Trapianto di cellule staminali emopoietiche 2022

E terapia cellulare

Andrea Bacigalupo

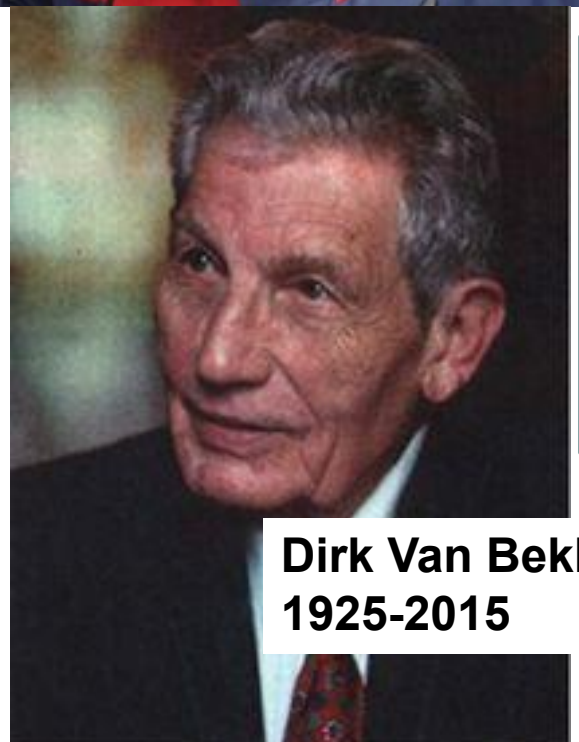
Istituto di Ematologia, Fondazione Policlinico Universitario A. Gemelli
Universita' Cattolica del Sacro Cuore
Roma

Jan van Rood
1926- 2017

HLA
BMDW
W

Don Metcalf
1929- 2014

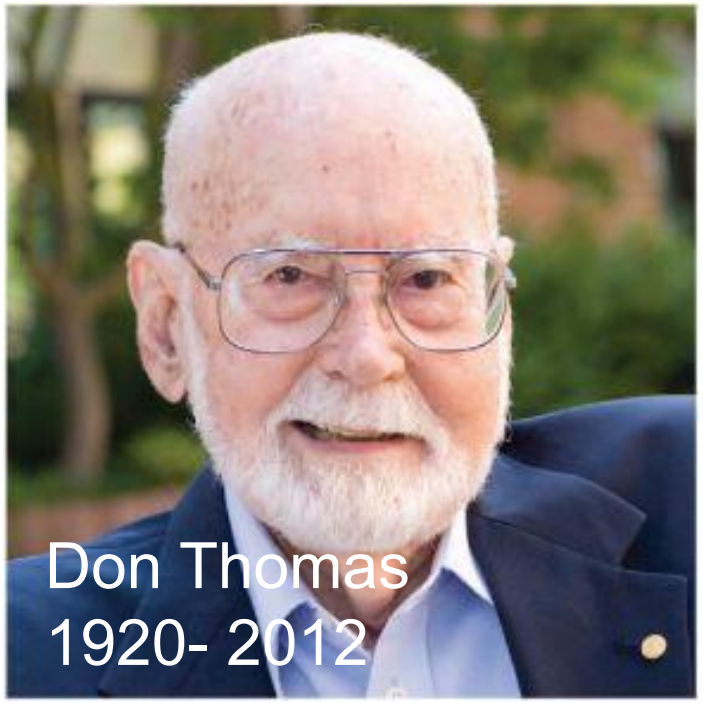
G-CSF
GM-CSF
M-CSF
EPO



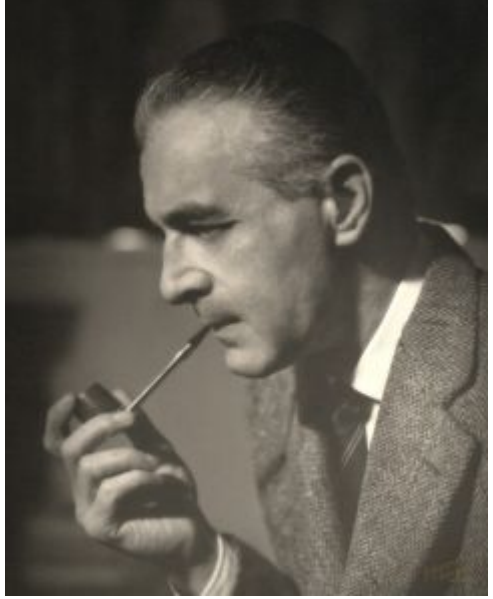
Dirk Van Bekkum
1925-2015

Mouse
mod
GvHD

Dog model
BMT
humans

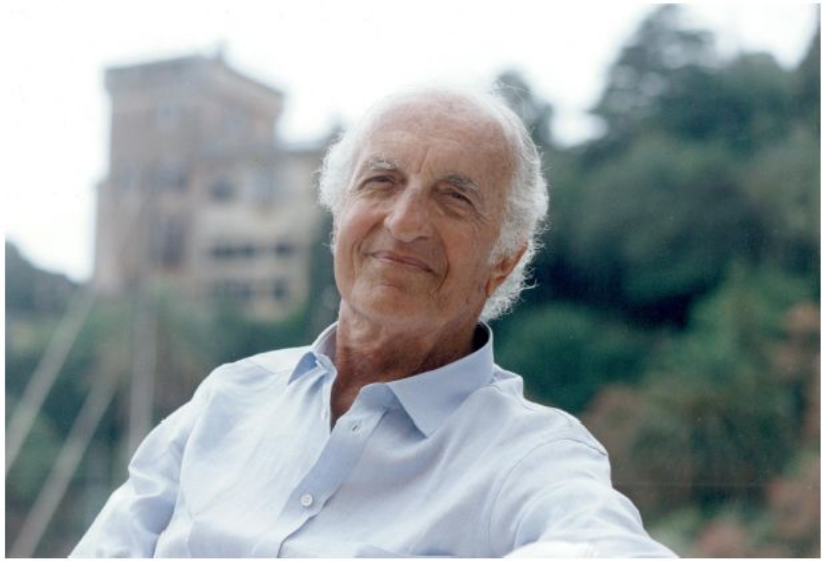


Don Thomas
1920- 2012



Ruggero Ceppellini : **HLA**

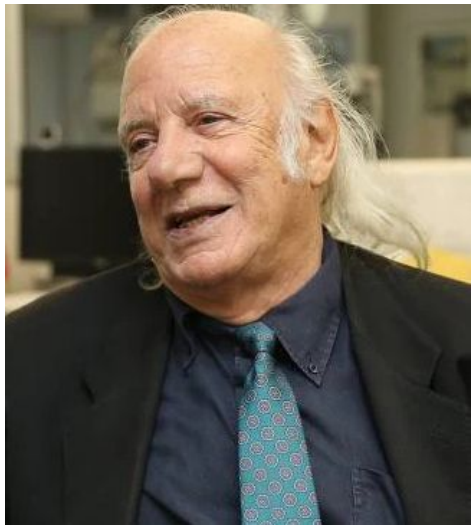
Alberto Marmont: **allogeneic HSCT**
Auto SCT in Autoimmune dis



Massimo Gianni : **mobil autol CD34+**

Massimo Martelli: **Haplo HSCT**

Guido Lucarelli : **HSCT in THAL**



Atomic Bomb Hiroshima (6/august/1945, 8:15 am)

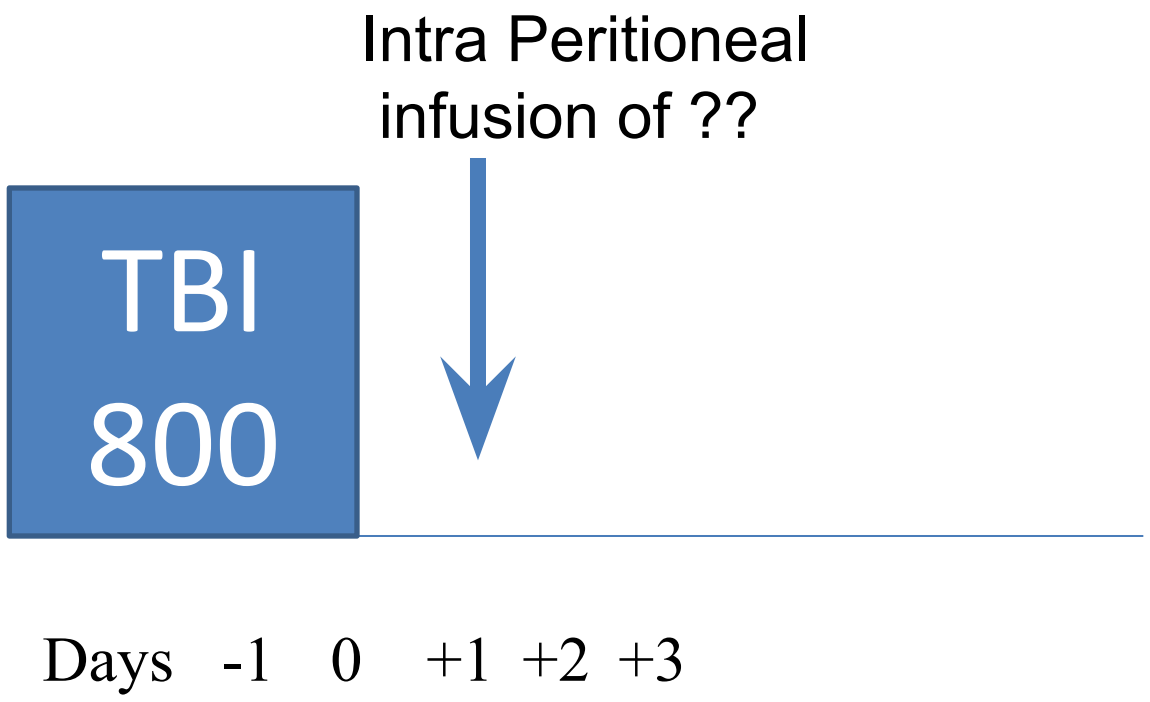
London 5 september 1945
Reuter correspondent Peter Bourchett sends a telegraph: the few survivors of Hiroshima (6.000 out of 250.000), one month after the bomb, **with no particular reason**, they start to feel ill
They loose their appetite, their hair falls, they have blu stains on their skin. They start bleeding and then they die.
(ANSA 21:15)

1945- 1950
Radiobiology

A new branch of medicine develops and it is called radiobiology : it studies the effect of gamma radiation

Mice are exposed to Cobalt 60 at increasing doses, to assess the lethal dose (LD30 LD50 LD70)
the dose is different from animal to animal (mouse, rat)
a dose of 6-10 Gy is lethal
the animals get sick after TBI – they stop eating- they loose weight – they develop pancytopenia- and they die

But what tissue would rescue the cytopenia??
Thymus? Liver? Spleen? Blood?



The Old England Lake Hotel, Windermere, UK

Aug.6.1950

Dear Miss Uphoff

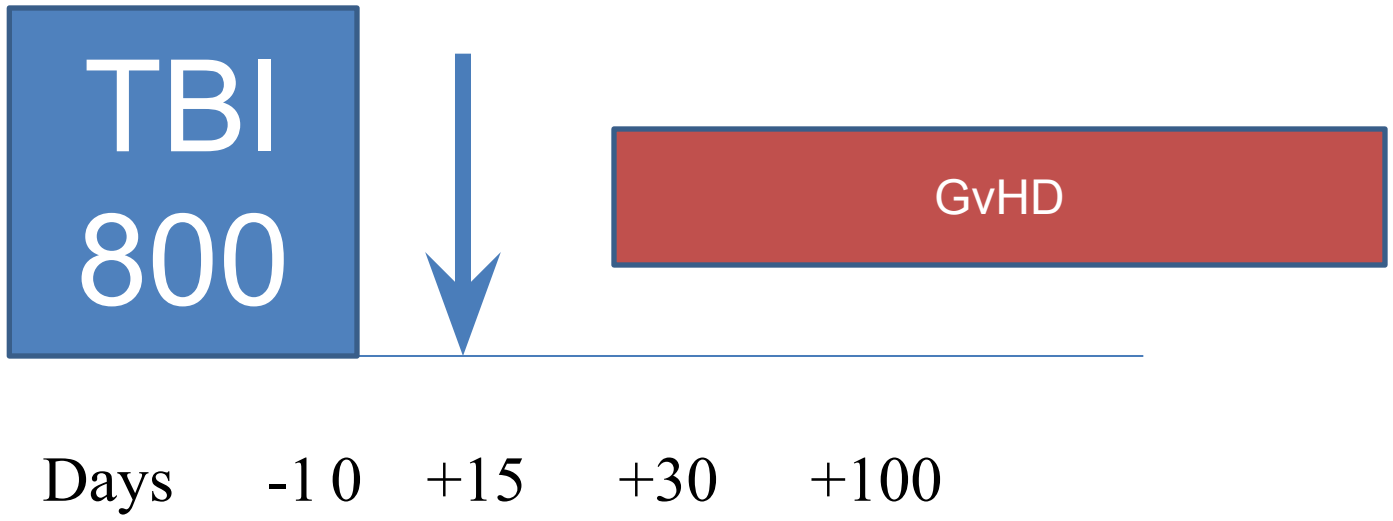
..after talking with many people I am beginning to get convinced that we should not only try transfusions in mice at different intervals after irradiation,

but also injection (intravenous) of a normal bone marrow suspension at different times after irradiation with the idea of repopulating the destroyed bone marrow.

As to the technique, it should not be too difficult to get some bone marrow out , as only little may be necessary to produce the effect…..

Egon Lorenz

i.v. BMT



TRANSPLANTATION
Vol. 9, No. 6
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A COMPENDIUM OF REPORTED HUMAN BONE MARROW TRANSPLANTS[1]

MORTIMER M. BORTIN

May and Sigmund Winter Research Laboratory, Mount Sinai Hospital, and Department of Medicine, Marquette School of Medicine, Milwaukee, Wisconsin 53233

TABLE 1. Results of 203 reported human bone marrow transplants

Disease	No. of patients	No. with no engraftment	No. with secondary disease	No. of allogeneic chimeras
Aplastic anemia	73	66	5	0
Leukemia	84	33	32	3
Malignant disease	31	23	1	1
Immune deficiency	15	3	11	7
Total	203	125	49	11[a]

[a] Three alive at the time of this report.

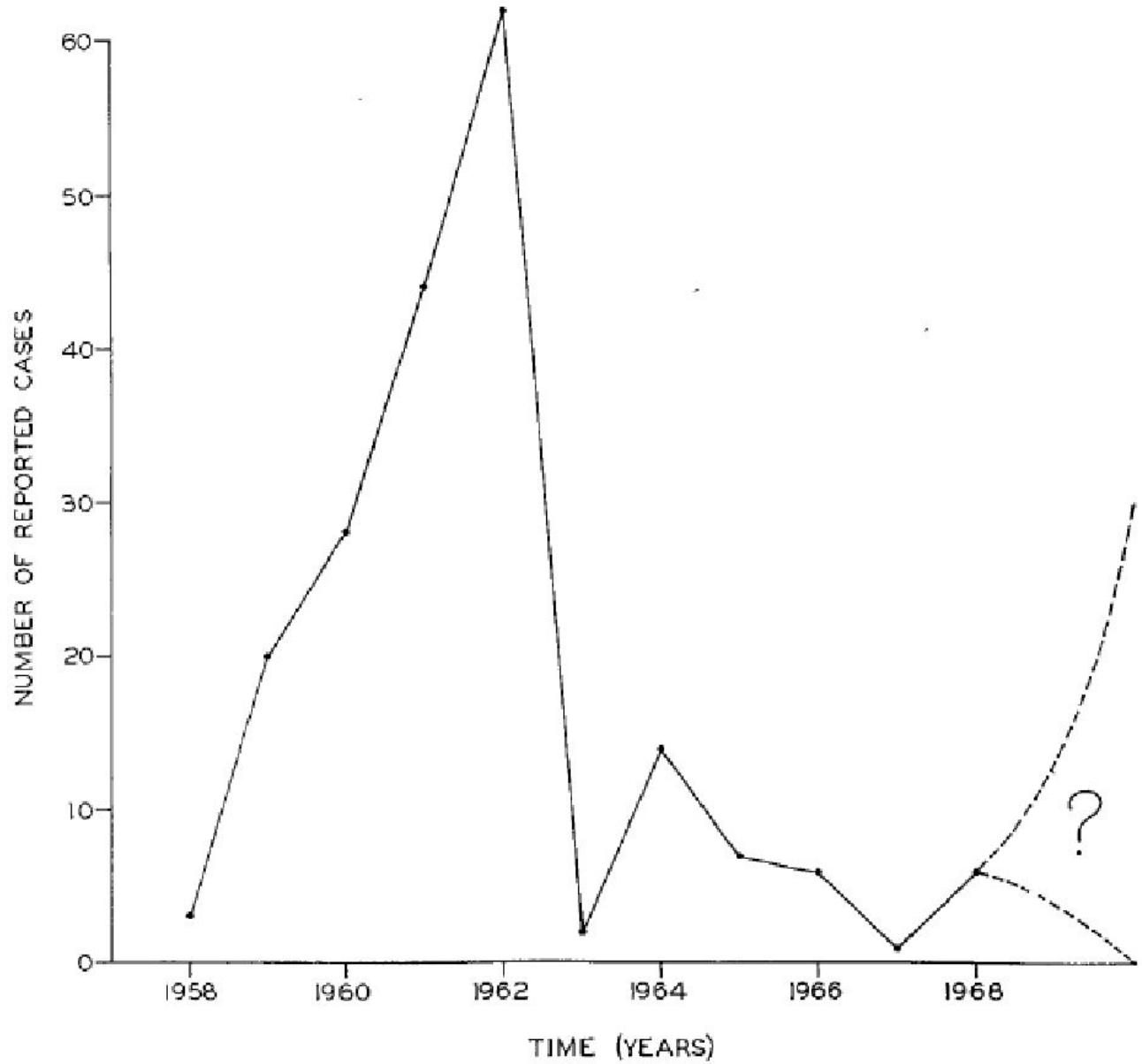
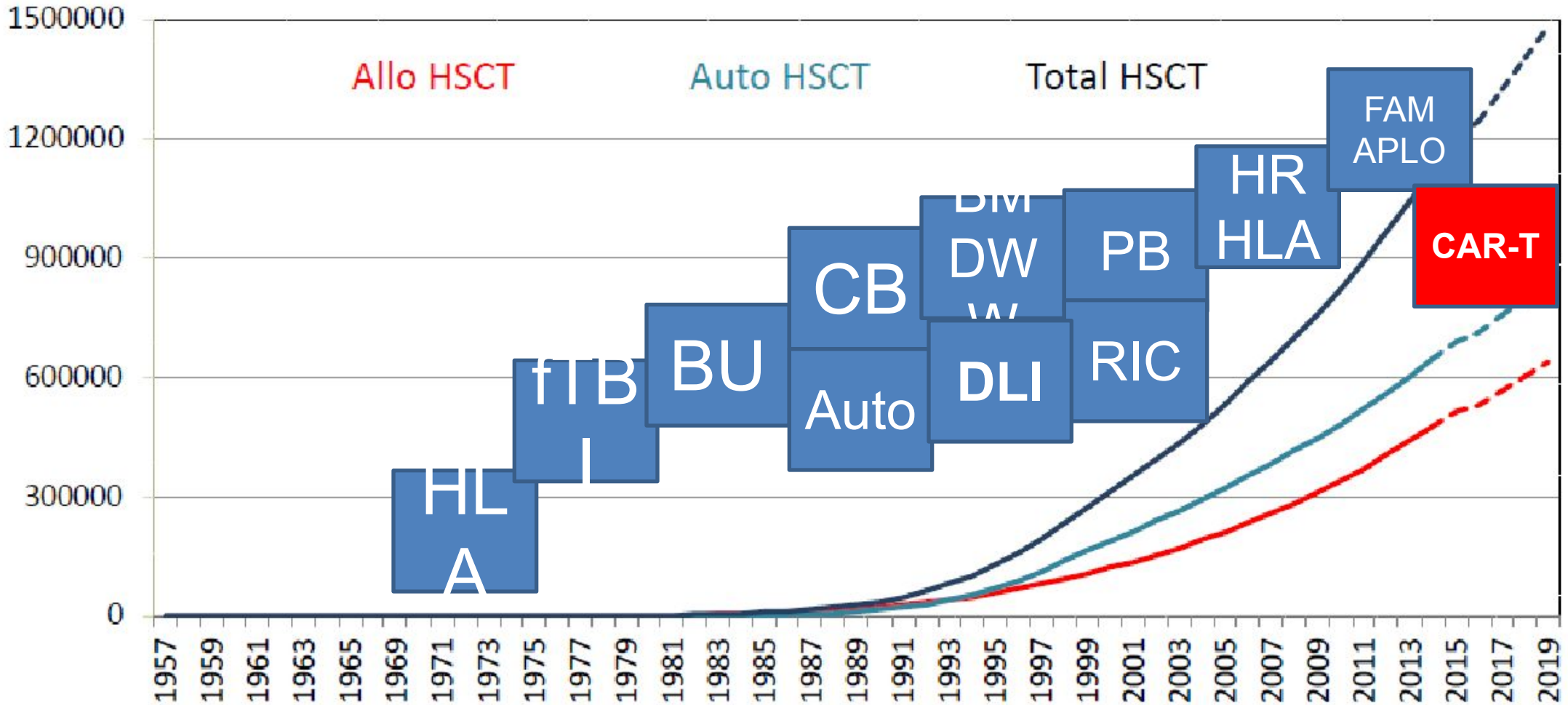


FIGURE 1. Reported human bone marrow transplants from 1958 to 1968.

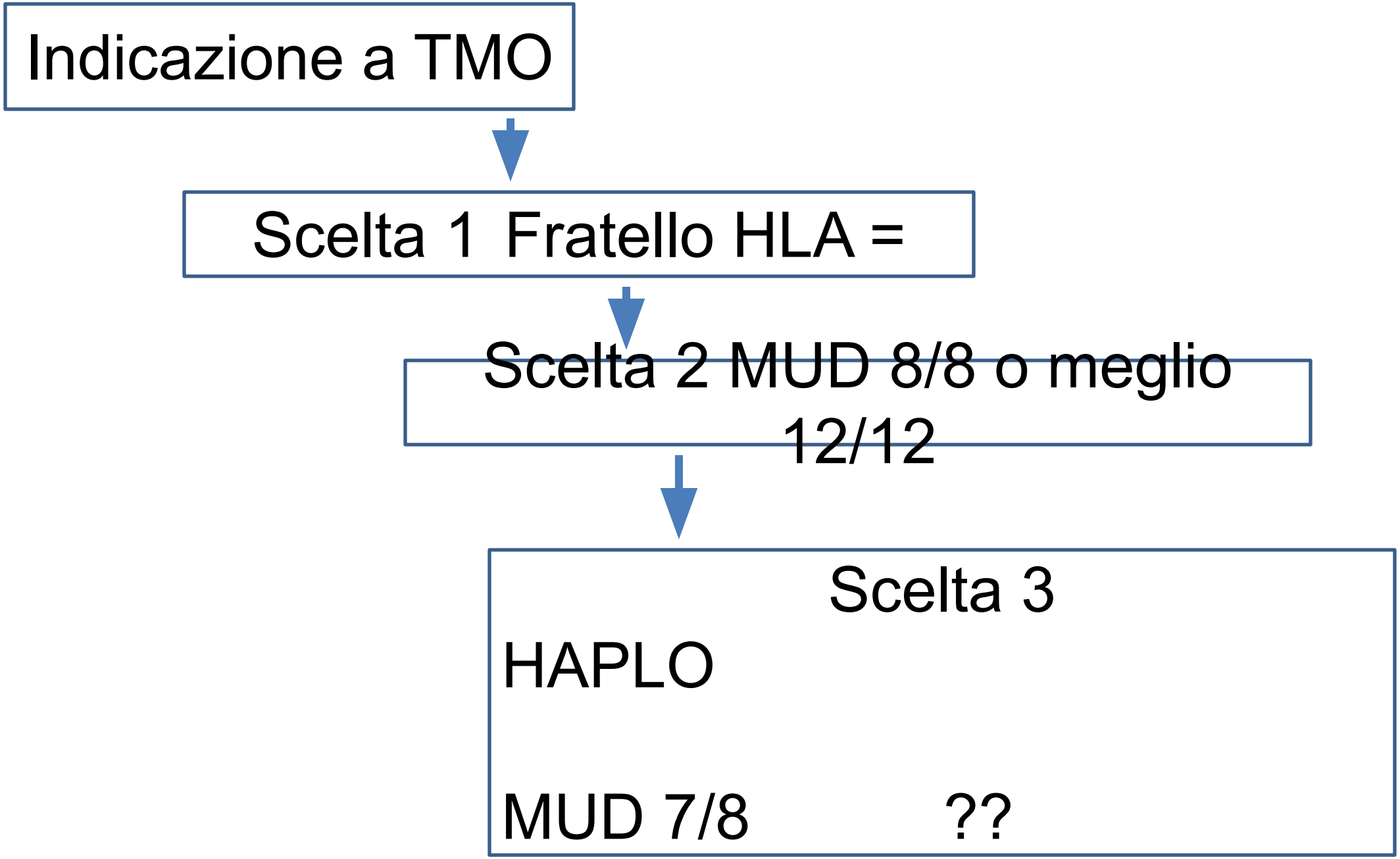
WBMT global survey: predicted activity 2020



HSCT allogenico 2021

HLA
best donor
HLA= sibling

Unrelated HLA=8/8 (A,B,C,DRB1)

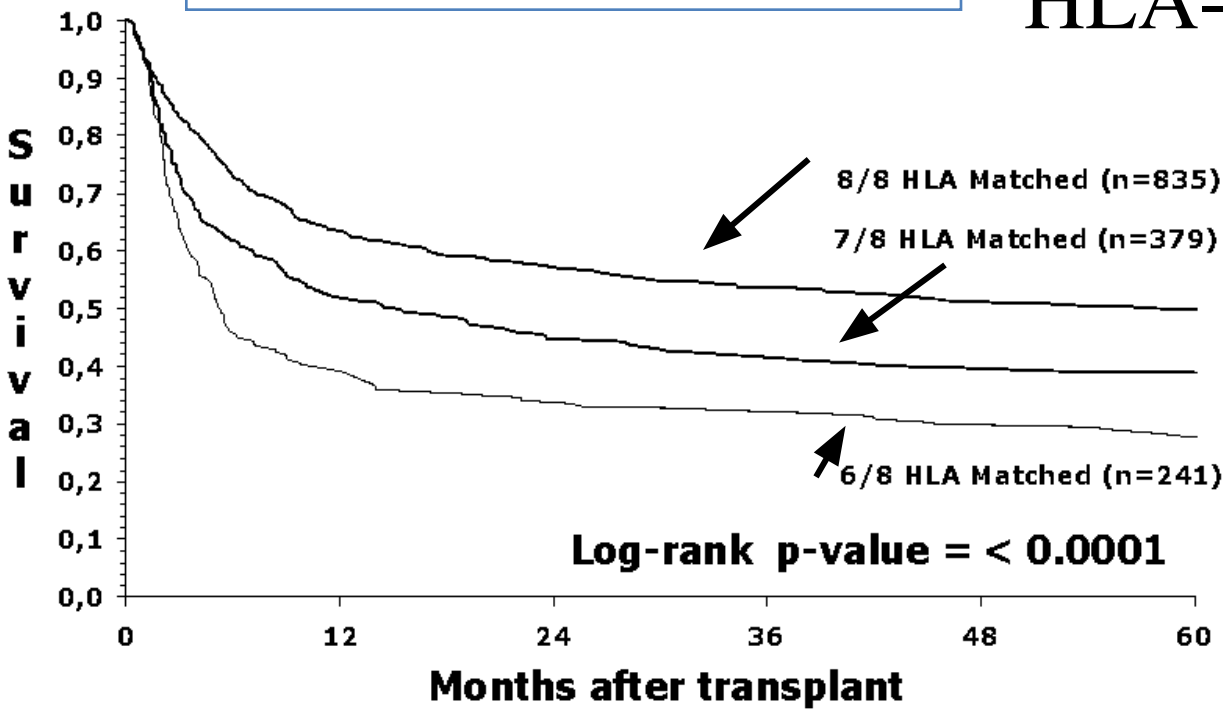

Indicazione a TMO
Scelta 1 Fratello HLA =
Scelta 2 MUD 8/8 o meglio 12/12
Scelta 3
HAPLO
MUD 7/8 ??

Early Stage Disease: Adverse impact of HLA mismatch

Lee et al, 2007

Each mm yield 10-11% worse survival

HLA-A ,B, C, DR



HLA 2022

 # miglior donatore Fratello HLA identico (se giovane (<60?)-sano)

 # seconda scelta MUD 8/8

 # terza scelta APLO o UD 7/8

 # poi Cordone Ombelicale

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 18, 2012 VOL. 367 NO. 16

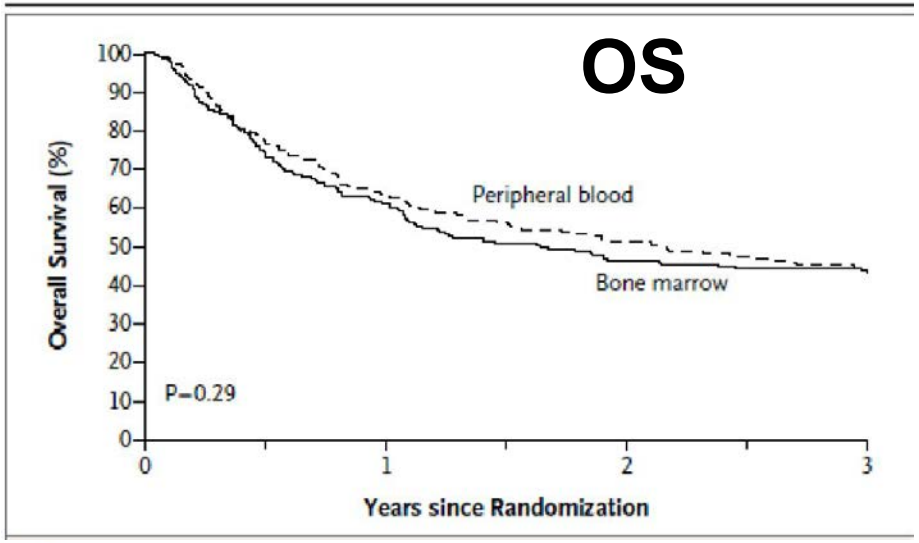
Peripheral-Blood Stem Cells versus Bone Marrow from Unrelated Donors

Claudio Anasetti, M.D., Brent R. Logan, Ph.D., Stephanie J. Lee, M.D., M.P.H., Edmund K. Waller, M.D., Ph.D., Daniel J. Weisdorf, M.D., John R. Wingard, M.D., Corey S. Cutler, M.D., M.P.H., Peter Westervelt, M.D., Ph.D., Ann Woolfrey, M.D., Stephen Couban, M.D., Gerhard Ehninger, M.D., Laura Johnston, M.D., Richard T. Maziarz, M.D., Michael A. Pulsipher, M.D., David L. Porter, M.D., Shin Mineishi, M.D., John M. McCarty, M.D., Shakila P. Khan, M.D., Paolo Anderlini, M.D., William I. Bensinger, M.D., Susan F. Leitman, M.D., Scott D. Rowley, M.D., Christopher Bredeson, M.D., Shelly L. Carter, Sc.D., Mary M. Horowitz, M.D., and Dennis L. Confer, M.D., for the Blood and Marrow Transplant Clinical Trials Network*

278 patients BONE MARROW

273 PERIPHERAL BLOOD

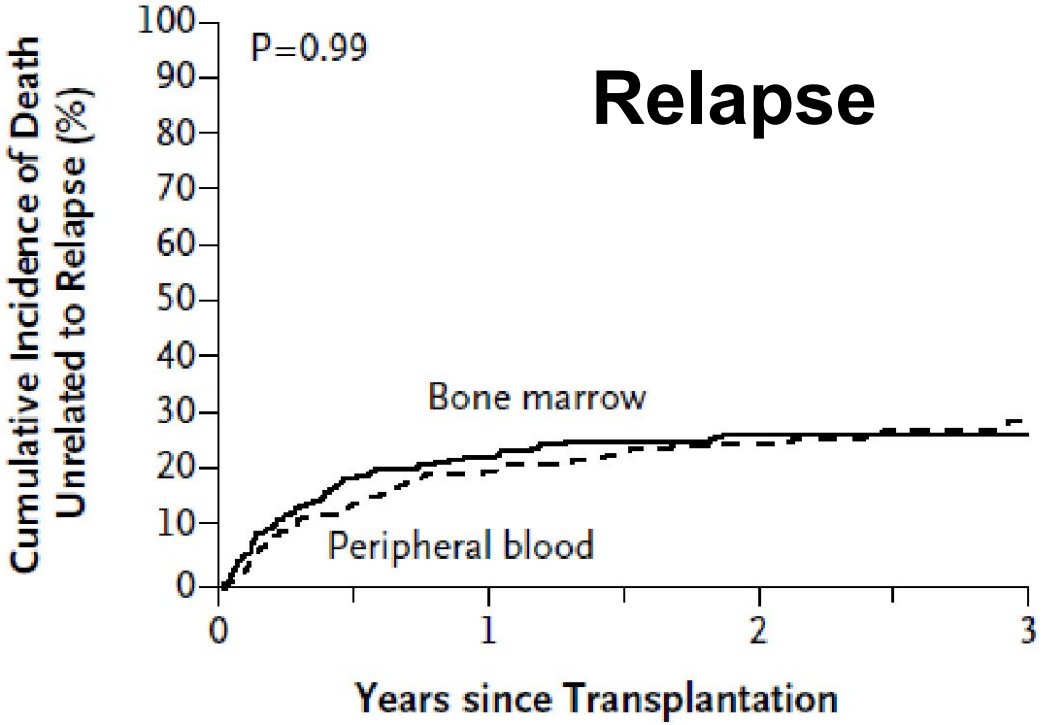
OS



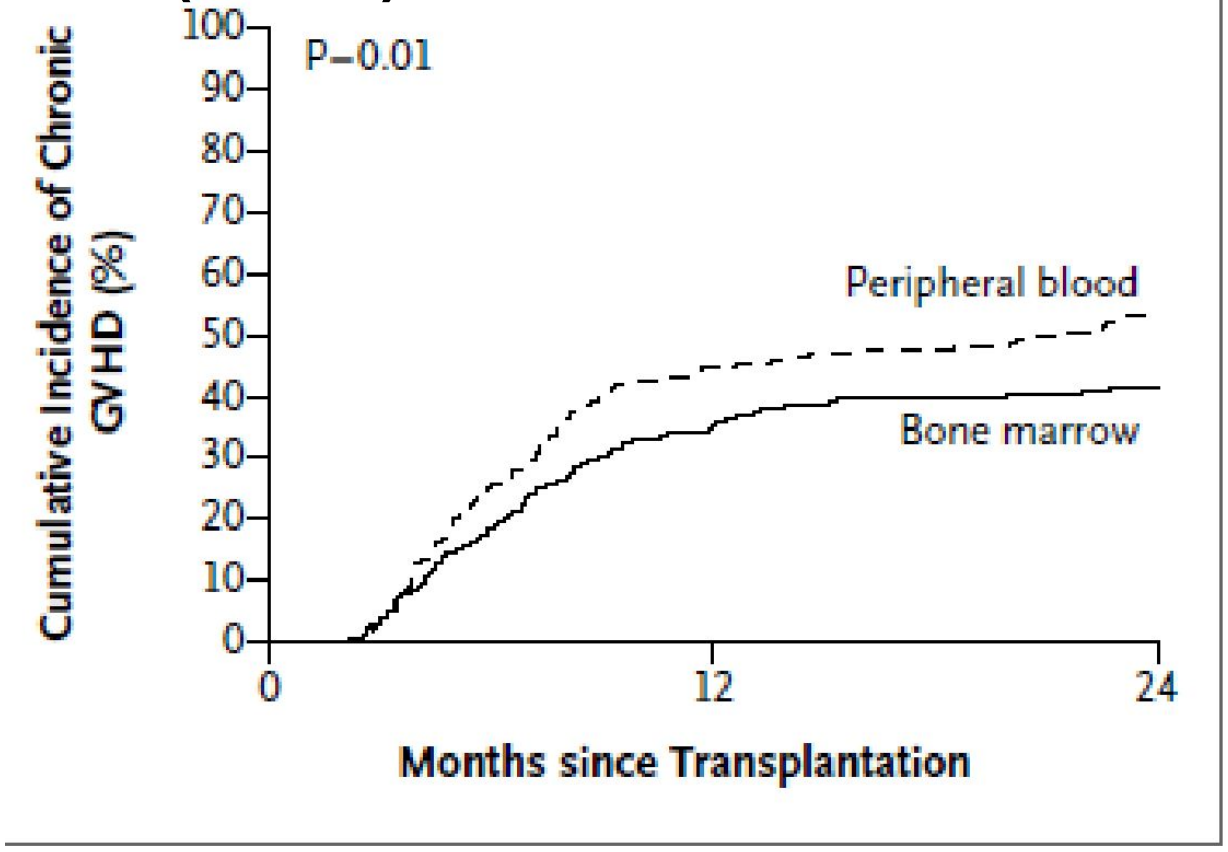
Chronic GvHD: 53% vs 41% (0.01)
Ext.cGvHD: 48% vs 32% (0.001)

C

Relapse



H



Published in final edited form as:
JAMA Oncol. 2016 December 01; 2(12): 1583–1589. doi:10.1001/jamaoncol.2016.2520.

Bone marrow is associated with better patient-reported outcomes than peripheral blood in survivors 5 years after unrelated donor transplantation

Stephanie J Lee, M.D.[1], **Brent Logan, Ph.D.**[2], **Peter Westervelt, M.D.**[3], **Corey Cutler, M.D.**[4], **Ann Woolfrey, M.D.**[5], **Shakila P. Khan, M.D.**[6], **Edmund K. Waller, M.D.**[7], **Richard T. Maziarz, M.D.**[8], **Juan Wu, M.S.**[9], **Bronwen Shaw, M.D.**[10], **Dennis Confer, M.D.**[11], **Mary M. Horowitz, M.D.**[10], and **Claudio Anasetti, M.D.**[12]

[1]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA

Conclusions and Relevance—Recipients of unrelated donor bone marrow have better psychological well-being, less burdensome chronic GVHD symptoms, and are more likely to return to work than recipients of peripheral blood at 5 years after transplantation. Bone marrow should be the standard of care for these types of transplant procedures.

Midollo o Periferico ?

 # studio randomizzato (evidenza grado I) dice che la sopravvivenza e' uguale , solo + cGvHD in PB

 # RECIDIVA e' uguale BM=PB

 # QOL migliore per BM a 5 anni

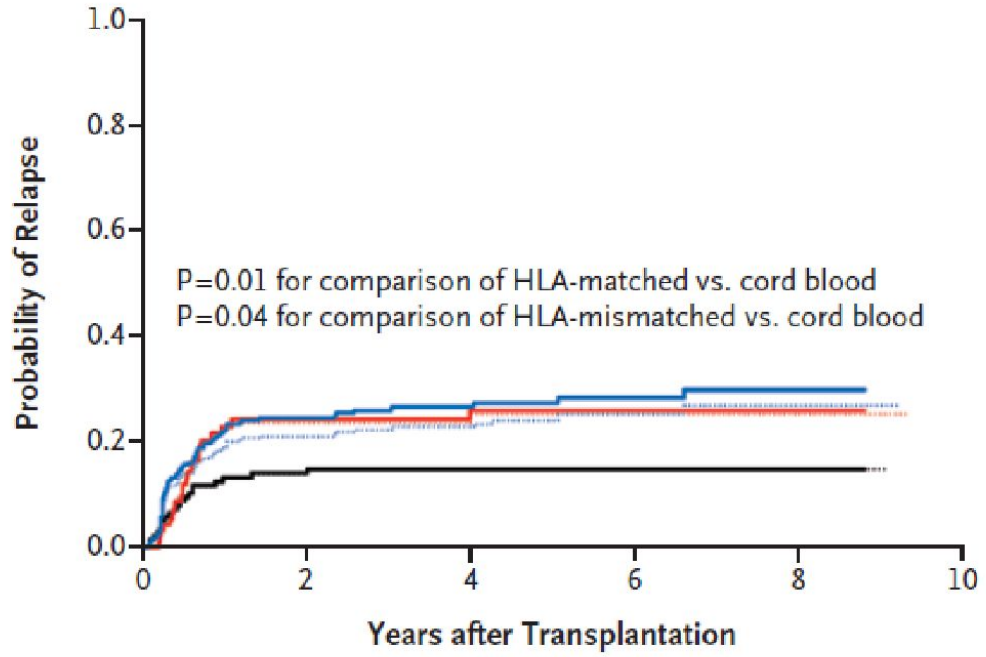
 # tutti usano periferiche (!! ??)

ORIGINAL ARTICLE

Cord-Blood Transplantation in Patients with Minimal Residual Disease

Filippo Milano, M.D., Ph.D., Ted Gooley, Ph.D., Brent Wood, M.D.,
Ann Woolfrey, M.D., Mary E. Flowers, M.D., Kristine Doney, M.D.,

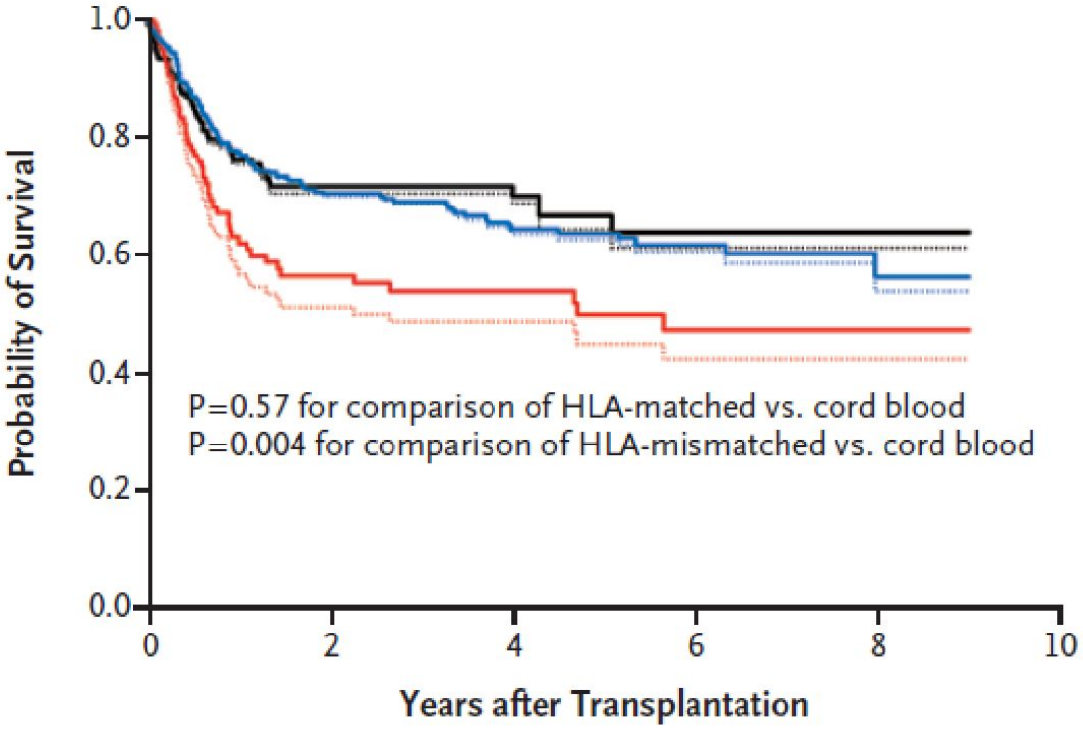
B Relapse



No. at Risk					
Cord blood	140	74	39	13	4
HLA-matched	344	161	87	35	11
HLA-mismatched	98	40	29	15	6

M.D.,

A Survival



Patients with MRD+ at Tx

Relapse is lowere

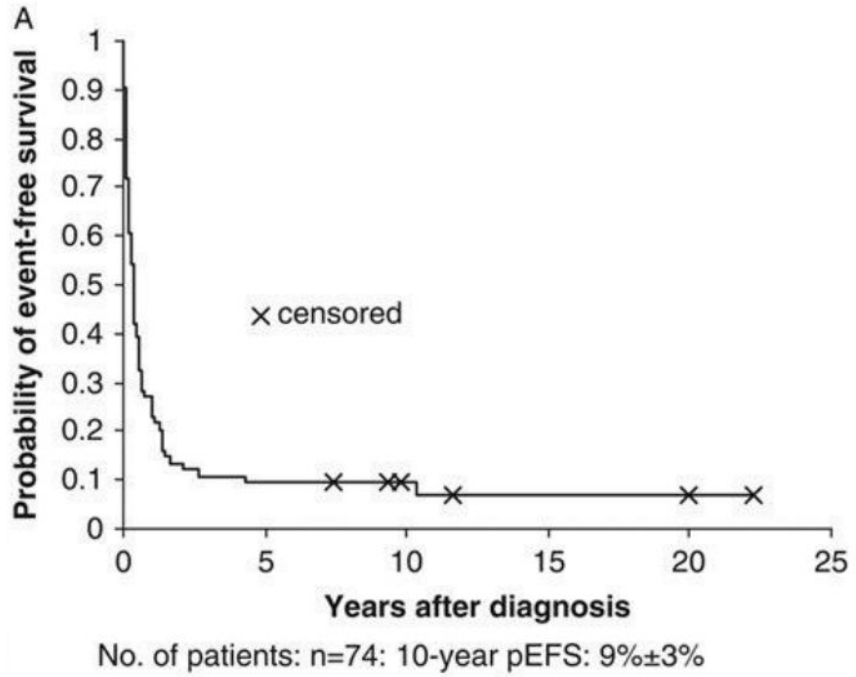
OS of CB as good as HLA=Tx
better than UD 7/8

Midollo o Periferico o Cordone?

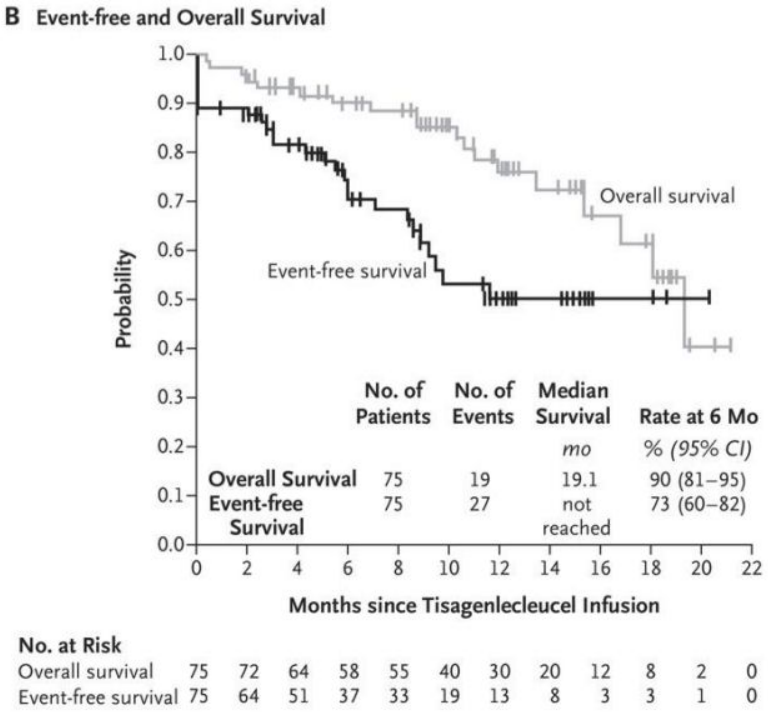
 # non dimentichiamo Cordone
Ottime sorgente di CSE e di GvL

Impact of Car-T Cells: Prognosis of 2nd or Greater Relapsed ALL

Courtesy of M Pulsipher
Keck school of Medicine
USC



10-30% remission rate
EFS 9%



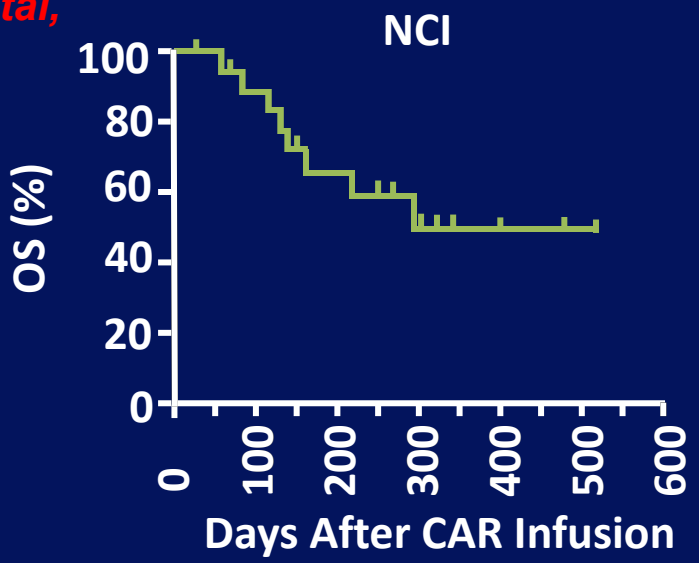
81% remission rate
EFS 73% 6 mo, 50% 12 mo

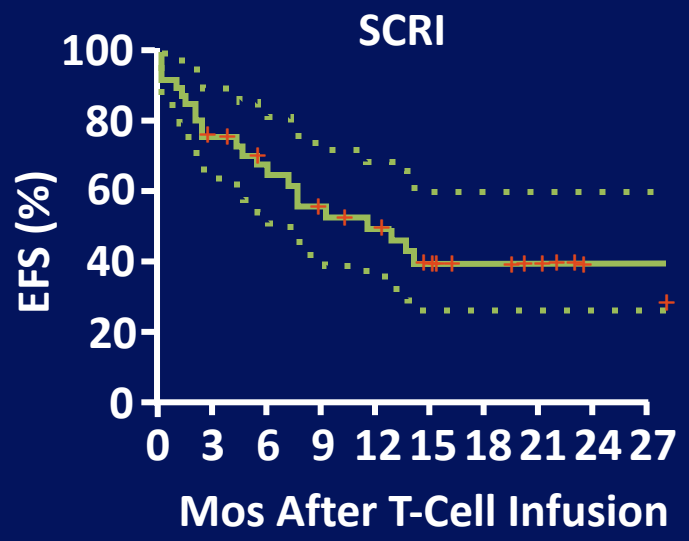
Reismuller B , JPHO 2013
Maude S,/Pulsipher/Grupp, NEJM 2018

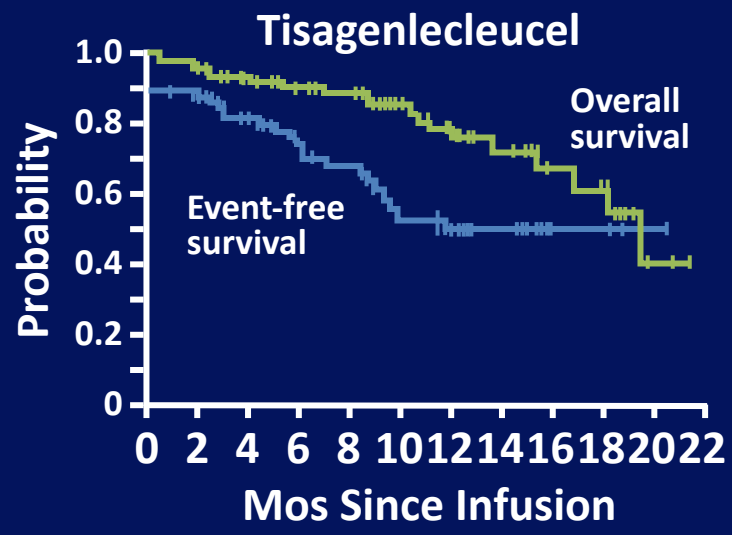
Clinical Course After CD19 CAR Therapy in R/R ALL

Courtesy of Peggy LU
Lu Daopei Hospital, China

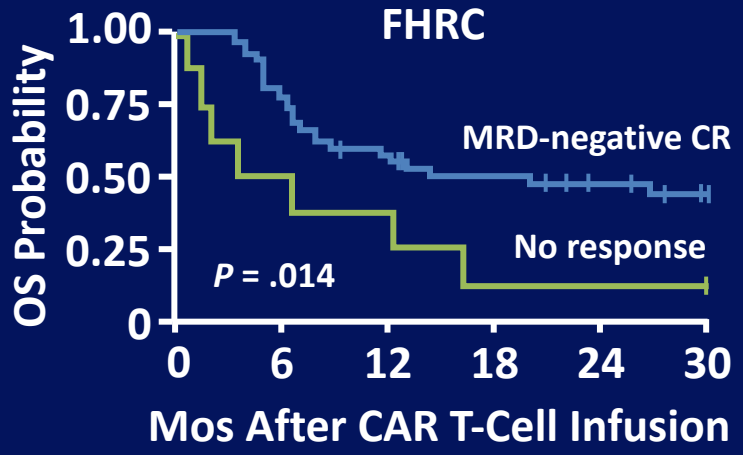
Pediatric ALL

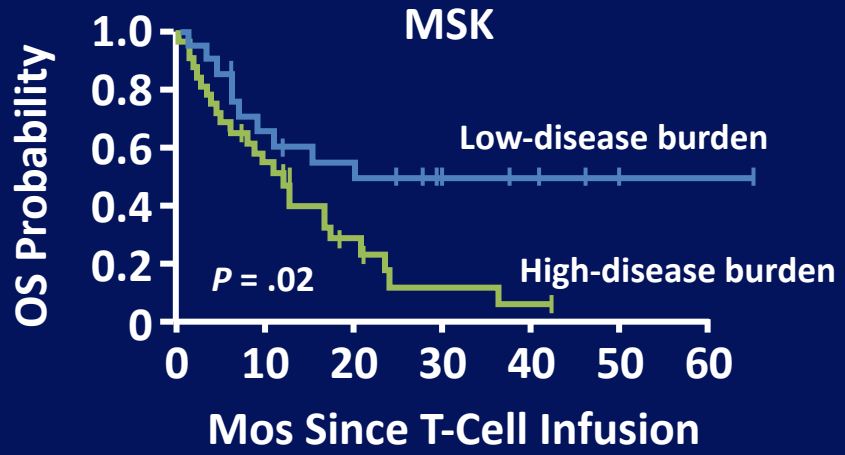






Adult ALL





Park. NEJM. 2018;378:449. Hay. Blood. 2019;133:1652. Maude. NEJM. 2018. Gardner. Blood 2017. Lee. Lancet. 2015.

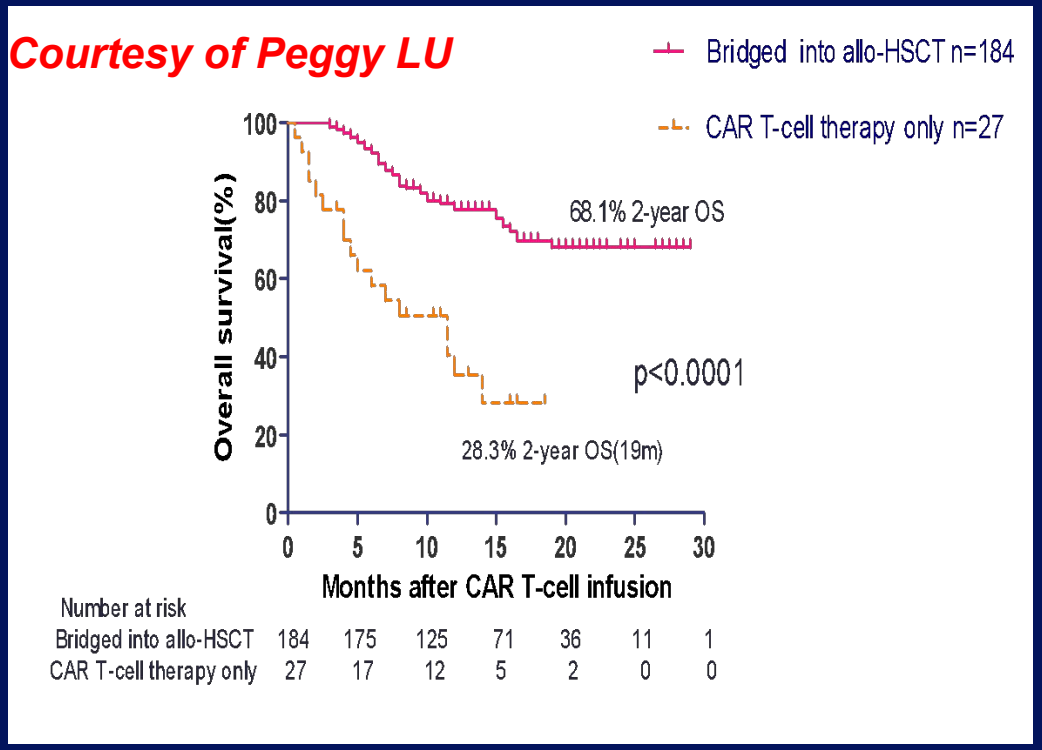
Slide credit: clinicaloptions.com

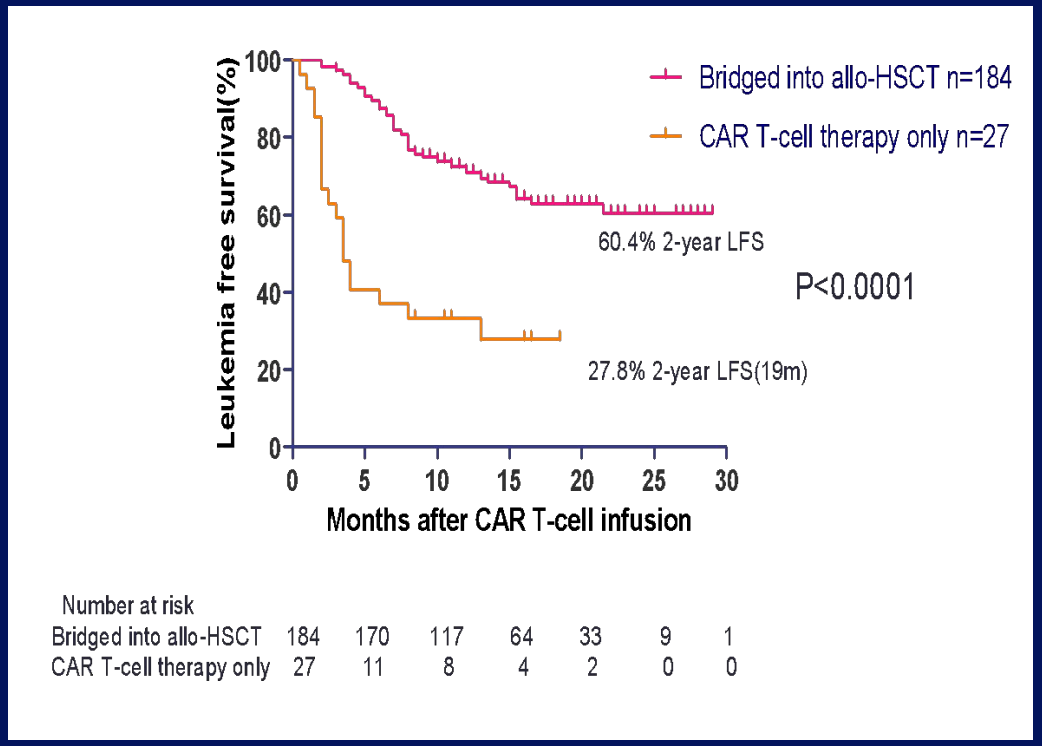
CAR-T Patients in Lu Daopei Hospital

Courtesy of Peggy LU

OS and LFS of Patients with or without Consolidation Allo-HSCT after CAR-T Cell Therapy (N=231)

Courtesy of Peggy LU





The OS and LFS were much higher in the group that had consolidative allo-HSCT compared to those that received CAR-T cell therapy alone (1-year OS of 77.8% vs. 35.4%, p<0.0001; 1-year LFS of 70.9% vs. 33.3%, p<0.0001; 2-year OS of 68.1% vs. 28.3% [19 months], p<0.0001; 2-year LFS of 60.4% vs. 27.8% [19 months], p<0.0001, respectively)

Jiang *et al. Biomarker Research* (2020) 8:66
https://doi.org/10.1186/s40364-020-00247-8

Biomarker Research

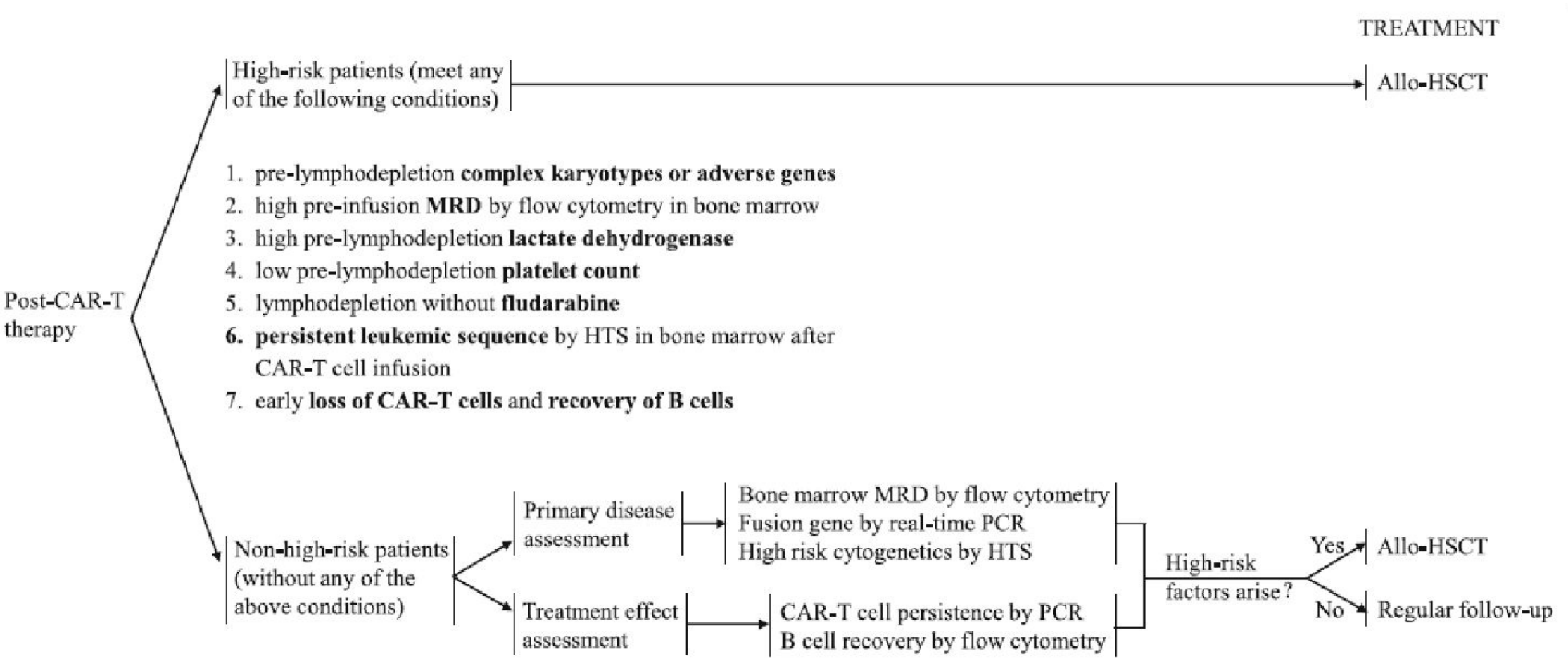


Fig. 1 Recommendation for the assessment and management of r/r B-ALL patients in anti-CD19 CAR T-cell therapy. MRD, minimal residual disease; HTS, high throughput sequencing; PCR, polymerase chain reaction

Summary: HCT Needed After CAR T Rx?

- HCT recommended for all patients after CD28 CAR T Rx
- HCT for pts receiving 4-1BB with demonstrated persistence
  - May improve EFS, no clear OS benefit
- Can we Predict relapse?
  - Pts with a hx of blina failure and high tumor burden at risk
  - Early loss (<6m) of B-cell aplasia = high risk of relapse
  - NGS-MRD>0 after CAR T = very high risk
  - Using these markers, we can identify pts who may benefit from HCT
  - A randomized trial of HCT for at risk vs. HCT for all is needed

MRD pos pre allo HSCT in ALL

Blinatumomab

CART CD19 ALLO :si' in paz alto rischio
e CAR-T CD28

fattibile, efficace metodo per
indurre CR
indurre MRD-

altro?

The NEW ENGLAND JOURNAL of MEDICINE

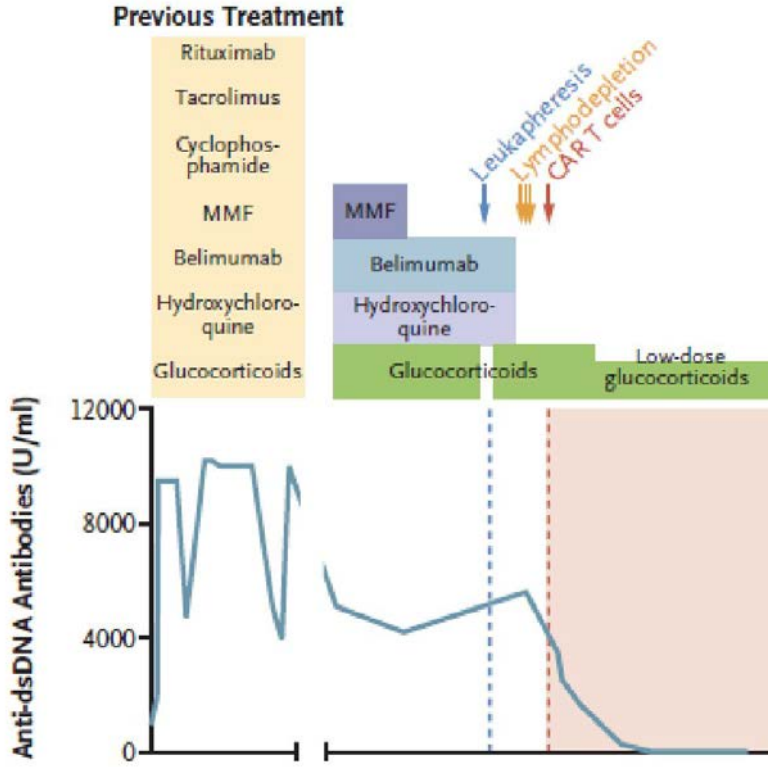
CORRESPONDENCE

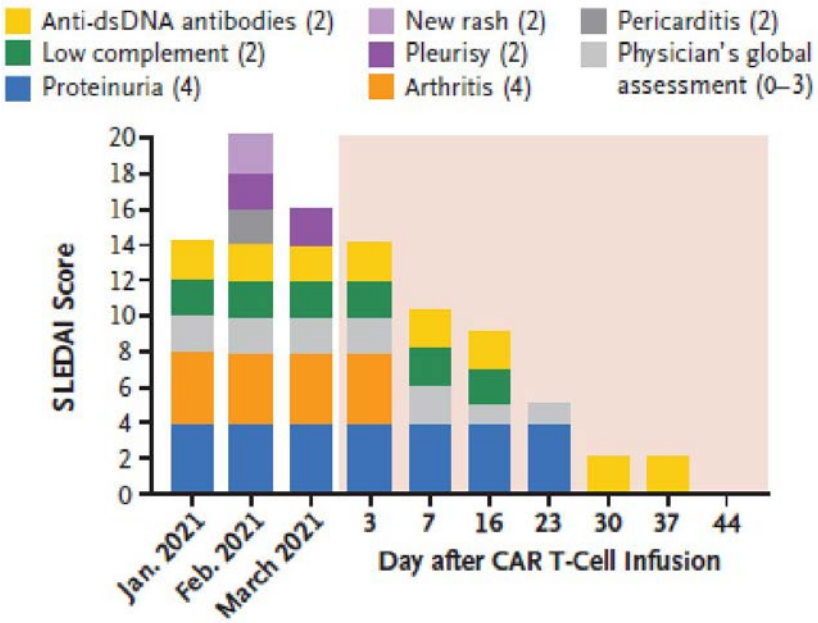
N ENGL J MED 385;6 NEJM.ORG AUGUST 5, 2021

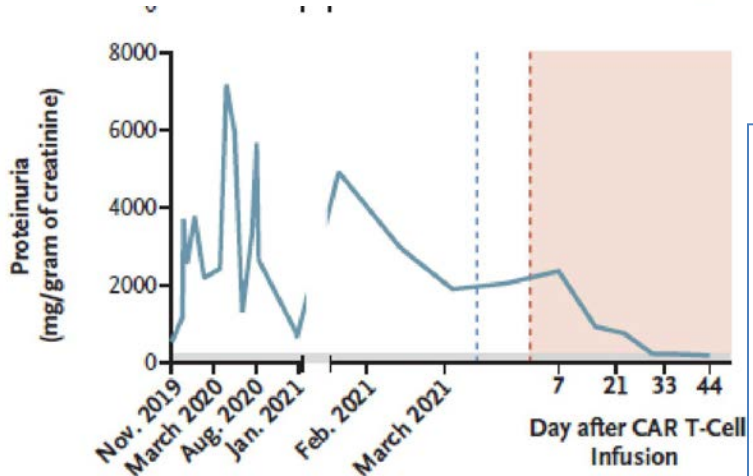
CD19-Targeted CAR T Cells in Refractory Systemic Lupus Erythematosus

Georg Schett et al, Erlangen , DE

F 20 yy
Refract SLE







Patient has been in unmaintained Steroid free- remission now for 1 year
SIX patients already followed
All six in in CR

A prospective phase 1 trial started

CART CD19 nel LES

efficacia straordinaria (in una pz refr anti-CD20)

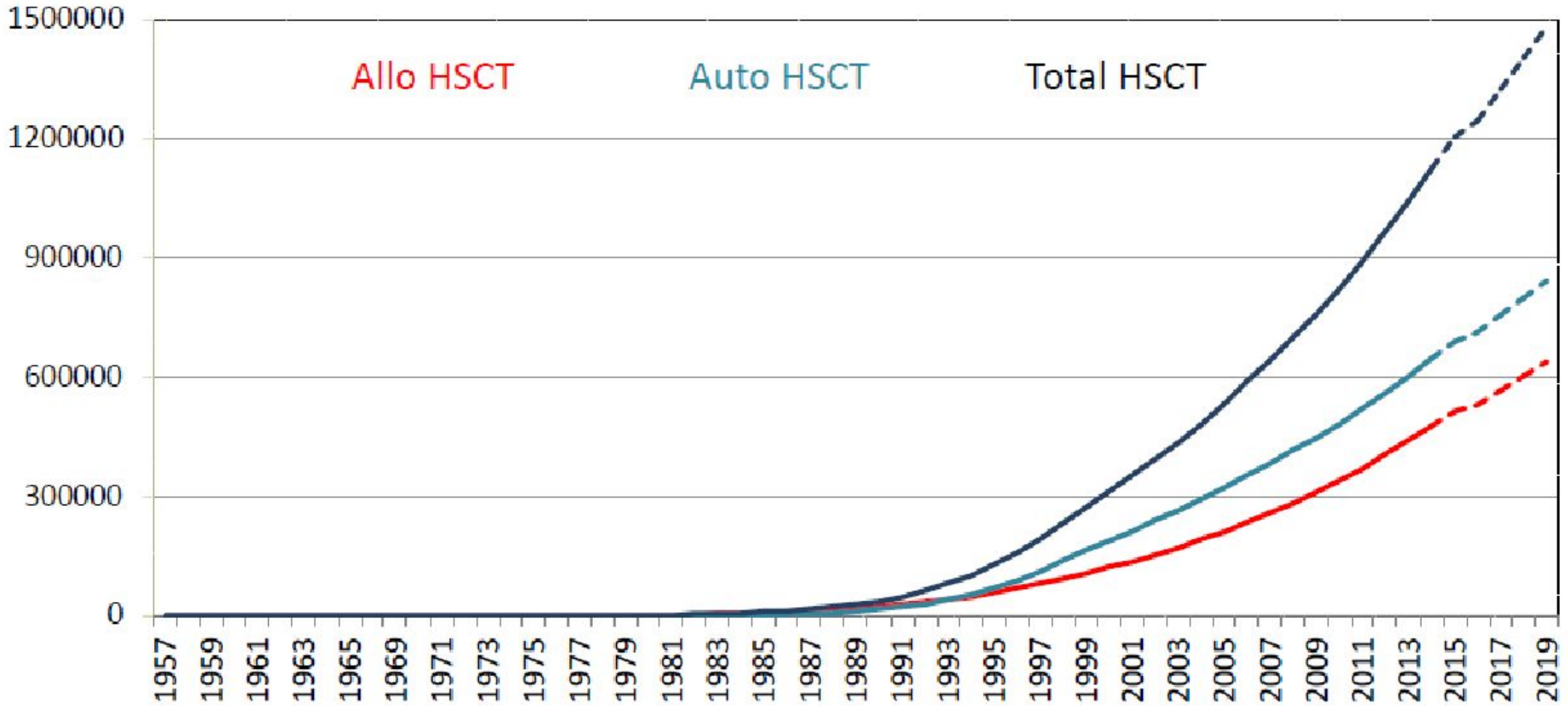
apertura sulla patogenesi
    eliminare cellule CD19+ (B cells? Plasmoblasts?)
    effetto anche se il TARGET resta ?

aprire a studi in altre connettiviti
    SLE, RA, SSc

autoimmunita' e' paragonabile ad un linfoma basso grado?

WBMT

HSCT : alive and well 50 years down the line and an Exciting Future in front of us !!!



Thank you for your attention