Place of SCT in the management of inherited marrow failure disorders

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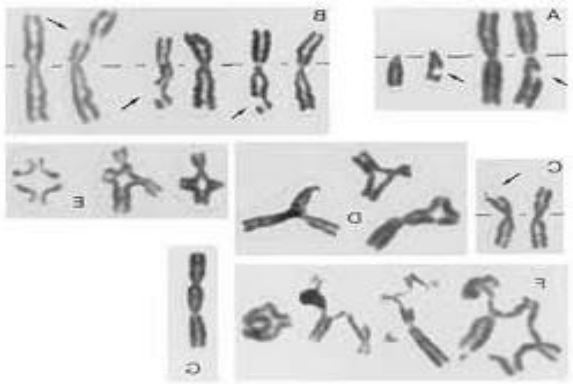
ERN-EuroBloodNet
Focus on BMF Syndromes
15th March 2022

- Fanconi Anemia (FA)
- Diamond Blackfan Anemia (DBA)
- Schwachman Diamond Sindrome (SDS)
- Telomere Biology Diseases (TBD)

Fanconi Anemia

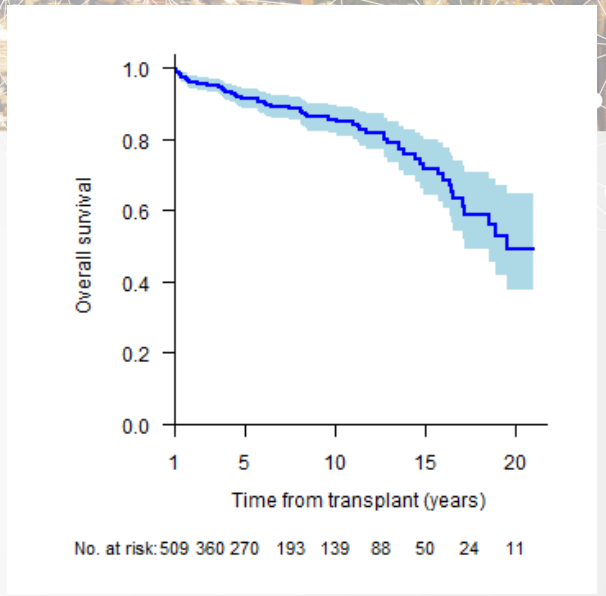
- Marrow failure +/- somatic malformations
- Increased risk of tumors (+ 700 AML, + 600 HNSCC + 6000 MDS)
- Incidence: 3 cases/million/year
- 22 genes so far (15 true FA genes)
- Progressive pancytopenia usually in the first decade of life.
- Diagnosis: Chromosomal fragility test DEB/MMC



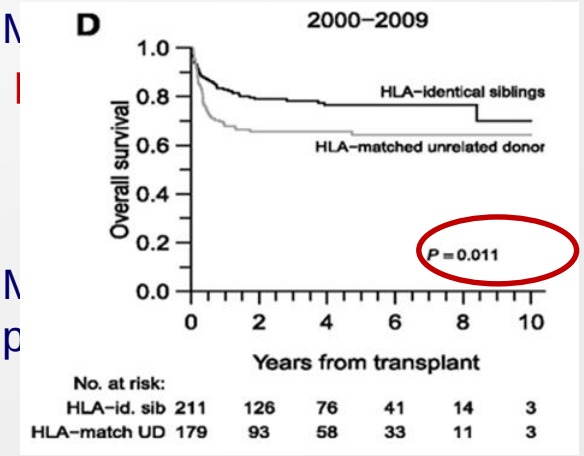
- NGS

HSCT

- 789 first SCT
- MRD (65%)
- Marrow as cell source 79%
- Conditioning Regimen
  - Fludarabine-based 29%
  - Irradiation 27%
  - T-cell depletion 41%



Ac GvHD
MSD vs MUD



Overall Survival

71% at 15 years
49% at 20 years
Follow-up 6 years

BM cells improve survival

R Peffault de Latour,…C Dufour SAAWP EBMT, Blood 2013

HSCT

- Causes of death

  GvHD 34%

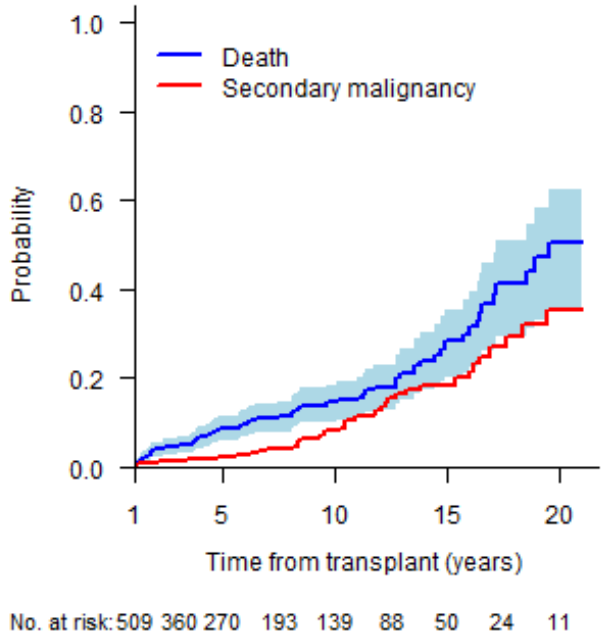
  Infections 27%

  Secondary malignancies 10%

- Negative impact on late tumors

  Use of PBSC
  Previous cGVHD
  MDS/AML

R Peffault de Latour & C Dufour EBMT, Blood 2013



- Late tumours

  40% develop tumours 15-20 years after SCT.

  Head & Neck SCC earlier, ~ 8 yrs after TAI & CY if GVDH

P Rosenberg,Blood 2005

SCT increases the risk and accelarates the appearance of late tumours

UK STUDY (1999-2018)

82 pts
median age 8.7 yrs
Median follow up 6.2 yrs (5-7.3)

42 MRD –
23 MUD - 6 MMUD
9 HAPLO

Most PBSC

69 BMF
11 MDS/leukemia

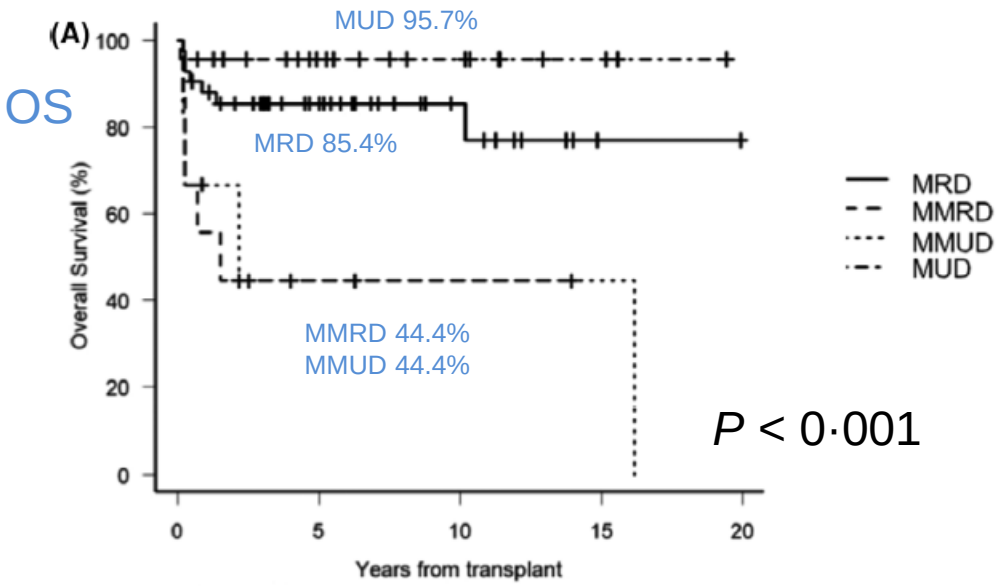
Conditioning regimen
FLU-CY 87%
TBI/TAI 13%

Serotherapy
Alemtuzumab 69.5%
ATG 22%

5y-OS: 79.9%

5y-cGVHD-free EFS: 75.4%
5y-NRM: 13.8%

Ac GvHDII-IV 6%
CGvHD 10%
3 pts secondary malignancies



$P < 0{\cdot}001$

Bernard F et al, UK Paediatric BMT group; Br J Haematol 2021; 193(4):804-813

Limited Resources Countries

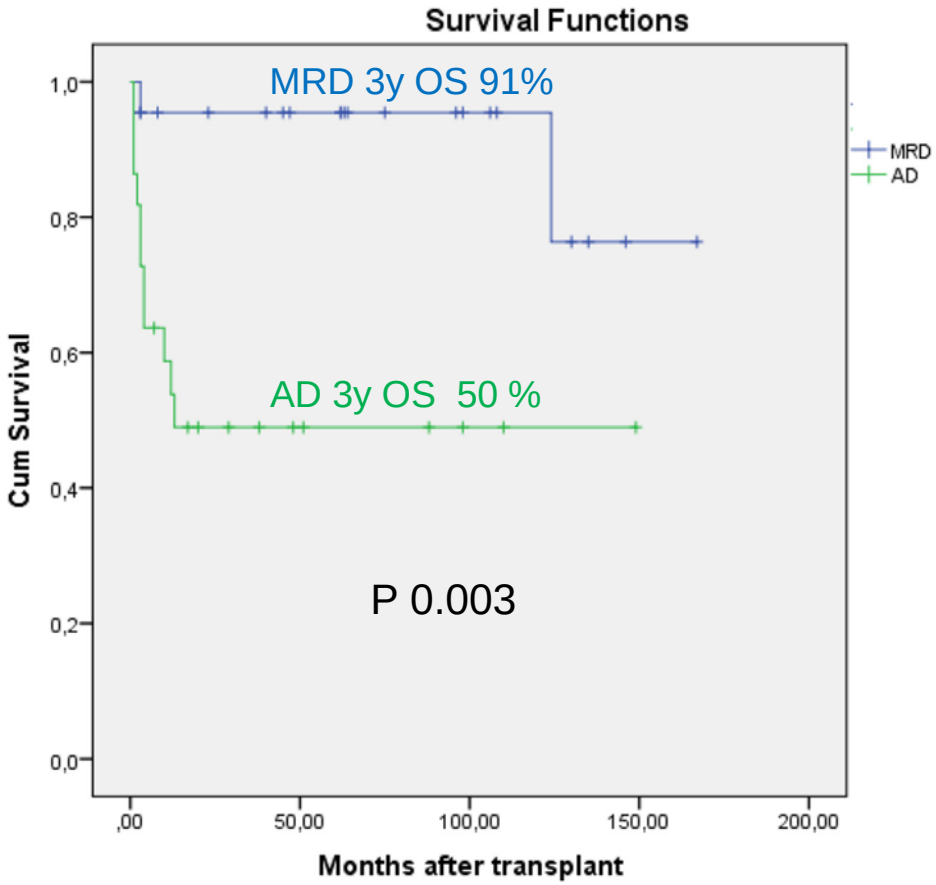
44 patients
22 MRD
22 AD

Radiation-free, reduced-intensity conditioning regimen (Flu, Cy, ATG)

Unmanipulated graft

Ac GvHD 13% in MSD
C GVHD 4% overall

Follow-up 3 years

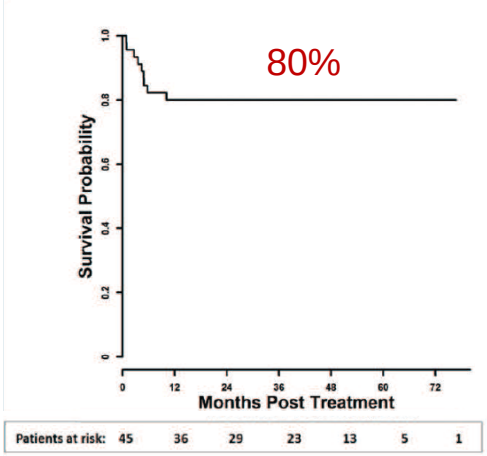


Tuysuz G et al, BBMT 25, 2017-23, 2019

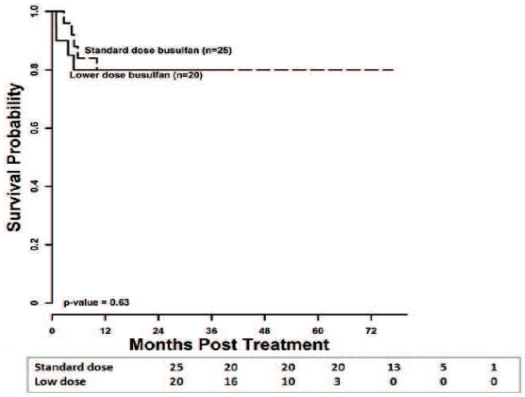
Alternative Donor

New York-Cincinnati protocol
45 pts
Follow-up 41 months
Bu, Cy, Flu, ATG, No irradiation
Source of cells: CD 34+ TCD PBSC

OS



OS by busulphan dose



Ac GvHD 6.7% at d 100, all I-II
cGVHD 6.6% limited
All responsive to treatment
Never lethal

Mehta P et al Blood 2017 Apr 20;129(16):2308-2315.

HAPLO PTCY

63 patients

Conditioning

only Flu 30mg/m2/dx5

TBI 200

Alemtuzumab/ATG d-8-5

CY post 25 mg/kg/d x 2d

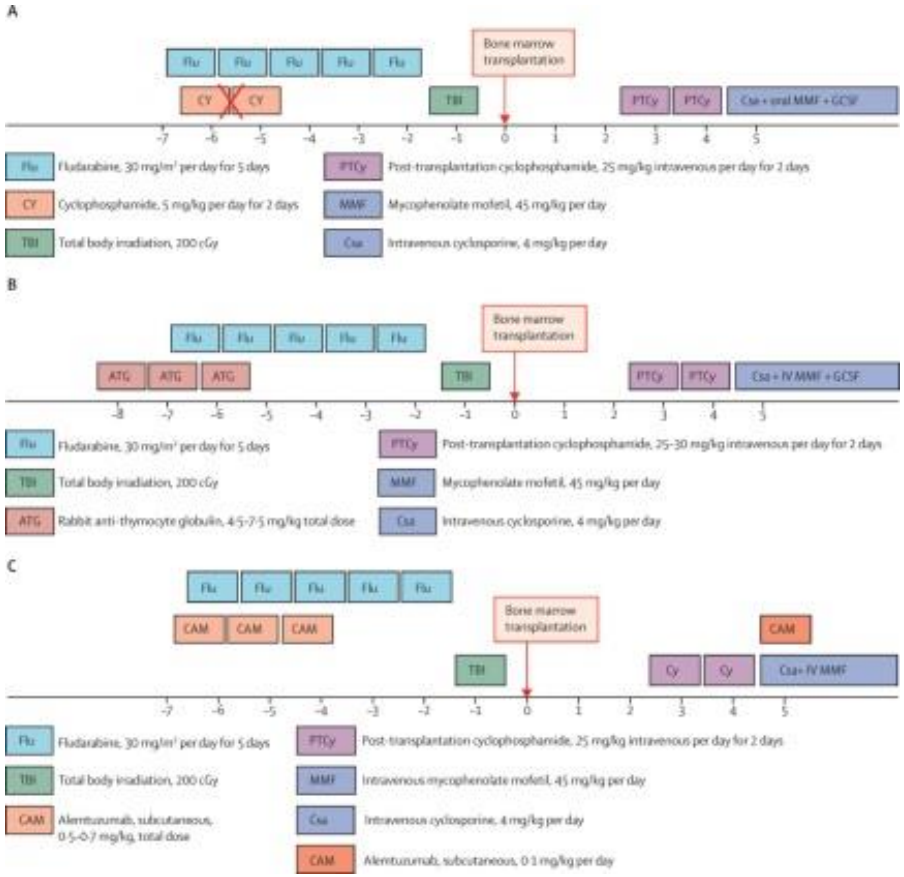
CsA + iv MMF

2-y OS 82%

(50% with no serotherapy p=0·015)

2-year Ac GvHD II-IV 28%

cGVHD 26%.



Bonfim C Lancet hematology, Vol 8, issue 3, March 2022, Pages e228-e236

HAPLO αb+/CD19+ depleted

24 pts
median age 8.6 yrs
Follow up 5.2 yrs

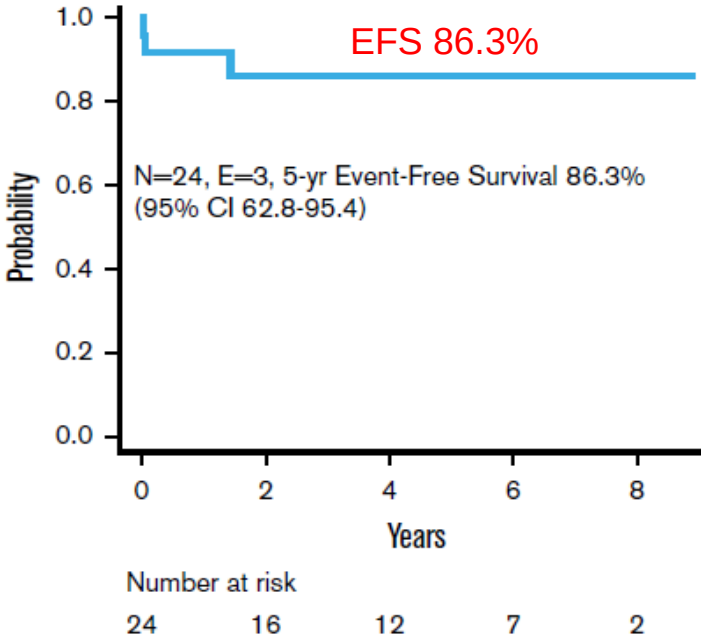
23 BMF
1 clonal evolution (RCC)

Flu-LD CY
+ TBI 200 cGy (except 3pts)
ATG -4-2
Rituximab -1

No GVHD prophylaxis post

5y OS 100%

Ac GvHD all 17%
cGVHD 5.5%
1 secondary malignancy

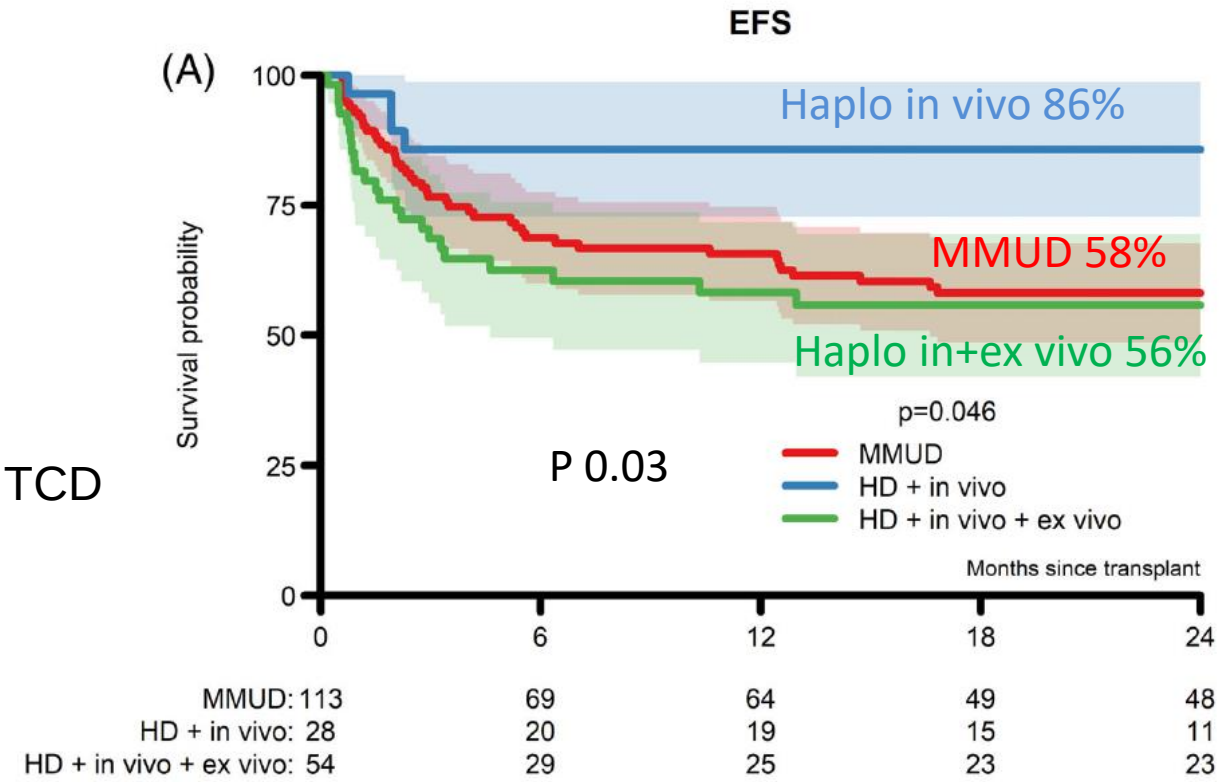


Strocchio L et al, Blood Adv. 2021, Mar 9;5(5):1333-1339

IN VIVO *vs* IN+EX VIVO TCD HAPLO HSCT

215 pts

MMUD 57.2%
HAPLO 42.7%
- 36% in vivo TCD
- 64% ex vivo+in vivo TCD



NRM no differences

aGVHD II-IV

MMUD 41%
HD + in vivo TCD 40%
HD + in vivo + ex vivo TCD 17%

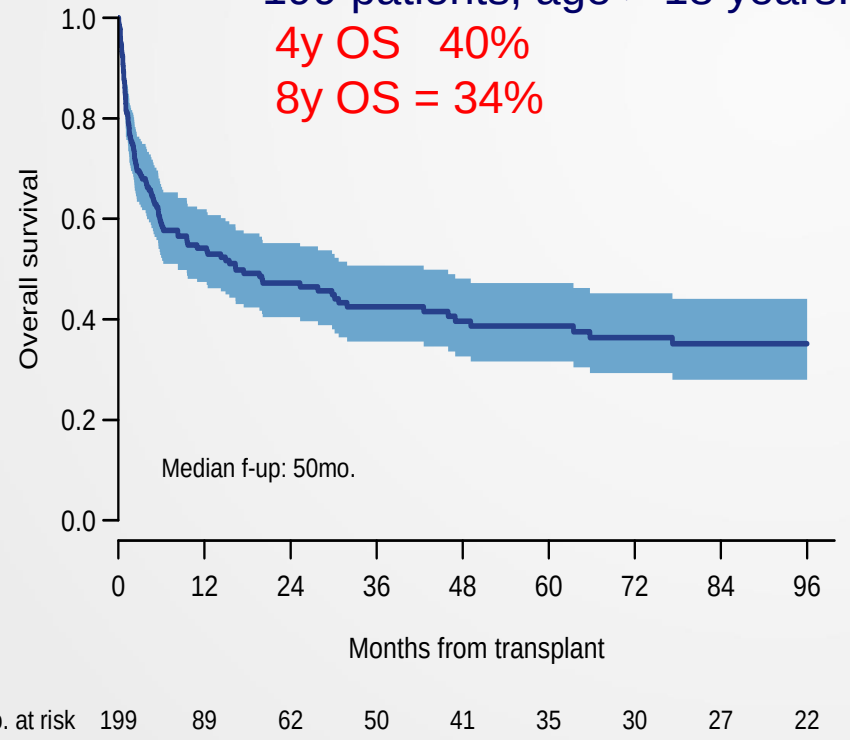
Zubicaray J et al, Am J Hematol. 2021 May 1;96(5):571-579. for SAAWP EBMT

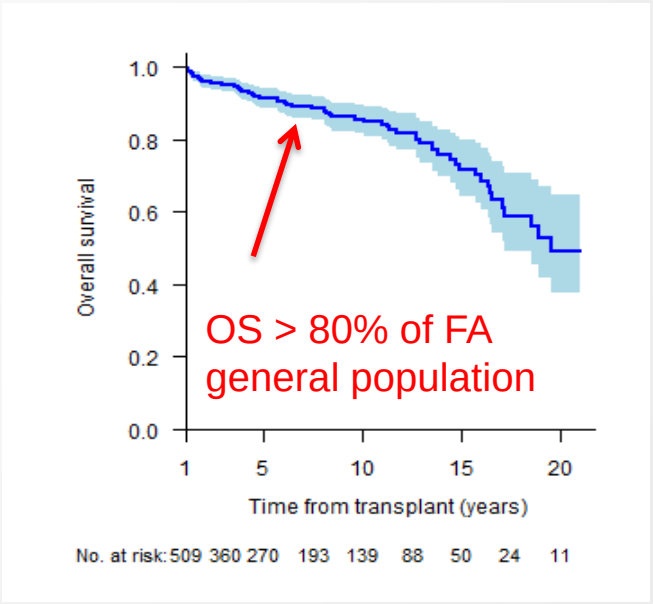
SCT in HIGH RISK PATIENTS
Adult FA

199 patients, age > 18 years.

4y OS 40%

8y OS = 34%

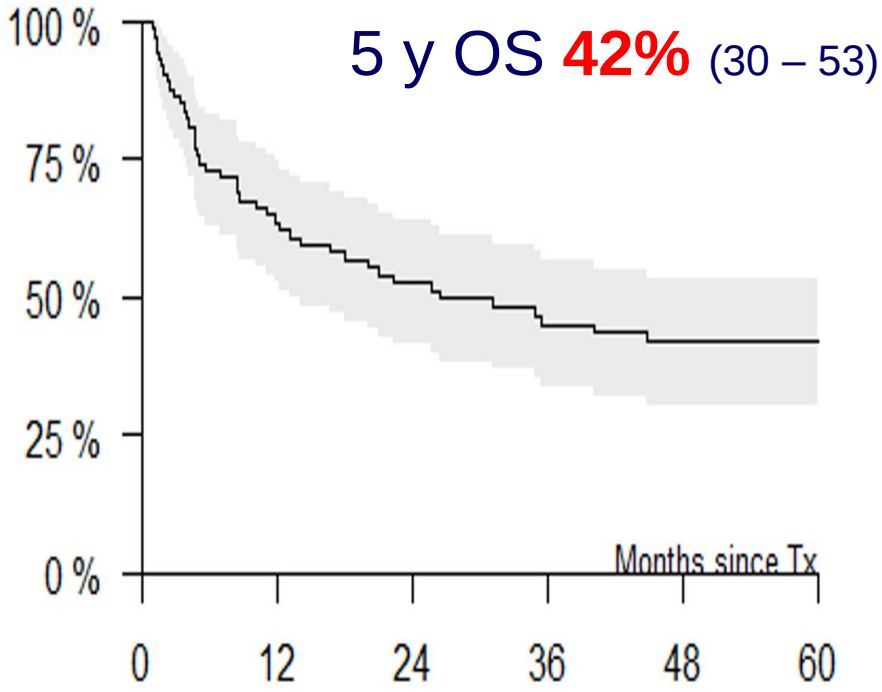




M Bierings for SAAWP EBMT & non EBMT, 2018, BrJ Haem; 180 (1): 00-9

HSCT IN HIGH RISK PATIENTS
FA with MSD/AML

74 FA pts 35 AML
35 MDS
4 cytog abn



Main Cause of death	N	%
➢ **Relapse or disease progression**	8	**19**
➢ **Not-relapse related**	34	**81**
• GvHD	15	35.7
• Infection	7	16.7
• Multi-organ failure	6	14.3
• Secondary malignancy/PTLD	2	4.8
• Other HSCT-related	4	9.5
Total	**42**	**100.0**

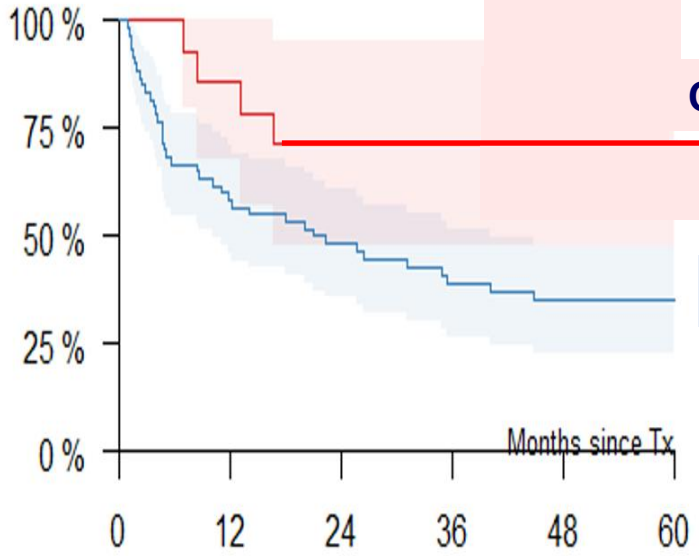
S.Giardino et al on behalf of *SAAWP & CMWP EBMT. Am J Hematol 20*

SCT IN HIGH RISK PATIENTS
FA with MSD/AML

EFFECT OF PRE-SCT REMISSION STATUS

5yr OS

92% of patients in CR was AL



CR **71%** (48-95)

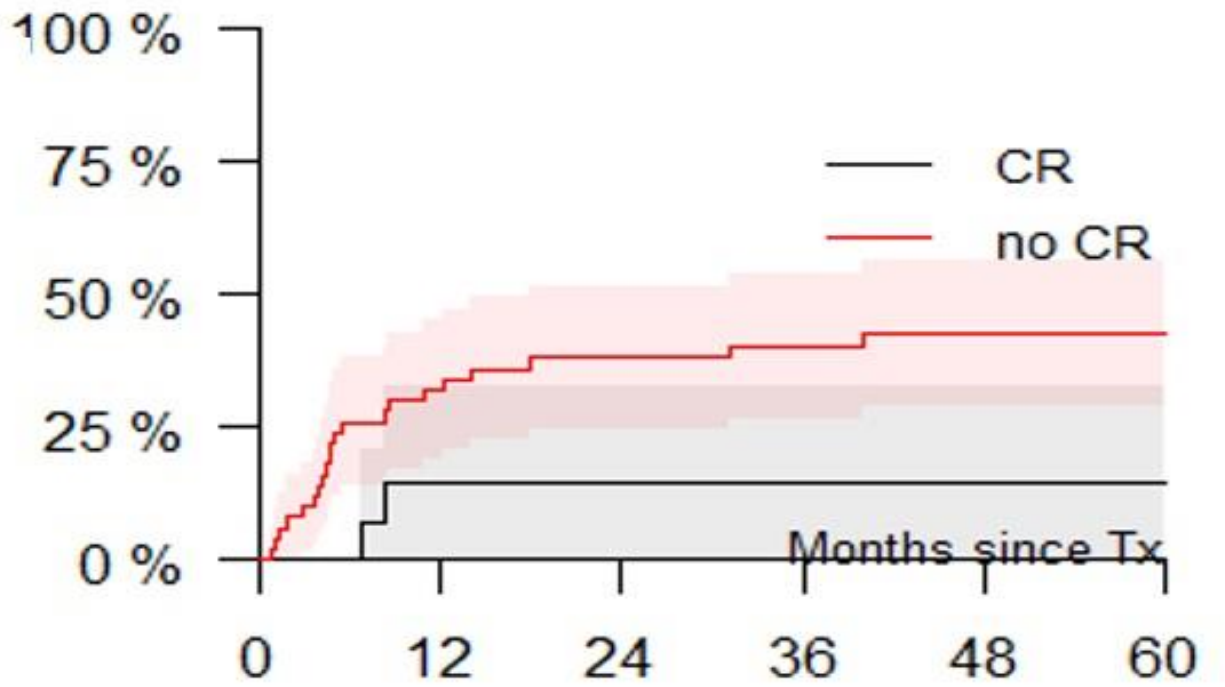
p = 0.03

no-CR **35%** (23-48)

S Giardino, SCT Unit. G.Gaslini Institute Genoa Italy, on behalf of SAAWP & CMWP EBMT. Am J Hematol 20

SCT IN HIGH RISK PATIENTS
FA with MSD/AML

EFFECT OF NON RELAPSE MORTALITY



P=0.05

OVERALL BETTER OUTCOME IF SCT IN REMISSION

S Giardino, SCT Unit. G.Gaslini Institute Genoa Italy, on behalf of SAAWP & CMWP EBMT. Am J Hematol 2019

Conditioning

MSD

Cyclophosphamide 40mg/Kg D-6 to D-2
Fludarabine 90mg/m2 D-5 to D-3
Cell source: BM
GvHD prophylaxis: CsA-MMF

95% OS at 2 yrs
15 % Ac GvHD Acute 3-4
10% Cr GvHD

Benajiba L et al, St Louis. Blood 2015

MUD

Cyclophospamide 40 mg/kg for 4 d
Fludarbine 120 mg/m2 for 4 days
ATG 7,5 mg/kg for 2 days
TBI 2 Gy (ATG for 4 days id <14 years)
Cell Source: BM
GvHD prophylaxis CsA MMF

Hopital St Louis, Paris

- MDS/AML/high risk clonal abnormalities (-7q,+3q, complex abn)

FLAG + SCT in aplastic phase
HD ARA C + SCT

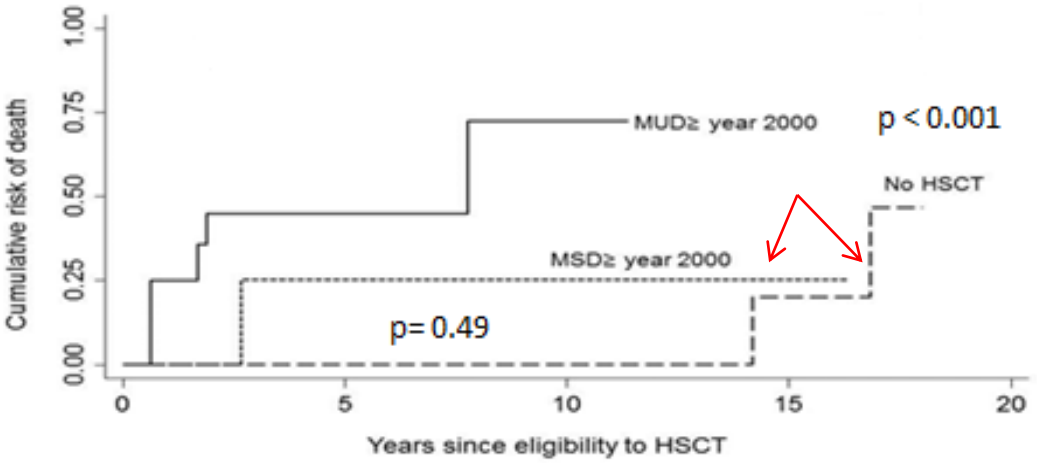
Need for data with thorough follow-up on NON transplanted FA patients
to compare
with transplanted FA patients

Consensus Statement from the 2nd Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects after Pediatric Hematopoietic Cell Transplantation

Dietz Ac et al , BBMT, 2017.01.075

- Cytopenia may stabilize or improve in about 1/3 of patients

- Patients tranplanted with MODERATE CYTOPENIA
- Follow-up 4.6 years



NON TRANSPLANTED PATIENT DO as MSD SCT but BETTER than MUD SCT

J Svahn et al for Aieop, Am J Hematol 2016, Jul;91(7):666-71

Diagnosis

Normal FBC +
No dysplasia +
No cytogenetic abn
+
No MDS/AML

Mild cytopenia +
No dysplasia +
No cytogenetic abn +
No MDS/AML

Moderate cytopenia +
No dysplasia +
No cytogenetic abn
Or+
No poor risk cytogenetic abn (+1q; -20q; -11q)

Severe cytopenia or dysplasia (10% blasts)
Or
poor risk cytogenetic abn (+3q; -7q; complex abn, RUNX1 mutation)

MDS (> 10% blasts) **or AML**

FBC every 6 months
BM studies every year

FBC every 3 months
BM studies every 6 mos

FBC every 6 weeks
BM studies every 3-4 months

SCT

Cytopenia becomes Moderate

Cytopenia becomes Moderate

-**NON FA MSD available**

↓

SCT

-**NO MSD available, but 10/10 MUD available**

↓

SCT as soon as moderate cytopenia progresses

-**NO MUD 10/10 available**

↓

Androgens ± supportive theraphy
Experimental treatments (Haplo, Cord SCTs, Gene therapy)

SCT from either MSD or MUD
Consider Haplo or Cord SCT if a donor is not found

Chemo therapy followed by SCT

∂BRCA2/FANCD1 patients should undergo a close monitoring and early premptive SCT once a donor is found.

Dufour C How I manage Fanconi Anemia, Br J haematol 2017 Jul;178(1):32-47

FA TAKE HOME MESSAGE

- HSCT is so far the only consistent option to restore hematopoiesis.
- Excellent survival in MRD setting also in middle-lower income countries.
- In recent cohorts Haplo equals MUD as for OS/EFD.
  PTCY same OS as ex vivo TCD
- HSCT increases cancer risk
- Pre-emptive HSCT not recommended
  Tight monitoring since diagnosis to intercept the “momentum”
- Moderate cytopenia, moderate shifting to severe
  Flu-based conditioning
- Tight lifetime monitoring after HSCT for malignancies.
- Follow up in “marrow failure” centres

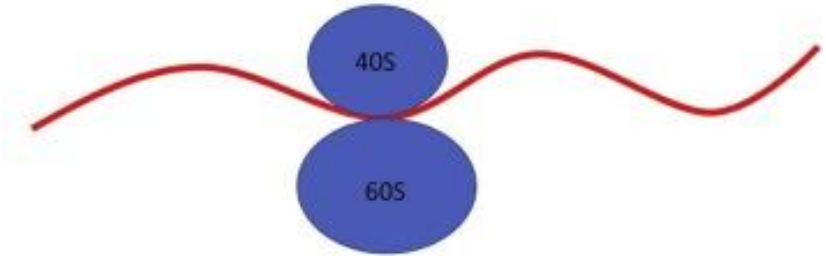
- Fanconi Anemia (FA)
- Diamond Blackfan Anemia (DBA)
- Schwachman Diamond Sindrome (SDS)
- Telomere Biology Diseases (TBD)

Diamond-Blackfan Anemia

Disorder of ribosomal synthesis

22+ genes identified so far. 20 ribosomal
90% of mutations in 6 genes *(RPS19, RPL5, RPS26, RPL11, RPL35A, and RPS24)*

Small ribosomal RNA:	Large ribosomal RNA:	Non-ribosomal:
RPS19, RPS10, RPS26, RPS24, RPS17, RPS7, RPS29, RPS28, RPS27, RPS20	RPL11, RPL5, RPL35A, RPL26, RPL15, RPL31, RPL27	GATA1 TSR2



Dietz Ac et al , BBMT, 2017 May;23(5):726-735, Eur J Med Genet 2017 Oct 26

Between 25- 35% of patients are gene orphan

Diamond-Blackfan Anemia

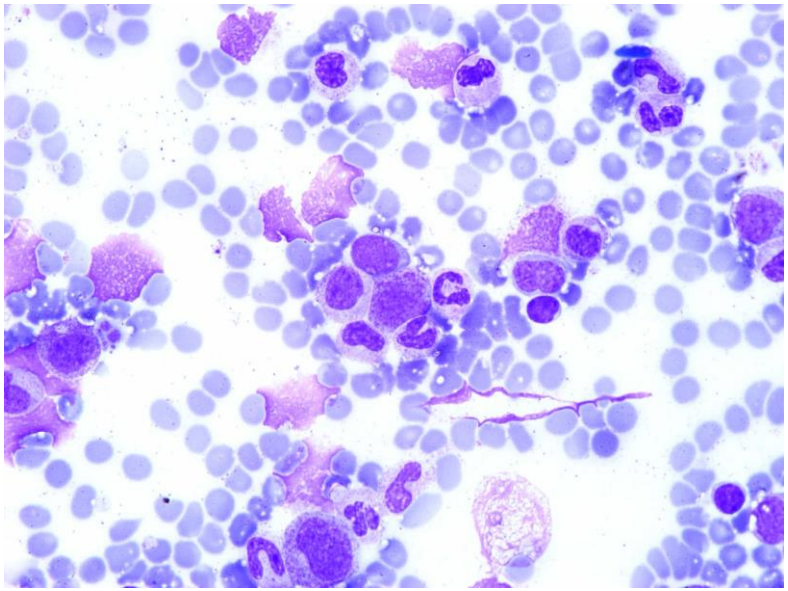
Incomplete penetrance and variable expression

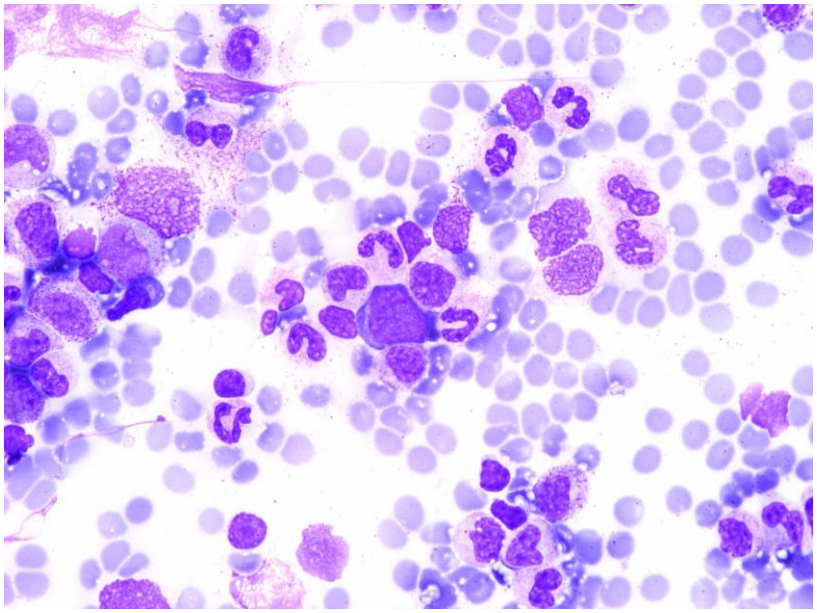
Macrocytic/normocytic anemia at birth or within first 6 months (ca 60%)

Reticulocytopenia

Elevated red cell ADA

Normocellular bone marrow with selective erythroid precursor deficiency





- Pre cancer disease

  O/E 4.75 for all cancers
  352 for MDS, 45 for colon K, 42 for osteosarcoma, 29 for AML

Vlachos A et al , ASH 2016

- Cancer risk in post SCT may be higher than in non SCT

Dietz AC et al , BBMT, 2017. May;23(5):726-735

SAAWP-EBMT STUDY (1985-2016)

Largest study ever
106 pts, median age at HSCT 6.8 yrs
Median follow up 5.6 yrs (4.3-7.4)

53% pre 2000

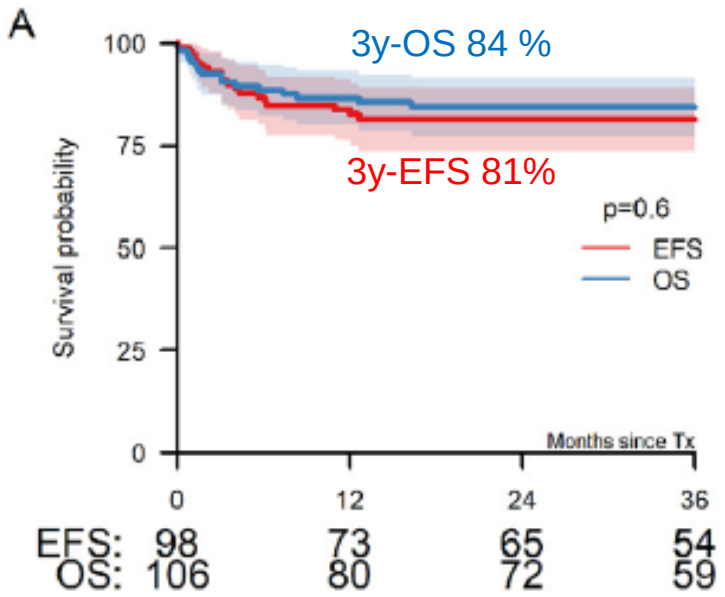
55% MSD 45% MUD/other relative
59% BM

62% > 20 RBC transfusion
77% iron overload

Previous treatment: 93% steroids, 11% epo

Transfusion dependency 70%;
AA 7%

Conditioning
84% Myeloablative (Bu or Treo-based)
16% Non myeloablative (Flu or Cy-based)

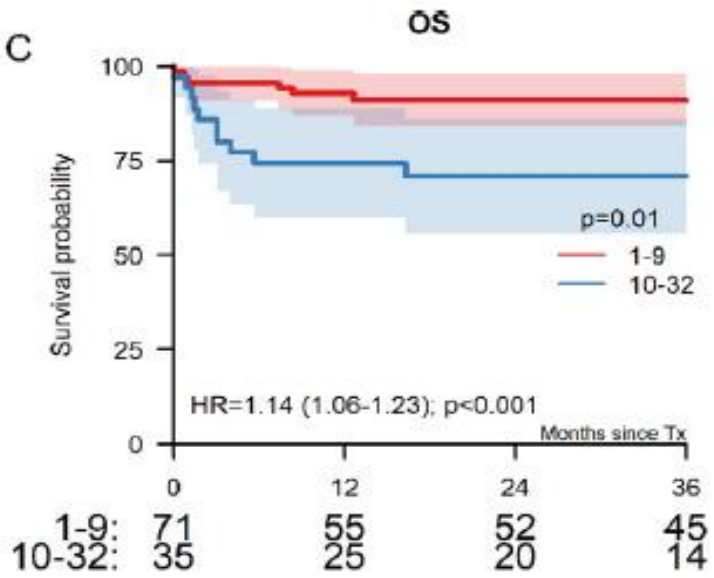


aGVHD II-IV 30%
ext cGVHD 15%

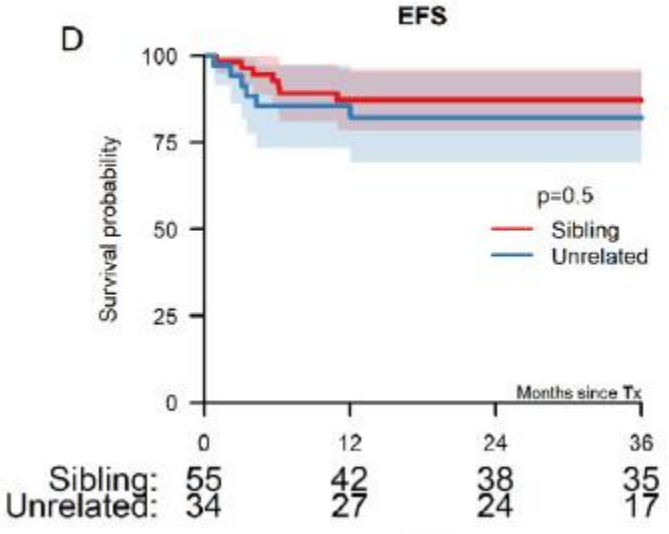
7 malign 5.5 yrs post HSCT

Miano M, Dufour C et al, Transplant Cell Ther. 2021 Mar;27(3):274.e1-274.e5.

SAAWP-EBMT STUDY (1985-2016)



Older pts worse outcome



No difference SIB *vs* MUD

Miano M, Dufour C et al, Transplant Cell Ther. 2021 Mar;27(3):274.e1-274.e5.

GERMAN- FRENCH STUDY

70 pts,
Median age 5.5 yrs, 74% <10 yrs old
Median follow up 4.5 yrs

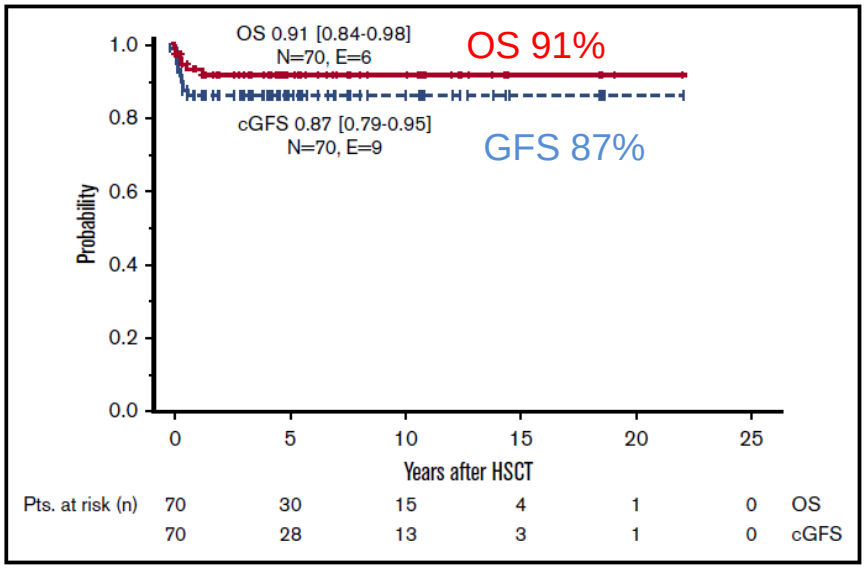
27% PRE 2000

64% MSD 36% MUD/MMUD
80% BM

81% > 20 RBC transfusion
77% iron overload

Transfusion dependency 95%;
Steroid dependency 2%;
Secondary MDS 2%

Conditioning regimen:
69% Bu-based
19% Treo-based
4% TBI-based
81% serotherapy



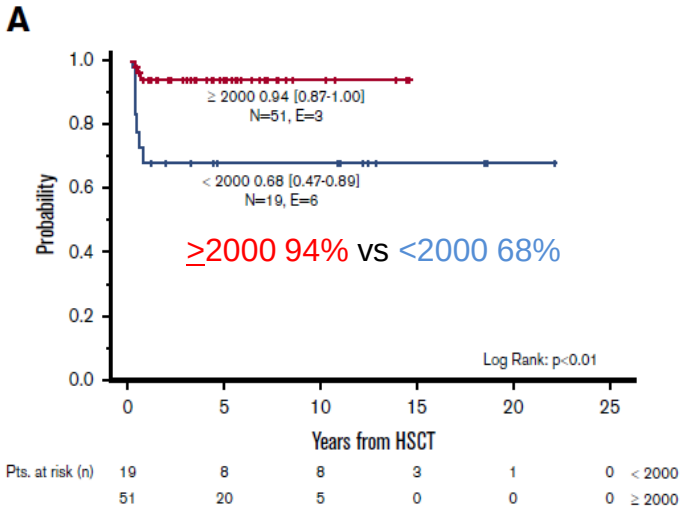
aGVHD II-IV 24%
cGVHD 11%

Major causes of death: TRM, infections

No malignancies reported

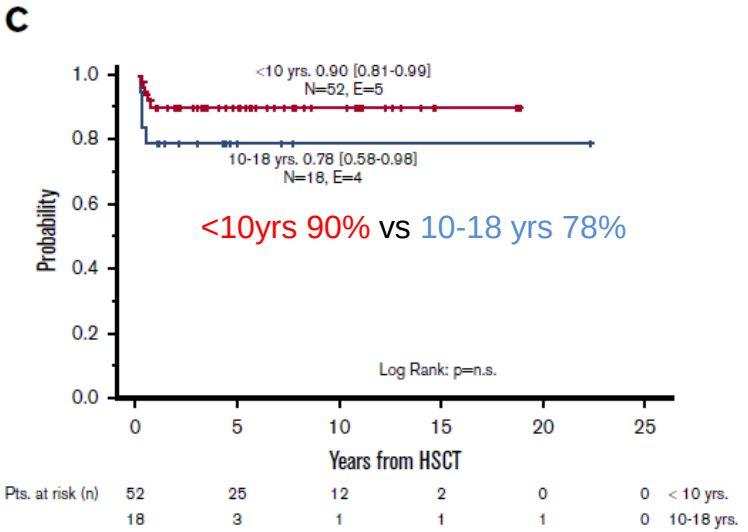
Strahm B et al, Blood Adv. 2020 Apr 8;4(8):1760-1769.

GERMAN- FRENCH STUDY



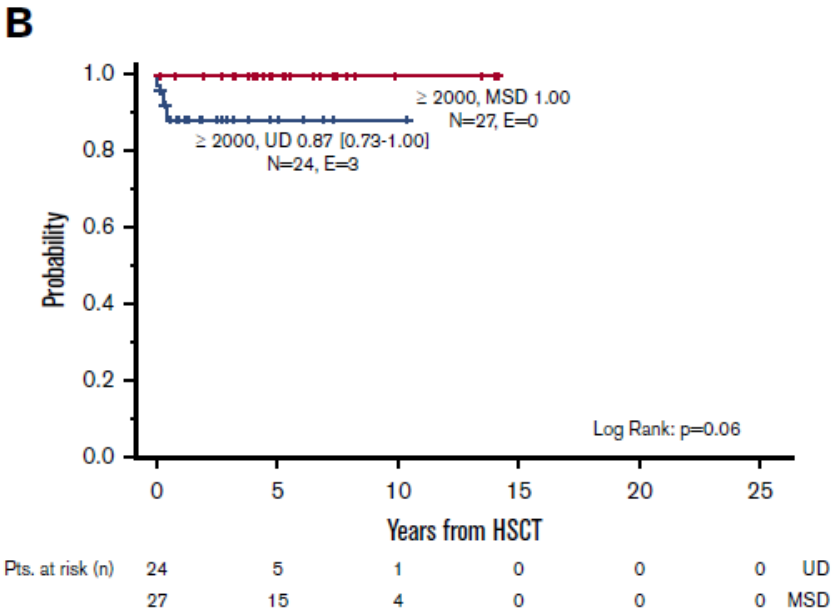
≥2000 94% vs <2000 68%

Pre 2000 worse GFS



<10yrs 90% vs 10-18 yrs 78%

Older pts worse GFS



SIB and MUD similar GFS

Overall similar results as EBMT

Small difference due to better patients selection

- Younger
- more post 2000

Strahm B et al, Blood Adv. 2020 Apr 8;4(8):1760-1769.

CURRENT RECOMMENDATIONS for SCT in DBA

- Steroid resistance
- Heavy side effects of steroid dependence
- Impossibility to “well transfuse & chelating” patients

- Genetic screen of donor if MSD SCT

- Need for appropriate chelation before SCT (iron liver <3 mcg/g dw) to reduce risk of SOS and infections

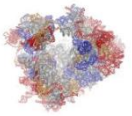
- Aggressive phlebotomy post–SCT to reduce the risk of late cardiac deaths

- Fanconi Anemia (FA)
- Diamond Blackfan Anemia (DBA)
- Shwachman Diamond Syndrome (SDS)
- Telomere Biology Diseases (TBD)

Shwachman Diamond Syndrome

Rare disease, 1: 153.000 newborns

Autosomal-recessive *(except for SRP54, autosomal-dominant)*



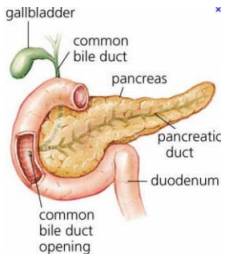
90% of cases mutations in SBDS gene (chr 7q11) impaired ribosomy assembly

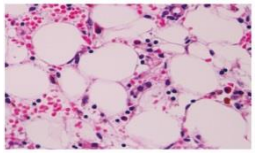
Other recently detected genes : EFL1, DNAJC21, SRP54

Clinical triad: skeletal abnormalities,

exocrine pancreatic insufficiency,

bone marrow dysfunction

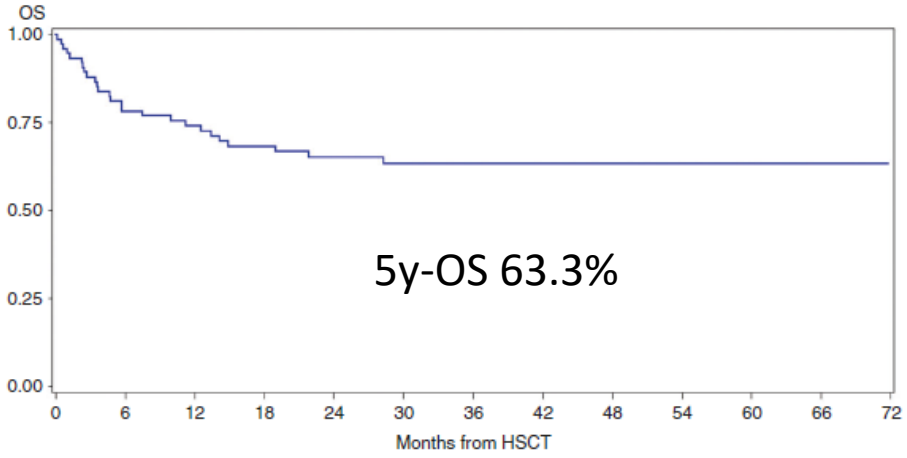




SAAWP EBMT STUDY (1988-2016)

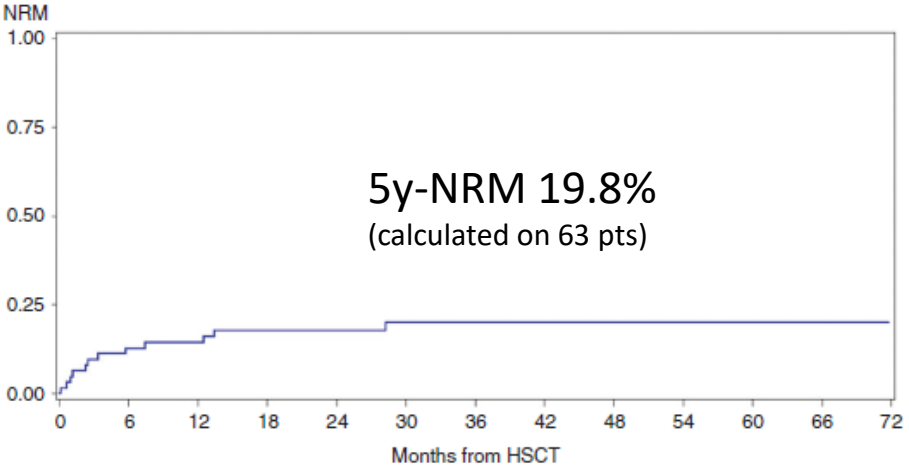
The largest study ever

74 pts, median age 8.7 yrs
20% >18 yrs
Median follow up 7.3 yrs



24% MSD/ 68% UD /8%others
70% BM

82% BMF
9% MDS
9% AML

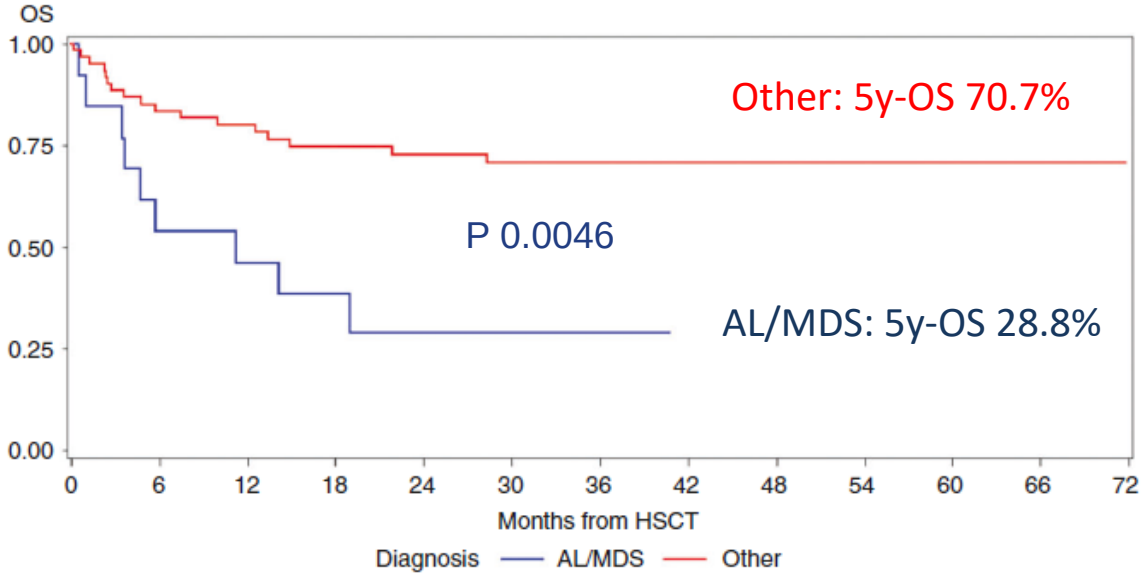


Conditioning regimen:
54% Myeloablative
46% RIC

aGVHD III-IV 44%
cGVHD 20%

Causes of death:
21 toxicity
7 progression/relapse

Cesaro S et al, Bone Marrow Transplant. 2020 Sep;55(9):1796-1809.



Worse OS in AL/MDS. Confirmed in MV

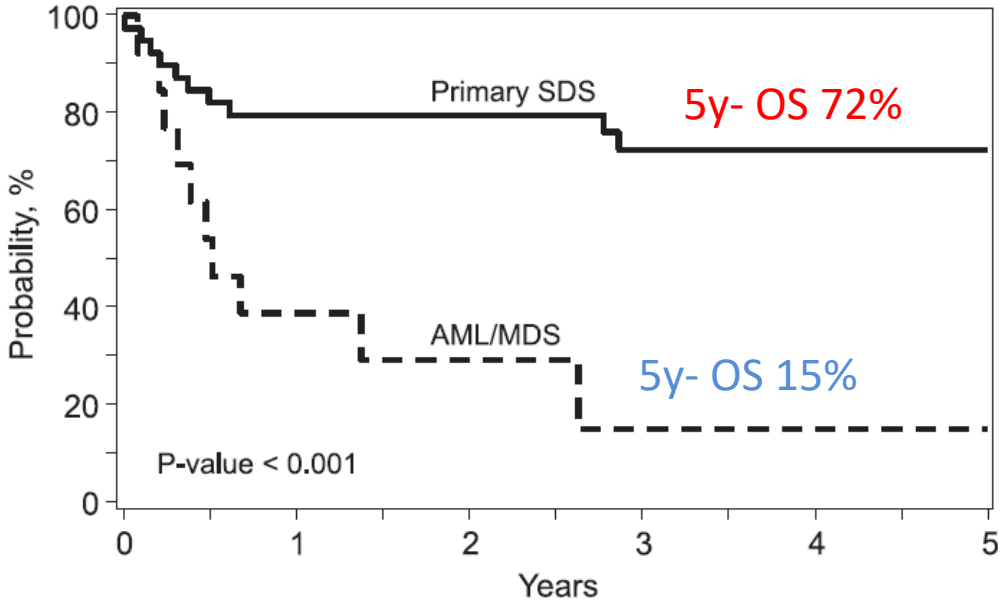
No difference in OS by

RIC *vs* MAC
MRD *vs* MUD,
TBI-based *vs* a no-TBI conditioning regimen

Cesaro S et al, Bone Marrow Transplant. 2020 Sep;55(9):1796-1809.

US RETROSPECTIVE ANALYSIS (2000-2017)

52 pts,
median age 11 yrs
Median follow up 5 yrs



<u>39 BMF</u>
Median age 7 yrs
16 MSD, 4 HAPLO, 15 MUD, 4 MUCB
27 BM, 6 PBSC, 6 UCB
Conditioning: 13 MAC - 26 RIC

aGVHD II-IV: BMF 26%
MDS/AML 46%

<u>13 MDS/AML</u>
Median age 18 yrs
3 MSD, 1 MMRD, 9 MUD
8 BM, 5 PBSC
Conditioning: 8 MAC – 5 RIC

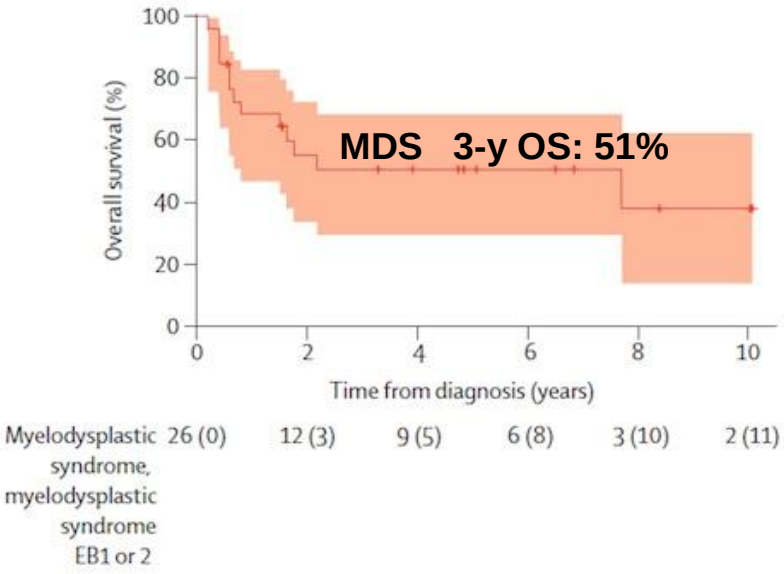
Causes of death:
BMF graft failure, GVHD, infections

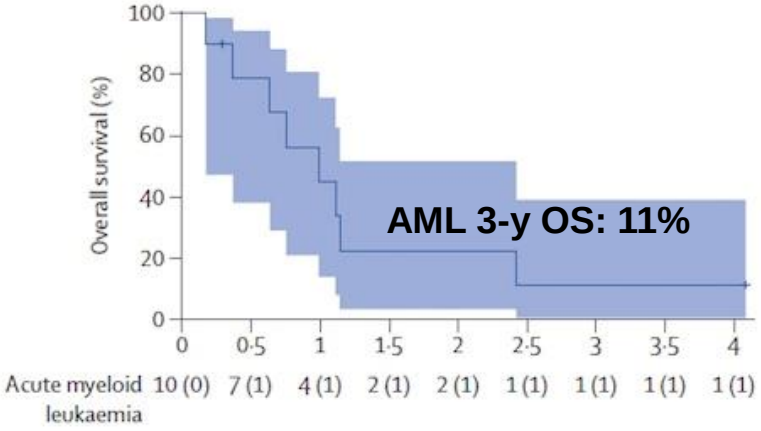
MDS/AML. recurrent/persistent disease
organ failure, VOD, infection

Myers K et al, Biol Blood Marrow Transplant. 2020;26(8):1446–1451

US/CANADIAN RETROSPECTIVE ANALYSIS OF MDS/AML

17 centers, 36 pts: 26 MDS, 10 AML





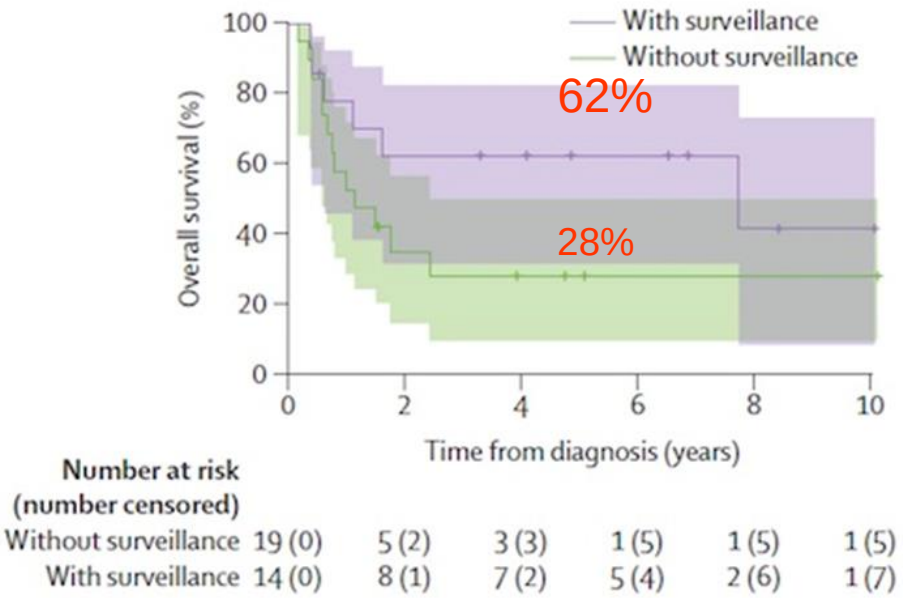
AML worse outcome *vs* MDS

Myers et al. Lancet Hematol 2019

Monitoring

3-y OS superior in SDS patients who underwent regular hematological surveillance

Myers et al. Lancet Hematol 2020



CURRENT RECOMMENDATIONS for SCT in SDS

- BMF, prior to overt MDS/leukemia
- Watch over comorbidities
- Monitoring is critical

- RIC preferred for BMF
- Chemotherapy-based myeloablative conditioning preferred for MDS/AML.

- Pre-HSCT cytoreduction with MDS/AML is an option but efficacy still debated.

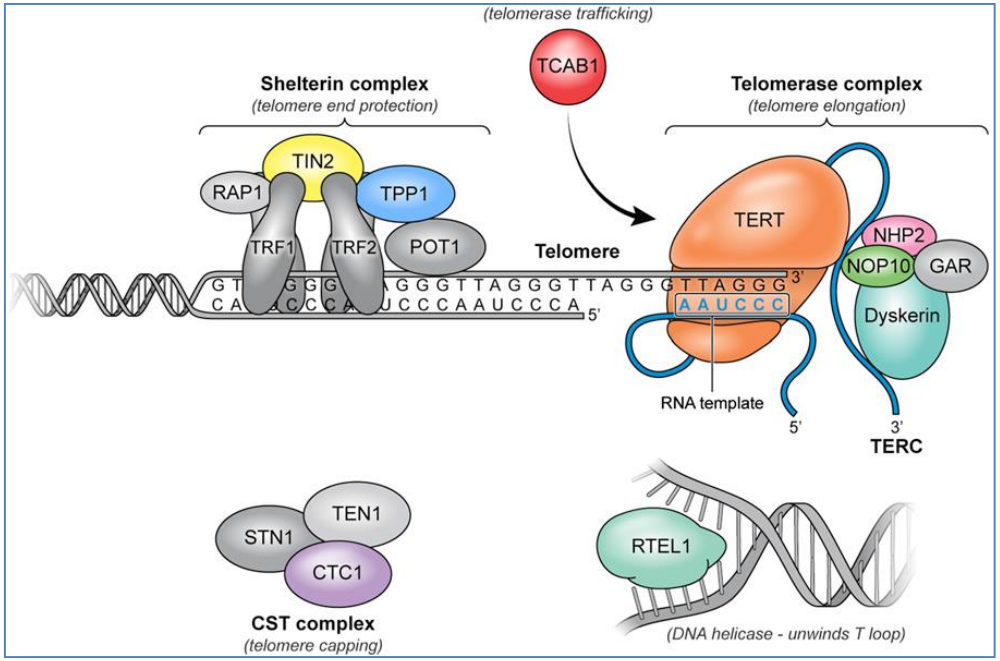
- Anti-leukemic chemotherapy, followed by a RIC-HSCT, can be considered in advanced MDS or AML patients.

- Fanconi Anemia (FA)
- Diamond Blackfan Anemia (DBA)
- Schwachman Diamond Sindrome (SDS)
- Telomere Biology Diseases (TBD)

TBD

- About 60% of patients has mutations in13 genes of shelterin-telomerase complex

DKC1 (25%)
TNF2 (12%)
TERC (5%)
TERT (5%)
USB1 (2%)
R TEL (2%)
CTC1 (1%)
NOLA2 (<1%)
NOLA 3 (<1%)
T CAB1 (WRAP 53) (<1%)
TPP1 (ACD) (<1%)
PARN (<1%)

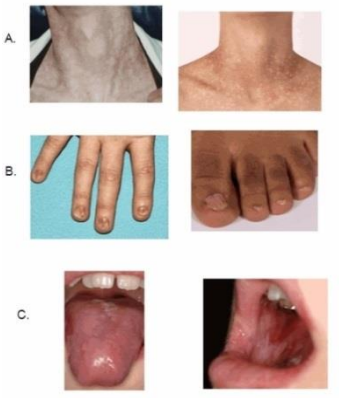


- X linked, autosomal dominant/recessive
- Variabile penetrance
- Remarkable shortening of the telomere

I Dokal, Eur J Hum Genet. 2015, D.Townsley, Blood 2014

TBD

- Variable combination, severity, and time of appearance of:
  - Marrow failure
  - Lung disease *(fibrosis)*
  - Liver disease *(cirrhosis)*
  - Skin, hair and nails abnormalities



Clinical phenotype may be **very misleading.**
Patients may have subtle and non-specific symptoms e.g.

- Minor lung or liver disease to differentiate from cryptogenic cirrhosis
- Isolated, mild marrow failure to differentiate from idiopathic AA (TERC & TERT mutations)

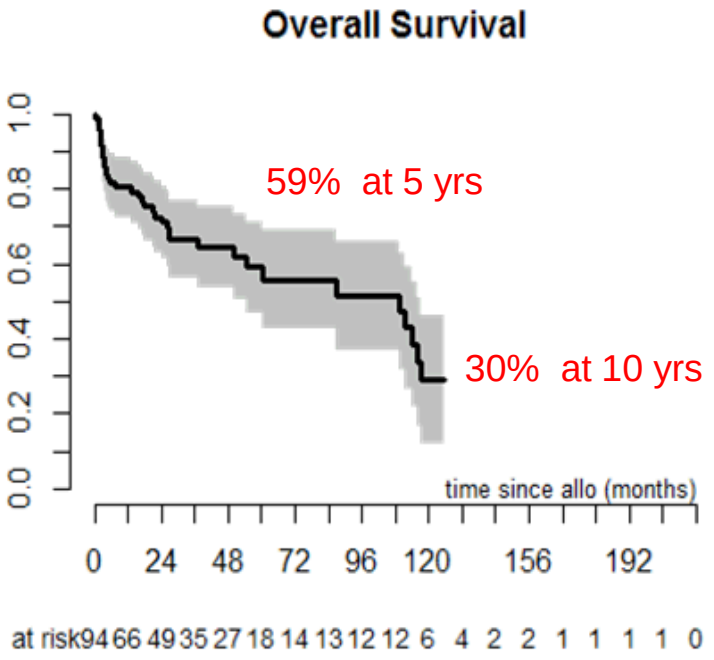
Probably about 5 % of apparently “idiopathic” AA with no clinical phenotype of DC has TERC e TERT mutations

EBMT/EWOG Study

94 patients, 64 males

- Median age at dx 5.8 years (0-33)
- Mixed populations and conditioning

- 51% MUD
- 25% MSD
- 25% MMD
- Mainly BM

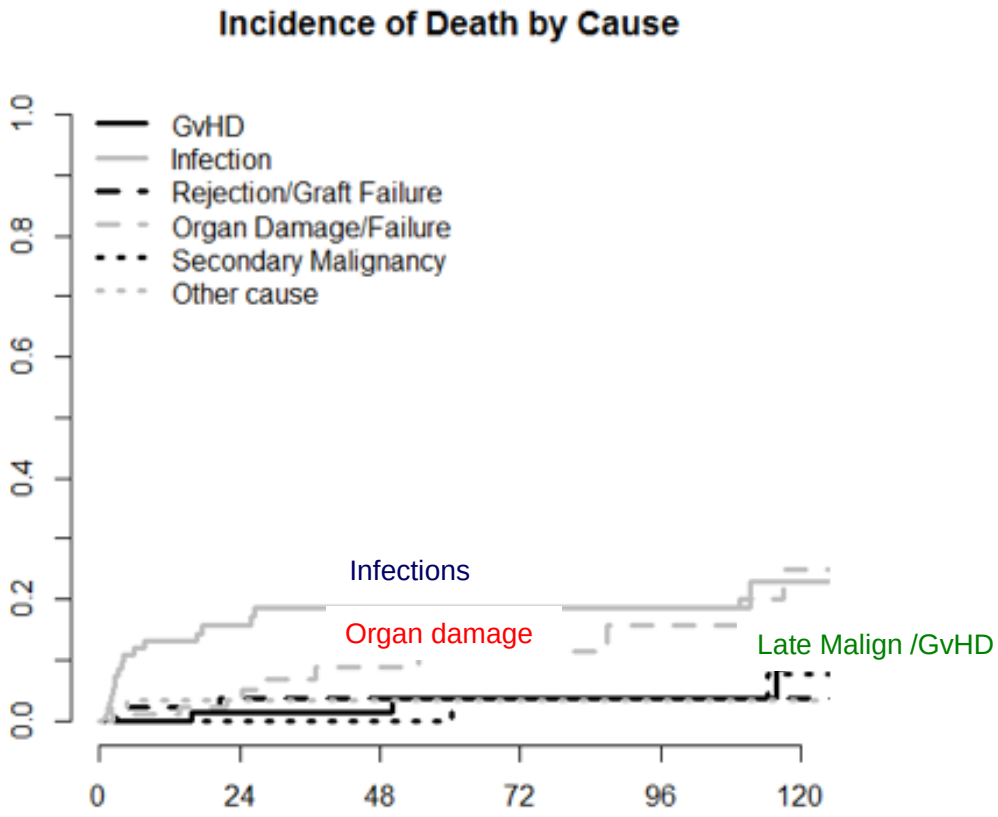


- Ac GVHD 18%
  cGVHD 31%

Higher if organ damage

F. Fioredda for SAAWP EBMT/EWOG Br J Hematology 2018

EBMT/EWOG Study



F. Fioredda for SAAWP EBMT/EWOG, submitted

SCT incresaes the risk of cancer of 5.7-fold *vs* **NON** SCT DC patients

Alter B, Blood 2016.334 (128),22

TBD

- Marrow failure and matched donor, family better than unrelated
- Careful evaluation of family donors (telomere length, mutation analysis)

- Before clonal evolution.
- No major organ damage.
- RIC with Flu
- Lifetime monitoring of organ functions and cancer surveillance

OVERALL in IBMFS

- In some IBMFS like FA, HSCT has a clear role.
- In others (DBA,TBD, SDS) possibly as second line option but case by case evaluation
- Very careful use of pre-emptive HSCT

- Tight monitoring since diagnosis to intercept the “momentum”
- Tight lifetime monitoring after HSCT for malignancies.
- Follow up in “marrow failure” centres

Many Thanks

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A Grossi
I Ceccherini

Patients and their families