WORKSHOP MIELOFIBROSI
IL TRAPIANTO

Quinta Giornata Fiorentina dedicata ai pazienti con malattie mieloproliferative croniche

Sabato 9 Maggio 2015

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TMO
AOU Careggi
Firenze

laboratorio congiunto sulle malattie mieloproliferative croniche

Mielofibrosi: Storia naturale

Decorso da indolente ad aggressivo

MF primitiva 1 per 100.000 secondarie 0.1 per 100.000

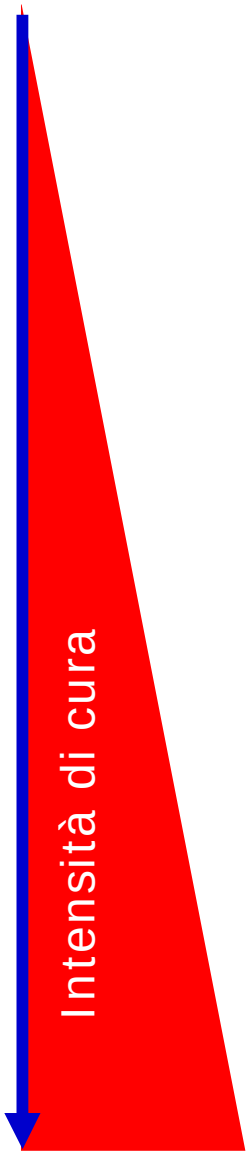
Il quadro è dominato dalla splenomegalia,dai sintomi sistemici, dalla insufficienza midollare con fibrosi, dalla iperplasia megacariocitaria o dalla leucocitosi

Si inizia il trattamento alla comparsa di sintomi

Età mediana di insorgenza: 62-66 anni

Mielofibrosi:Terapia

- **Sola Osservazione**
- **Terapia orientata per problemi:**
  - **Anemia: steroidi, androgeni, EPO, thalidomide lenalidomide pomalidomide supporto trasfusionale**
  - **Mieloproliferazione: idrossiurea**
  - **Piastrinopenia: trasfusioni**
  - **Splenomegalia: Idrossiurea, splenectomia, Radioterapia**
  - **Emopoiesi extramidollare: radioterapia chirurgia**
  - **Trombosi: ASA, anticoagulanti**
  - **Sintomi costituzionali: steroidi a basse dosi**
- **Inibitori di m-Tor**
- **Inibitori JAK-2 (Ruxolitinib ……..)**
- **Trapianto allogenico di cellule emopoietiche**

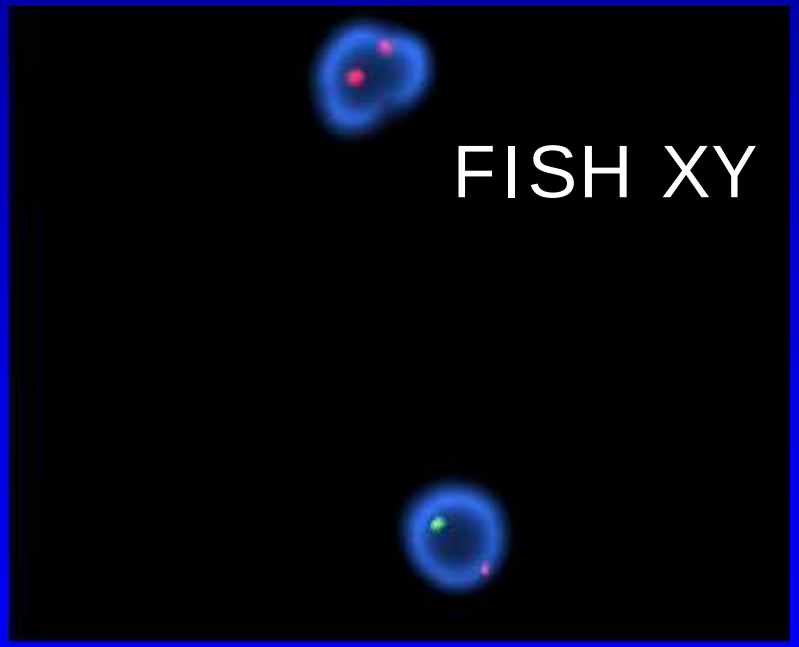


Mielofibrosi: Obbiettivi terapeutici

TRAPIANTO DI CELLULE EMOPOIETICHE
UNICA OPPORTUNITÀ DI
GUARIGIONE

SCOPO DEL TRAPIANTO

CHIMERA



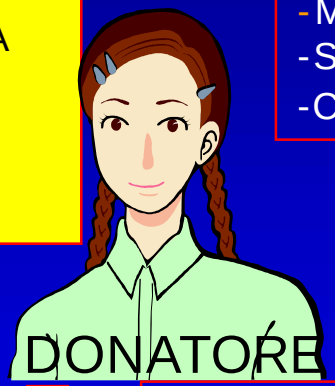
TMO
FIRENZE

TRAPIANTO DI CELLULE STAMINALI EMOPOIETICHE

TERAPIA DI CONDIZIONAMENTO
- ERADICARE LA MALATTIA
- FARE SPAZIO
- IMMUNOSOPPRESSIONE
- CHIMERISMO

FONTI DI CELLULE STAMINALI:
- MIDOLLO OSSEO
- SANGUE PERIFERICO
- CORDONE OMBELICALE

PAZIENTE



DONATORE

APLASIA

CHIMERA

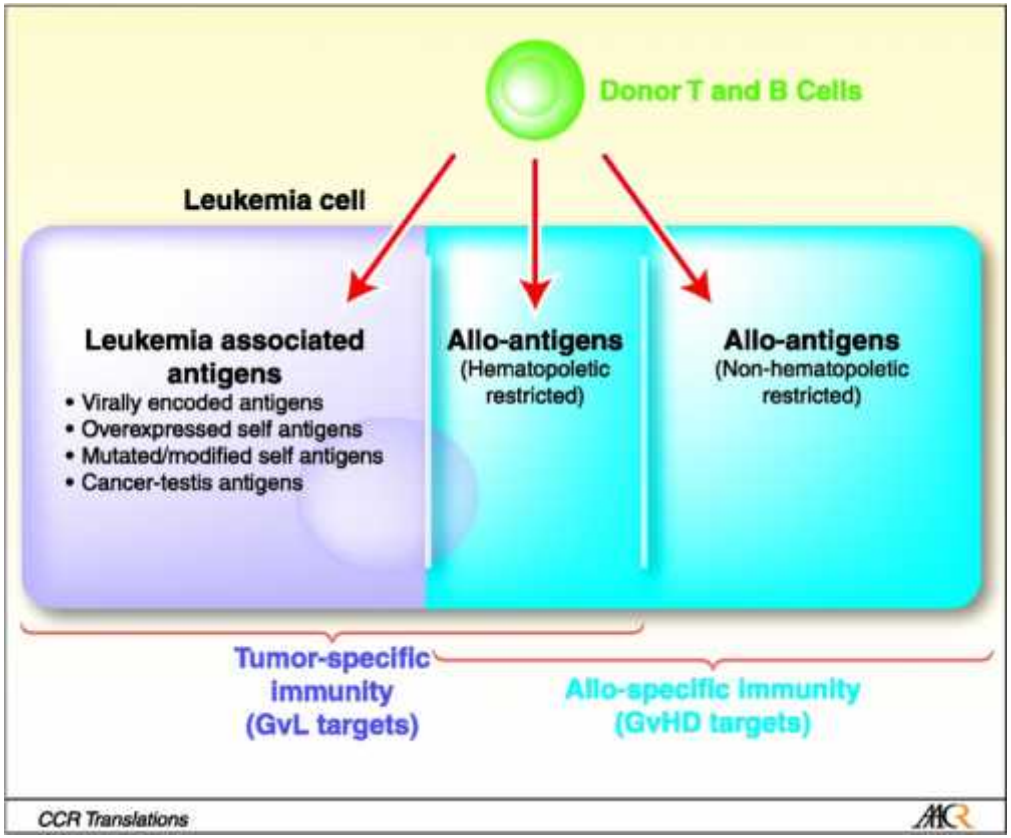
TERAPIA IMMUNOSOPPRESSIVA

DLI

TMO FIRENZE

Graft *vs* Malattia

After allogeneic HSCT, donor T- and B-cell responses to leukemia cells can be directed against three categories of antigens.



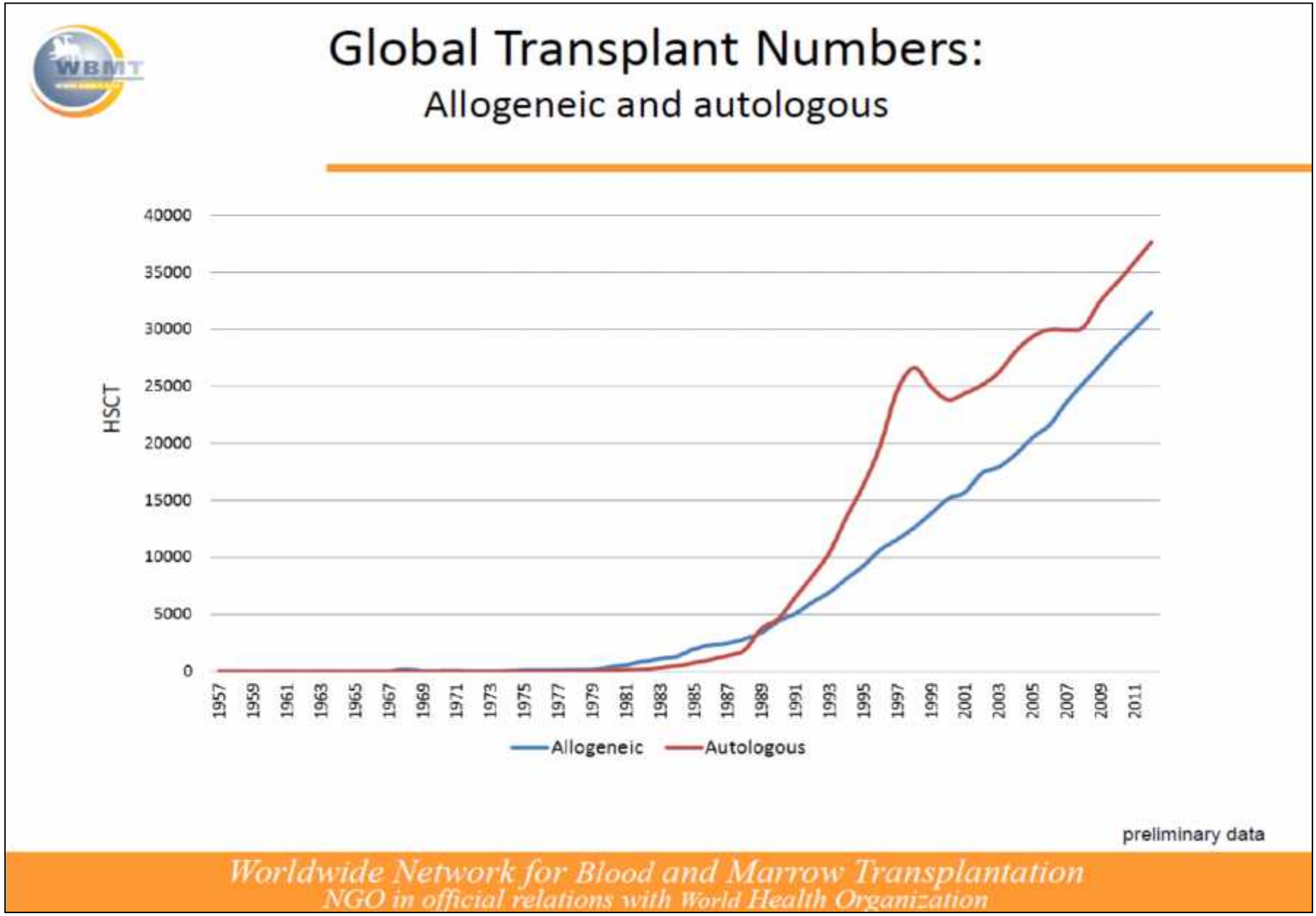
Wu C J , Ritz J Clin Cancer Res 2009;15:4515-4517

GVM PROVE

- Basso rischio di recidiva in cGvHD
- Alto rischio di recidiva nei T depleti
- Ottenimento della RC con DLI

Clinical Cancer Research

>1.000.000 trapianti effettuati



THE EBMT REGISTRY HAS REACHED A TOTAL OF

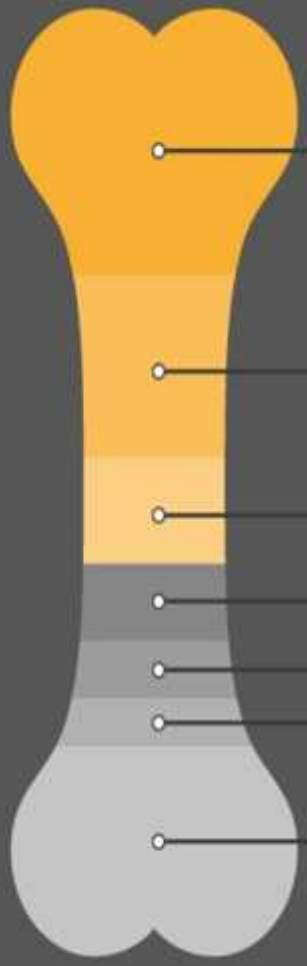
500,000

TRANSPLANTS

Here are some interesting facts about them

DIAGNOSED DISEASES

Allogeneic



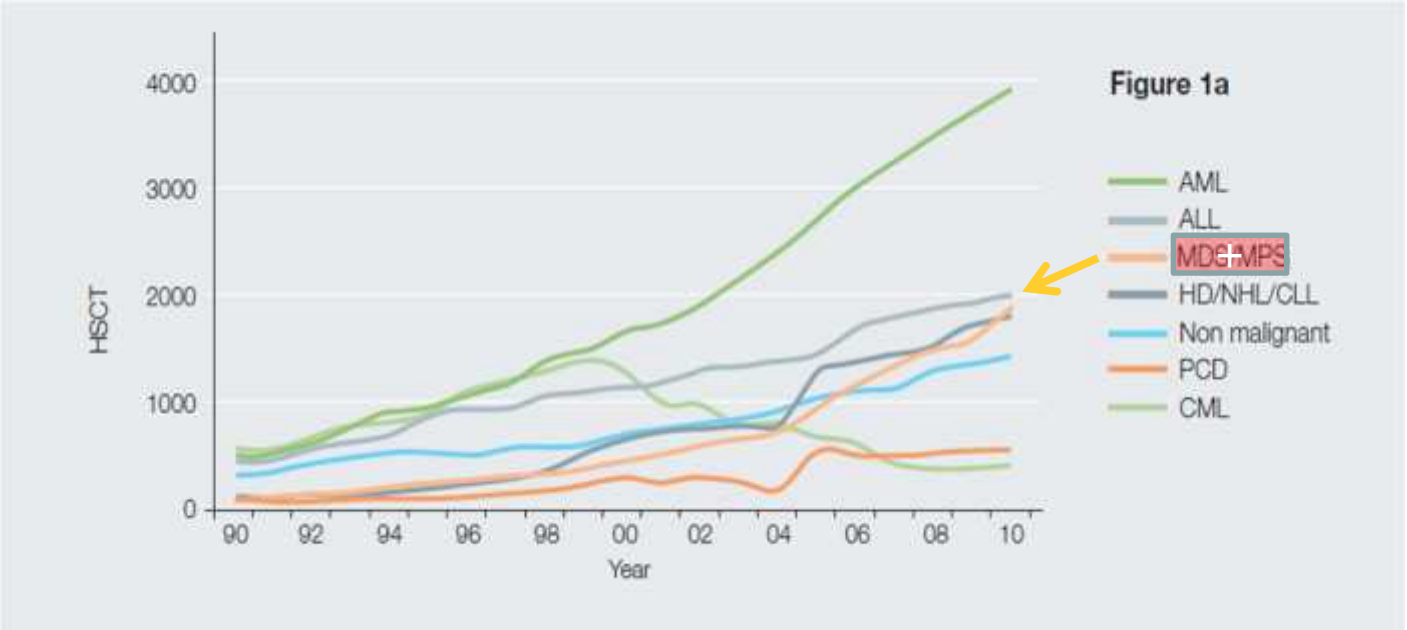
- 28% Acute Myeloid Leukaemia
- 19% Acute Lymphoblastic Leukaemia
- 11% Chronic Myeloid Leukaemia
- 8% Myelodysplastic syndrome
- 6% Bone marrow failure
- 5% Non-Hodgkin Lymphoma
- 22% Other

Autologous

- 31% Multiple myeloma
- 29% Non-Hodgkin Lymphoma
- 10% Solid tumour (excluding Breast)
- 10% Hodgkin's Lymphoma
- 6% Acute Myeloid Leukaemia
- 4% Breast cancer
- 9% Other

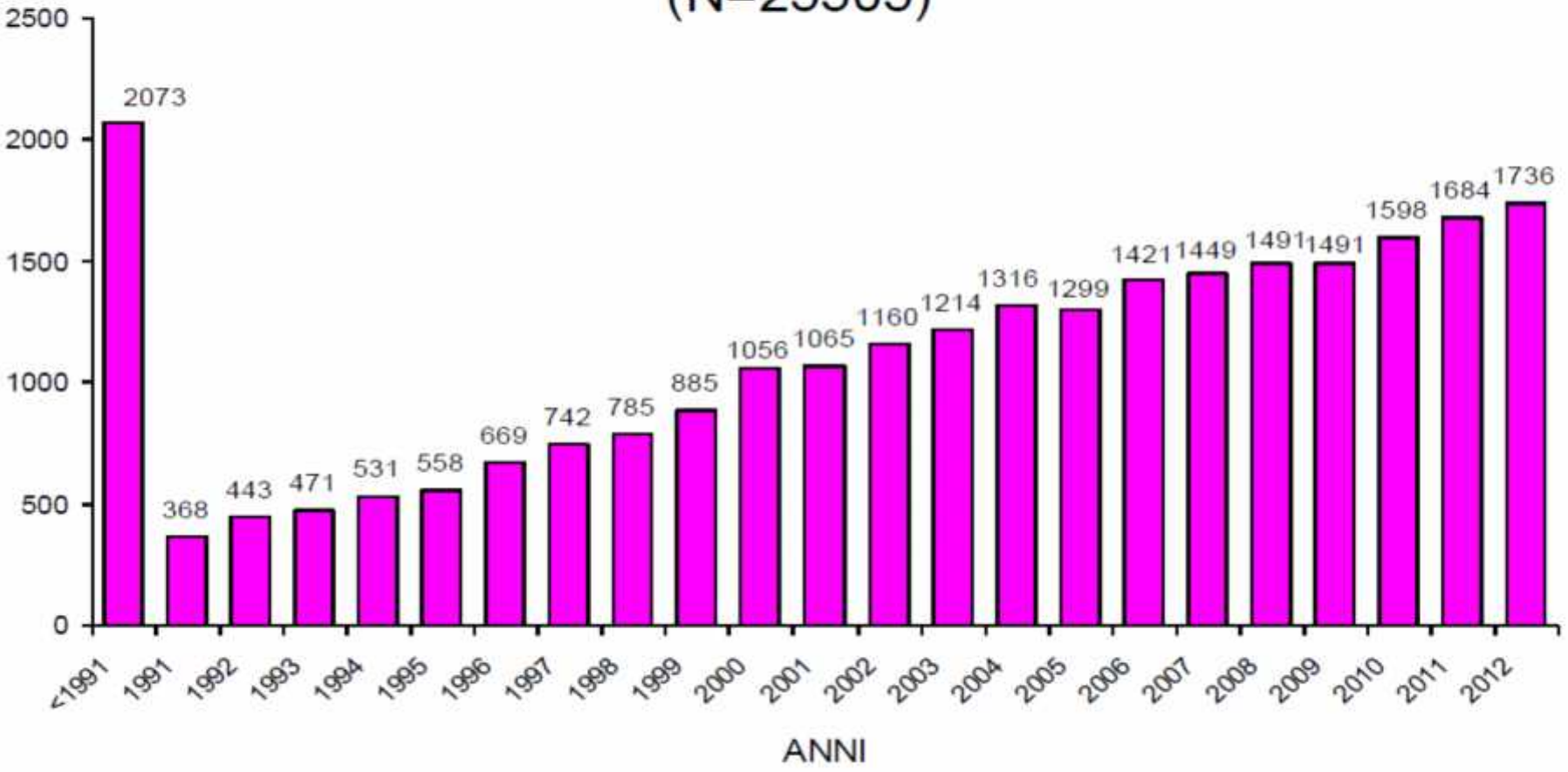
EBMT

TRAPIANTO DA DONATORE



GITMO Trapianto Allogenico

Allotrapianti registrati
(N=25505)

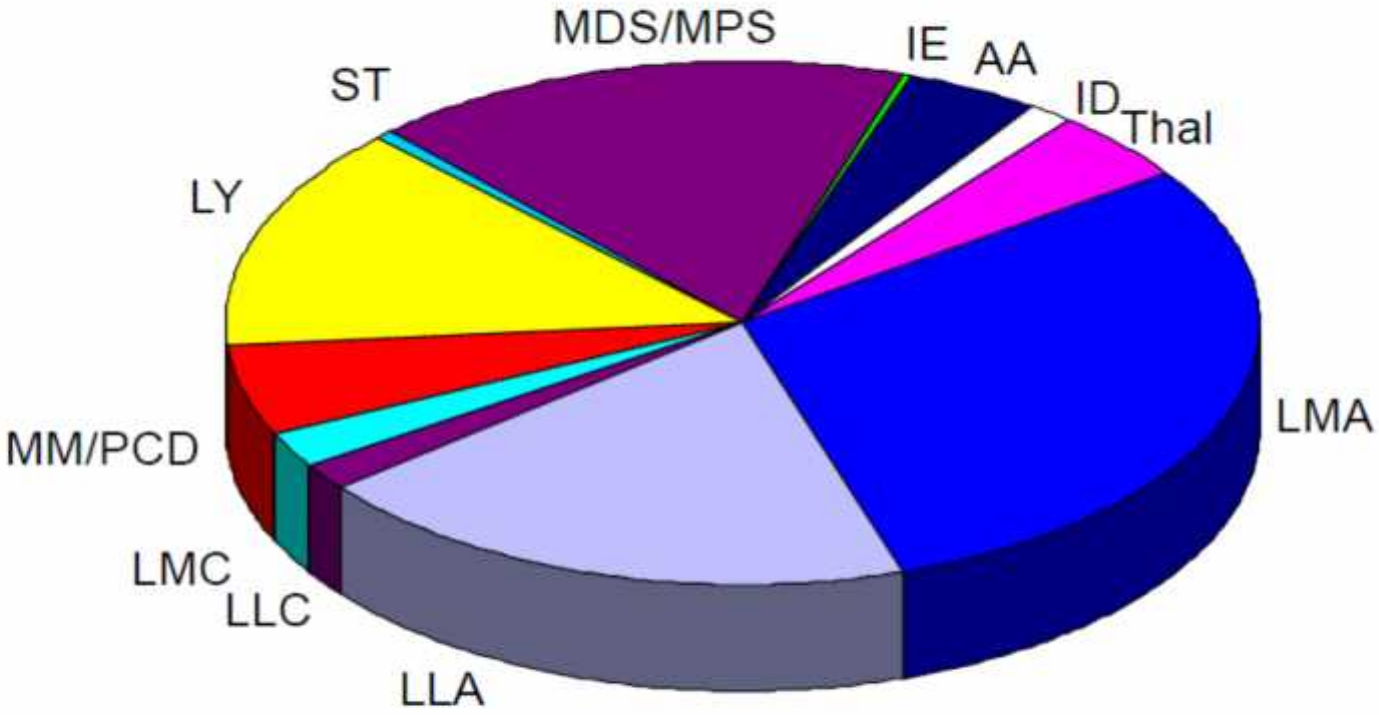


GITMO

GITMO Trapianto Allogenico

Numero Trapianti per principali Patologie

Attività 2012



n=501	Leucemia Mieloide Acuta	n=323	Leucemia Linfatica Acuta
n=32	Leucemia Linfatica Cronica	n=37	Leucemia Mieloide Cronica
n=91	MielMult/Plasmacell	n=238	Linfomi
n=10	Tumori Solidi	n=282	MDS/MPS
n=9	Errori genetici	n=69	Anemia Aplastica
n=24	Immunodeficienze	n=74	Talassemia

MF2010= 11

GITMO

Perché così pochi trapianti nella mielofibrosi ?

Il trapianto ha un costo biologico elevato!

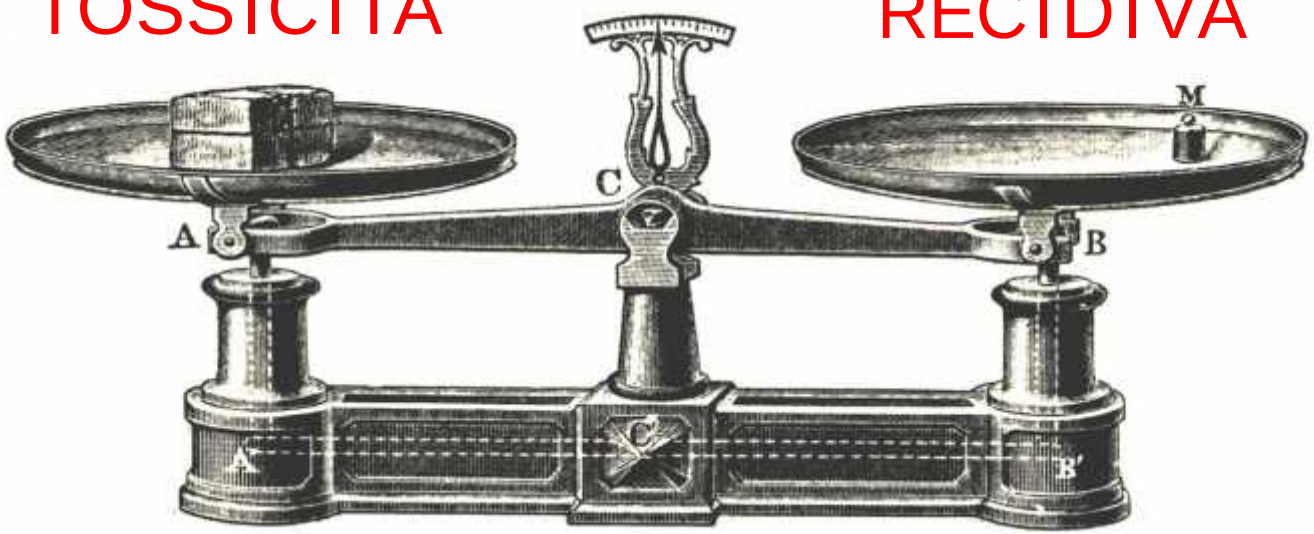
GUARIGIONE

- Tipo di trapianto
- Età
- Comorbidità

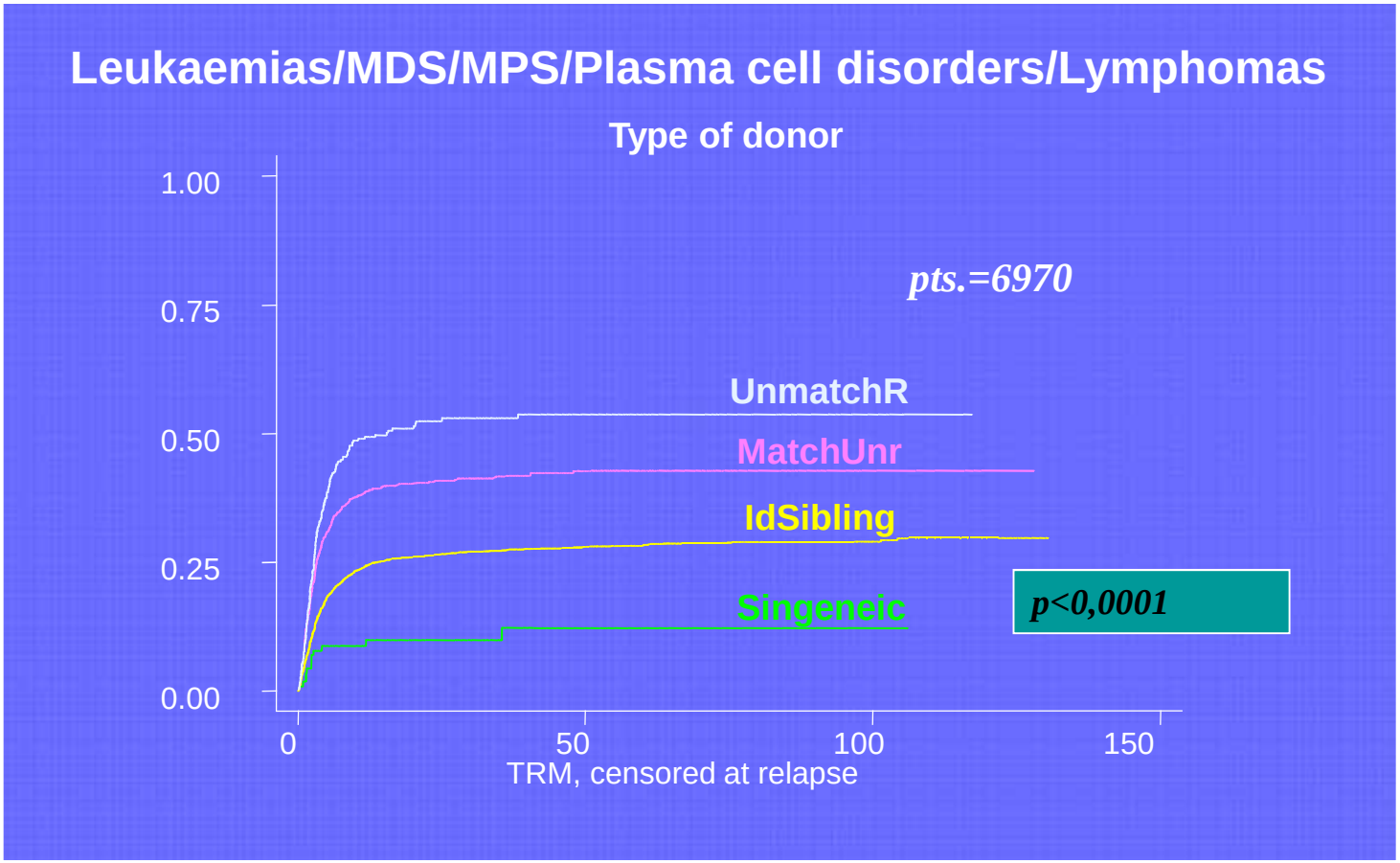
- Fase avanzata
- Malattia refrattaria

TOSSICITA'

RECIDIVA



RISCHIO TRAPIANTOLOGICO 1990-2001



TRAPIANTO MASSIMALE

L' INTENSITÀ DEL TRAPIANTO È PROPORZIONALE AL RISCHIO TRAPIANTOLOGICO

TRAPIANTO CONVENZIONALE MASSIMALE

Necessità di limitare l' indicazione al TMO a:

- Giovani
- Patologie alto rischio
- Basso rischio trapiantologico

TRAPIANTI AD INTENSITA' RIDOTTA

Possibilità di TMO per:

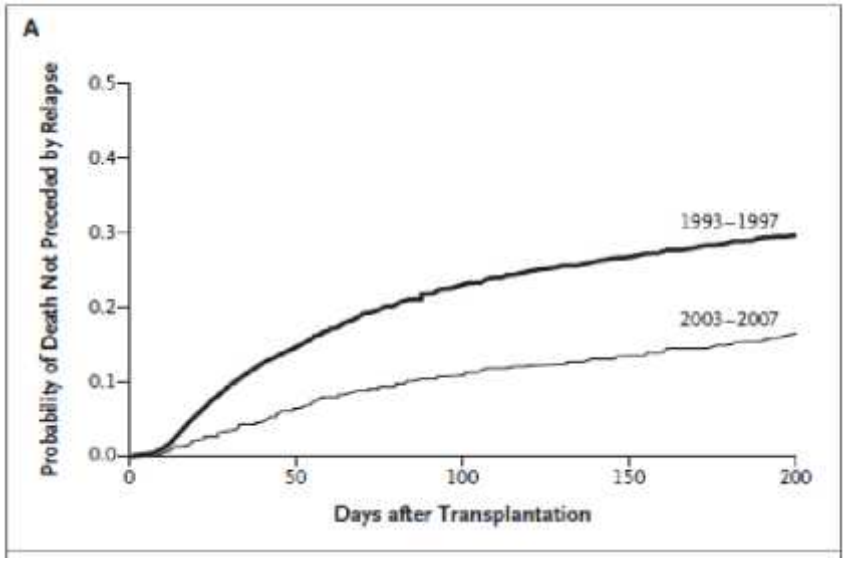
- Meno giovani
- Comorbidità
- Più alto rischio trapiantologico

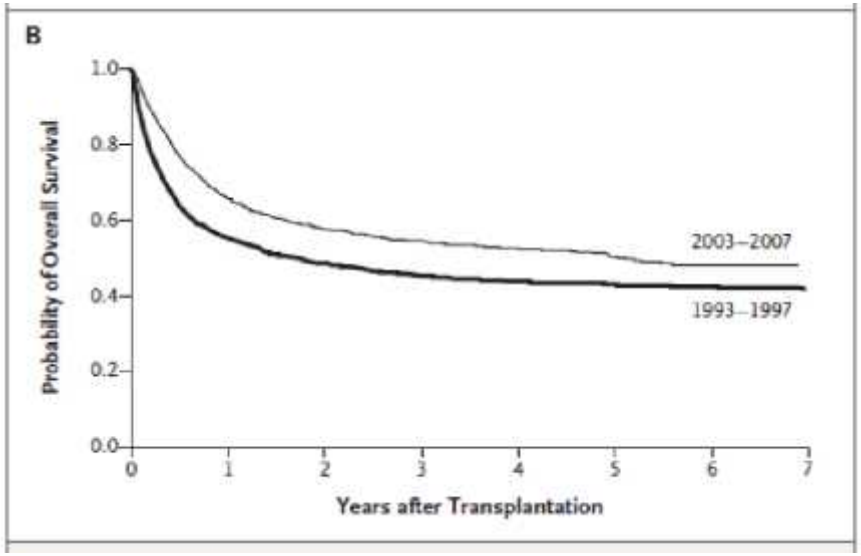
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 25, 2010 VOL. 363 NO. 22

Reduced Mortality after Allogeneic Hematopoietic-Cell Transplantation

Ted A. Gooley, Ph.D., Jason W. Chien, M.D., Steven A. Pergam, M.D., M.P.H., Sangeeta Hingorani, M.D., M.P.H., Mohamed L. Sorror, M.D., Michael Boeckh, M.D., Paul J. Martin, M.D., Brenda M. Sandmaier, M.D., Kieren A. Marr, M.D., Frederick R. Appelbaum, M.D., Rainer Storb, M.D., and George B. McDonald, M.D.





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

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

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

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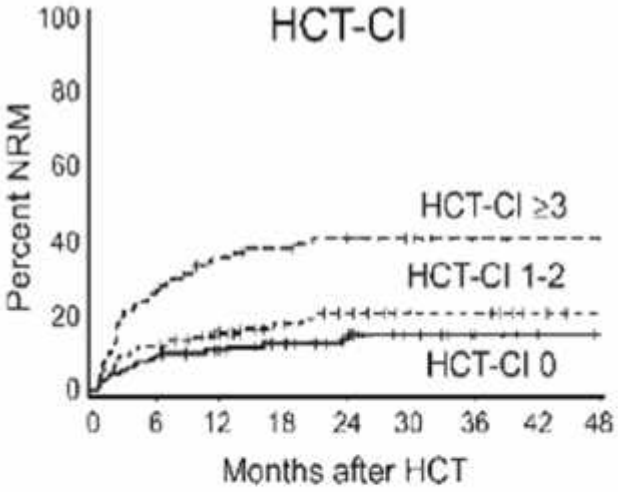
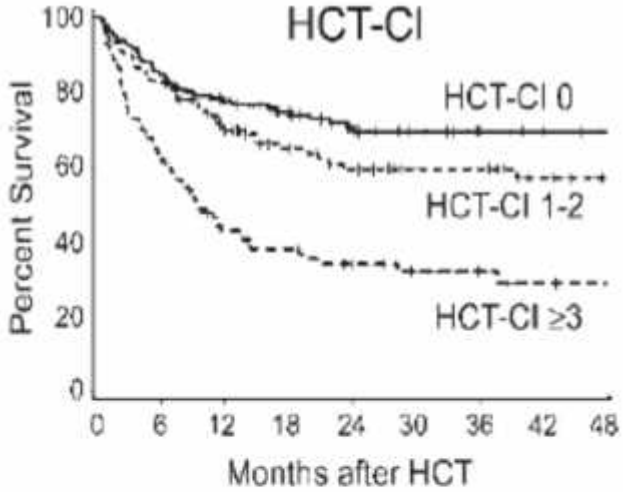
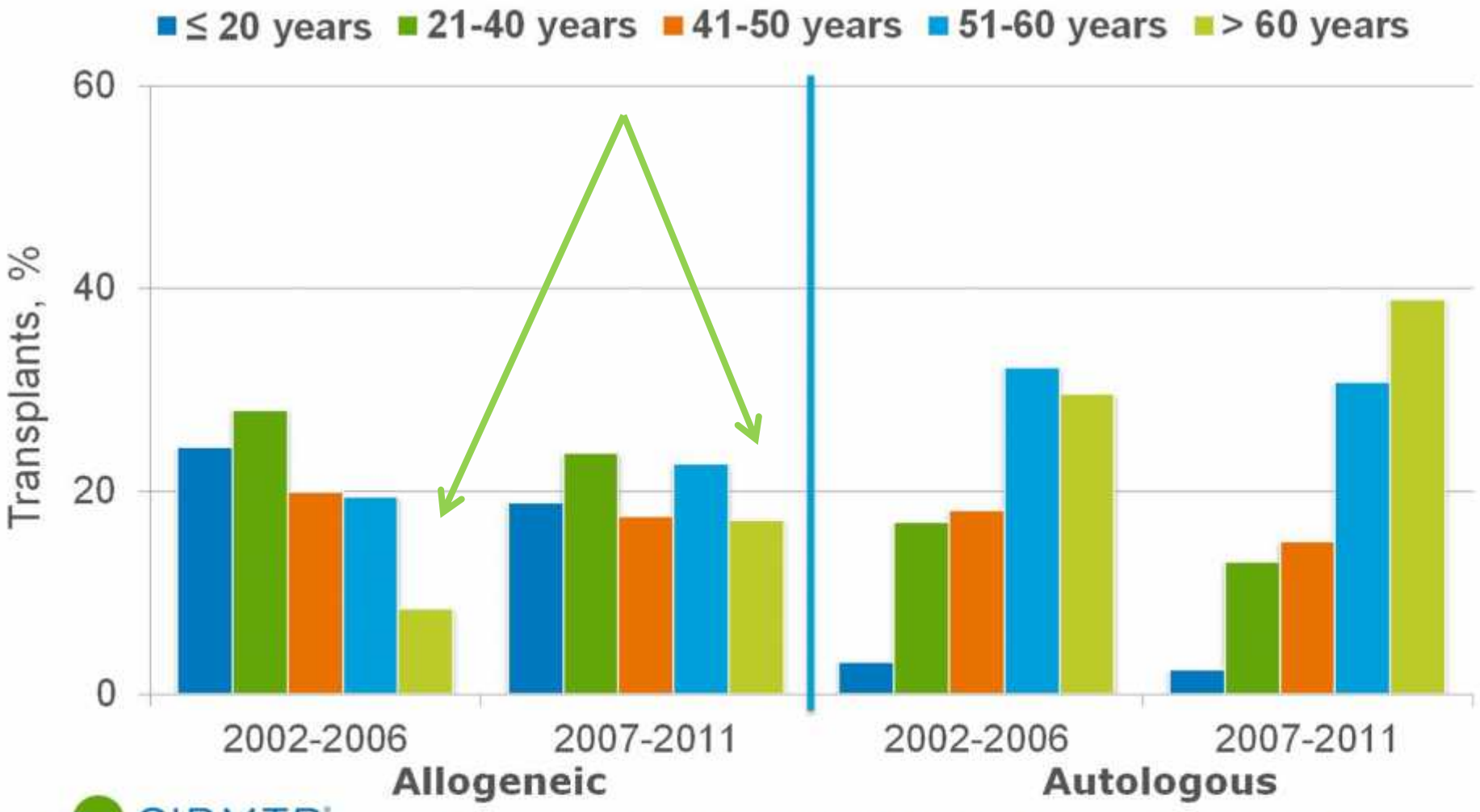




		NRM		Survival	
Score	No.	HR* (95% CI)	2-year, %	HR* (95% CI)	2-year, %
0	38	1.0	14	1.0	71
1 to 2	34	1.42 (0.8-2.7)	21	1.31 (0.8-2.0)	60
3 or more	28	3.54 (2.0-6.3)	41	2.69 (1.8-4.1)	34

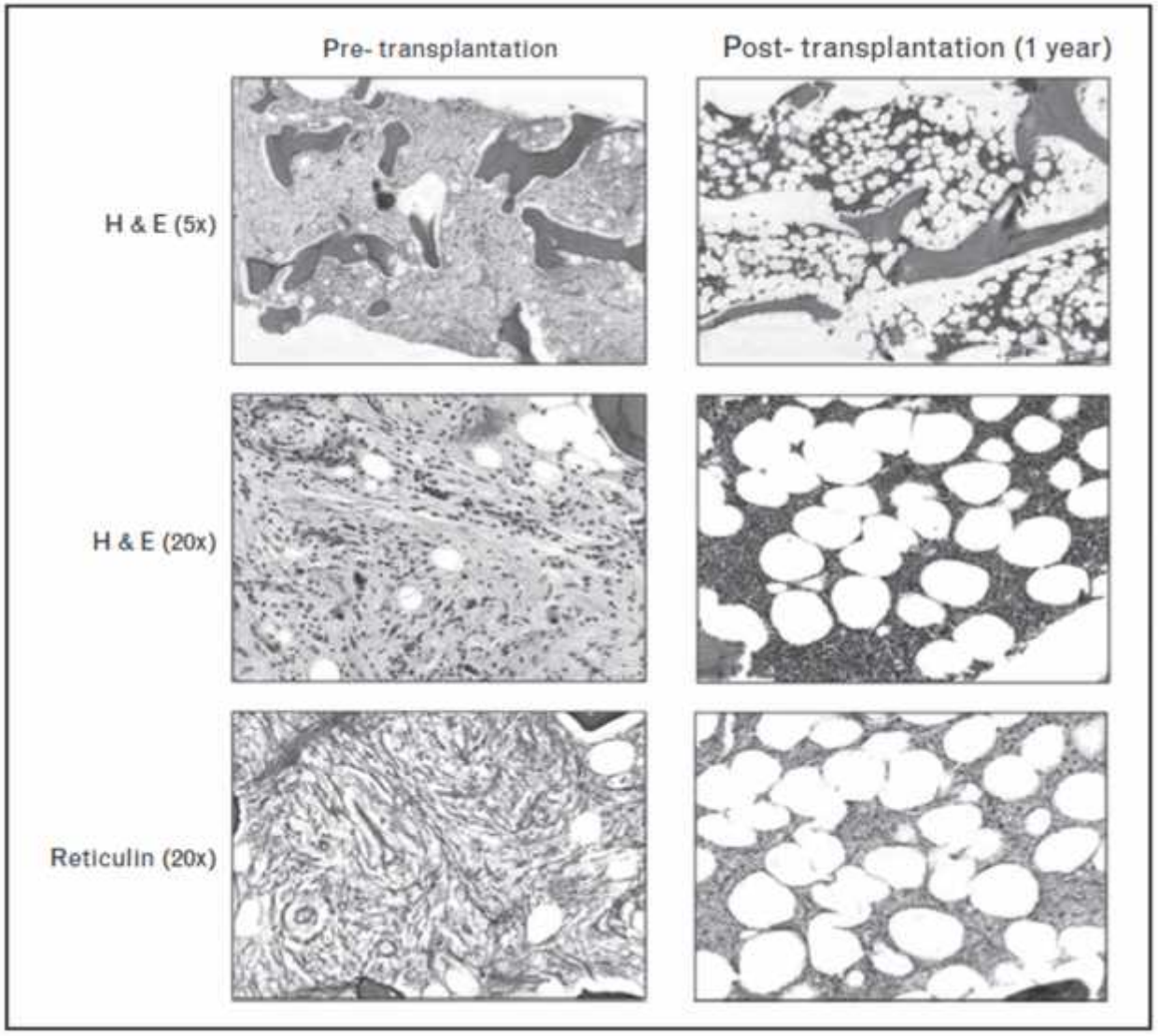
Trends in Transplants by Type and Recipient Age*



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

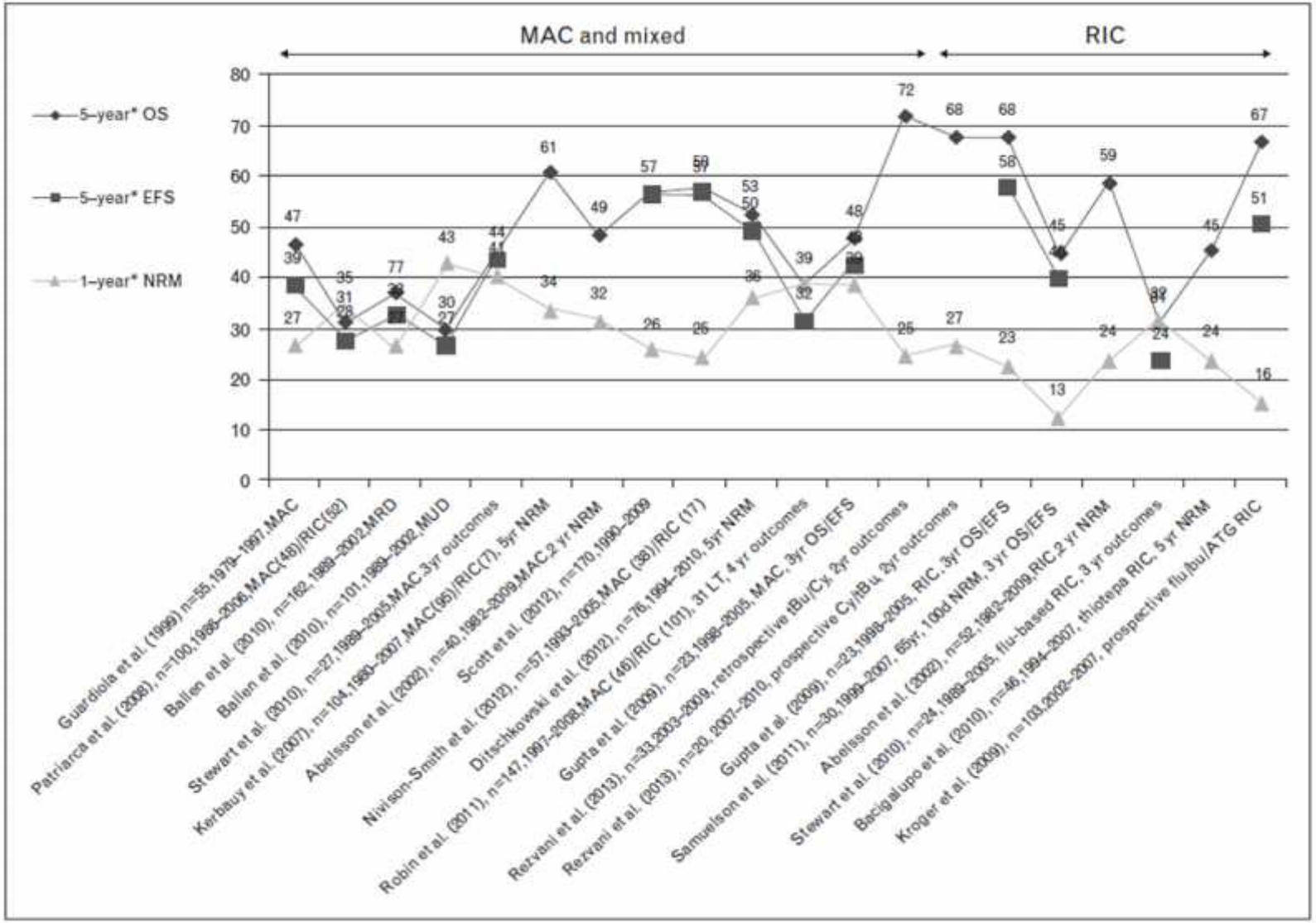
*Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma

RISULTATI DEL TRAPIANTO



Allogeneic transplantation for myelofibrosis Babushok and Hexner **Curr Opin Hematol** 2014, 21:114–122

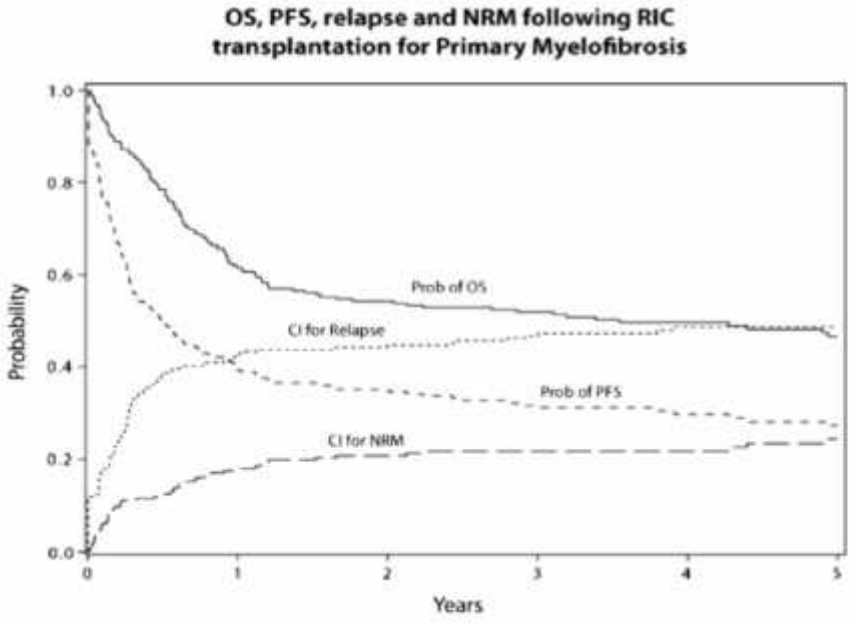
RISULTATI DEL TRAPIANTO

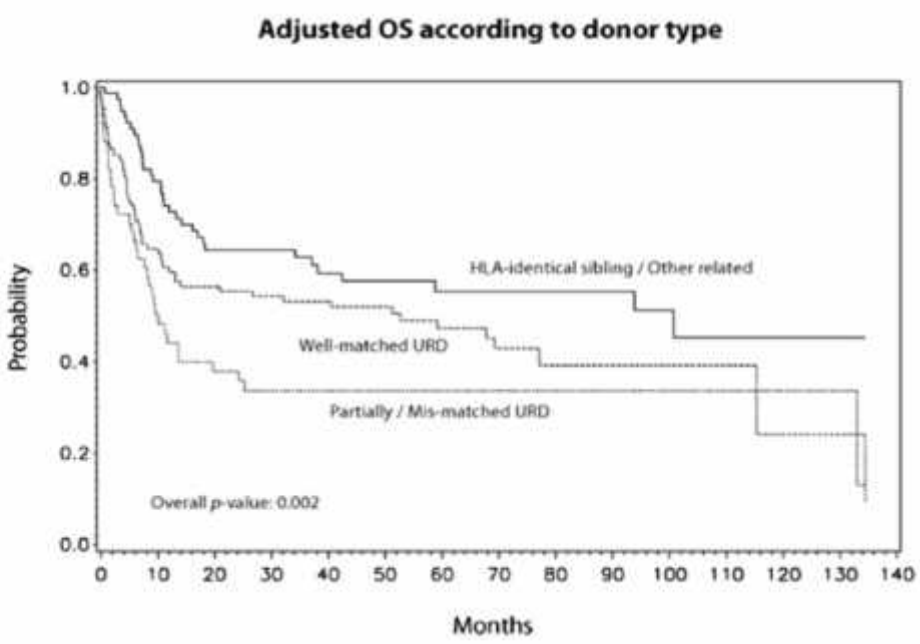


Allogeneic transplantation for myelofibrosis Babushok and Hexner **Curr Opin Hematol** 2014, 21:114–122

Reduced-Intensity Hematopoietic Cell Transplantation for Patients with Primary Myelofibrosis: A Cohort Analysis from the Center for International Blood and Marrow Transplant Research

Vikas Gupta [1,*], Adriana K. Malone [2], Parameswaran N. Hari [3],





Biol Blood Marrow Transplant 20 (2014) 89–97

Allogeneic Stem Cell Transplantation for Myelofibrosis with Leukemic Transformation: A Study from the Myeloproliferative Neoplasm Subcommittee of the CMWP of the European Group for Blood and Marrow Transplantation

Haefaa Alchalby [1], Tatjana Zabelina [1], Thomas Stübig [1],

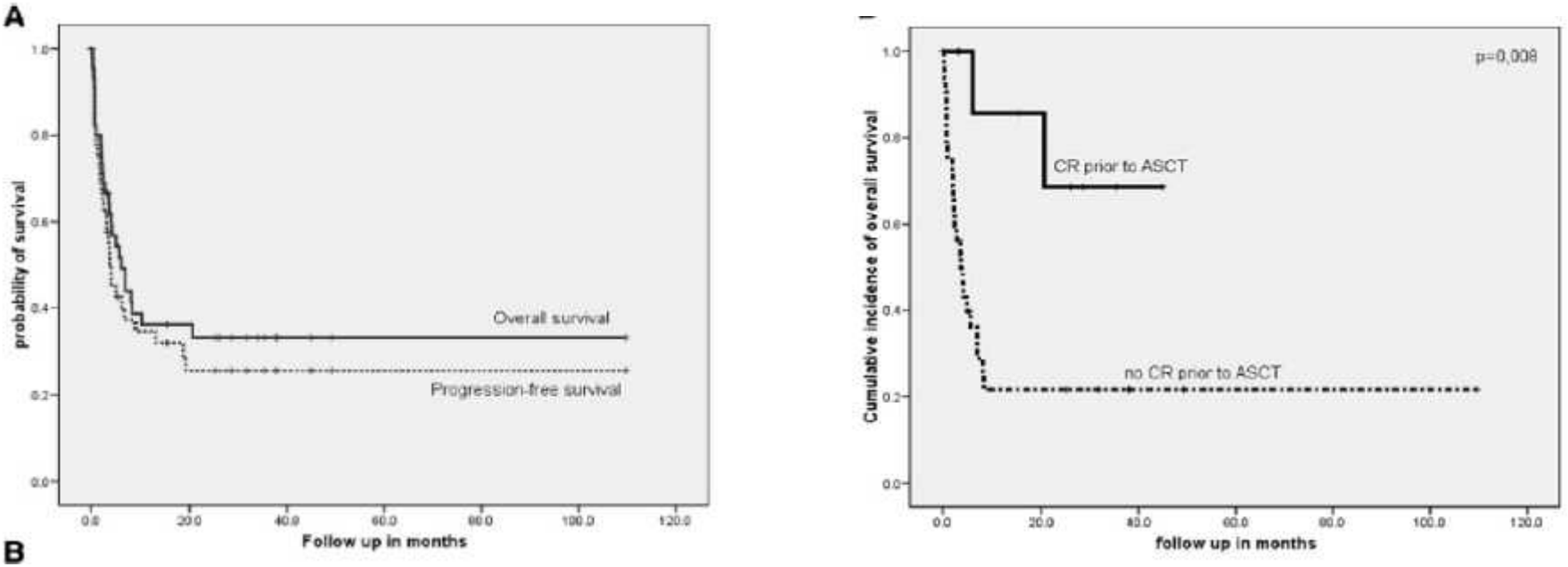
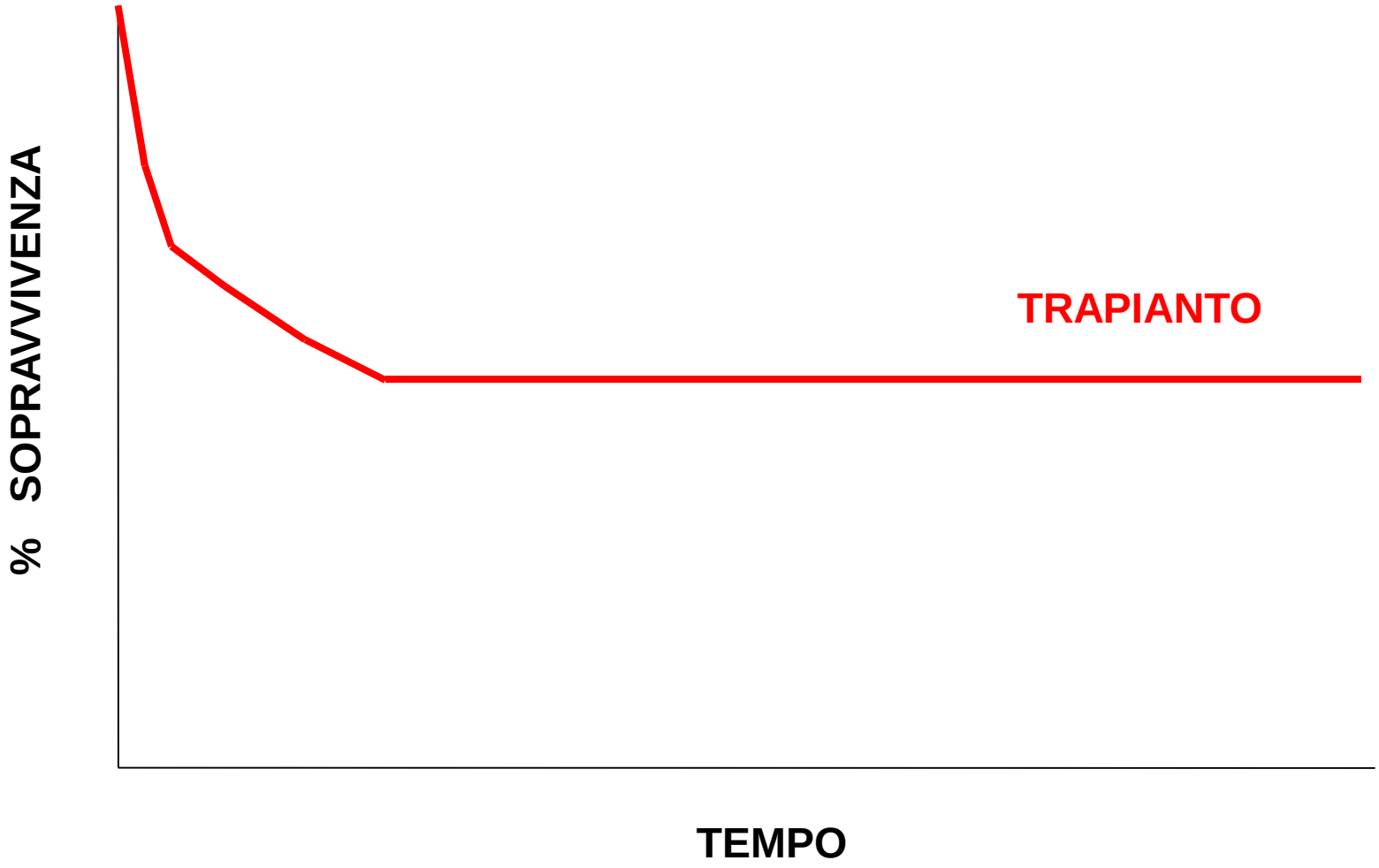


Figure 1. (A) OS and PFS after ASCT for MF transformed to acute leukemia. (B)

OTTIMIZZARE I RISULTATI I

IDENTIFICARE IL MOMENTO MIGLIORE PER IL TRAPIANTO

IL DILEMMA DEL TRAPIANTO



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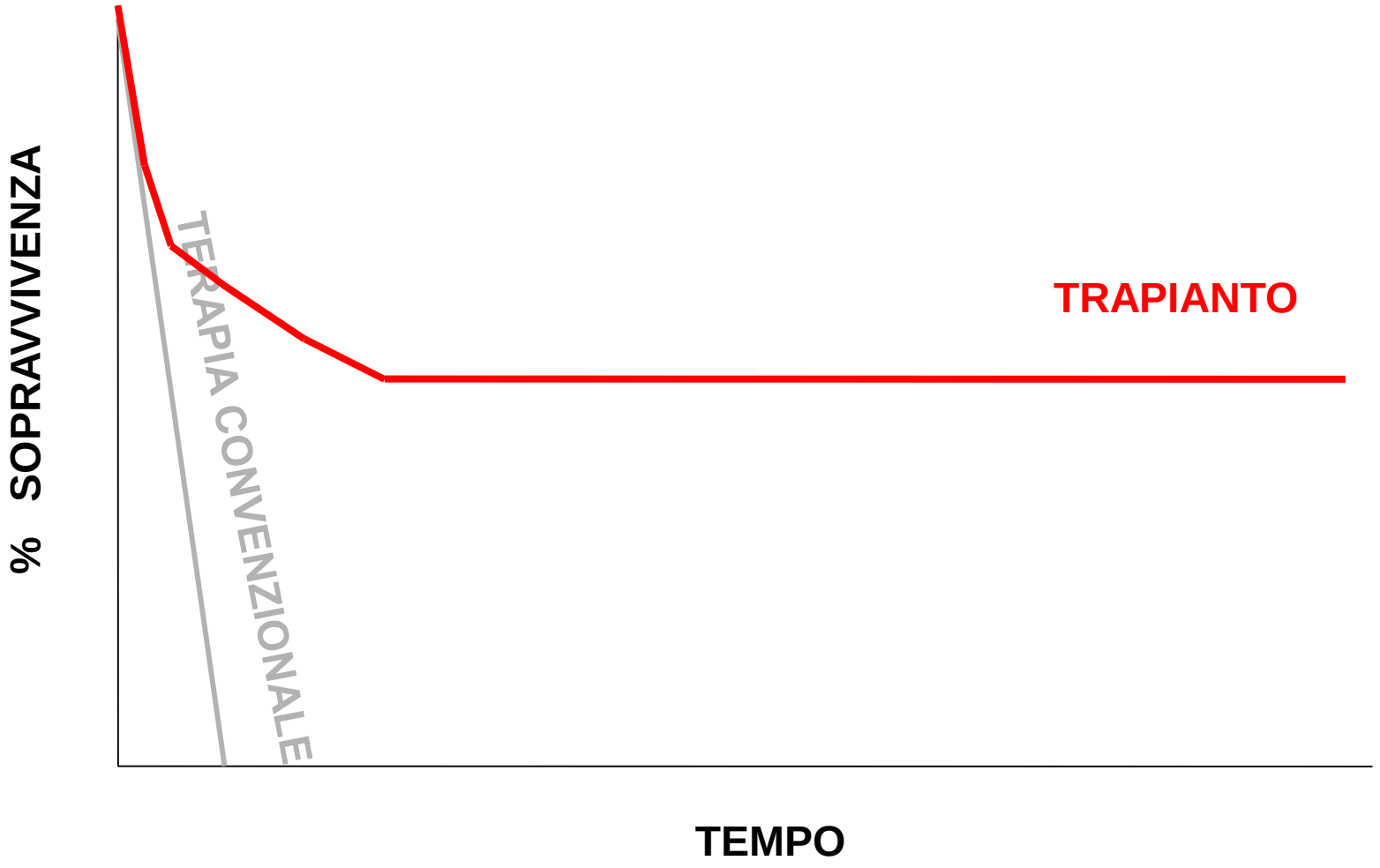

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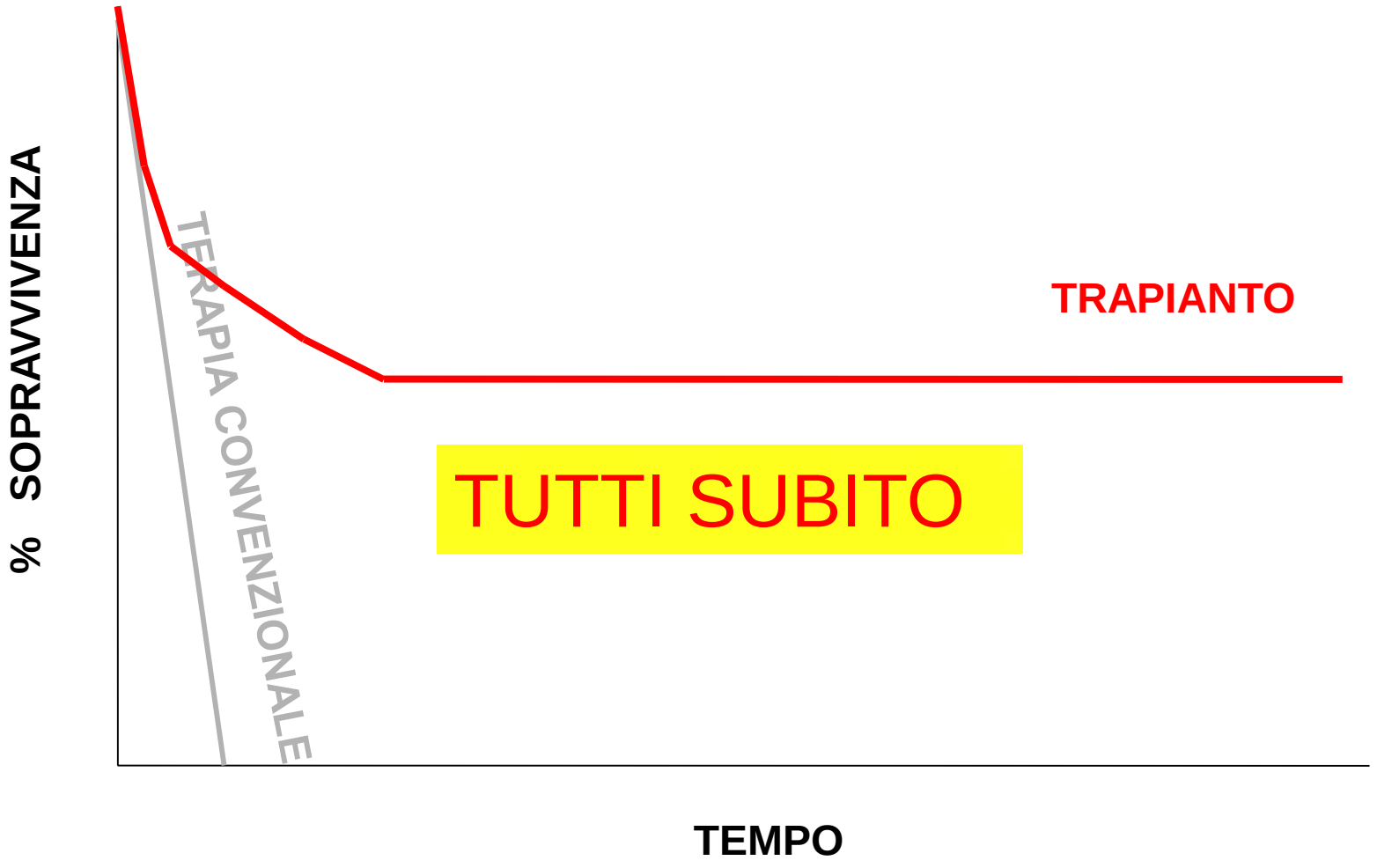

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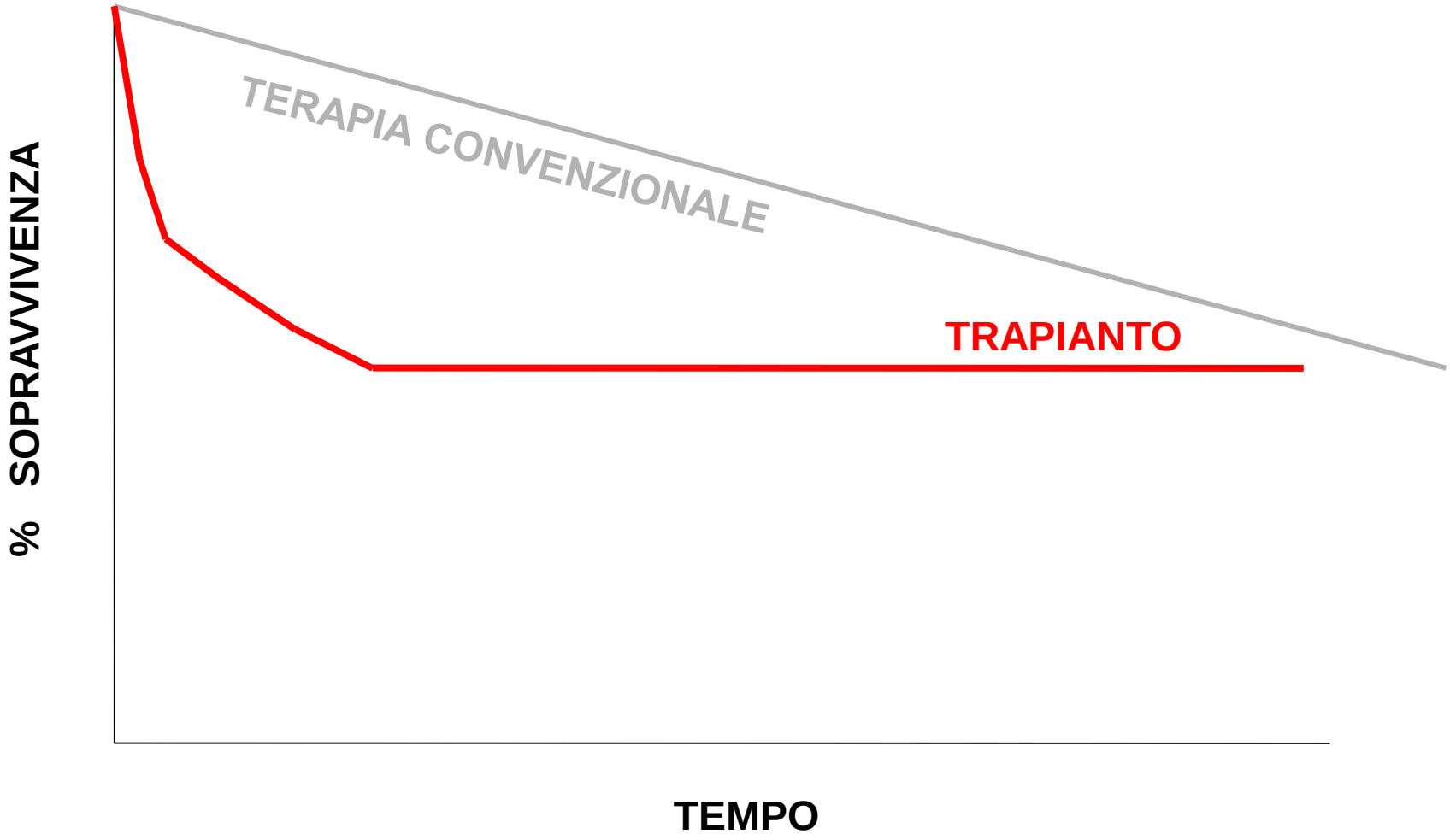

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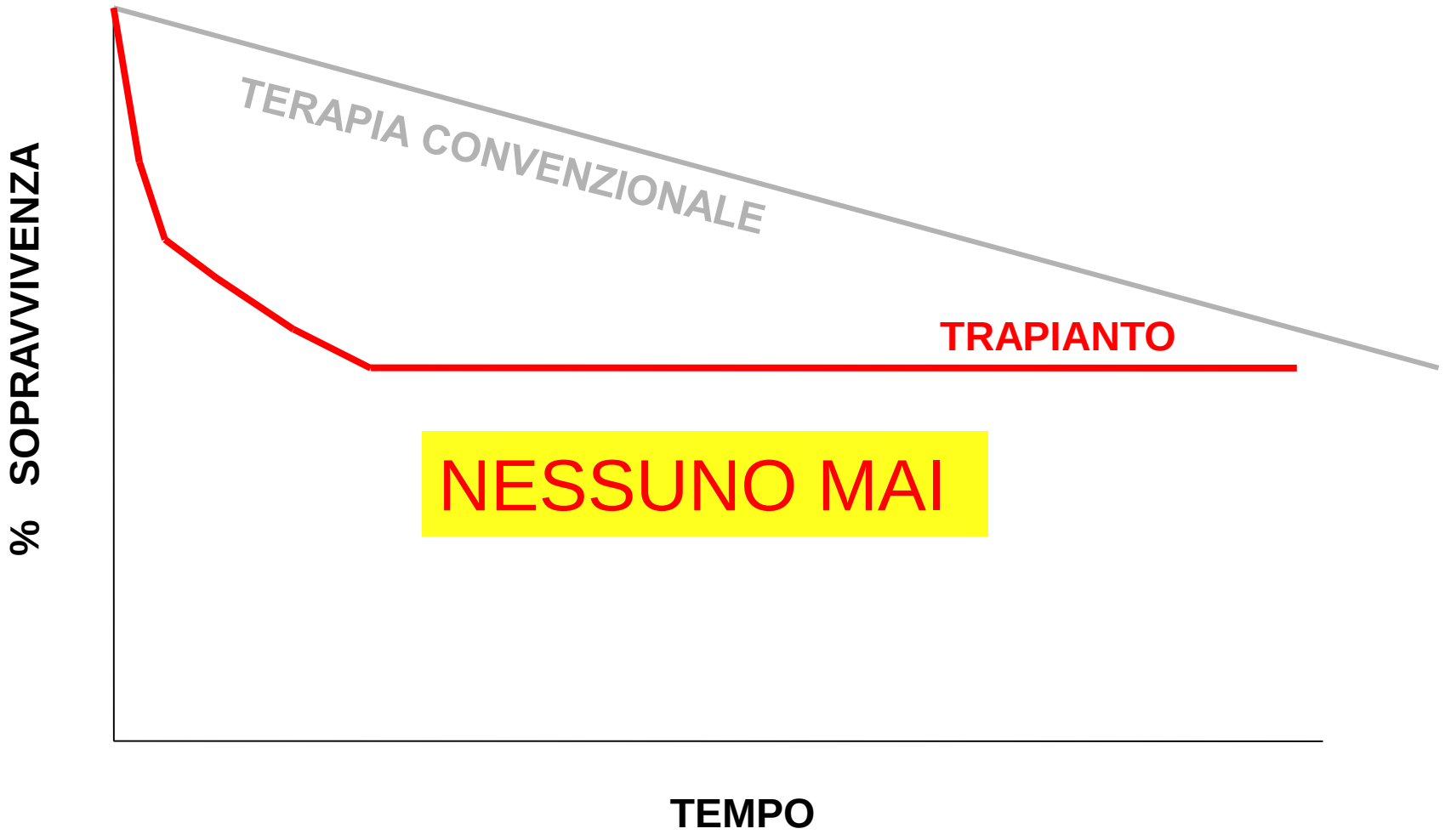

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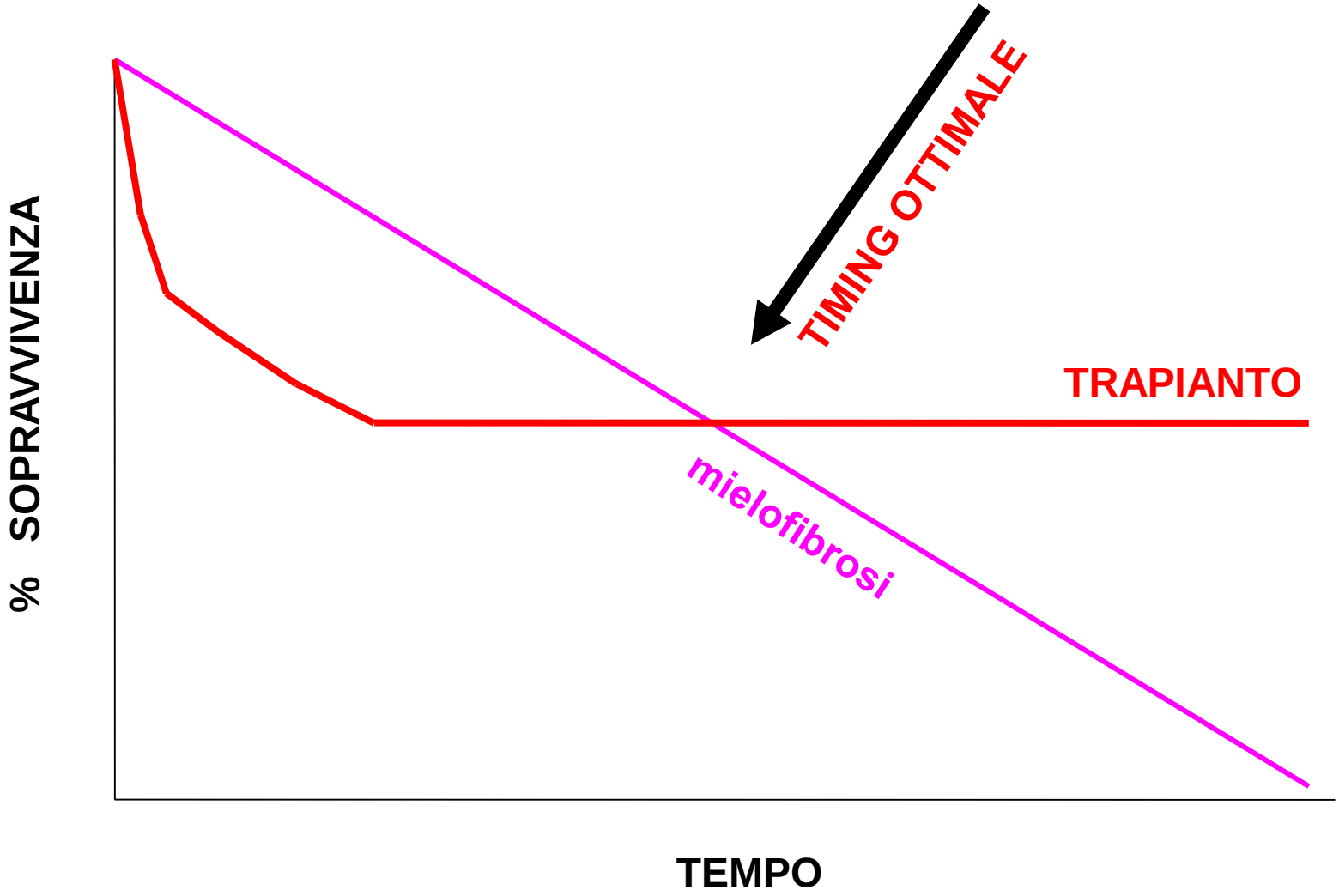

OTTIMIZZARE I RISULTATI II

QUALI PAZIENTI TRAPIANTARE

FATTORI PROGNOSTICI MF

DIPSS Plus: A Refined Dynamic International Prognostic Scoring System for Primary Myelofibrosis That Incorporates Prognostic Information From Karyotype, Platelet Count, and Transfusion Status

Naseema Gangat, Domenica Caramazza, Rakhee Vaidya, Geeta George, Kebede Begna, Susan Schwager, Daniel Van Dyke, Curtis Hanson, Wenting Wu, Animesh Pardanani, Francisco Cervantes, Francesco Passamonti, and Ayalew Tefferi

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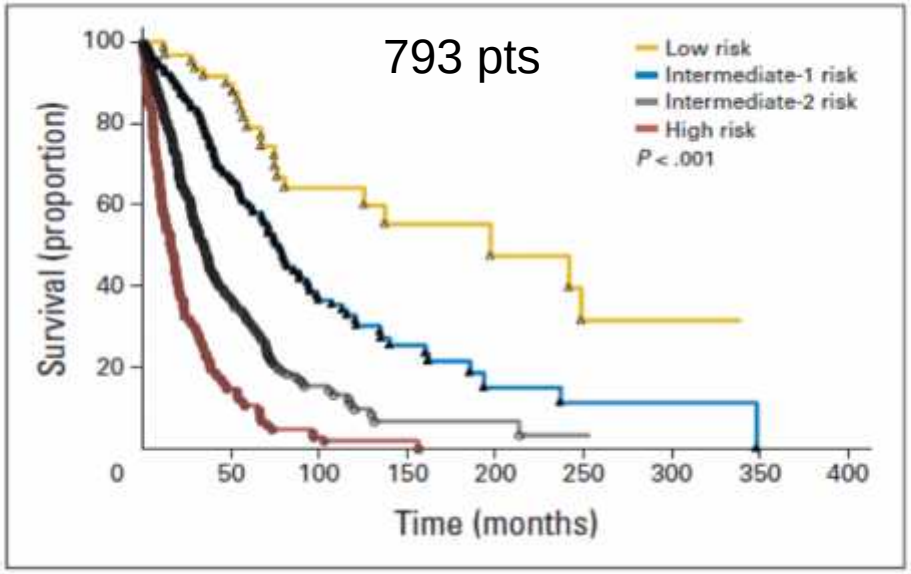
JOURNAL OF CLINICAL ONCOLOGY



DIPSS

Clinical feature	Points
Age > 65 years	1
Constitutional symptoms[1]	1
Hb < 10 g/dl	2
WBC count > 25 x 10^9/l	1
Peripheral blasts ≥ 1%	1

DIPSS-Plus

Clinical feature	Points
DIPSS-low	0
DIPSS-int-1	1
DIPSS-int-2	2
DIPSS-high	3
PLUS	
Unfavourable karyotype[2]	1
Transfusion dependence	1
Platelet < 100 000/μl	1

Prognostic category	Points	Median survival (mo)
Low	0	185
Intermediate-1	1	78
Intermediate-2	2–3	35
High	4–6	16

Allogeneic transplantation for myelofibrosis: for whom, when, and what are the true benefits?

Curr Opin Hematol 2014, 21:114–122

Daria Babushok and Elizabeth Hexner

Very high risk (over 80% 2-year mortality) [11]

Clinical feature	Points
Monosomal karyotype	1
Inv(3)/t(17q)	1
Other unfavourable karyotype[2]	0.5
Peripheral blasts > 9%	0.5
WBC ≥ 40^9/L	0.5

Prognostic category	Points	Median survival (mo)
Very high risk	≥1	9

Accelerated phase (median survival ≤ 12 months) [10]

Clinical feature	Points
Any abnormality of Chr 17	1
Blood/bone marrow blasts ≥ 10%	1
Platelets <50 000/μl	1

Prognostic category	Points	Median survival (mo)
Accelerated phase	≥1	≤12

Leukemic transformation (DIPSS-Plus) [9]

Clinical feature	Points
Platelets < 50 000/μl	1
Unfavourable karyotype[1]	1

Prognostic category	Points	Leukemic transformation rate (5-year, 10-year)
Low risk	0	6%, 12%
High risk	≥1	18%, 31%

Leukemic transformation (Tefferi *et al.*) [12]

Clinical feature	Points
Very high risk karyotype[2]	2
Blasts ≥ 2%	1
Platelets ≤ 50 000/μl	1

Prognostic category	Points	Leukemic transformation rate (3-year)
Low	0	3%
Intermediate	1	10%
High	≥2	35%

Leukemic transformation (Quintás *et al.*) [13]

Clinical feature	Points
Worst karyotype[3]	1
Blasts ≥ 10%	1

Prognostic category	Points	Leukemic transformation rate (1-year)
Low risk	0	2%
High risk	≥1	13%

Leukemic transformation (Barbui *et al.*) [14]

Clinical feature	Points
Blasts > 1%	4
Age > 65	2
hs-CRP > 7 mg/l	2

Prognostic category	Points	8-year leukemia-free survival
Low	0	88%
Intermediate	2–4	43%
High	6–8	32%

Clonal molecular changes of adverse prognostic significance in myelofibrosis [15]

Mutations in: *ASXL1, EZH2, SRSF2, IDH1, IDH2*

The Dynamic International Prognostic Scoring System for myelofibrosis predicts outcomes after hematopoietic cell transplantation

Bart L. Scott,[1,2] Ted A. Gooley,[1,2] Mohamed L. Sorror,[1,2] Andrew R. Rezvani,[1,2] Michael L. Linenberger,[1,2] Jonathan Grim,[1] Brenda M. Sandmaier,[1,2] David Myerson,[1,2] Thomas R. Chauncey,[1-3] Rainer Storb,[1,2] Veronika Buxhofer-Ausch,[4] Jerald P. Radich,[1,2] Frederick R. Appelbaum,[1,2] and H. Joachim Deeg[1,2]

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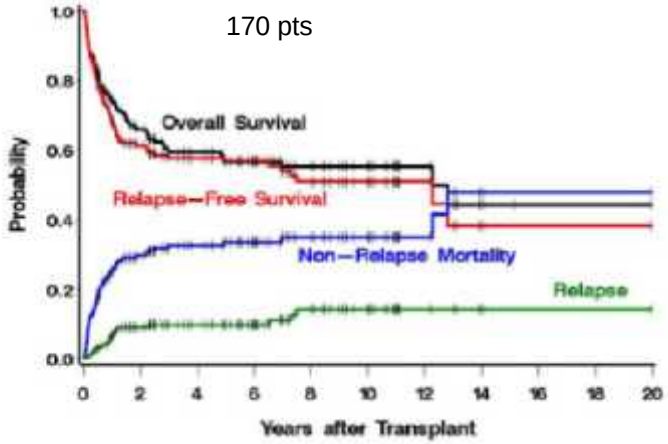
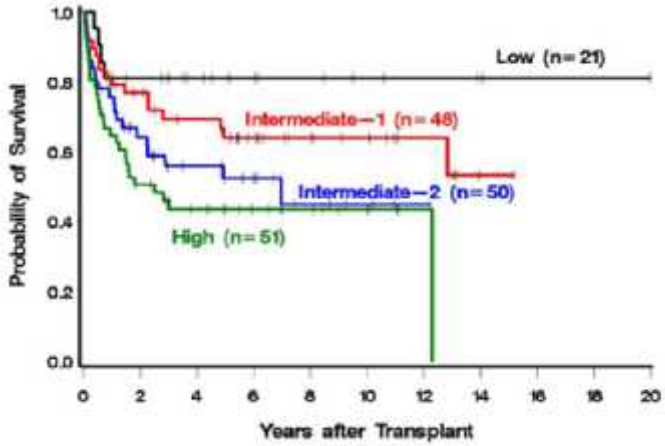
170 pts





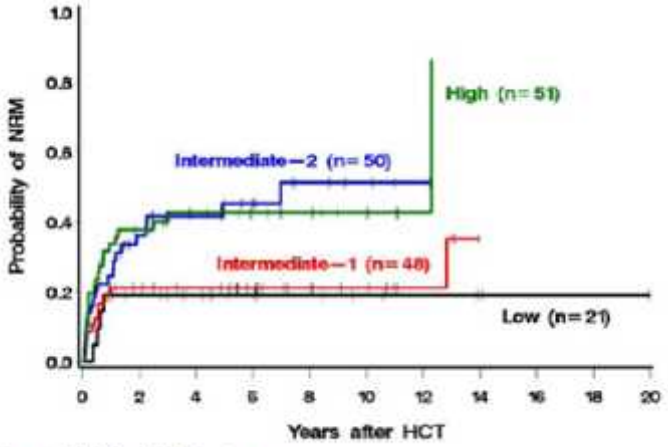


Figure 3. NRM by DIPSS category.

CONFRONTO TMO vs NO TMO

Impact of allogeneic stem cell transplantation on survival of patients less than 65 years with primary myelofibrosis

Nicolaus Kröger, Toni Giorgino, Bart L. Scott, Markus Ditschkowski, Haefaa Alchalby, Francisco Cervantes, Alessandro Vannucchi, Mario Cazzola, Enrica Morra, Tatjana Zabelina, Margherita Maffioli, Arturo Pereira, Dietrich Beelen, H. Joachim Deeg and Francesco Passamonti

	Allogeneic SCT			Conventional therapy		
Number of patients	n = 188			n = 255		
Median age at diagnosis	50 years (20-65)			55 years (18-65)		
DIPSS	at transplant			at diagnosis *		
low risk	n = 22			n = 125		
intermediate-1	n = 38			n = 75		
intermediate-2	n = 84			n = 52		
high risk	n = 44			n = 3		
Gender						
male	n = 108			n = 154		
female	n = 80			n = 101		
Time from diagnosis to transplant	1.2 year (0.0-22.2)					
Conditioning regimen						
RIC	n = 91					
MAC	n = 97					
Donor						
matched unrelated or mismatch related	n = 102					
matched related	n = 86					
Survival proportion (95% CI)	Year			Year		
	1	5	10	1	5	10
low risk	100%	69% (48-99)	60% (38-95)	98% (96-100)	95% (90-99)	92% (86-99)
intermediate-1	78% (55-100)	52% (33-83)	41% (24-70)	97% (93-100)	77% (67-89)	63% (51-77)
intermediate-2	82% (68-98)	50% (37-67)	32% (21-48)	77% (67-88)	41% (32-54)	11% (5-22)
high risk	65% (46-92)	32% (19-56)	27% (15-49)	67% (30-100)	11% (3-44)	1% (0-10)

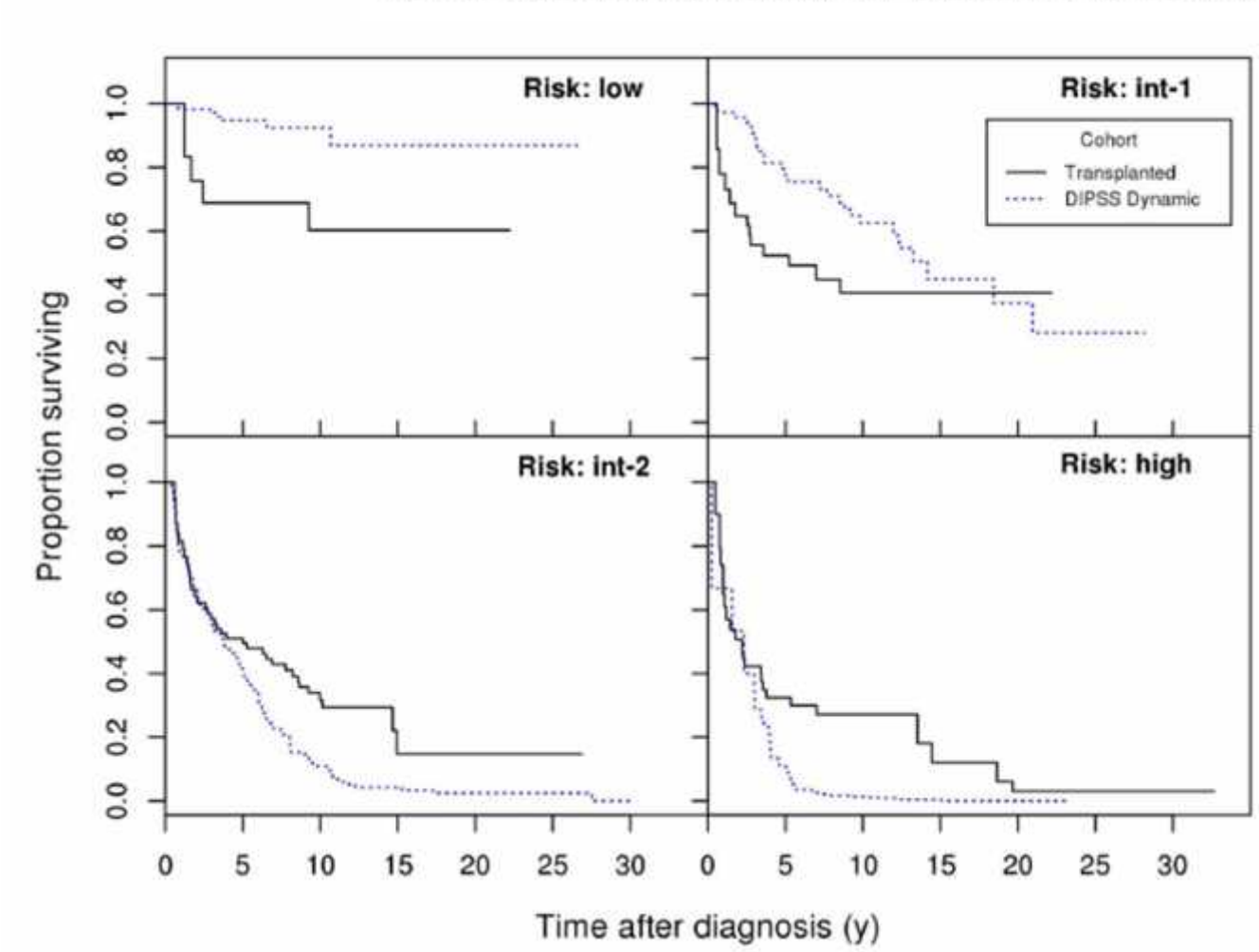
438 pazienti

188 trapiantati
255 non trapiantati

blood Prepublished online March 17, 2015

CONFRONTO TMO vs NO TMO

The net benefit of transplant versus non–transplant is marked in higher risk patients.



NO TMO

SI TMO

Figure 1: Survival probabilities for the four subgroups (DIPSS low, int-1, int-2, high). DIPSS score is taken at SCT (solid, transplant cohort) or at the indicated time (dotted, non-transplant cohort). Time (horizontal axis) elapses from diagnosis.

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OTTIMIZZARE I RISULTATI III

PARTECIPARE AL PROGRESSO SCIENTIFICO

Prospective , phase II randomized study to compare busulfan-fludarabine reduced-intensity conditioning (RIC) with thiotepa-fludarabine RIC regimen prior to allogeneic transplantation of hematopoietic cells for the treatment of myelofibrosis

Comitato scientifico:
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Alessandro Rambaldi
Alberto Bosi
Renato Fanin
Francesca Patriarca

Centro Coordinatore:
Clinica Ematologica di Udine

Promoter: GITMO
Ufficio sperimentazioni cliniche : Sonia Mammoliti
CRO: Mario Negri Sud

Inclusion criteria :

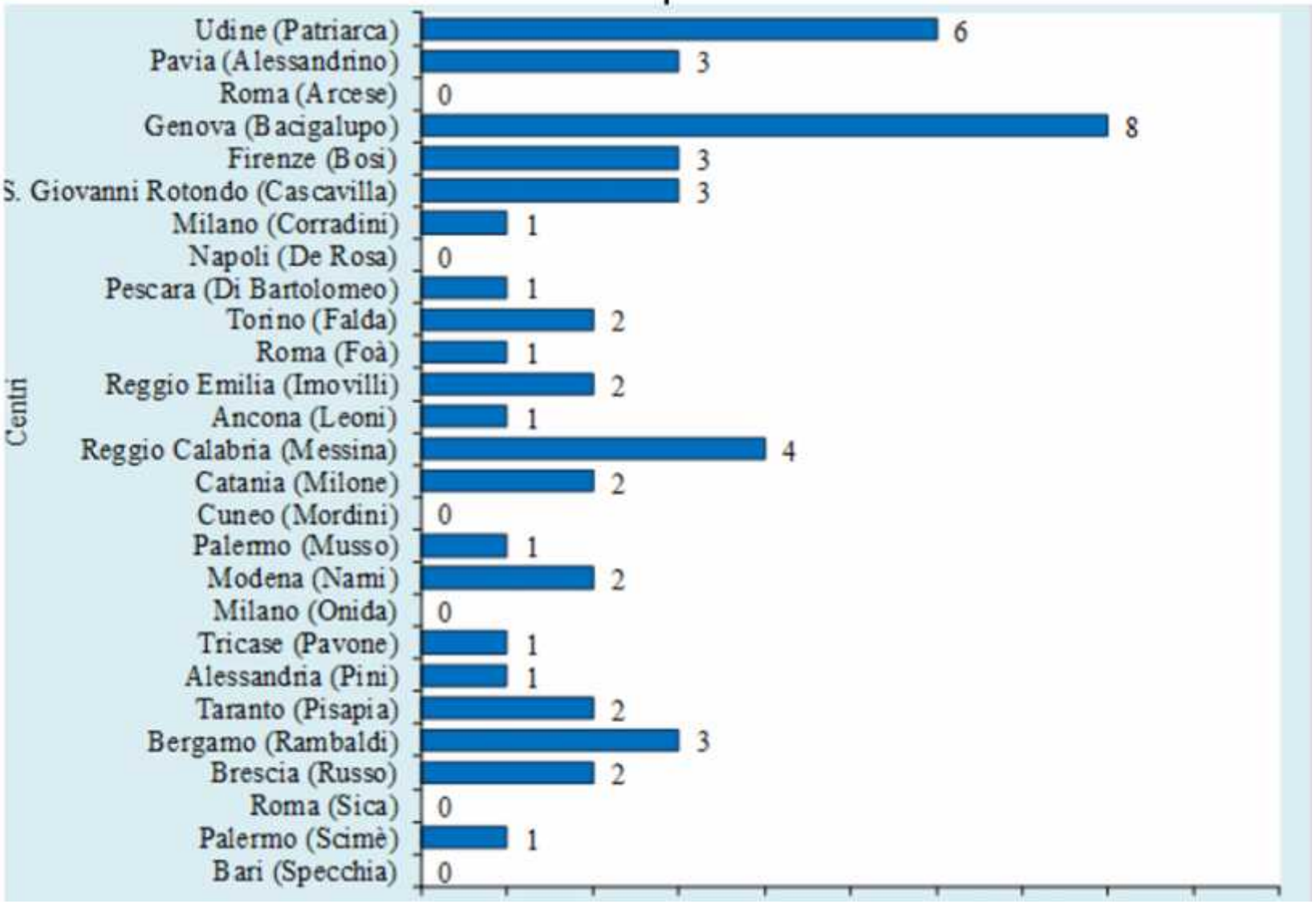
- Age ≥ 18 ≤ 70 years
- Primary or secondary myelofibrosis after essential thrombocytemia or polycyhemia vera
- One of the following unfavourable prognostic factors: Hb <10 g/dL or leucocytes > 25 x 10^9/L or > 1% circulating blasts or constitutional symptoms
- PS (Karnofsky)≥ 60%
- HCT-CI < 5
- HLA-identical sibling donor or
- HLA-identical unrelated donor by high resolution DNA-based HLA-A,-B,-C, DRB1 typing or one allele mismatched (class I) unrelated donor

Exclusion criteria:

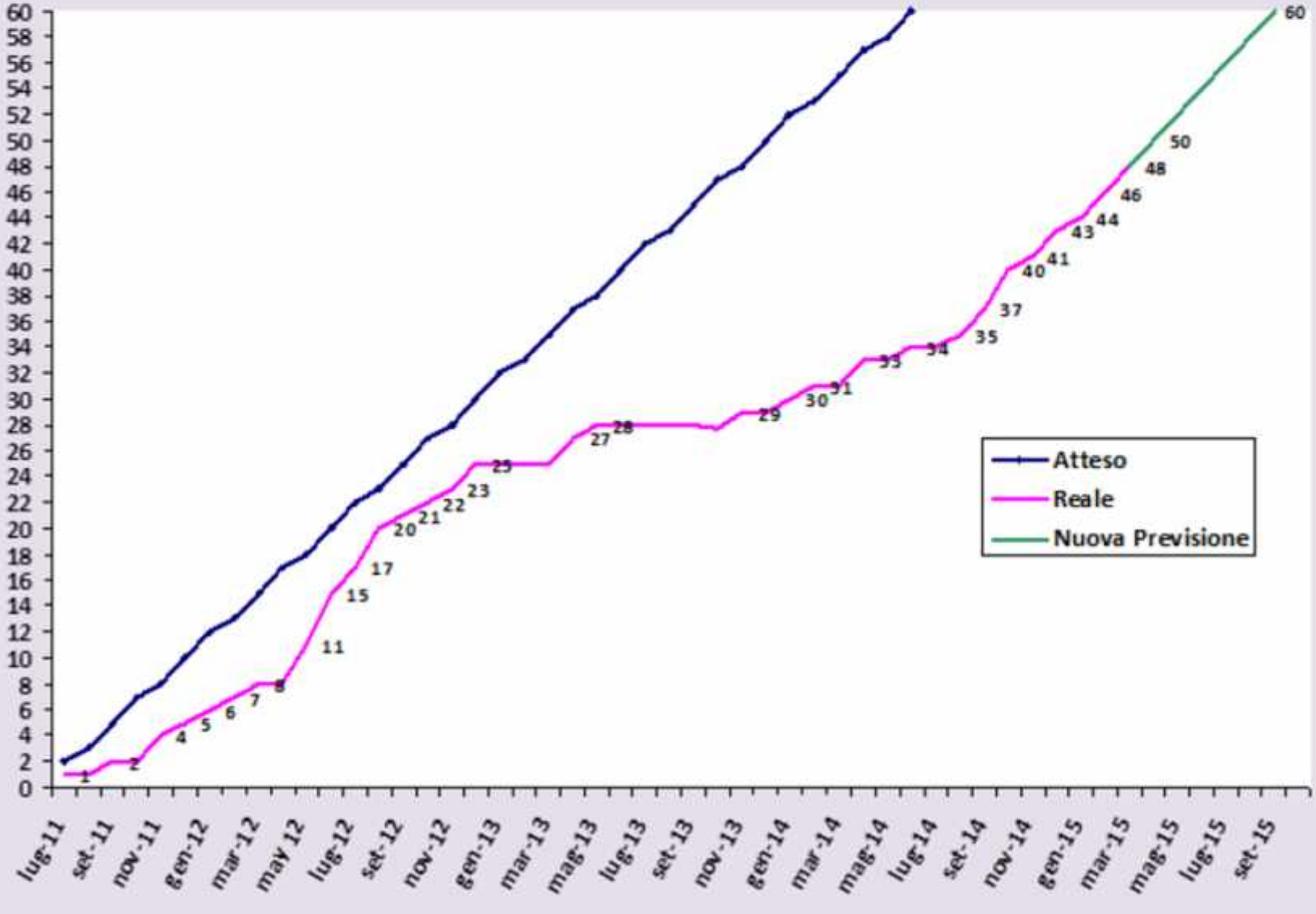
- ≥ 20% blasts in the peripheral blood and/or marrow
- Severe organ damage, active infections, pregnancy etc

GITMO MF2010

Pazienti arruolati: n. 50
Centri partecipanti: n. 27
Centri arruolanti: n. 21



Accrual Generale



- Non si osservano particolari sbilanciamenti nei due bracci

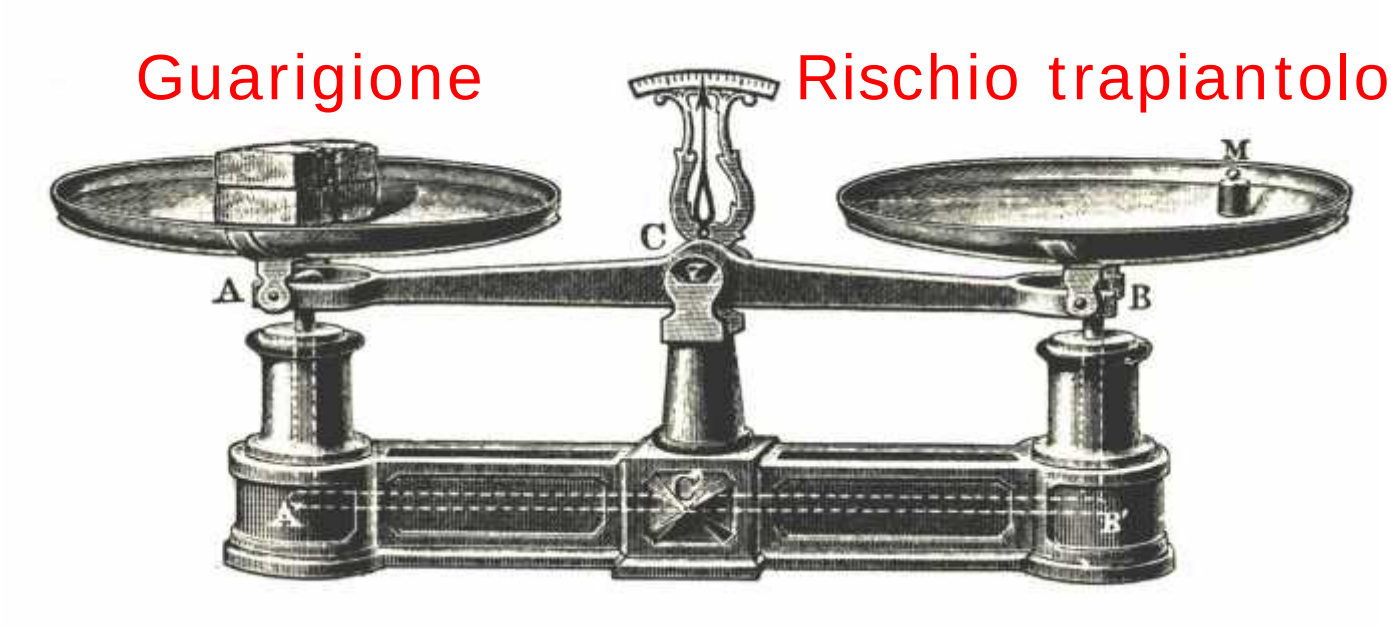
- La valutazione degli Eventi Avversi Severi non evidenzia tossicità inattese in relazione causale con la terapia sperimentale

CONCLUSIONI I

TRAPIANTO

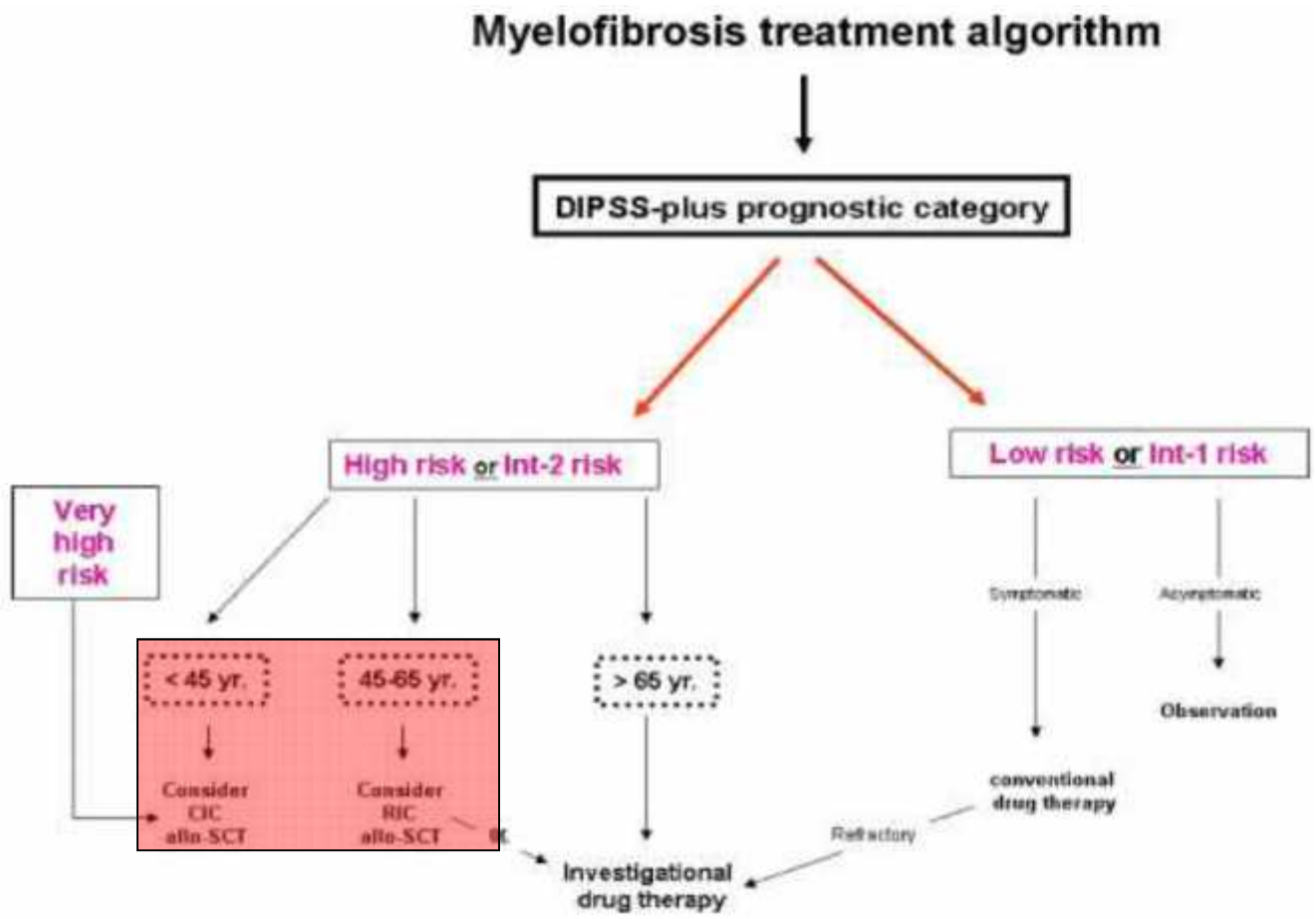
Guarigione

Rischio trapiantologico



- Pazienti a rischio di trasformazione leucemica
- Pazienti con attesa di vita significativamente ridotta

CONCLUSIONI II



2015

- HR e Int-2 età < 70 aa
- Int-1 < 65 aa se refrattari, citogenetica sf, bl >2% e dipendenza da trasfusioni

?

Ayalew Tefferi **Am. J. Hematol. 88:142–150, 2013.**

CONCLUSIONI III

Mielofibrosi: TRAPIANTO

- A chi ? Int 2 e Alto rischio < 70 aa
- Come ? studio GITMO MF 2010
- Quando? All'ingresso nella categoria di rischio
  e prima della perdita della indicazione


GRAZIE