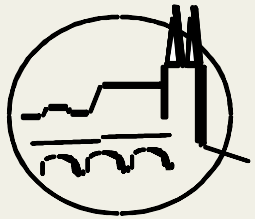
Haploidente HSCT bei Sichelzellkrankheit



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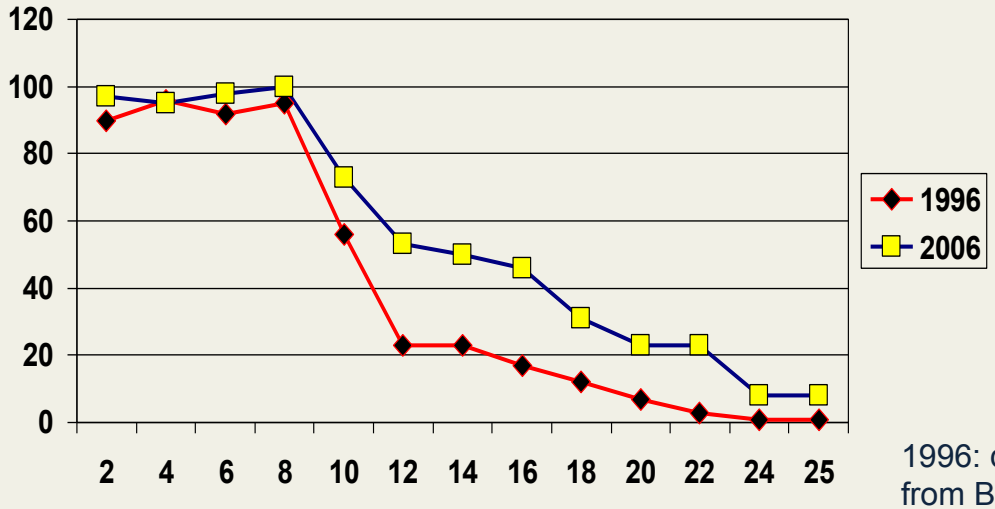
Hemoglobinopathies are the largest patient population with an absolute indication for SCT

5% of the world's population are healthy carriers of a gene for sickle-cell disease or thalassaemia.

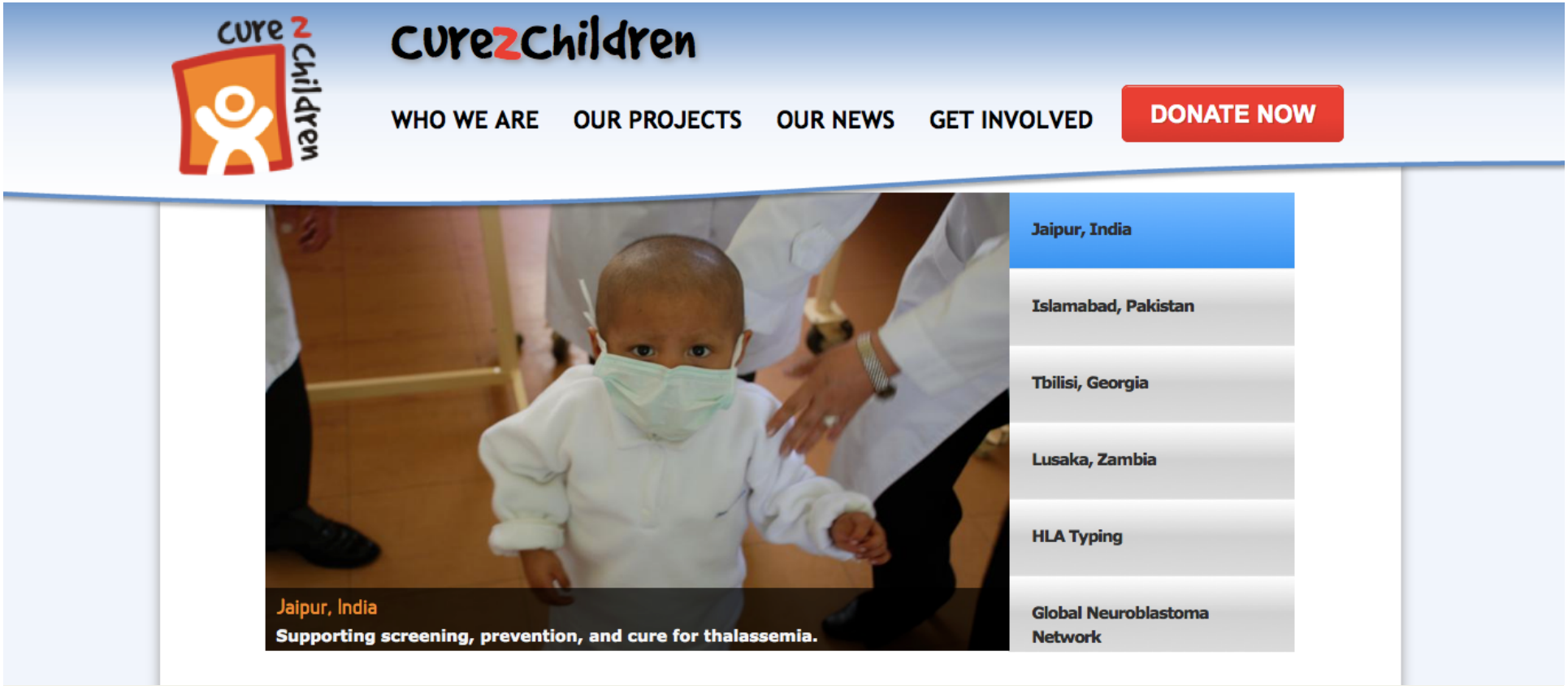
Hemoglobinopathies

Severe Thalassemia

- **>100.000** new children are born each year in Middle east and South-Asia
- Global disease burden **~ 1 million**
- In spite of advances in supportive care the majority may not live beyond age 20 years

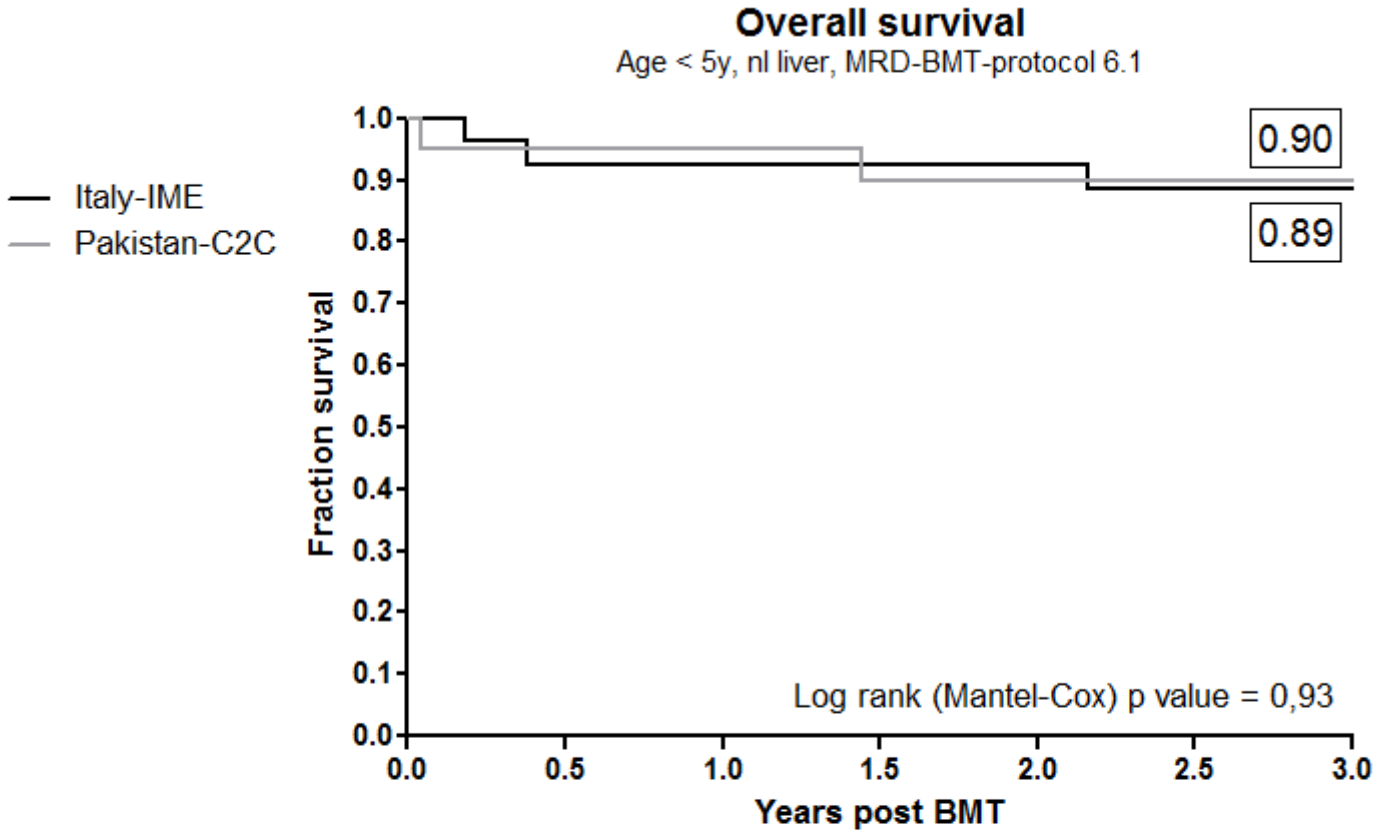


1996: data from HBB Karachi, 2006: data from BTIHS, Karachi



Mission

Cure2Children (C2C) is a non-profit, apolitical, and secular organization providing support for the care of children with cancer and severe blood disorder in developing countries.



Years of follow up	0	0,5	1	1,5	2	2,5	3
Number at risk Italy-IME	27	26	25	25	24	23	21
Number at risk Pakistan-C2C	20	20	20	19	12	9	2

Events Italy-IME 3 deaths: At 65 days (aGVHD), 4.5 months (aGVHD) and 2.2 years (cGVHD)

Events Pakistan-C2C 2 deaths: at 14 days (sepsis) and 10 months (graft failure/sepsis)

Cost of supportive care *vs.* SCT

Cost of supportive therapy for Thalassaemia

Blood transfusions	800 USD
Chelation	2.000 USD
Investigations	100 USD
Miscellaneous expenditures	100 USD
Total cost per year	**3.000 USD**

Cost of BMT for Thalassaemia

BMT in Pakistan **15.000 USD**

BMT in Italy (120.000 USD)

The cost of BMT is equivalent to a few years of supportive therapy!

Hemoglobinopathies

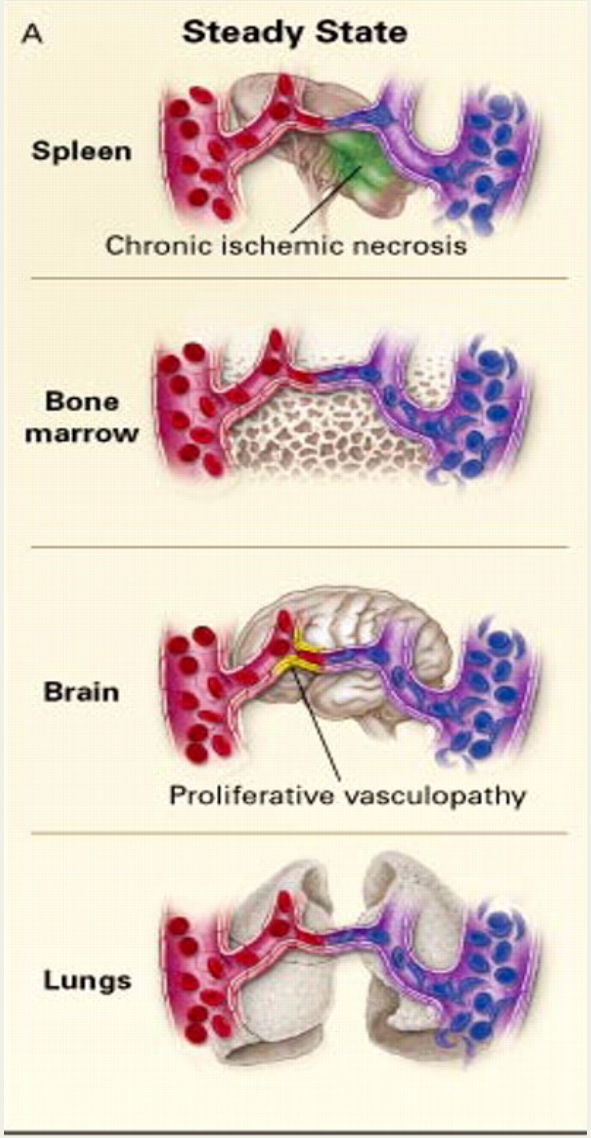
Sickle cell disease (SCD)

- Over 300 000 newborns with severe forms of SCD , the majority in low and middle income countries.
- Mortality rate 50-80% within first 5 years of age due to infection complication

World Health Organization

Major Complications of SCD patients

- Asplenia
  - Splenic sequestration, infectious risk
- Vaso-occlusive crisis
  - Pain
- Acute chest syndrome
  - Mortality risk
  - Chronic lung disease/pulm. artery HTN
- Recurrent priapism
- Osteonecrosis, Osteomyelitis
- Sickle-Nephropathy
- **Cerebral vasculopathy**
  - 50% risk at 14yrs
  - Overt strokes (11% <20yrs., 24% <45yrs)
  - Silent strokes, cognitive deficiency



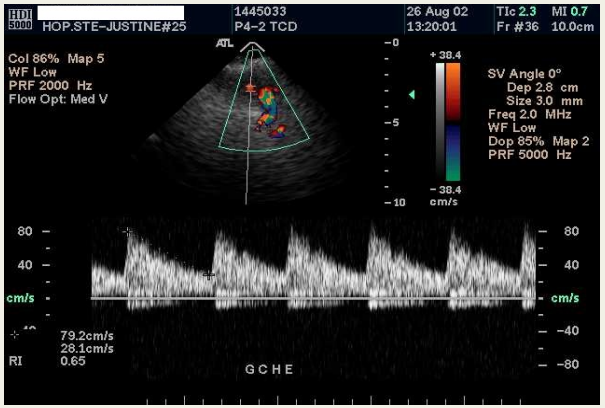
Orah Platt NEJM 2000

Standard medical care of SCD

- Parental training
- Immunizations (incl. Meningo-/Pneumocci)
- Penicillin-Prophylaxis
- Aggressive antibiotic management
- Oxygen and pain management
- Transfusions
- Hydroxyurea
- TCD screening
- Neuro-cognitive testing

Detection of patients at risk of stroke

- **TAMMX* velocities**
  - Normal < 170 cm/sec
  - Conditional: 170-199 cm/sec
  - Abnormal ≥ 200 cm/sec
  - **Velocities ≥ 200 cm/sec: predictive of a 40% stroke risk within 3 years**
  - Risk reduced to **2%** when velocities are **normal** (< 170 cm/sec)



Time-averaged mean of maximum velocities (TAMMX)

Adams et al ; NEJM 1992 and Ann Neurol 1997

Irritating facts in stroke prevention...

- Aggressive cTF programs can reduce stroke (Adams, et al, STOP-I trial, NEJM 1998)
- But only when continued (Adams, et al, STOP-II trial, NEJM 2005)
- HbS levels below 30% does not abolish completely the risk of recurrent strokes (Pegelow et al, J. Pedtr., 1995)
- Radiologic progression of vascular lesions not influenced by cTF (Brousse et al, 2005, Ann Hematol)

Can Hydroxyurea prevent strokes?

SWiTCH trial interrupted by DSMB!

- **Multicenter randomized Phase III**

Results:

	TF/Chelation	Hydroxyurea/Phlebotomy
Incidence of stroke	0%	**10%**
Liver iron content	**Equivalent!**	

Allogeneic SCT is the only definitive cure for SCD...

Allogeneic SCT is the only definitive cure for SCD

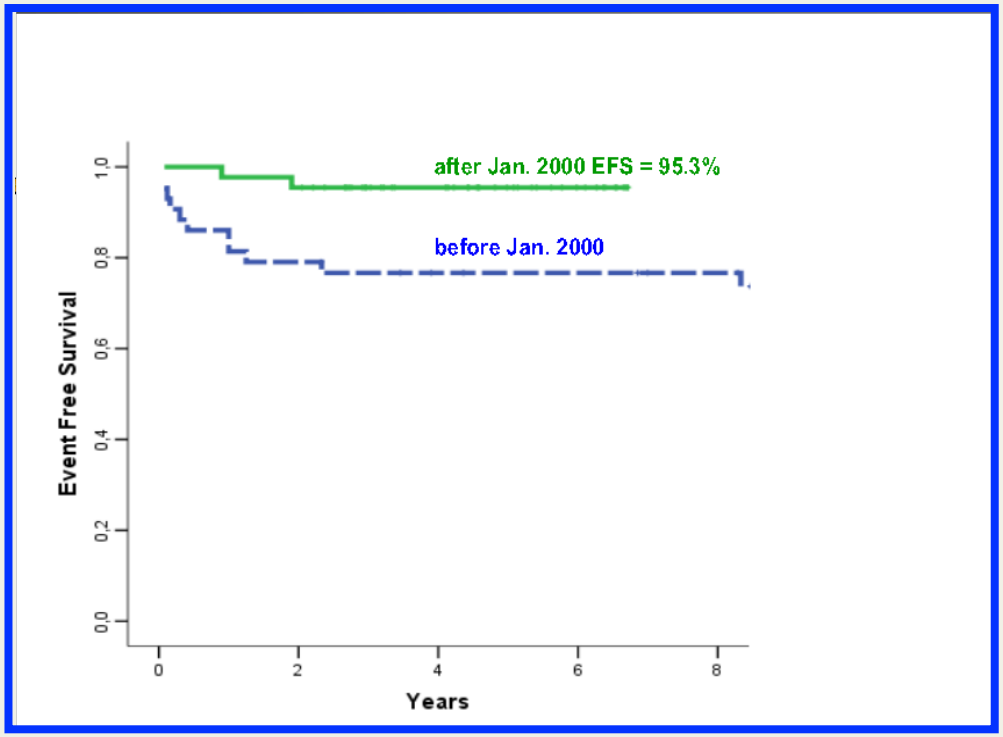
- **Things to consider:**
  - TRM
  - GvHD
  - Graft rejection in heavily transfused patients
  - PRES and other cerebral vascular complications
  - VOD in liver fibrosis/hepatic siderosis
  - Nephropathy
  - Infertility

Promising results in SCT with geno-identical donors

Indication: symptomatic young sickle cell patients
Donor: geno-identical donor
Conditioning: Myeloablative conditioning regimen

- **Iv Busulfan (BU)**
- **Cyclophosphamide (CY) 200 mg/kg**
- **Rabbit ATG 10-20 mg/kg**

- **TRM (n=6) was primarily related to GVHD (n=4) and not to conditioning**
- **Chance of cure of at least of 95% since 2000 (n=147)**

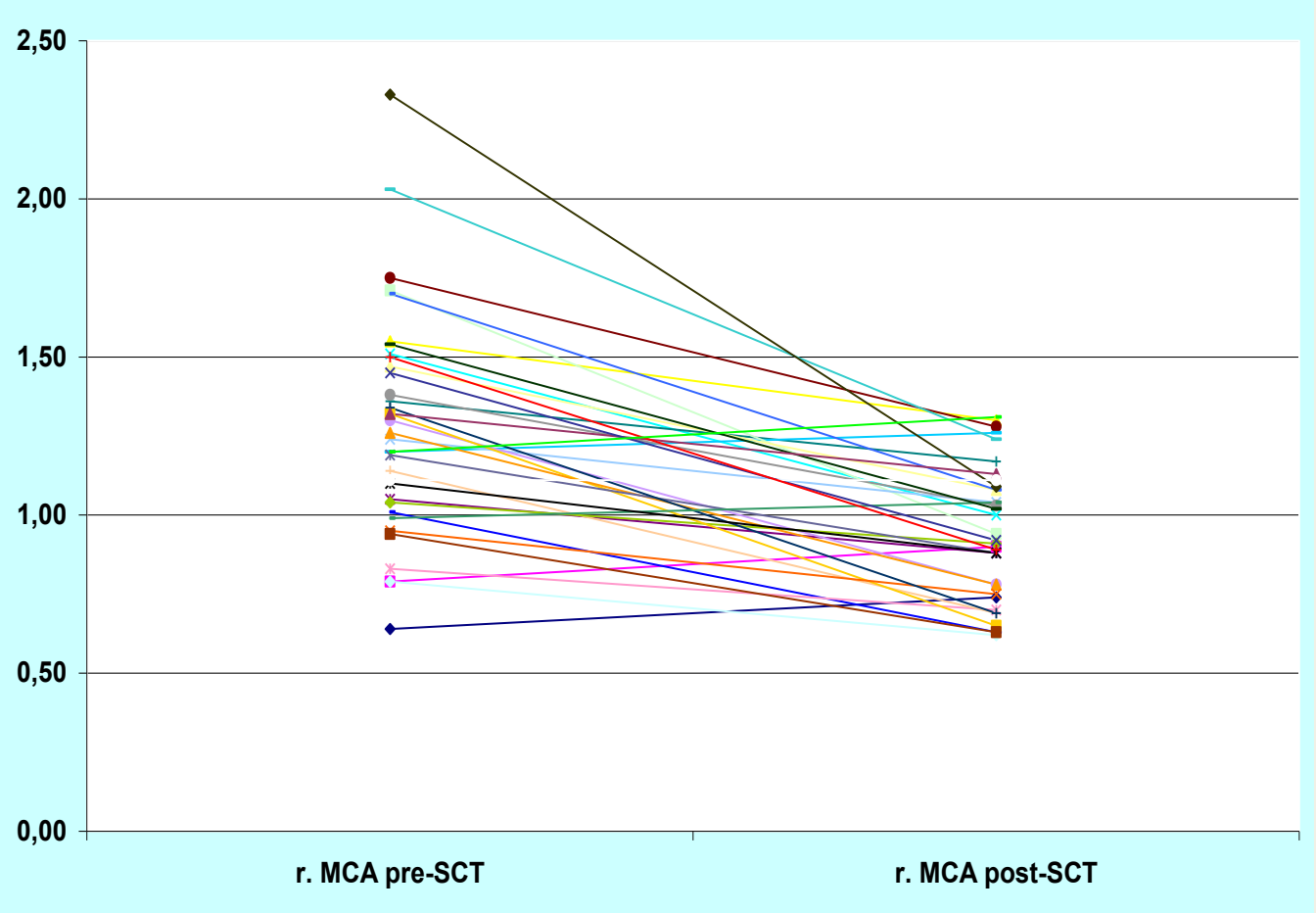


Bernaudin et al. Blood 2007

Société Française de Greffe de Moelle et de thérapie cellulaire

Outcome of arterial velocities

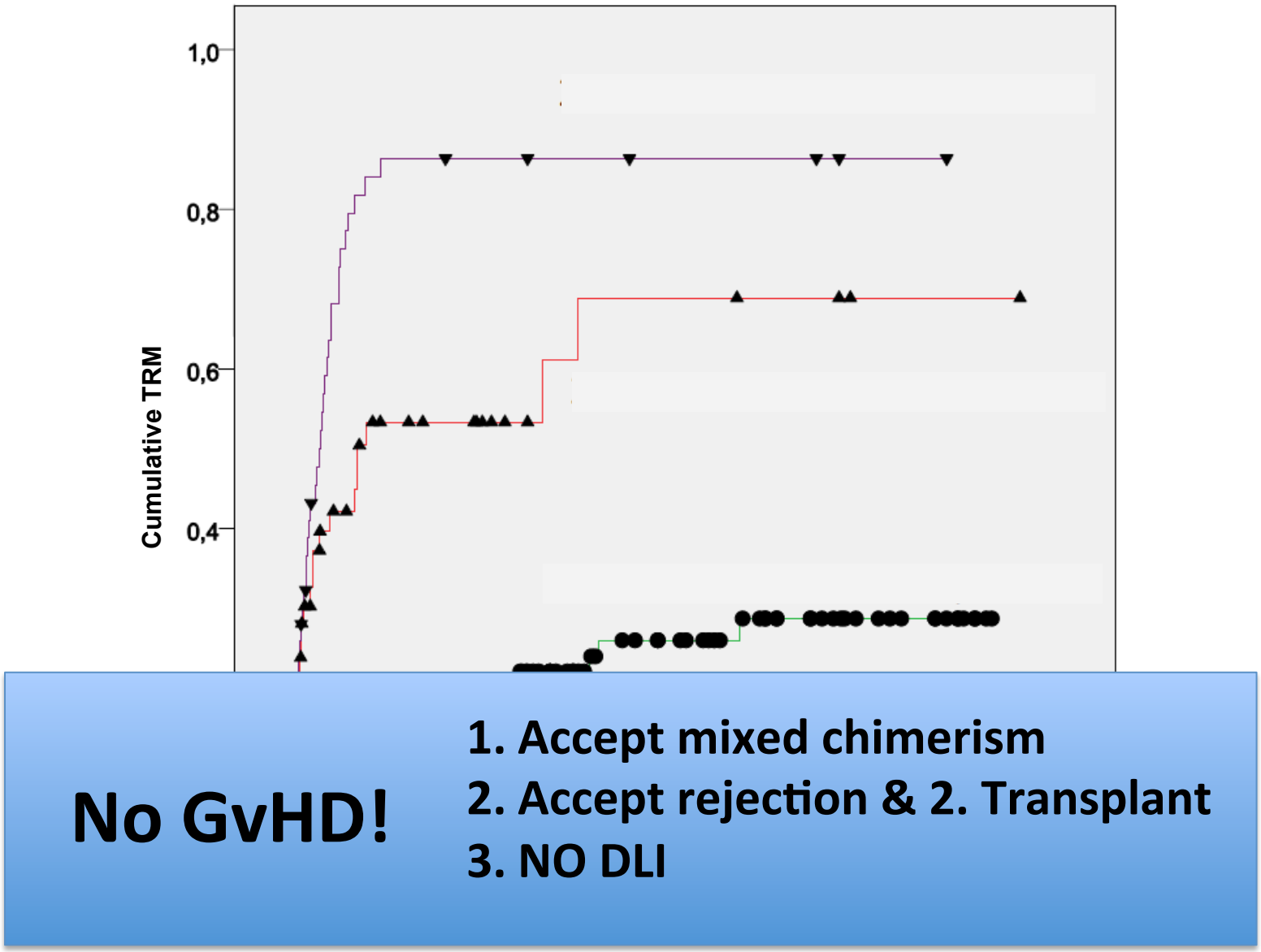
- **Significantly reduced TAMMX 1 year after transplant in 49 assessable patients *(p<0.001)***



Bernaudin et al, 2011

What are our expectations from a successful SCT in SCD?

- Conditioning regimen
  - Non-toxic
  - Immunosuppressive
  - Myeloabative (?)
- Immediate donor availability
- Quick and sustained engraftment
- Low TRM

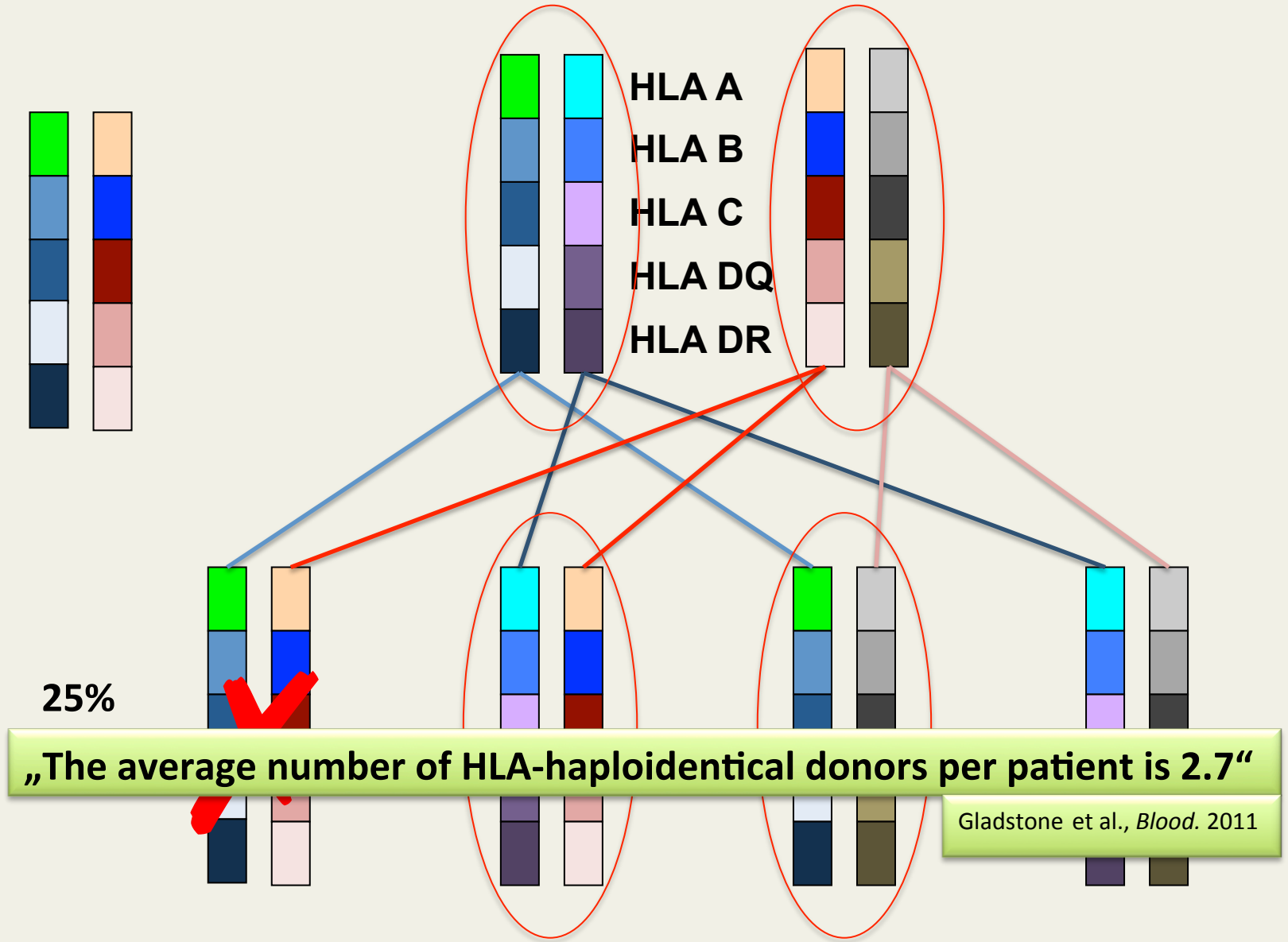


No GvHD!

1. Accept mixed chimerism
2. Accept rejection & 2. Transplant
3. NO DLI

What if a MSD or MUD donor is not available?

Haploidentical SCT



„The average number of HLA-haploidentical donors per patient is 2.7“

Gladstone et al., *Blood.* 2011

Haploidentical SCT

Pro‘s

- Immediate donor availibility (average 2,7/patient)
- High cell dose
- Low GvHD rate
- Fast neutrophil and PLT engraftment

Con‘s

- Delayed immune reconstitution (?)
- High risk for TRM (?)
- High rate of graft rejection and GvhD (?)
- Expense (?)

Haploidentical SCT, 2014

- Major developments in the last years
  - CD34 pos. Selection („Megadose“: >1x10^6 CD34), 1995
  - CD3/CD19 depleted SCT, 2003
  - α/β depleted SCT, 2010
  - Post-SCT Cyclophosphamide, 2010 (1963)
  - CD45RA depleted SCT, 2015 (?)
  - Post-SCT Cyclophosphamide + T cell depletion

GvHD?

Graft versus Host Disease in Haplo-SCT?

- **CD34+:**
  - Grades II-IV acute GVHD 11%
  - Grades II-IV chronic GVHD 14%

Ciceri F, *Blood,* 2008

- **CD3/CD19 depleted:**
  - Grades II-IV acute GVHD 46%
  - Grades II-IV chronic GVHD 18%

Federmann B, *Haematologica,* 2011

- **α/β depleted:**
  - Grades I-II aGvHD skin only in 26% (n=50)
  - Limited cGvhD (skin only) in 4%

Bertaina et al, *EBMT* 2014, PH-O106

- **Post SCT Cy:**
  - 100-day cumulative incidence of grade aGVHD II-IV : 32%

Brunstein et al, Blood, 2011

Transplantation of CD3/CD19 depleted allografts from haploidentical family donors in paediatric leukaemia

- N=46
- Conditioning: Flu (Clo), TT, Mel, ATG
- Graft: CD3/CD19 depleted (CliniMACS)

- Results:
  - Engraftment Rate: 87%

Incidence of a/cGvhD in haplo-SCT is low

  - **No a**GvHD in 48%
  - Grade 1 aGvHD in 26%
  - Grade 2 aGvHD in 19,5%
    - **Grade 3 & 4 aGvHD in 6,5% (II – IV: 26%)**
  - **Chronic GvHD:**
    - Overall in 21%
    - Limited disease in 9%
      - **Extensive disease in 11%**

Lang et al, BJH, 2014

Incidence of acute GvHD (Day+100) in allogeneic HSCT recipients

Defibrotide prevention trial
(prospective, controlled, randomized)

Day+100 Incidence aGvHD grades II-IV	Control arm N = 117
Graft from Mismatched donors	11/31 (35.5%)
Graft from Matched donors	32/86 (37.2%)
Graft from Mismatched Unrelated donors	5/21 (23.8%)
Graft from Matched Unrelated donors	20/61 (32.8%)

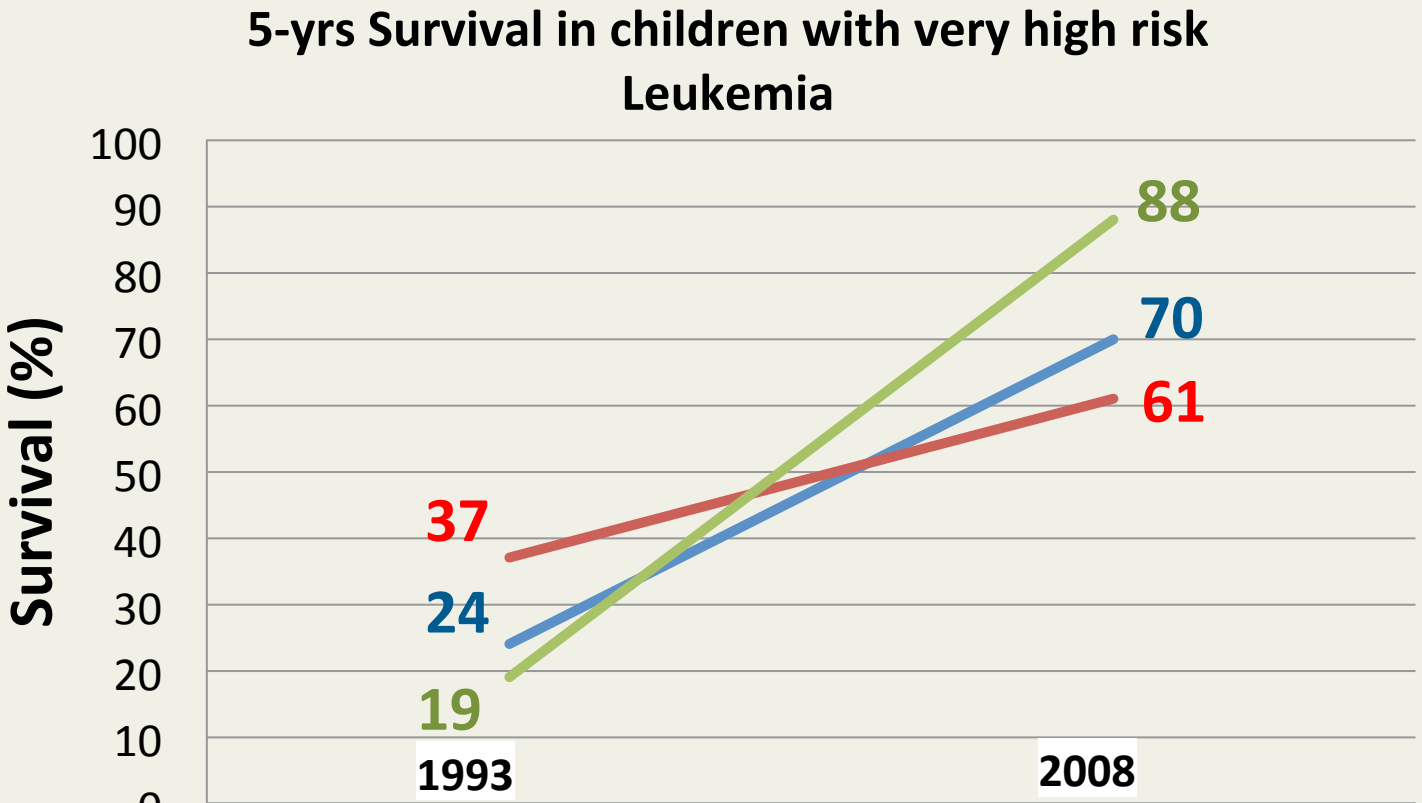
Corbacioglu et al, Lancet 2012

Comparability of
OS, DFS, Relapse
between MRD, MSD and Haplo?

PT SCT Cy	MRD (n=115)	MUD (n=99)	Haplo (n=45)
OS at 36 months (%)	71	58	**58**
DFS at 36 months (%)	47	46	**55**
Inicidence of relapse (%)	35	38	**36**

Bashey, et al Blood 2011

Progress in 5-yrs survival

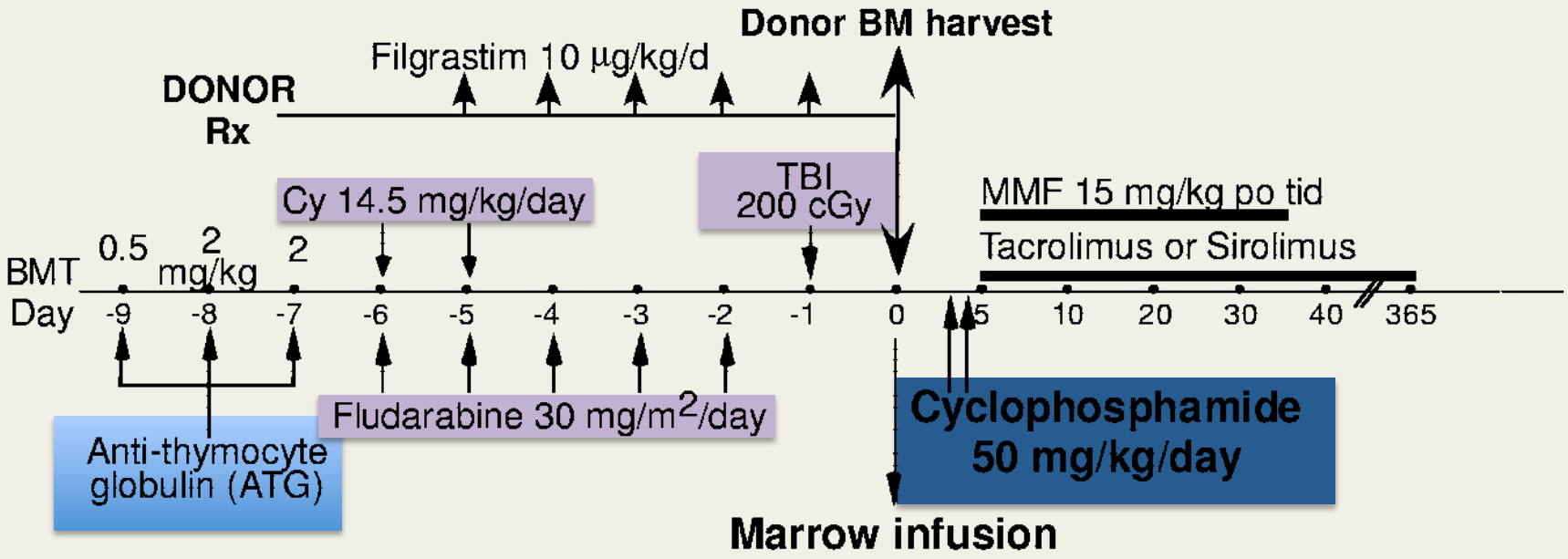


	1	2
MSD	24	70
MUD	37	61
Haplo	19	88

Leung W et al., Blood 2011

Expenses?

Post-transplant Cyclophosphamide PT-CY



Double unrelated cord blood *vs.* haploidentical BM?

Results of 2 parallel phase 2 trials (adult leukemia/lymphoma pts)

RIC: Flu, Cy, 200TBI

	1-yr non-relapse mortality	d100 II-IV GVHD	Median ANC recovery (>500)	Median plt recovery (>20K)	Graft failure	Stem cell source cost
dUCB (50 pts)	**24%**	**40%**	**d15**	**d30**	**12%**	>60K USD
Haplo BMT (50 pts)	**7%**	**32%**	**d16**	**d24**	**2%**	0

Brunstein et al. *Blood* 2011;118:282

PT-CY or CD34+ SCT?

	PT-CY (n=32)	TCD (n=33)
Engraftment Rate	94%	81%
Non-Relapse Mort.	**16%**	**42%**
OS	**64%**	**30%**
PFS	**50%**	**30%**
aGvHD II-IV	20%	11%
cGvHD	7%	18%

N=65 adult pts. with hem. malignancies

- Excellent immune reconstitution with PT-CY

Ciurea et al, Biol Blood Marrow Transplant. 2012

Prospects

Partially matched related (haploidentical) SCT for SCD

	Mortality	III-IV GVHD	Graft failure
PT-CY BMT (14 pts: 15-42 yrs)	**0%**	**0%**	**43%**

Bolanos-Meade et al. Blood 2012;118:282

Haploidentical SCT, 2013-14

- 100% Donor availability
- Low incidence of GvHD
- Comparable incidence of OS, DFS, RR
- Simplified access to SCT procedures
  - PT-Cy with BM
  - CliniMACS Prodigy® cell separation system (Miltenyi)

The donor selection process: Is it time for a change?

Type of donor	Chance
1. Matched sibling donor, 8/8 or 10/10	25%
2. Mismatched related (haploidentical) donor	≈100%
3. Matched unrelated donor, 10/10, 9/10	50% - 0%
4. Cord Blood	50% - 0%

Delayed SCT due to lack of a suitable donor increases risk of

- TRM
- GvHD
- Graft rejection in heavily transfused patients
- Complications assoc. with vasculopathy
  - PRES and other cerebral vascular complications
  - VOD in liver fibrosis/hepatic siderosis
  - Nephropathy and other complications of cont. conservative care

German SCD Transplant Registry

Tasks:

Collect all German SCD SCT activity in one database

- Donor selection
- Indications
- Conditioning
- Immunosuppression
- Chimerism

Collect all SCT related complications

- Rejection
- TRM
- GvHD
- Neurological Complications (PRES et al)
- VOD
- Fertility
- Et al

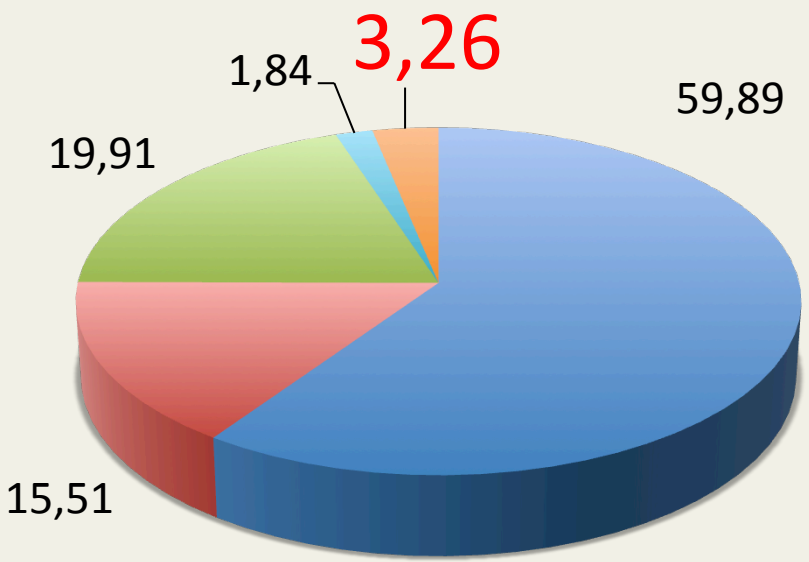
medac

„Die normative Kraft des Faktischen“

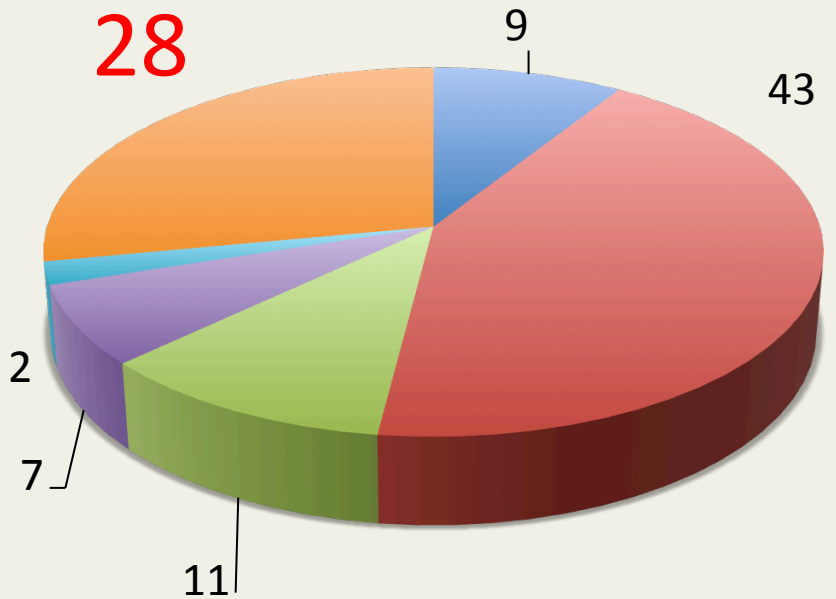
G. Jellinek (1851-1911)

Transplant Survey

EBMT, 2012 (%)



China, 2010 (%)



Autologous MRD MUD MMUD UCB Haplo

Passweg et al, BMT, 2014

Huang, Am J Blood Res 2011