*Incontri Bresciani di Radioterapia Oncologica – Edizione 2010*
*Brescia Meetings in Radiation Oncology – 2010 Edition*

Hodgkin and Non Hodgkin Lymphomas:
a new Role for Radiation Therapy?

# The reasons to use TBI: from Biology to Clinical Applications

Andrea Riccardo Filippi
Radiation Oncology Unit
AOU S. Giovanni Battista – Torino, Italy

# Presentation Outline

- Background of myeloablative TBI
- Myeloablative TBI clinical applications
- The role of TBI in non-myeloablative approaches
- New conditioning regimens?

# Phases of Myeloablative Approaches to Allografting

| *Components* | *Purpose* |
| --- | --- |
| **1. Myeloablative conditioning pretransplant** | **Host immunosuppression**<br>**Eradication of underlying disease**<br>**Creation of Marrow Space** |
| **2. Stem Cell Graft** | **Rescue from myelosuppression**<br>**Establishment of normal hematopoiesis**<br>**Graft-versus-tumor** |
| **3. Postgrafting immunosuppression** | **Prevent rejection**<br>**Control of GVHD** |
| **4. Discontinuation immunosuppression** | **Achievement of tolerance** |

# To achieve the goals of step 1

- Chemotherapy: myelotoxic-stem cells toxic + immunosuppressive → agents like busulfan, melphalan, BCNU + Cyclophosphamide, Fludarabine, ATG
- Radiation Therapy: high dose TBI
- A combination of CT and RT

# Theoretical advantages of combining CT-RT (compared to CT only)

- No sparing of sanctuaries
- No cross resistance with other agents
- No need of detoxificatio/excretion fully functional mechanisms

# Classic Conditioning Regimens

CY/TBI

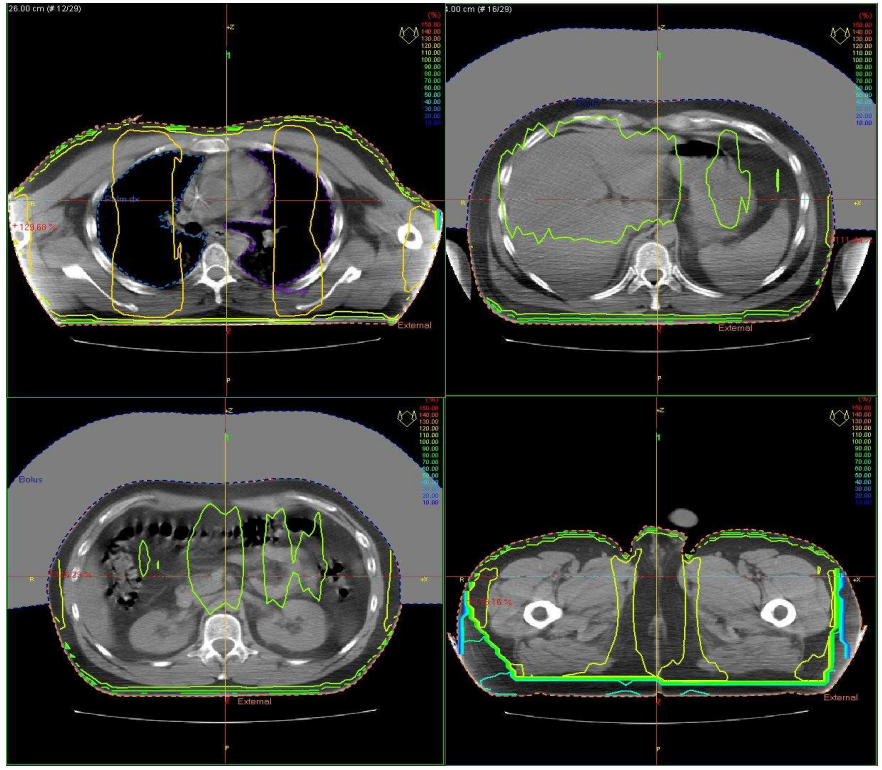
- CY 60 mg/kg days –6 e –5
- Total Body Irradiation days –3 –2 e –1, for a total dose of 10-14,4 Gy

BU/CY

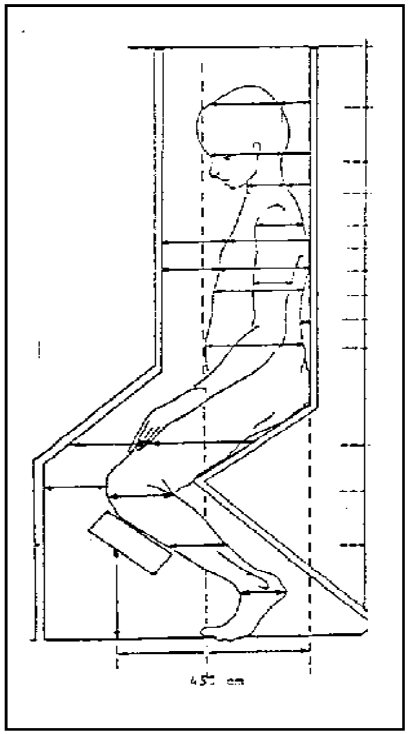
- BU 4 mg/kg/die per os in 4 daily doses from –9 to –6
- CY 50 mg/kg dal gg –5 al gg –2

# 12 Gy in 6 fractions over 3 days: a standard approach

Treatment planning elaborated on CT scan



Conventional AP/PA technique Gantry at 270° Collimator at 45°

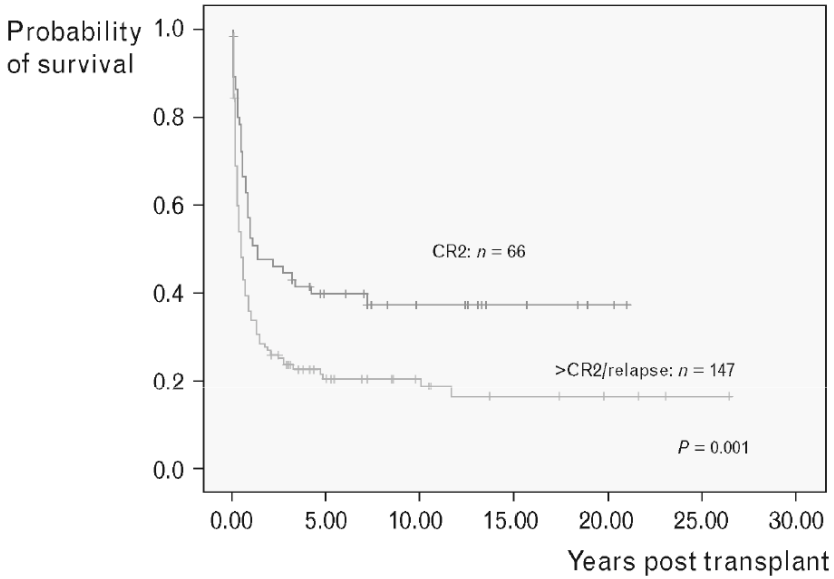


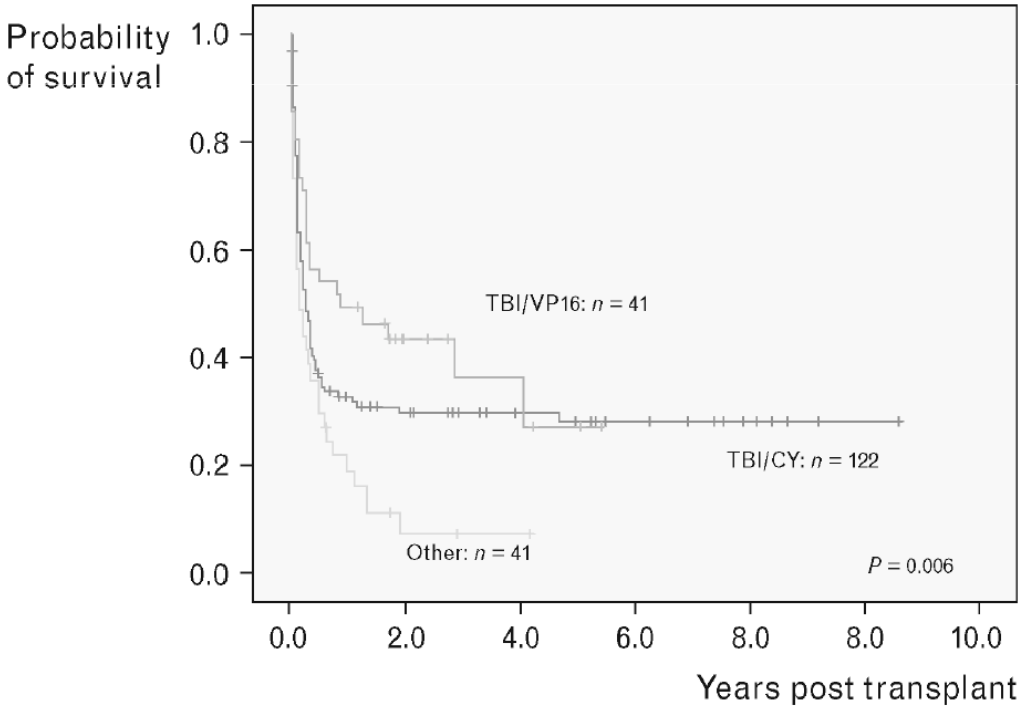
# Clinical Experiences of allogeneic transplantation with TBI conditioning

- High-risk AML
- High-Risk ALL
- Relapsed-refractory Lymphomas/Chronic Lymphatic Leukemia

# TBI Containing regimens vs. other in ALL

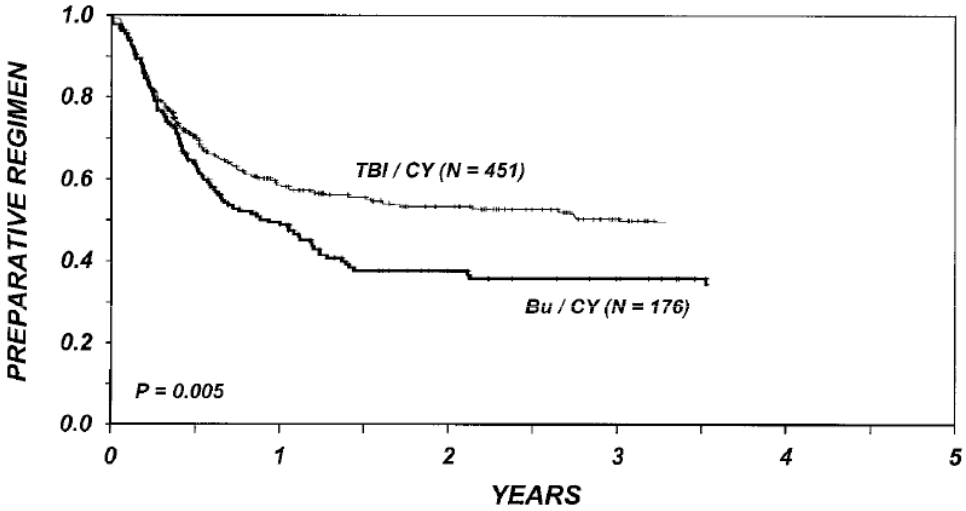
## Munich Experience (1975-2009)



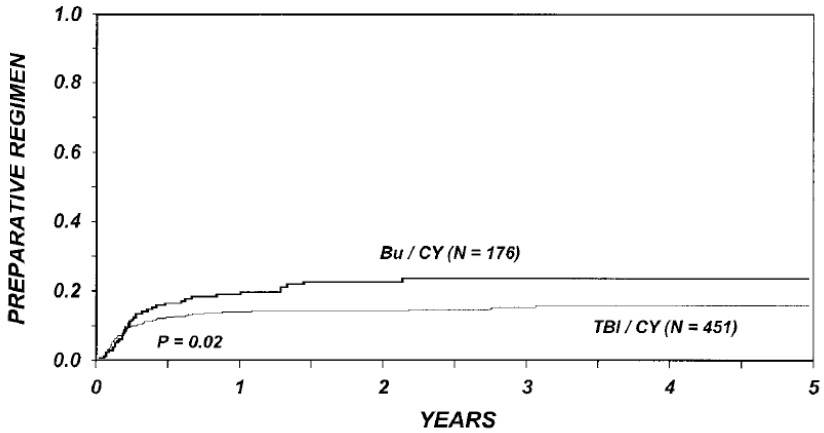




Kolb et al, 2009

# TBI/CY vs. BU/CY in pediatric ALL




TRM




Davies et al, 2000

# Impact of Conditioning Regimen in Allogeneic Hematopoetic Stem Cell Transplantation for Children with Acute Myelogenous Leukemia beyond First Complete Remission: A Pediatric Blood and Marrow Transplant Consortium (PBMTC) Study

*India Y. Sisler,[1] Elizabeth Koehler,[1] Tatsuki Koyama,[1] Jennifer A. Domm,[1] Robin Ryan,[2] John E. Levine,[3] Michael A. Pulsipher,[4] Paul R. Haut,[5] Kirk R. Schultz,[6] Douglas S. Taylor,[7] Haydar A. Frangoul[1]*

Results in AML are probably different in pediatric patients

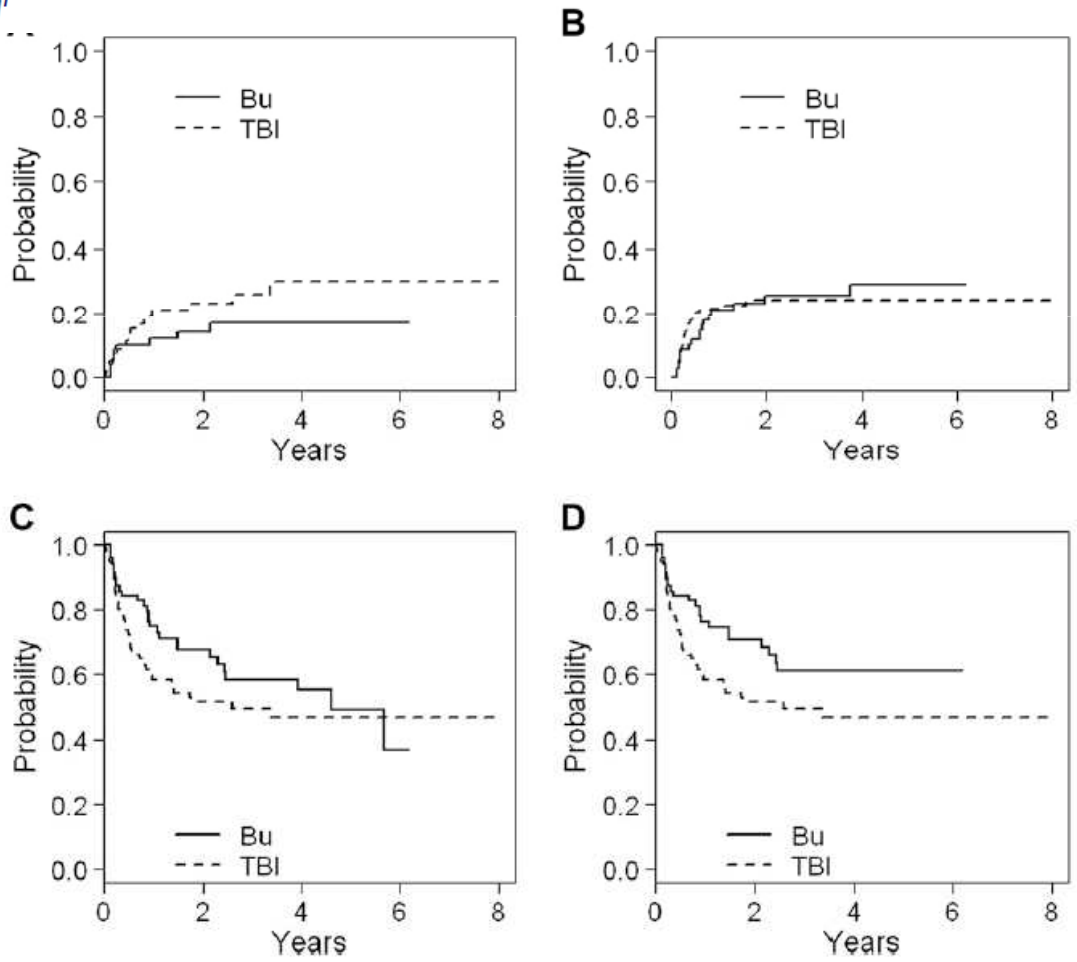


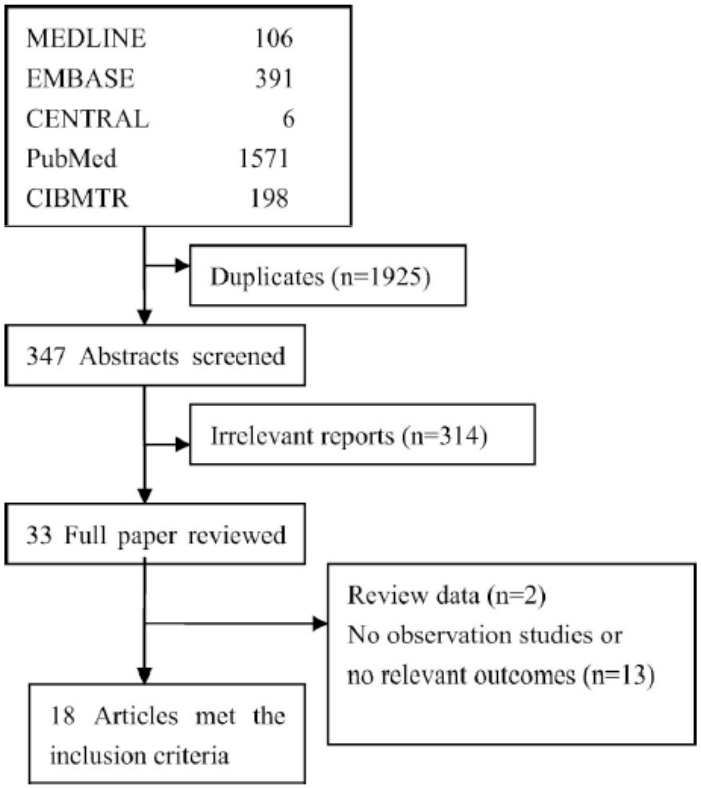

**Figure 1.** TRM (A), incidence of relapse (B), EFS (C), and OS (D).

# A meta-analysis?

**Total body irradiation plus cyclophosphamide *versus* busulphan with cyclophosphamide as conditioning regimen for patients with leukemia undergoing allogeneic stem cell transplantation: a meta-analysis**

XU SHI-XIA[1], TANG XIAN-HUA[1], XU HAI-QIN[1], FENG BO[1], & TANG XIANG-FENG[2]

[1]*Department of Medical Information and* [2]*Department of Pediatrics, Navy General Hospital, Beijing, China*




Leukemia and Lymphoma 2010

# Selected Trials

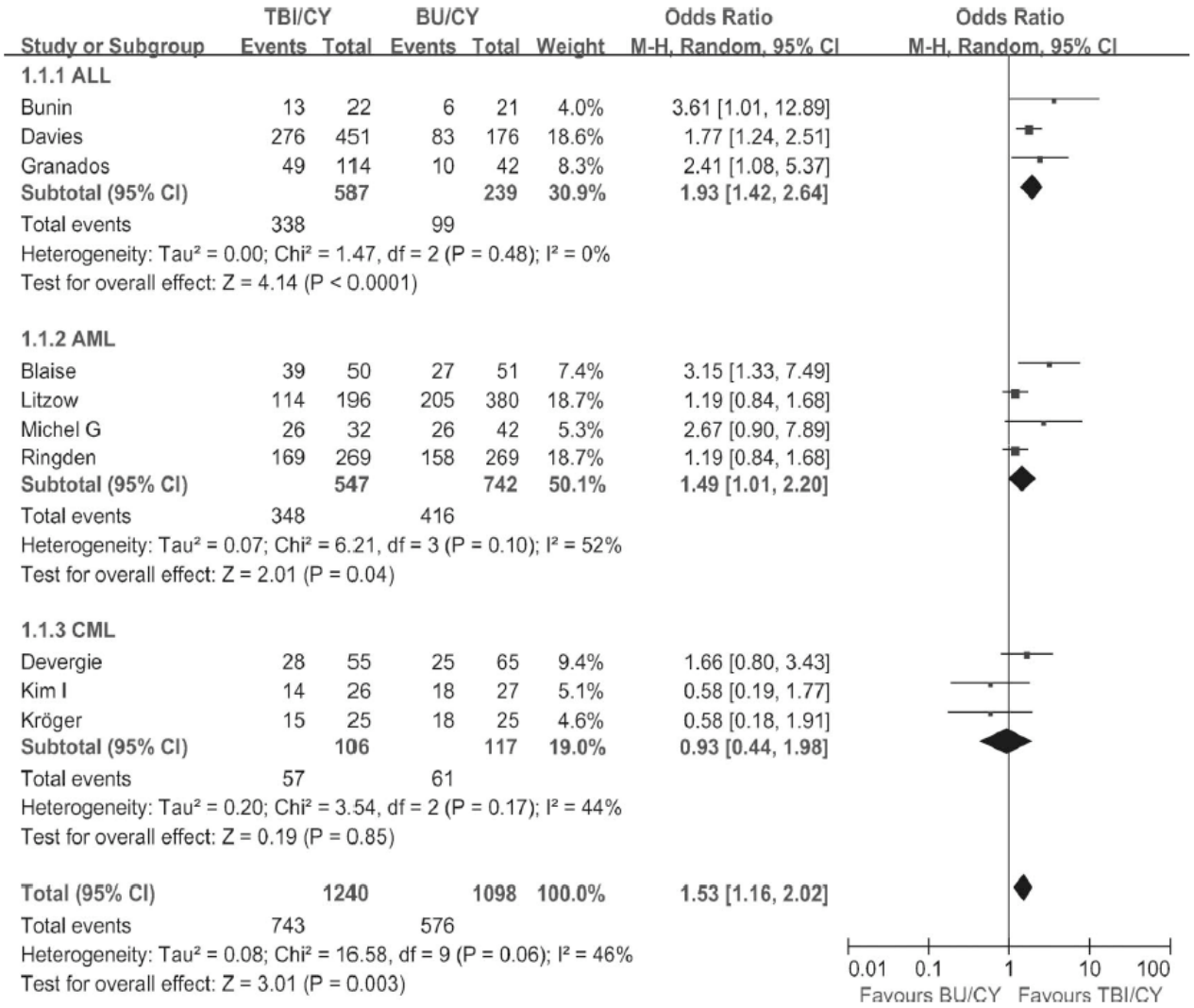
Table I. Characteristics of included studies.

| Reference | TBI/BU (no. of patients) | Dose of TBI/BU | Age (yr) | Diseases | GVHD prophylaxis | Source of HSC | Follow-up (yr) |
|---|---|---|---|---|---|---|---|
| Wingard *et al.* [10] | 23/24 | fTBI 3Gy × 4, BU/CY4, BU:16 mg/kg(O) | 1.8–11.9 | ALL,AML, NHL, etc. | NA | Auto-and allogeneic BM | 2 |
| Blaise *et al.* [11] | 50/51 | fTBI 12Gy, BU/CY2, BU:16 mg/kg(O) | 32 ± 8 | AML | CsA + MTX | Allogeneic BM | 2 |
| Clift *et al.* [12] | 69/73 | fTBI 2Gy × 6, BU/CY2, BU:16 mg/kg(O) | 6–55 | CML | CsA + MTX | id sib BM | 4 |
| Michel *et al.* [13] | 32/42 | fTBI/CY, BU/CY2, BU/CY4, BU:16 mg/kg(O) | 0–16 | AML | CsA + MTX | id sib BM | 2 |
| Devergie *et al.* [14] | 55/65 | fTBI 10 Gy × 1 or 2Gy × 6, BU/CY2, BU:16 mg/kg(O) | 10–54 | CML | CsA + MTX ± MoAb | id sib BM | 5 |
| Ringdén *et al.* [15] | 391/391 | TBI/CY, BU/CY2, BU/CY4 | Unlimited | ALL, AML | CsA + MTX | id sib BM | 2 |
| Micheal *et al.* [16] | 32/42 | TBI 10Gy × 1 or fTBI 11–15Gy, BU/CY2, BU/CY4, BU:16 mg/kg(O) | 8.5 ± 1.5 | AML | CsA + MTX | id sib BM | 7 |
| Ringden *et al.* [17] | 79/88 | TBI 10Gy × 1 or fTBI 12Gy, BU/CY2, BU:16 mg/kg(O) | 2–55 | ALL, AML, CML | CsA + MTX | id sib BM | 7 |
| Granados *et al.* [18] | 114/42 | fTBI 10–12Gy, BU/CY2, BU:16 mg/kg(O) | 2–59 | ALL | CsA + MTX | Auto- or id sib SC | 4 |
| Davies *et al.* [19] | 451/176 | fTBI 10–12Gy, BU/CY2, BU:16 mg/kg(O) | 0.5–19.9 | ALL | CsA ± MTX ± other | id sib BM | 3 |
| Kröger *et al.* [20] | 25/25 | fTBI 2Gy × 6, BU/CY2, BU:16 mg/kg(O) | 19–57 | CML | CsA + MTX + ATG | Unrelated SC | 3 |
| Kim *et al.* [21] | 26/27 | fTBI 1.65Gy × 8, BU/CY2, BU:16 mg/kg(O) | 17–50 | CML | CsA + MTX | id sib BM | 5 |
| Litzow *et al.* [22] | 200/381 | fTBI 11–14Gy, BU/CY2, BU:16 mg/kg(O) | 20–57 | AML | CsA + MTX | Allogeneic BM | 5 |
| Holmstrom *et al.* [23] | 21/24 | TBI 10Gy × 1, BU/CY4, BU:16 mg/kg(O) | 2–16 | AML, ALL, CML | CsA ± MTX | Allogeneic SC | 2 |
| Bunin *et al.* [24] | 22/21 | fTBI 2Gy × 6, BU/CY2, BU:16 mg/kg(O) | <21 | ALL | CsA + MTX | Allogeneic SC | 3 |
| Zhang *et al.* [25] | 23/21 | TBI 7.5–8.5Gy × 1, BU/CY2, BU:16 mg/kg(O) | 14–42 | AML, ALL, CML | CsA + MTX | id sib PBSC | 3 |
| Lähteenmäki *et al.* [26] | 26/18 | fTBI 10Gy, BU/CY2, BU/CY4, BU:16 mg/kg(O) | 0.99–7 | ALL, AML | CsA + MTX or TCD | Related or unrelated SC | 5 |
| Smedler and Winiarski [27] | 12/10 | TBI 10Gy × 1 or 4 Gy × 3, BU/CY2, BU/CY4, BU:16 mg/kg(O) | 0.4–3.6 | ALL, AML, CML, non-malignant | NA | Allogeneic SC | 6.5 |

yr, year; No, number; HSC, Hematopoietic stem cell; HLA, human leukocyte antigen; Bu, busulphan; Cy, cyclophosphamide; fTBI, fractionated total body irradiation; TBI, total body irradiation; ALL, acute lymphoblastic leukemia; CML, chronic myelocytic leukemia; AML, acute myelogenous leukemia; NHL, non-Hodgkin lymphoma; BM, bone marrow; GVHD, graft-*versus*-host disease; NA, not applicable; CsA, cyclosporine; MTX, methotrexate; MoAb, mono-clone antibody; id sib, identical sibling; SC, stem cell; PBSC, peripheral blood stem cell.

Shi-Xia et al, Leukemia and Lymphoma 2010

# DFS for acute leukemias: TBI/Cy vs. Bu/Cy




Shi-Xia et al, 2010

# TBI/Cy or Bu/CY?

- TBI/CY and BU/CY are the 2 gold standards
- TBI/CY : lower relapse rates for acute leukemias, expecially ALL → higher DFS (risk of CNS relapse?)
- With BU/CY: slightly higher risk of TRM (higher VOD risk, higher HC risk)
- TBI/CY: higher late toxicity, expecially in children (impaired development)
- TBI/CY: higher IP risk (unconfirmed when fractionation and lung shielding are used)
- Study limits: heterogeneous studies, small numbers, various pre-transplant regimens

# CT/RT Conditioning: a toxic treatment

## ACUTE SIDE EFFECTS

- Alopecia*
- Nausea and vomiting*
- Oral mucositis*
- Pancytopenia*
- Veno-occlusive disease of the liver
- Interstitial pneumonitis
- Diarrhea*
- Infection due to neutropenia
- Gastrointestinal hemorrage
- Hemorragic cystitis
- Cardiomyopathy
- Dermatitis
- Peripheral neuropathy
- Acute renal failure
- Pancreatitis
- Parotitis

## DELAYED EFFECTS

- Cataracts
- Infertility*
- Hypothyroidism
- Radiation nephritis
- Secondary malignancies
- Impaired growth and development in children/psychosocial problems
- Osteoporosis
- Restrictive lung disease

Strahlentherapie
und Onkologie

**Supplement Article**

Late Toxicity in Children Undergoing Hematopoietic Stem Cell Transplantation with TBI-containing Conditioning Regimens for Hematological Malignancies

Umberto Ricardi[1], Andrea Riccardo Filippi[1], Eleonora Biasin[2], Patrizia Ciammella[1], Angela Botticella[1], Pierfrancesco Franco[1], Andrea Corrias[3], Elena Vassallo[2], Riccardo Ragona[1], Franca Fagioli[2]

***Almost invariably occur after high-dose regimens**

# Transplant-Related Mortality

- With conventional allo-BMT, expected non-relapse mortality (NRM) @ day 100 is 23%, @ 1 year is 30% (FHCRC, Blood 2004)
- There is a strong correlation with a direct adverse effect of conditioning (Cy-TBI, Busulfan-TBI)

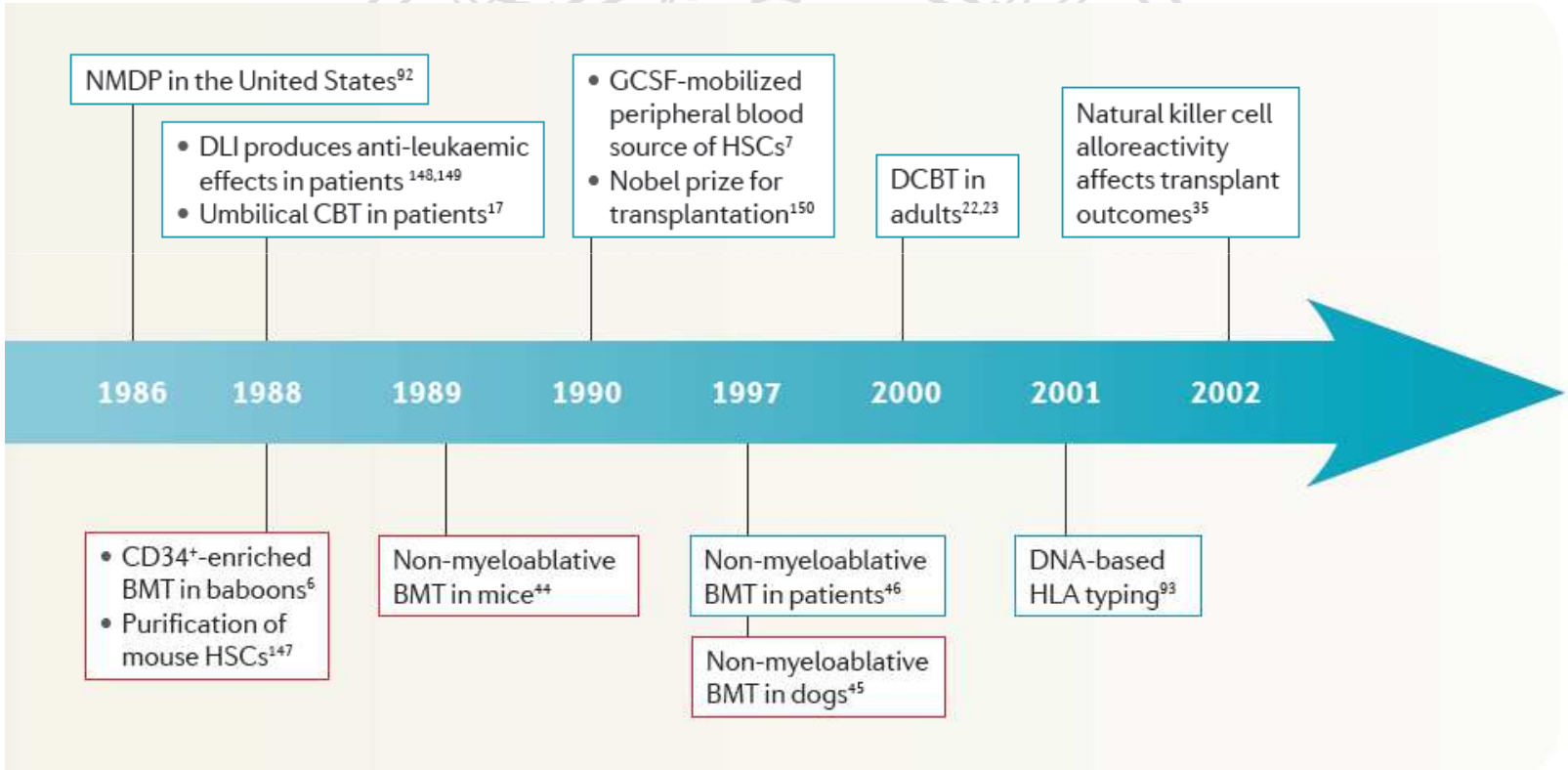
Consequential restriction in allo-BMT indications

# Median Ages at HSCT vs. Ages at Diagnoses

| Disease | Allogeneic HSCT Recipients (FHCRC) | | At Diagnoses (SEERS) |
|---|---|---|---|
| | Related Donor | Unrelated Donor | |
| CML | 40 | 36 | 67 |
| AML | 28 | 33 | 68 |
| NHL | 33 | 35 | 65 |
| MM | 45 | 45 | 70 |
| CLL | 51 | 46 | 71 |
| HD | 29 | 28 | 34 |
| MDS | 40 | 41 | 68 |
| Overall | 40(n=1428) | 35(n=1277) | __ |

***Sandmaier Keystone 2001***

# An alternative way:
# Reduced Intensity Conditioning

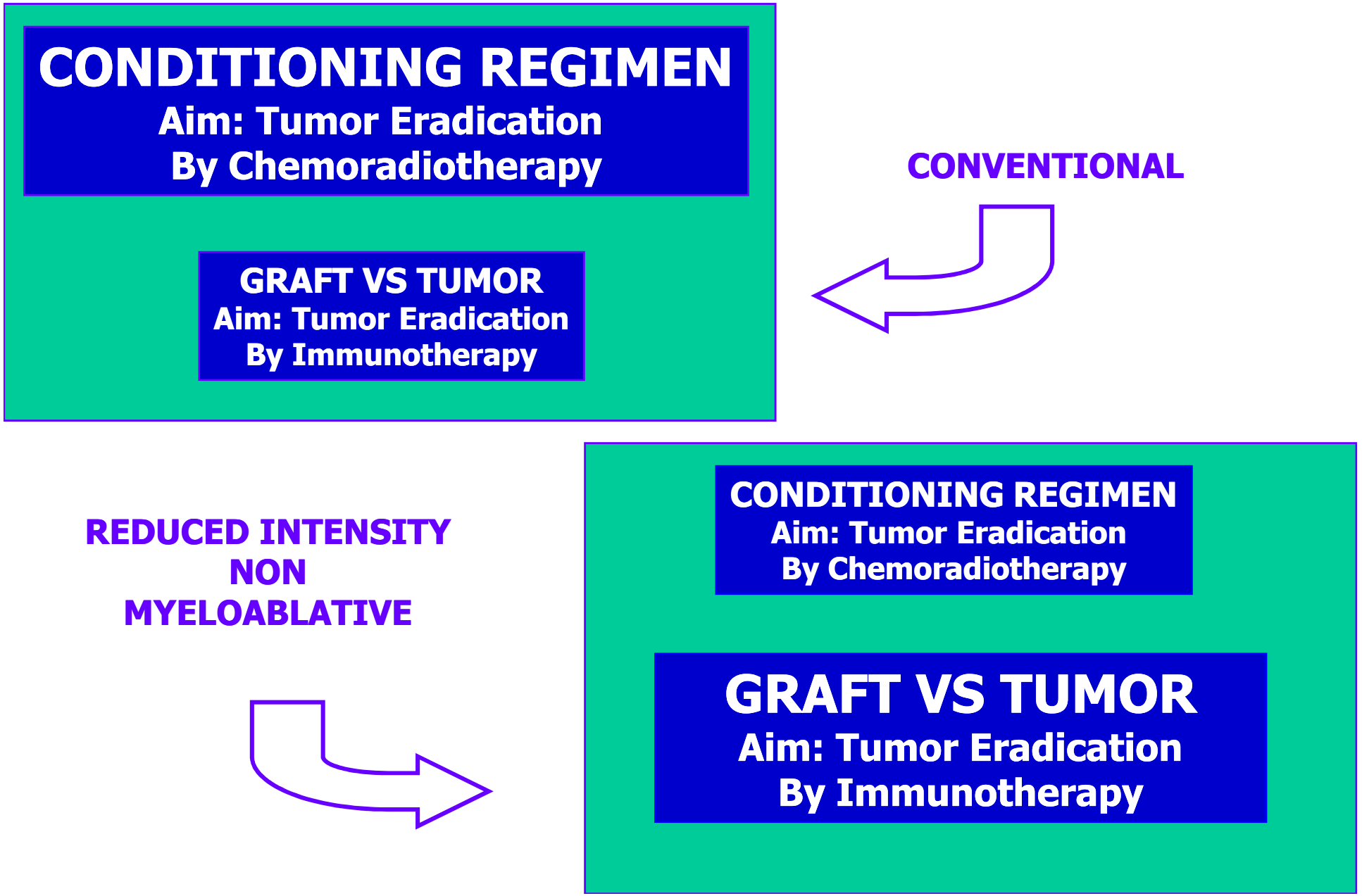



Jenq R, Nat Rev Cancer 2010

# A new approach to allografting

1. High Dose Regimen
   - eradicate malignancy
   - create space
   - suppress host immunity
2. Stem Cell Graft
   - rescue from pancytopenia
3. GVHD Prevention
   - post-grafting immunosuppression
   - T cell depletion

1. Non Myeloablative Regimen
   - not aimed at eradicate malignancy
   - not aimed at creating space
   - suppress host immunity
2. Stem Cell Graft
   rescue from pancytopenia
3. GVHD Prevention
   - potent post-grafting immunosuppression to overcome HVG barriers
   - T cell depletion


CONDITIONING REGIMEN
Aim: Tumor Eradication
By Chemoradiotherapy
GRAFT VS TUMOR
Aim: Tumor Eradication
By Immunotherapy
CONVENTIONAL
REDUCED INTENSITY
NON
MYELOABLATIVE
CONDITIONING REGIMEN
Aim: Tumor Eradication
By Chemoradiotherapy
GRAFT VS TUMOR
Aim: Tumor Eradication
By Immunotherapy

# Role of low dose TBI in non-myeloblative allografting

Low-dose TBI administered in a single fraction before BMT

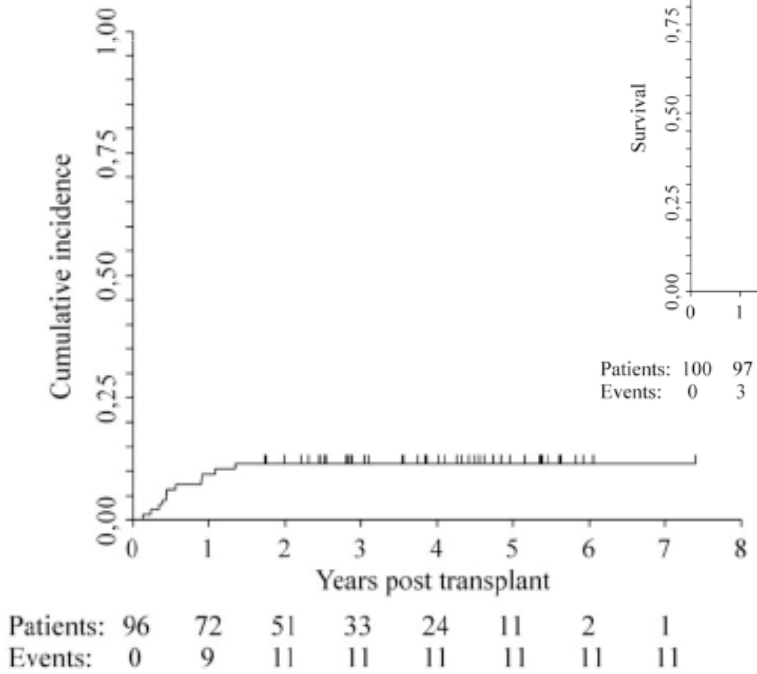
Post-grafting immunosuppression with MMF and CSP

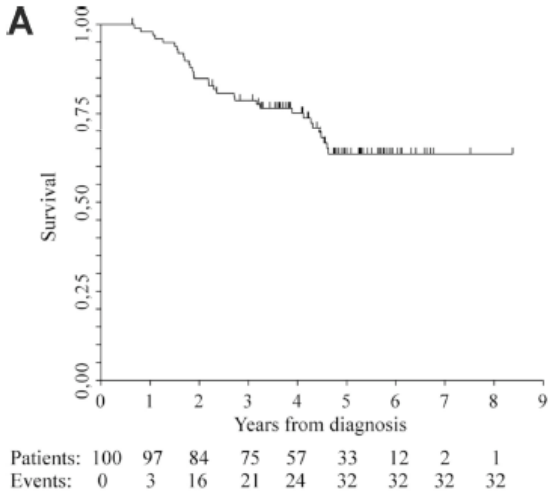
Induction of GVT and control of GVHD

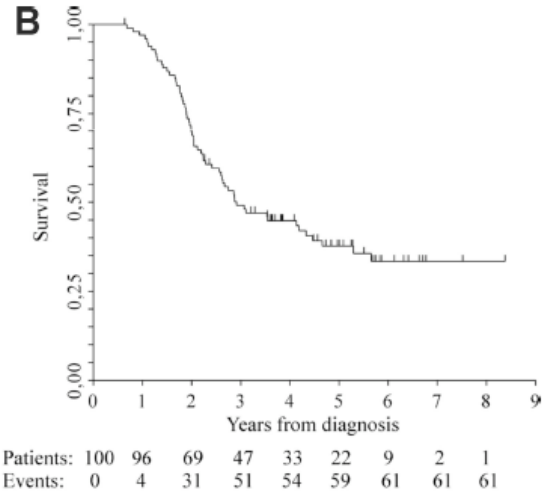
# RIC with 2 Gy TBI/Flu: experience in MM

## Nonmyeloablative allografting for newly diagnosed multiple myeloma: the experience of the Gruppo Italiano Trapianti di Midollo

Benedetto Bruno,[1] Marcello Rotta,[1] Francesca Patriarca,[2] Daniele Mattei,[3] Bernardino Allione,[4] Fabrizio Carnevale-Schianca,[5] Roberto Sorasio,[1] Alessandro Rambaldi,[6] Marco Casini,[7] Matteo Parma,[8] Pasqua Bavaro,[9] Francesco Onida,[10] Alessandro Busca,[11] Luca Castagna,[12] Edoardo Benedetti,[13] Anna Paola Iori,[14] Luisa Giaccone,[1] Antonio Palumbo,[1] Paolo Corradini,[15] Renato Fanin,[2] David Maloney,[16] Rainer Storb,[16] Ileana Baldi,[17] Umberto Ricardi,[18] and Mario Boccadoro[1]

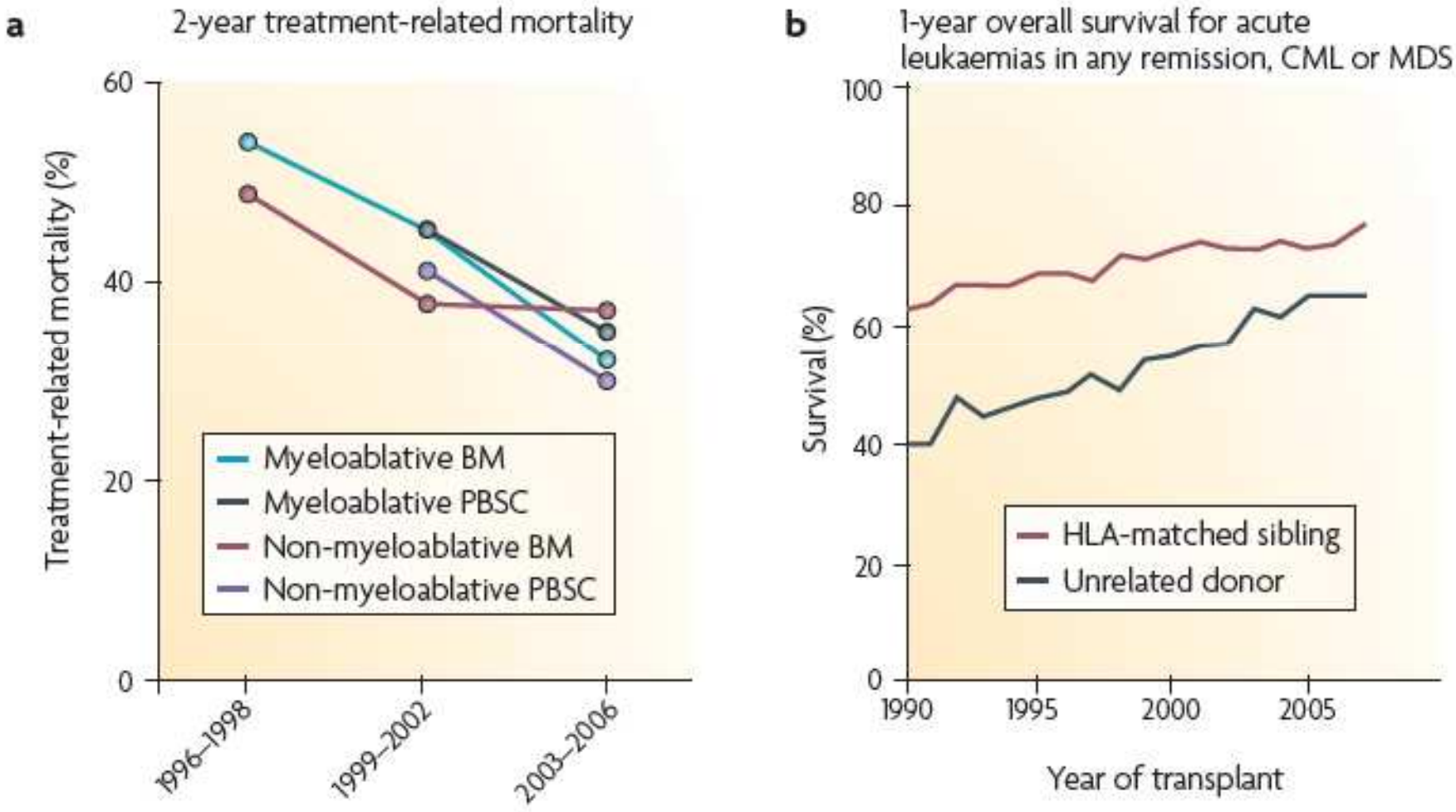



Bruno B et al, Blood 2008

# Lower TRM and higher OS




Jenq, Nat Rev Cancer, 2010

# Alternative RIC strategies: intermediate conditioning

**The Addition of 400 cGY Total Body Irradiation to a Regimen Incorporating Once-Daily Intravenous Busulfan, Fludarabine, and Antithymocyte Globulin Reduces Relapse Without Affecting Nonrelapse Mortality in Acute Myelogenous Leukemia**

*James A. Russell,[1] William Irish,[2] Alexander Balogh,[1] M. Ahsan Chaudhry,[1] Mary Lynn Savoie,[1] A. Robert Turner,[3] Loree Larratt,[3] Jan Storek,[1] Nizar J. Bahlis,[1] Christopher B. Brown,[1] Diana Quinlan,[1] Michelle Geddes,[1] Nancy Zacarias,[1] Andrew Daly,[1] Peter Duggan,[1] Douglas A. Stewart[1]*

**400 cGy TBI with fludarabine for reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation**

RM Sobecks[1], R Dean[1], LA Rybicki[2], J Chan[1], KS Theil[3], R Macklis[4], S Andresen[1], M Kalaycio[1], B Pohlman[1], C Ferraro[1], K Cherni[1], J Sweetenham[1], E Copelan[1] and BJ Bolwell[1]

*[1]Department of Hematologic Oncology and Blood Disorders, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA; [2]Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH, USA; [3]Department of Clinical Pathology, Cleveland Clinic, Cleveland, OH, USA and [4]Department of Radiation Oncology, Cleveland Clinic, Cleveland, OH, USA*

# Alternative RIC strategies: intermediate conditioning

Allogeneic transplantation improves the overall and progression-free survival of Hodgkin lymphoma patients relapsing after autologous transplantation: a retrospective study based on the time of HLA typing and donor availability

Barbara Sarina,[1] Luca Castagna,[1] Lucia Farina,[2] Francesca Patriarca,[3] Fabio Benedetti,[4] Angelo M. Carella,[5] Michele Falda,[6] Stefano Guidi,[7] Fabio Ciceri,[8] Alessandro Bonini,[9] Samantha Ferrari,[10] Michele Malagola,[11] Enrico Morello,[12] Giuseppe Milone,[13] Benedetto Bruno,[14] Nicola Mordini,[15] Simonetta Viviani,[16] Alessandro Levis,[17] Laura Giordano,[18] Armando Santoro,[1] and Paolo Corradini,[2,19] for Gruppo Italiano Trapianto di Midollo Osseo

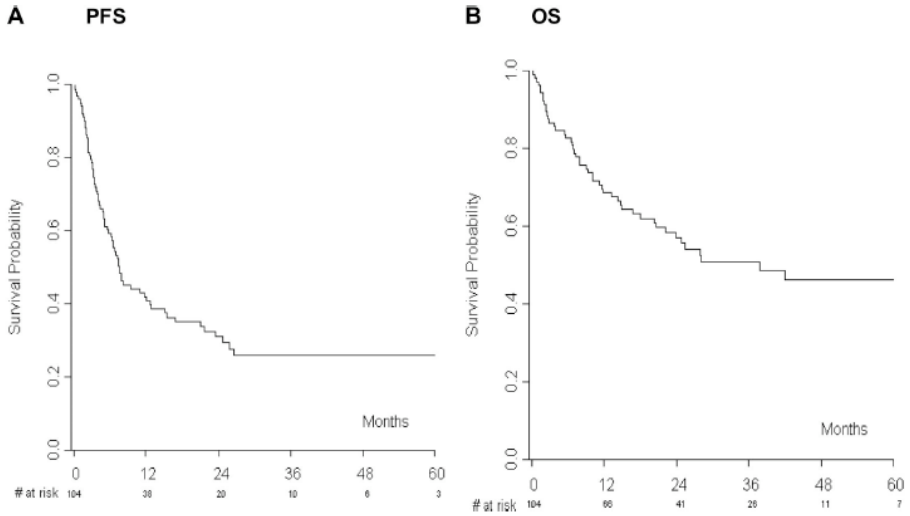



**Table 2. Conditioning regimens**

| Conditioning regimen | No. of patients |
|---|---|
| Fludarabine (90 mg/m$^2$) + melphalan (100-140 mg/m$^2$) ± ATG | 15 |
| Thiotepa (10 mg/kg) + cyclophosphamide (100 mg/kg) ± ATG | 11 |
| Fludarabine (60 mg/m$^2$) + cyclophosphamide (60 mg/kg) + thiotepa (10 mg/kg) | 49 |
| Fludarabine (150 mg/m$^2$) + busulfan (8 mg/kg) | 2 |
| Thiotepa (5 mg/kg) + cyclophosphamide (100 mg/kg) + melphalan (70 mg/m$^2$) + ATG or alemtuzumab | 6 |
| Fludarabine (120 mg/m$^2$) + cyclophosphamide (60 mg/kg) + thiotepa (10 mg/kg) + alemtuzumab + TBI 2 Gy | 6 |
| Fludarabine (120 mg/m$^2$) + cyclophosphamide (900 mg/m$^2$) | 11 |
| Fludarabine (90 mg/m$^2$) + TBI 2 Gy | 4 |

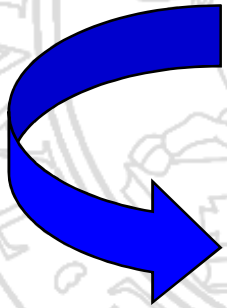
Sarina et al, Blood 2010

# TBI: Different Options in 2010

- Classic Myeloblative Approach in ALL ped/adult, and selected AML→ TBI 12 Gy/6 fractions
- Reduced Intensity classic approach for MM, CLL in CR → TBI 2 GY single fraction
- Intermediate Reduced Intensity regimens: when you need higher rates of disease eradication, not too toxic conditioning → TBI 4 Gy single fraction, 8 Gy 4 fractions

We’re still using TBI, at standard or different doses: can we imagine further applications of RT prior to allo-BMT?

Due to the fact that acute grade II-IV GVHD is still the main toxic event in the first 100 days post allo-BMT



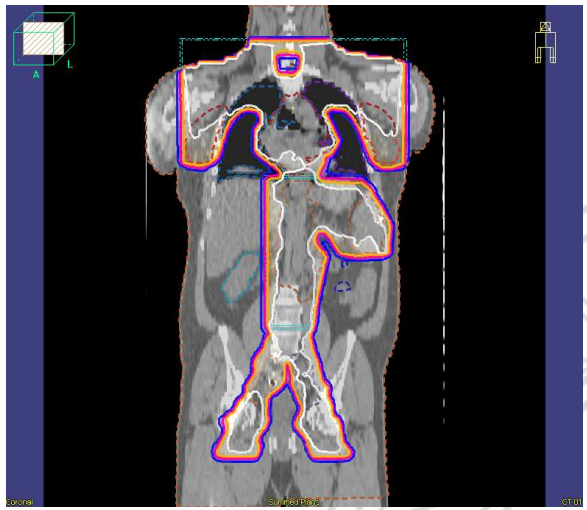
**“Protective” Conditioning ?**

# Back to biology: from generalized towards selected immuno-suppression

**Predominance of NK1.1$^+$TCR$\alpha\beta^+$ or DX5$^+$TCR$\alpha\beta^+$ T Cells in Mice Conditioned with Fractionated Lymphoid Irradiation Protects Against Graft-Versus-Host Disease: "Natural Suppressor" Cells[1]**

**Fengshuo Lan,* Defu Zeng,* Masanori Higuchi,* Philip Huie,† John P. Higgins,† and Samuel Strober[2]***

**J Immunol. 2001**

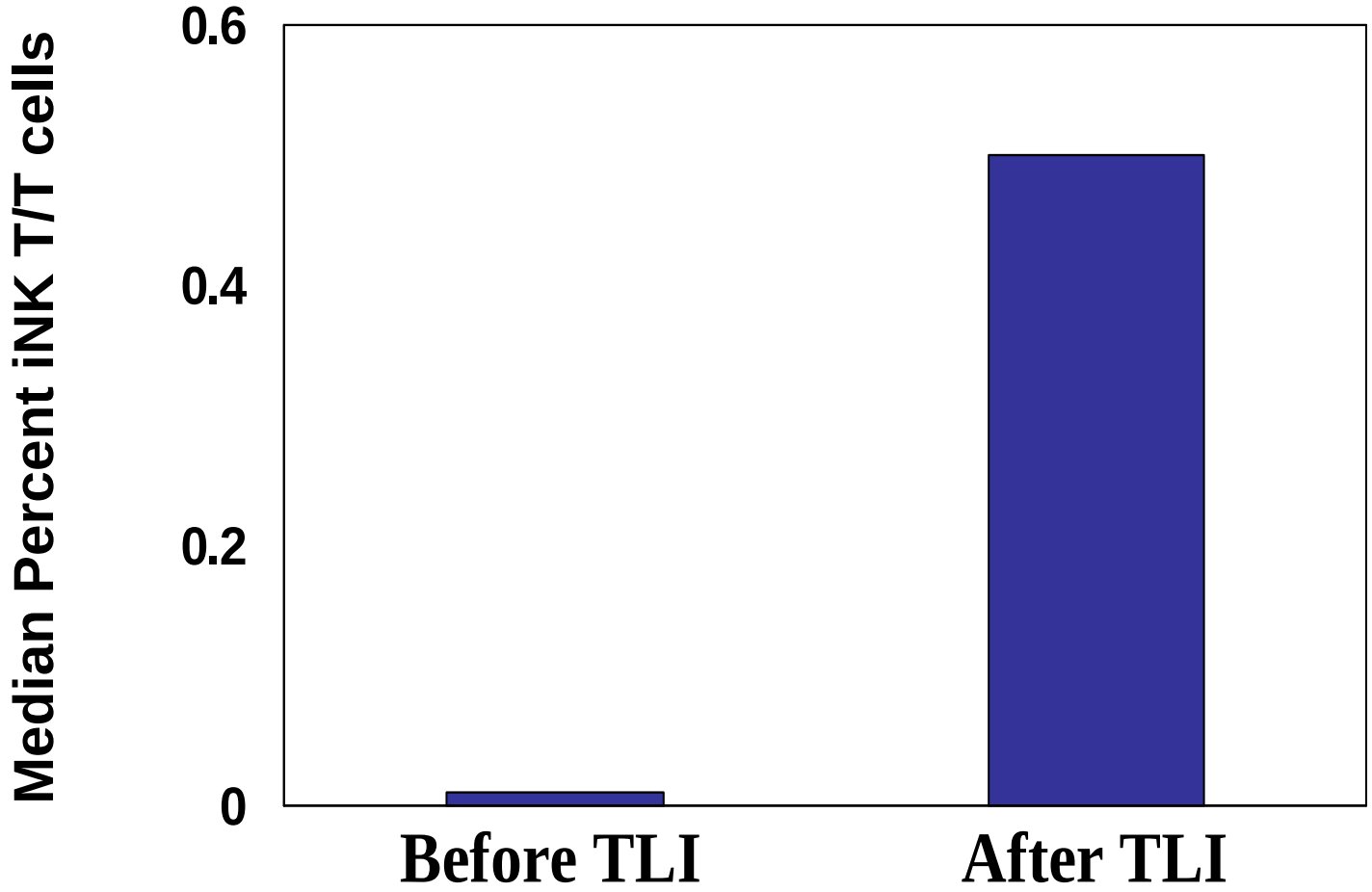


# TLI and ATG conditioning regimen: immunological basis

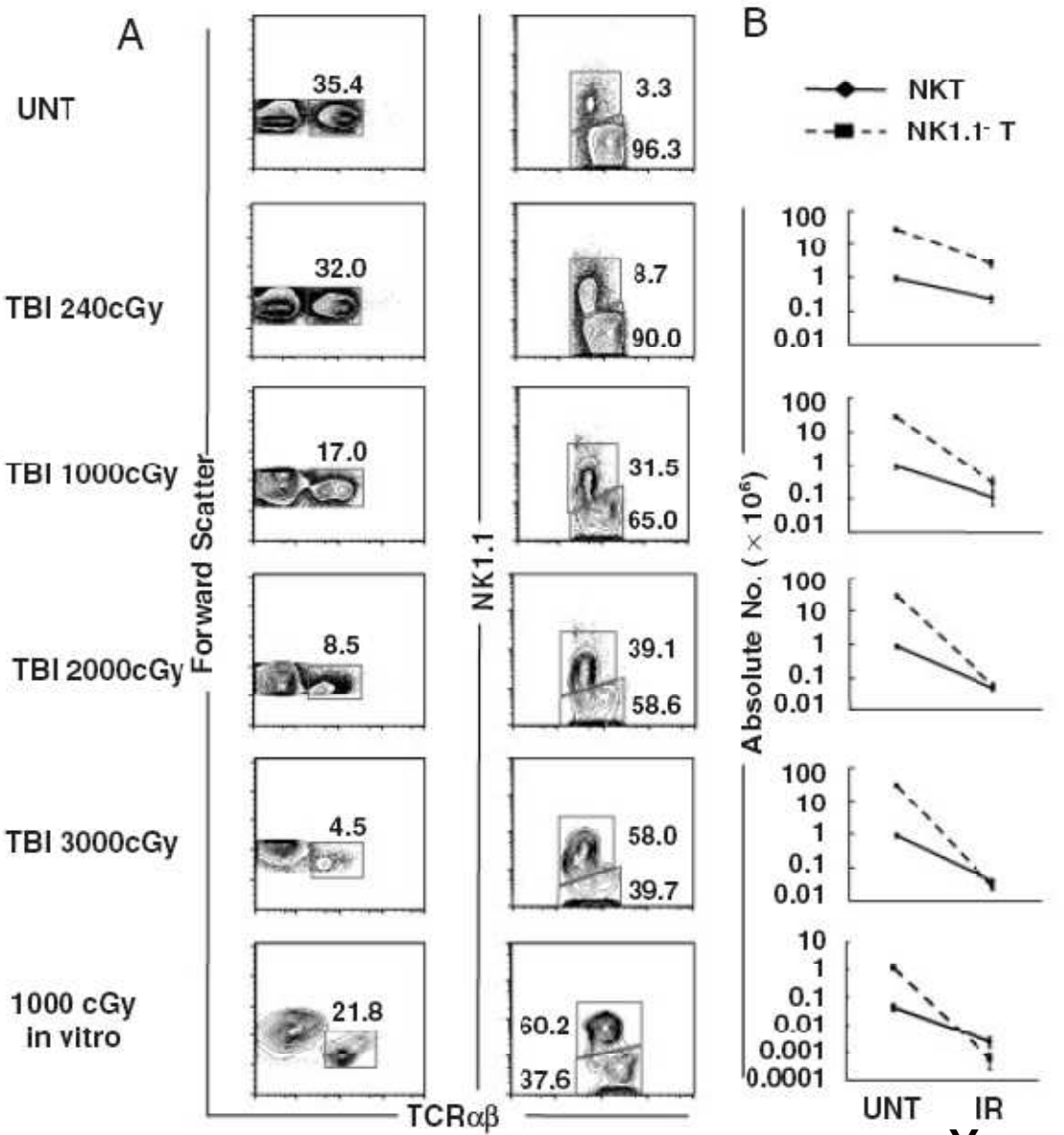
Favoring **host** regulatory NK T cells:

→ polarizing **donor** T cells towards secretion of cytokines like interleukin-4
→ promoting expansion of **donor** CD4+CD25+ Fox P3+ T regulatory cells

# Increased percent of iNK T cells/All T cells in peripheral blood of patients receiving TLI and ATG

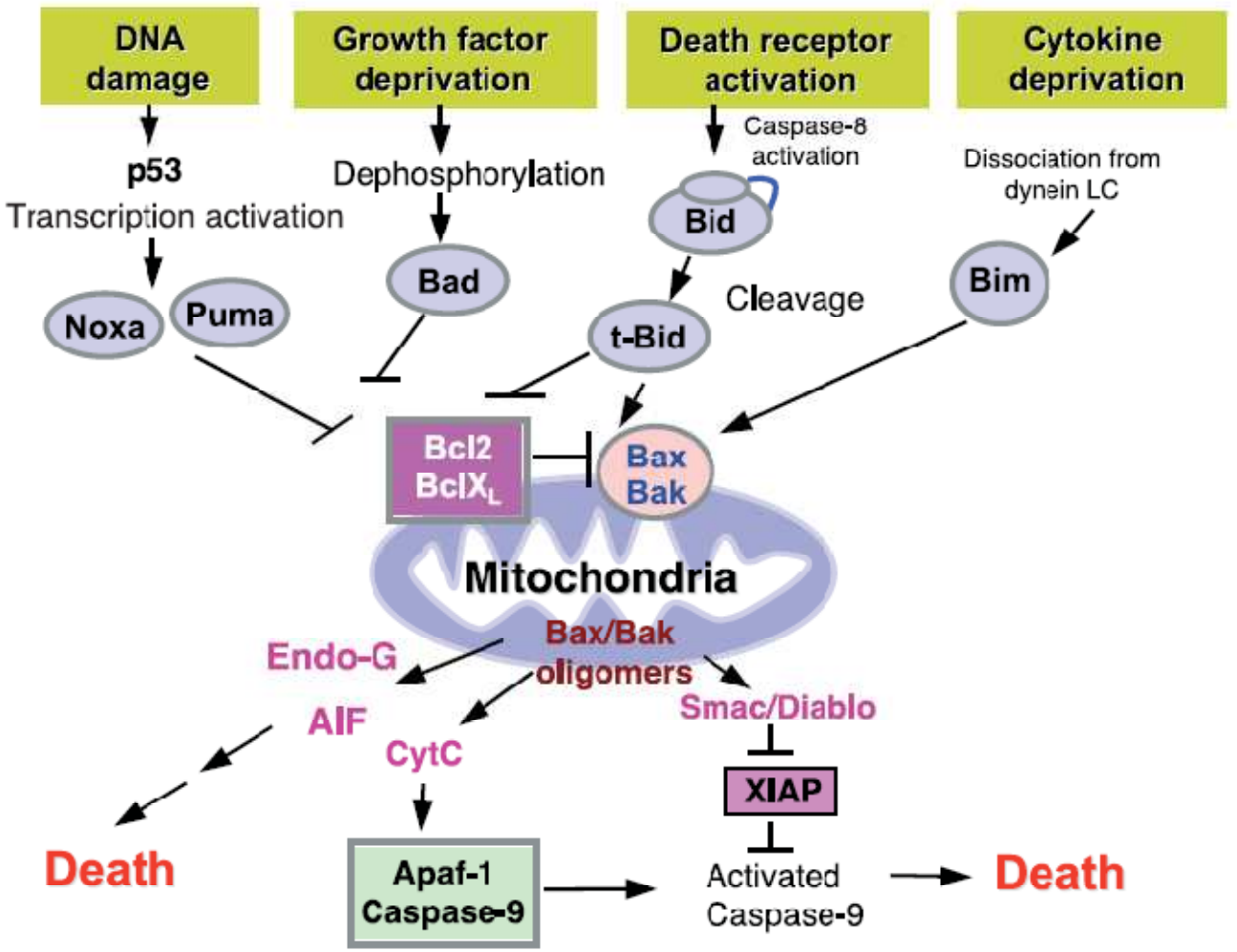


# NK T Cells are Radiation Resistant



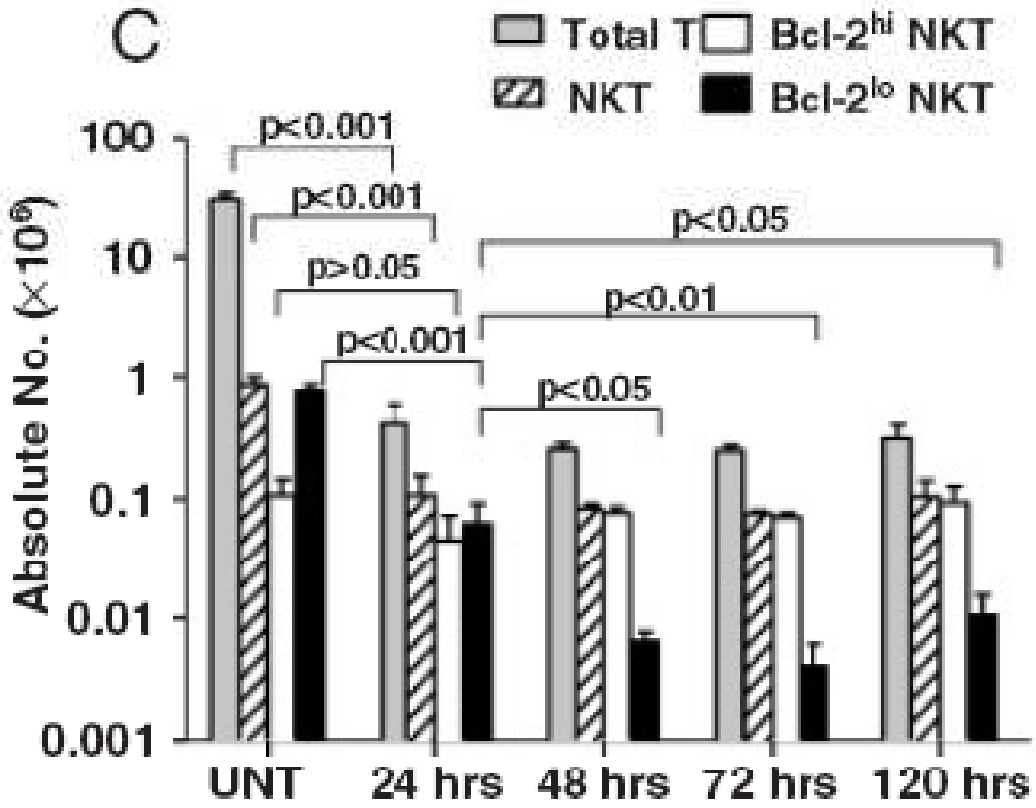

Yao et al, J Immunol 2009

# Role of Bcl-2



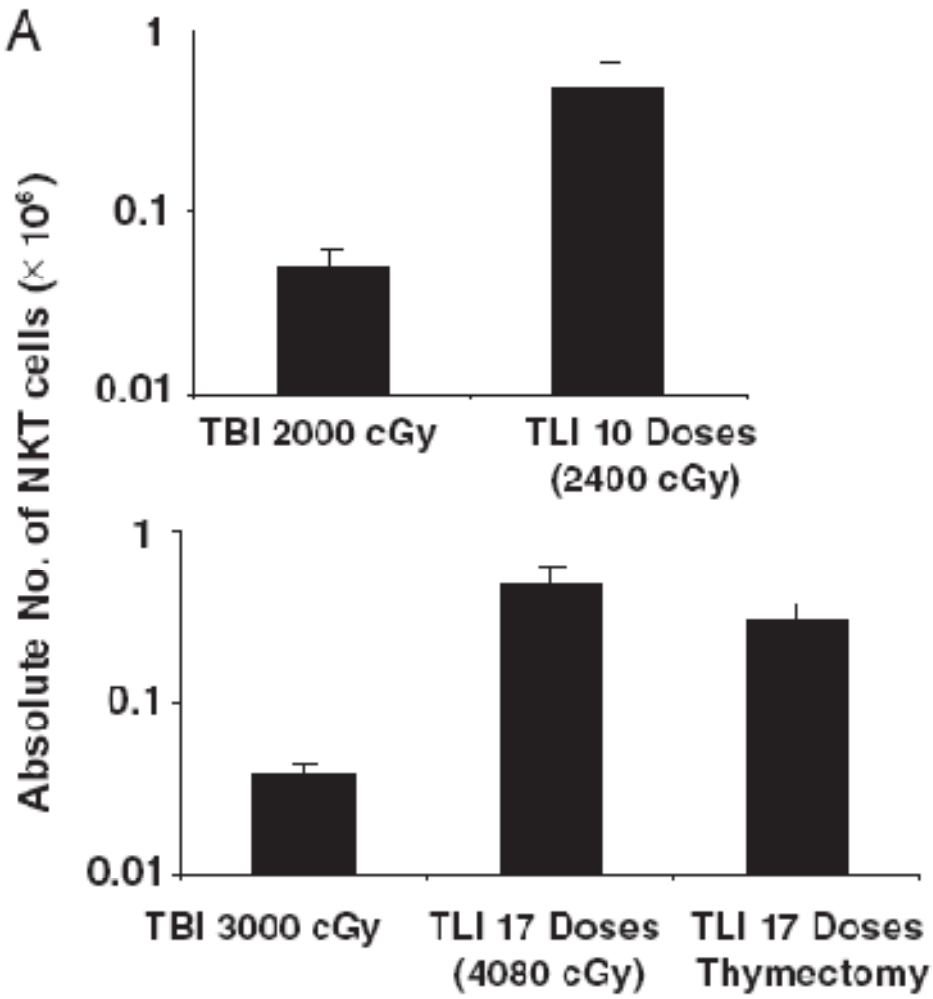

Kim, Cancer 2005

# Radio-resistance of NKT cells depends on Bcl-2 expression




Yao et al, J Immunol 2009

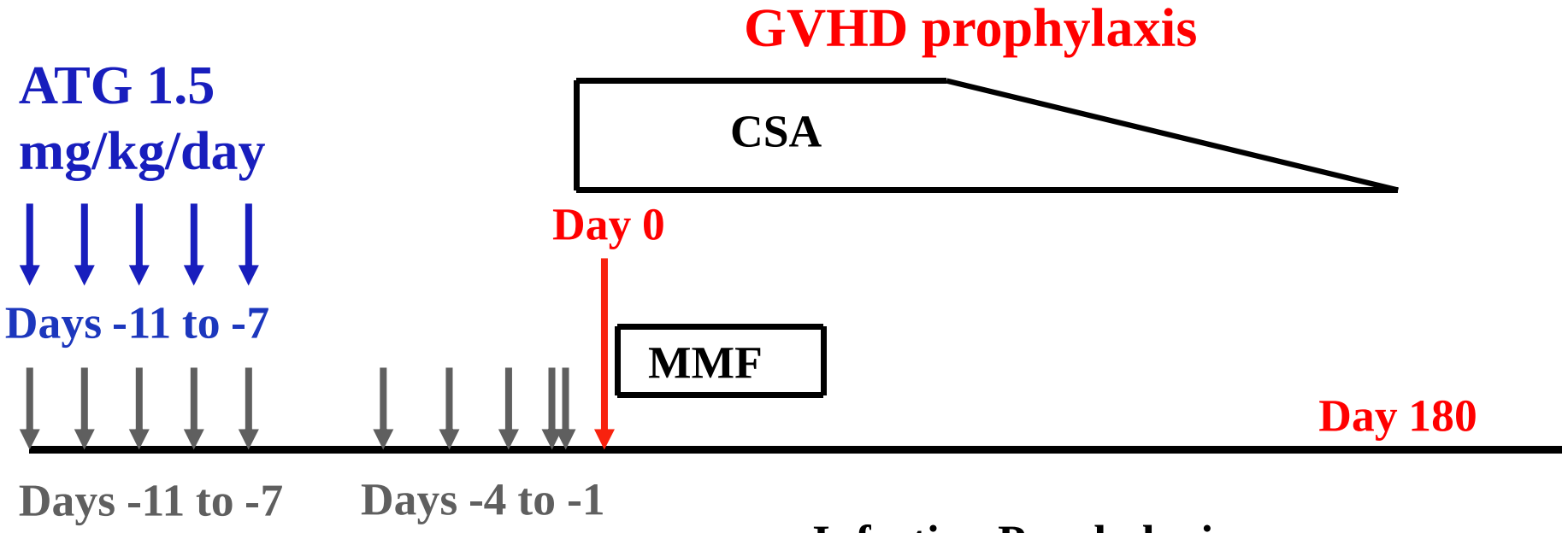
# Differences between TBI and TLI




Yao et al, J Immunol 2009

# TLI/ATG as conditioning regimen to allo-SCT

# The Stanford protocol




**Infection Prophylaxis**

**HSV: if +ve acyclovir 400 mg BID**

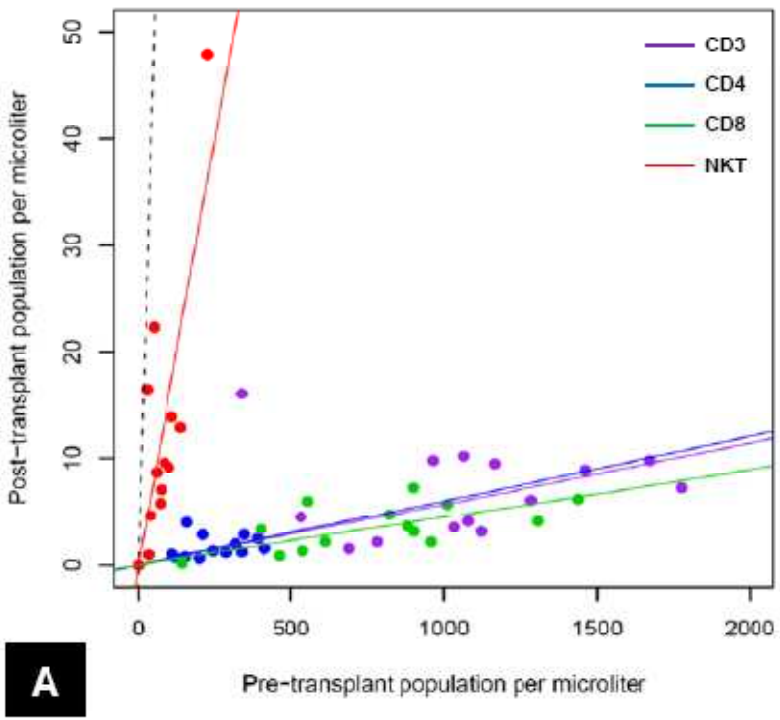
**CMV: blood PCR weekly**

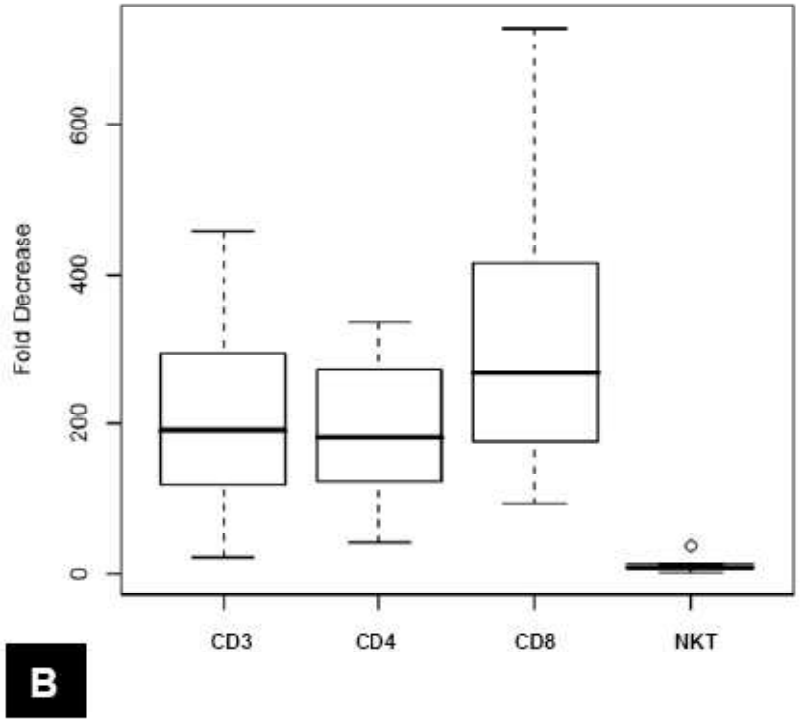
**EBV: blood PCR every 2 weeks**

**PCP: Septra DS BID weekends D+42**

**Fungus: if prior infection or URD**

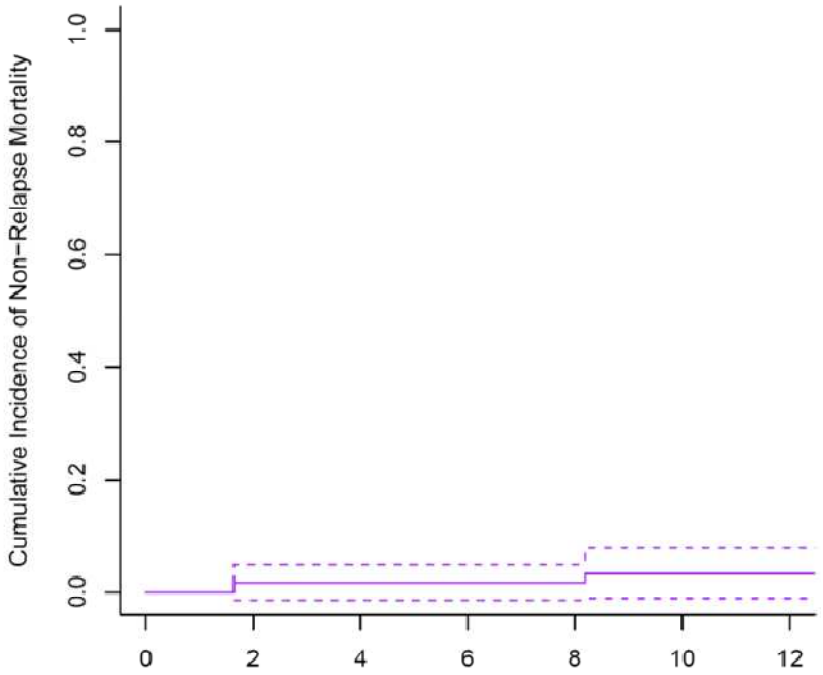
# 2009 trial up-date: effect of TLI plus ATG on circulating T-cells subsets

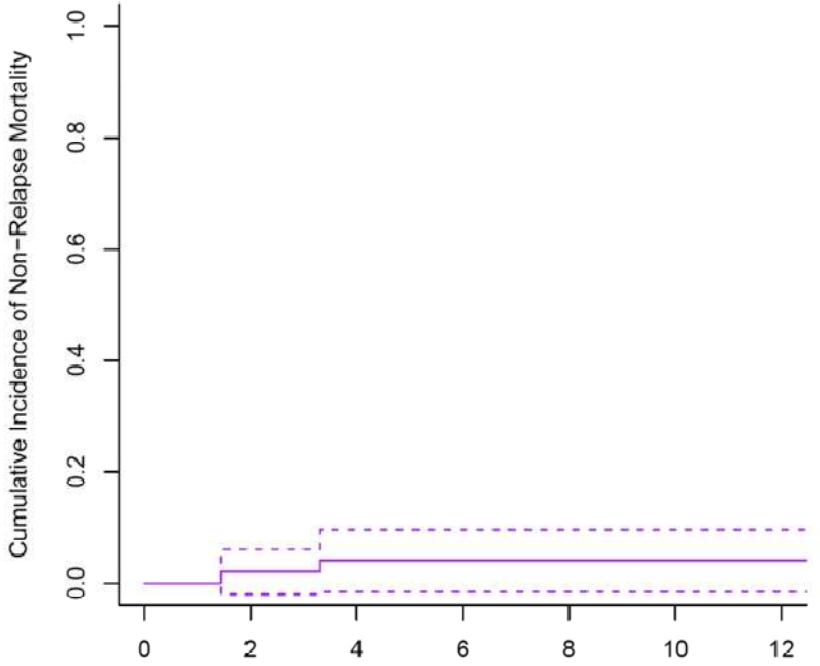



Kohrt et al, Blood 2009

# 2009 trial up-date: CI of aGVHD




**Kohrt et al, Blood 2009**

# Remarks

- Myeloablative TBI is still a gold standard for conditioning in ALL/AML
- Non-myeloablative TBI is a major component of non-myeloablative regimens
- TLI is feasible and safe but should be reserved to patients in clinical trials (and performed by RO trained in hemato-oncology)
- Biological basis and mechanisms of immunomodulation after RT continue to be object of investigation