בחירת טיפול מכין להשתלת מח עצם מתורם

סיגל גריסרו
המחלקה להשתלות מח עצם
הדסה עין כרם

conditioning regimen → Two functions:

- Reduce the tumor burden—when the disease is neoplastic
- suppress the recipient's immune system, to allow engraftment of donor's stem cells

Traditionally- these goals have been achieved by:
Supra lethal doses of total body irradiation (TBI) and chemotherapeutic agents.

Graft-Versus-tumor [GVT] effect:

Immunologic reactions of donor cells against malignant host cells

→ Reduced-intensity Conditioning -RIC

and Nonmyeloablative - NMA conditioning regimens

→ HCT applicable to older and medically infirm patients.

How to choose….

Conditioning regimens choice is influenced by:

Patient related factors:

Age

performance status

comorbidities

Disease related factors:

Malignant/non malignant

disease risk

remission status

disease sensitivity to GVT

Roles of the conditioning regimen before HSCT

Eradicate Malignant cells

Eradicate host hematopoiesis
Suppress host immunity

DISEASE CONTROL

ENGRAFTMENT

Challenge:
Limit toxicity
Max efficacy

RIC / MAC

Roles of the graft

Graft-versus tumor

Restore donor's hematopoiesis
Graft-versus host's hematopoiesis

DISEASE CONTROL

ENGRAFTMENT

Conditioning regimens characteristics to consider :

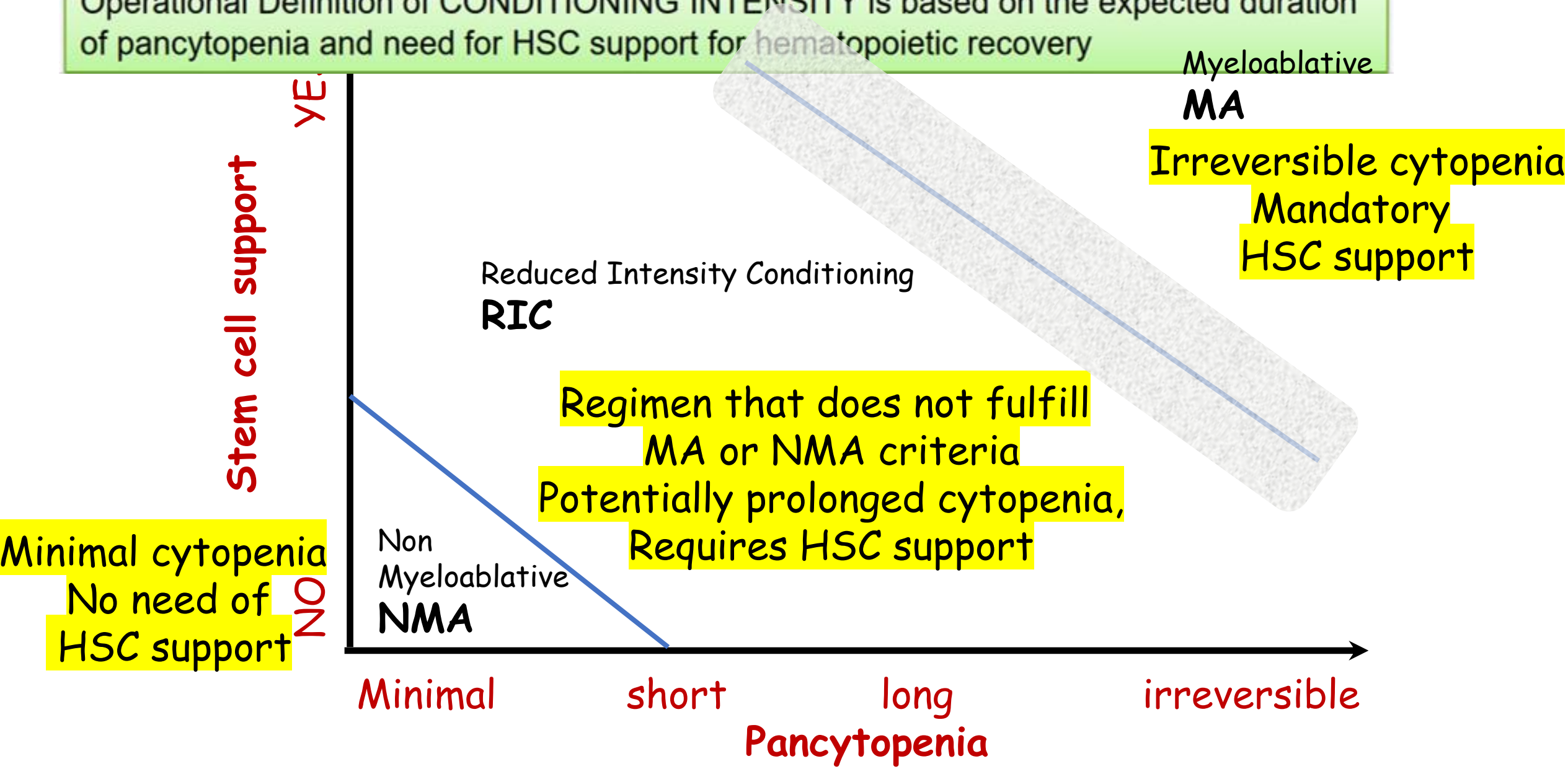
- Intensity = MAC/RIC/NMA
- TBI /non TBI
- GVHD prophylaxis
- Myeloablation / immunoablation

Conditioning regimens characteristics to consider :

- **Intensity = MAC/RIC/NMA**
- TBI /non TBI
- GVHD prophylaxis
- Myeloablation / immunoablation

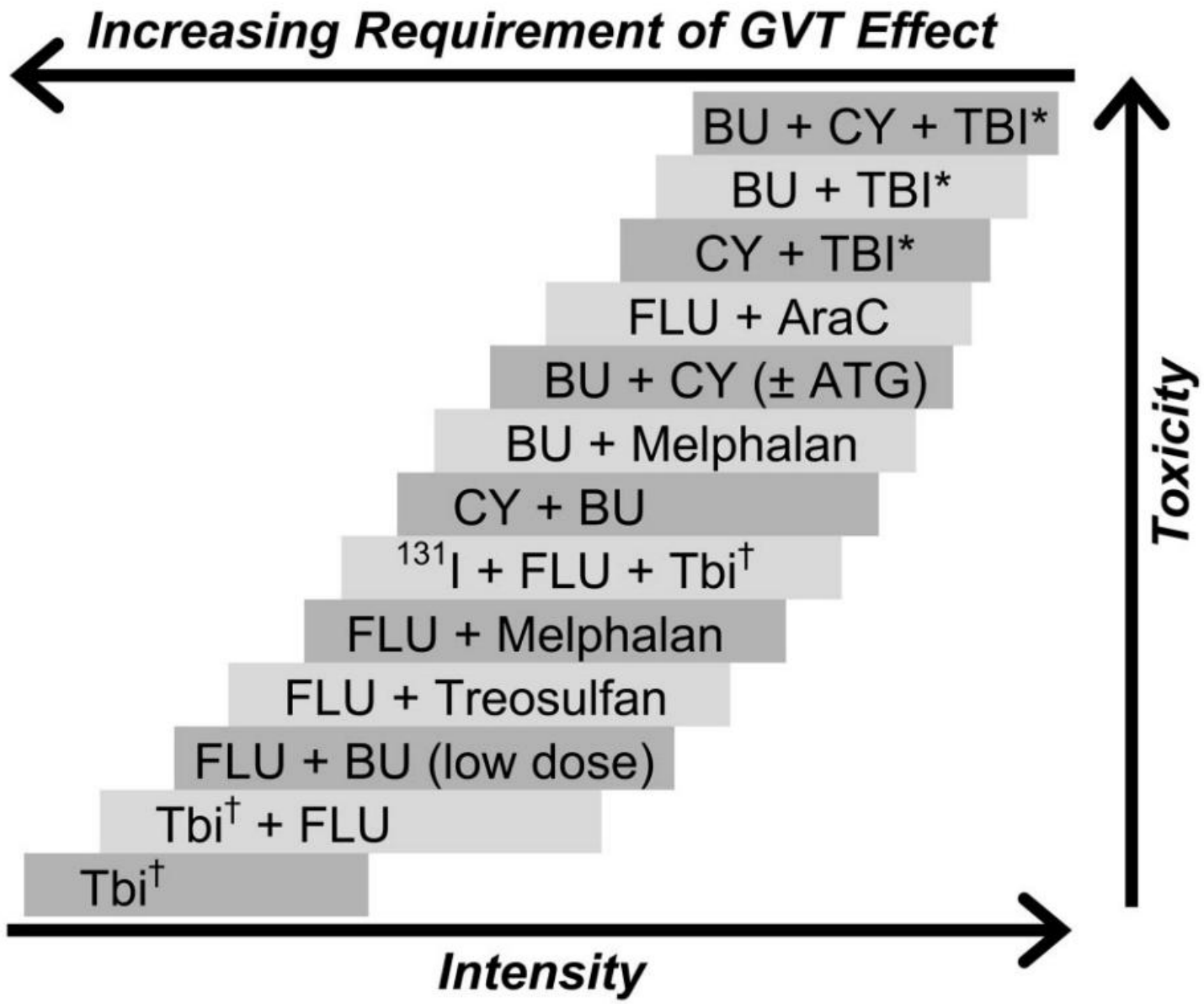
Regimens Intensity Definition:

Operational Definition of CONDITIONING INTENSITY is based on the expected duration of pancytopenia and need for HSC support for hematopoietic recovery



Myeloablative Conditioning - MAC	**Reduced Intensity Conditioning – RIC & Non Myelo Ablative NMA**
TBI >5 Gy (single) or >8 Gy (fractionated)	TBI ≤5 Gy (single) or TBI ≤8 Gy (fractionated)
Busulfan (BU) >7.2 mg/kg IV (or >9.0 mg/kg PO)	BU ≤7.2 mg/kg IV or ≤9.0 mg/kg PO
BU >300 mg/m2 IV (or 375 mg/m2 PO)	BU ≤300 mg/m2 IV or ≤375 mg/m2 PO
Mel >150 mg/m2	Mel ≤150 mg/m2
Thiotepa (TT) ≥ 10 mg/kg	TT < 10 mg/kg
Treosulfan (Treo) >30,000 mg/m2 (or >30 g/m2)	Treo ≤30 g/m2

rely on GVT effect



Selected conditioning regimens of different dose intensities.
*High-dose TBI (800-1320 cGy).
†Low-dose TBI (200-400 cGy).

- What differentiates RIC regimens from myeloablative regimens

  is that the dose of **alkylating agents** or **TBI** is generally reduced by **≥30%**

Limitations the above definition:

- **- "intensity"** was defined on the basis of grade of reversible and

  irreversible **myelotoxicity** rather than of **non-hematologic toxicity** →

  Early Non Relapse Mortality
- Ignores the additional intensity of purine analogs used for immune-ablation
- Less well-defined terms, such as "**reduced toxicity**" , "**hyper-intensive**"

  "**augmented reduced intensity**"

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https://doi.org/10.1038/s41409-020-0803-y

ARTICLE

Redefining and measuring transplant conditioning intensity in current era: a study in acute myeloid leukemia patients

This article has been corrected since Advance Online Publication and a correction is also printed in this issue

Alexandros Spyridonidis[1] · Myriam Labopin[2] · Bipin N. Savani[3] · Riitta Niittyvuopio[4] · Didier Blaise[5] · Charles Craddock[6] · Gerard Socié[7] · Uwe Platzbecker[8] · Dietrich Beelen[9] · Noel Milpied[10] · Jan J. Cornelissen[11] · Arnold Ganser[12] · Anne Huynh[13] · Laimonas Griskevicius[14] · Sebastian Giebel[15] · Mahmoud Aljurf[16] · Eolia Brissot[2] · Florent Malard[2] · Jordi Esteve[17] · Zinaida Peric[18] · Frédéric Baron[19] · Annalisa Ruggeri[20] · Christoph Schmid[21] · Maria Gilleece[22] · Norbert-Claude Gorin[2] · Francesco Lanza[23] · Roni Shouval[24] · Jurjen Versluis[12] · Gesine Bug[25] · Yngvar Fløisand[26] · Fabio Ciceri[27] · Jamie Sanz[28] · Ali Bazarbachi[29] · Arnon Nagler[30] · Mohamad Mohty[2]

Assigned intensity weight scores for frequently used conditioning regimen components.

Used their sum to generate the **Transplant Conditioning Intensity (TCI) score**.

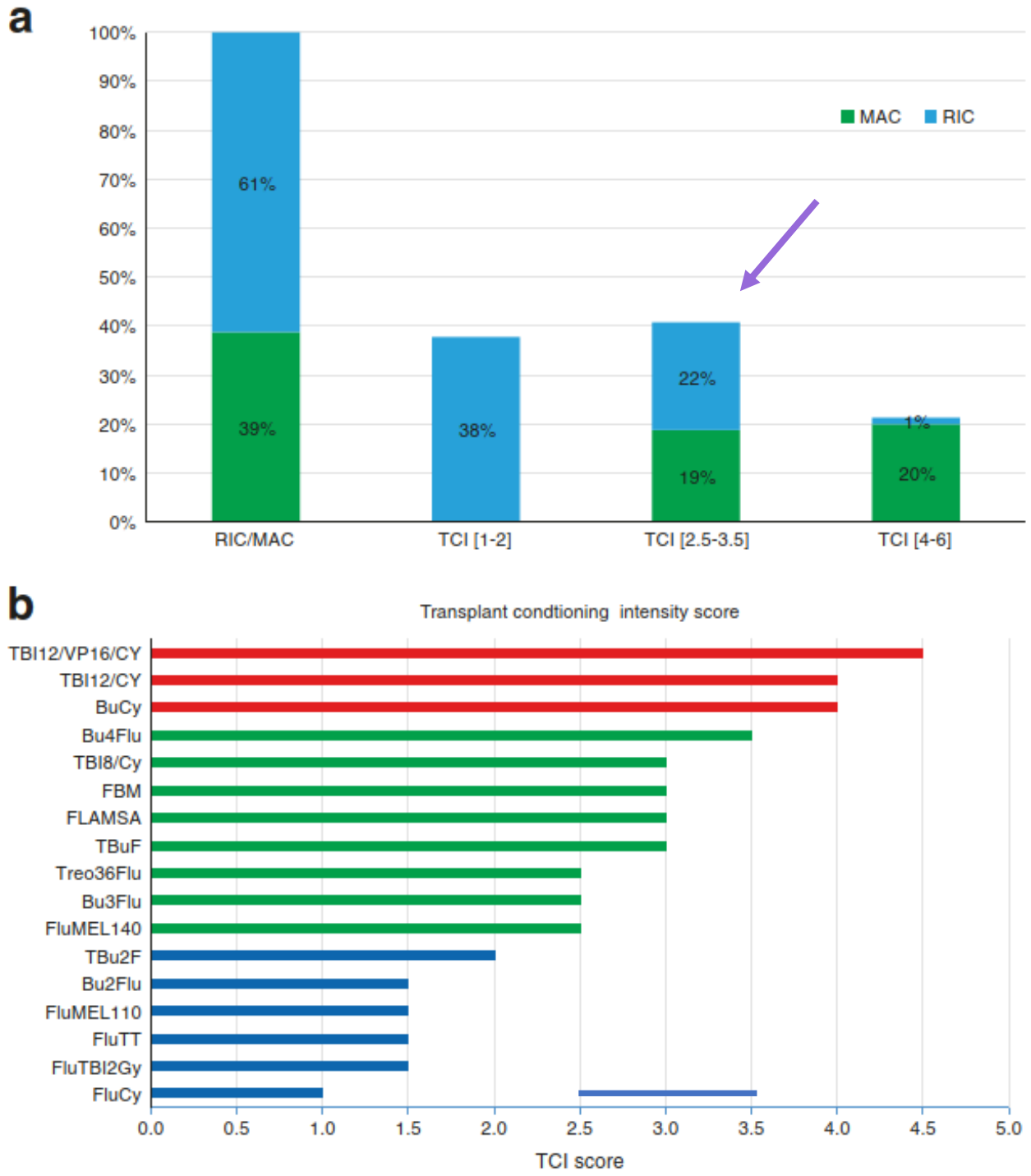
Retrospectively tested the impact of TCI on 8255 adult (45–65 years) AML 1CR

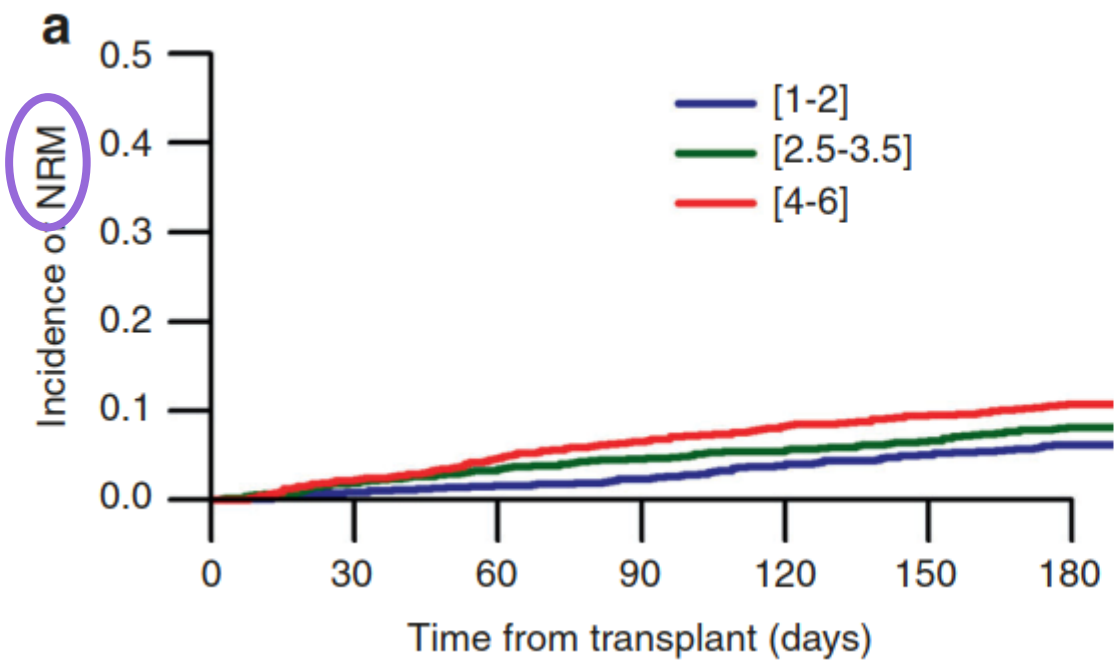
3-group TCI risk scheme :low [1–2] intermediate [2.5–3.5] high [4–6]

TCI grouping was highly and better **predictive for early (day 100 and 180) NRM, 2-year NRM and relapse** as compared with the RIC/MAC classification.

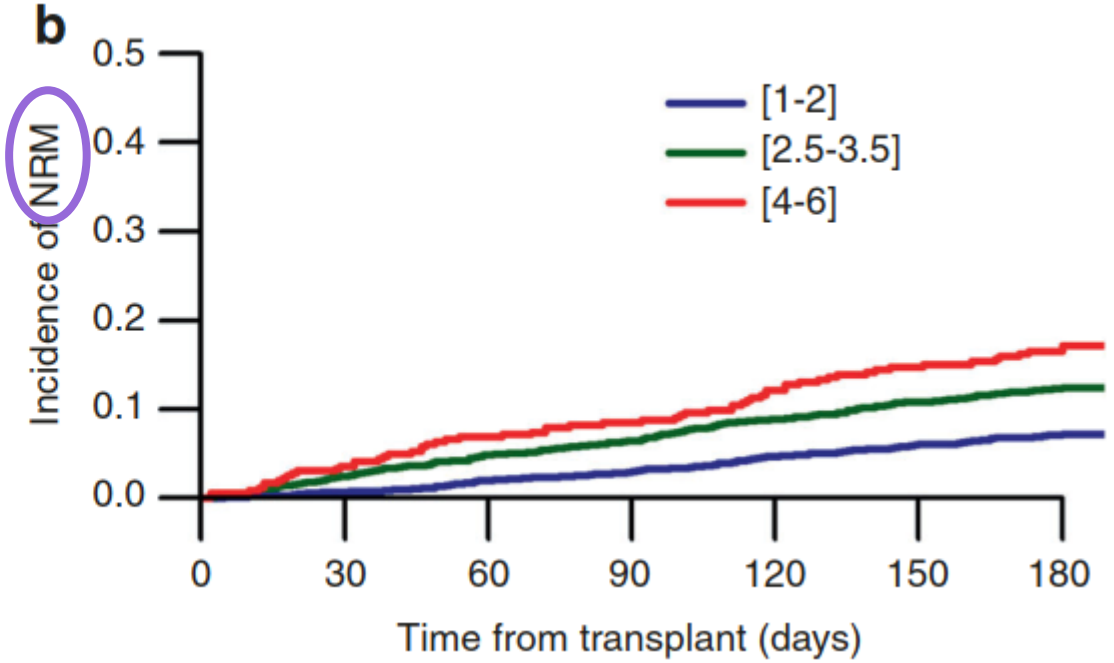
Component	Dose level			Added points for each dose level
	Low	Intermediate	High	
TBI fractionated (Gray)	≤5	6–8	≥9	1
Busulphan (mg/kg)	≤6.4 iv & ≤8 po	9.6 iv & 12 po	12.8 iv & 16 po	1
Treosulfan (g/m2)	30	36	42	1
Melphalan (mg/m2)	<140	≥140	≥200	1
Thiotepa (mg/kg)	<10	≥10	≥20	0.5
Fludarabine (mg/m2)	≤160	>160		0.5
Clofarabine (mg/m2)	≤150	>150		0.5
Cyclophosphamide (mg/kg)	<90	≥90		0.5
Carmustine (mg/m2)	≤250	280–310	≥350	0.5
Cytarabine (g/m2)	<6	≥6		0.5
Etoposide (mg/kg)	<50	≥50		0.5

iv intravenously, *po* per os, *TBI* total body irradiation.


a
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
MAC
RIC
61%
39%
38%
22%
19%
1%
20%
RIC/MAC
TCI [1-2]
TCI [2.5-3.5]
TCI [4-6]
b
Transplant condtioning intensity score
TBI12/VP16/CY
TBI12/CY
BuCy
Bu4Flu
TBI8/Cy
FBM
FLAMSA
TBuF
Treo36Flu
Bu3Flu
FluMEL140
TBu2F
Bu2Flu
FluMEL110
FluTT
FluTBI2Gy
FluCy
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
TCI score



aged 45–55 years at transplant



aged 55–65 years at transplant

TCI Identifies a distinct intermediate subgroup consisting RIC and MAC regimens that had identical outcomes in all aspects:

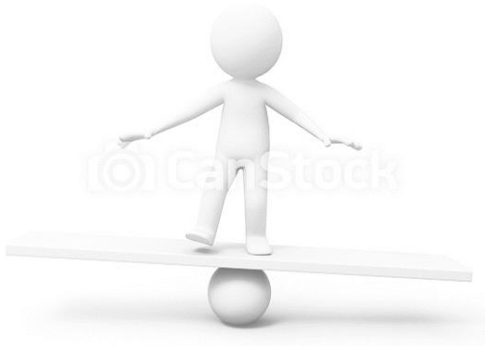
Table 6 The intermediate TCI [2.5–3.5] group.

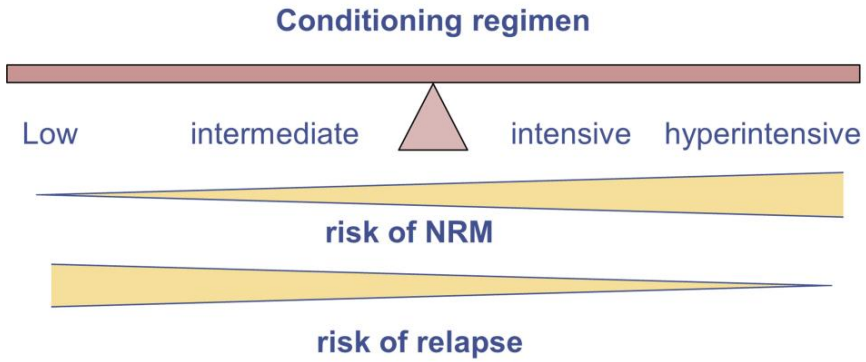
RIC/MAC	*N*	NRM @ day 100	NRM @ day 180	NRM	Relapse	LFS	OS
RIC	1819	6.9% [5.8–8.1]	10.9% [9.5–12.4]	18.7% [16.9–20.6]	24.5% [22.4–26.6]	56.8% [54.4–59.3]	62.2% [59.8–64.6]
MAC	1552	5.7% [4.6–6.9]	10.1% [8.7–11.7]	17% [15.0–19.0]	26.2% [23.9–28.5]	56.8% [54.2–59.5]	61.2% [58.6–63.8]
p value		0.15	0.43	0.02	0.05	0.92	0.62

Intermediate TCI [2.5–3.5] group

Probably captured the so called “reduced toxicity conditioning” regimens specifically designed to optimize dose intensity while safely minimizing NRM

Do we use TCI – low/ intermediate/ high? -------No



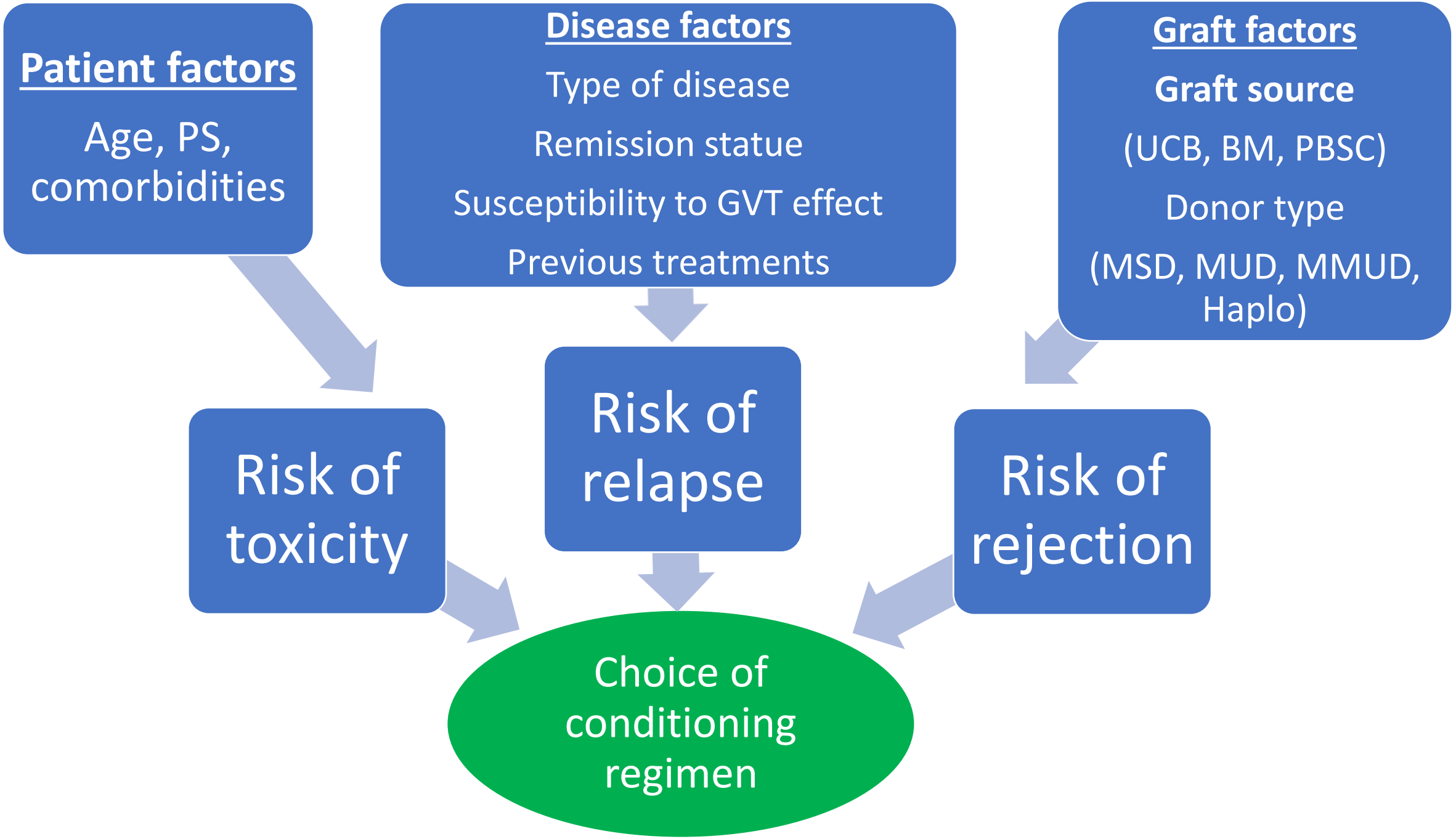


Risk of toxicity

Risk of relapse

Risk of rejection

Choice of conditioning regimen


Patient factors
Age, PS, comorbidities
Disease factors
Type of disease
Remission statue
Susceptibility to GVT effect
Previous treatments
Graft factors
Graft source
(UCB, BM, PBSC)
Donor type
(MSD, MUD, MMUD, Haplo)
Risk of toxicity
Risk of relapse
Risk of rejection
Choice of conditioning regimen

Common toxicities of standard MAC regimens

- Prolonged aplasia → risks of infections,bleeding
- GI toxicity: mucositis, nausea/vomiting, diarrhea
- Organ toxicities:

  - Liver: Sinusoidal obstruction syndrome (SOS)

  - Lungs: Pneumonitis

- Cytokine storm → risk of acute GVHD
- Long-term: Infertility

  Iatrogenic menopause/andropause

  2nd malignancies

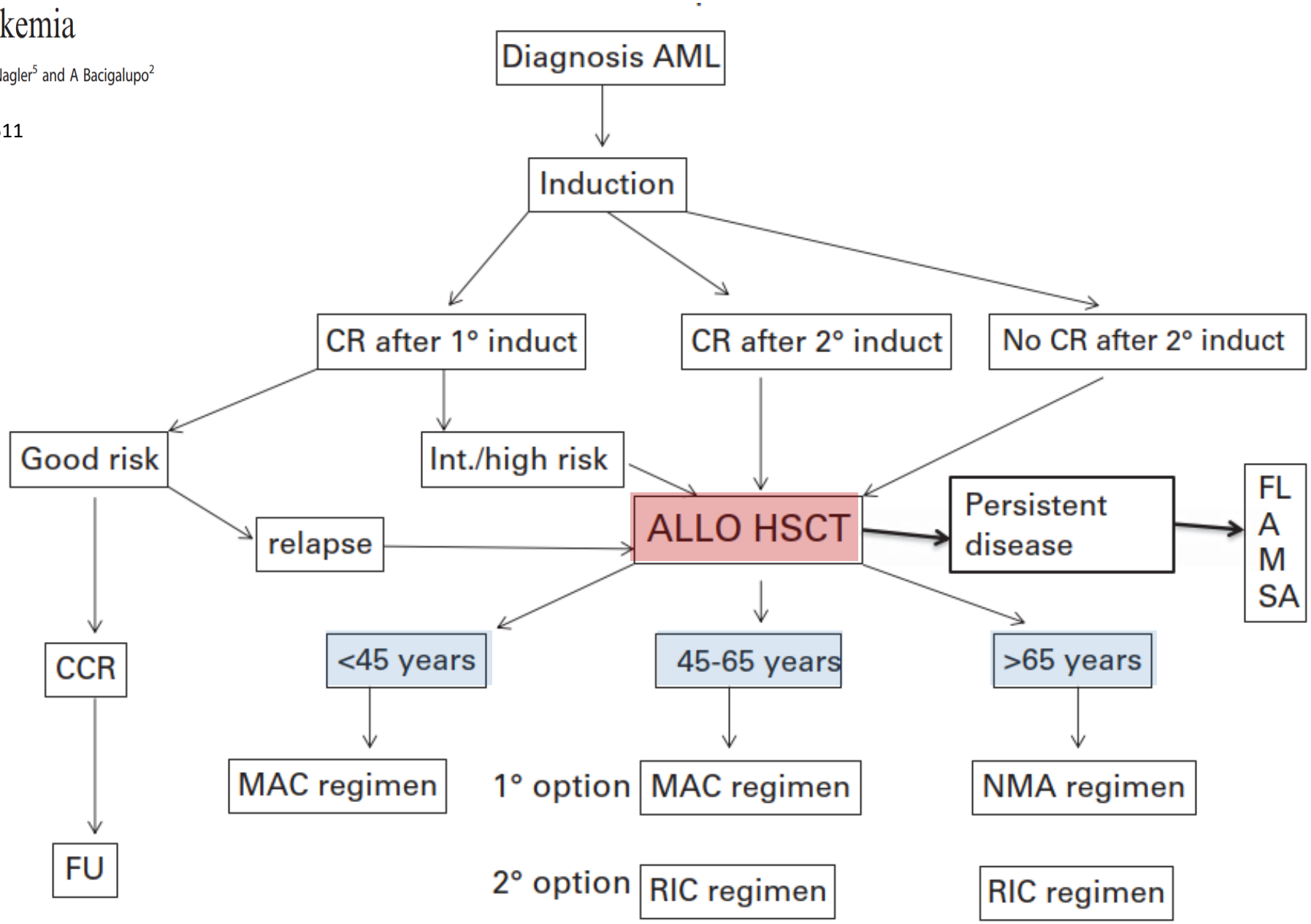
REVIEW

Conditioning regimens for allogeneic hematopoietic stem cell transplants in acute myeloid leukemia

YS Jethava[1], S Sica[2], B Savani[3], F Socola[1], M Jagasia[3], M Mohty[4], A Nagler[5] and A Bacigalupo[2]

Bone Marrow Transplantation (2017) 1504 – 1511

fitness



How to evaluate fitness?

- **Age**

  ≤ 45 y: MAC

  > 45 y: RIC

But also depends on:

- **Performance** status (Karnofsky, ECOG)
- **Comorbidities**
- **Organ-specific toxicity risk**

Hematopoietic cell transplantation (HCT)–specific comorbidity index: a new tool for risk assessment before allogeneic HCT

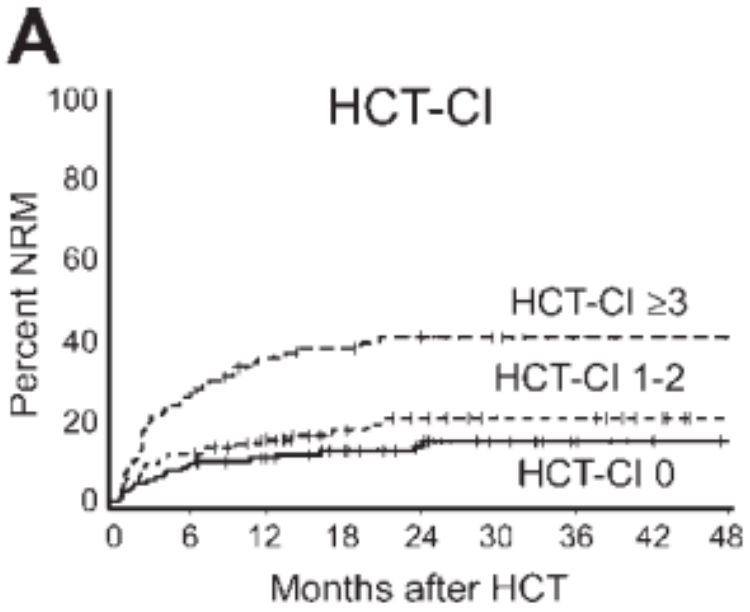
Mohamed L. Sorror, Michael B. Maris, Rainer Storb, Frederic Baron, Brenda M. Sandmaier, David G. Maloney, and Barry Storer

BLOOD, 15 OCTOBER 2005 VOLUME 106, NUMBER 8

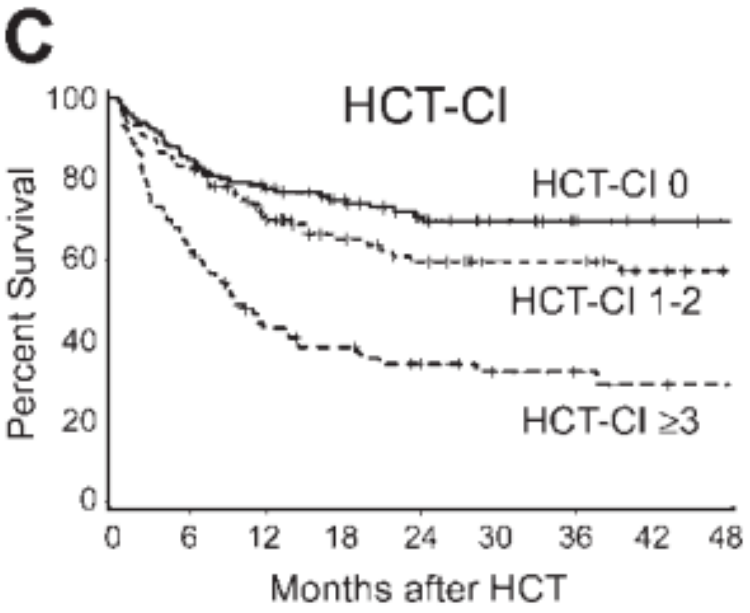
Table 4. Definitions of comorbidities included in the HCT-CI and HCT-CI scores compared with original CCI scores

Comorbidity	Definitions of comorbidities included in the new HCT-CI	HCT-CI weighted scores	Original CCI scores*
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1	0
Cardiac‡	Coronary artery disease,§ congestive heart failure, myocardial infarction, or EF ≤ 50%	1	1
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1	0
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1	1
Psychiatric disturbance†	Depression or anxiety requiring psychiatric consult or treatment	1	Not included
Hepatic, mild‡	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN	1	1
Obesity†	Patients with a body mass index > 35 kg/m^2	1	Not included
Infection†	Requiring continuation of antimicrobial treatment after day 0	1	Not included
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2	1
Peptic ulcer	Requiring treatment	2	1
Moderate/severe renal‡	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2	2
Moderate pulmonary‡	DLco and/or FEV_1 66%-80% or dyspnea on slight activity	2	1
Prior solid tumor‡	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3	2
Heart valve disease	Except mitral valve prolapse	3	0
Severe pulmonary‡	DLco and/or FEV_1 ≤ 65% or dyspnea at rest or requiring oxygen	3	1
Moderate/severe hepatic‡	Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN	3	3

NRM



survival



VOLUME 32 · NUMBER 29 · OCTOBER 10 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Comorbidity-Age Index: A Clinical Measure of Biologic Age Before Allogeneic Hematopoietic Cell Transplantation

Mohamed L. Sorror, Rainer F. Storb, Brenda M. Sandmaier, Richard T. Maziarz, Michael A. Pulsipher, Michael B. Maris, Smita Bhatia, Fabiana Ostronoff, H. Joachim Deeg, Karen L. Syrjala, Elihu Estey, David G. Maloney, Frederick R. Appelbaum, Paul J. Martin, and Barry E. Storer

Data from 3,033 consecutive recipients of HLA-matched grafts from five institutions.

All patients should be evaluated with the **composite comorbidity/age score**, as well as appropriate features of their primary disease for selection of the most beneficial transplantation strategy

Patients with comorbidity/age scores of **0 to 2** had comparable mortality risks regardless of conditioning regimens.
Patients with scores of **3 to 4 and 5** had statistically significant **higher mortality risks after high-dose** versus nonmyeloablative regimens.

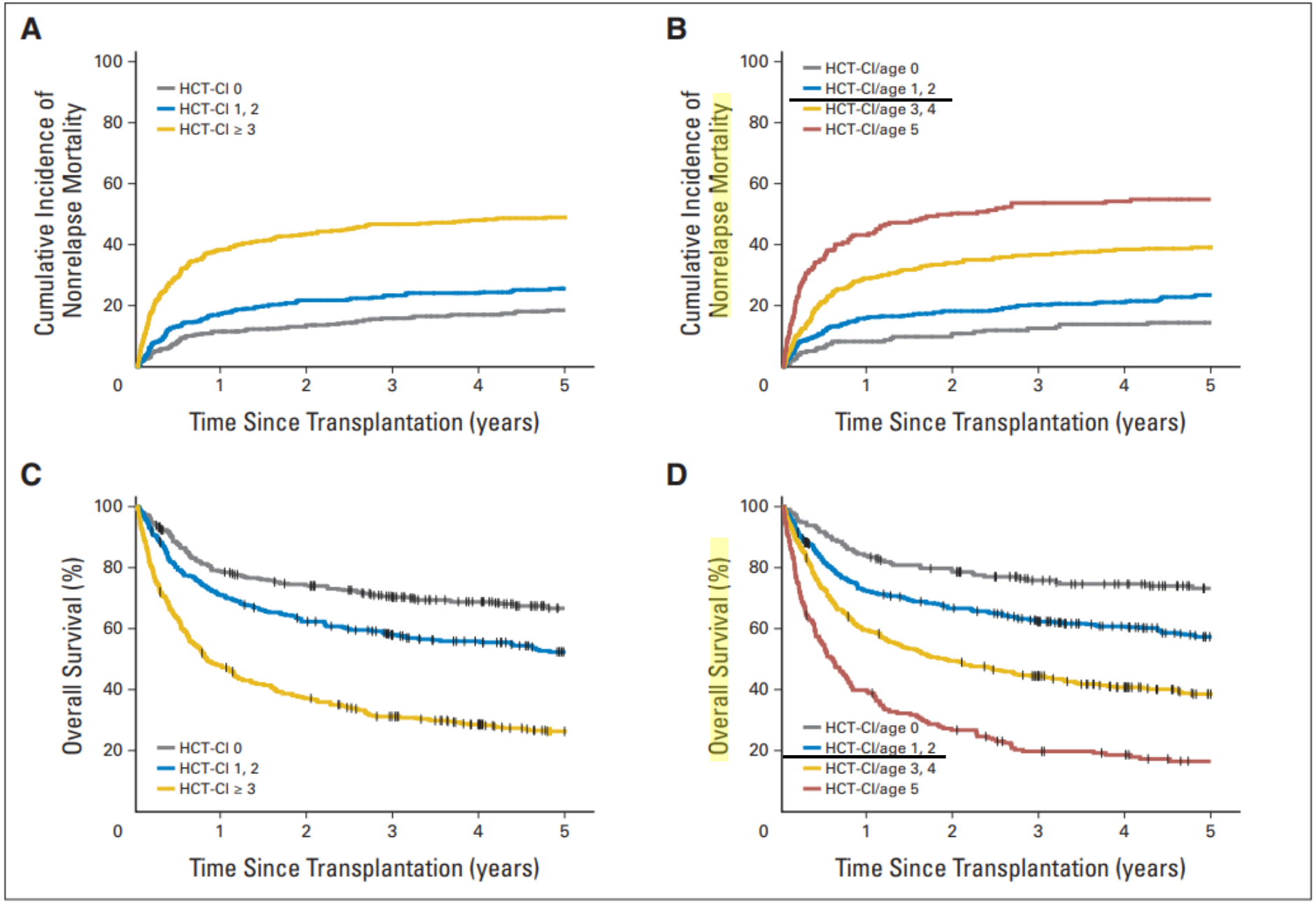
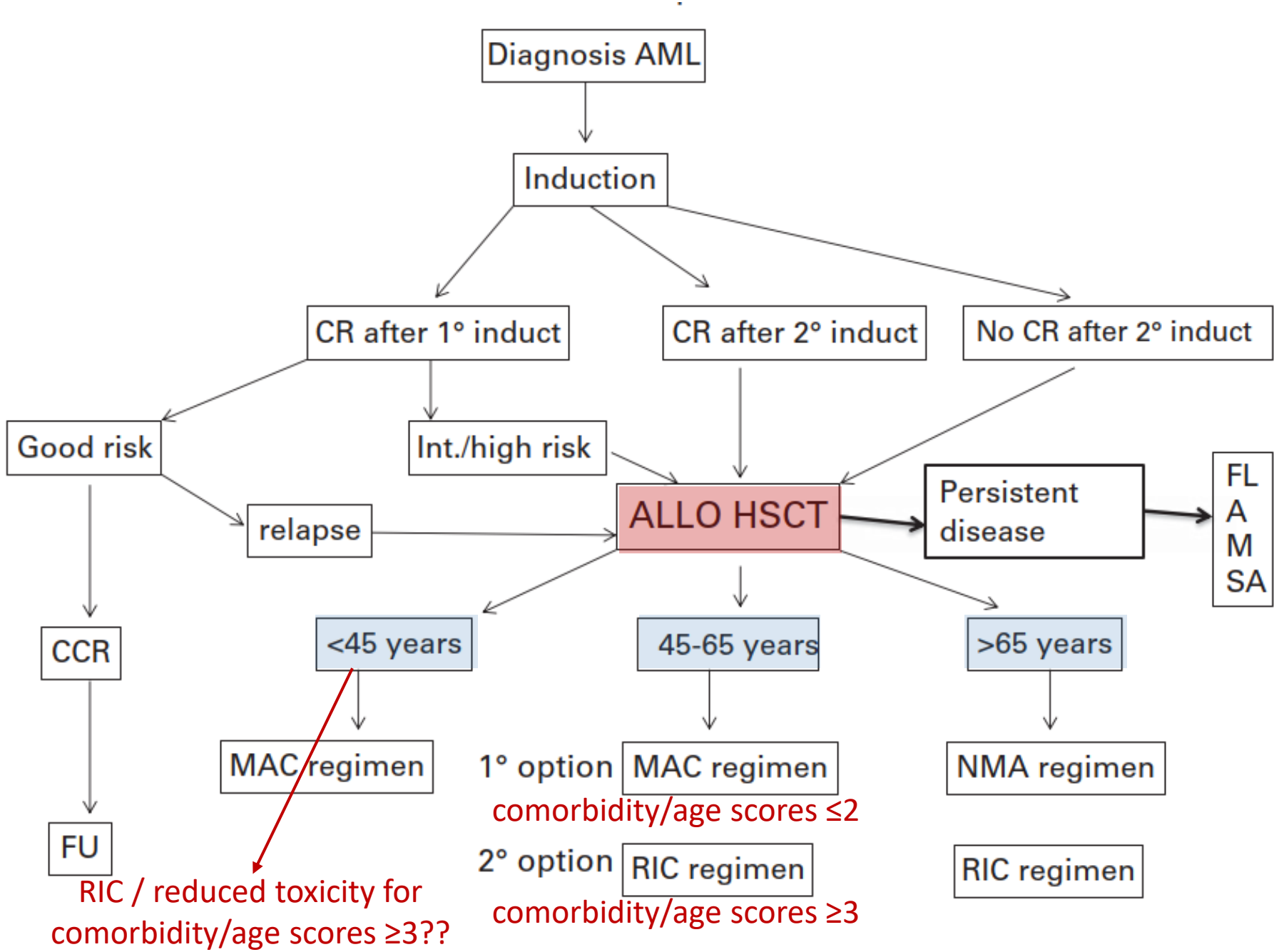


Fig 2. Comparisons of outcome stratifications by the hematopoietic cell transplantation–comorbidity index (HCT-CI) and the composite comorbidity/age index (HCT-CI/age). (A, B) Cumulative incidences of nonrelapse mortality and (C, D) Kaplan-Meier estimates of overall survival among patients of the validation set (n = 1,180) as stratified by (A, C) the HCT-CI and (B, D) the composite comorbidity/age index.

Age adjusted HCT CI


Diagnosis AML
Induction
CR after 1° induct
CR after 2° induct
No CR after 2° induct
Good risk
Int./high risk
relapse
ALLO HSCT
Persistent disease
FL
A
M
SA
CCR
<45 years
45-65 years
>65 years
MAC regimen
1° option
MAC regimen
NMA regimen
comorbidity/age scores ≤2
2° option
RIC regimen
RIC regimen
FU
RIC / reduced toxicity for comorbidity/age scores ≥3??
comorbidity/age scores ≥3

Prospective randomized studies comparing different condition regimen intensities exist only **for AML & MDS**

Table 1. **Characteristics and results of prospective randomized trials comparing different intensities and toxicity of conditioning regimens.**

Trial	Population	Regimen		RFS % (*P*)	Relapse % (*P*)	NRM % (*P*)	OS % (*P*)
Toxicity reduced MAC *vs.* MAC or RIC							
Rambaldi *et al.*[20]	AML Age >40 y	BuFlu (MAC)	BuCy (MAC)	40 *vs.* 47 (ns)	24 *vs.* 21 (ns)	8 *vs.* 18 (0.03)	27 *vs.* 35 (ns)
Bornhäuser *et al.*[16]	AML CR1 Age 18-60 y IR/HR cytogenetics	8 GyTBIFlu (MAC)	12 GyTBI/Cy (MAC)	58 *vs.* 56 (ns)	28 *vs.* 26 (ns)	13 *vs.* 18 (ns)	61 *vs.* 58 (ns)
Beelen *et al.*[24]	AML/MDS Age ≥50 y and/or CI >2/KPS >60%	TreoFlu (MAC)	BuFlu (RIC)	64 *vs.* 50 (0.001)	25 *vs.* 23 (ns)	11 *vs.* 23 (0.05)	71 *vs.* 56 (0.01)
RIC *vs.* NMA							
Blaise *et al.*[2]	Hematologic malignancies	BuFlu (RIC)	FluTBI (NMA)	35 *vs.* 23 (ns)	27 *vs.* 54 (<0.01)	38 *vs.* 22 (0.03)	41 *vs.* 41 (ns)
RIC *vs.* MAC							
Ringdén *et al.*[90]	AML/CML Age ≤60 y	BuFlu (RIC) incl n=4 CML (NMA)	BuCy(MAC)	NR	12 *vs.* 35 (ns)	11 *vs.* 11 (ns)	76 *vs.* 62 (ns)
Scott *et al.*[26]	AML/MDS in CR Age 18-65 y	BuFlu; FluMel (RIC)	BuFlu; BuCy; TBICy (MAC)	47 *vs.* 68 (<0.01)	48 *vs.* 14 (<0.001)	4 *vs.* 16 (<0.01)	78 *vs.* 68 (0.07)
Kröger *et al.*[25]	MDS/sAML Age 18-60 y UD Age 18-65 RD	BuFlu (RIC)	BuCy (MAC)	62 *vs.* 58 (ns)	17 *vs.* 15 (ns)	17 *vs.* 25 (ns)	76 *vs.* 63 (0.08)
RIC *vs.* sequential RIC							
Craddock *et al.*[14]	AML /MDS Age 18-75 y	FLAMSA-Bu (seq RIC)	Bu/Flu or Mel/Flu (RIC)	54 *vs.* 49 (ns)	27 *vs.* 30 (ns)	21 *vs.* 17 (ns)	61 *vs.* 59 (ns)

RIC: reduced intensity conditioning; MAC: myeloablative conditioning; NMA: nonmyeloablative; RFS: relapse-free survival; NRM: non-relapse mortality; OS: overall survival; (s)AML: (secondary) acute myeloid leukemia; CML: chronic myeloid leukemia; CR: complete remission; Cy: cyclophosphamide; Treo: treosulfan; Flu: fludarabine; TBI: total body irradiation; Bu: busulfan; IR: intermediate-risk; HR: high-risk; Mel: melphalan; MDS: myelodysplastic syndrome; UD: unrelated donor; RD: related donor; ns: not significant; y: years; CI: comorbidity index; KPS: Karnofsky performance status; NR: not reported; seq: sequential.

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BMT Clinical trial network – JCO 2017
RIC vs MAC
AML/MDS in CR

MAC – better RFS, more NRM.

MAC-Cause Off Death: GVHD(50%)
RIC-Cause Off Death : Relapse(86%)

Survival benefit of MAC: AML, high-risk, CI-0

The **wide basis** for current clinical consensus statements with regards to conditioning intensity in AML/MDS draws on data from **retrospective comparisons**

Table 2. **Selected retrospective registry comparisons of conditioning intensity in acute myeloid leukemia/myelodysplastic syndromes.**

Trial	Registry	Population	N	LFS/RFS	Relapse	NRM	OS
				%, RIC *vs.* MAC (*P*)			
Aoudjhane *et al.*[30]	EBMT	AML Age >50 y	722	40 *vs.* 47 (ns)	↑41 *vs.* 24 (<0.01)	18 *vs.* 32↑ (<0.01)	44 *vs.* 46 (ns)
Martino *et al.*[13]	EBMT	AML/MDS Blasts <10%	878	48 *vs.* 54 (ns)	↑34 *vs.* 24 (0.01)	18 *vs.* 22 (ns)	53 *vs.* 56 (ns)
Luger *et al.*[34]	CIBMTR	AML/MDS Age 18-69 y	5179	30 *vs* 33 (ns)	↑40 *vs* 32* (<0.01)	29 *vs* 29 (ns)	33 *vs* 34 (ns)

MAC: TBI doses >10 Gy or busulfan doses >8 mg/kg
RIC: fludarabine + TBI (<2 Gy) or busulfan doses <8 mg/kg.

MAC: Bu/CY TBI/CY
RIC: fludarabine + busulfan doses <8 mg/kg

retrospective studies in AML/MDS:
Increased risk of relapse after RIC and a higher NRM after MAC,
while **overall survival appeared to be similar** comparing both intensities.

Impact of Conditioning Intensity of Allogeneic Transplantation for Acute Myeloid Leukemia With Genomic Evidence of Residual Disease

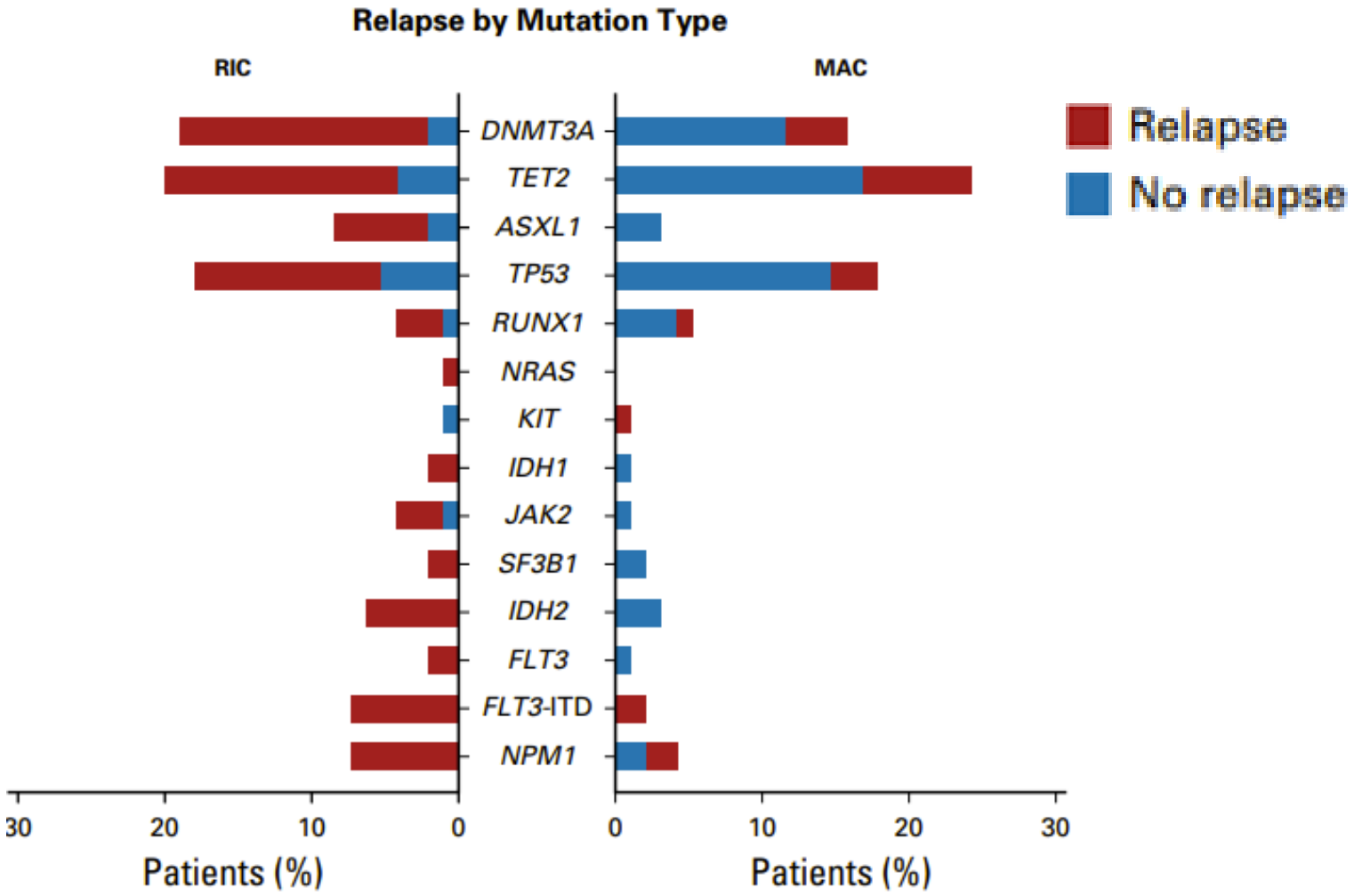
Journal of Clinical Oncology
Volume 38, Issue 12 1273

Christopher S. Hourigan, DM, DPhil[1]; Laura W. Dillon, PhD[1]; Gege Gui, ScM[1]; Brent R. Logan, PhD[2]; Mingwei Fei, MSc[2]; Jack Ghannam, BS[1]; Yuesheng Li, PhD[1]; Abel Licon, MS[3]; Edwin P. Alyea, MD[4]; Asad Bashey, MD[5]; H. Joachim Deeg, MD[6]; Steven M. Devine, MD[7]; Hugo F. Fernandez, MD[8]; Sergio Giralt, MD[9]; Mehdi Hamadani, MD[10]; Alan Howard, PhD[7]; Richard T. Maziarz, MD[11]; David L. Porter, MD[12]; Bart L. Scott, MD[6]; Erica D. Warlick, MD[13]; Marcelo C. Pasquini, MD[2]; and Mitchell E. Horwitz, MD[14]

Whether modulation of the intensity of the alloHCT conditioning regimen in patients with AML who test positive for MRD can prevent relapse?

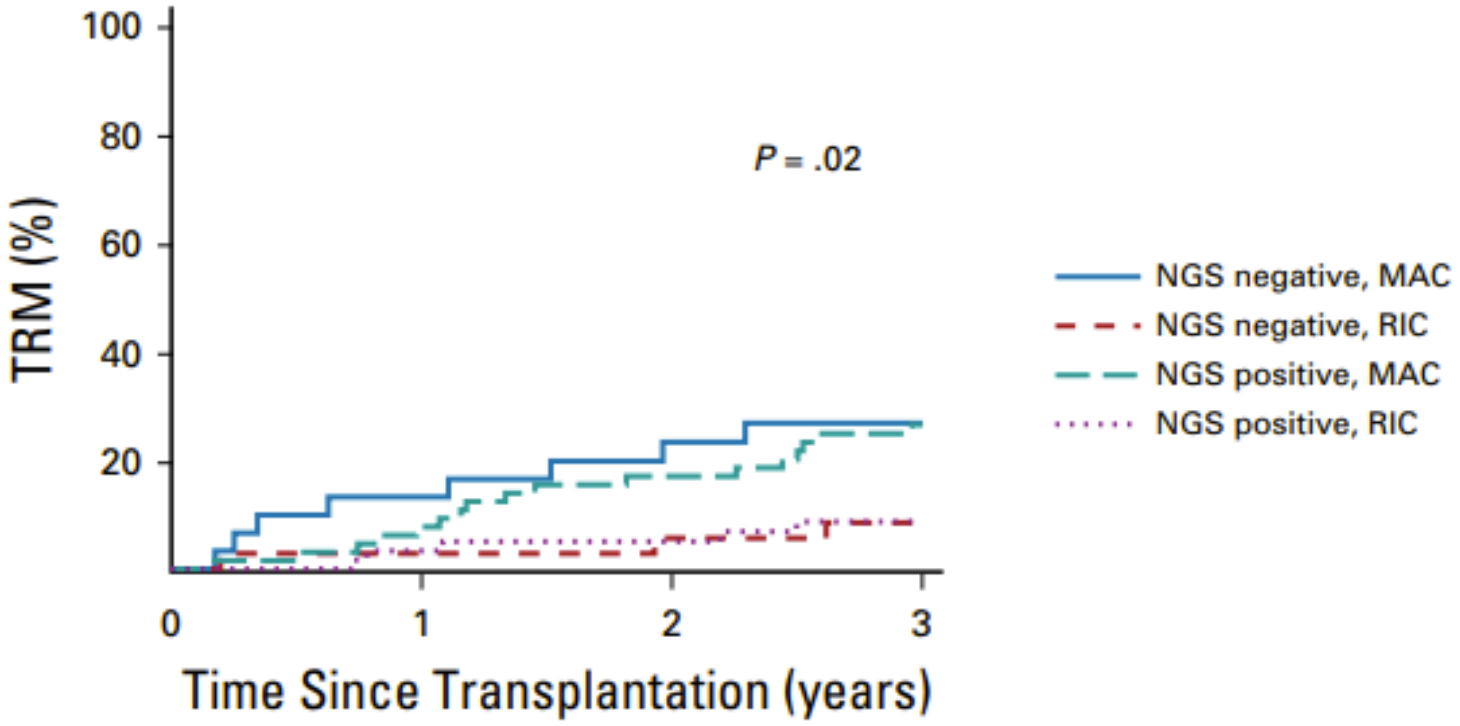
N=190 AML, morphologic CR : randomly assigned to MAC vs RIC

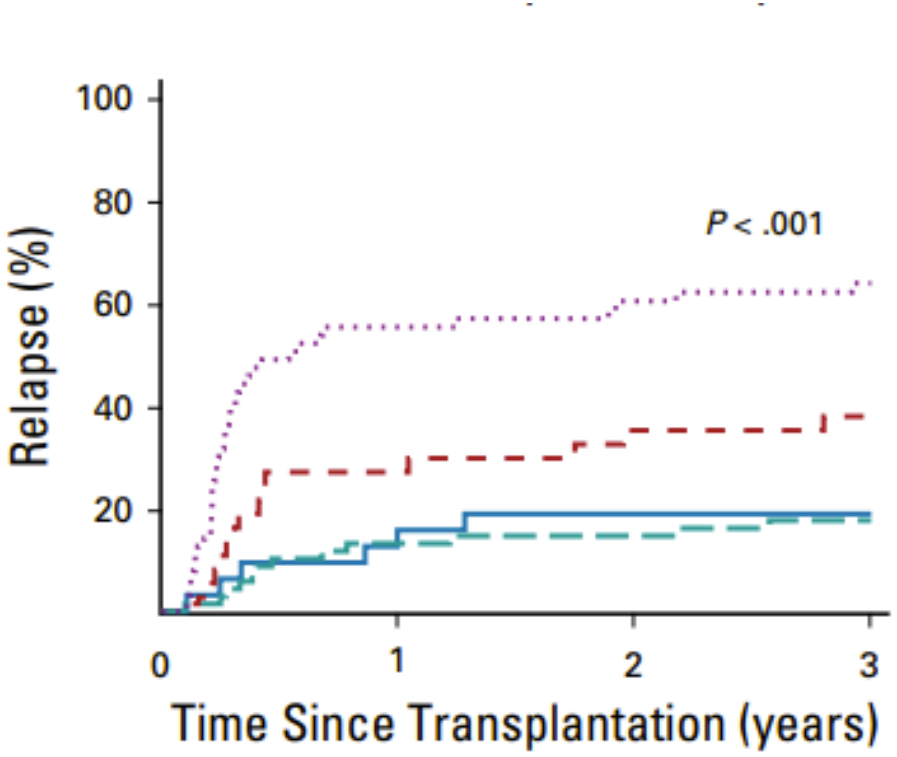
Preconditioning NGS for ASXL1, DNMT3A, FLT3, IDH1, IDH2, JAK2, KIT, NPM1, NRAS, RUNX1, SF3B1, TET2,TP53 → **MRD**



The percentage of patients with mutations in each gene separated by conditioning intensity and excluding those with TRM

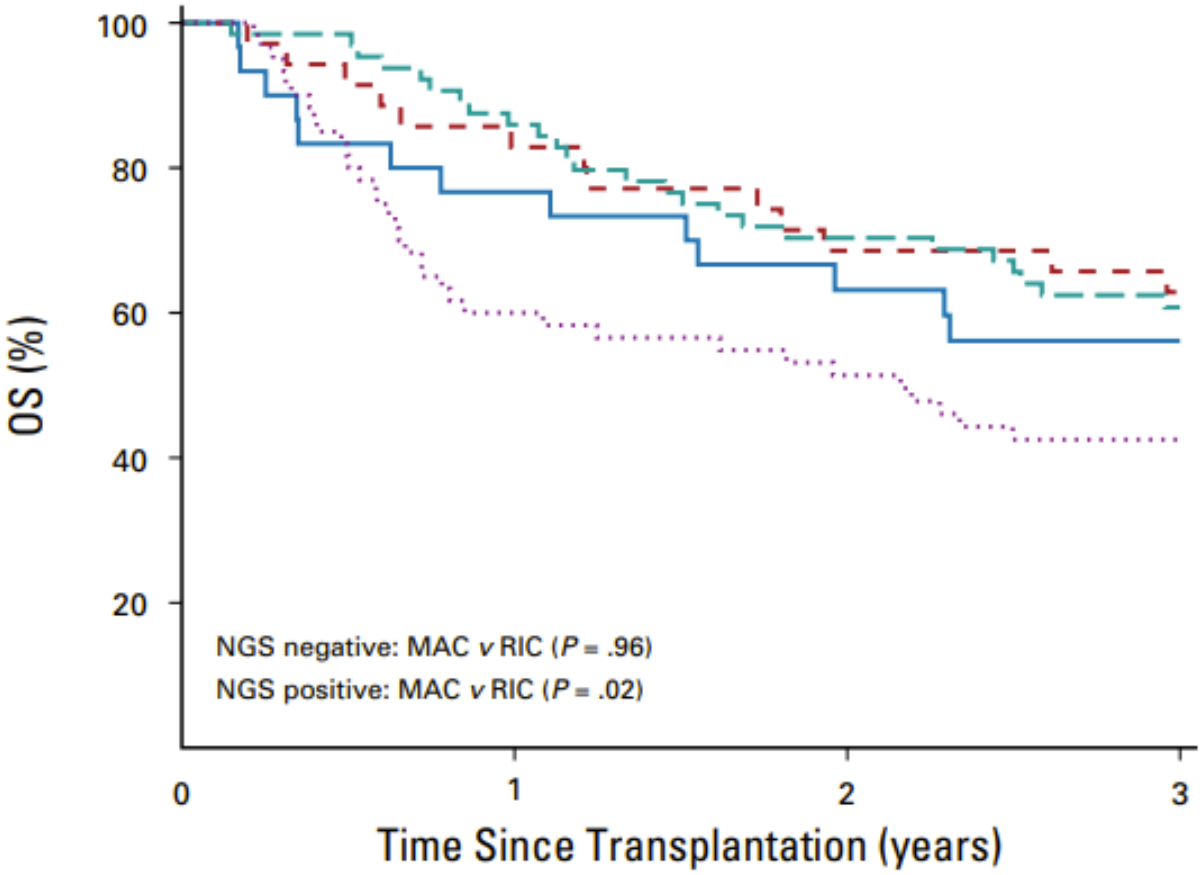
differences in whether a patient experienced relapse v no relapse were observed on the basis of RIC vs MAC





TRM was significantly higher MAC v RIC
No difference on the basis of mutational status (P = .8)

RIC :higher relapse rate than MAC
Highest rate occurring in RIC NGS+



<u>NGS negative:</u>

OS did not differ on the basis of conditioning intensity (3-year OS, 63% RIC v 56% MAC; P = .96).

<u>NGS positive:</u>

OS worse in RIC (3-year OS, 43%) v MAC (3-year OS 61% ; P = .02).

→Support for higher intensity when MRD+

For AML and MDS:

- The overall quality of evidence for the optimal conditioning intensity is low.
- For higher-risk patients, MAC appeared to provide some benefit.
- Data synthesis on the level of individual patient data may be of additional value.

Myelo ablative Conditioning regimens for AML/MDS:

- TBI ⟷ Non TBI (how we achieve myeloablation)
- Bu Cy ⟷ Bu Flu? (how we achieve immune ablation)

TBI ⟷ Non TBI

TBI remains an **important component** of the conditioning regimen in patients with AML

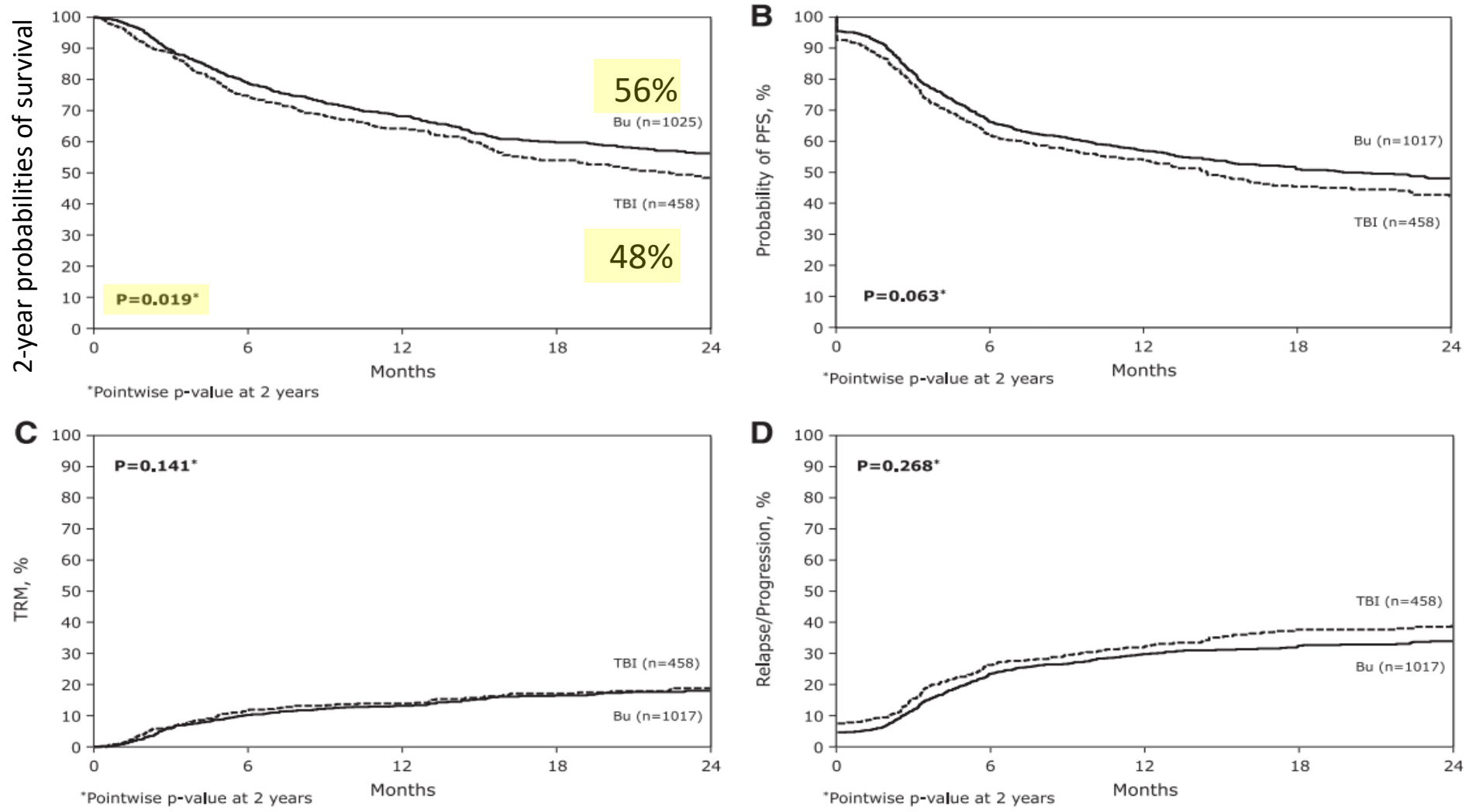
Factors limiting the use of TBI:

age, previous radiation therapy, comorbidities, higher incidence of acute GVHD and logistical problems delivering TBI.

A **prospective study** by Bredeson et al: (BLOOD, 5 DECEMBER 2013 x VOLUME 122, NUMBER 24)

MA BU vs MA TBI-based regimens in myeloid malignancies were compared.

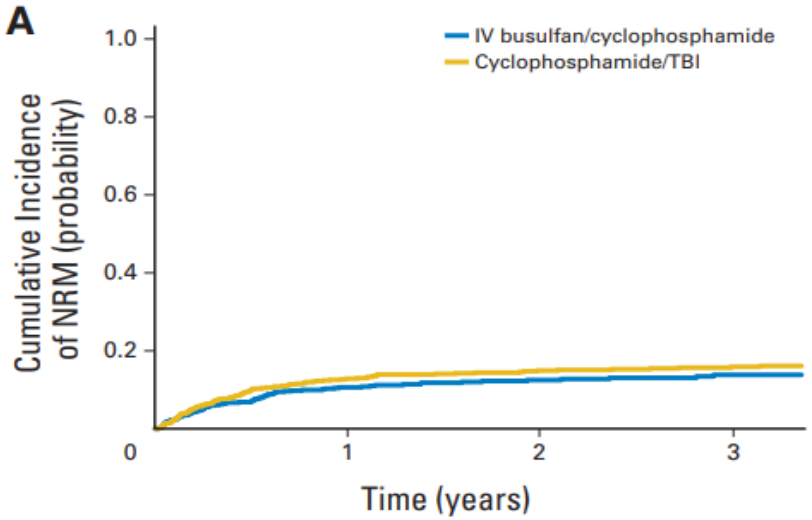
A total of 1483 patients undergoing transplantation for myeloid malignancies (IV-BU, N = 1025; TBI, N = 458)

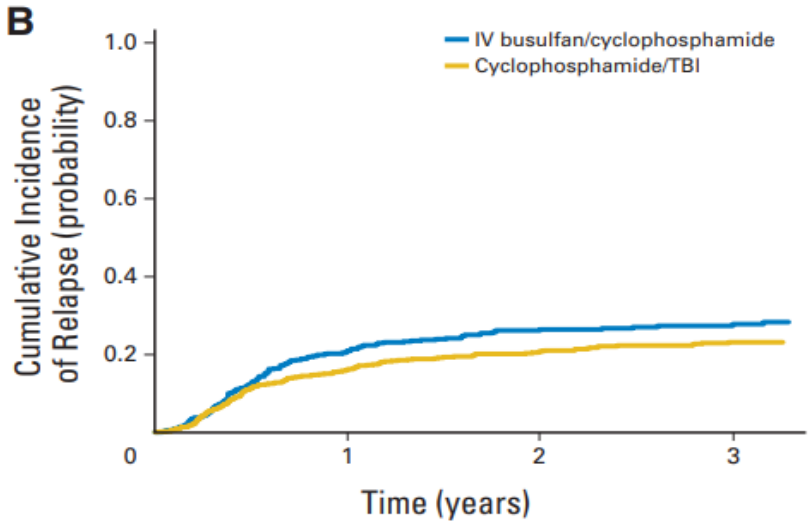


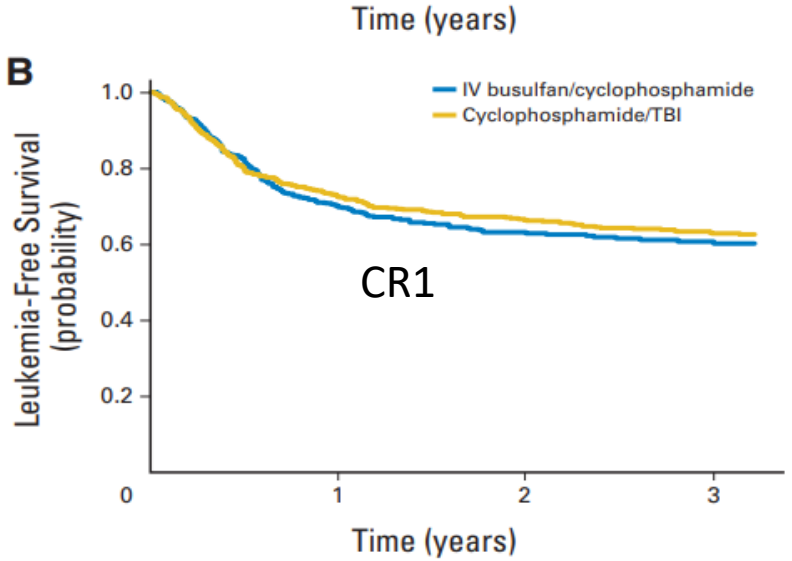
Compared with TBI, IV-BU resulted in superior survival with no increased risk for relapse or TRM.

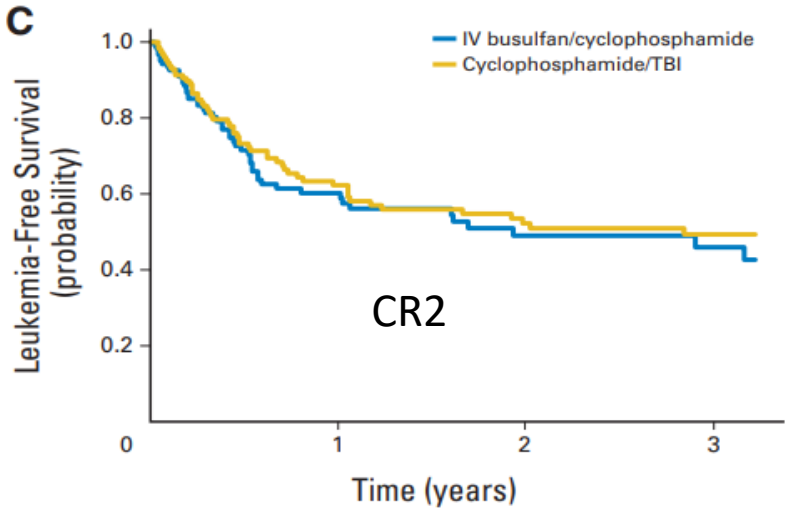
Allogeneic HSCT for AML in Remission: **Retrospective Comparison** of IV Busulfan Plus Cyclophosphamide (Cy) Versus Total-Body Irradiation Plus Cy As Conditioning Regimen— A Report From the ALWP. Arnon Nagler et.al

Bu/Cy (n 795) Cy/TBI (n 864) – No difference (NRM, Relapse, LFS in CR1 or CR2)









Bone Marrow Transplantation (2016) **51,** 232–240

www.nature.com/bmt

ORIGINAL ARTICLE

Busulfan fludarabine vs busulfan cyclophosphamide as a preparative regimen before allogeneic hematopoietic cell transplantation: systematic review and meta-analysis

S Ben-Barouch[1,2], O Cohen[1,2], L Vidal[2,3], I Avivi[1,2] and R Ram[1,2]

Meta analysis: 1830 patients conducted between the years 2003 and 2015

Lower risk for ↓**NRM at 100 days** in patients given Bu–Flu.
The risks of ↓ **SOS and infections** were lower in patients given Bu–Flu.
Engraftment kinetics, risk of grade 3–4 mucositis, **GvHD, relapse and NRM** at the end of the study were all **similar** between the two groups.

→ Similar efficacy profiles, whereas toxicity is lower with the Bu–Flu regimen.

ELSEVIER

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

ALL

Full Length Article Analysis

F. Khimani et al. / Transplantation and Cellular Therapy 27 (2021) 620.e1–620.e9

Impact of Total Body Irradiation-Based Myeloablative Conditioning Regimens in Patients with Acute Lymphoblastic Leukemia Undergoing Allogeneic Hematopoietic Stem Cell Transplantation: Systematic Review and Meta-Analysis

Farhad Khimani[1,*], Mudit Dutta[2], Rawan Faramand[1], Taiga Nishihori[1], Ariel Perez Perez[1], Erin Dean[1], Michael Nieder[1], Lia Perez[1], Asmita Mishra[1], Hany Elmariah[1], Marco Davila[1], Leonel Ochoa[1], Melissa Alsina[1], Aleksandr Lazaryan[1], Nelli Bejanyan[1], Doris Hansen[1], Michael Jain[1], Frederick Locke[1], Hien Liu[1], Joseph Pidala[1], Bijal Shah[3], Rahul Mhaskar[4]

[1] Department of Blood and Marrow Transplant and Cellular Immunotherapy, H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida
[2] Morsani College of Medicine, University of South Florida, Tampa, Florida
[3] Department of Malignant Hematology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida
[4] Department of Internal Medicine, Morsani College of Medicine, University of South Florida, Tampa, Florida

systematic review to assess the efficacy of **TBI-based versus chemotherapy** only-based myeloablative conditioning regimens (N=5000)

TBI-based regimens showed evidence of **benefit** compared with chemotherapy only-based conditioning regimens:

Relapse (relative risk [RR], 0.82; 95% confidence interval [CI], 0.72 to 0.94; 6 studies, 5091 patients)

OS (hazard ratio [HR], 0.76; 95% CI, 0.64 to 0.89; 7 studies, 4727 patients)

PFS (HR, 0.74; 95% CI, 0.63 to 0.85; 7 studies, 4727 patients).

The **TBI-based** regimen **did not increase** the likelihood of **grade II-IV acute GVHD** (RR, 1.12; 95% CI, 0.92 to 1.36; 5 studies, 4996 patients) **or chronic GVHD** (RR, 1.10; 95% CI, 1.00 to 1.21; 5 studies, 4490 patients), **or NRM** (RR, 0.94; 95% CI, 0.69 to 1.28; 6 studies, 4522 patients).

TBI-based regimens were associated with an **increased risk of grade III-IV acute GVHD** (RR, 1.29; 95% CI, 1.01 to 1.63; 3 studies, 3675 patients).

This systematic review represents evidence supporting the use of TBI-based conditioning regimen in patients undergoing allo-HCT for ALL who are candidates for myeloablative conditioning, as it offers better OS, PFS, and less relapse with acceptable NRM.

The acceptable approach:

- TBI approach can be safely applied,
  especially in adult patients who are able to tolerate myeloablative therapy, age <40 years.

- Studies have shown a higher NRM, up to 36%, in alloHCT recipients age >35 years.

- Caution should be exercised when using TBI-based myeloablative conditioning regimens in older patients.

Biology of Blood and Marrow Transplantation 12:438-453 (2006)

1083-8791/06/1204-0007$32.00/0
doi:10.1016/j.bbmt.2005.12.029

ASBMT
American Society for Blood and Marrow Transplantation

CY TBY vs. VP16 TBI (BFM pediatric……)

A Comparison of Cyclophosphamide and Total Body Irradiation with Etoposide and Total Body Irradiation as Conditioning Regimens for Patients Undergoing Sibling Allografting for Acute Lymphoblastic Leukemia in First or Second Complete Remission

David I. Marks,[1] Stephen J. Forman,[2] Karl G. Blume,[3] Waleska S. Pérez,[4] Daniel J. Weisdorf,[5] Armand Keating,[6] Robert Peter Gale,[7] Mitchell S. Cairo,[8] Edward A. Copelan,[9] John T. Horan,[10] Hillard M. Lazarus,[11] Mark R. Litzow,[12] Philip L. McCarthy,[13] Kirk R. Schultz,[14] David D. Smith,[2] Michael E. Trigg,[15] Mei-Jie Zhang,[4] Mary M. Horowitz[4]

298 patients with acute lymphoblastic leukemia in CR1 or CR2 HLA-matched sibling.
4 groups were compared (retrospective):
Cy-TBI<13Gy (n 217) Cy-TBI>13Gy (n 81) VP16-TBI<13Gy (n 53) VP16-TBI>13Gy (n 151)

Transplant-Related Mortality did not differ by conditioning regimen.
In **CR1**, there were no significant differences in relapse**, LFS, or OS**.
In CR2:
In comparison with Cy-TBI<13Gy, the risks of **relapse**, **treatment failure** and **mortality** tended to be **lower** with **etoposide** (regardless of TBI dose) or with **TBI doses >13Gy**.

For both CR1 and CR2 transplantations, causes of death were similar among the groups; Relapse accounted for 47% of deaths.

MSD allo for ALL in CR2, there is an advantage in substituting VP16 for Cy or, when Cy is used, in increasing the TBI dose to >13 Gy.

Bone Marrow Transplantation (2019) 54:798–809
https://doi.org/10.1038/s41409-018-0373-4

REVIEW ARTICLE

Hematopoietic stem cell transplantation for adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission: a position statement of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT)

Sebastian Giebel[1] · David I. Marks[2] · Nicolas Boissel[3] · Frederic Baron[4] · Sabina Chiaretti[5] · Fabio Ciceri[6] · Jan J. Cornelissen[7] · Michael Doubek[8] · Jordi Esteve[9] · Adele Fielding[10] · Robin Foa[5] · Norbert-Claude Gorin[11,12] · Nicola Gökbuget[1,3] · Helene Hallböök[13] · Dieter Hoelzer[14] · Elena Paravichnikova[15] · Josep-Maria Ribera[16] · Bipin Savani[17] · Anita W. Rijneveld[7] · Christoph Schmid[18] · Ulla Wartiovaara-Kautto[19] · Mohamad Mohty[10,11] · Arnon Nagler[10,20] · Hervé Dombret[3]

consensus paper, summarize available evidence and reflect current clinical practice in major European study groups.

TBI-based myeloablative conditioning is the **preferable** one in **young** patients.

TBI may be combined with either **Cy or etoposide**.

In centers with limited access to TBI, **chemotherapy-based** conditioning using either i.v. **busulfan or thiotepa may be considered**.

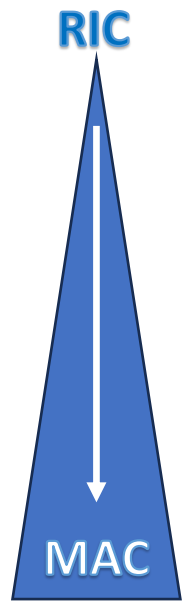
For **elderly** patients or patients with **comorbidities RIC** based on either TBI or chemotherapy is recommended.

- The therapeutic benefit of allogeneic HCT is largely derived from the immune **graft vs malignancy (GVM) effect.**
- Donor immune cells eradicate residual malignant cells that may survive the preparative regimen.
- **Sensitivity of malignancy to GVM** effect varies among different diseases, and depends on the diagnosis, tumor burden immune escape mechanisms and proliferation rate.

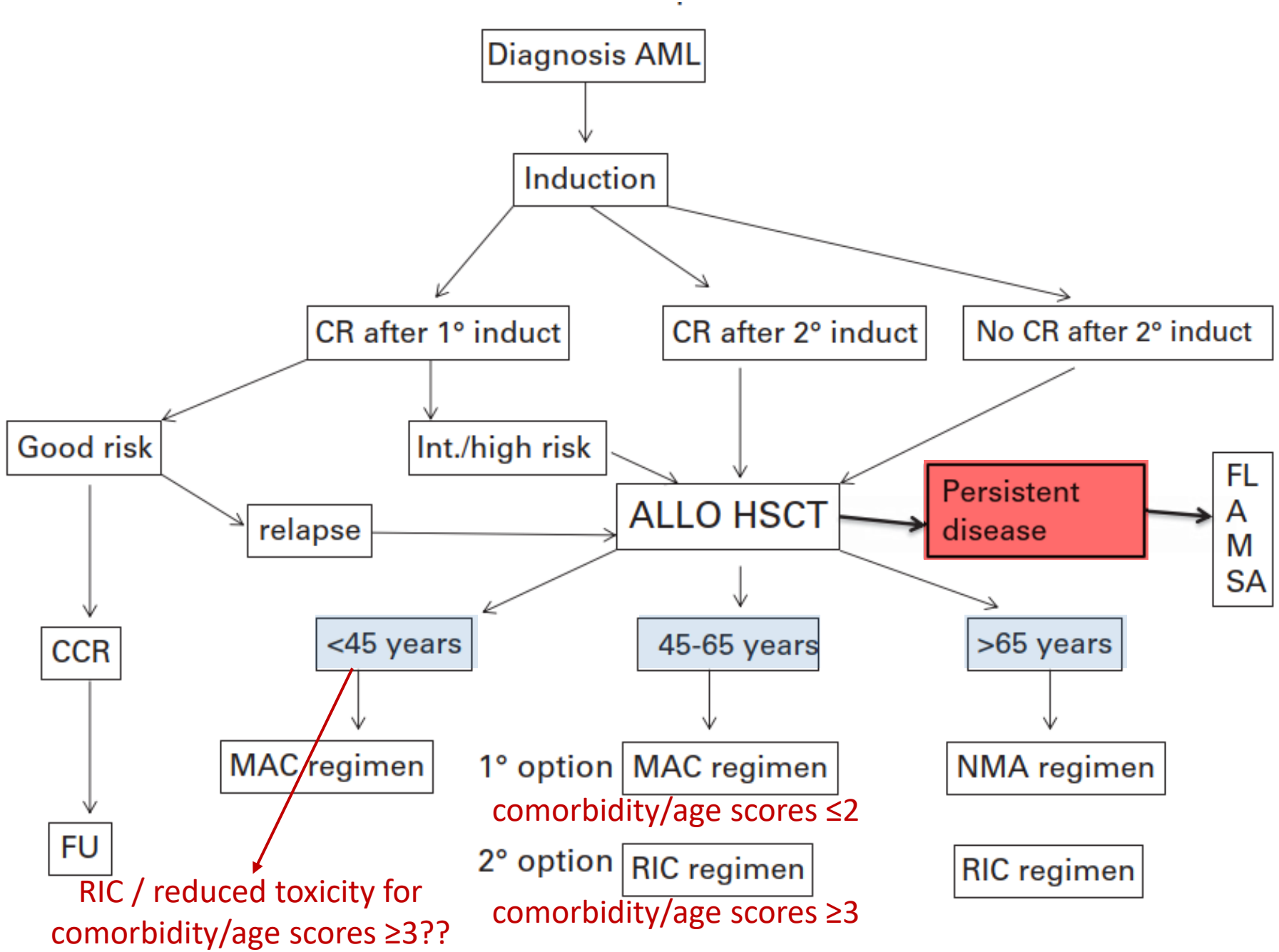
Table 1. Disease sensitivity to GVM effects

Highly sensitive	CML CLL Low-grade lymphoma Mantle cell lymphoma
Intermediate sensitivity	AML Intermediate-grade lymphoma Hodgkin's lymphoma Plasma cell myeloma
Relatively insensitive	ALL High-grade lymphoma

Abbreviation: GVM = graft versus malignancy.



- **RIC and NMA** regimens provide sufficient immunosuppression to achieve engraftment and allow GVM effects to eradicate the malignancy.
- Utilize the **least toxic regimen that can achieve the optimal therapeutic result.**
- **RIC** and NMA regimens are indicated for **diagnoses that are highly sensitive to GVM** effects.
- In diagnoses where higher-dose intensity improves eradication of malignancy, RIC regimens should be reserved for **elderly patients or those with comorbidities** who could not tolerate an ablative regimen.
- RIC highly used for **myeloma, chronic phase CML and lymphoma** patients.


Diagnosis AML
Induction
CR after 1° induct
CR after 2° induct
No CR after 2° induct
Good risk
Int./high risk
relapse
ALLO HSCT
Persistent disease
FL
A
M
SA
CCR
<45 years
45-65 years
>65 years
MAC regimen
1° option
MAC regimen
comorbidity/age scores ≤2
NMA regimen
2° option
RIC regimen
RIC regimen
comorbidity/age scores ≥3
FU
RIC / reduced toxicity for
comorbidity/age scores ≥3??

FLAMSA-Based Reduced-Intensity Conditioning versus Myeloablative Conditioning in Younger Patients with Relapsed/Refractory Acute Myeloid Leukemia with Active Disease at the Time of Allogeneic Stem Cell Transplantation: An Analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

sequential regimen

Eduardo Rodríguez-Arbolí[1,*], Myriam Labopin[2], Johanna Tischer[3], Arne Brecht[4], Arnold Ganser[5], Jürgen Finke[6], Igor Wolfgang Blau[7], Nicolaus Kröger[8], Peter Kalhs[9], Edouard Forcade[10], Donald Bunjes[11], Alexandros Spyridonidis[12], Bipin Savani[13], Arnon Nagler[14], Mohamad Mohty[2]

Biol Blood Marrow Transplant 26 (2020) 2165–2173

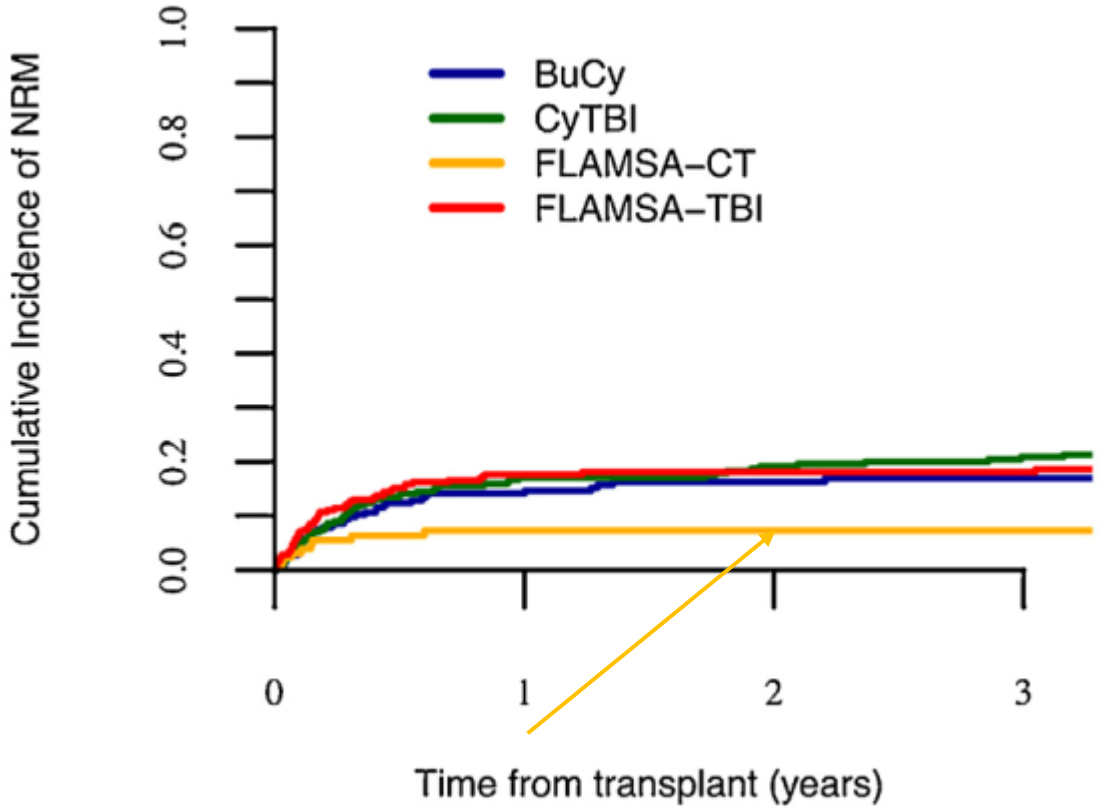
registry-based analysis:

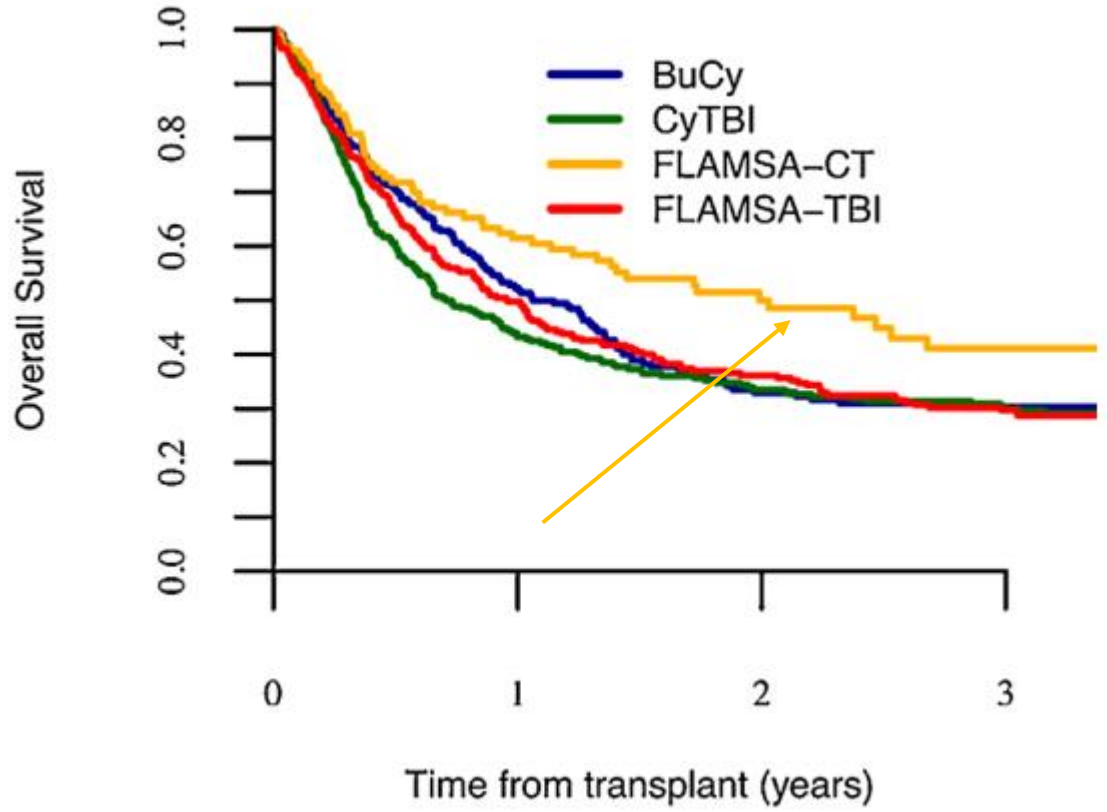
1018 patients med age 39 y (range, 18 to 50).

258 Bu/Cy, 314 Cy/TBI, 318 FLAMSA-TBI, 128 FLAMSA-RIC med. follow-up 50 months.

2-year relapse incidence 54% LFS 30%, GRFS 21%

were not significantly different between cohorts.





↓2-year NRM in the FLAMSA-RIC group 7% versus 16% in Bu/Cy, 19% in Cy/TBI, and 18% in FLAMSA-TBI;

↑ 2-year OS - 50% in FLAMSA –RIC versus 33% in Bu/Cy, 34% in Cy/TBI, and 36% in FLAMSA-TBI;

FLAMSA RIC may be a preferred conditioning regimen in patients with active R/R AML

Conditioning regimens are composed of combinations:

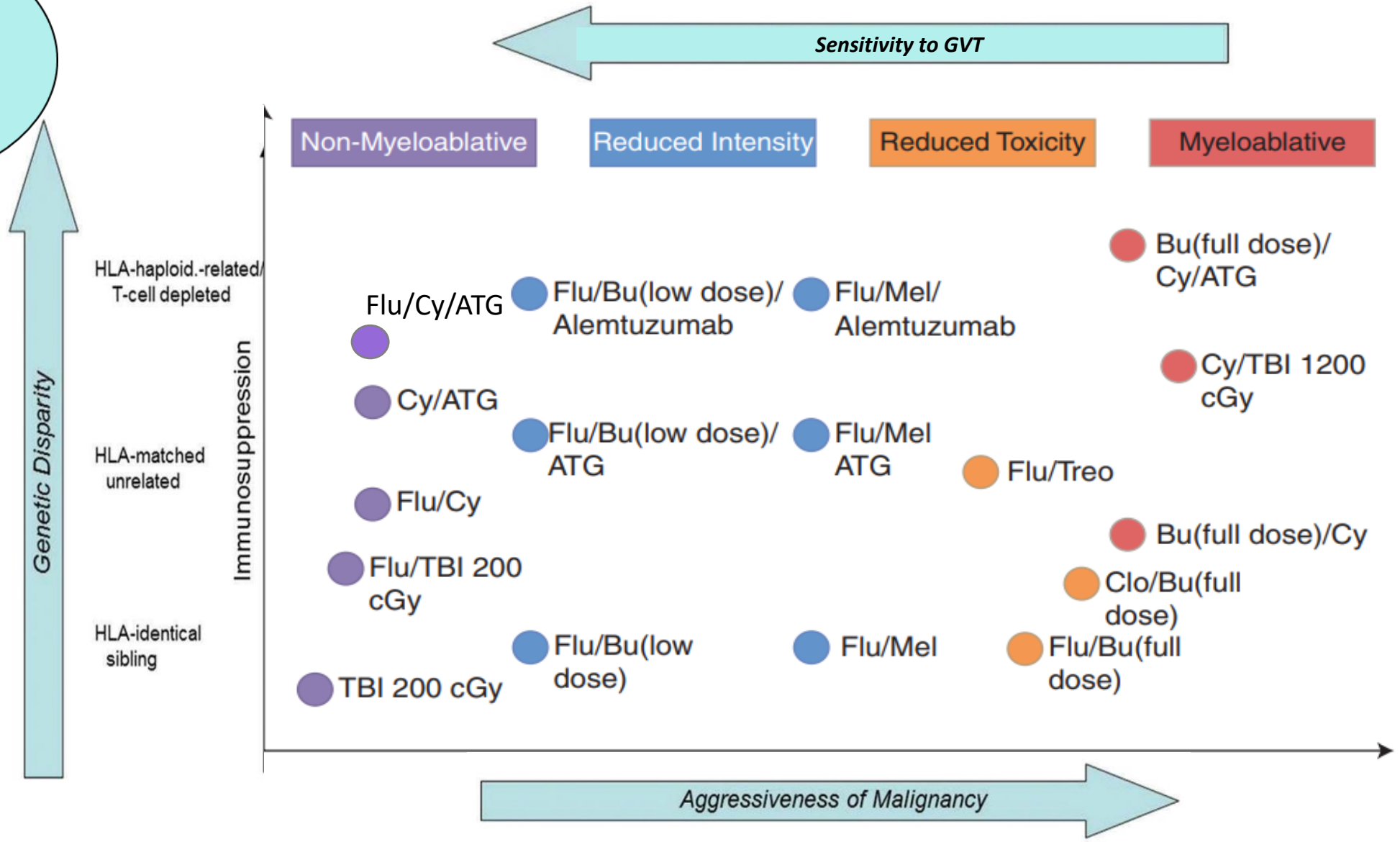
Myelo ablation:

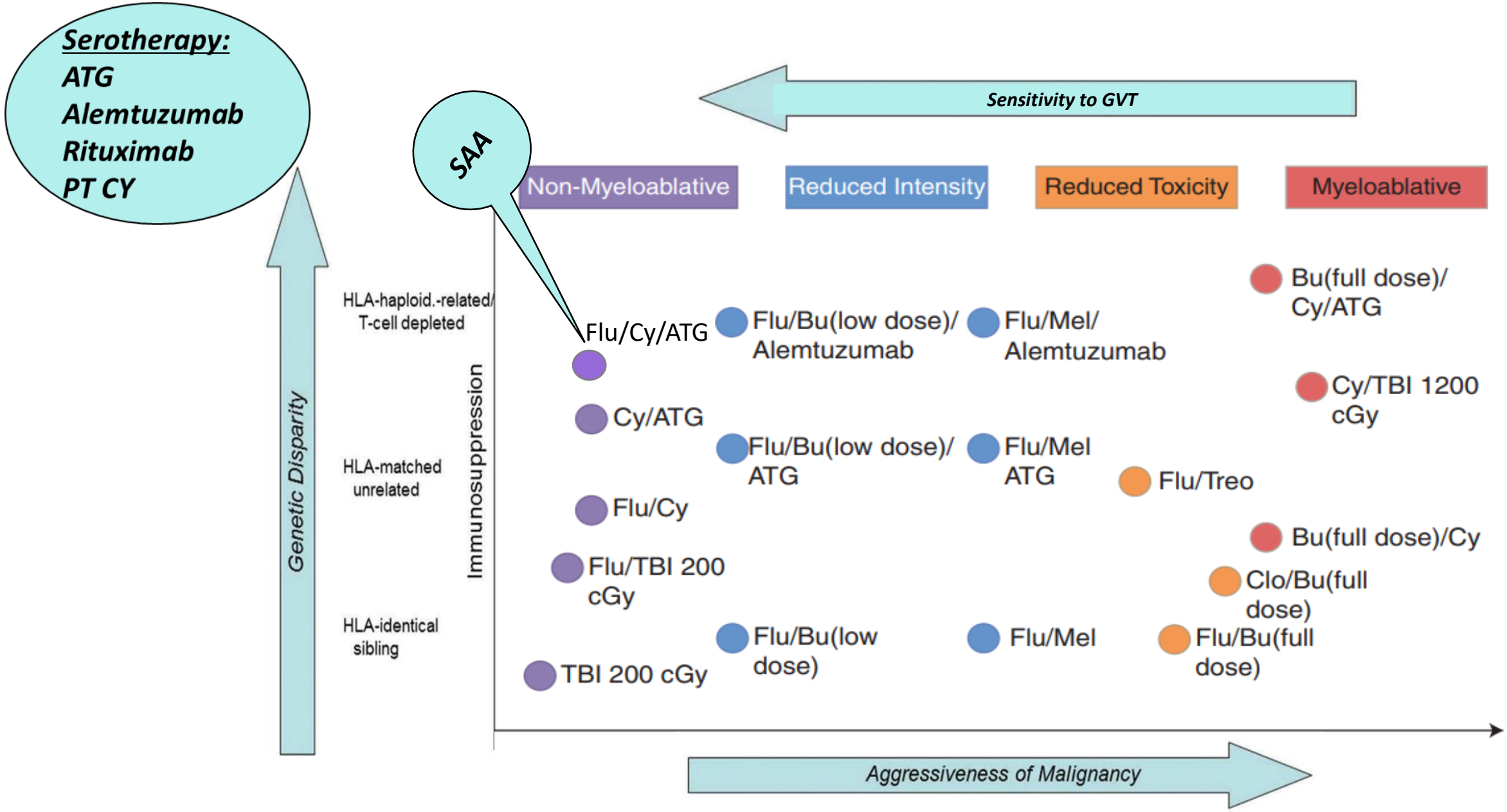
High dose alkylating agents:
Busulphan, Melphalan, Treosulfan, Cyclophosphamide
High dose TBI

Immune ablation:

Purine analogs – fludarabine
Cyclophosphamide
Lympholytic agents – alemtuzumab, rituximab, ATG – anti thymocytic globulin
Anti GVHD medications - Calcinorine inhibitors (CSA FK), low dose MTX,
mTOR inhibitor (sirolimus)
Very low dose TBI

Serotherapy:
ATG
Alemtuzumab
Rituximab
PT CY




Serotherapy:
ATG
Alemtuzumab
Rituximab
PT CY
SAA
Sensitivity to GVT
Non-Myeloablative
Reduced Intensity
Reduced Toxicity
Myeloablative
Genetic Disparity
Immunosuppression
HLA-haploid.-related/ T-cell depleted
HLA-matched unrelated
HLA-identical sibling
Flu/Cy/ATG
Flu/Bu(low dose)/ Alemtuzumab
Flu/Mel/ Alemtuzumab
Bu(full dose)/ Cy/ATG
Cy/TBI 1200 cGy
Cy/ATG
Flu/Bu(low dose)/ ATG
Flu/Mel ATG
Flu/Treo
Flu/Cy
Bu(full dose)/Cy
Flu/TBI 200 cGy
Clo/Bu(full dose)
Flu/Bu(low dose)
Flu/Mel
Flu/Bu(full dose)
TBI 200 cGy
Aggressiveness of Malignancy

Severe Aplastic Anemia:
More patient undergo TX as 1st line

Survival after allogeneic transplantation in children is excellent
In adults, organ toxicity and graft failure were higher - ↑ morbidity &mortality

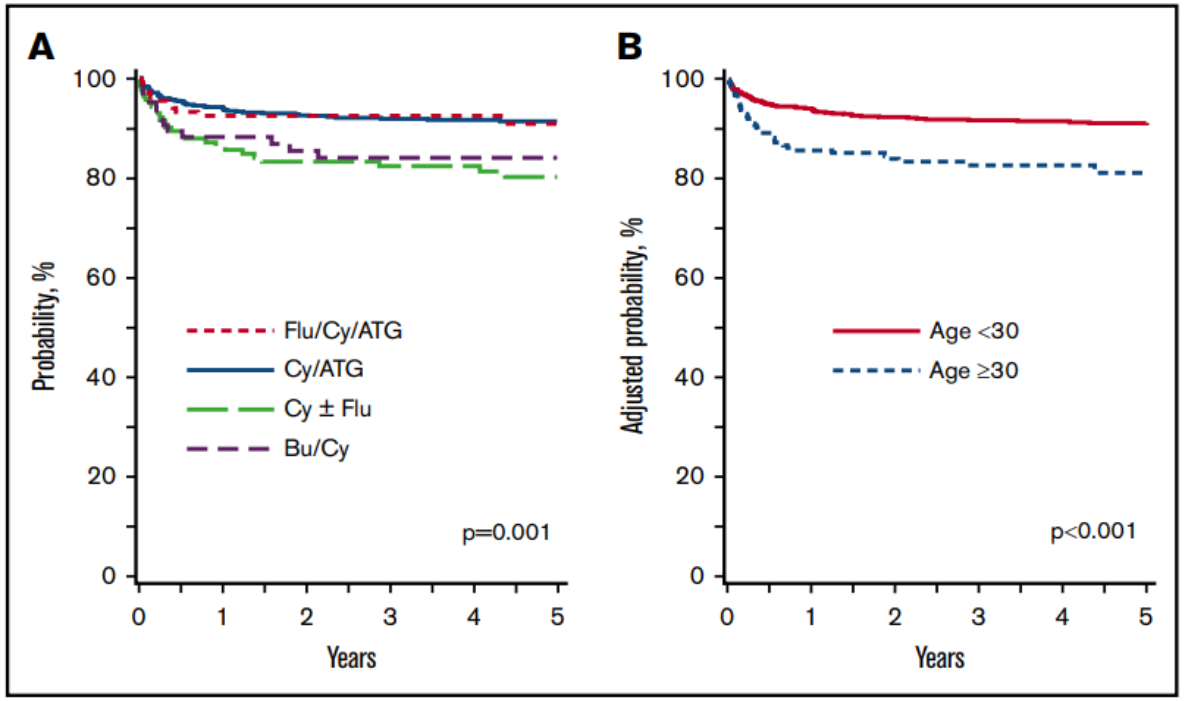
Given the rarity of SAA, there are no randomized trials that have compared transplant-conditioning regimens.

Choice of conditioning regimens for bone marrow transplantation in severe aplastic anemia

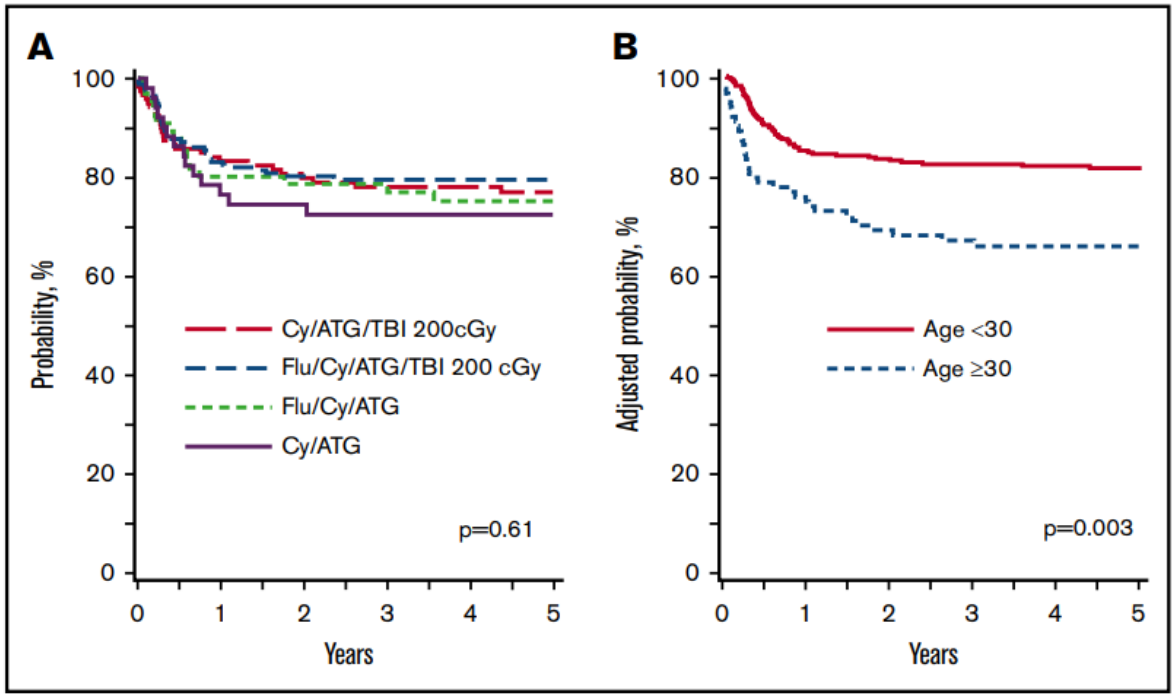
BEJANYAN et al 22 OCTOBER 2019 • VOLUME 3, NUMBER 20 blood advances

CIBMTR - Data on consecutive allo BMT (2000-2014)
MSD – N=955 MUD&MMUD – N= 409

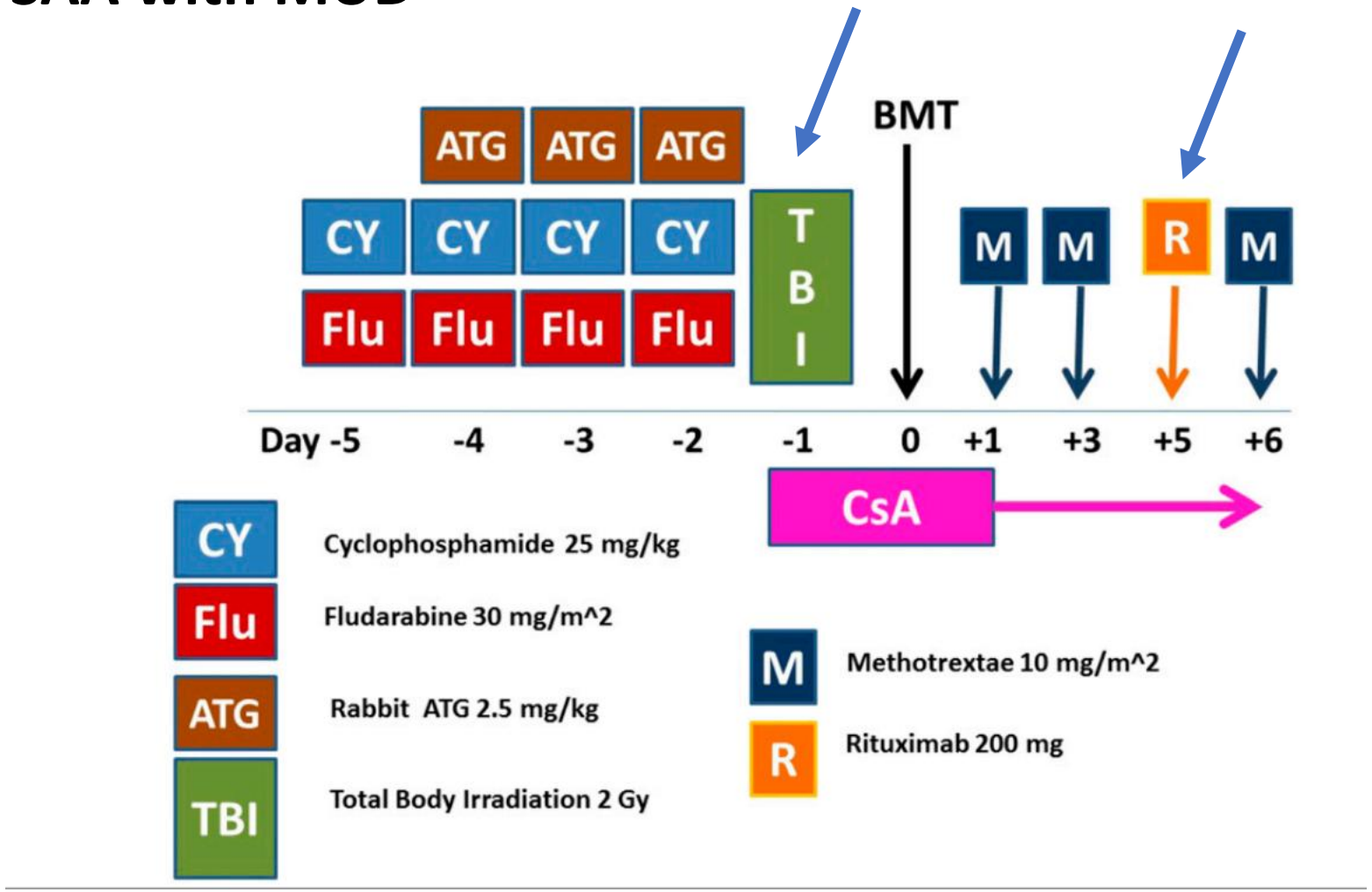
matched sibling



Matched & mismatche URD



Conditioning SAA with MUD



Andrea Bacigalupo Hematology 2018

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