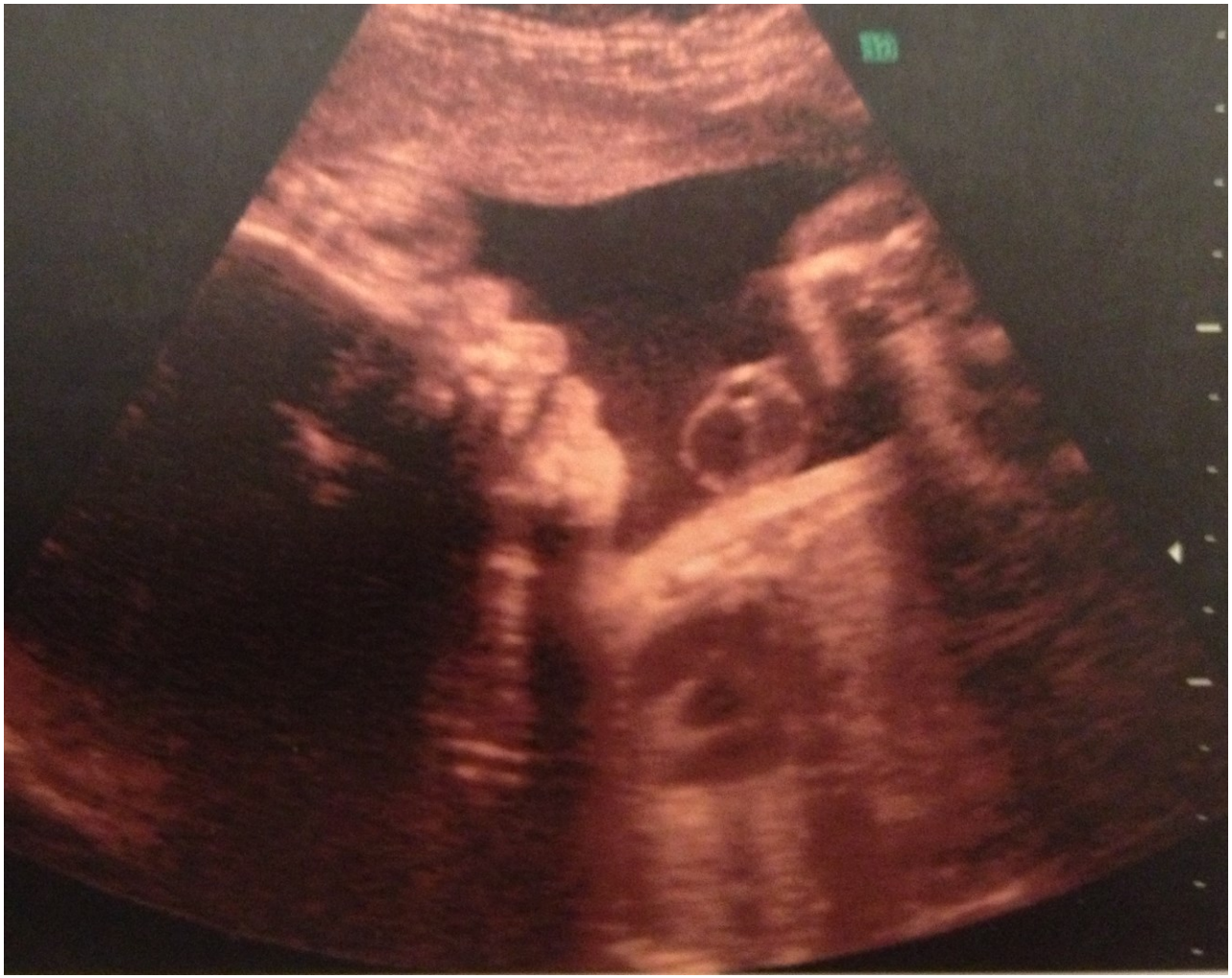
Adapted from Giralt et al.[104,105] AraC, cytarabine; ATG, antithymocyte globulin; BU, busulfan; CY, cyclophosphamide; FLU, fludarabine; Ida, idarubicin; MEL, melphalan.


Increasing Requirement of GVT Effect
BU + CY + TBI*
BU + TBI*
CY + TBI*
FLU + AraC
BU + CY (± ATG)
BU + Melphalan
CY + BU
131I + FLU + Tbi†
FLU + Melphalan
FLU + Treosulfan
FLU + BU (low dose)
Tbi† + FLU
Tbi†
Toxicity
Intensity

# Reduced Intensity Conditioning Regimen

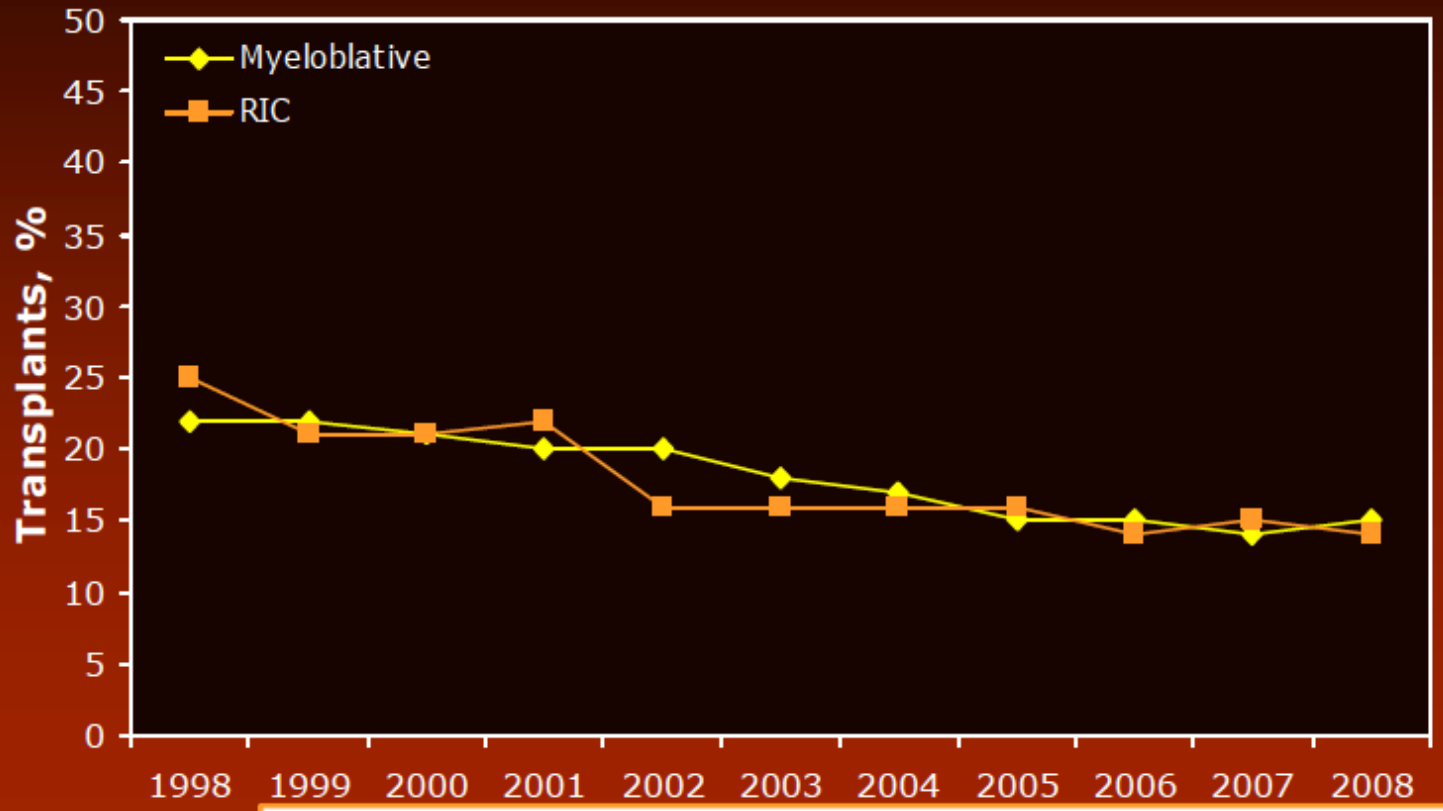
- Advantages
  - Decreased acute toxicity
  - Application to older and/or morbid patients
- Disadvantages
  - Loss/decrease in anti-tumor activity from cytotoxic chemotherapy/radiation

# Fertility preservation



# 100-day Mortality after Allogeneic Transplantation, 1998-2008

## - by conditioning intensity -

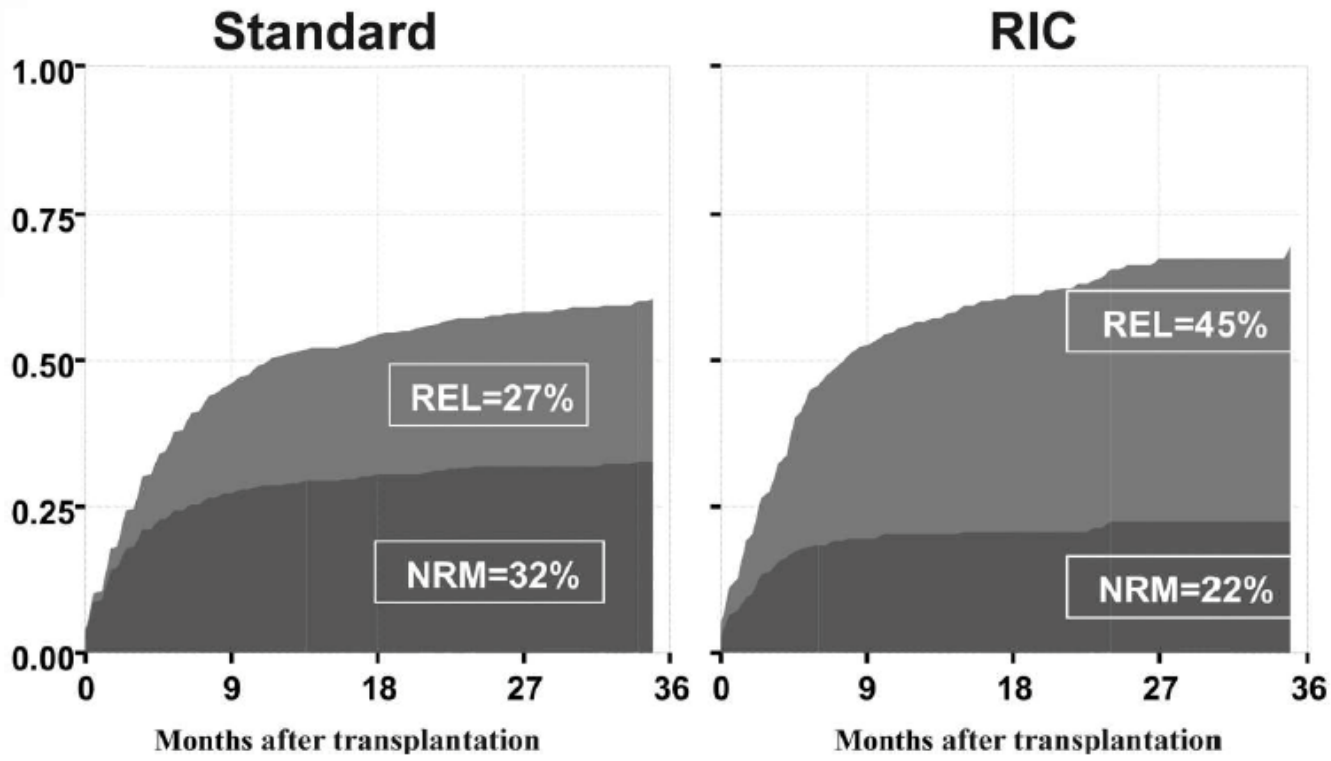



CIBMTR®

**Early mortality has improved for allogeneic transplants in general.**

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

## NRM and REL cumulative incidence estimates (36-month) from a competing risk model, estimated separately for both conditioning regimens for MDS




*Martino, R. et al. Blood 2006;108:836-846*

# The Conditioning Masterchef

- Immnosuppressive
- Myeloablative

- Active on Leukemia

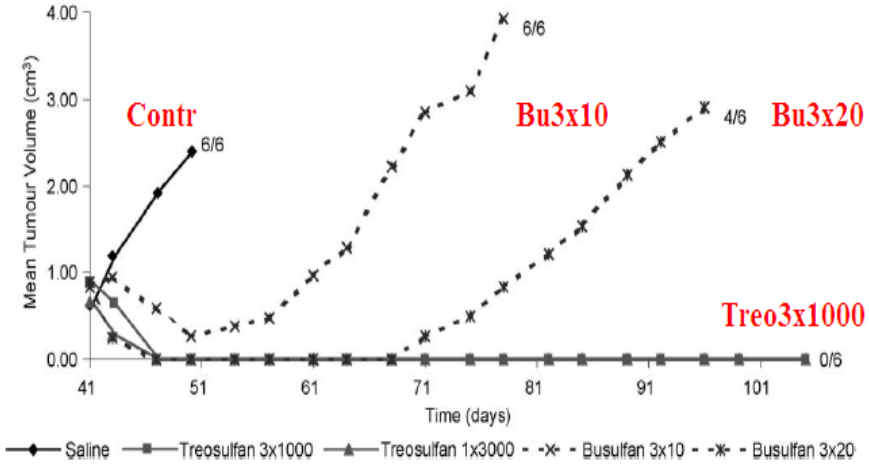
- Low extra-hematologic toxicity

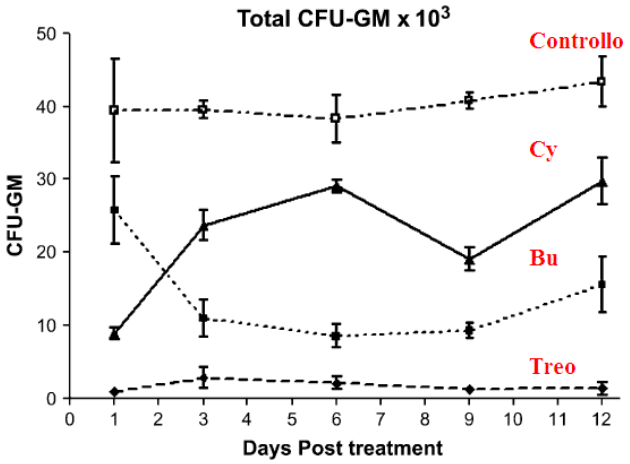
- Finacially sustainable

**= Fludarabine + Alkylating agent**

# Treosulfan

Alkylating agent
Structural analog of Busulfan
Prodrug, soluble in water
Stem cell toxicity
Immunosuppressive activity
In vitro anti leukemia activity



# Treosulfan-based conditioning before hematopoietic SCT: more than a BU look-alike

I Danylesko, A Shimoni and A Nagler

**Table 1** Comparative properties of alkylating agents

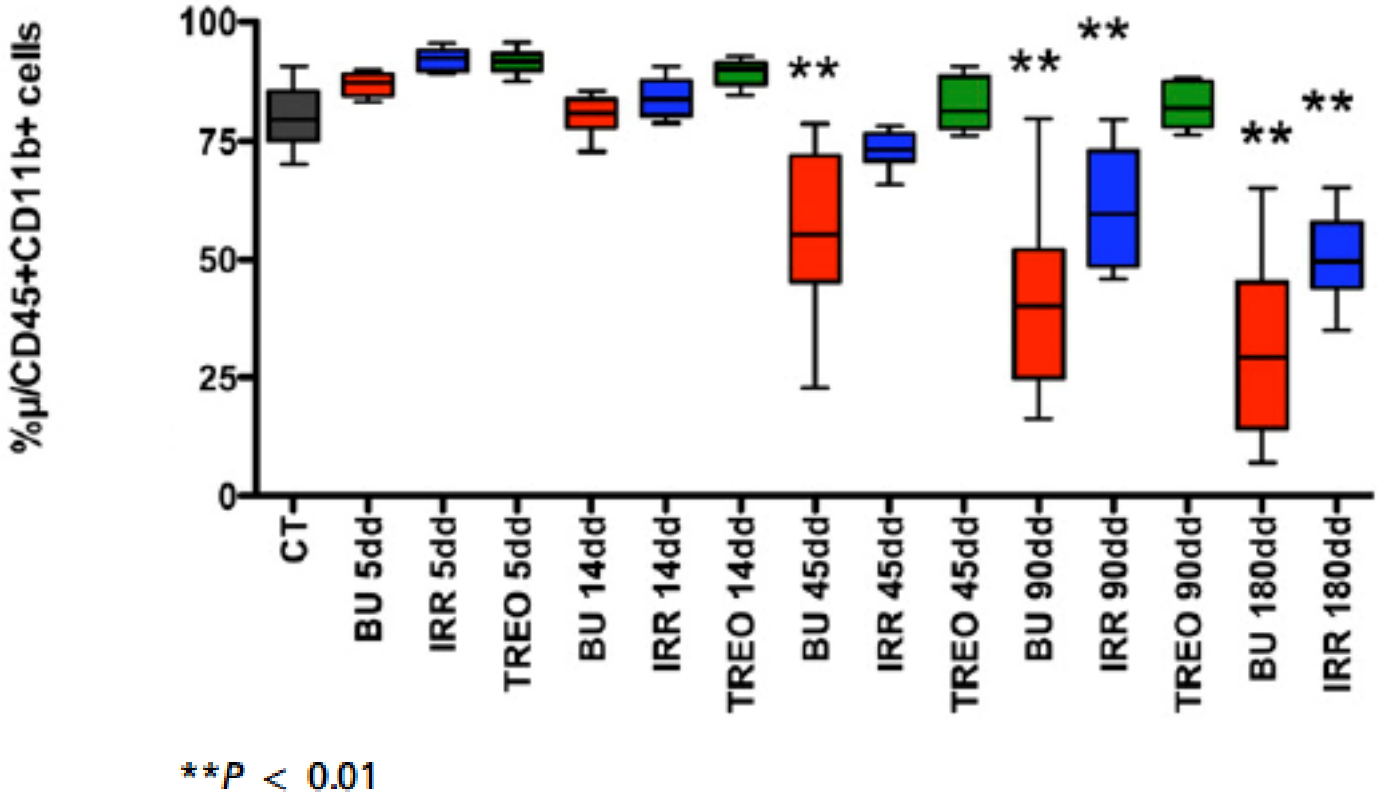
| *Properties* | *BU* | *Treosulfan* | *Melphalan* | *Cytoxan* |
|---|---|---|---|---|
| *Immunosuppression* | | | | |
| *In vitro* | −[26] | +++[25] | − | ++[81] |
| *In vivo* | −[84] | +++[30] | −[83] | ++[82] |
| Distribution | Liver, lung, brain, kidney[84] | Kidneys[23] | Kidneys + spontaneus chemical degradation[83] | Kidney, hepatic bioactivation85 |
| Liver toxicity and VOD | +++[86] | +[41] | −[85] | +++[85] |
| Pneumonitis | ++[87–89] | − | − | + |
| Hemorrhagic cystitis | +[87–89] | − | − | +++[85] |
| Convulsion | +++[87–89] | +[43] | − | − |
| Mucositis | ++ | ++[41,43] | +++[83,90] | − |
| Cardiotoxicity | − | − | − | ++[85] |
| BM suppression | +++[91] | +++ | +++ | ++ |

Abbreviations: CNS = central nervous system; VOD = veno-occlusive disease.

**Bone Marrow Transplantation (2011)**, 1–10

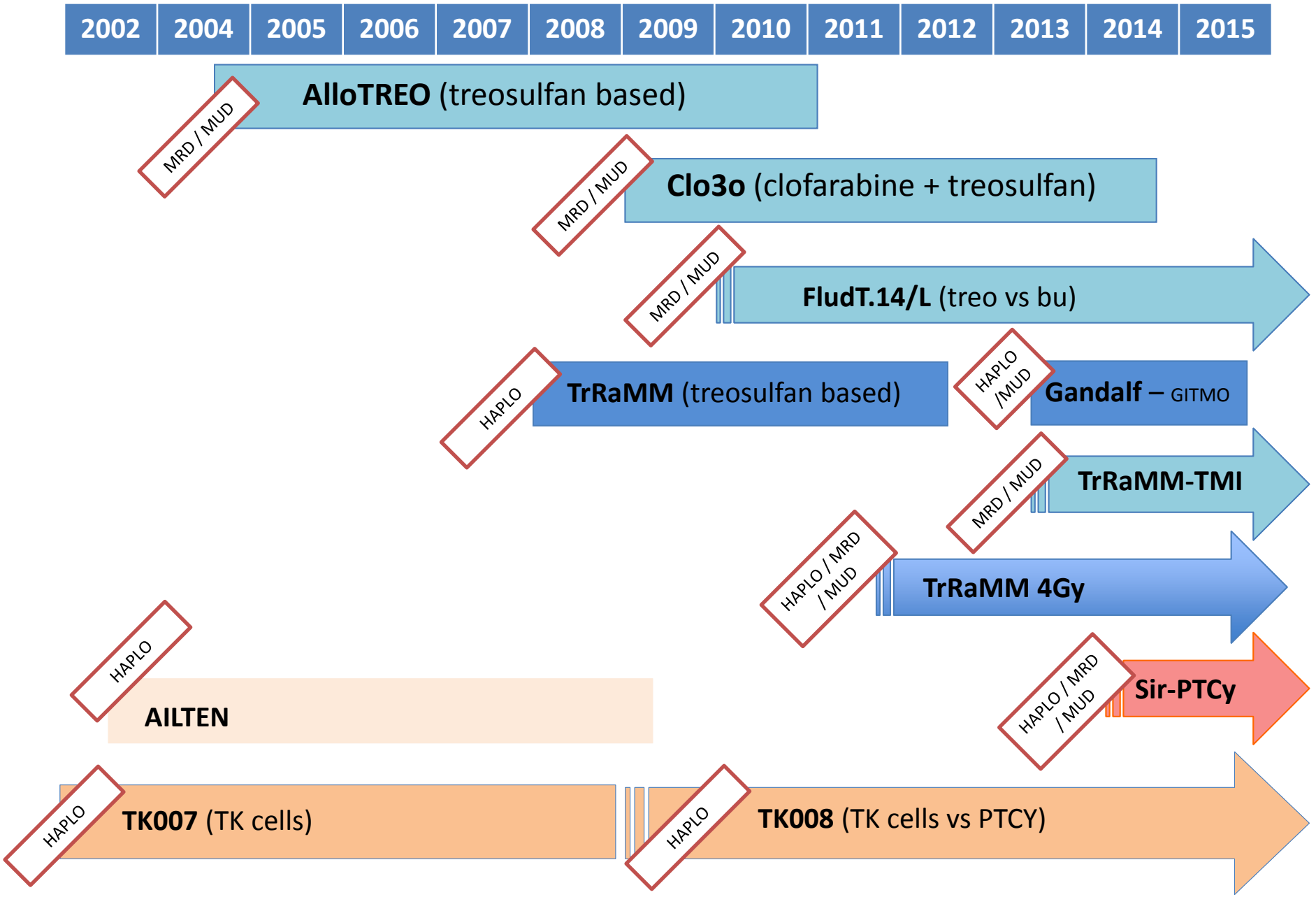
# Brain conditioning is instrumental for successful microglia reconstitution following hematopoietic stem cell transplantation

Alessia Capotondo[a,b], Rita Milazzo[a,b], Letterio Salvatore Politi[c,d], Angelo Quattrini[e], Alessio Palini[f], Tiziana Plati[a], Stefania Merella[a], Alessandro Nonis[g], Clelia di Serio[g], Eugenio Montini[a], Luigi Naldini[a,b], and Alessandra Biffi[a,1]




$^{**}P < 0.01$

# San Raffaele Allogeneic Plan



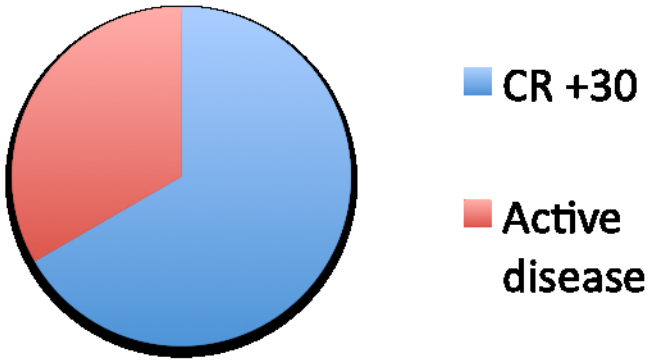
# Treosulfan-fludarabine-ATG-F based reduced-toxicity conditioning regimen: multicentre "Allo-Treo" study, results in 183 patients with haematological malignancies

**Alessandro Crotta, Alessandro Lorusso, Giovanni Martinelli, Sergio Cortelazzo, Maria Beatrice Pinazzi, Giorgio La Nasa, Roberto Foà, Stella Santarone, Alessandro Rambaldi, Andrea Gallamini, Renato Fanin, Francesco Merli, Angelo Michele Carella, Consuelo Corti, Annalisa Ruggeri, Magda Marcatti, Maria Teresa Lupo Stanghellini, Andrea Assanelli, Carlo Messina, Massimo Bernardi, Fabio Ciceri, Jacopo Peccatori**

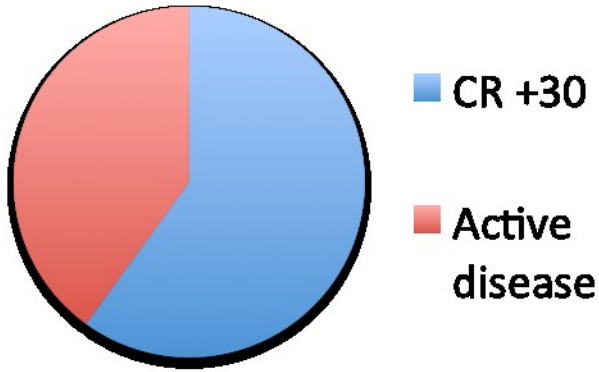
| | -6 | -5 | -4 | -3 | -2 | -1 | 0 | .... |
|---|---|---|---|---|---|---|---|---|
| Treosulfan 14 g/m$^2$ | X | X | X | | | | | |
| Fludarabine 30 mg/m$^2$ | X | X | X | X | X | | | |
| ATG Fresenius* 10 mg/kg | | | X | X | X | | | |
| Rituximab* 500 mg | | | | | | X | | |
| Allo-SCT | | | | | | | X | |
| Cyclosporine + MTX | | | | | | X | X | X |

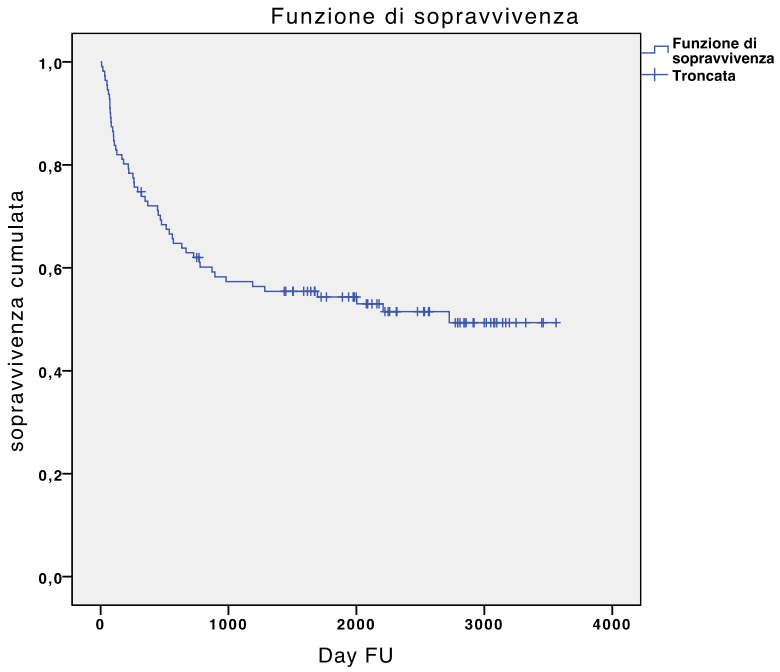
* only in MUD

## AML (30 patients)




## ALL (10 patients)

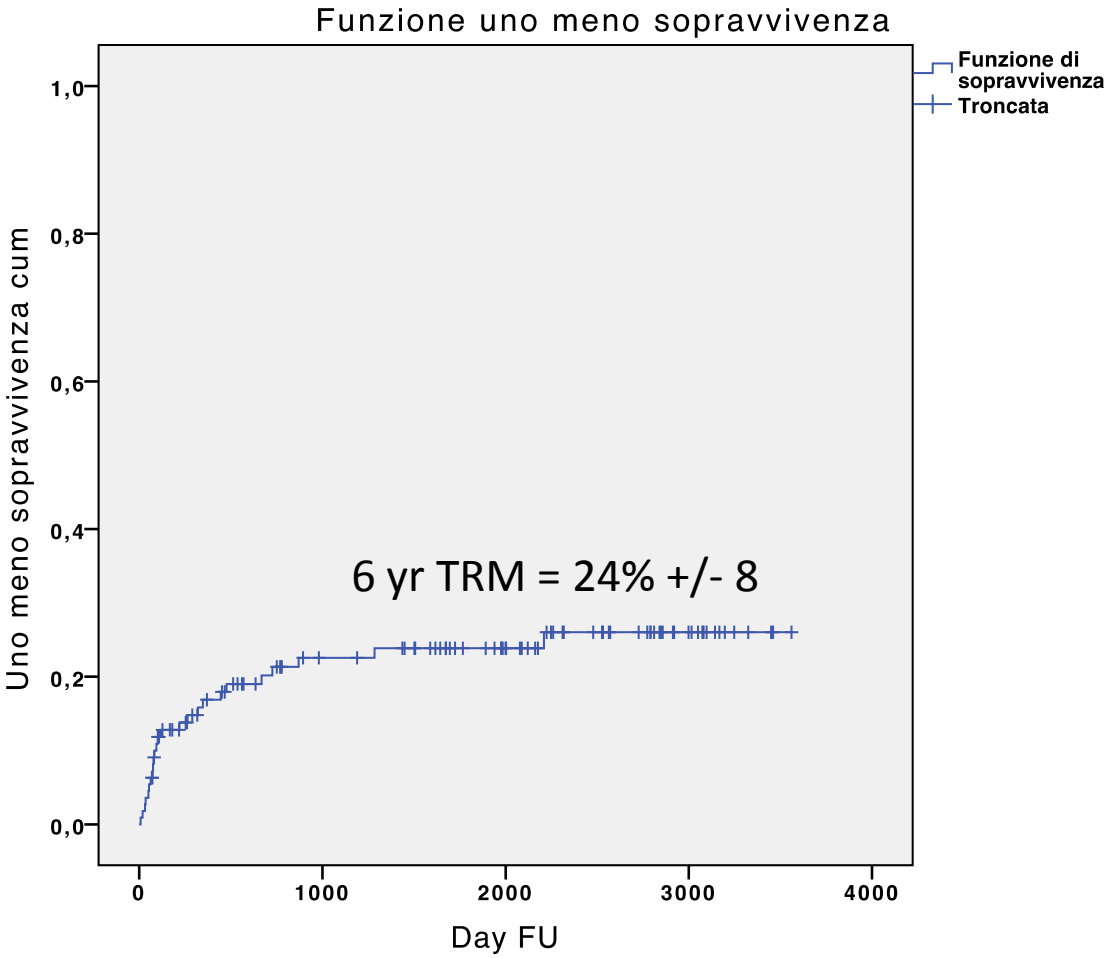


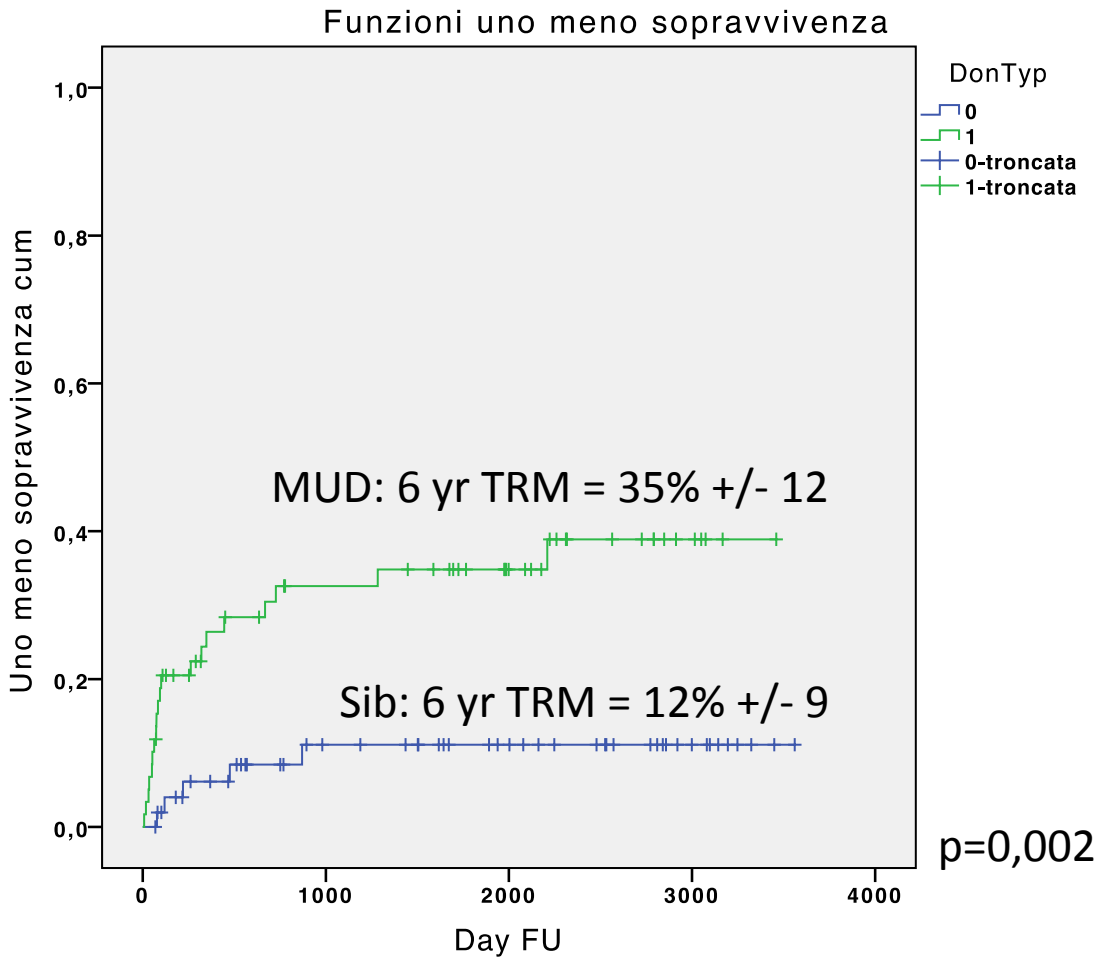

**OS**

Median follow-up: 6,3 years (317-3561) n=111

# TRM

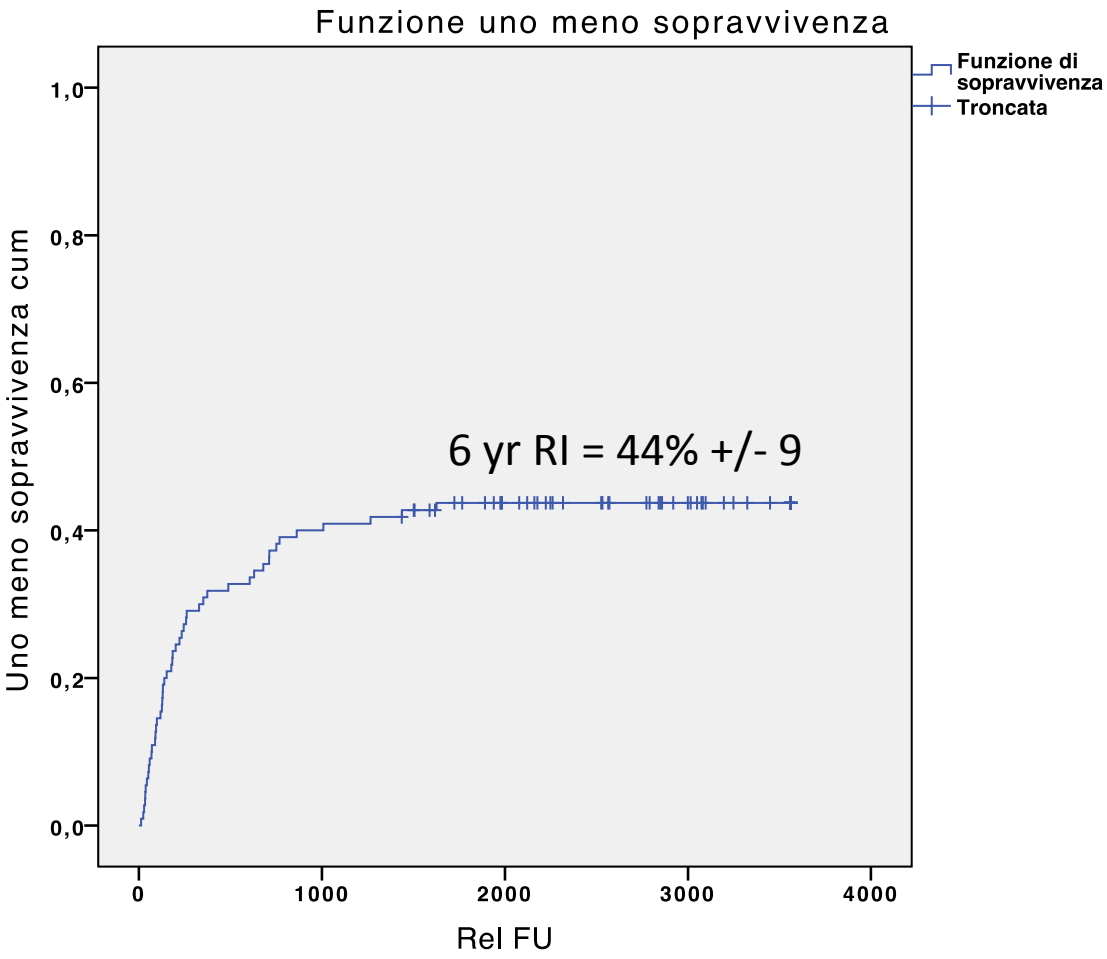

Funzione uno meno sopravvivenza
Funzione di sopravvivenza
Troncata
Uno meno sopravvivenza cum
1,0
0,8
0,6
0,4
0,2
0,0
6 yr TRM = 24% +/- 8
0
1000
2000
3000
4000
Day FU

# TRM by donor

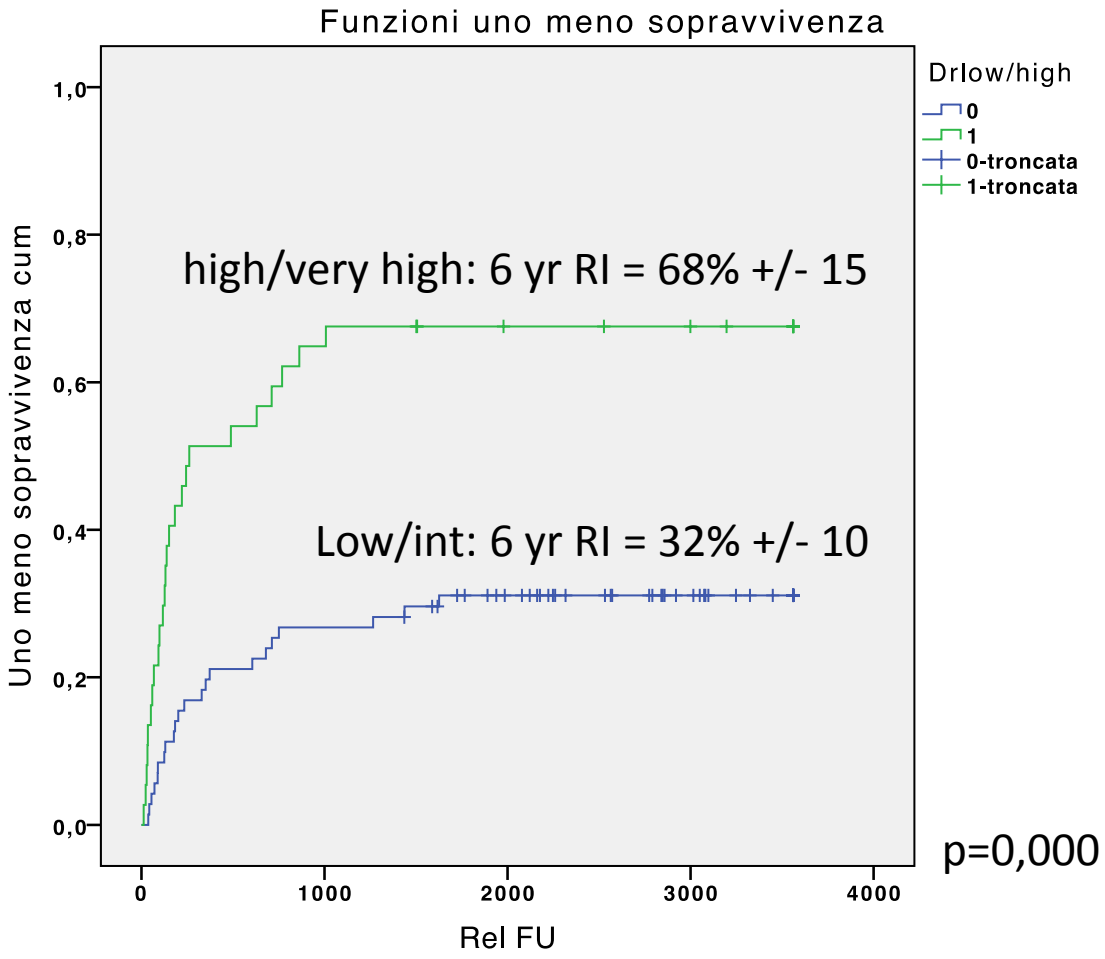



p=0,002

# Relapse Incidence

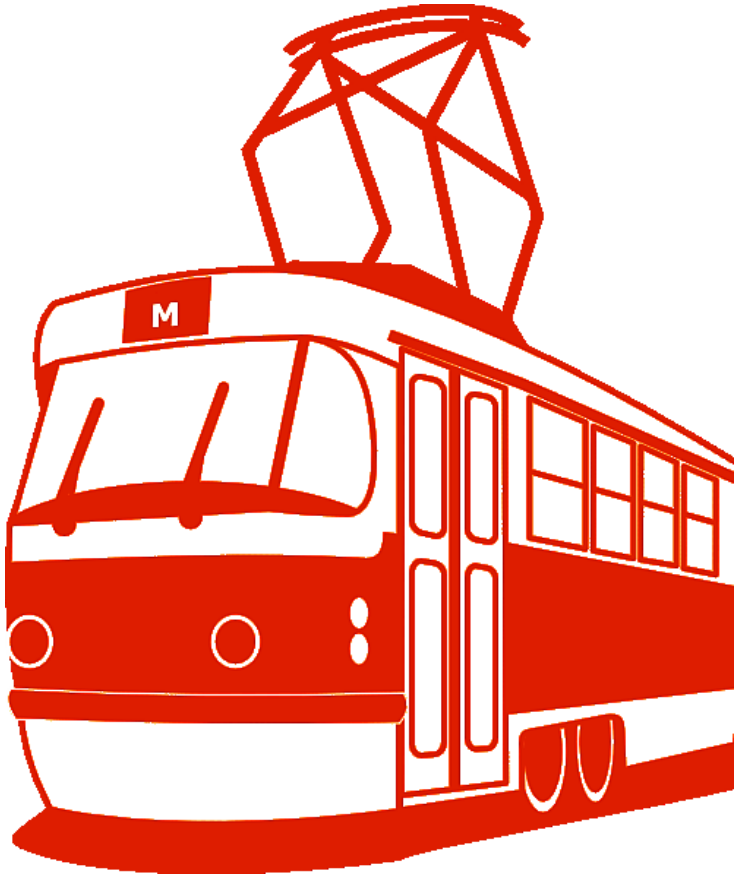


# Relapse incidence by DRI




p=0,000

# TrRaMM




**Treosulfan-based conditioning and Rapamycin-ATG-F-based GvHD prophylaxis prior to unmanipulated allogeneic haematopoietic stem cell transplantation from a mismatched donor in patients with high risk haematological malignancies**

TrRaMM

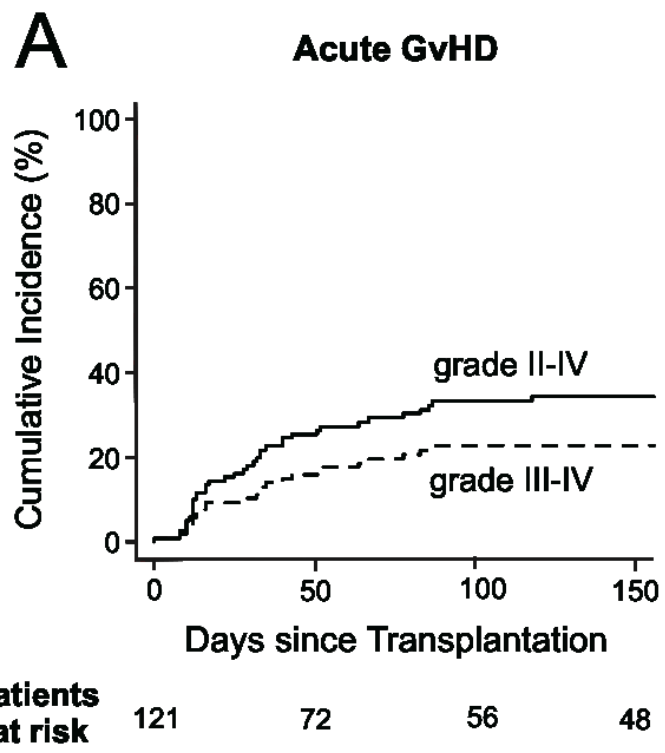
**Eudract 2007-5477-54**

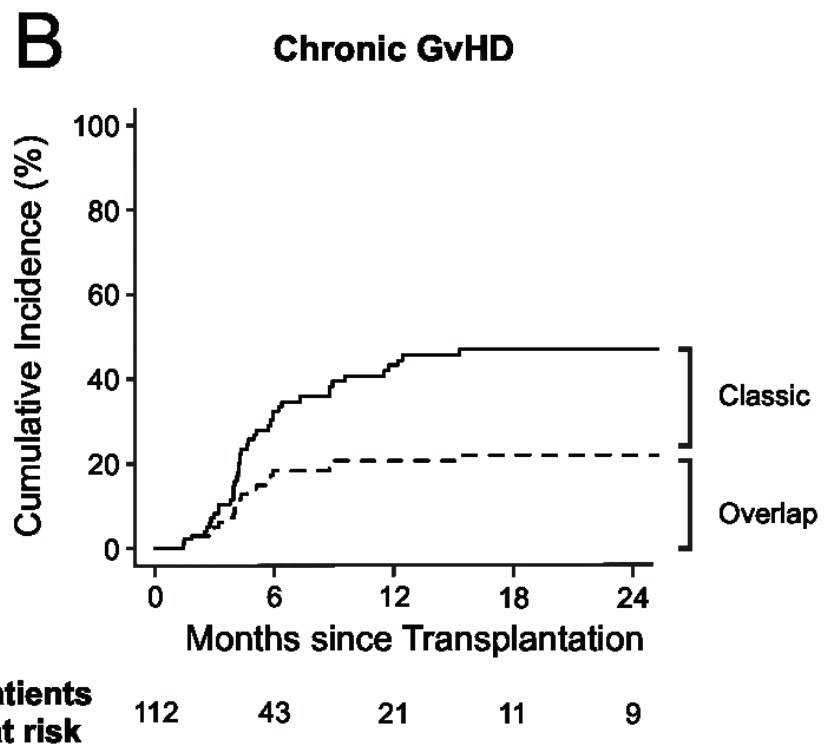
*Peccatori et al. Leukemia.* 2015 Feb. 29(2):396-405.

# Treatment Schedule

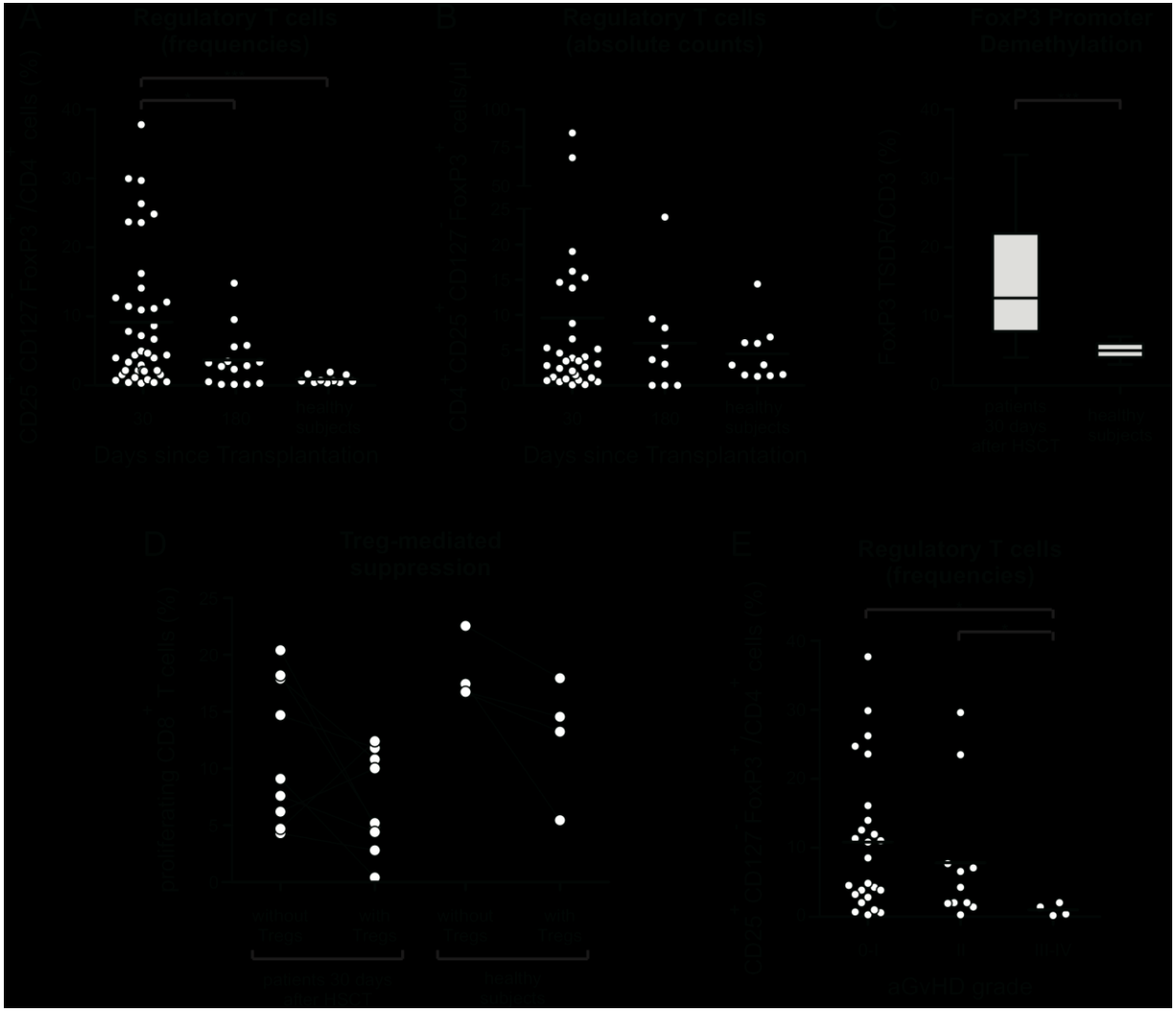
| | -6 | -5 | -4 | -3 | -2 | -1 | 0 | …. |
|---|---|---|---|---|---|---|---|---|
| Treosulfan 14 g/m$^2$ | X | X | X | | | | | |
| Fludarabine 30 mg/m$^2$ | X | X | X | X | X | | | |
| ATG Fresenius 10 mg/kg | | | X | X | X | | | |
| Rituximab 500 mg | | | | | | X | | |
| Haplo-PBSC | | | | | | | X | |
| Rapamycin | X | X | X | X | X | X | X | X |
| MMF | | | | | | | X | X |

# GvHD

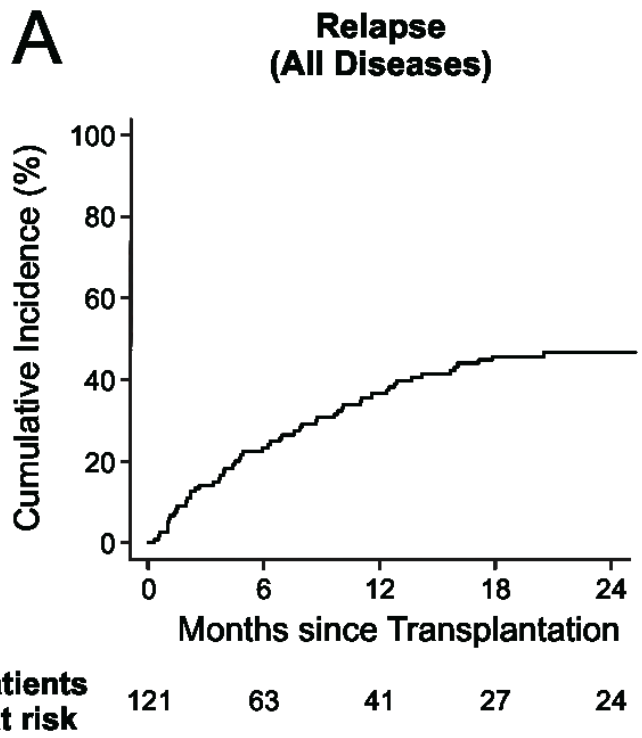

A
Acute GvHD
Cumulative Incidence (%)
100
80
60
40
20
0
grade II-IV
grade III-IV
0
50
100
150
Days since Transplantation
Patients at risk
121
72
56
48

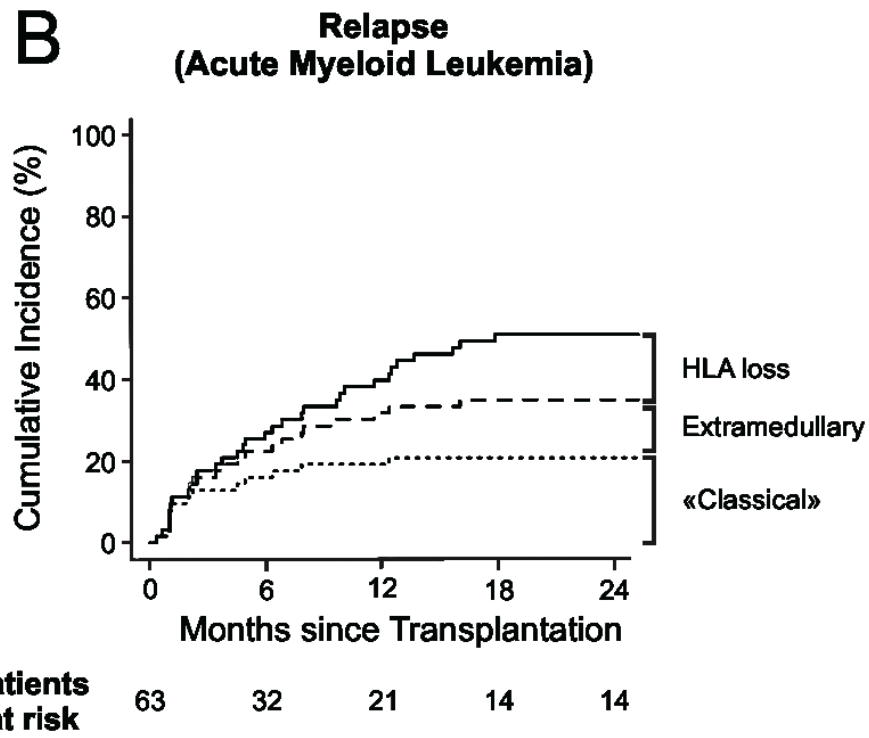

B
Chronic GvHD
Cumulative Incidence (%)
100
80
60
40
20
0
Classic
Overlap
0
6
12
18
24
Months since Transplantation
Patients at risk
112
43
21
11
9

# Treg and GvHD

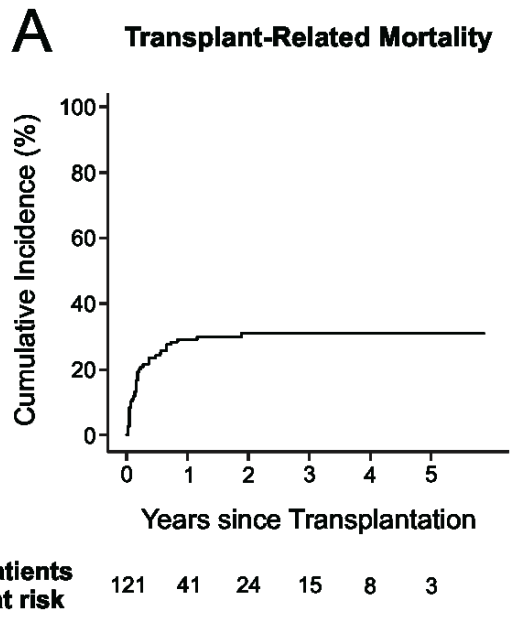


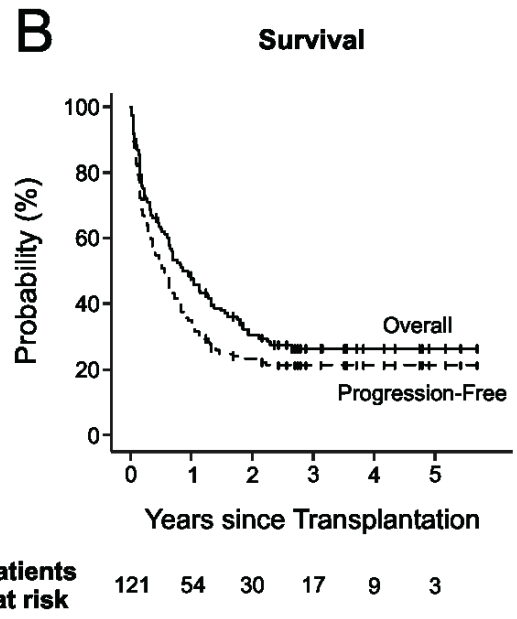
# Relapse

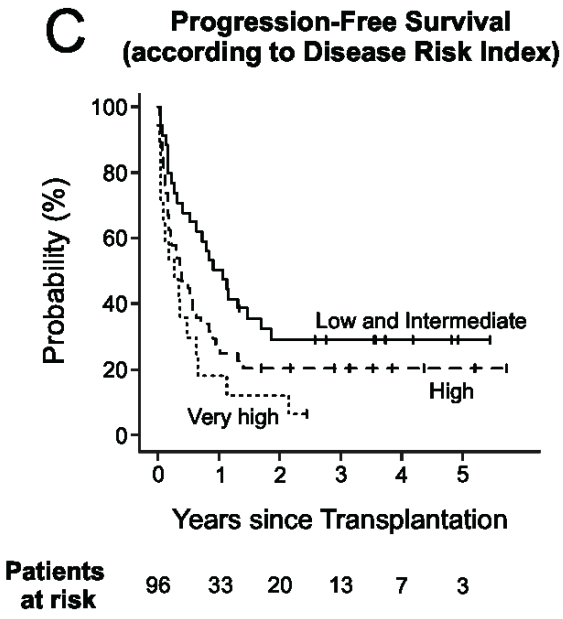

A
Relapse
(All Diseases)
Cumulative Incidence (%)
100
80
60
40
20
0
0
6
12
18
24
Months since Transplantation
Patients at risk
121
63
41
27
24


B
Relapse
(Acute Myeloid Leukemia)
Cumulative Incidence (%)
100
80
60
40
20
0
0
6
12
18
24
Months since Transplantation
HLA loss
Extramedullary
«Classical»
Patients at risk
63
32
21
14
14

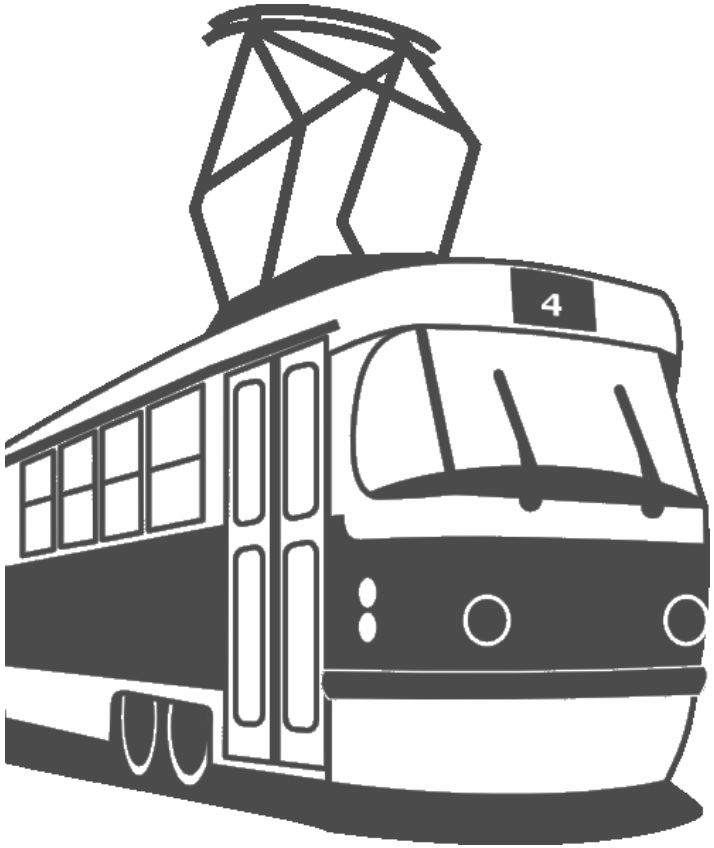
# Outcome


A
Transplant-Related Mortality
Cumulative Incidence (%)
100
80
60
40
20
0
0 1 2 3 4 5
Years since Transplantation
Patients at risk 121 41 24 15 8 3


B
Survival
Probability (%)
100
80
60
40
20
0
Overall
Progression-Free
0 1 2 3 4 5
Years since Transplantation
Patients at risk 121 54 30 17 9 3


C
Progression-Free Survival
(according to Disease Risk Index)
Probability (%)
100
80
60
40
20
0
Low and Intermediate
High
Very high
0 1 2 3 4 5
Years since Transplantation
Patients at risk 96 33 20 13 7 3

# TrRaMM 4Gy




**Treosulfan-based conditioning and Rapamycin-ATG-F-based GvHD prophylaxis prior to unmanipulated allogeneic haematopoietic stem cell transplantation from a mismatched donor in patients with high risk haematological malignancies**

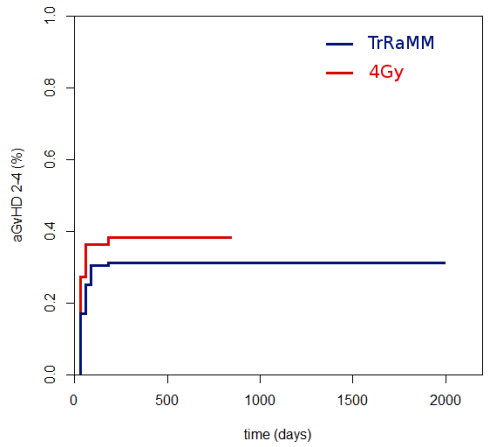
TrRaMM 4Gy

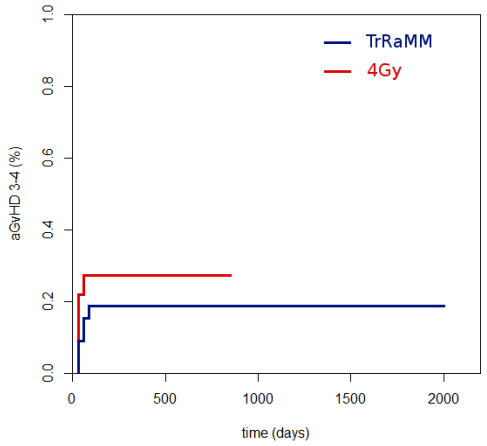
**Eudract 2011-001534-42**

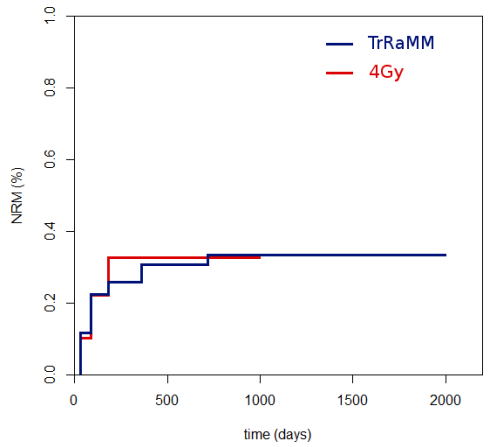
# Treatment Schedule

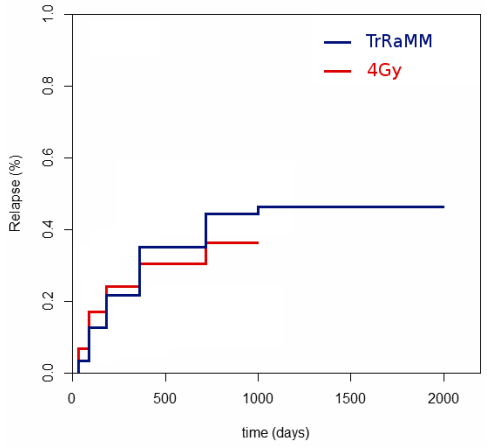
| | -6 | -5 | -4 | -3 | -2 | -1 | 0 | …. |
|---|---|---|---|---|---|---|---|---|
| Treosulfan 14 g/m$^2$ | X | X | X | | | | | |
| Fludarabine 30 mg/m$^2$ | X | X | X | X | X | | | |
| ATG Fresenius 10 mg/kg | | | X | X | X | | | |
| Rituximab 500 mg | | | | | | X | | |
| **TBI 2 Gy** | | | | | | **X** | **X** | |
| Haplo-PBSC | | | | | | | X | |
| Rapamycin | X | X | X | X | X | X | X | X |
| MMF | | | | | | | X | X |

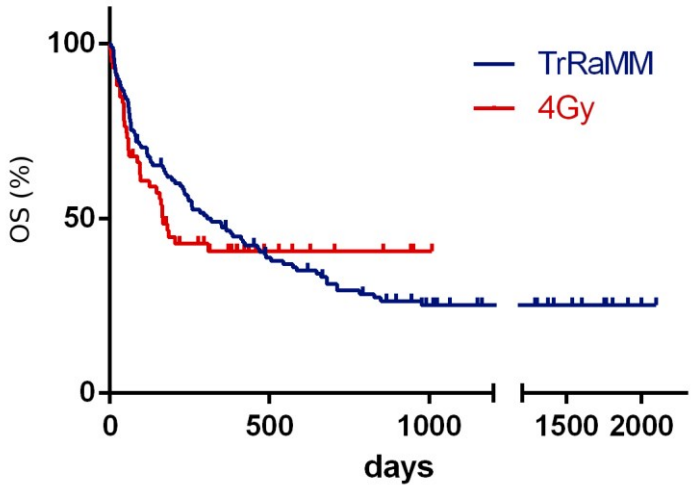
# TrRaMM *vs* TrRaMM 4Gy



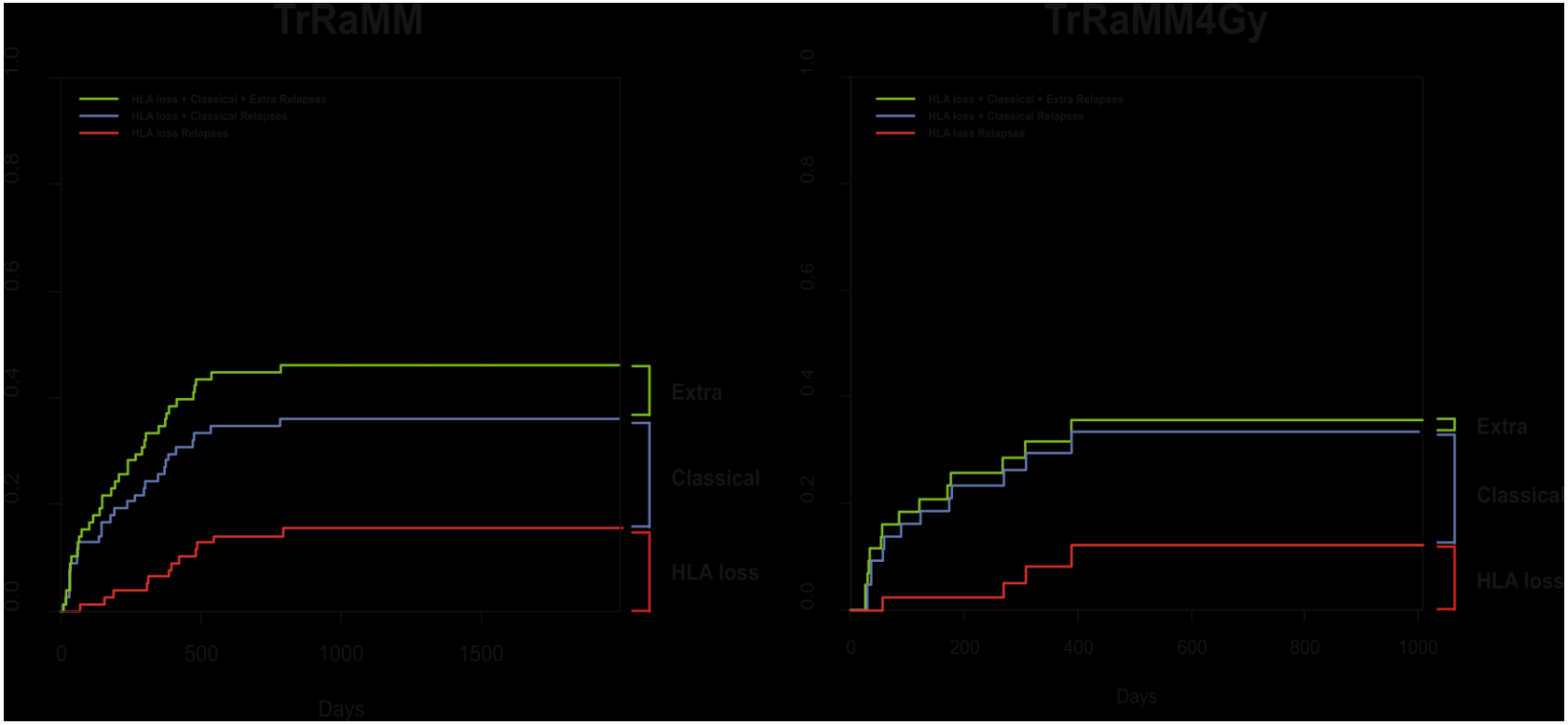



# TrRaMM *vs* TrRaMM 4Gy



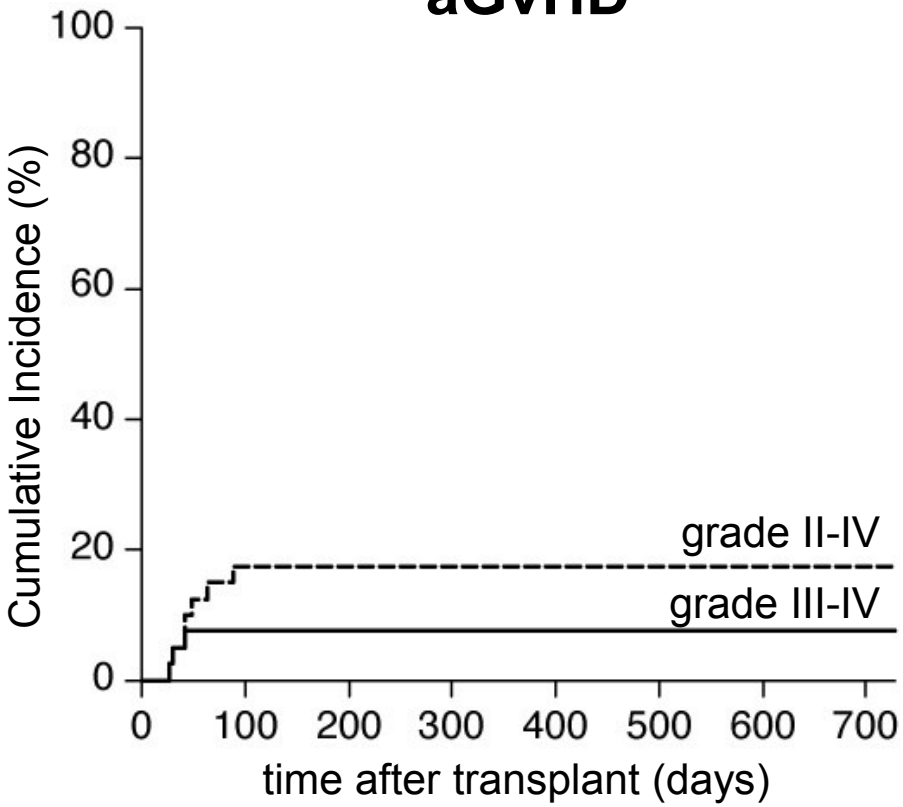
# New Generation TrRaMM Protocol: "Sir PT-Cy"

| | -6 | -5 | -4 | -3 | -2 | -1 | 0 | +3 | +4 | +5 |
|---|---|---|---|---|---|---|---|---|---|---|
| Treosulfan 14 g/m$^2$ | X | X | X | | | | | | | |
| Fludarabine 30 mg/m$^2$ | X | X | X | X | X | | | | | |
| **Melphalan 70 mg/m$^2$** | | | | | **X** | **X** | | | | |
| Haplo-PBSC | | | | | | | X | | | |
| **Cyclophosphamide 50 mg/kg** | | | | | | | | **X** | **X** | |
| Rapamycin | | | | | | | | | | X… |
| MMF | | | | | | | | | | X… |

*Cieri et al. Biol Blood Marrow Transplant. 2015 Aug;21(8):1506-14.*

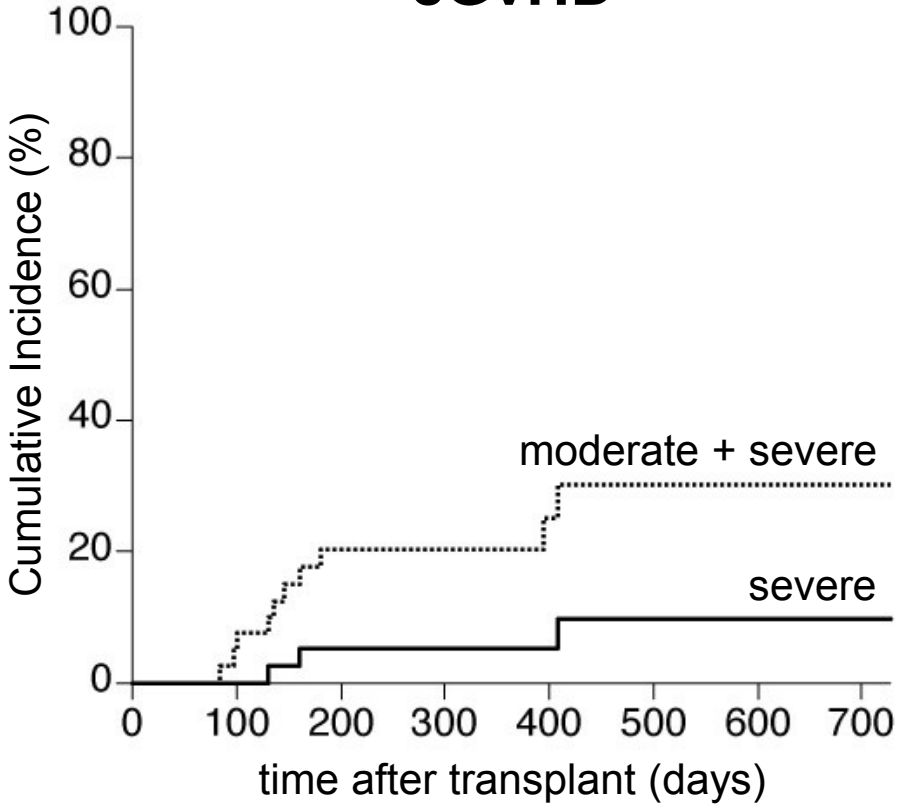
# GvHD incidence

## aGvHD



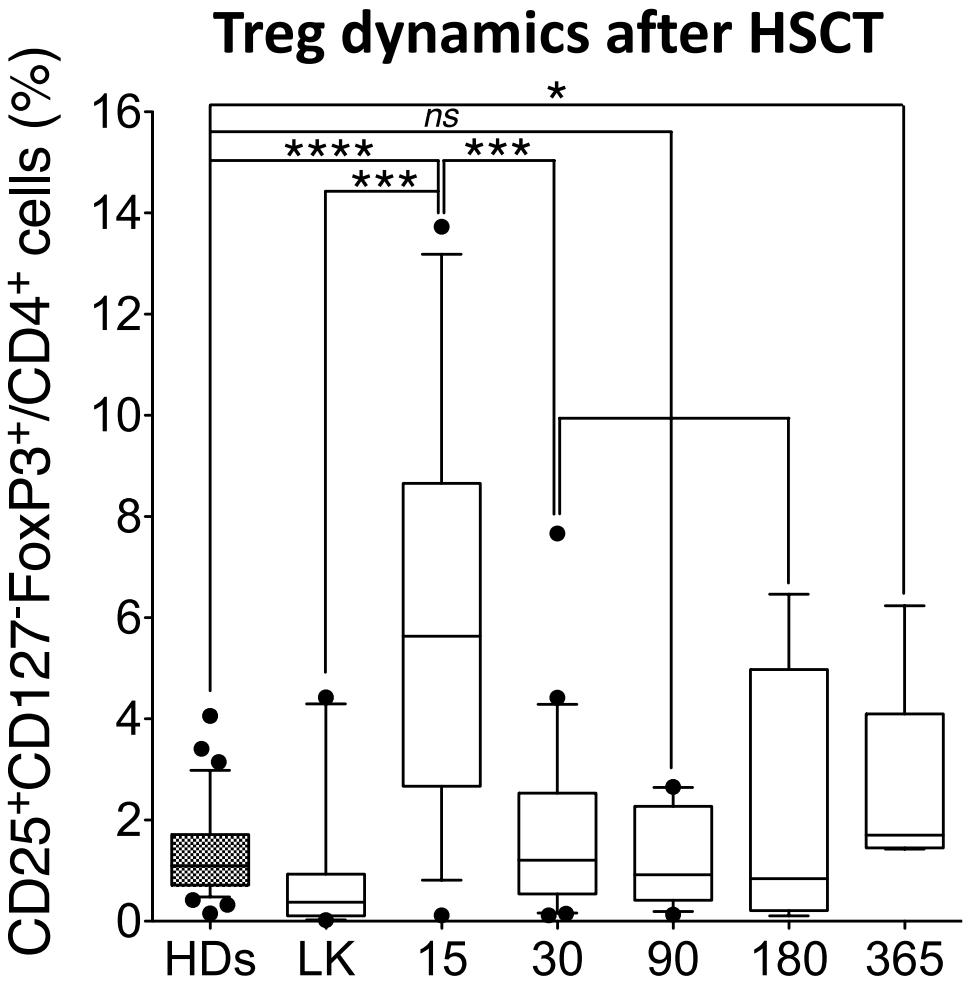

| @ day 100 | CI | St.E. |
|---|---|---|
| **grade II-IV** | 17.5% | 6.1 |
| **grade III-IV** | 7.5% | 4.2 |

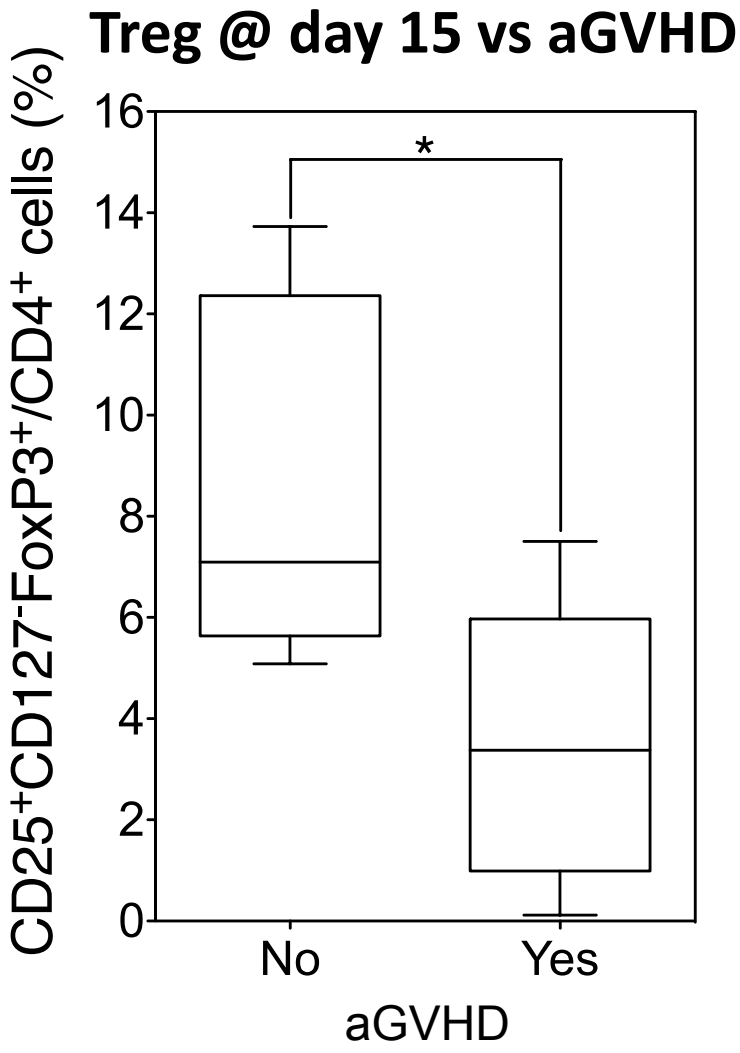
## cGvHD




| @1y | CI | St.E. |
|---|---|---|
| **moderate + severe** | 20.34% | 6.6 |
| **severe** | 5.1% | 3.6 |

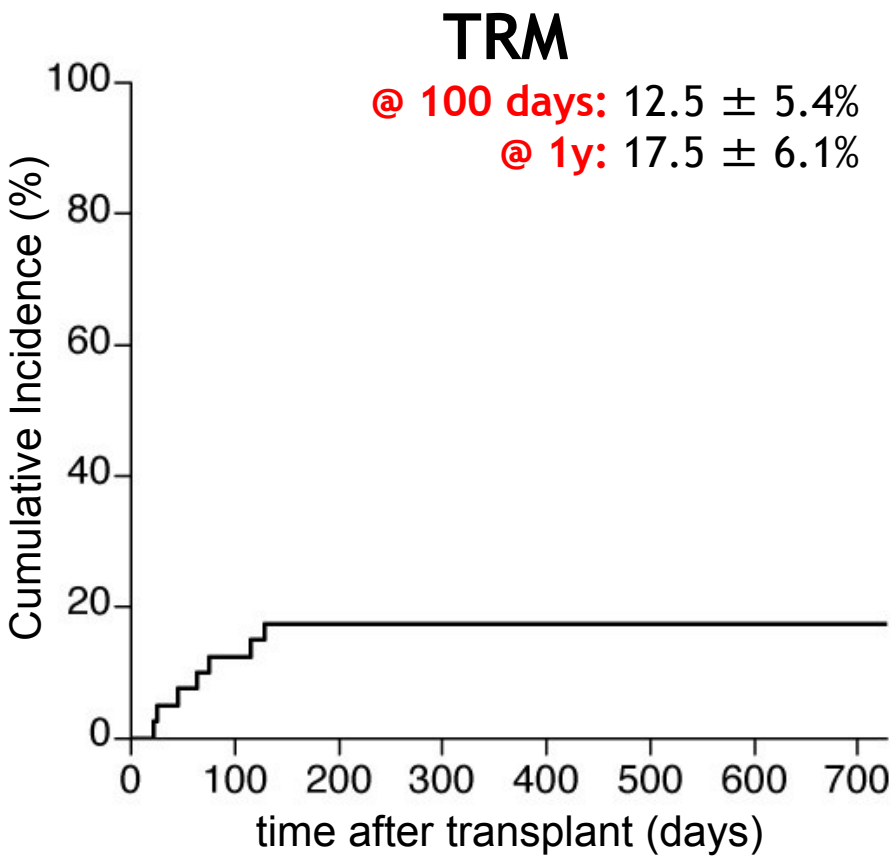
# Treg dynamics



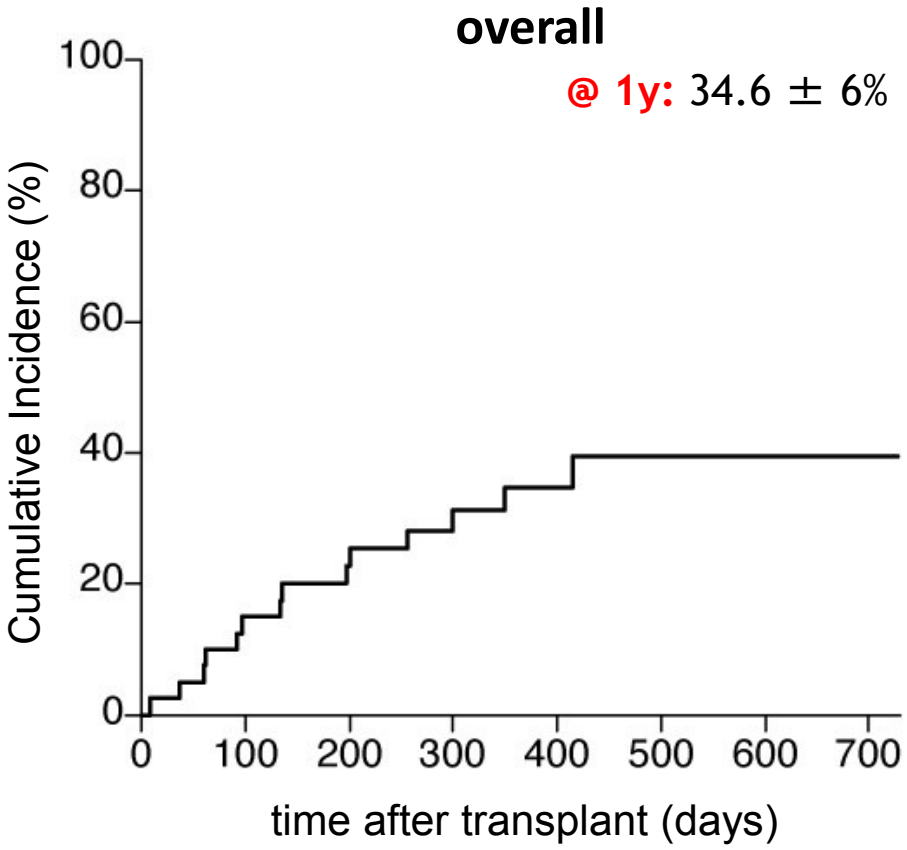



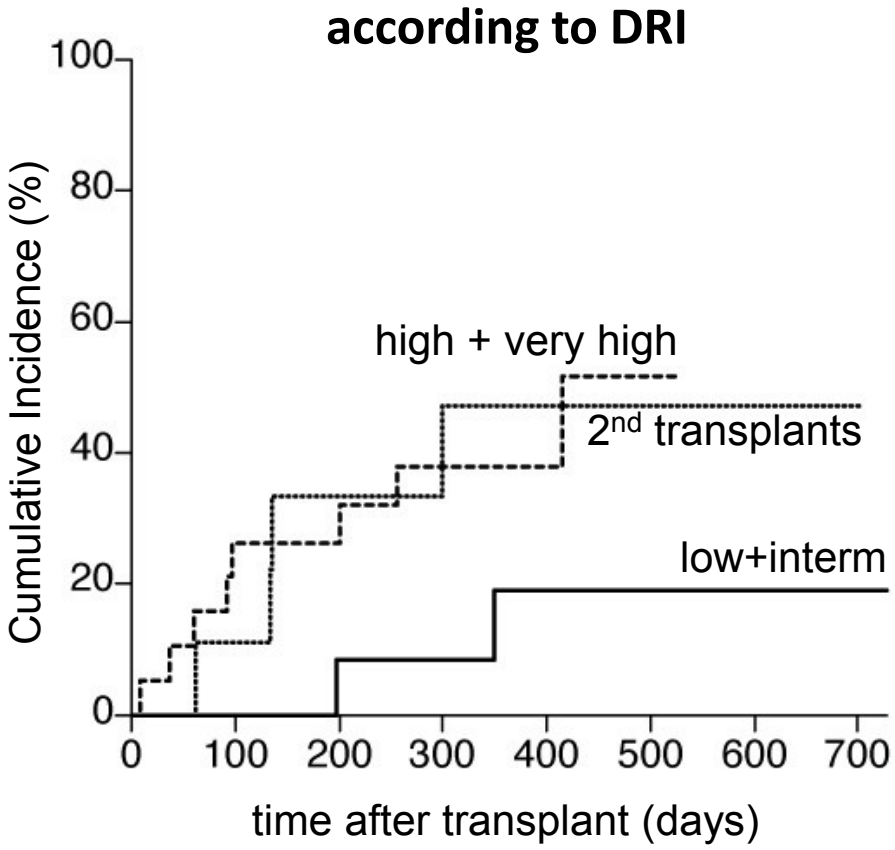
# Complications and TRM

| | |
|---|---|
| **Mucositis grade III** | 6 |
| **PRES** | 1 |
| **Hemorrhagic cystitis** | |
| Mild | 4 |
| Requiring treatment | 5 |
| **Severe bacterial infections** | |
| G- sepsis | 2 |
| Tbc | 1 |
| Unknown etiology | 2 |
| **Viral infections** | |
| CMV reactivation (CMV disease) | 22 (6) |
| EBV reactivation | 6 |
| HHV6 positivity | 25 |
| Other | 1 (Enterovirus) |
| **Invasive fungal infections** | |
| Prior to HSCT | 11 (possible = 5, probable = 6) |
| After HSCT | 5 (possible = 1, probable = 4) |



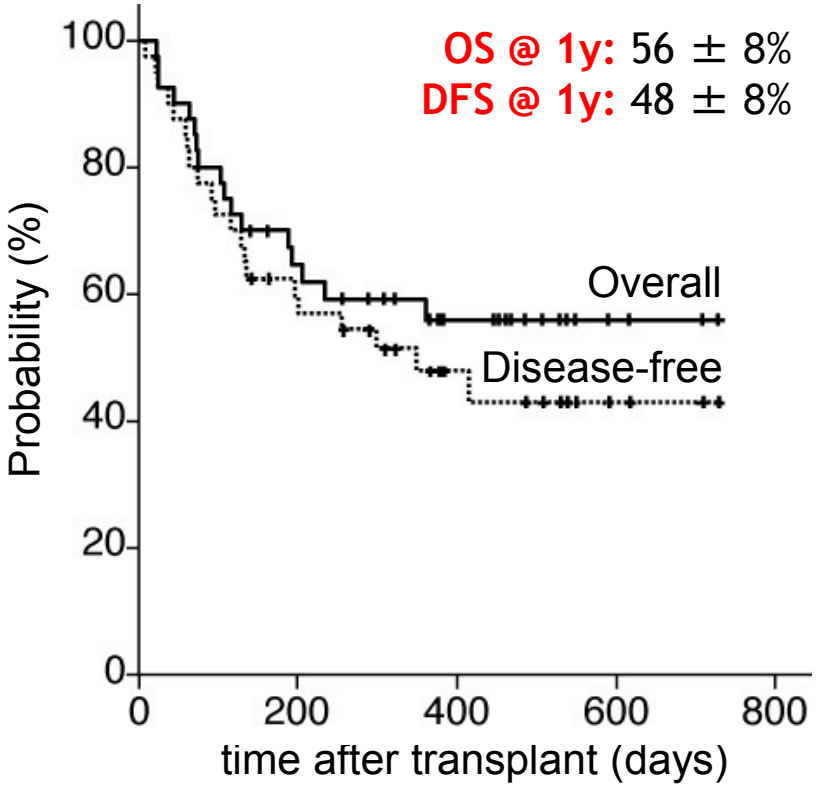
# Relapse


overall
@ 1y: 34.6 ± 6%
Cumulative Incidence (%)
100
80
60
40
20
0
0
100
200
300
400
500
600
700
time after transplant (days)

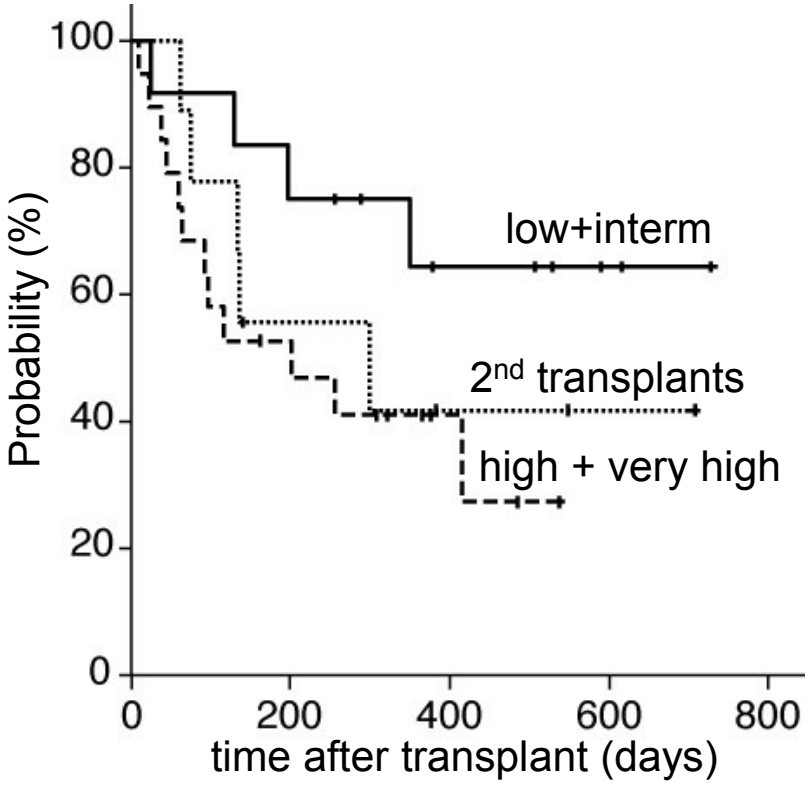

according to DRI
Cumulative Incidence (%)
100
80
60
40
20
0
high + very high
2nd transplants
low+interm
0
100
200
300
400
500
600
700
time after transplant (days)

# Survival

## Overall




## DFS according to DRI



# Next Generation TrRaMM Protocol: "TTF PT-Cy"

| | -6 | -5 | -4 | -3 | -2 | -1 | 0 | +3 | +4 | +5 |
|---|---|---|---|---|---|---|---|---|---|---|
| Treosulfan 14 g/m$^2$ | X | X | X | | | | | | | |
| **Thiotepa 5 mg/kg** | | | | **X** | **X** | | | | | |
| Fludara 30 mg/m$^2$ | X | X | X | X | X | | | | | |
| Haplo-PBSC | | | | | | | X | | | |
| Cyclophosphamide 50 mg/kg | | | | | | | | X | X | |
| Rapamycin | | | | | | | | | | X… |
| MMF | | | | | | | | | | X… |

# Clofarabine and treosulfan as conditioning for allogeneic hematopoietic stem cell transplantation from matched related and unrelated donors: **the Clo3o trial**

# Clo3o

## Conditioning regimen

**Clofarabine** 40 mg/m$^2$ day -6 → -2

**Treosulfan** 14 g/m$^2$ day -6 → -4

## Graft versus Host Disease (GvHD) prophylaxis

**Thymoglobuline** 1.5/2.5 mg/kg* day -4 → -2

**Rituximab** 200 mg/mq day -1

**Cyclosporine** 3 mg/kg from day -1

**Methotrexate** 15/10/10 mg/m$^2$ day +1/+3/+6

*according to HLA match

# Patients characteristics

| | All transplants | MRD transplants | MUD transplants |
|---|---|---|---|
| **Total number** | **44** | **22** | **22** |
| *Patient characteristics* | | | |
| Median age at HSCT, years (range) | 47 (13-69) | 43 (13-61) | 50 (16-69) |
| Male sex, n (%) | 22 (50%) | 9 (41%) | 13 (59%) |
| *Disease diagnosis, n (%)* | | | |
| Acute myeloid leukaemia | 36 (82%) | 17 (77%) | 19 (86%) |
| Myelodisplastic syndrome | 3 (7%) | 3 (14%) | 0 |
| Acute lymphoblastic leukaemia | 5 (11%) | 2 (9%) | 3 (14%) |
| *Status at transplant, n (%)* | | | |
| First complete remission | 16 (36%) | 8 (36%) | 8 (36%) |
| Other complete remission | 9 (20%) | 4 (18%) | 5 (23%) |
| Active disease | 16 (36%) | 7 (32%) | 9 (41%) |
| Upfront | 3 (8%) | 3 (14%) | 0 |
| *Comorbidities (HCT-CI) § , n (%)* | | | |
| 0 | 15 (34%) | 10 (45%) | 5 (23%) |
| 1-2 | 12 (27%) | 5 (23%) | 7 (32%) |
| 3-4 | 17 (39%) | 7 (32%) | 10 (45%) |
| *Disease Risk Index (DRI) ¶, n (%)* | | | |
| Low | 1 (2%) | 1 (4%) | 0 |
| Intermediate | 26 (59%) | 14 (64%) | 12 (55%) |
| High | 13 (30%) | 5 (23%) | 8 (36%) |
| Very High | 4 (9%) | 2 (9%) | 2 (9%) |
| *CMV serostatus (host/donor) , n* | | | |
| negative/negative | 2 | 0 | 2 |
| negative/positive | 2 | 1 | 1 |
| positive/negative | 11 | 3 | 8 |
| positive/positive | 29 | 18 | 11 |
| *Donor-recipient HLA matching, n (%)‡* | | | |
| *MRD* | | | |
| (10/10) | -- | 22 (100%) | -- |
| *MUD* | | | |
| (8/10) | -- | -- | 1 (4%) |
| (9/10) | -- | -- | 7 (32%) |
| (10/10) | -- | -- | 14 (64%) |

*Peccatori et al, in preparation*

# Toxicities

| All grade > 2 adverse events | n (%) | Max CTCAE grade |
|---|---|---|
| Febrile neutropenia | 32 (73) | 3 |
| Liver enzymes | 12 (27) | 4 |
| Septic shock | 8 (18) | 5 |
| Mucositis | 6 (14) | 4 |
| Pneumonia | 5 (11) | 5 |
| Skin lesions[§] | 3 (7) | 4 |
| CNS infection | 3 (7) | 4 |
| Hematuria/cystitis | 2 (5) | 3 |
| Nausea | 1 (2) | 3 |
| Pleural effusion | 1 (2) | 3 |
| VOD | 1 (2) | 3 |
| DVT | 1 (2) | 3 |
| Arrhythmia | 1 (2) | 3 |
| CNS bleeding | 1 (2) | 5 |
| Microangiopathy | 1 (2) | 3 |
| Hypocalcemia | 1 (2) | 3 |

Of note:

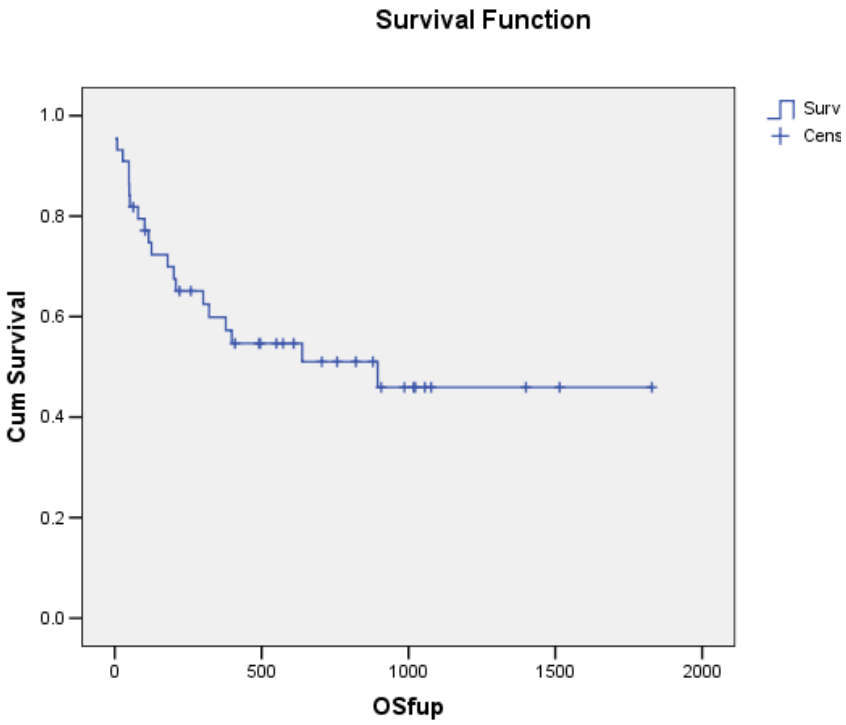
- Reversible hepatic damage and body weight gain: most frequent side effects
- Skin rash after clofarabine frequently observed, but reversible and of low severity in the vast majority of cases (only 3 patients with severe cutaneous lesions)
- Creatinine increase in 5 pts (maximal severity grade of 2)

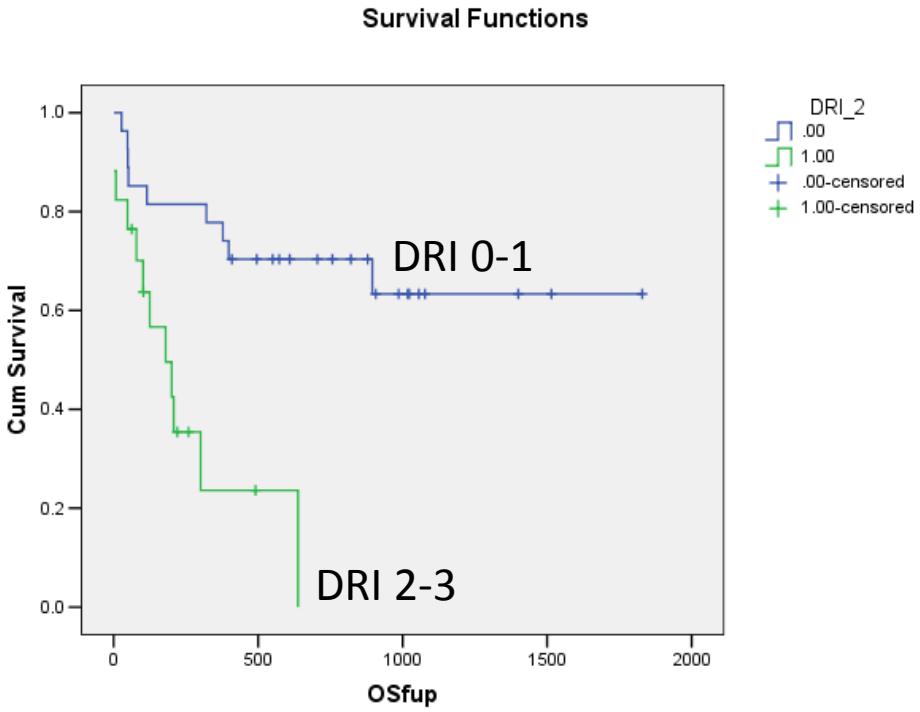
*Peccatori et al, in preparation*

# Results

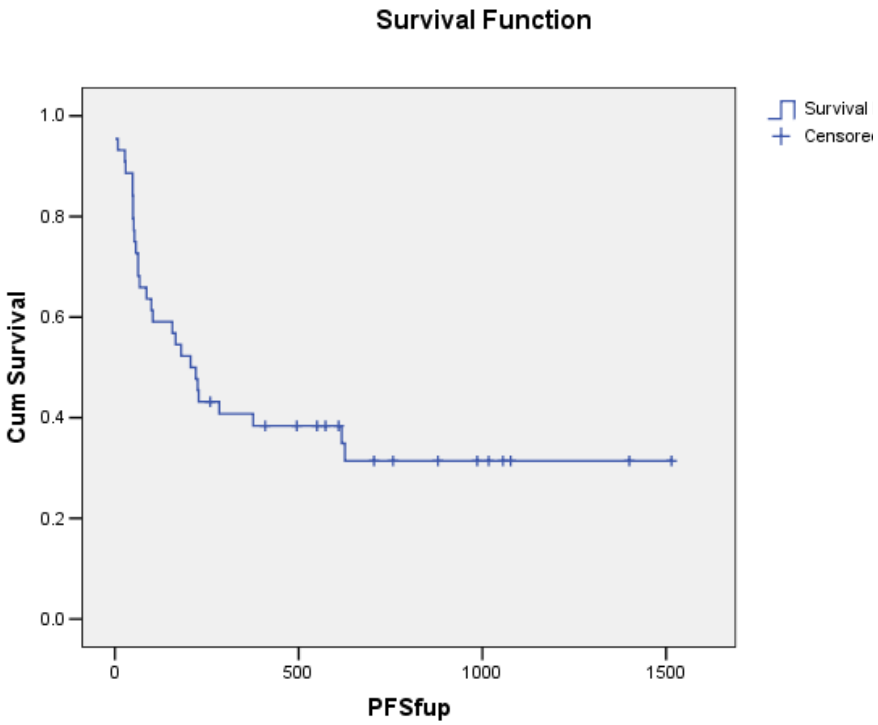
- ✓ Rapid engraftment and full donor chimerism at day 30 in 100% pts
- ✓ 2-year transplant related mortality: 18%
- ✓ Grade 2-4 acute GvHD: 16%
- ✓ Chronic GvHD: 19%
- ✓ 2-year overall survival: 51%
- ✓ 2-year progression free survival: 31%
- ✓ 2-year relapse incidence: 50%

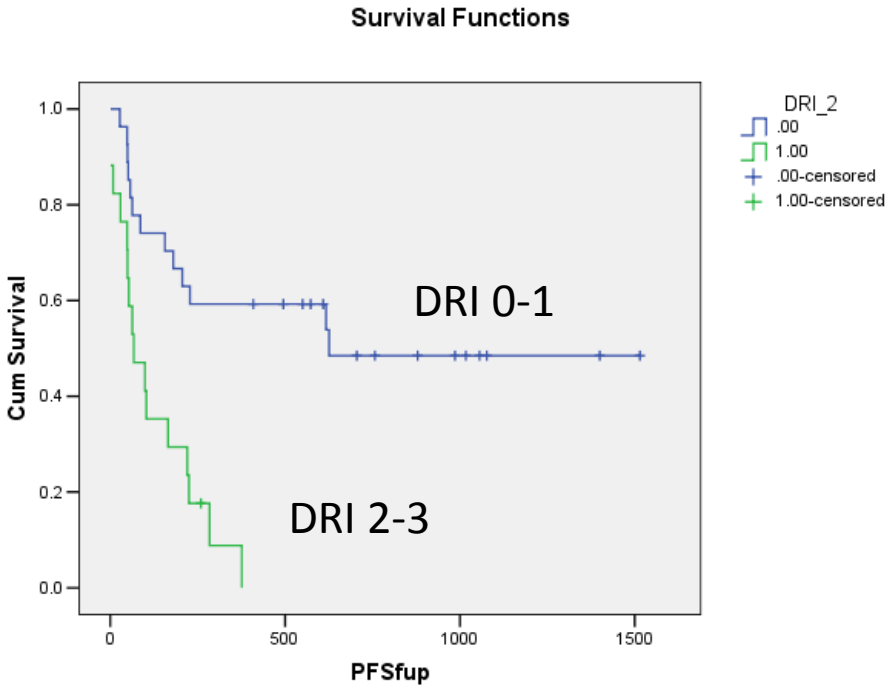
# The impact of disease status: OS



# The impact of disease status: PFS



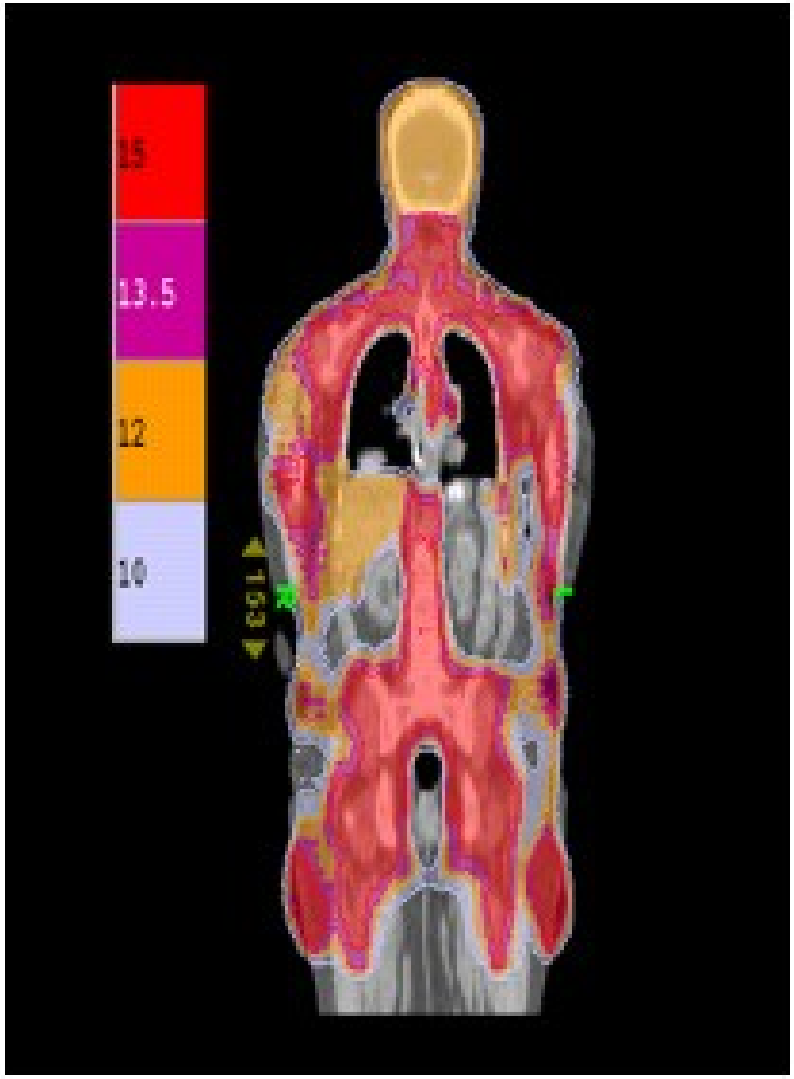
# Conclusions

Treosulfan and Clorafabine combination is feasible, safe and allows a prompt engraftment. The considerable relapse incidence in patients with poor prognostic risk factors is still a major issue and could be addressed through the modulation of *in vivo* T-cell depletion

# From TBI towards TMI

- A more targeted form of TBI delivery is needed to allow for dose escalation with acceptable toxicities and treatment-related mortality rates.
- TMI (Tomotherapy Hi-Art system) alone escalated to 18 Gy before dose limiting toxicities were observed (Somlo G, *Clin Cancer Res* 2011)
- TMI at 12 Gy combined with Flu/Mel was associated with acceptable toxicities (Rosenthal J, *Blood* 2011)

# TMI with concurrent CT




- Target structures bone, lymph nodes and testes received 15 Gy
- Spleen and splenic-hilar lymph nodes, liver, porta-hepatic lymph nodes, ribs, sternum, brain and skull received 12 Gy (Jeffrey YC Wong, Int J Radiation Oncol Biol Phys 2012)

# TMI with concurrent CT

At 13.5 Gy dose-limiting toxicities were observed

**Table 2** Toxicities observed in first 30 days

| | Trial 1 TMI + CY + VP16 | | | Trial 2 TMI + BU+ VP16 | |
|---|---|---|---|---|---|
| Toxicity | 12 Gy (n=3) | 13.5 Gy (n=3) | 15 Gy (n=6) | 12 Gy (n=18) | 13.5 Gy (n=2) |
| NCI Grade 3 | | | | | |
| Mucositis | 1 | | 6 | 15 | 1 |
| Fatigue | 1 | 1 | 6 | 15 | 2 |
| Anorexia | 1 | 2 | 4 | 6 | |
| Nausea | 1 | | 3 | 8 | |
| Vomiting | | | 1 | 2 | |
| Diarrhea | | | | 3 | |
| NCI Grade 4 or Bearman Grade 3 | | | | | 1- mucositis<br>1- hepatic (SOS) |

*Abbreviations:* SOS = sinusoidal obstructive syndrome; TMI + CY + VP16 = total marrow irradiation + cyclophosphamide + etoposide.

(Jeffrey YC Wong, Int J Radiation Oncol Biol Phys 2012)

# TrRaMM - TMI

Monocentric, non-randomized, non-controlled open-label **phase I/II** trial
to evaluate the **feasibility, safety and efficacy**
of **treosulfan, fludarabine + TMI** as conditioning therapy prior to allogeneic SCT,
in patients with advanced haematological malignancies
with a related matched donor.
*To reduce the incidence of aGvHD, a Rapamycin-based GvHD prophylaxis has been chosen.*

The aim is to demonstrate a **feasibility** of the treatment with TMI with an escalated dose of radiation, associated to a **clinical benefit** compared to historical data
on HLA-matched (sibling or MUD) transplantation.

# TrRaMM - TMI

**INCLUSION CRITERIA**

- Patients with high risk haematological malignancies such as:
- **any AML beyond CR1**
- **any ALL beyond CR1**
- **MM at any relapse/progression, except refractory disease**

- Karnofsky Index $\geq$ 80 %
- Age $\leq$ 70 years
- Adequate contraception in female patients of child-bearing potential.
- Written informed consent

- **Availability of a matched related donor (MRD) sibling/MUD (10/10 HLA match)**

# TrRaMM - TMI

| **Conditioning Regimen** | Day | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | -9 | -8 | -7 | -6 | -5 | -4 | -3 | -2 | -1 | 0 | | |
| **Treosulfan i.v. 14 g/m² within 120 minutes** | | | | X | X | X | | | | | | |
| Fludarabine i.v., 30 mg/m² within 30 minutes | | | | X | X | X | X | X | | | | |
| ATG- Fresenius® (S) i.v., 5/0* mg/kg BW | | | | | | X | X | X | | | | |
| Mabthera- Roche® i.v., 200/0* mg/m2 | | | | | | | | | X | | | |
| **TMI (8-10-12) 2 Gy BID (minimum 6 hours interval)*** | | | | | | | **X** | **X** | **X** | **X** | | |
| Allogeneic stem-cell transplantation | | | | | | | | | | X | | |
| Rapamycin po 4 mg/day starting dose (target level for sirolimus 8-15 ng/ml) | | | X | X | X | X | X | X | X | X | | |
| Mycophenolate 10 mg/kg tid po (Maximun dose 720 mg/tid) | | | | | | | | | X | X | | |

# TrRaMM - TMI

| | |
|---|---|
| **Primary endpoints:** | Dose finding approach:<br>For each dose step at least **three PTs** will be treated;<br>2 months interval before increasing the prescribed dose in order to monitore the acute toxicity<br>In case of dose-limiting toxicity (**DLT**), other 3 PTs will be enrolled in the same dose level<br>No further step when the rate of toxicity $\geq$ 2/6<br>The acceptable dose level will guarantee a toxicity rate < 2/6.<br>**Stopping rule:**<br>**If the rate of Gr 4 extra-haematological toxicity will be > 20%, it means more than the double rate, that is expected in this population, the study will be stopped.**<br>The study will be stopped if more than 8 extra-haematological Gr 4 toxic events will be observed.<br><br>Efficacy: to determine the probability of being alive and with normal engraftment at +30 after transplant.<br>A total of 18 patients will be necessary to reject a H0 = 0.50 with H1 = 0.80. A minimum of 13 patients have to be alive and with correct engraftment, with a alpha=0.0.5 and power = 0.80. |

# Candidate agents for maintenance of remission post Allo-SCT

- Hypomethylating agents
- FLT3 inhibitors
- Histone deacethylase inhibitors
- Lenalidomide and other IMIDs
- Monoclonal antibodies (CD20, CD19, CD33)
- Cells – educated or not

# The maintenance agent

1- Active against the disease.

2- Not too toxic.

3- Not myelotoxic (or with tolerable myelotoxicity).

4- Can be given early after transplant.

5- Influence donor cells favorably.

6- Increase immunogenicity of malignant cells.

# Hypomethylating Agents – Potential Effects

- Increased expression of tumor-associated antigens ie CTA (Roman-Gomez, 2007) Tatjana Stankovic et al. Goodyear et al.
- Increased expression of KIR ligands on hematopoietic cells (Liu, 2009)
- Recovery of reduced expression of HLA class I, II and III antigens on tumor cells (Campoli & Ferrone, 2008) (Pinto et al – 1984)
- Increased expression of known Minor antigens (Hambach, 2009)
- Affect microRNA function - inhibition of oncogenes

↑ GVL

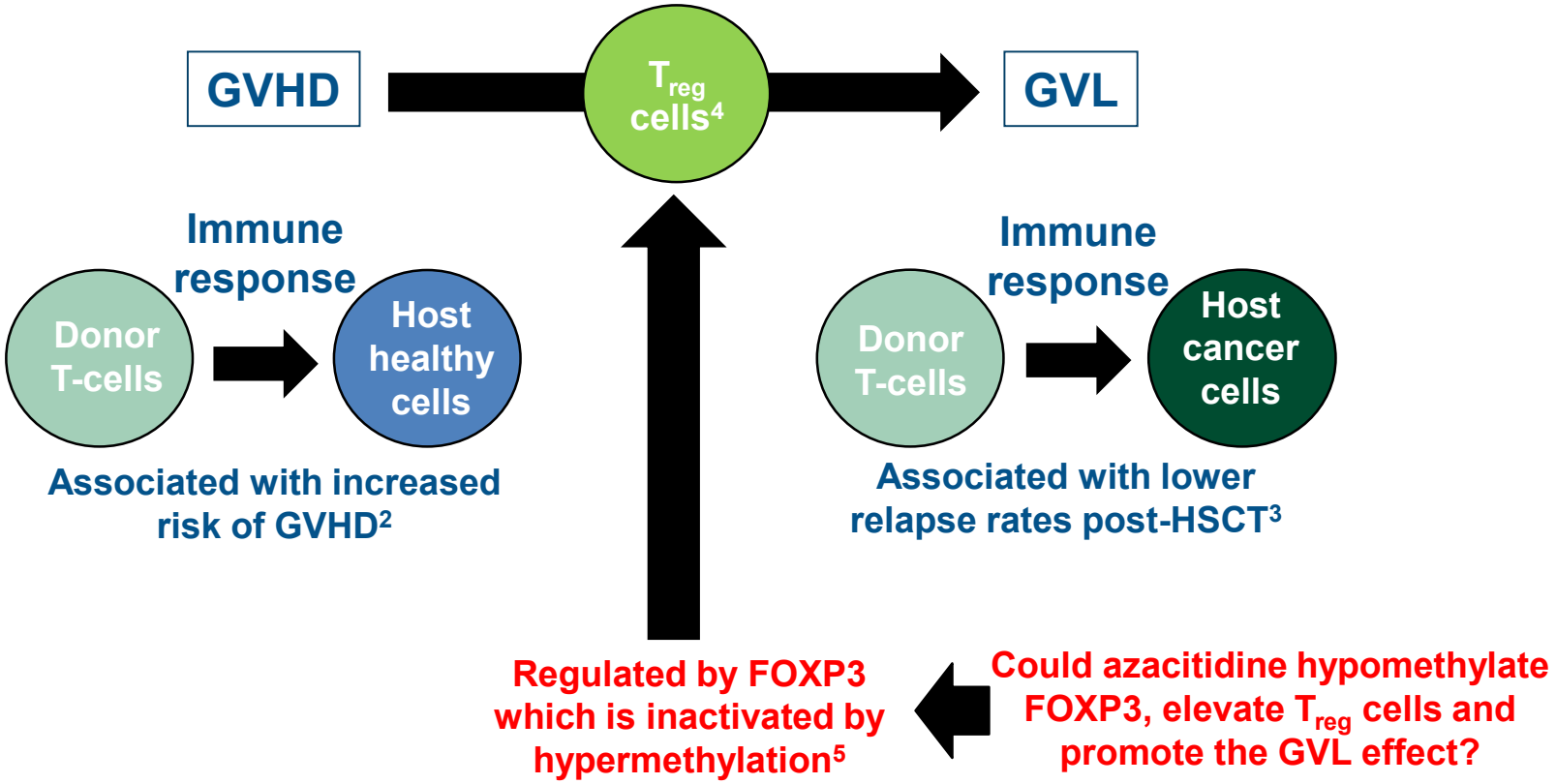
- Increased FoxP3 expression and $T_{reg}$ generation (Polansky, 2008) (Choi et al. 2010) (Sanchez-Abarca et al. 2010) (John DiPersio et al. Goodyear et al. Blood 2011).
- Modification of CDR3-TCR on T helper

Tolerance without affecting relapse ?

GvHD? GvL?

# Biological rationale for treating patients with azacitidine post-HSCT

**It has been hypothesised that azacitidine post-HSCT could promote the graft–versus-leukaemia (GVL) effect and reduce graft–versus-host disease (GVHD)[1]**




1. Jabbour E, et al. Cancer 2009;1115:1899–905; 2. Weiden PL, et al. N Engl J Med 1979;300:1068–73
3. Ringden O, et al. Br J Haematol 2009;147:614–33; 4. Edinger M, et al. Nat Med 2003;9:1144–50
5. Floess S, et al. PLoS Biol 2007;5:e38

# Maintenance Therapy With Low-Dose Azacitidine After Allogeneic Hematopoietic Stem Cell Transplantation for Recurrent Acute Myelogenous Leukemia or Myelodysplastic Syndrome

## A Dose and Schedule Finding Study

Marcos de Lima, MD[1]; Sergio Giralt, MD[1]; Peter F. Thall, PhD[2]; Leandro de Padua Silva, MD[1]; Roy B. Jones, MD[1]; Krishna Komanduri, MD[3]; Thomas M. Braun, PhD[4]; Hoang Q. Nguyen, PhD[2]; Richard Champlin, MD[1]; and Guillermo Garcia-Manero, MD[5]

- CR at day 30
- creatinine <1.6 mg/dL,
- bilirubin <1.6 mg/dL,
- ALT 3 upper limit of normal,
- platelet count >15,
- absolute neutrophil count (ANC) >1,000

- No bleeding, uncontrolled infection, or grade III/IV acute GVHD.
- If not eligible for treatment during the first 3 months post-transplant, patients went off protocol.

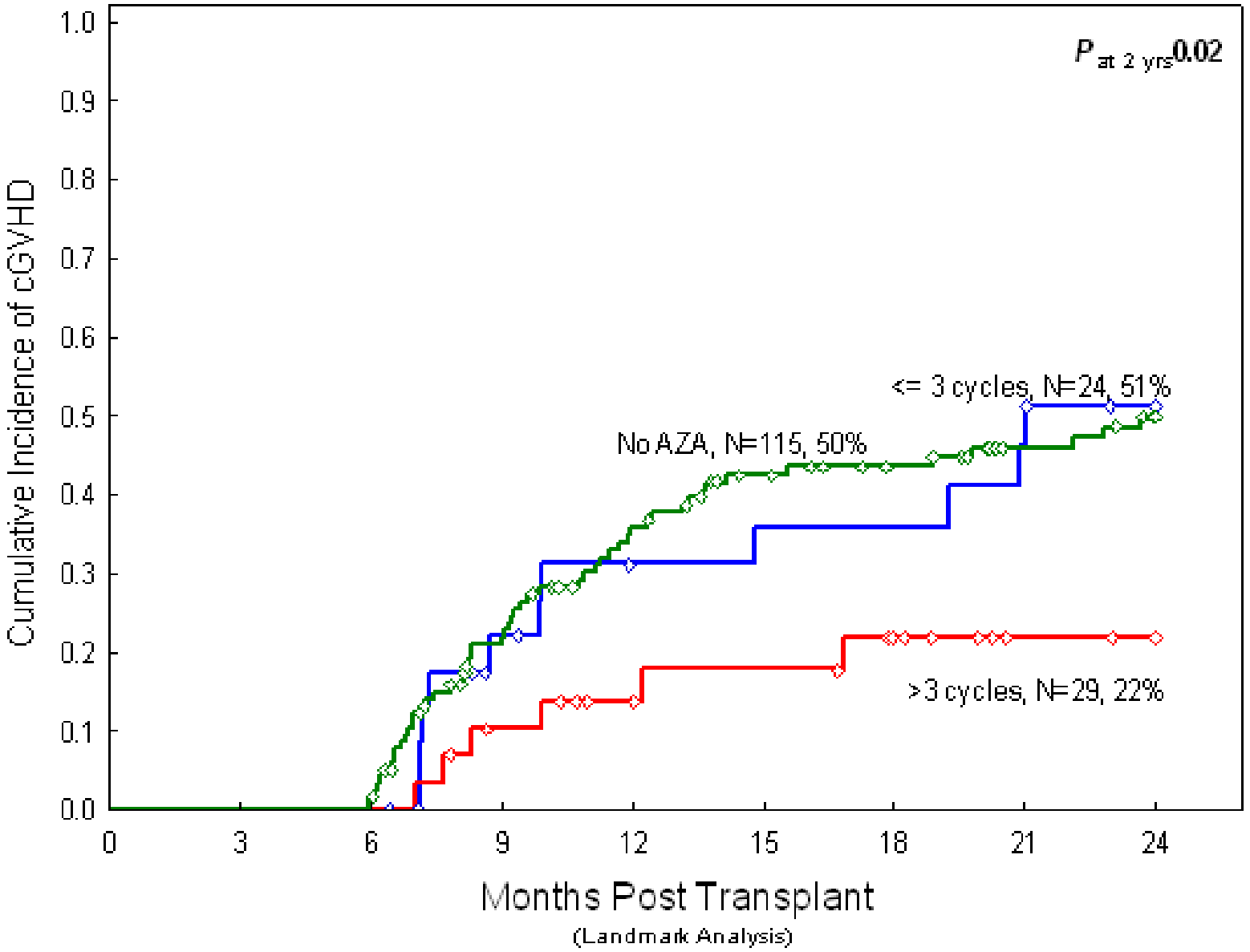
Cancer December 1, 2010

# Protocol 2005-0417

- Azacitidine was well tolerated
- Approximately 60% of the patients (heavily pre-treated, refractory etc) were able to receive at least one cycle
- At least 4 cycles at 32 mg/$m^2$ could be delivered.
- Randomized protocol: 32 mg/$m^2$ daily X 5 days, every 30 days, for 1 year, versus no maintenance.

# Low dose AZA and cGVHD

Cumulative incidence of cGVHD. 6-month landmark analysis.



# Conclusions

- Maintenance therapy may contribute to the treatment of patients with AML/MDS.

- Hypomethylating agents may modulate GVL and GVHD after allogeneic transplantation.

- The post transplant scenario, once the realm of GVHD trials, may provide an ideal arena to improve disease control now that new therapies (cellular and otherwise) are available.

Biol Blood Marrow Transplant 21 (2015) 1761–1769

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

# Maintenance Therapy with Decitabine after Allogeneic Stem Cell Transplantation for Acute Myelogenous Leukemia and Myelodysplastic Syndrome

Iskra Pusic [1,*], Jaebok Choi [1], Mark A. Fiala [1], Feng Gao [2], Matthew Holt [1], Amanda F. Cashen [1], Ravi Vij [1], Camille N. Abboud [1], Keith E. Stockerl-Goldstein [1], Meghan A. Jacoby [1], Geoffrey L. Uy [1], Peter Westervelt [1], John F. DiPersio [1]

# Drug Therapy Post Allo-Transplant

- AML
  - FLT3 (ITD and D835)
    - 20-30% of pts, poor prognosis, most pts go to allo-SCT
    - Ongoing Phase III study (CALGB10603) with PKC412 vs placebo during induction and consolidation and maintenance.
    - Available FLT3 inhibitors: PKC412, MLN518, CEP701
  - Gemtuzumab ozogamicin (GO)
    - High incidence of VOD when used post ablative SCT
    - May be able to administer GO post NST

# Drug Therapy Post Allo-Transplant

- Ph+ leukemias
  - CP-CML
    - Most patients transplanted are refractory to 1st and 2nd generation TKIs
  - AP/BP-CML
    - Reasonable to add imatinib or dasatinib post SCT
      - Small number of pts in the upfront setting
  - Ph+ ALL
    - Except for pts with T315I, many pts currently receive a TKI post SCT
    - Many pan-ABL inhibitors are currently in trials for pts with a T315I

Biol Blood Marrow Transplant 21 (2015) 1714–1720

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

# Haploidentical Hematopoietic Stem Cell Transplantation as a Platform for Post-Transplantation Cellular Therapy

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# Grazie!!!!