Azienda Ospedaliero Universitaria Careggi

FONDAZIONE CAREGGI ONLUS

Settima
Giornata Fiorentina
dedicata ai pazienti con
malattie mieloproliferative
croniche

Sabato 13 Maggio 2017

CRIMM
Centro di Ricerca e Innovazione per le
Malattie Mieloproliferative
AOU Careggi

UNIVERSITÀ DEGLI STUDI FIRENZE

Programma Clinical Molecular Oncology
AGIMM
AIRC

Trapianto

Stefano Guidi

TMO
AOU Careggi
Firenze

Mielofibrosi: Storia naturale

Decorso da indolente ad aggressivo

MF primitiva 1 per 100.000 secondarie 0.1 per 100.000

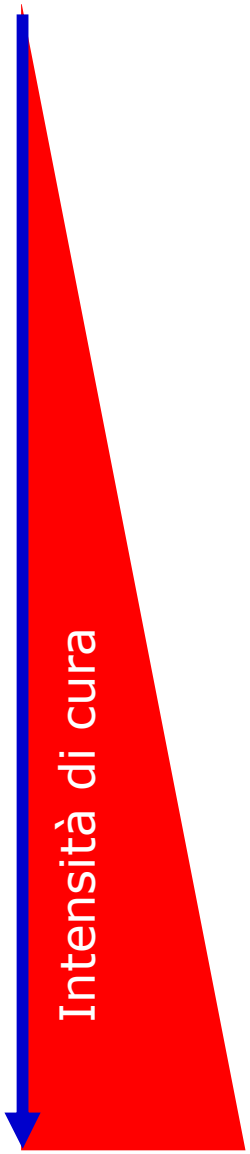
Il quadro è dominato dalla splenomegalia,dai sintomi sistemici, dalla insufficienza midollare con fibrosi, dalla iperplasia megacariocitaria o dalla leucocitosi

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 trasfusioni
  - 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 ……..)
- Inibitori delle Istondeacetilasi
- Trapianto allogenico di cellule emopoietiche



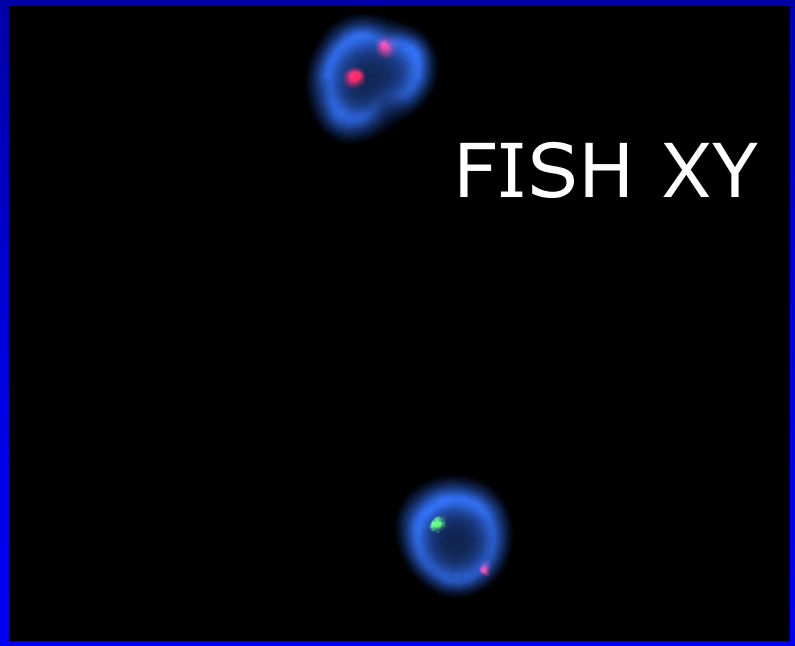
ASSENZA DI STUDI CONTROLLATI FRA TRAPIANTO E ALTRE TERAPIE

Mielofibrosi: Obbiettivi terapeutici

TRAPIANTO DI CELLULE EMOPOIETICHE
UNICA OPPORTUNITÀ DI
GUARIGIONE

SCOPO DEL TRAPIANTO

CHIMERA

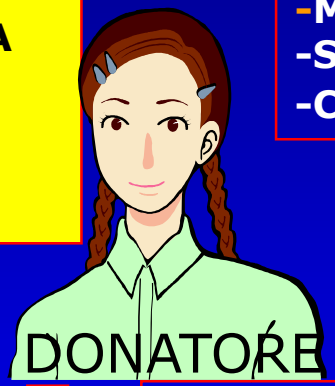


FISH XY

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**



DONATORE

APLASIA

CHIMERA

PAZIENTE

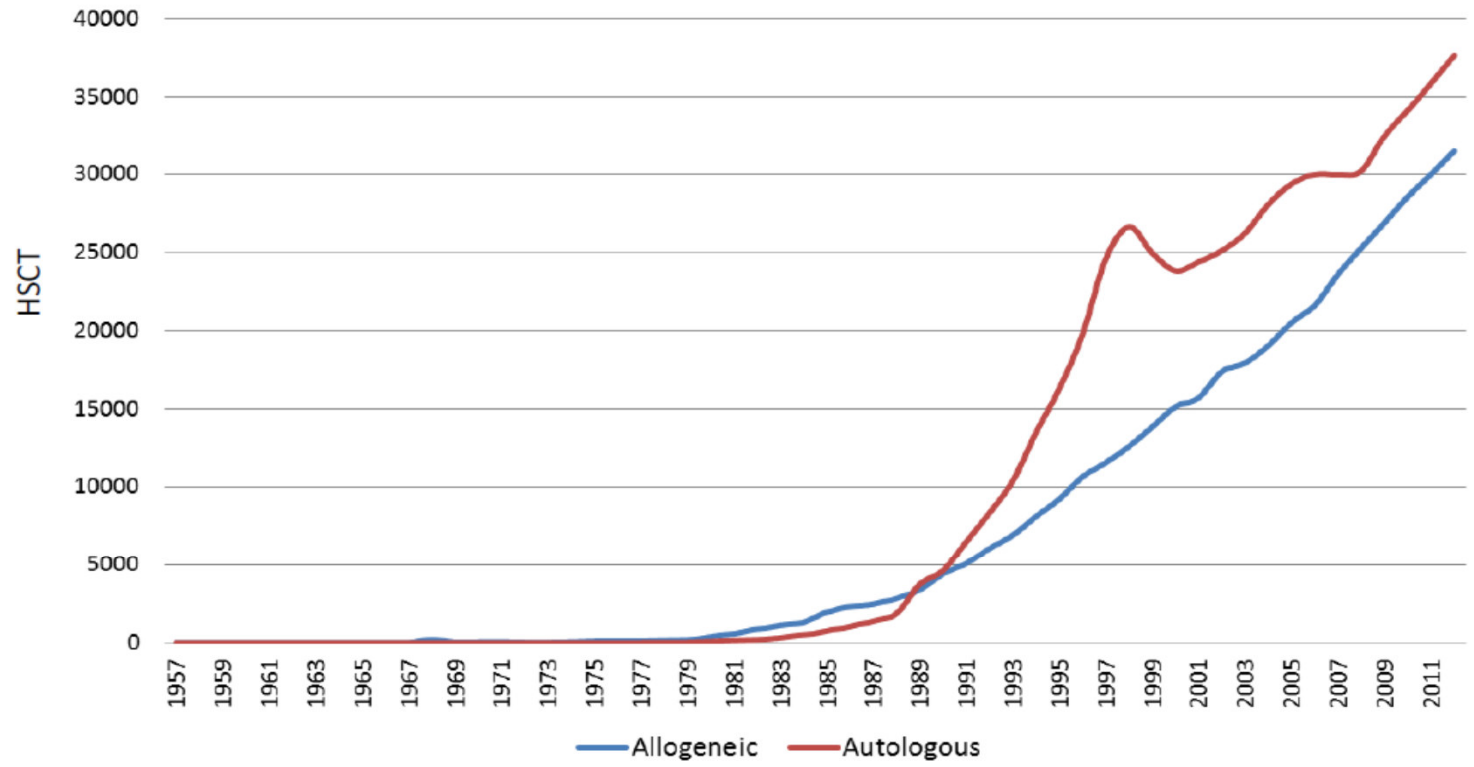
TERAPIA IMMUNOSOPPRESSIVA

DLI

>1.000.000 trapianti effettuati 12/2012

Global Transplant Numbers:

Allogeneic and autologous

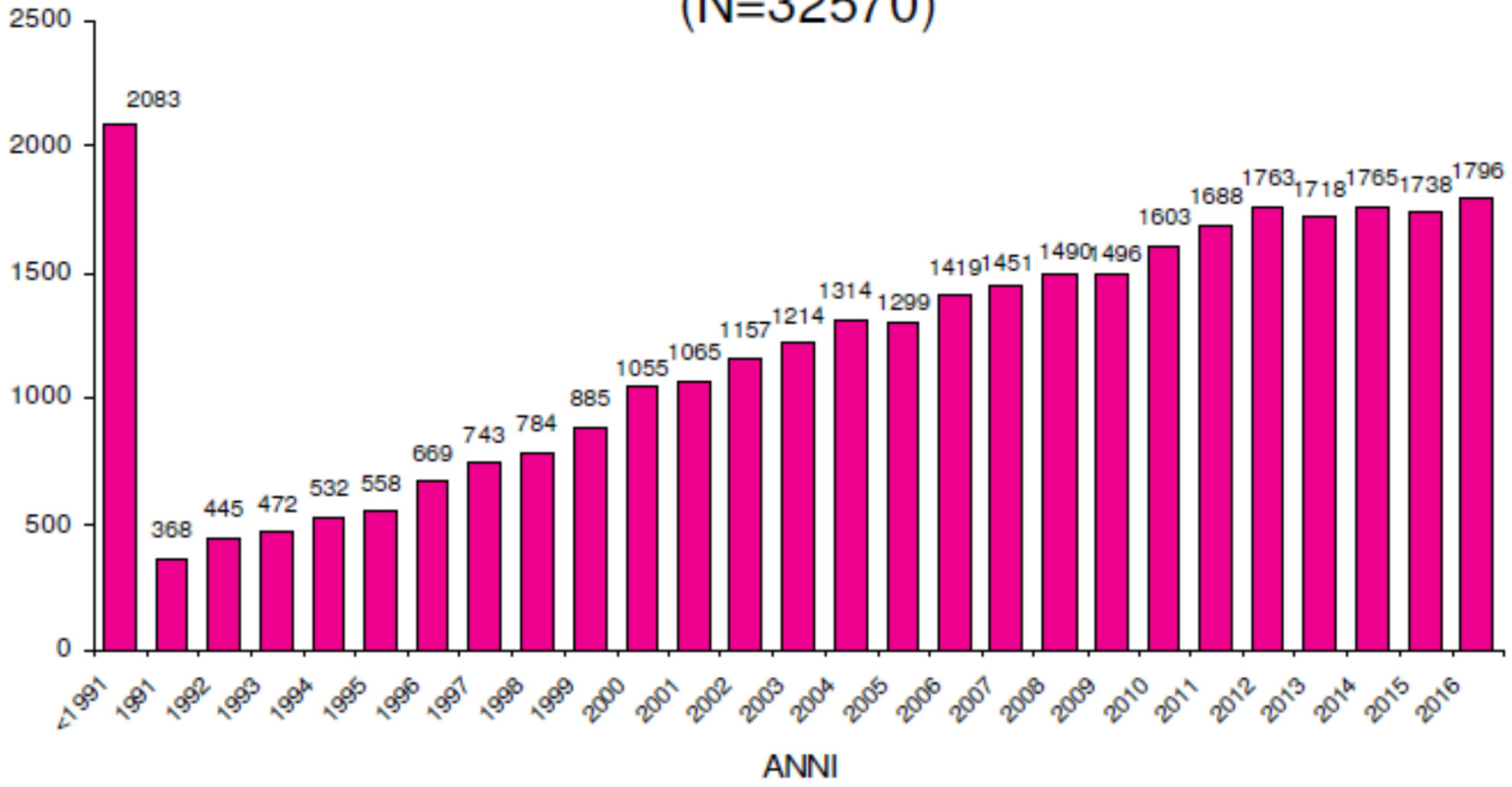


preliminary data

Worldwide Network for Blood and Marrow Transplantation
NGO in official relations with World Health Organization

GITMO Trapianto Allogenico

Allotrapianti registrati
(N=32570)



al 22 marzo 2017

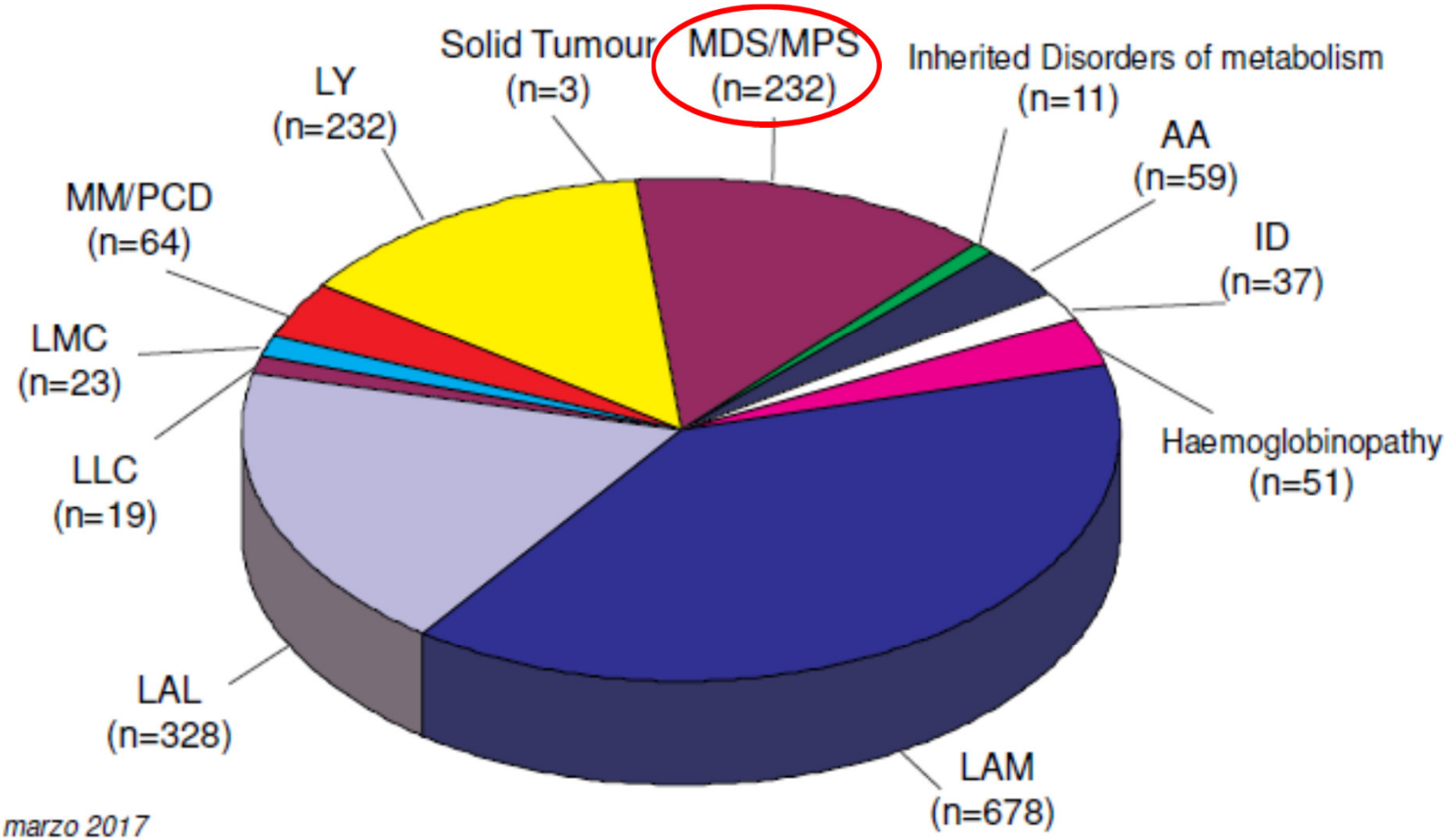
GITMO

GITMO Trapianto Allogenico

Numero Trapianti per principali Patologie

Attività 2016

MF2010= circa 10-15per anno



al 22 marzo 2017

GITMO

Perché così pochi trapianti nella mielofibrosi ?

Il trapianto ha un costo biologico elevato!

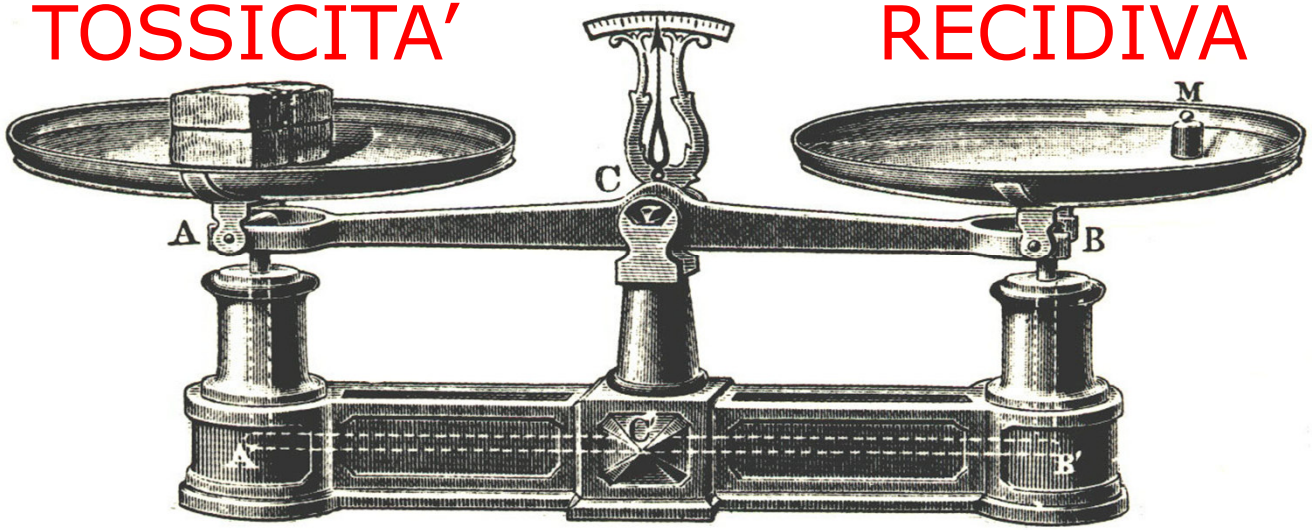
GUARIGIONE

- Età
- Malattie associate

- Fase avanzata
- Malattia refrattaria
- Trasformazione bl

SCO, aploidentico, volontario non familiare, fratello id

TOSSICITA’ RECIDIVA



LA SORGENTE DI CELLULE INFLUENZA L’ ESITO DEL TRAPIANTO

Rischio Trapiantologico Score Europeo

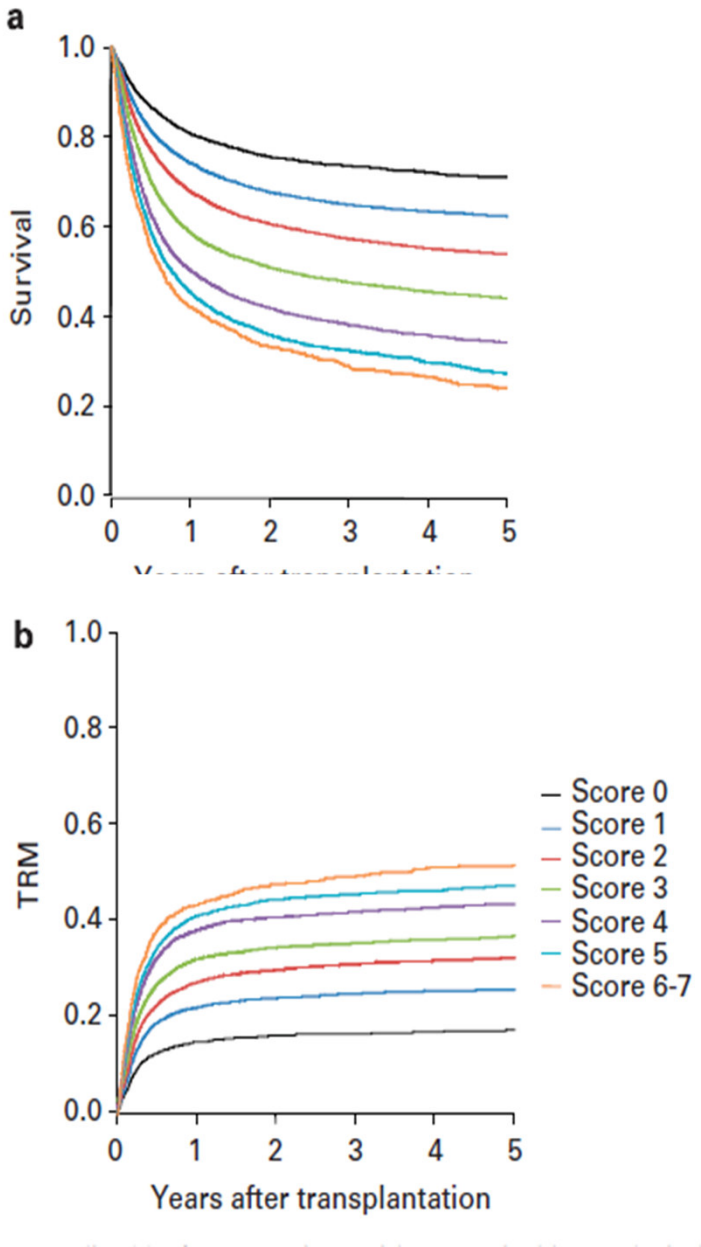
The EBMT risk score

A Gratwohl

Table 1 EBMT risk score definition

Risk factor	*Score points*
Age of the patient, years	
<20	0
20–40	1
>40	2
Disease stage[a]	
Early	0
Intermediate	1
Late	2
Time interval from diagnosis to transplant, months[b]	
<12	0
>12	1
Donor type[c]	
HLA-identical sibling donor	0
Unrelated donor, other	1
Donor recipient sex combination[c]	
All other	0
Female donor, male recipient	1

Bone Marrow Transplantation (2011),



Indice di comorbidità

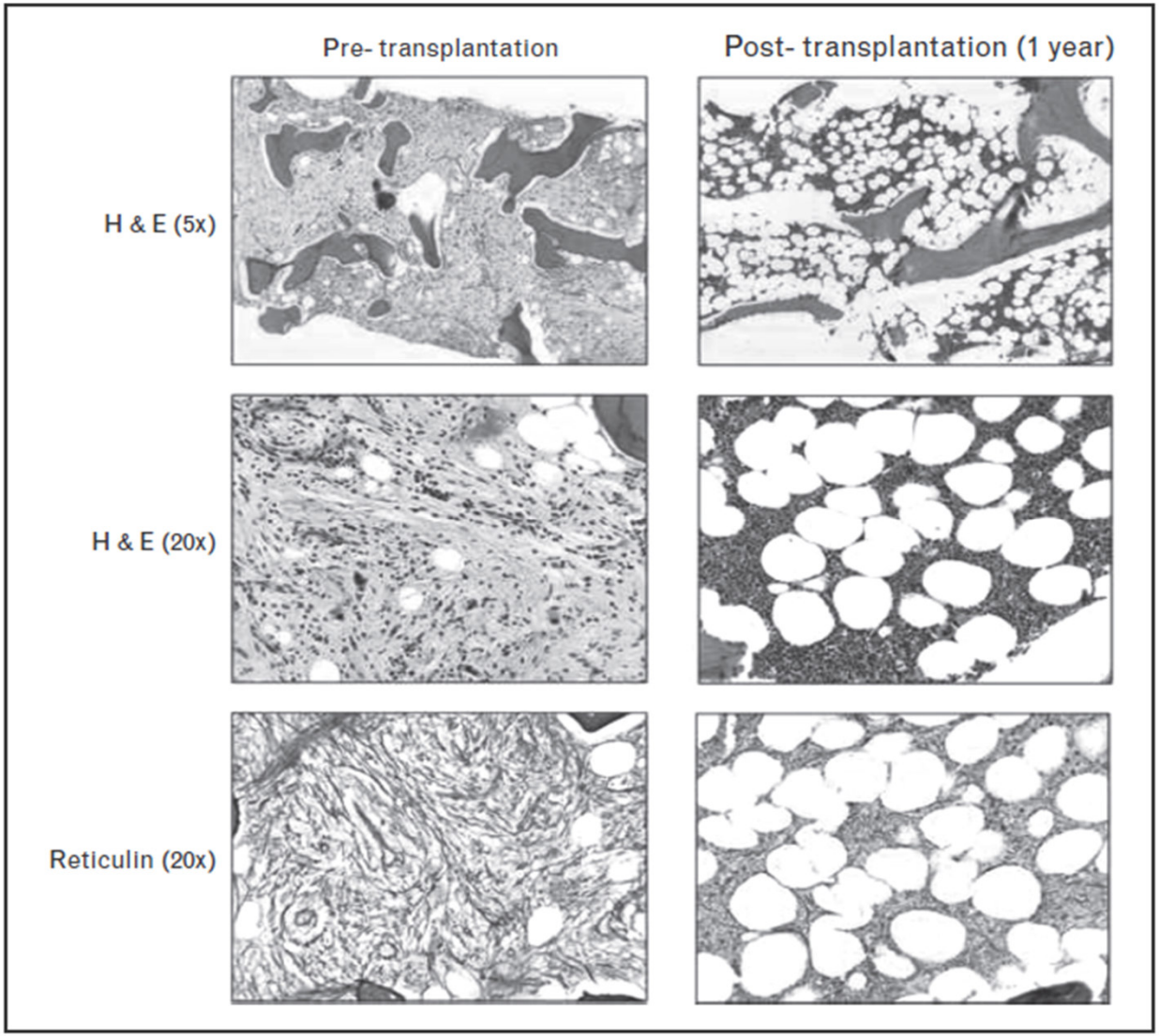
Hematopoietic cell transplantation (HCT)–specific comorbidity index: a new tool for risk assessment before allogeneic HCT

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

BLOOD, 15 OCTOBER 2005 • VOLUME 106, NUMBER 8

Normalizzazione del midollo

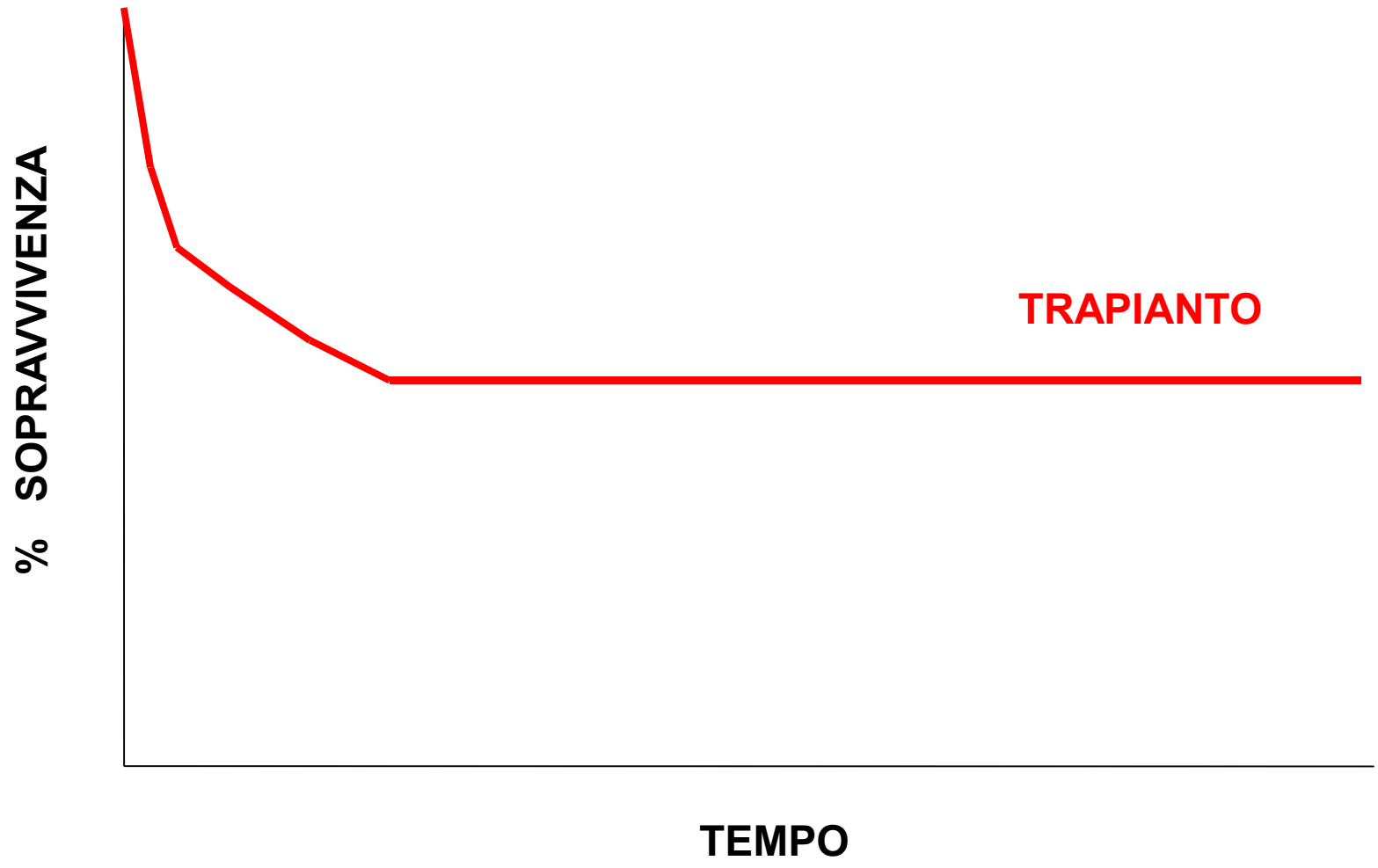


Allogeneic transplantation for myelofibrosis Babushok and Hexner **Curr Opin Hematol** 2014, 21:114–122

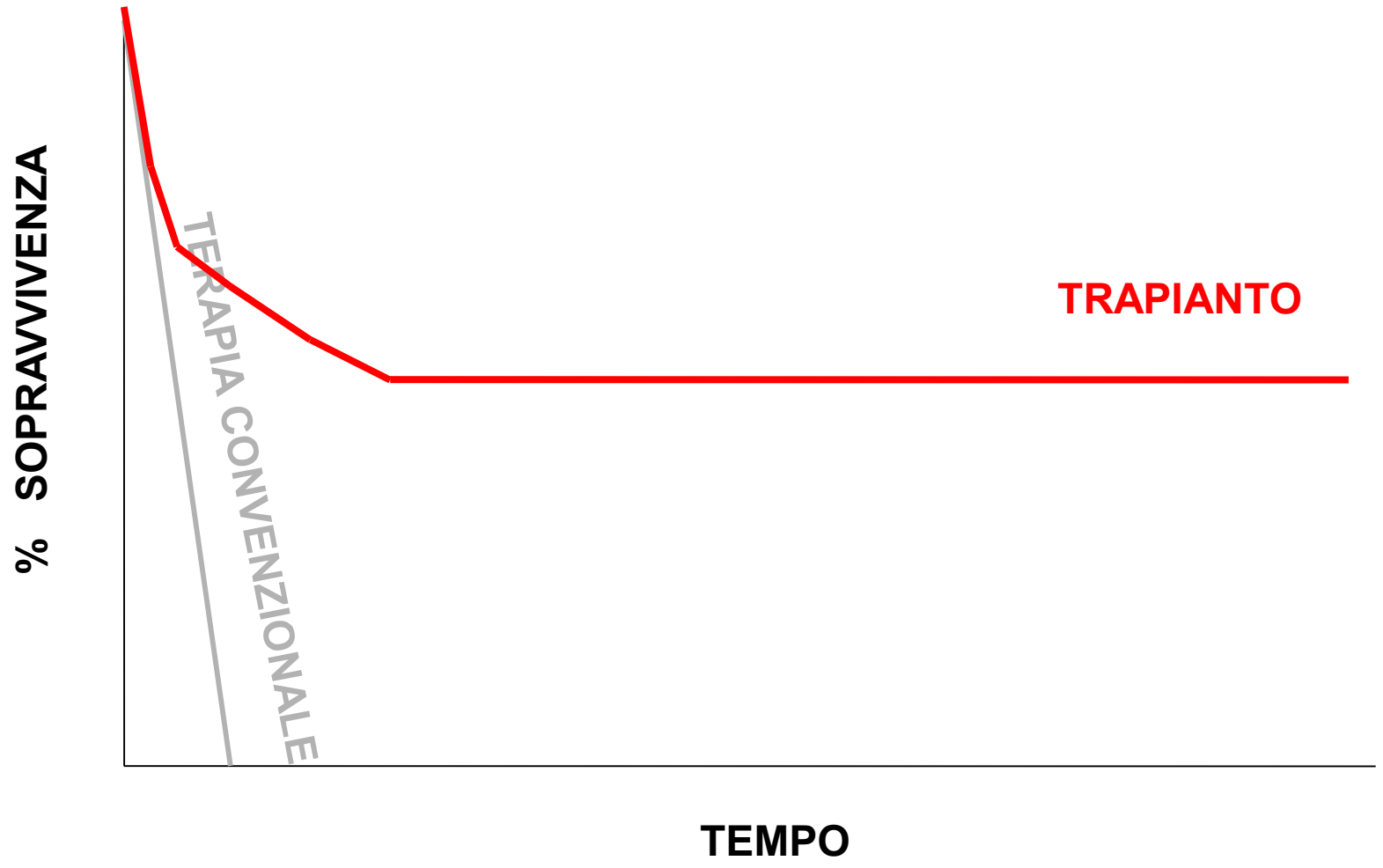
OTTIMIZZARE I RISULTATI I

IDENTIFICARE IL MOMENTO MIGLIORE PER IL TRAPIANTO

IL DILEMMA DEL TRAPIANTO



IL DILEMMA DEL TRAPIANTO



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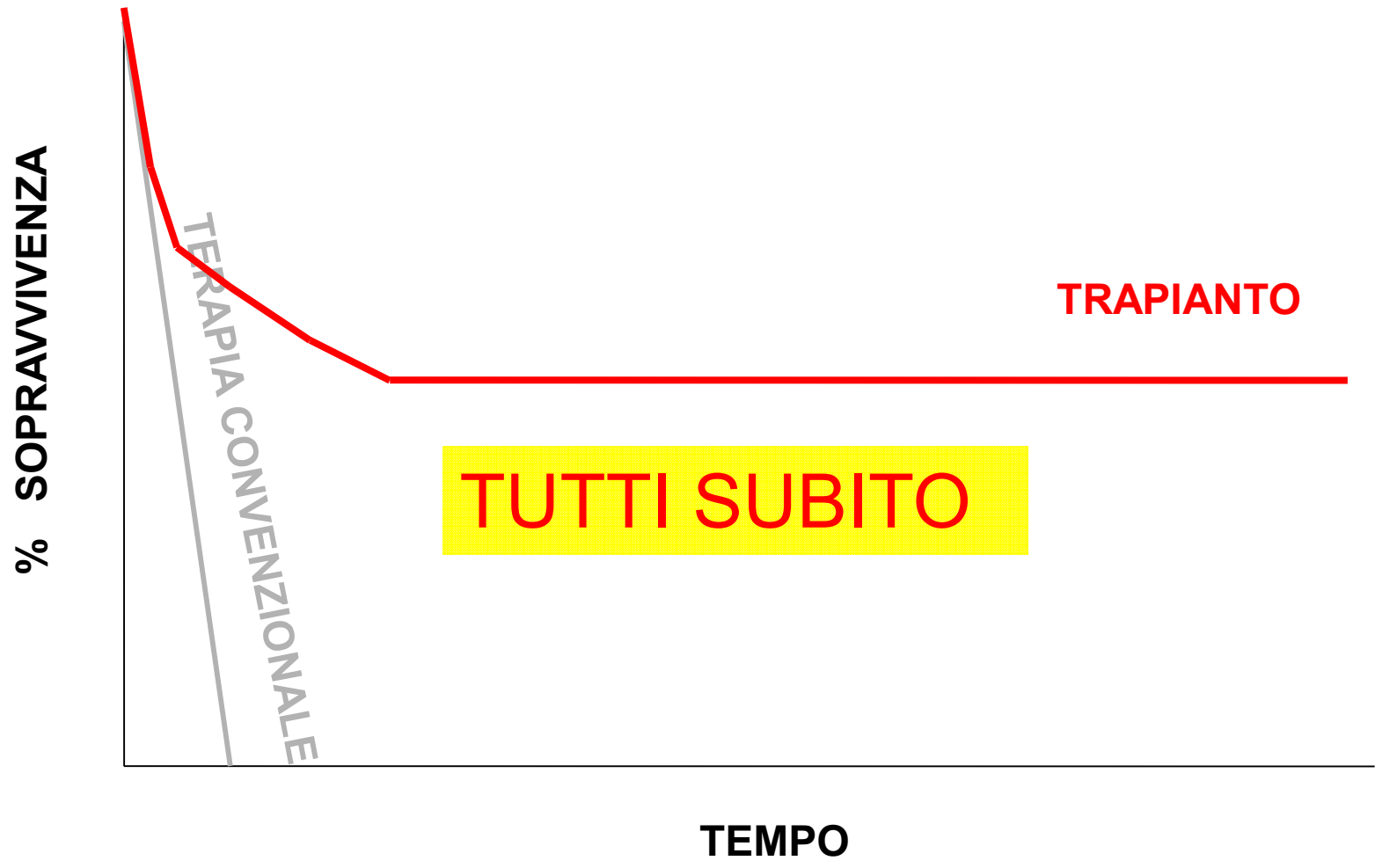

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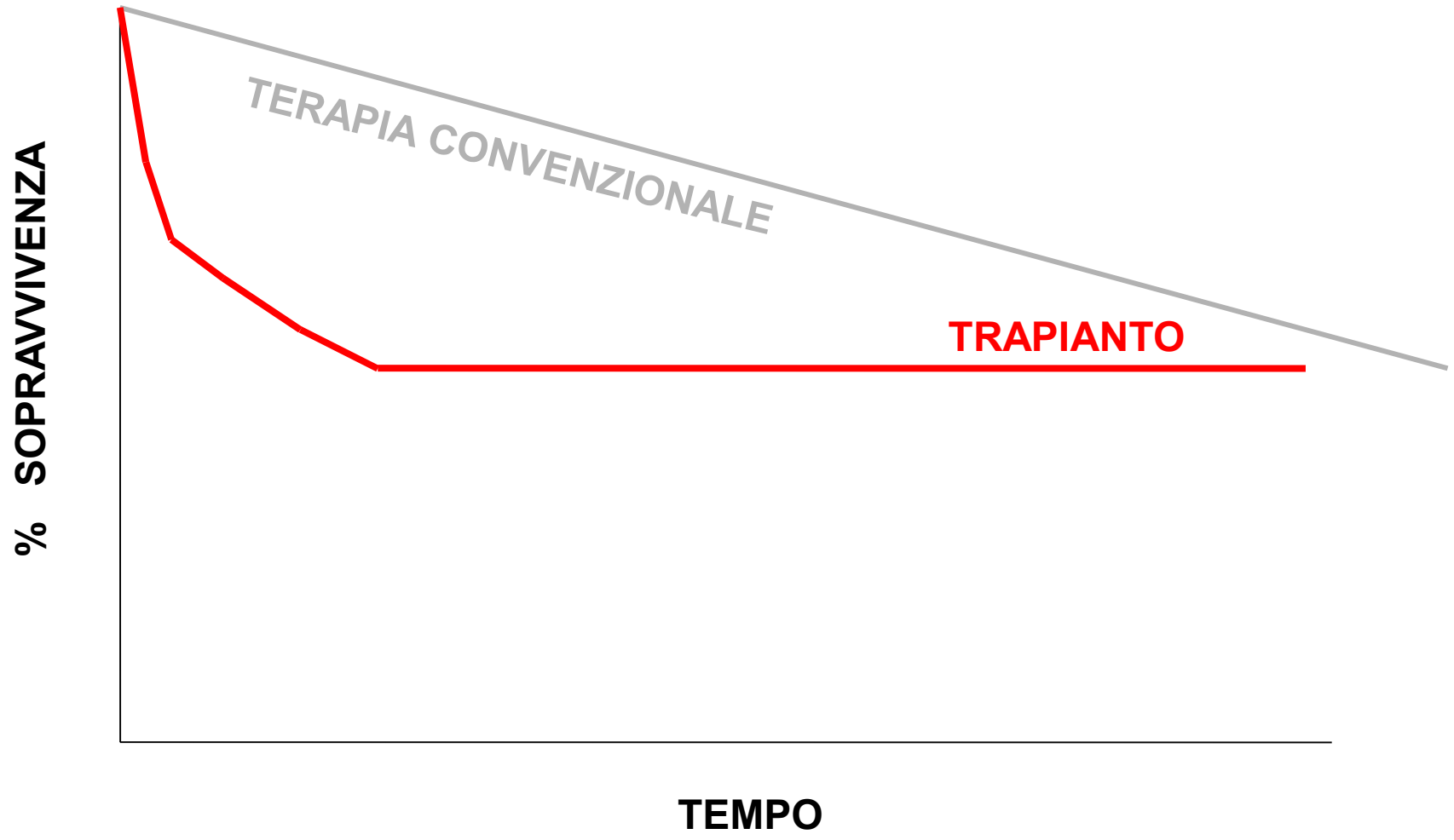

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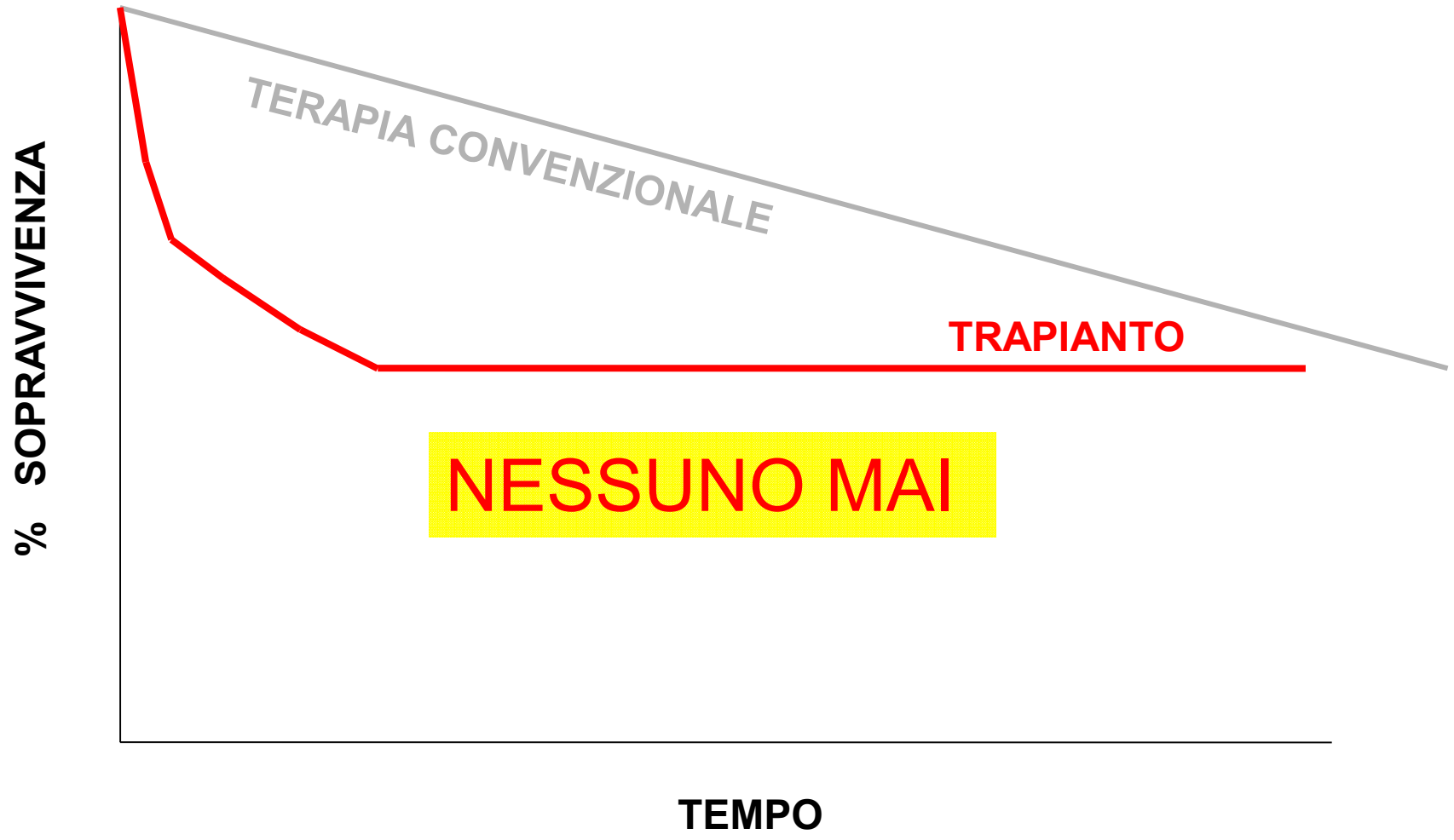
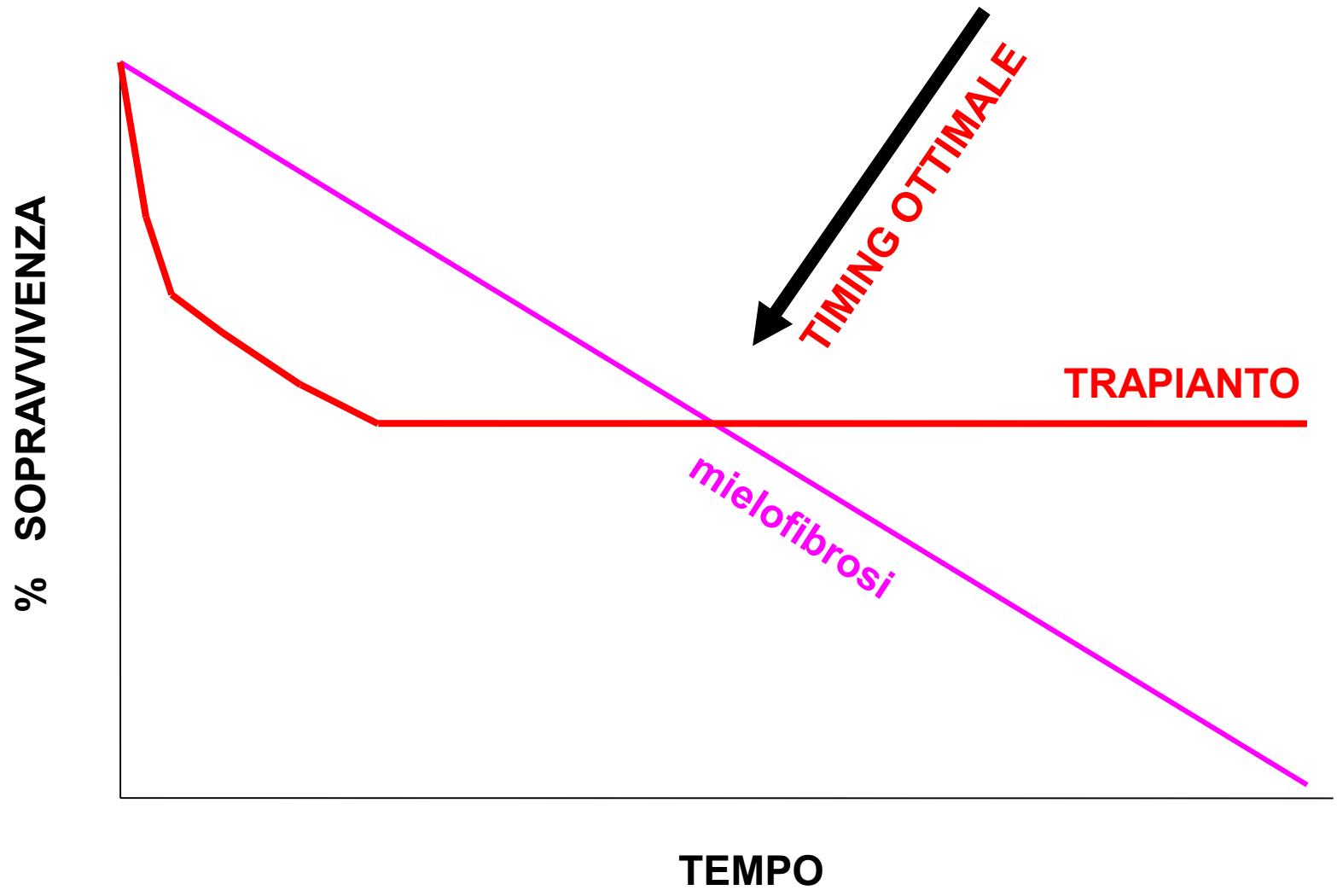


NESSUNO MAI

IL DILEMMA DEL TRAPIANTO



OTTIMIZZARE I RISULTATI II

QUALI PAZIENTI TRAPIANTARE

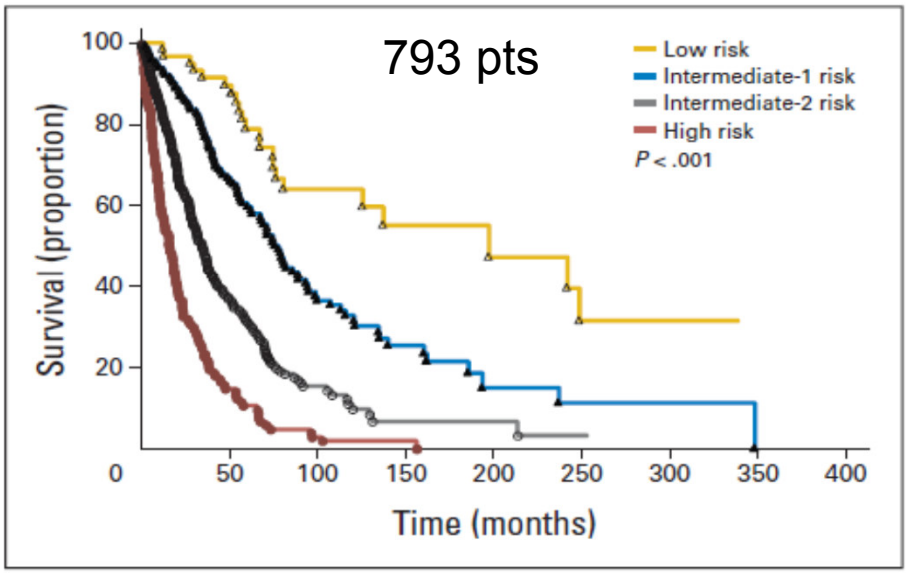
ATTESA DI VITA RIDOTTA < 5 aa

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

VOLUME 29 · NUMBER 4 · FEBRUARY 1 2011

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

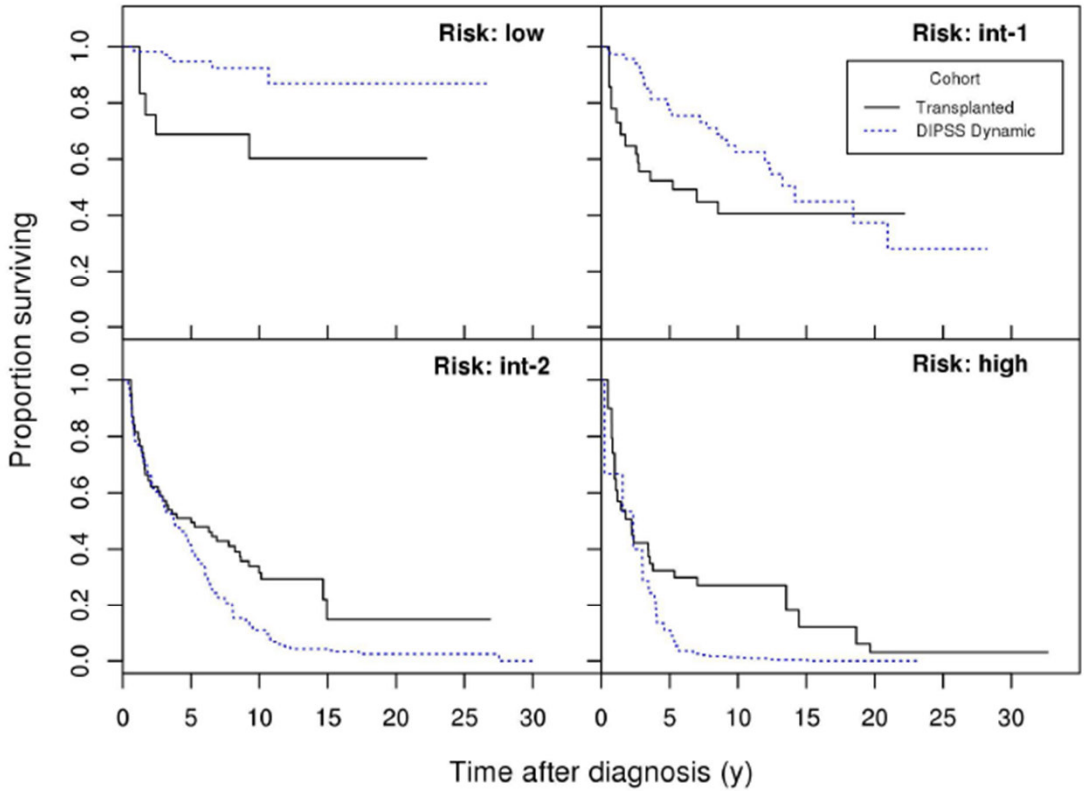
Clinical feature	Points
DIPSS-low	0
DIPSS-Int-1	1
DIPSS-Int-2	2
DIPSS-high	3
PLUS	
Unfavourable karyotype[2]	1
Transfusion dependence	1
Platelet < 100 000/µl	1

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

CONFRONTO Trapianto/non Trapianto

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



NO TMO 190 pts

SI TMO 248 pts

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.

blood Prepublished online March 17, 2015

OTTIMIZZARE I RISULTATI III

PARTECIPARE AL PROGRESSO SCIENTIFICO

Studio prospettico randomizzato di confronto fra regime di condizionamento a ridotta intensità (RIC) busulfan-fludarabine con thiotepa-fludarabina per trapianto allogenico di cellule staminali emopoietiche nella terapia della mielofibrosi

Comitato scientifico:
Andrea Bacigalupo
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

GITMO MF2010

Criteri di inclusione :

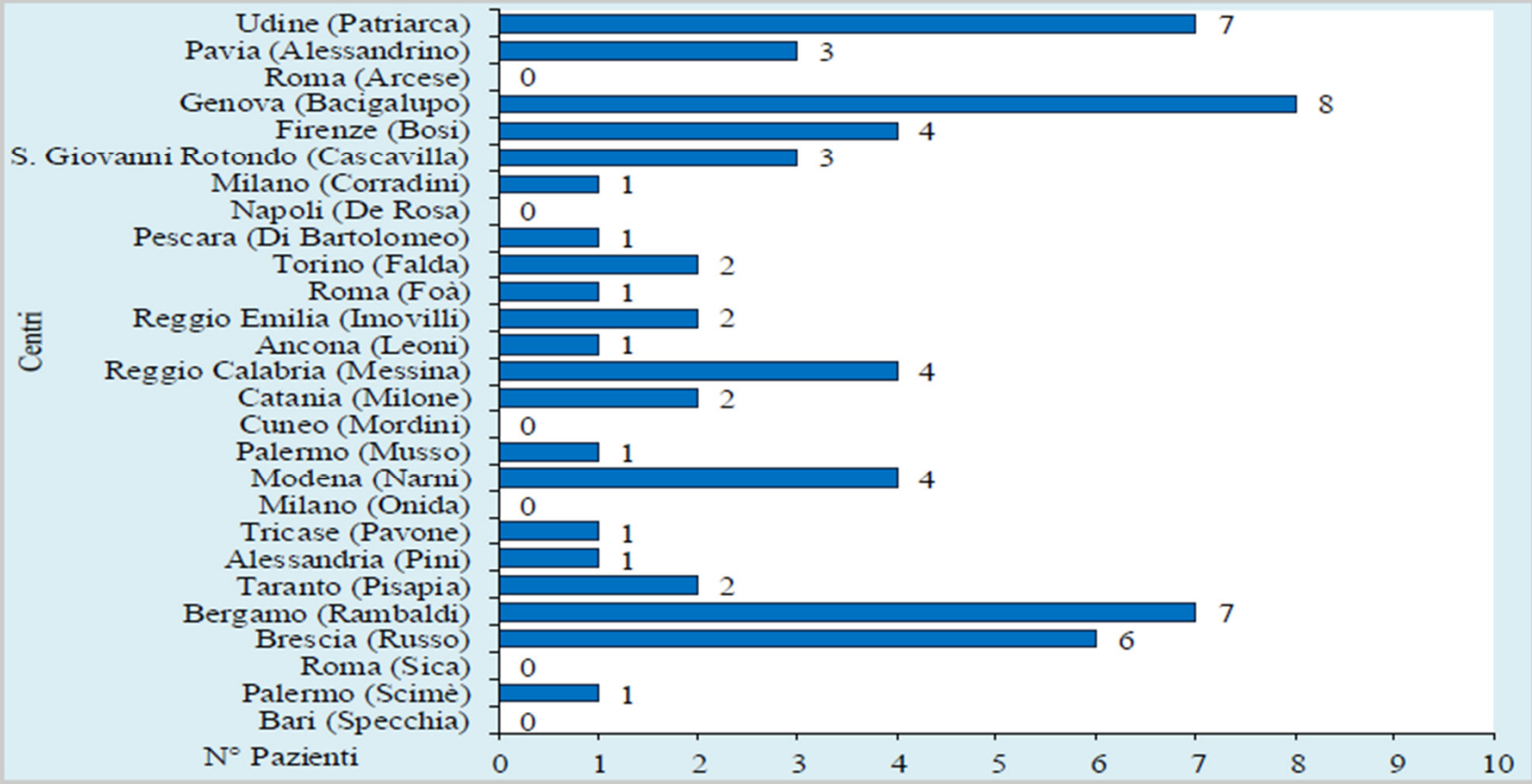
- Malattia con fattori prognostici sfavorevoli
- Disponibilità di un donatore almeno 7/8
- Indice di comorbidità < a 5
- Buon performance status

Criteri di esclusione

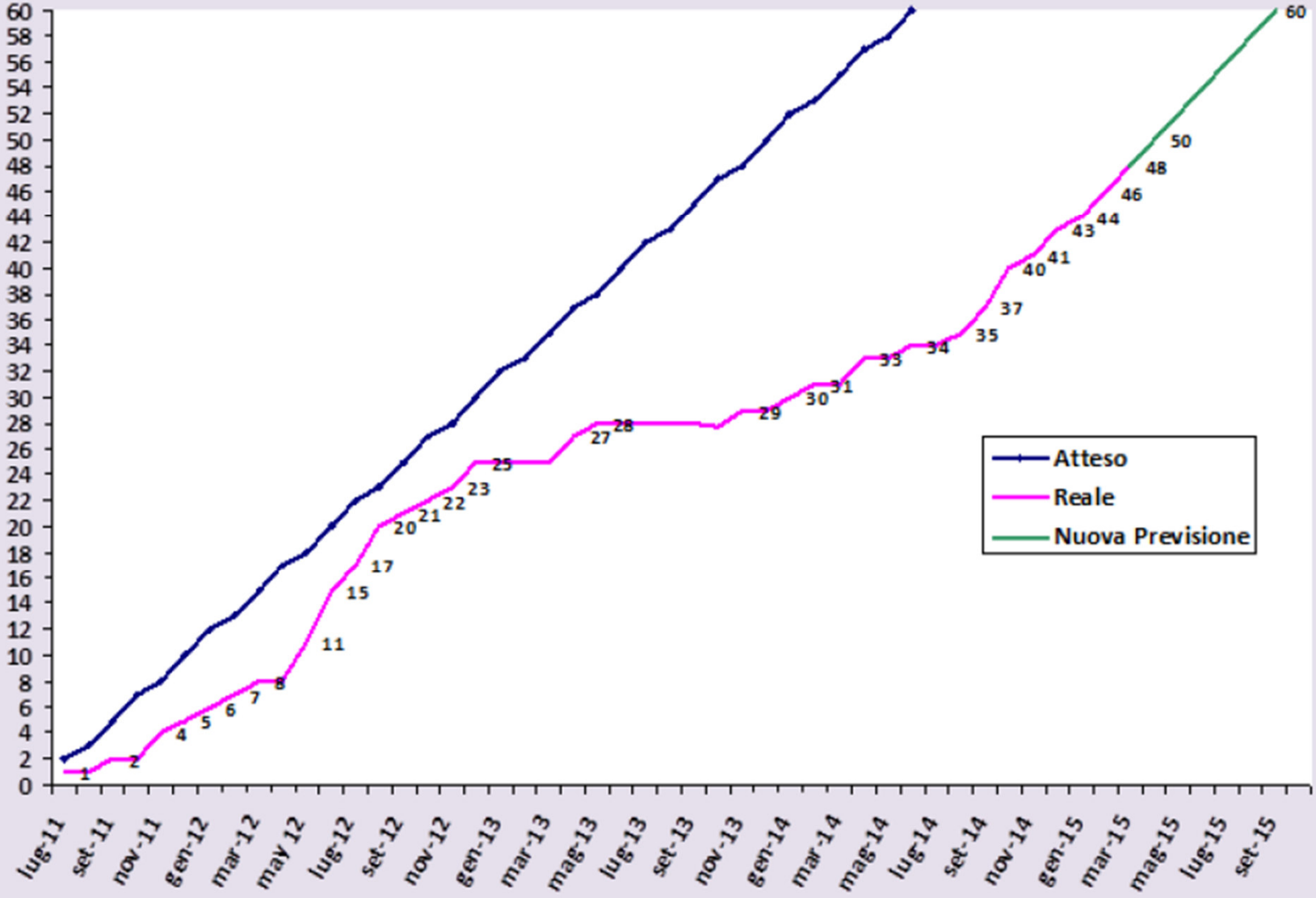
- Blasti > 20%
- Danno d' organo severo/infezione etc

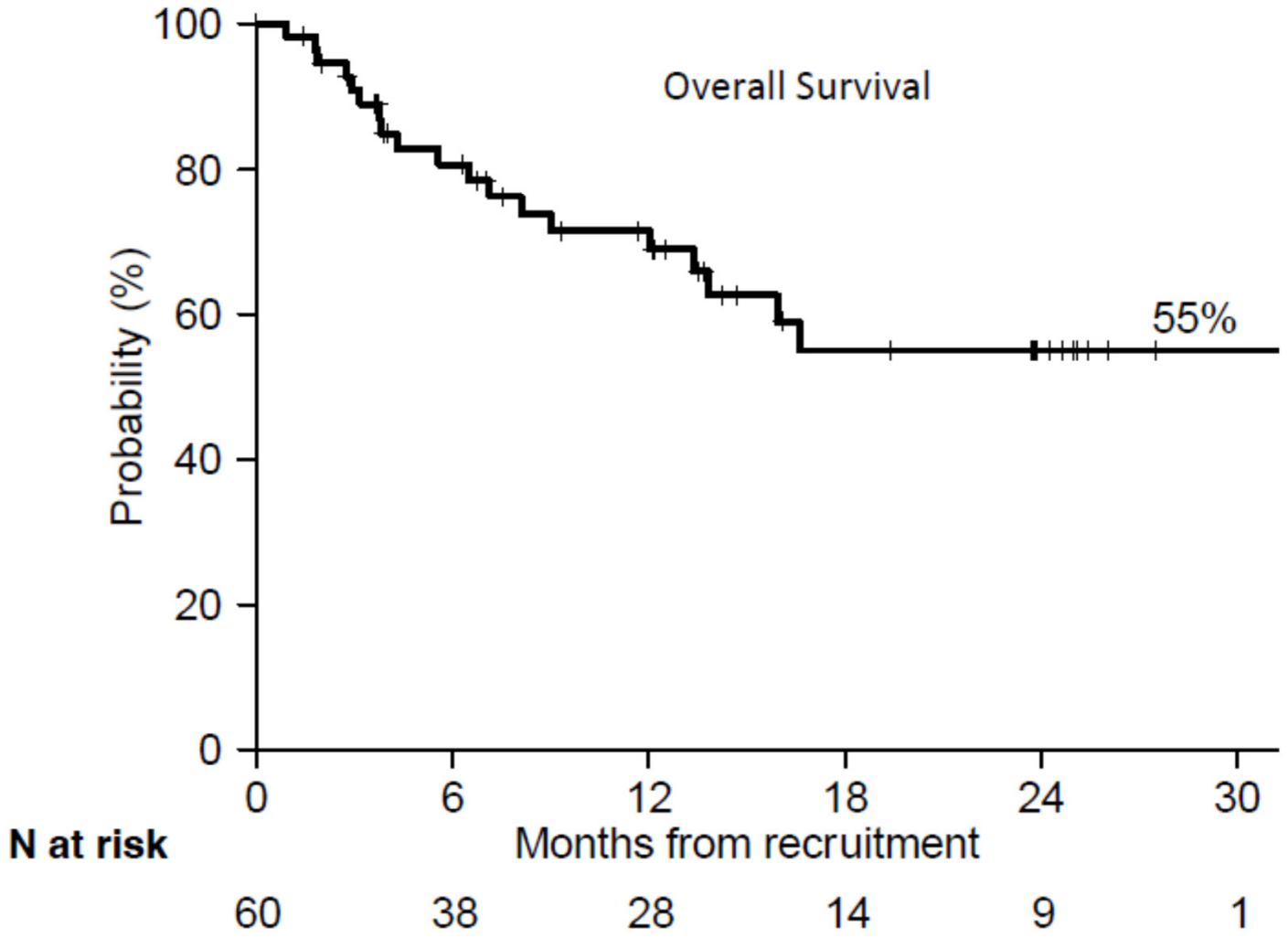
GITMO MF2010

Pazienti arruolati: n. 62
Centri partecipanti: n. 27
Centri arruolanti: n. 21



Accrual Generale




Overall Survival
Probability (%)
100
80
60
40
20
0
55%
0
6
12
18
24
30
Months from recruitment
N at risk
60
38
28
14
9
1

GITMO MF2010

Risultati preliminari per pazienti giunti a 12 mesi postrapianto

- NRM tipo donatore Fratello id 24% vs MUD 31%

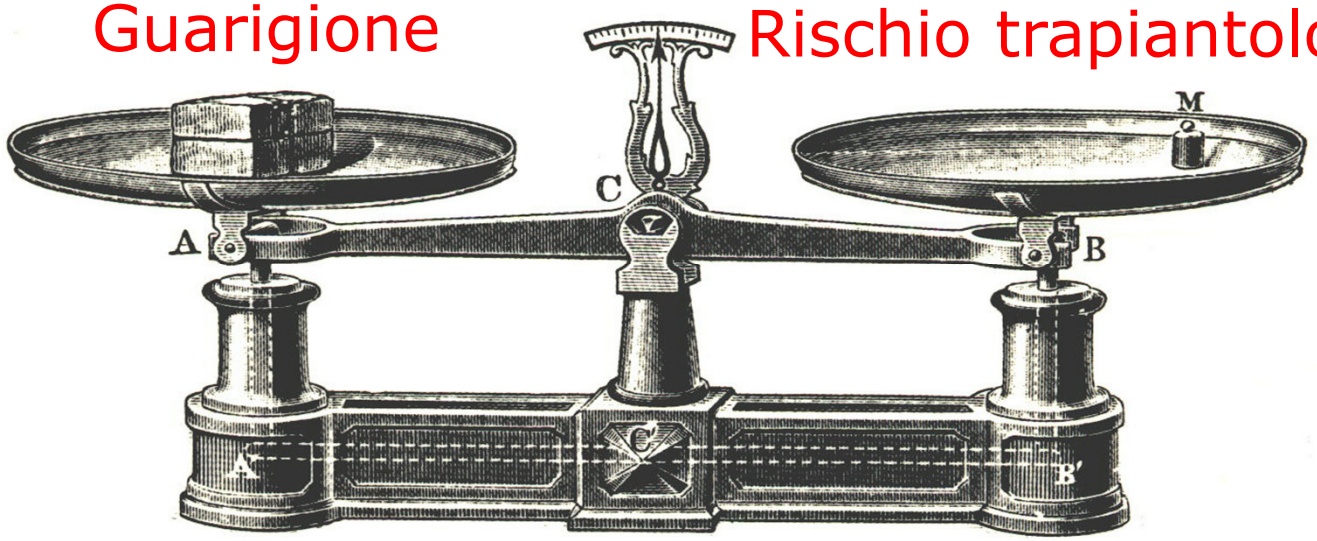
	TTFLU	BUFLU
• Tossicità NRM	21 %	27%
• aGvHD	24 %	40%
• Soprav. no malattia 12m	69 %	48%
• Inefficacia	21 %	38%
• Sopravvivenza generale	80 %	61%

CONCLUSIONI I

IL TRAPIANTO IMPATTA SULLA QUALITA' DI VITA

Guarigione

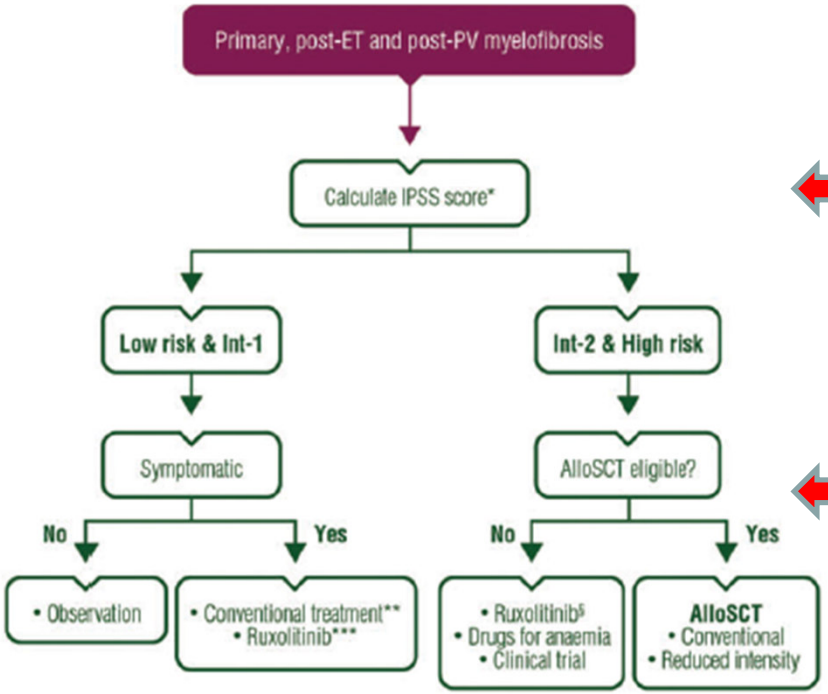
Rischio trapiantologico



- Pazienti a rischio di trasformazione leucemica
- Pazienti con attesa di vita significativamente ridotta
- Pazienti in condizioni di tollerare il Trapianto di CSE

CONCLUSIONI II

PRIORITA'



1) Calcolare il rischio IPSS

2) Valutare l'idoneità TMO

3) Identificazione donatore

Linee guida Europee 2015

Indication and management of allogeneic stem cell transplantation in primary myelofibrosis: a consensus process by an EBMT/ELN international working group

NM Kröger[1], JH Deeg[2], E Olavarria[3], D Niederwieser[4], A Bacigalupo[5], T Barbui[6], A Rambaldi[7], R Mesa[8], A Tefferi[9], M Griesshammer[10], V Gupta[11], C Harrison[12], H Alchalby[1], AM Vannucchi[13], F Cervantes[14], M Robin[15], M Ditschkowski[16], V Fauble[17], D McLornan[12,18], K Ballen[19], UR Popat[20], F Passamonti[21], D Rondelli[22] and G Barosi[23]

- Tutti i pazienti a intermedio-2 o alto rischio IPSS, DIPSS or DIPSS+, sono candidabili a un trapianto da donatore se idonei.

- Pazienti a rischio intermedio -1 max 65 anni se presentano:
  - anemia refrattaria trasfusioni dipendente
  - blastosi periferica < 2%
  - citogenetica sfavorevole

- Pazienti a basso rischio non sono candidabili a trapianto allogenico

Leukemia (2015),

2017

Emerging treatments for classical myeloproliferative neoplasms

Alessandro M. Vannucchi[1] and Claire N. Harrison[2]

Table 1. Recommendations on selection and preparation measures for patients with MF referred to HSCT, as developed by the European Leukemia Net/International Working Group–Myeloproliferative Neoplasms Research and Treatment panel

Recommended	Indicated*	Not recommended
Patient selection		
Patients with intermediate-2-risk or high-risk disease according to IPSS, DIPSS, or DIPSS-plus, and age <70 y	Patients with intermediate-1-risk disease and age <65 y if they present with either refractory, transfusion-dependent anemia or more than 2% blasts in peripheral blood or adverse cytogenetics	Patients with low-risk disease
	Patients with intermediate-1-risk disease if they are triple negative, ASXL1 positive, or both	Patients in blast transformation
	Patients in blast transformation after achieving a partial or complete remission of leukemia with debulking therapy	
Pretransplant management		
Iron chelation therapy in severely iron overloaded patients only	Ruxolitinib treatment of patients with a symptomatic spleen and/or constitutional symptoms	Splenic irradiation–splenectomy (case-by-case decision)

*Not a strong recommendation, but case-by-case approach.

Indicazioni nuove : Pazienti a richio intermedio -1 che siano tripli negativi (JAK,CALR,MPL) e/o ASXL1 positivi ma valutandoli caso per caso .

Controindicazioni: trasformazione blastica e basso rischio

CONCLUSIONI III

- A chi ? Int 2 e Alto rischio < 70 aa in buone condizioni, <2015
  Int 1 < 65aa, trasfusioni, BI < 2%, citogentica sf. 2015
  tripli negativi (JAK,CARL,MPL) e/o ASXL1 mutati 2017

- Come ? Condizionamento : studio GITMO MF2010
  Tipo Donatore: Fratello HLA id/MUD 8/8/Aploidentico

- Quando? All'ingresso nella categoria di rischio
  Prima della perdita della indicazione

Indication and management of allogeneic stem cell transplantation in primary myelofibrosis: a consensus process by an EBMT/ELN international working group

NM Kröger[1], JH Deeg[2], E Olavarria[3], D Niederwieser[4], A Bacigalupo[5], T Barbui[6], A Rambaldi[7], R Mesa[8], A Tefferi[9], M Griesshammer[10], V Gupta[11], C Harrison[12], H Alchalby[1], AM Vannucchi[13], F Cervantes[14], M Robin[15], M Ditschkowski[16], V Fauble[17], D McLornan[12,18], K Ballen[19], UR Popat[20], F Passamonti[21], D Rondelli[22] and G Barosi[23]

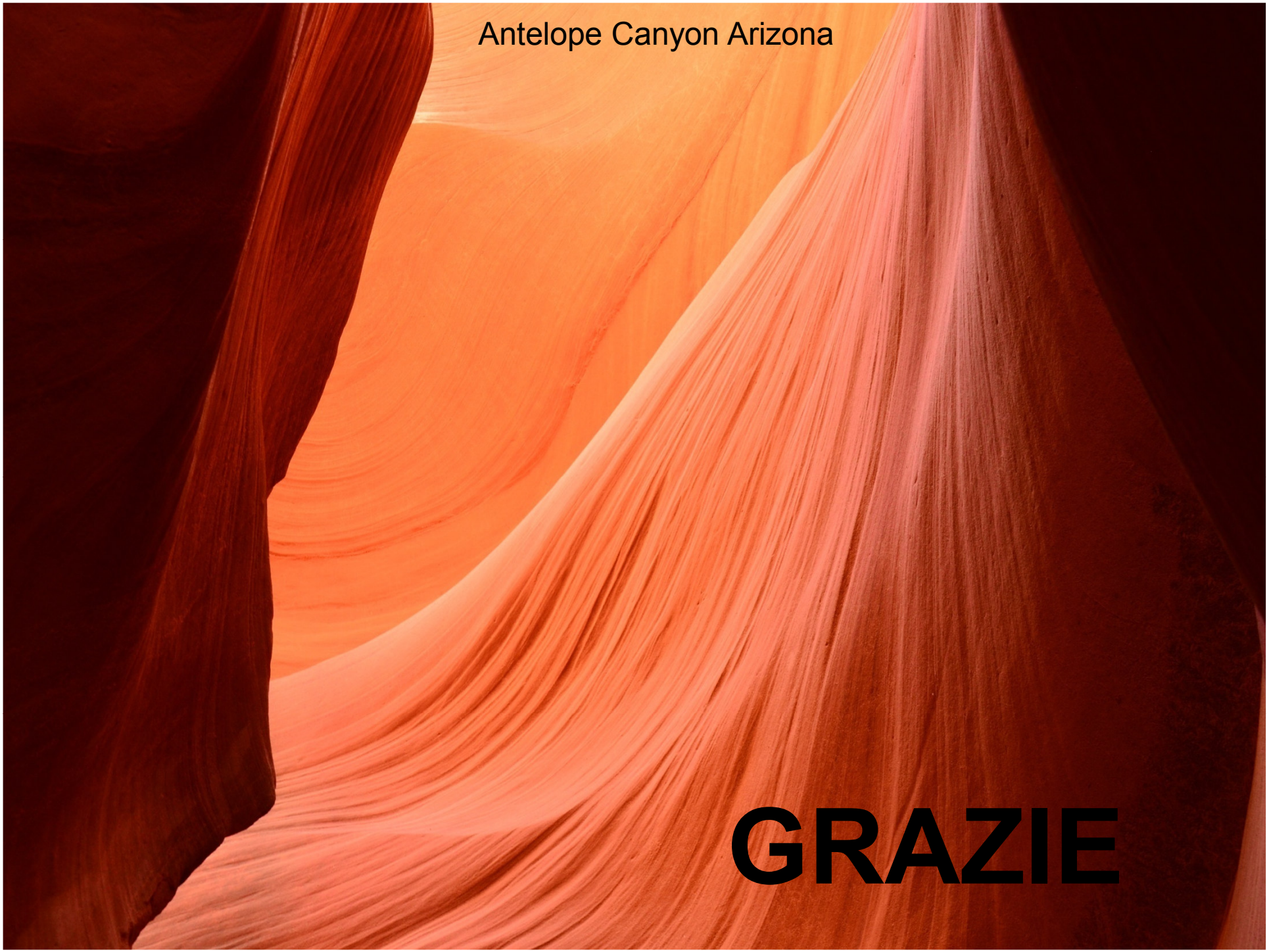
Leukemia (2015),

Annals of Oncology Vannucchi et al. Volume 26 | Supplement 5 | September 2015

Emerging treatments for classical myeloproliferative neoplasms

Alessandro M. Vannucchi[1] and Claire N. Harrison[2]

BLOOD, 9 FEBRUARY 2017 • VOLUME 129, NUMBER 6


Antelope Canyon Arizona
GRAZIE