MaRIH
Filière de santé Maladies Rares Immuno-Hématologiques

4ème Journée Nationale Maladies Rares Immuno-Hématologiques

Paris,
June 7th 2018

Matched unrelated upfront transplantation in idiopathic aplastic anemia?

Yes

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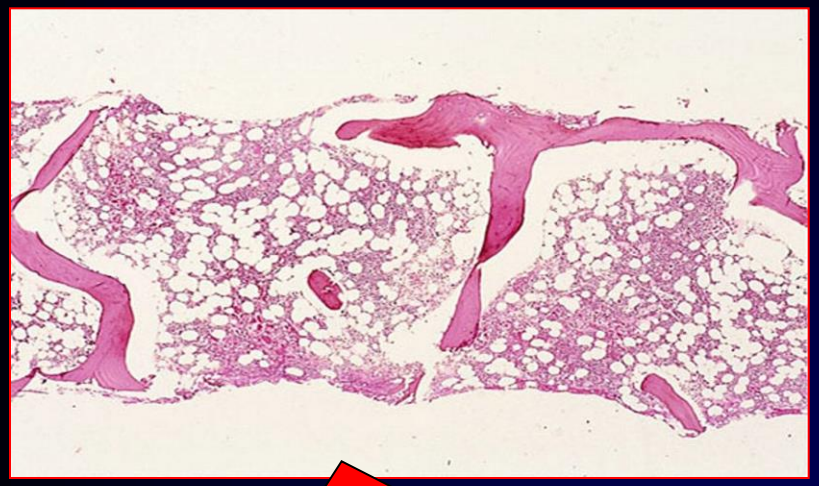
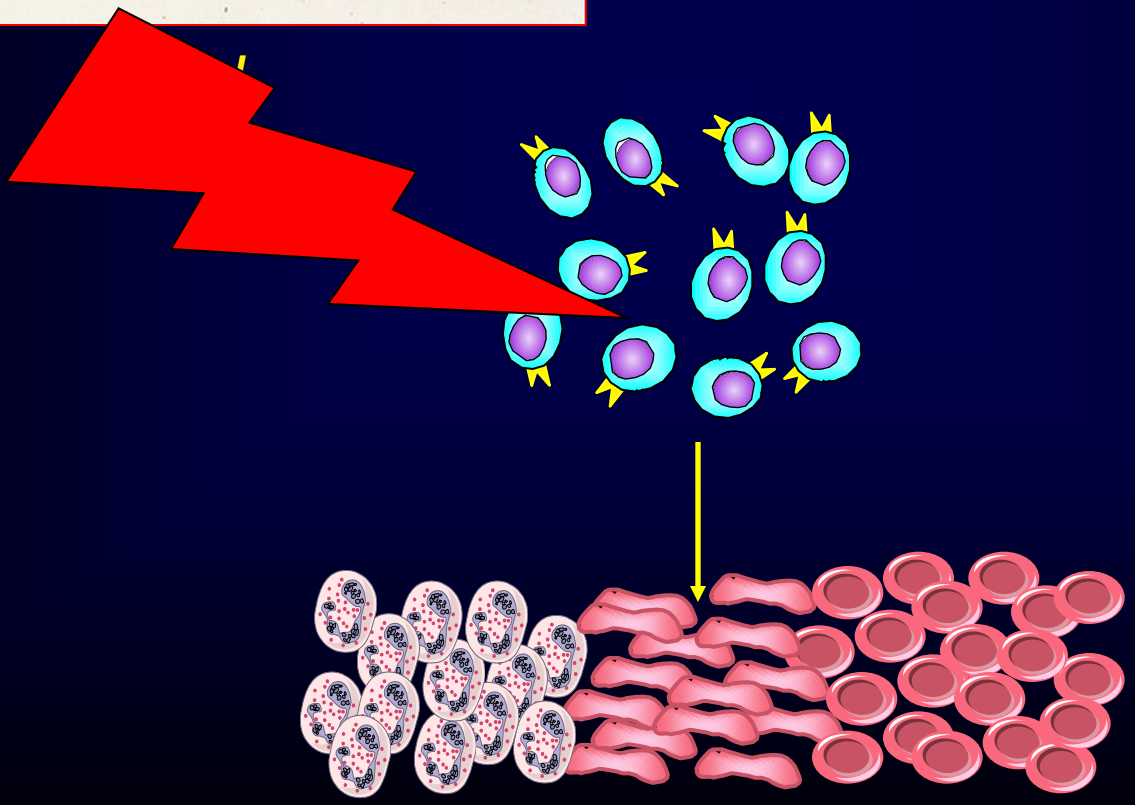
Federico II University of Naples

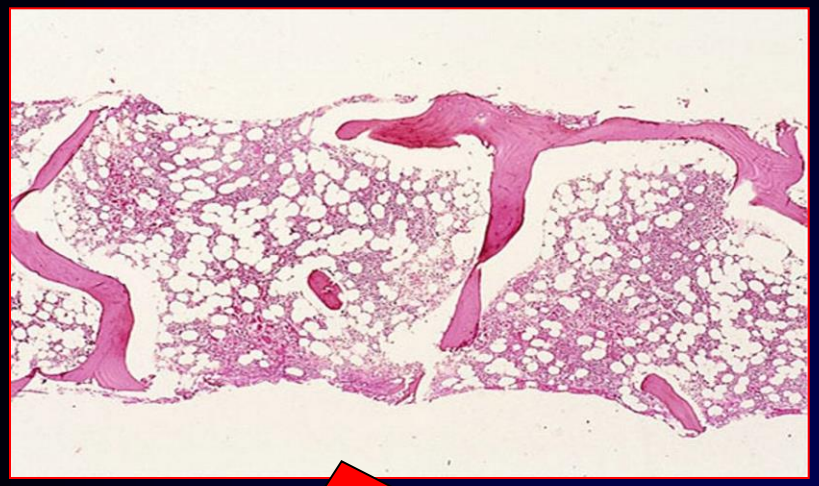
Azienda Ospedaliera Universitaria Federico II
Integrata con il Servizio Sanitario Regionale

Aplastic anemia

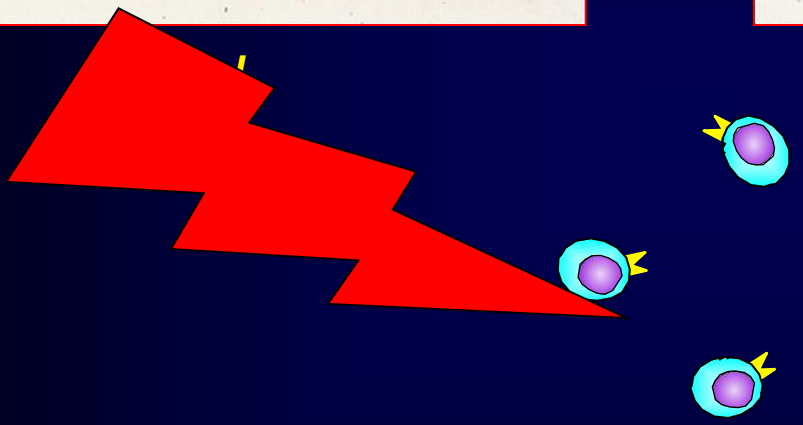




Aplastic anemia



Marrow aplasia

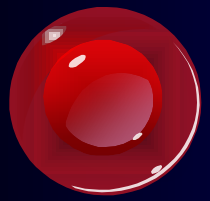


Contraction of stem cell pool

Cytopenia

Pathophysiology of aplastic anemia

Hematopoietic stem cell



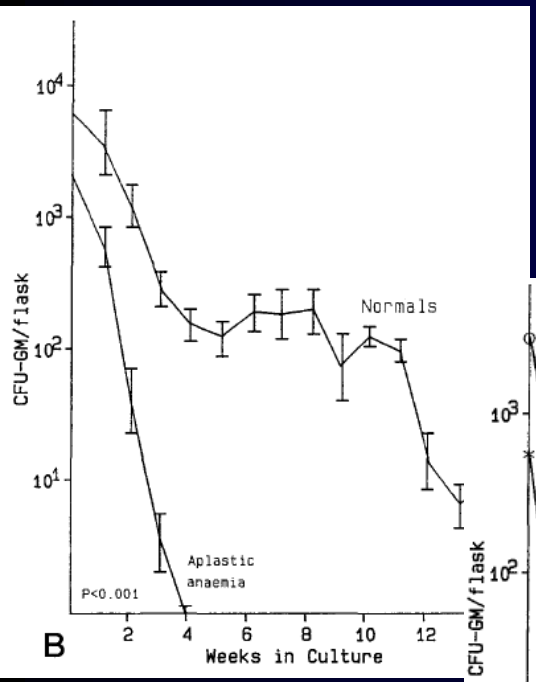
Hematopoietic stem cells in AA

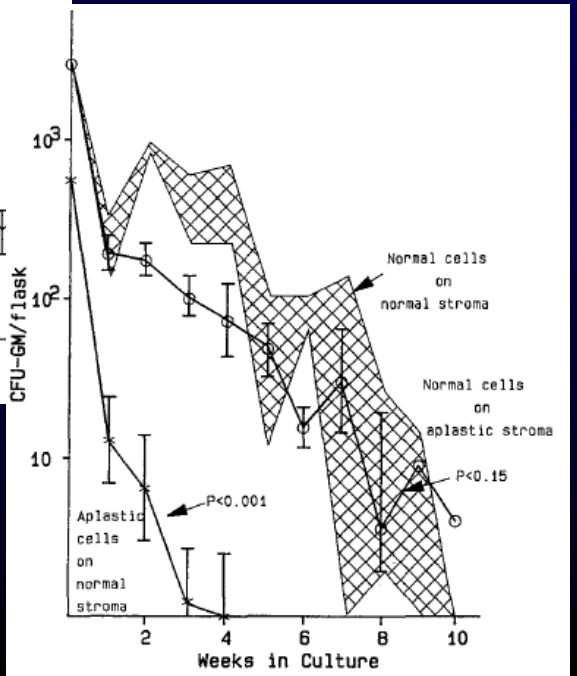
Hematopoietic progenitor cultures

blood 1990 76: 1748-1757

The hematopoietic defect in aplastic anemia assessed by long-t marrow culture

JC Marsh, J Chang, NG Testa, JM Hows and TM Dexter

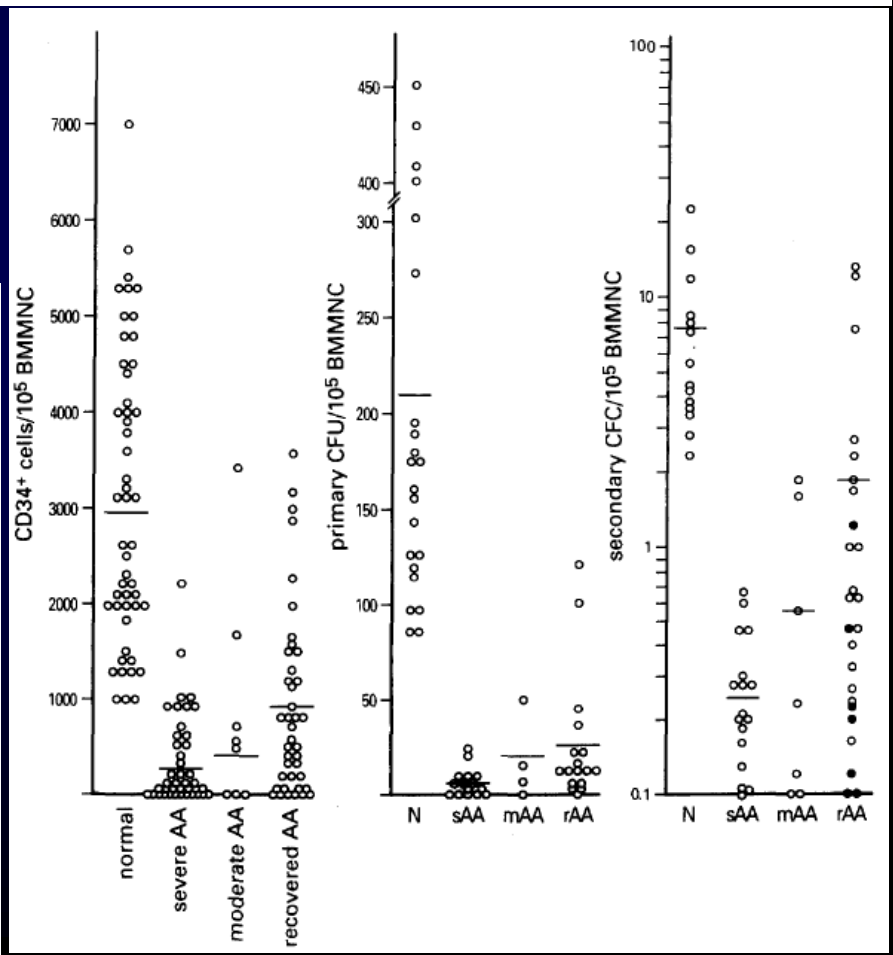




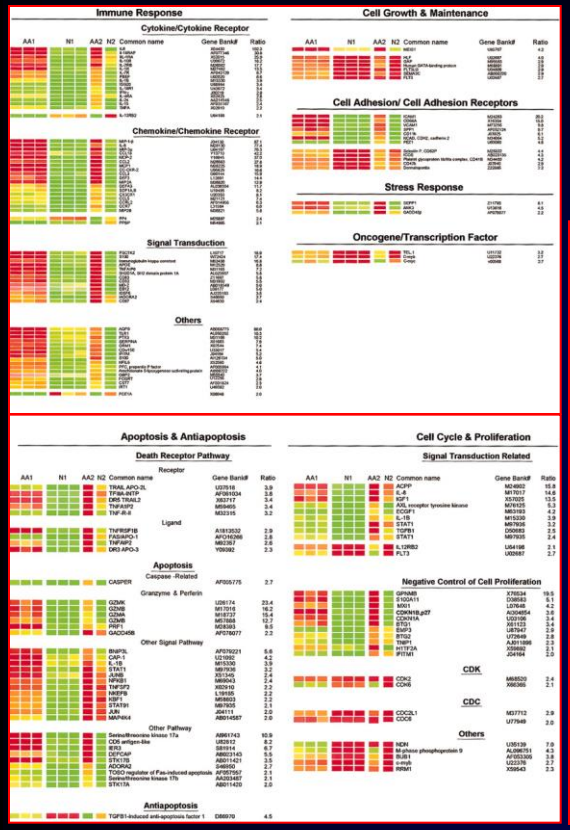
blood 1996 88: 1983-1991

A severe and consistent deficit in marrow and circulating primitive hematopoietic cells (long-term culture-initiating cells) in acquired aplastic anemia

JP Maciejewski, C Selleri, T Sato, S Anderson and NS Young



GENE EXPRESSION PROFILING IN CD34+ FROM AA PATIENTS

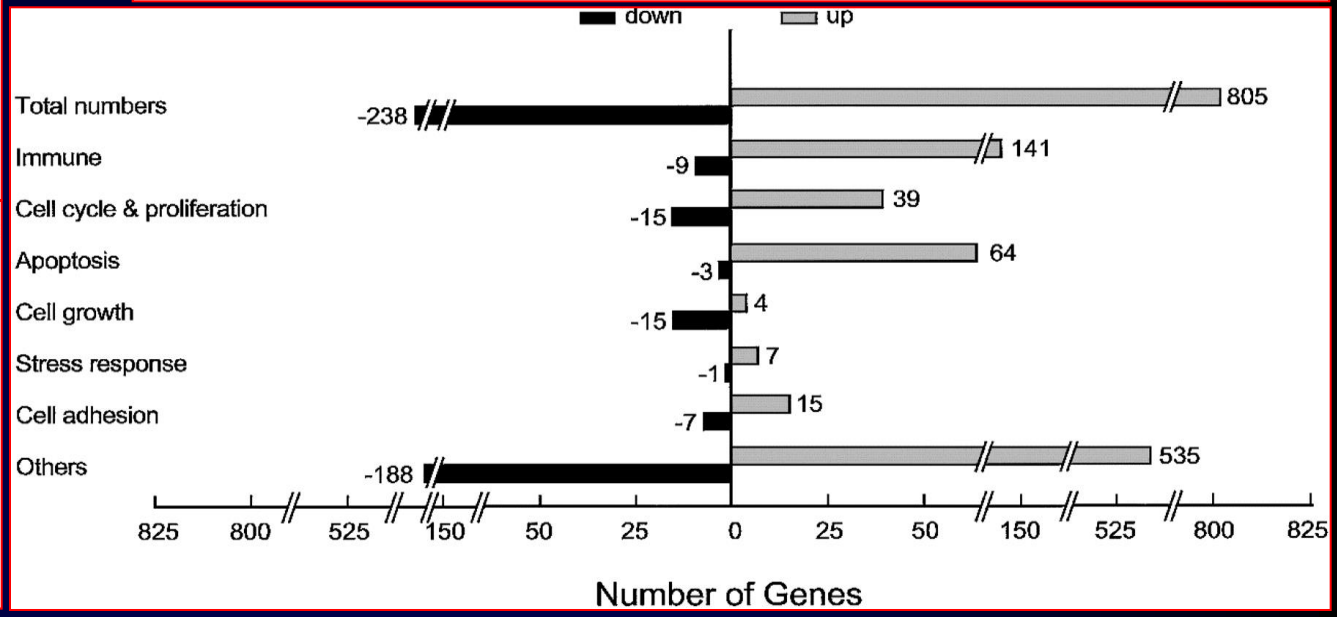


RED CELLS

BLOOD, 1 JANUARY 2004 • VOLUME 103, NUMBER 1

Gene expression profiling in CD34 cells to identify differences between aplastic anemia patients and healthy volunteers

Weihua Zeng, Guibin Chen, Sachiko Kajigaya, Olga Nunez, Alexandra Charrow, Eric M. Billings, and Neal S. Young



Over-expressed

- Apoptosis
- Stress response
- Cytokine/chemokine transduction
- Defense/immune response genes
- Cell cycle/proliferation inhibitors

Down-expressed

- Cell cycle/proliferation promoters

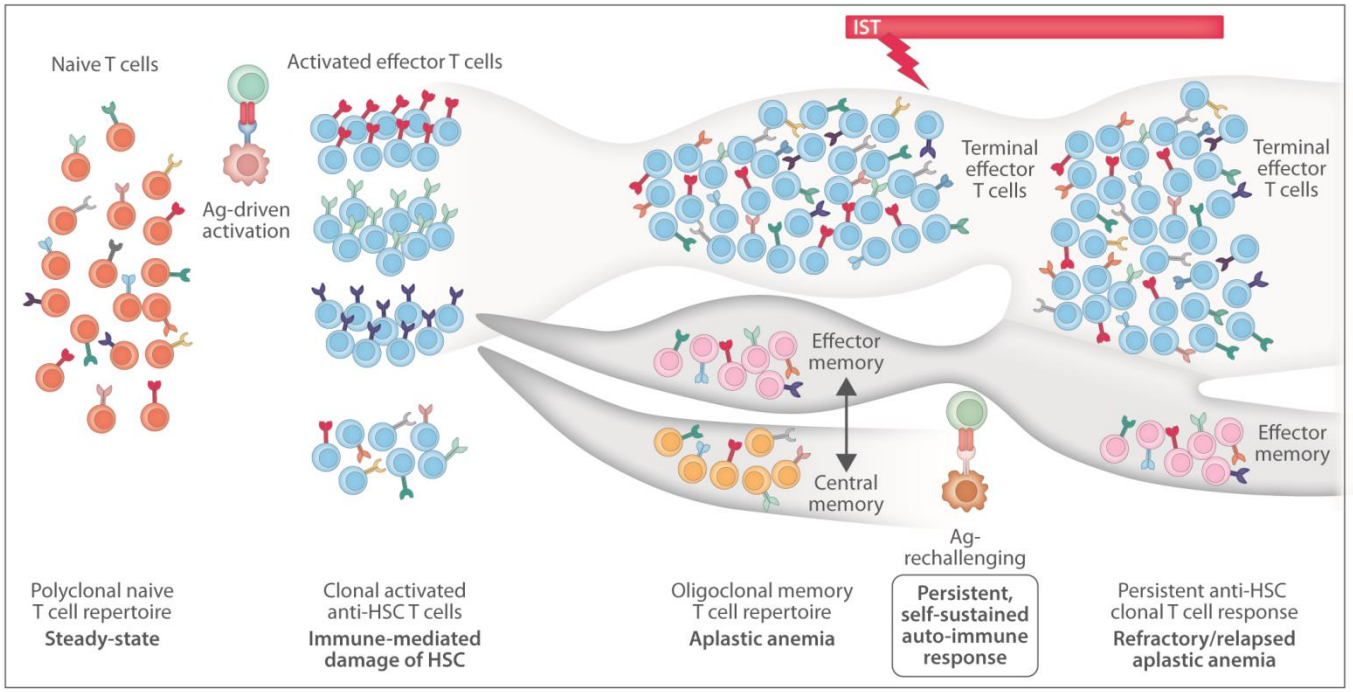
"…the transcriptome analysis of HSC in AA is consistent with the presence of stressed, immunologically activated or dying target cells rather than of an intrinsically abnormal population."

Molecular Tracking of Pathogenic Clonotypic T-cells

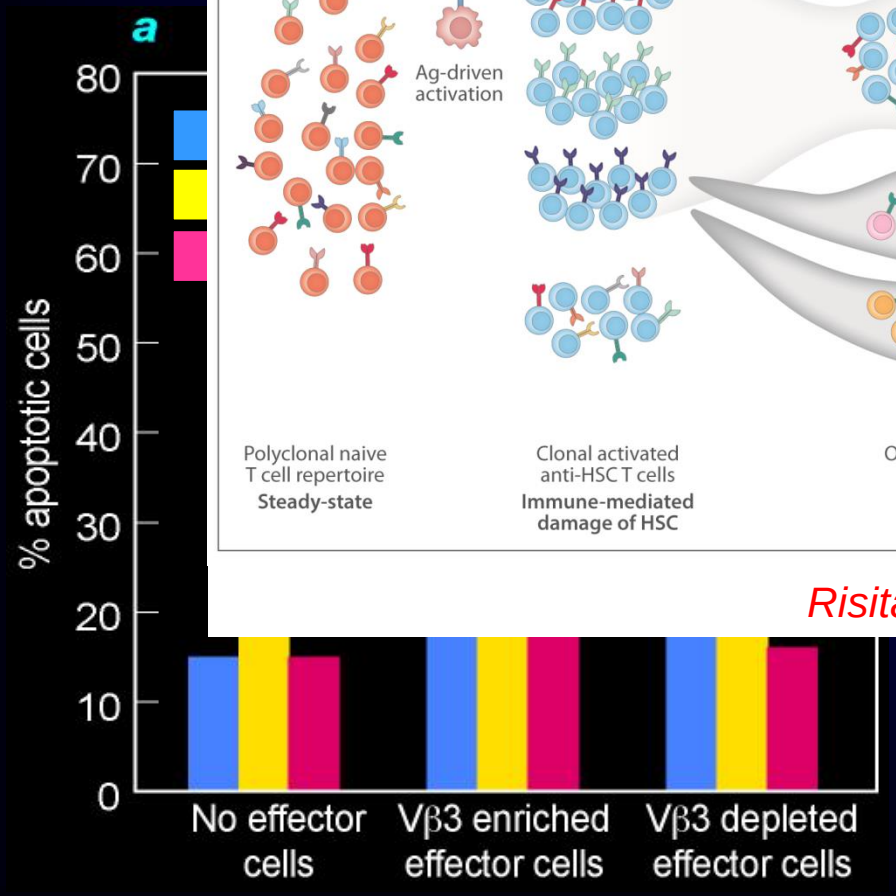
Lancet 2004; 364: 355–64 Mechanisms of Disease

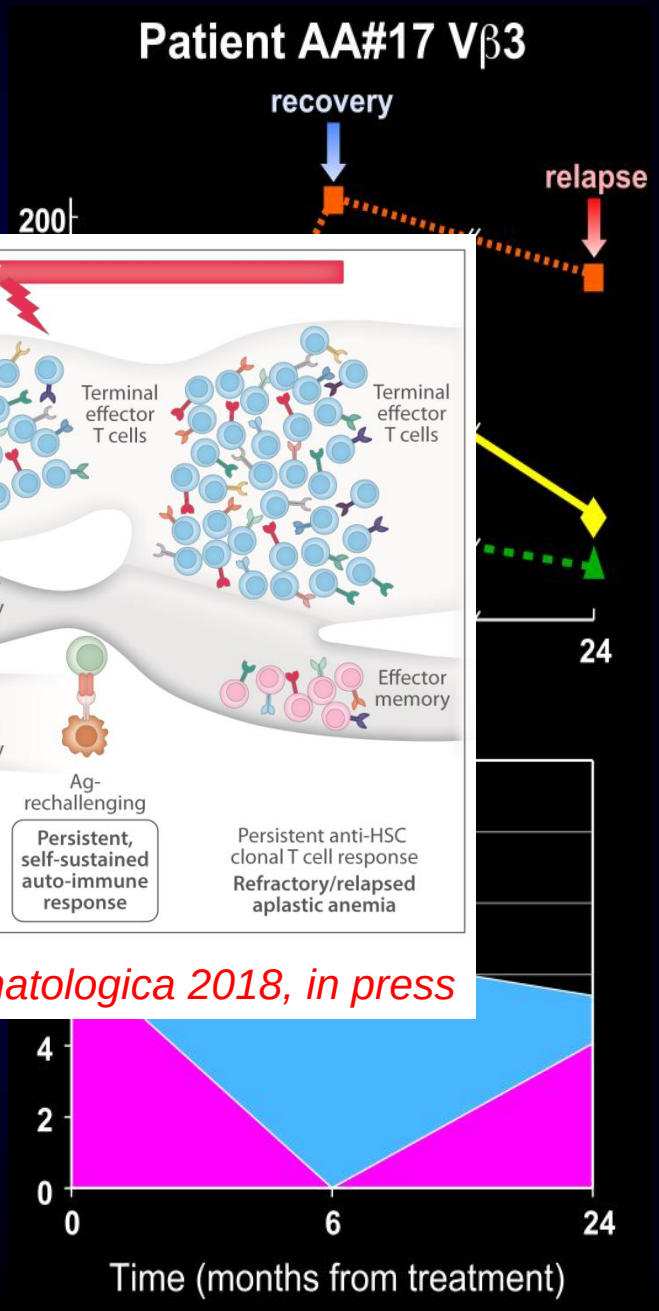
In-vivo dominant immune responses in aplastic anaemia:
molecular track
by TCR β-CDR3

Antonio M Risitano, Ja



Risitano, Haematologica 2018, in press

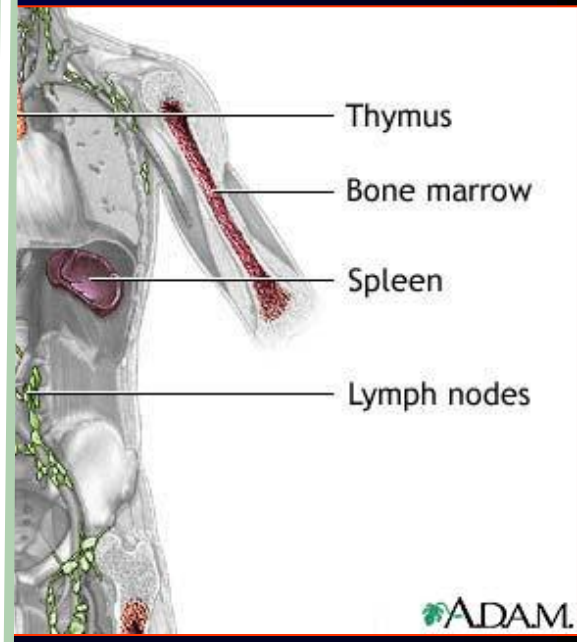




Pathophysiology of aplastic anemia

Hematopoietic stem cell

The immune system



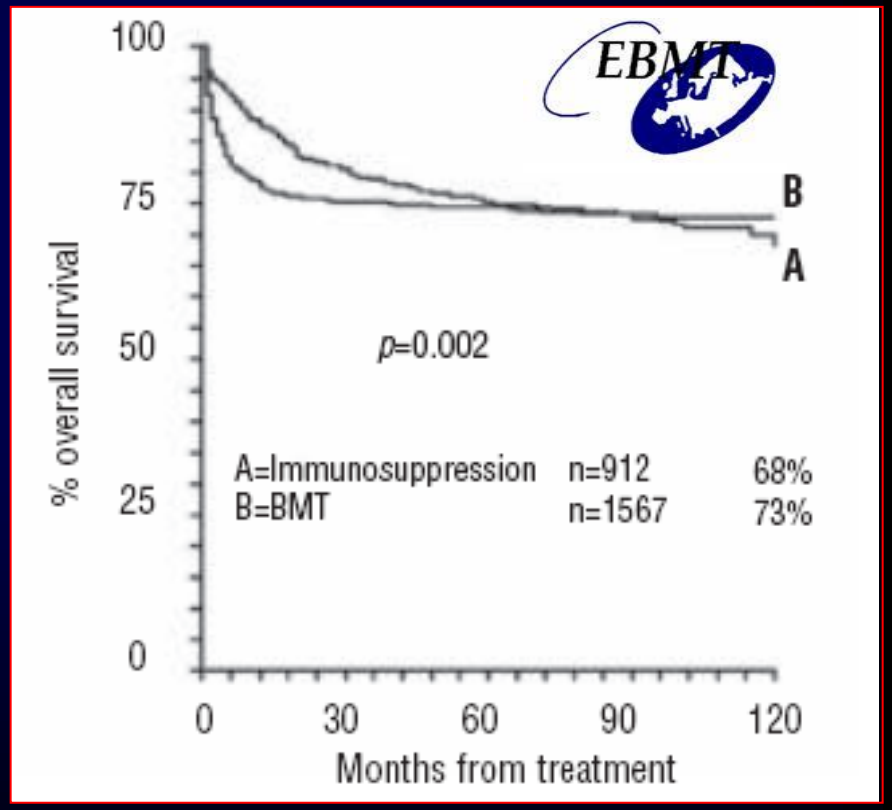
To transplant or not to transplant?

IST HSCT

Original Article

Outcome of patients with acquired aplastic anemia given first line bone marrow transplantation or immunosuppressive treatment in the last decade: a report from the European Group for Blood and Marrow Transplantation

Anna Locasciulli, Rosi Oneto, Andrea Bacigalupo, Gerard Socié, Elisabeth Korthof, Albert Bekassy, Hubert Schrezenmeier, Jakob Passweg, Monika Führer
on the Behalf of the Severe Aplastic Anemia Working Party of the European Blood and Marrow Transplant Group (SAA-WP, BMT).



Locasciulli et al, Haematologica 2007

To transplant or not to transplant?

LATE EVENTS IN AA

	IST	*HSCT*
✓ CsA dependence	++	++
✓ Relapse	+++	+
✓ Clonal evolution	++	-
✓ Sec. cancers	+/-	+
✓ GvHD	-	+++
✓ Avasc. osteon. (AVN)	++	+++
✓ Metabolic	++	+++
✓ Cardiovascular	+/-	+
✓ Endocrine	+	++
✓ QoL	+	++

IST HSCT

To transplant or not to transplant?

Upfront unrelated transplantation: is it an option?

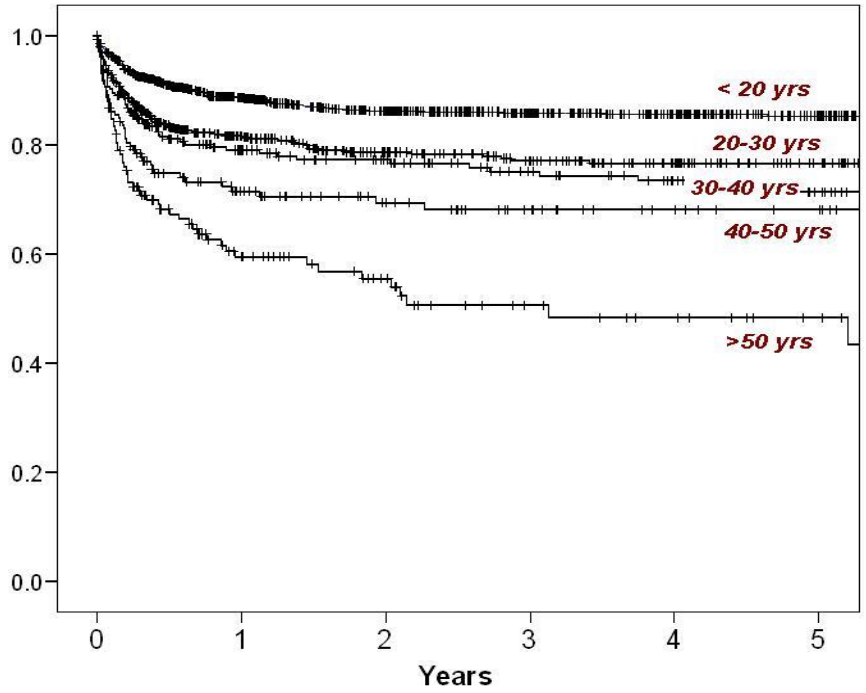
IST HSCT

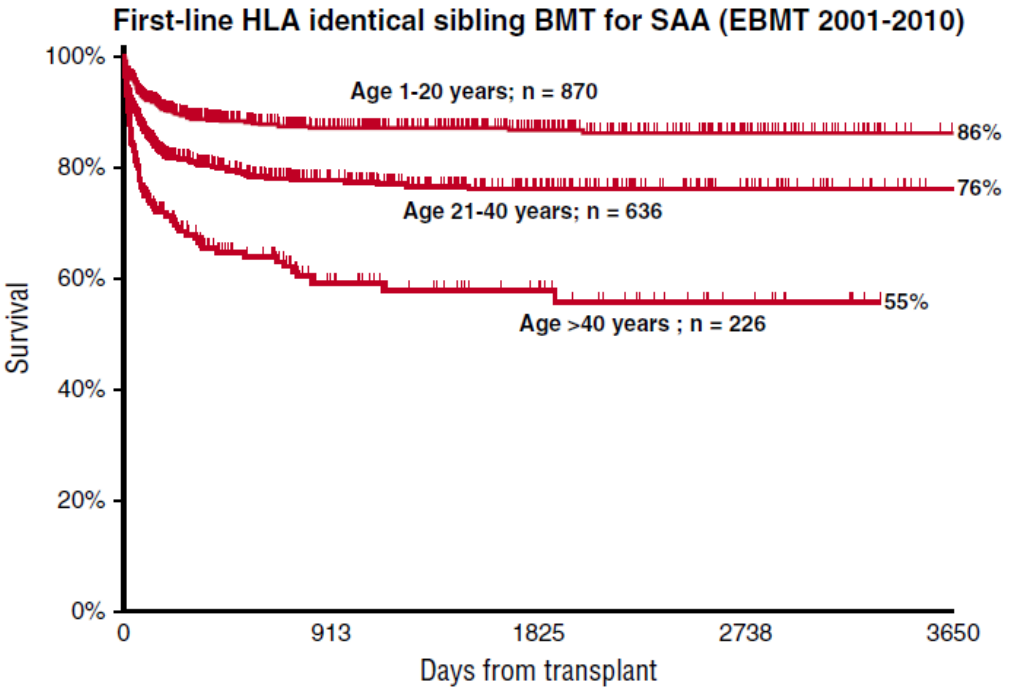
Matched related HSCT for AA

The impact of age

How I treat acquired aplastic anemia

Andrea Bacigalupo

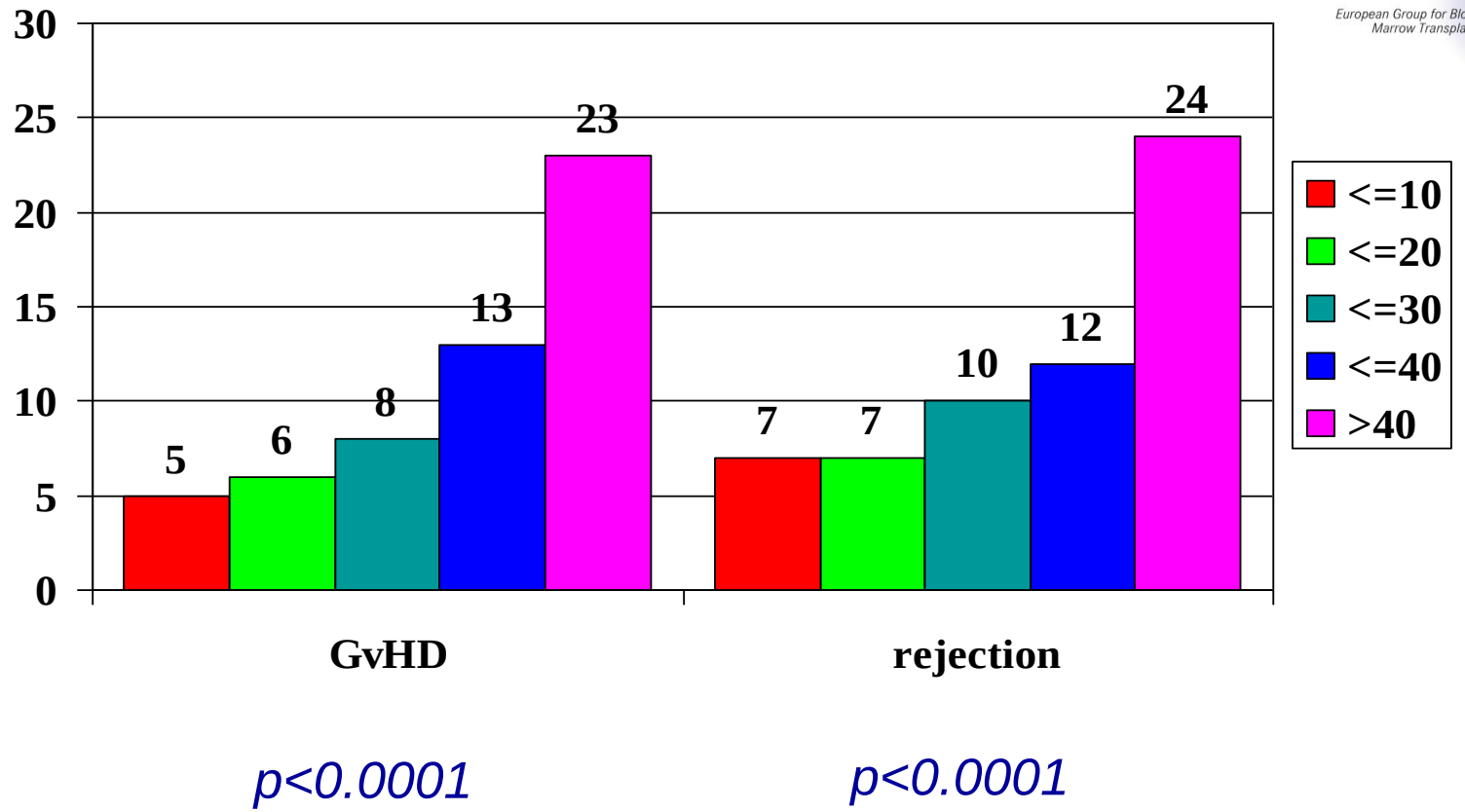




SAA-EBMT registry, update July 2012; Bacigalupo, Blood 2017

Matched related HSCT for AA

The impact of age



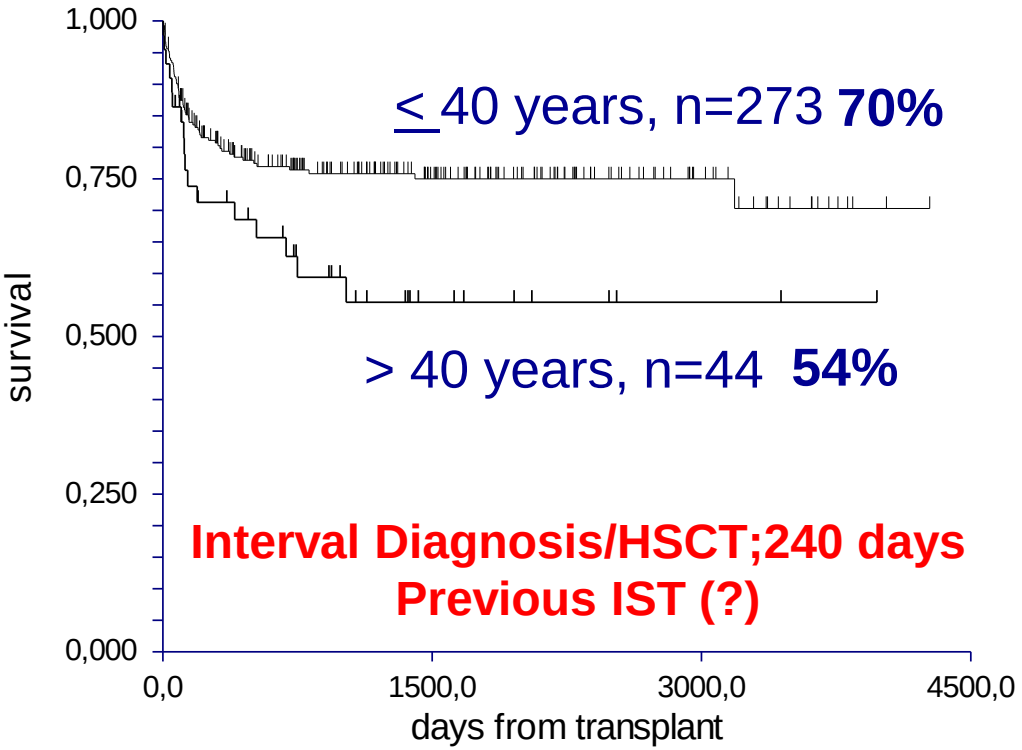
p<0.0001

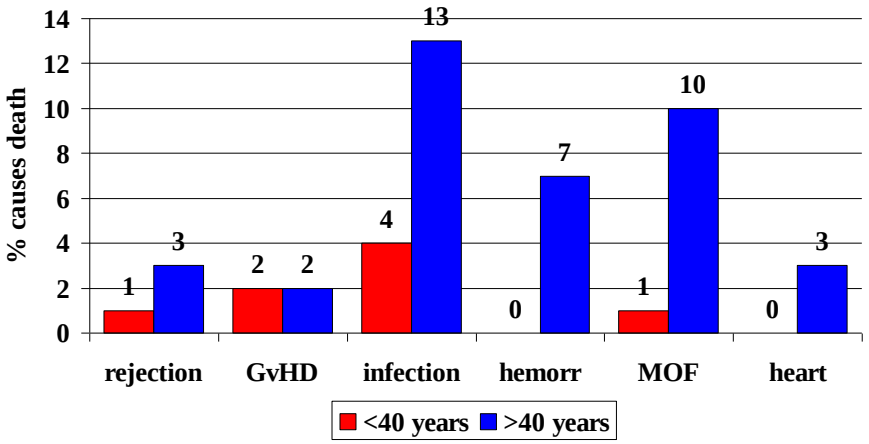
p<0.0001

SAA-EBMT registry, update July 2012

Matched related HSCT for AA

The impact of age

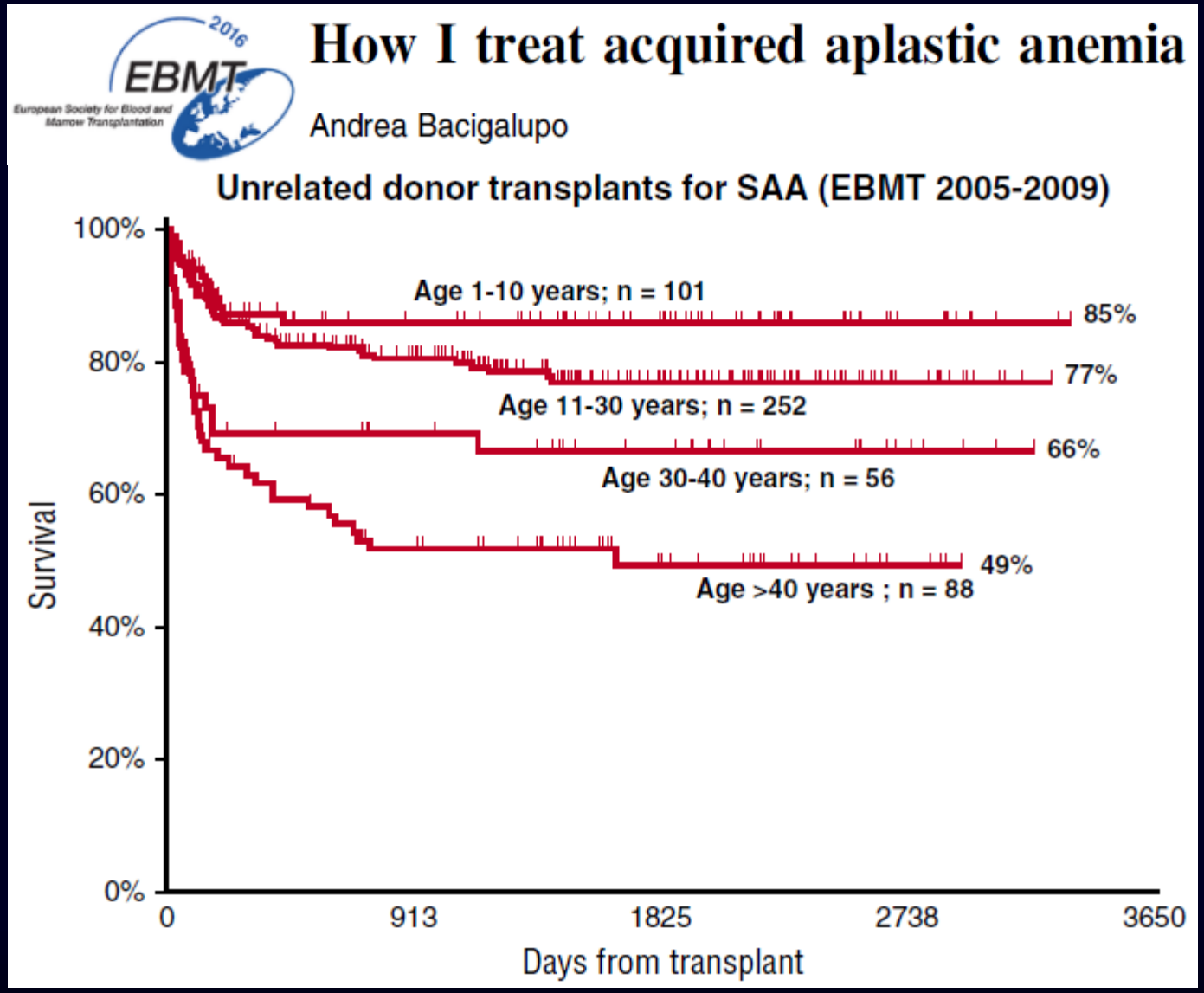




Unpublished data, courtesy of Gerard Sociè and Regis Peffault de Latour

Matched unrelated HSCT for AA

The impact of age



Bacigalupo, Blood 2017

IST for AA

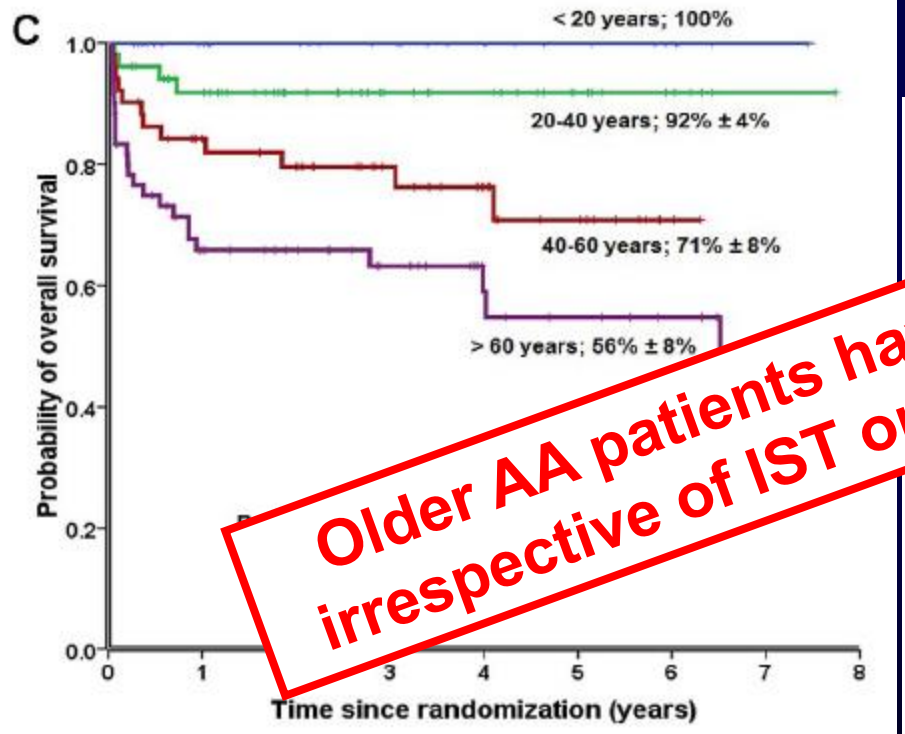
The impact of age

blood

2011 117: 4434-4441
Prepublished online January 13, 2011;
doi:10.1182/blood-2010-08-304071

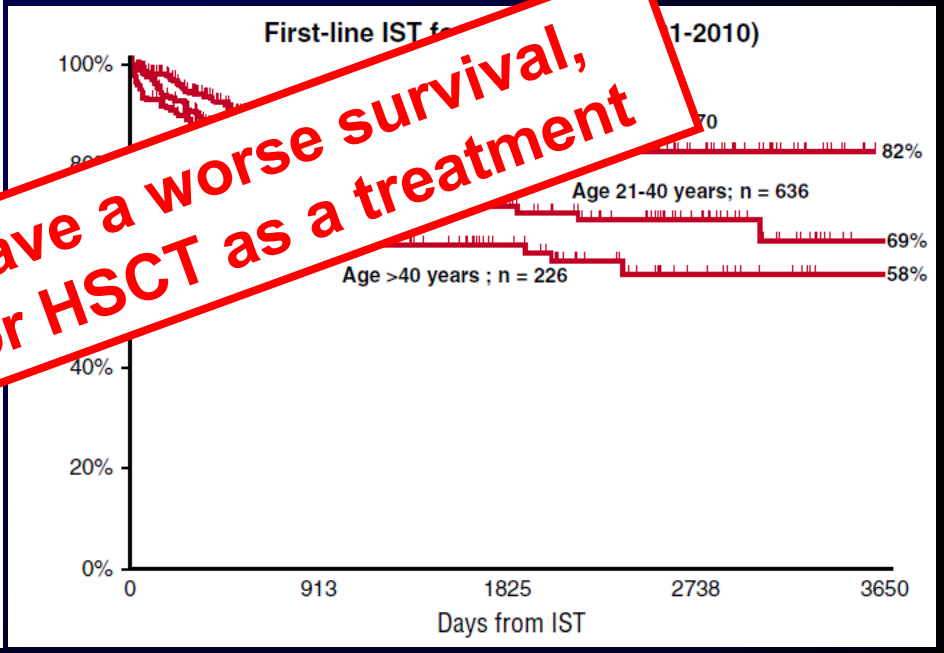
A randomized controlled study in patients with newly diagnosed severe aplastic anemia receiving antithymocyte globulin (ATG), cyclosporine, with or without G-CSF: a study of the SAA Working Party of the European Group for Blood and Marrow Transplantation

André Tichelli, Hubert Schrezenmeier, Gérard Socié, Judith Marsh, Andrea Bacigalupo, Ulrich Dührsen, Anke Franzke, Michael Hallek, Eckhard Thiel, Martin Wilhelm, Britta Höchsmann, Alain Barrois, Kim Champion and Jakob R. Passweg



How I treat acquired aplastic anemia

Andrea Bacigalupo



Older AA patients have a worse survival, irrespective of IST or HSCT as a treatment

- ✓ **N=192, Jan 2008-Jul 2008**
- ✓ **6y OS 76%, 6y EFS v42%**
- ✓ **No difference between arms**

Tichelli et al, Blood 2011; Bacigalupo, Blood 2017

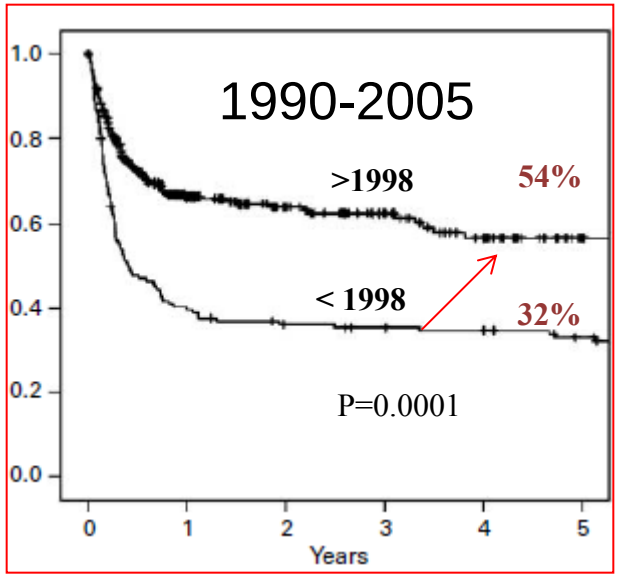
Matched unrelated HSCT for SAA

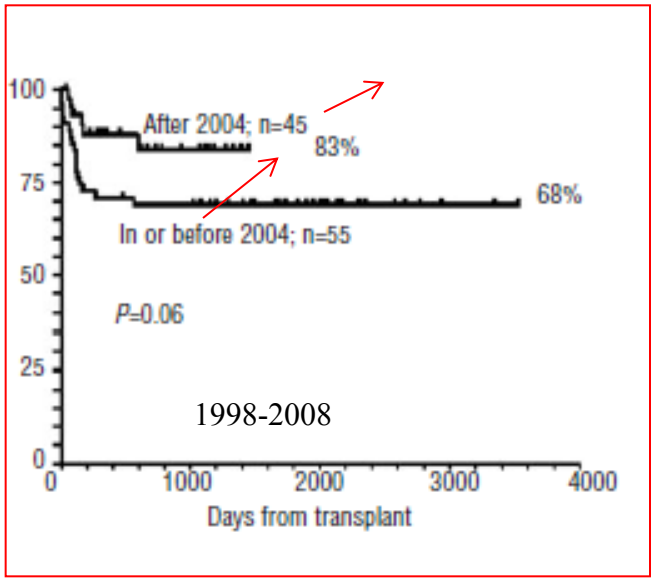
Improvement over time

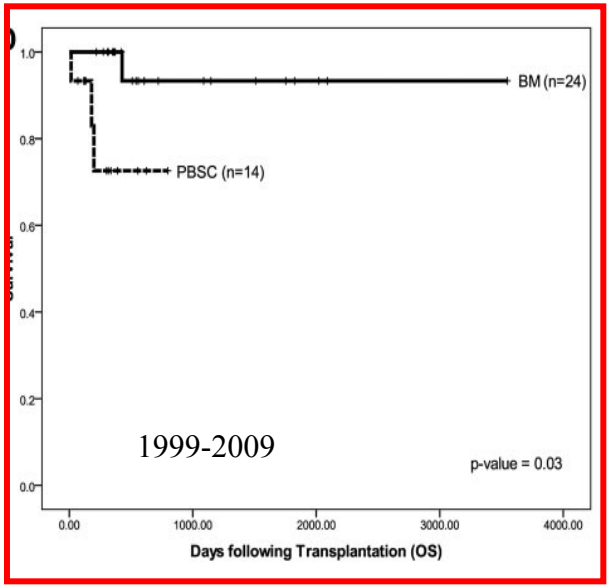
Viollier R et al.
SAA WP-EBMT
(498 pts most part II line treatment)

Bacigalupo A et al
SAA WP EBMT
(100 pts II line treatment)

Marsh J et al
(50 pts)







BMT 2008

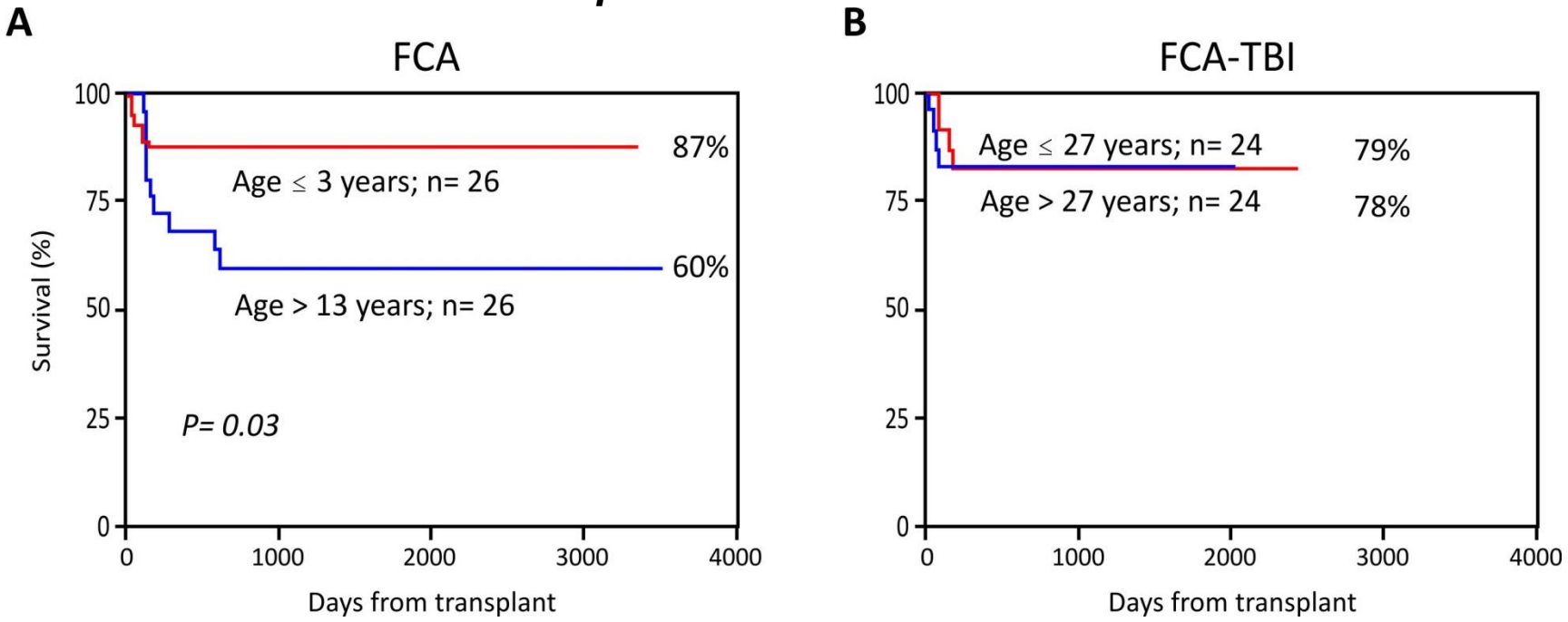
Haematologica 2010

Blood 2011

92% SCT within 2 yrs from dx

Matched unrelated HSCT for SAA

Improvement over time



FCA regimen:

Fludarabine 30 mg/m^2 on days -6, -5, -4, and -3,
Cyclophosphamide 300 mg/m^2 on days -6, -5, -4, and -3,
Antithymocyte globulin 3.75 mg/kg on days -6, -5, -4, and -3.

FCA-TBI regimen:

Fludarabine 30 mg/m^2 on days -6, -5, -4, and -3,
Cyclophosphamide 300 mg/m^2 on days -6, -5, -4, and -3, and
Antithymocyte globulin 3.75 mg/kg/on days -4 and -3
TBI 2 Gy.

GvHD prophylaxis

cyclosporine A and methotrexate (days +1, +3, and +6)

Bacigalupo et al, Haematologica 2010

Matched unrelated HSCT for AA

Is it still worse than MRD?

Articles Stem Cell Transplantation

Current outcome of HLA identical sibling versus unrelated donor transplants in severe aplastic anemia: an EBMT analysis

Andrea Bacigalupo,[1] Gerard Socié,[2] Rose Marie Hamladji,[3] Mahmoud Aljurf,[4] Alexei Maschan,[5] Slawomira Kyrcz-Krzemien,[6] Alicja Cybicka,[7] Henrik Sengelov,[8] Ali Unal,[9] Dietrich Beelen,[10] Anna Locasciulli,[11] Carlo Dufour,[12] Jakob R. Passweg,[13] Rosi Oneto,[1] Alessio Signori[14] and Judith C.W. Marsh;[15] for the Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (WPSAA-EBMT)

N=1448 AA receiving HSCT between 2005-2009

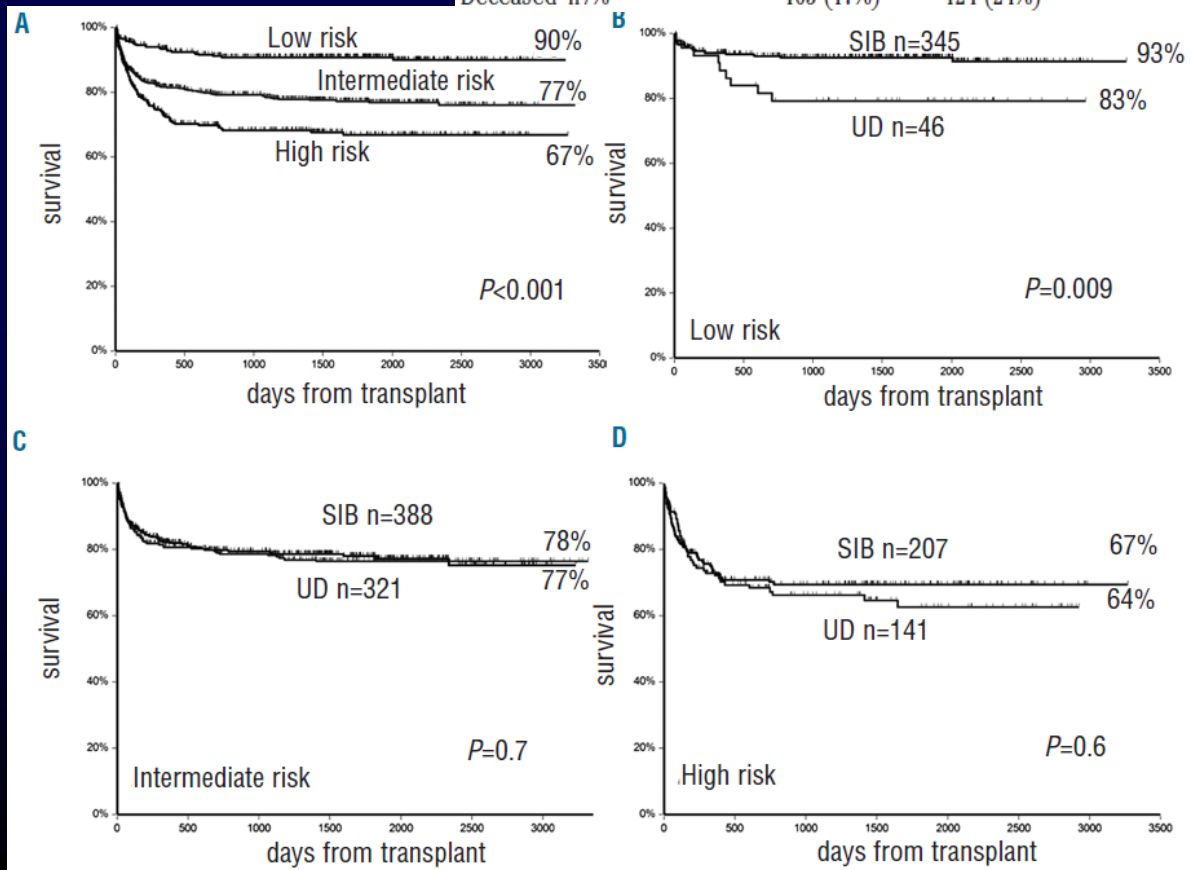
- ✓ MRD n=904
- ✓ MUD n= 508

Risk factors

- ✓ Interval >180dd
- ✓ PB
- ✓ Age
- ✓ No ATG
- ✓ CMV status

Table 2. Outcome of HLA identical sibling and unrelated donor grafts.

Source N.	Sibling 940	Unrelated 508	P
Engraftment	91%	91%	0.9
Acute GvHD II-IV	13%	25%	<0.0001
Acute GvHD III-IV	5%	10%	<0.0001
Chronic GvHD	14%	26%	<0.0001
Extensive chronic GvHD	6%	11%	0.002
Patients surviving	777 (83%)	384 (76%)	
Deceased n /%	163 (17%)	124 (24%)	

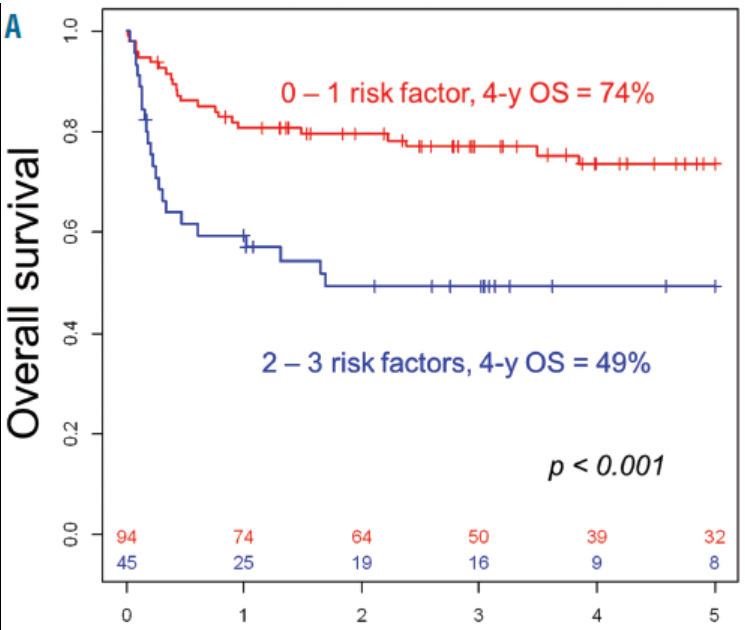


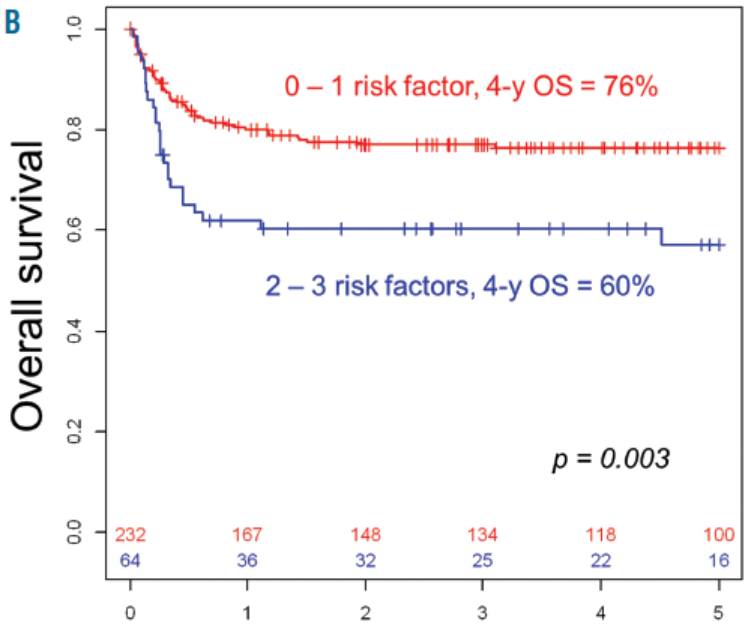
Matched unrelated HSCT for AA

Factors affecting the outcome

Table 3. Univariate and multivariate analyses of overall survival in the study population.

		Univariate analysis			Multivariate analysis*	
	4-y	[95%CI]	P	HR	[95%CI]	P
Age at allo-HSCT						
≤ 30 years (n = 93)	70%	[61-81]	0.037	1		
> 30 years (n = 46)	57%	[44-74]		2.39	[1.23-4.66]	0.011
Time from diagnosis to allo-HSCT						
≤ 12 months (n = 58)	77%	[65-90]	0.017	1		
> 12 months (n = 81)	58%	[48-70]		2.18	[1.09-4.37]	0.027
HLA matching						
10/10 (n = 113)	68%	[59-78]	0.196	1		
9/10 (n = 26)	57%	[40-80]		2.14	[1.05-4.38]	0.036
Predictive score						
0 or 1 risk factor (n = 94)	74%	[65-84]	< 0.001	1		
2 or 3 risk factors (n = 45)	49%	[36-67]		3.04	[1.64-5.62]	<0.001





Devillier et al, Haematologica 2016

Matched related HSCT for SAA

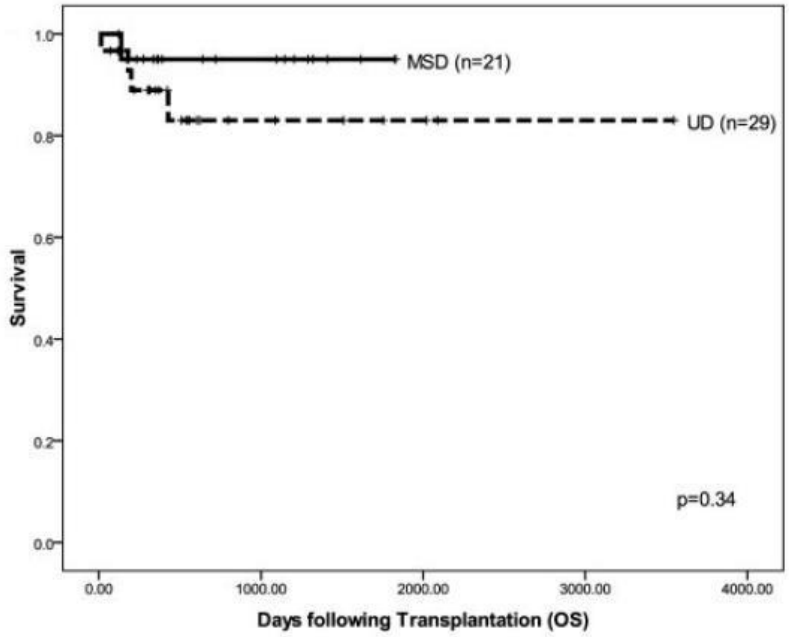
Novel conditioning regimens: the FCC

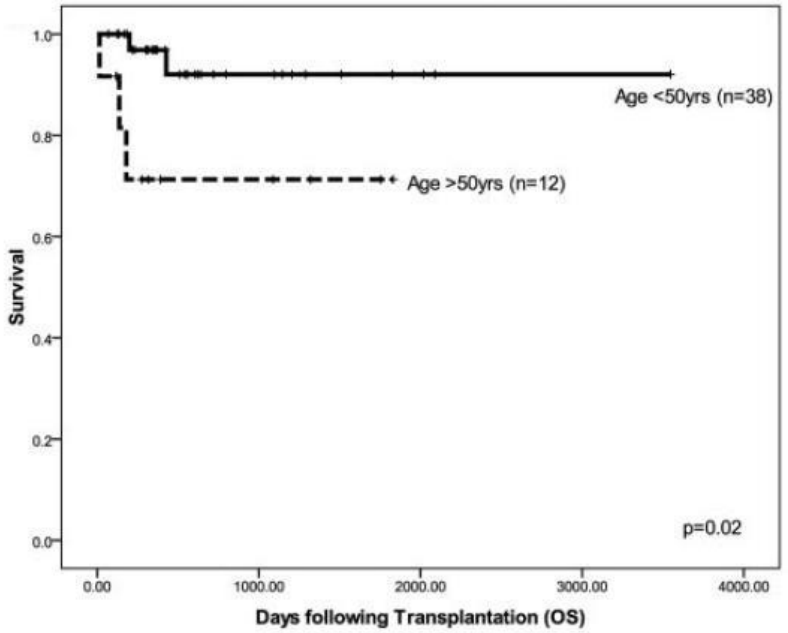
blood

2011 118: 2351-2357
Prepublished online April 25, 2011;
doi:10.1182/blood-2010-12-327536

Alemtuzumab with fludarabine and cyclophosphamide reduces chronic graft-versus-host disease after allogeneic stem cell transplantation for acquired aplastic anemia

Judith C. Marsh, Vikas Gupta, ZiYi Lim, Aloysius Y. Ho, Robin M. Ireland, Janet Hayden, Victoria Potter, Mickey B. Koh, M. Serajul Islam, Nigel Russell, David I. Marks, Ghulam J. Mufti and Antonio Pagliuca





Multicenter retrospective study: conditioning with Alemtuzumab + Fludara + Cyclophosph.

- 50 patients (21 MSD), median age 35 years (8-62), 12 patients ≥50 years
- Median time interval to HSCT: MSD 6 months

Marsh J. et al. Blood. 2011;118:2351-2357.

Matched related HSCT for SAA

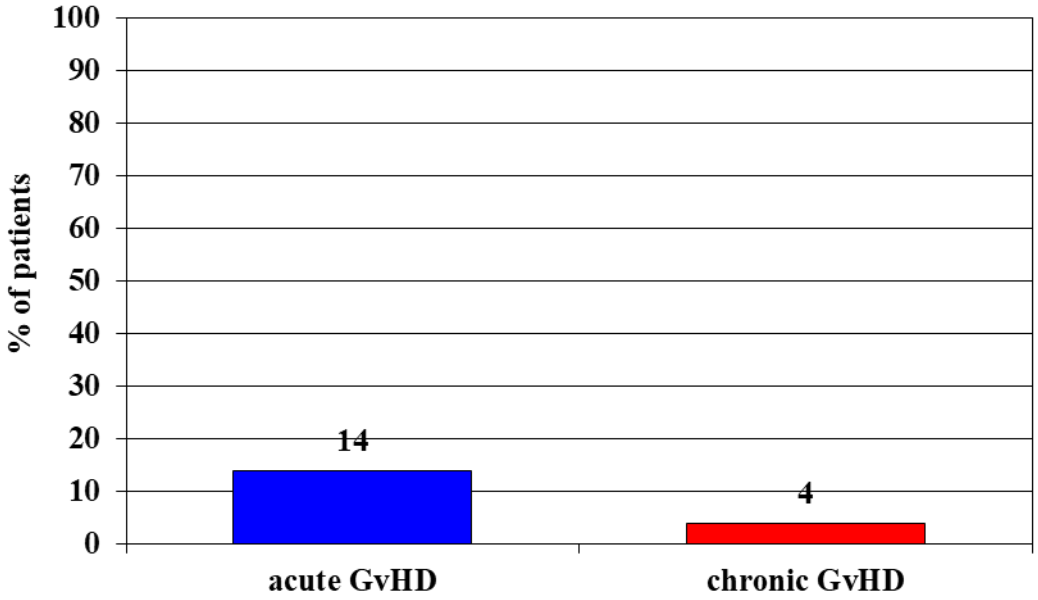
Novel conditioning regimens: the FCC

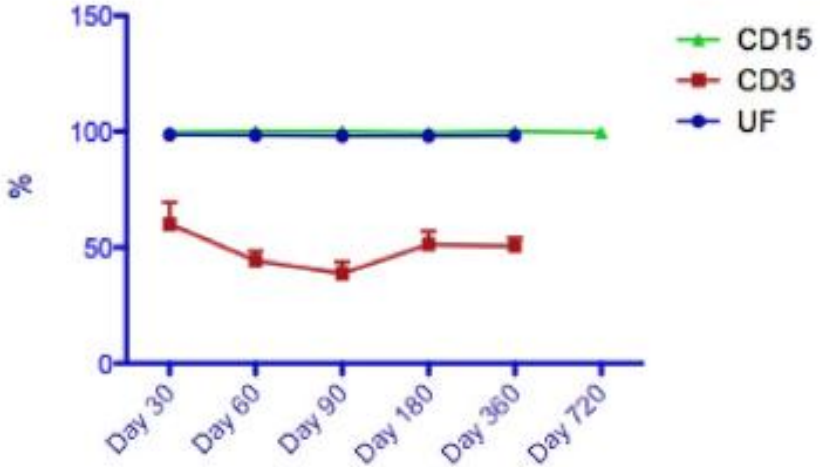
blood

2011 118: 2351-2357
Prepublished online April 25, 2011;
doi:10.1182/blood-2010-12-327536

Alemtuzumab with fludarabine and cyclophosphamide reduces chronic graft-versus-host disease after allogeneic stem cell transplantation for acquired aplastic anemia

Judith C. Marsh, Vikas Gupta, ZiYi Lim, Aloysius Y. Ho, Robin M. Ireland, Janet Hayden, Victoria Potter, Mickey B. Koh, M. Serajul Islam, Nigel Russell, David I. Marks, Ghulam J. Mufti and Antonio Pagliuca





Marsh J. et al. Blood. 2011;118:2351-2357.

The dose of CTX

Cyclophosphamide conditioning in patients with severe aplastic anaemia given unrelated marrow transplantation: a phase 1–2 dose de-escalation study

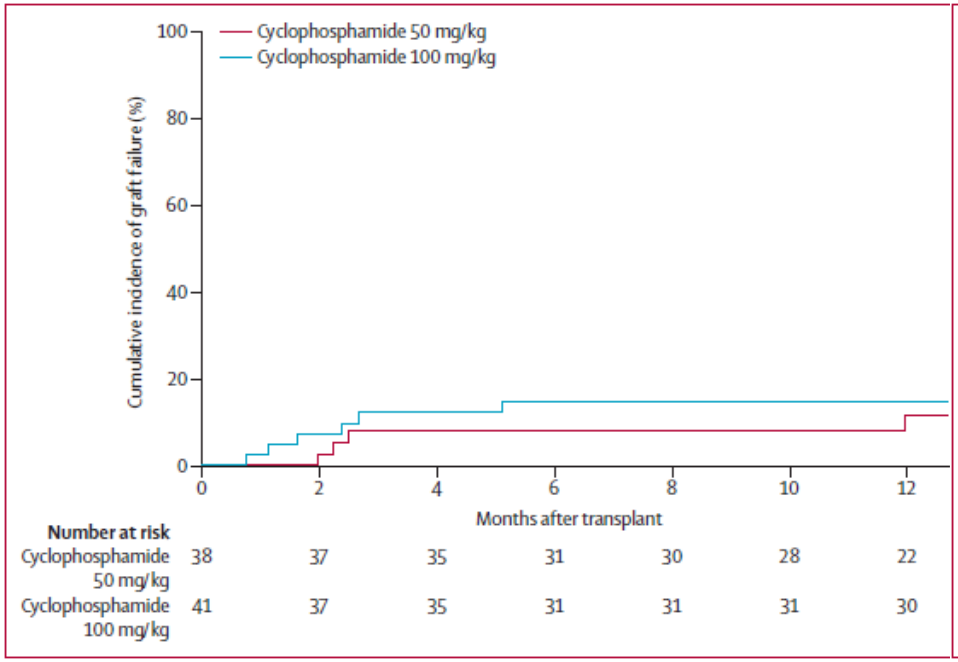
Paolo Anderlini, Juan Wu, Iris Gersten, Marian Ewell, Jakob Tolar, Joseph H Antin, Roberta Adams, Sally Arai, Gretchen Eames, Mitchell E Horwitz, John McCarty, Ryotaro Nakamura, Michael A Pulsipher, Scott Rowley, Eric Leifer, Shelly L Carter, Nancy L DiFronzo, Mary M Horowitz, Dennis Confer, H Joachim Deeg, Mary Eapen**

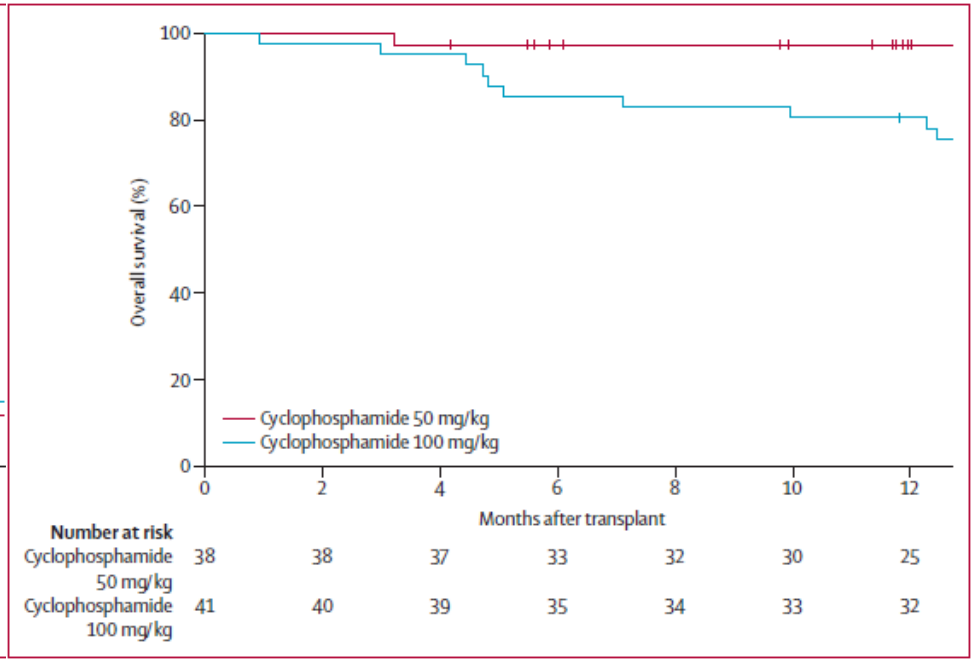
Phase 1		Phase 2	
Cyclophosphamide 150 mg/kg	6	Cyclophosphamide 150 mg/kg	8
Cyclophosphamide 100 mg/kg	6	Cyclophosphamide 100 mg/kg	35
Cyclophosphamide 50 mg/kg	6	Cyclophosphamide 50 mg/kg*	33
Cyclophosphamide 0 mg/kg	3	Total	96

	Cyclophosphamide 50 mg/kg (n=38)	Cyclophosphamide 100 mg/kg (n=41)
Graft failure, primary and secondary	3 (8%)	6 (15%)
Survival	37 (97%)	39 (95%)
Major regimen-related toxicity* (grade 3 or higher)	4 (11%)	9 (22%)
Alive and engrafted	35 (92%)	35 (85%)

Data are number (%). *Defined as severity of grade 4 in any organ system or grade 3 for pulmonary, cardiac, renal, oral, mucosal, or hepatic toxicity, in keeping with the approach adopted in Deeg and colleagues.[6]

Table 3: **Outcomes at day 100 in the cyclophosphamide 50 mg/kg and 100 mg/kg cohorts**

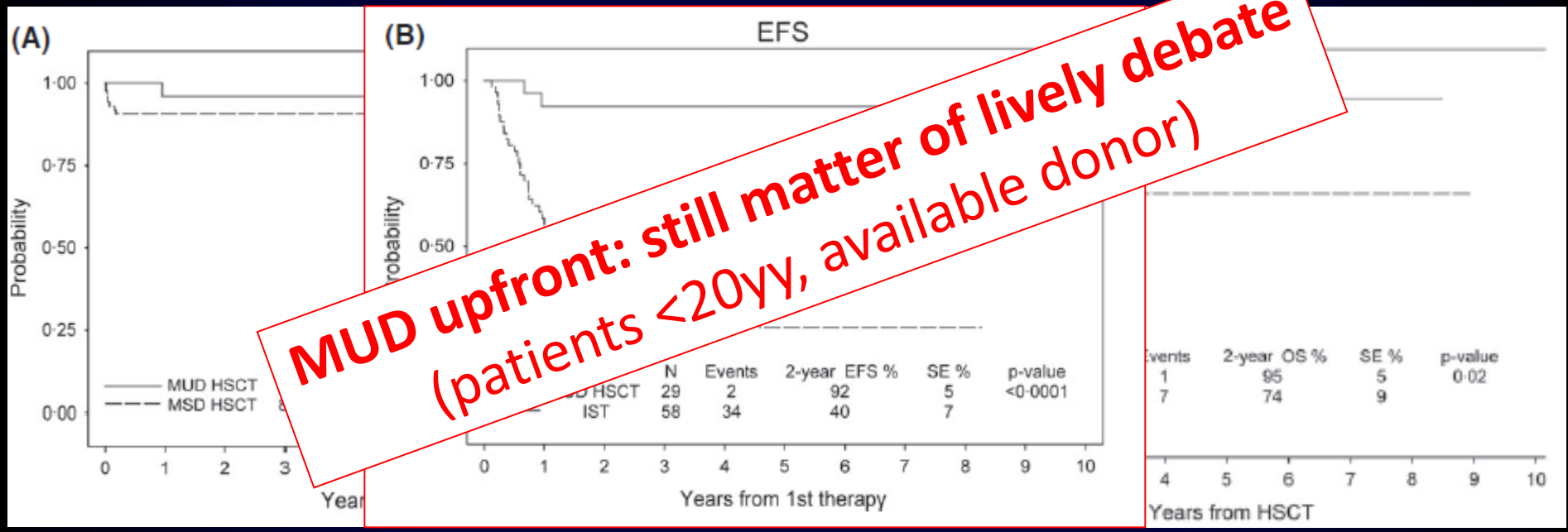




bjh research paper

Similar outcome of upfront-unrelated and matched sibling stem cell transplantation in idiopathic paediatric aplastic anaemia. A study on behalf of the UK Paediatric BMT Working Party, Paediatric Diseases Working Party and Severe Aplastic Anaemia Working Party of EBMT

© 2015 John Wiley & Sons Ltd
British Journal of Haematology, 2015, **171**, 585–594

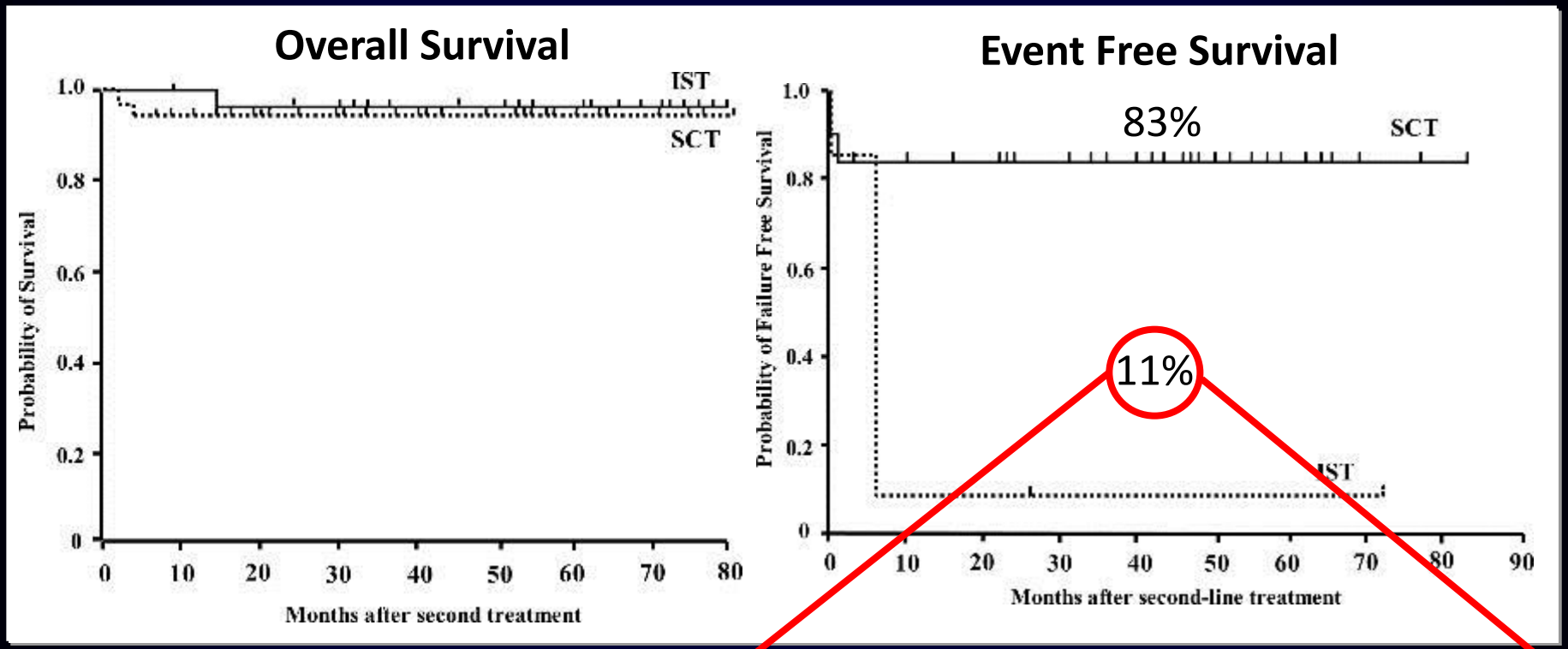


MUD upfront: still matter of lively debate
(patients <20yy, available donor)

- ✓ N=29, pediatric (median age 8.4 yy, range 1-19)
- ✓ 10/10 MUD (5 were 9/10), FCC protocol
- ✓ 2y OS 96%, 2y DFS 92%
  - 1y cGVHD 19% (limited)
  - 1 graft failure, 1 death (idiopathic pneumonia syndrome)

The choice of 2nd line therapy
Pediatric patients

Prospective multicenter trial / Refractory pediatric patients only



Second IST and EFS

No response / CSA dependance / Relapse

Clonal evolution

Kosaka Y *et al*, Blood 2008

IST vs BMT as first-line therapy for SAA

Pros and cons

IST

Pros

- ✓ Low treatment-related morbidity and mortality
- ✓ Off the shelf therapy
- ✓ Minimal impact on QoL
- ✓ BMT still an option as 2nd line therapy
- ✓ Improved results with eltrombopag?

Cons

- ✓ Longer interval to hematological recovery
- ✓ Risk of clonal evolution
- ✓ Risk of relapse
- ✓ Low rate of cure

BMT

Pros

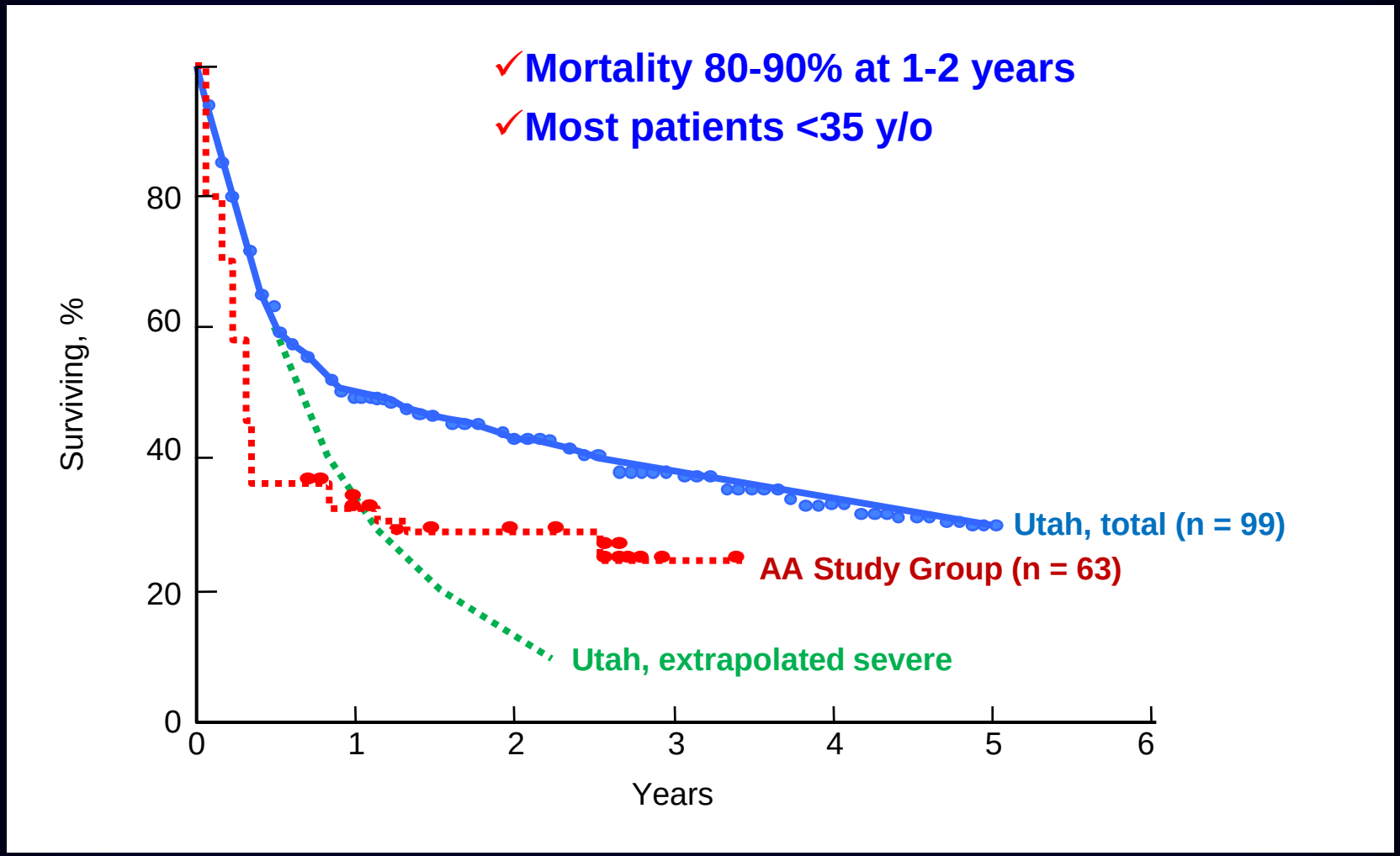
- ✓ High rate of cure
- ✓ Shorter intervals to hematological recovery
- ✓ Low risk of relapse (or clonal evolution)
- ✓ Outcome significantly improved with latest strategies (e.g., FCC)

Cons

- ✓ High transplant-related morbidity and mortality
- ✓ Risk of GvHD
- ✓ Possible impact on QoL
- ✓ Time to procedure (e.g., donor recruitment)

Aplastic anemia: the natural history

In the '70s almost always a fatal disease



Camitta et al, Blood 1979; 53:504
Williams et al, Sem Hematol 1973; 10:195

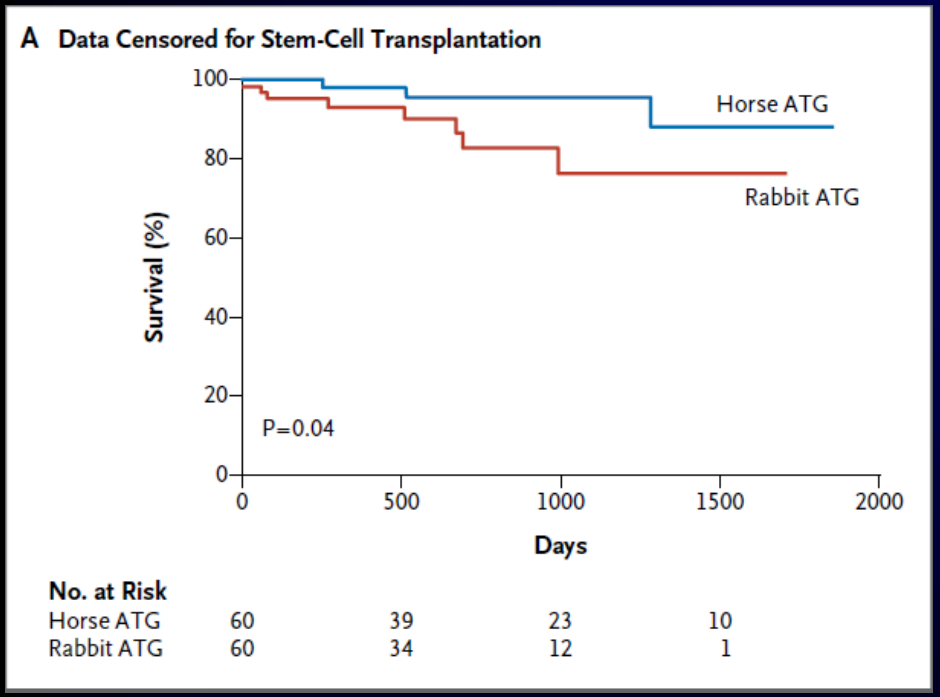
NEJM

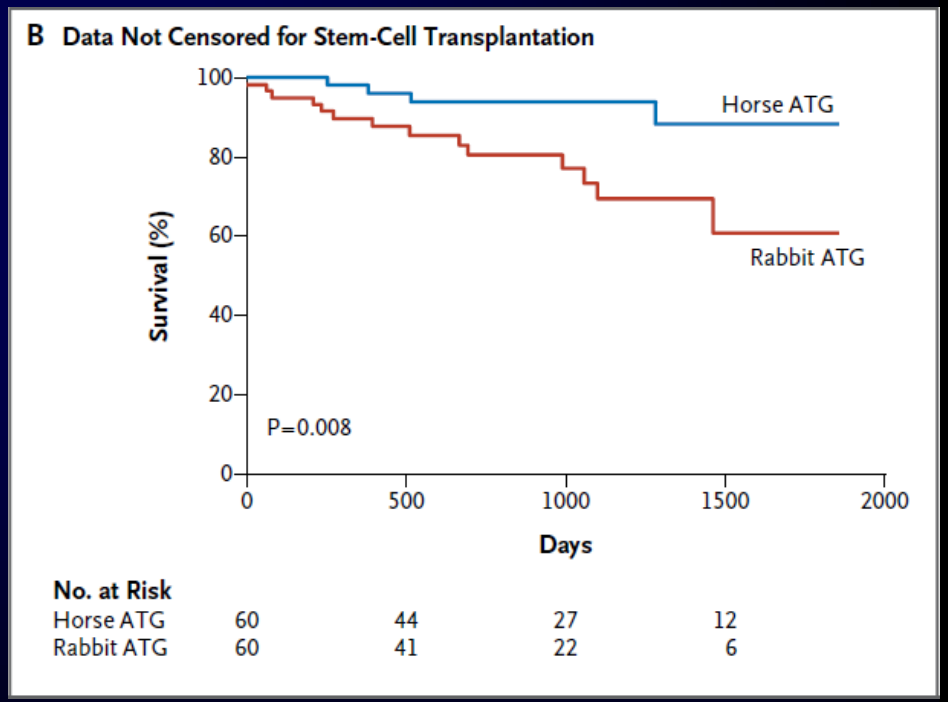
Horse versus Rabbit Antithymocyte Globulin in Acquired Aplastic Anemia

Phillip Scheinberg, M.D., Olga Nunez, R.N., B.S.N., Barbara Weinstein, R.N., Priscila Scheinberg, M.S., Angélique Biancotto, Ph.D., Colin O. Wu, Ph.D., and Neal S. Young, M.D.

NEJM 2011

- ✓ *Phase III prospective randomized study, first-line treatment*
- ✓ *hATG + CyA (n=60) vs rATG + CyA (n=60)*
- ✓ *OR @ 6m 68% vs 37% (p<0.001)*





rATG is inferior to hATG in first line treatment of SAA, as indicated by hematological response and survival

Aplastic anemia and immunusoppressive treatment

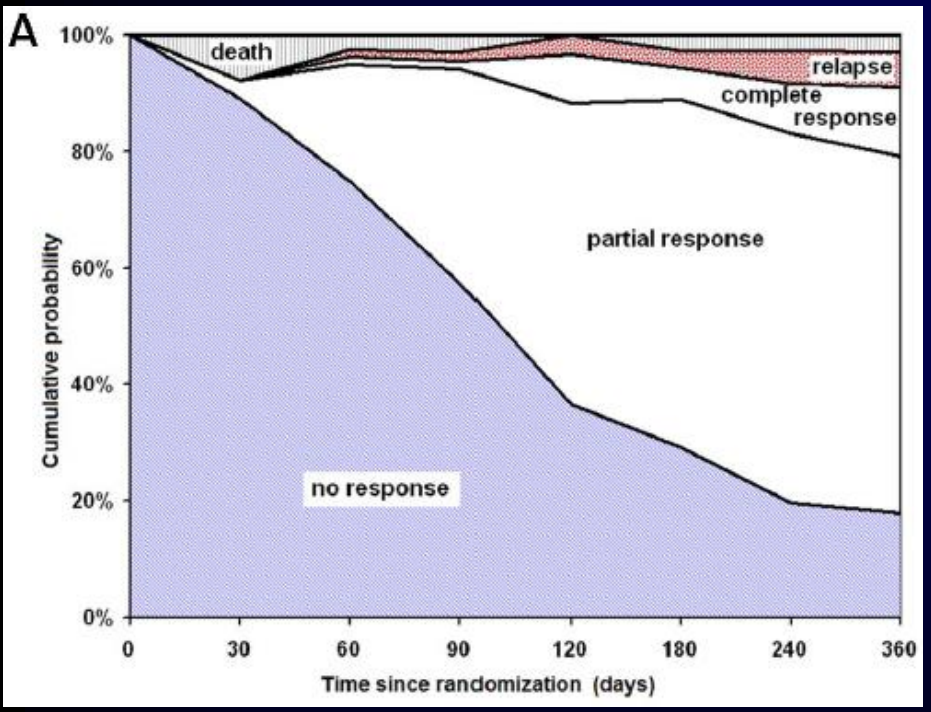
The "quality" of hematological response

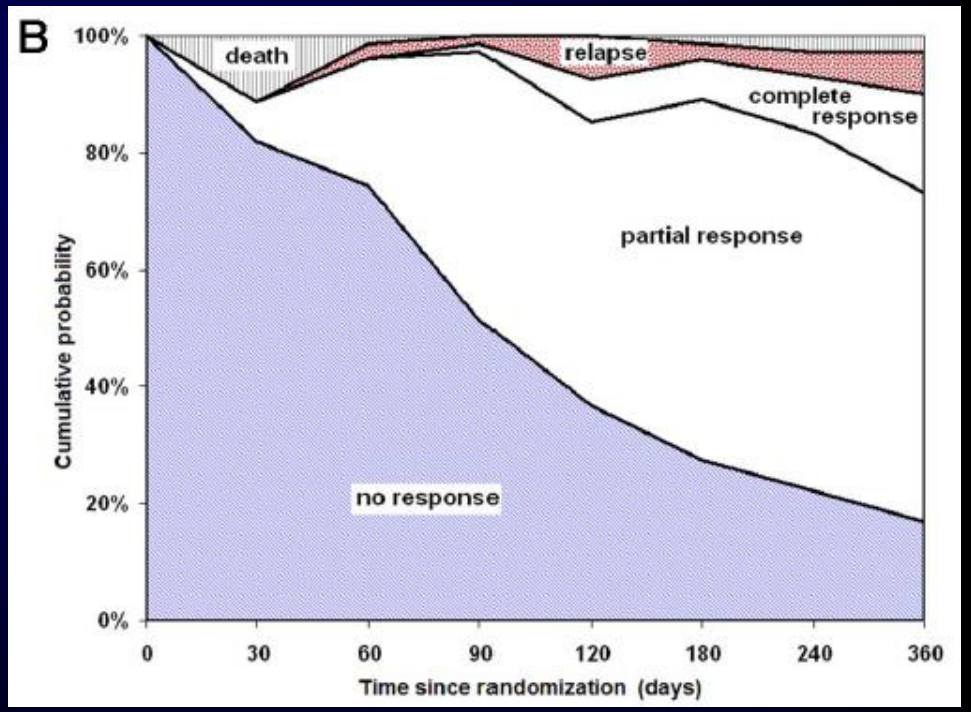
blood

2011 117: 4434-4441
Prepublished online January 13, 2011;
doi:10.1182/blood-2010-08-304071

A randomized controlled study in patients with newly diagnosed severe aplastic anemia receiving antithymocyte globulin (ATG), cyclosporine, with or without G-CSF: a study of the SAA Working Party of the European Group for Blood and Marrow Transplantation

André Tichelli, Hubert Schrezenmeier, Gérard Socié, Judith Marsh, Andrea Bacigalupo, Ulrich Dührsen, Anke Franzke, Michael Hallek, Eckhard Thiel, Martin Wilhelm, Britta Höchsmann, Alain Barrois, Kim Champion and Jakob R. Passweg

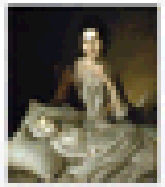




- ✓ Very low rate of complete response (about 10%)
- ✓ High rate of relapse (30-40%)

Tichelli et al, Blood 2011

JAMA



2003

Antithymocyte Globulin and Cyclosporine for Severe Aplastic Anemia

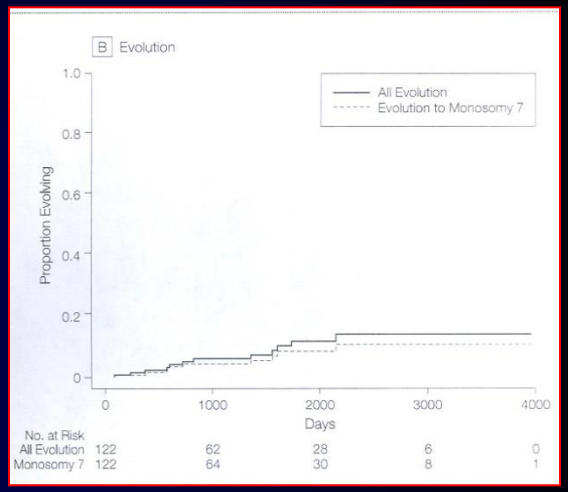
Association Between Hematologic Response and Long-term Outcome

Stephen Rosenfeld, MD
Dean Follmann, PhD
Olga Nunez, RN
Neal S. Young, MD

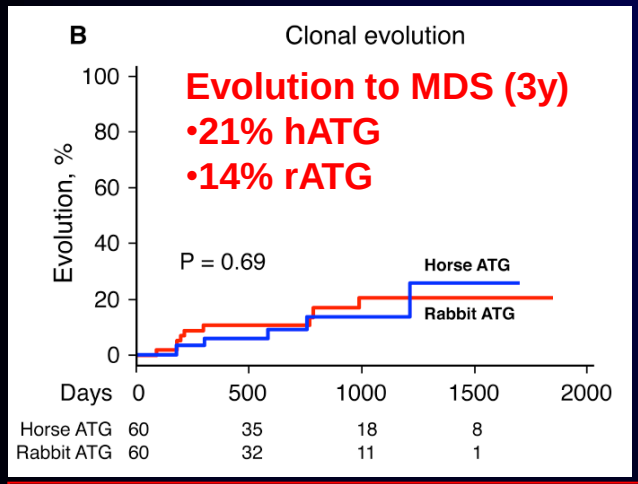
n=112

hATG x 4 (40mg/kg)
+ CsA x 6 m

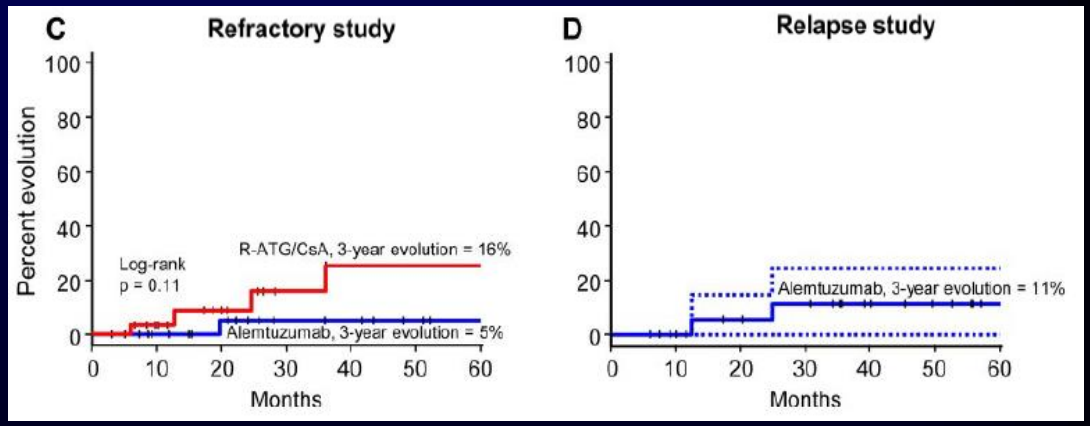
Clonal evolution (3y)
- **11% MDS (especially 7-)**
- **10% PNH**



NEJM 2011



Blood 2012



In all recent studies, the incidence of clonal evolution is about 10%, regardless the specific treatment

The actual meaning of somatic mutations in hematology

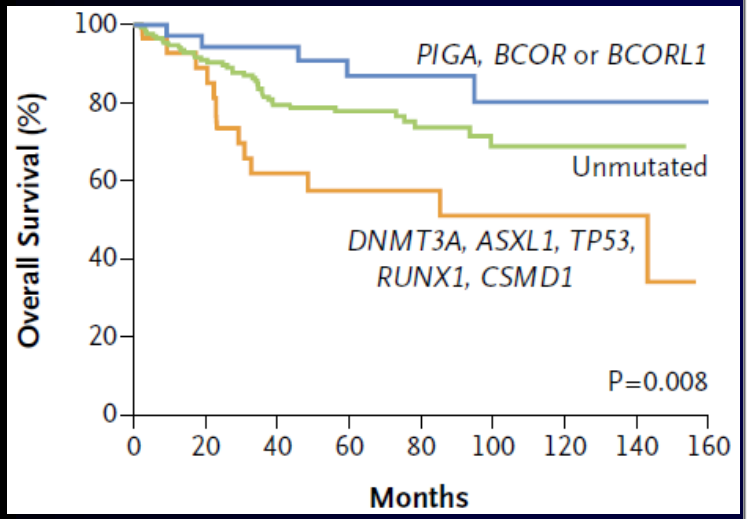
Do all mutations imply cancer (especially in marrow failure)?

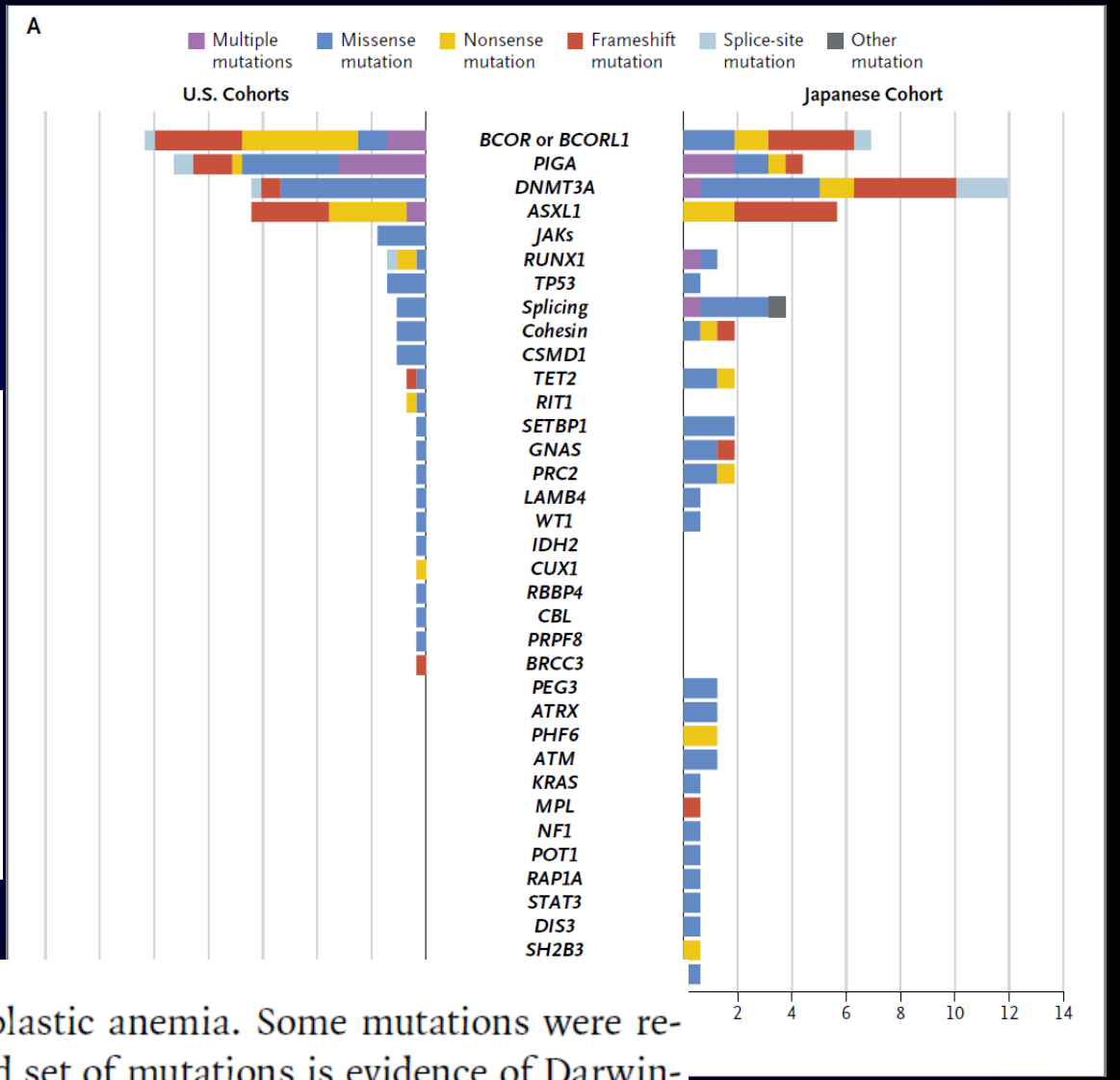
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Somatic Mutations and Clonal Hematopoiesis in Aplastic Anemia

T. Yoshizato, B. Dumitriu, K. Hosokawa, H. Makishima, K. Yoshida, D. Townsley, A. Sato-Otsubo, Y. Sato, D. Liu, H. Suzuki, C.O. Wu, Y. Shiraishi, M.J. Clemente, K. Kataoka, Y. Shiozawa, Y. Okuno, K. Chiba, H. Tanaka, Y. Nagata, T. Katagiri, A. Kon, M. Sanada, P. Scheinberg, S. Miyano, J.P. Maciejewski, S. Nakao, N.S. Young, and S. Ogawa





CONCLUSIONS

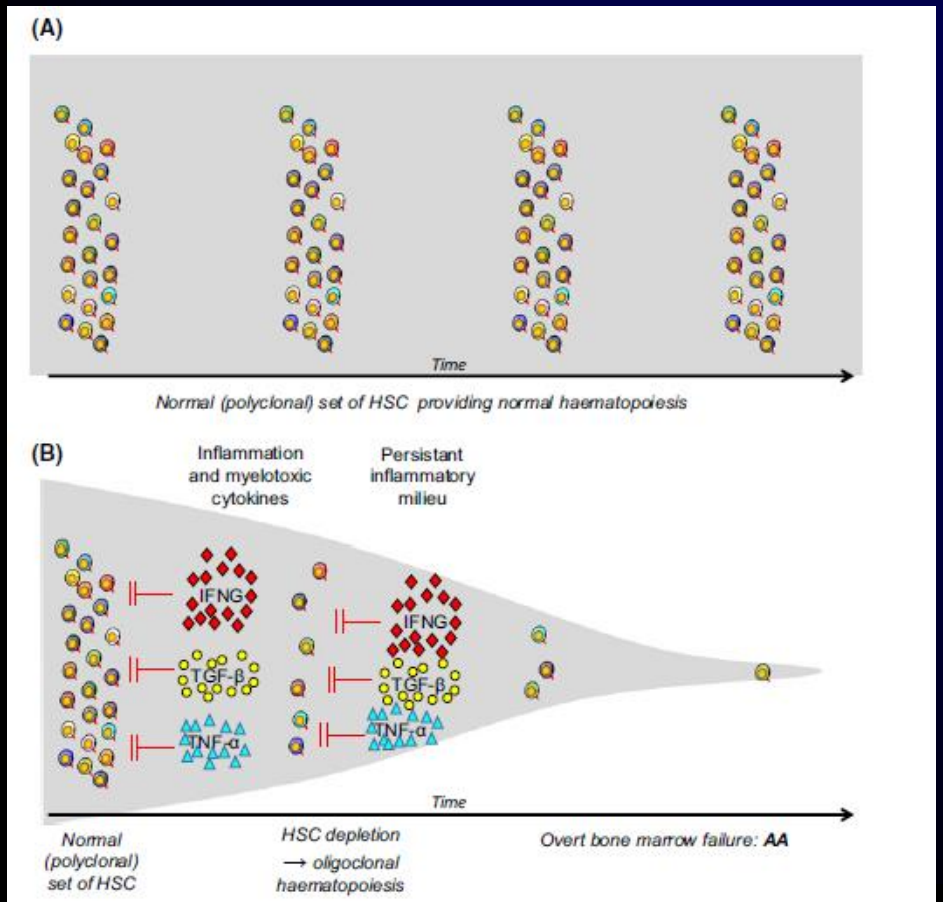
Clonal hematopoiesis was prevalent in aplastic anemia. Some mutations were related to clinical outcomes. A highly biased set of mutations is evidence of Darwinian selection in the failed bone marrow environment. The pattern of somatic clones in individual patients over time was variable and frequently unpredictable.

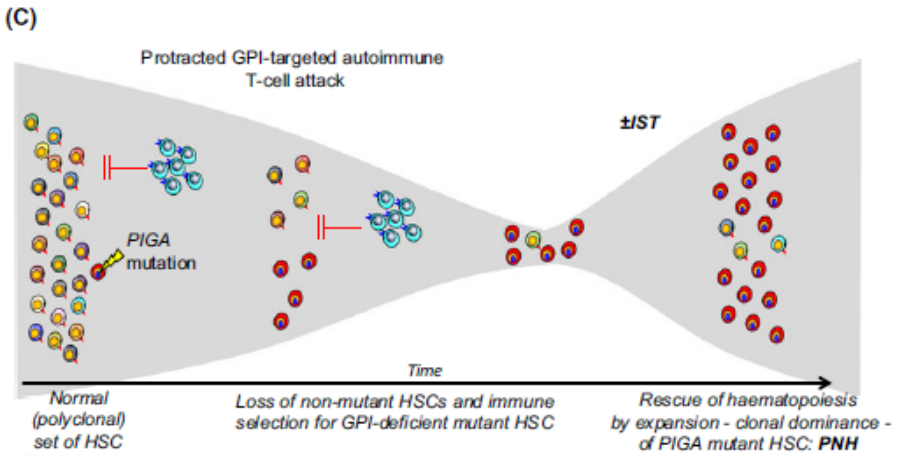
bjh review

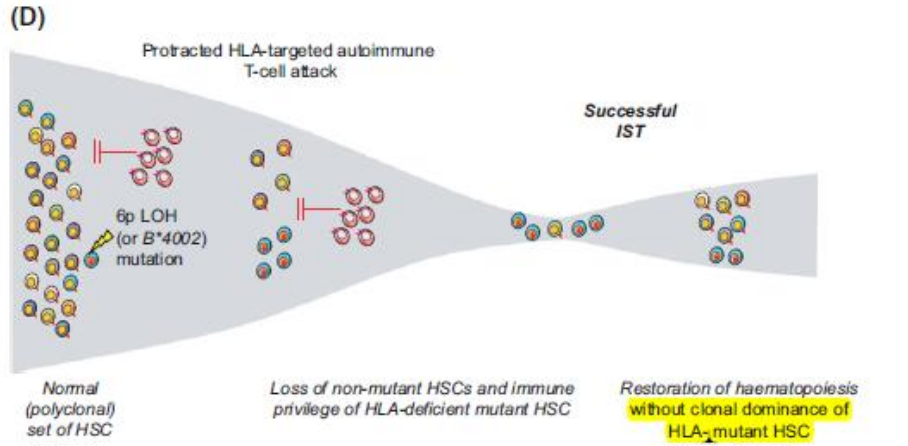
Advances in understanding the pathogenesis of acquired aplastic anaemia

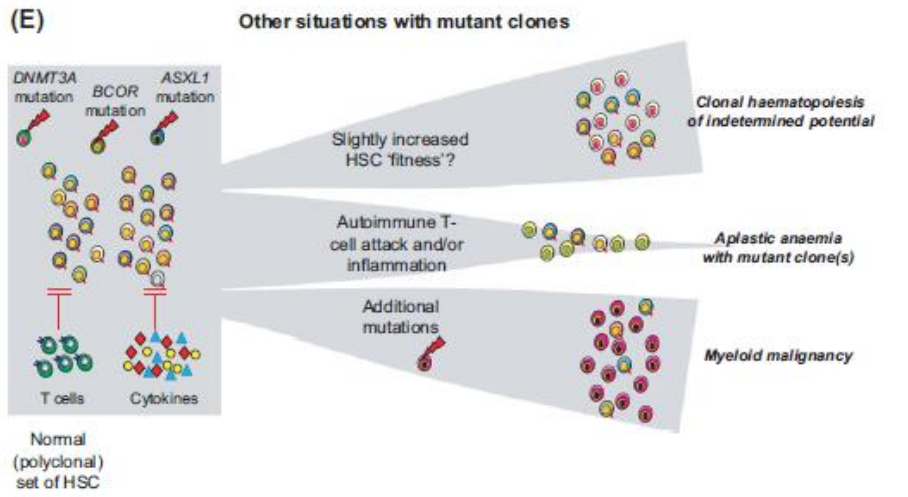
Lucio Luzzatto[1] and Antonio M. Risitano[2]

Fig 4. Dynamics of haematopoiesis in different situations.









ELTROMBOPAG IN SAA

Frontline treatment

ORIGINAL ARTICLE

Eltrombopag Added to Sta
Immunosuppression for Aplast

Danielle M. Townsley, M.D., Phillip Scheinberg, M.D., Th
Ronan Desmond, M.D., Bogdan Dumitriu, M.D., O
Barbara Weinstein, B.S.N., Janet Valdez, P.A., Jennif
Xingmin Feng, Ph.D., Marie Desierto, B.S., Harshraj L
Margaret Bevans, Ph.D., Colin Wu, Ph.D., Andre Laroch
Katherine R. Calvo, M.D., Cynthia E. Dunbar, M.D., and N

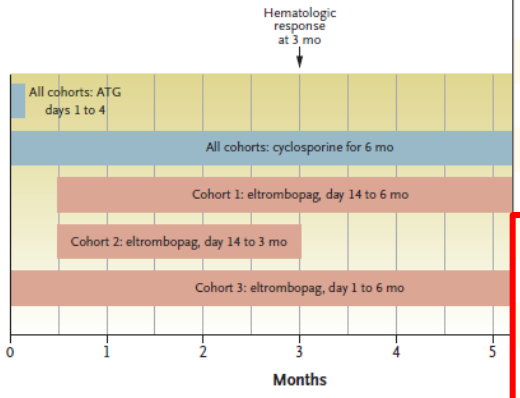


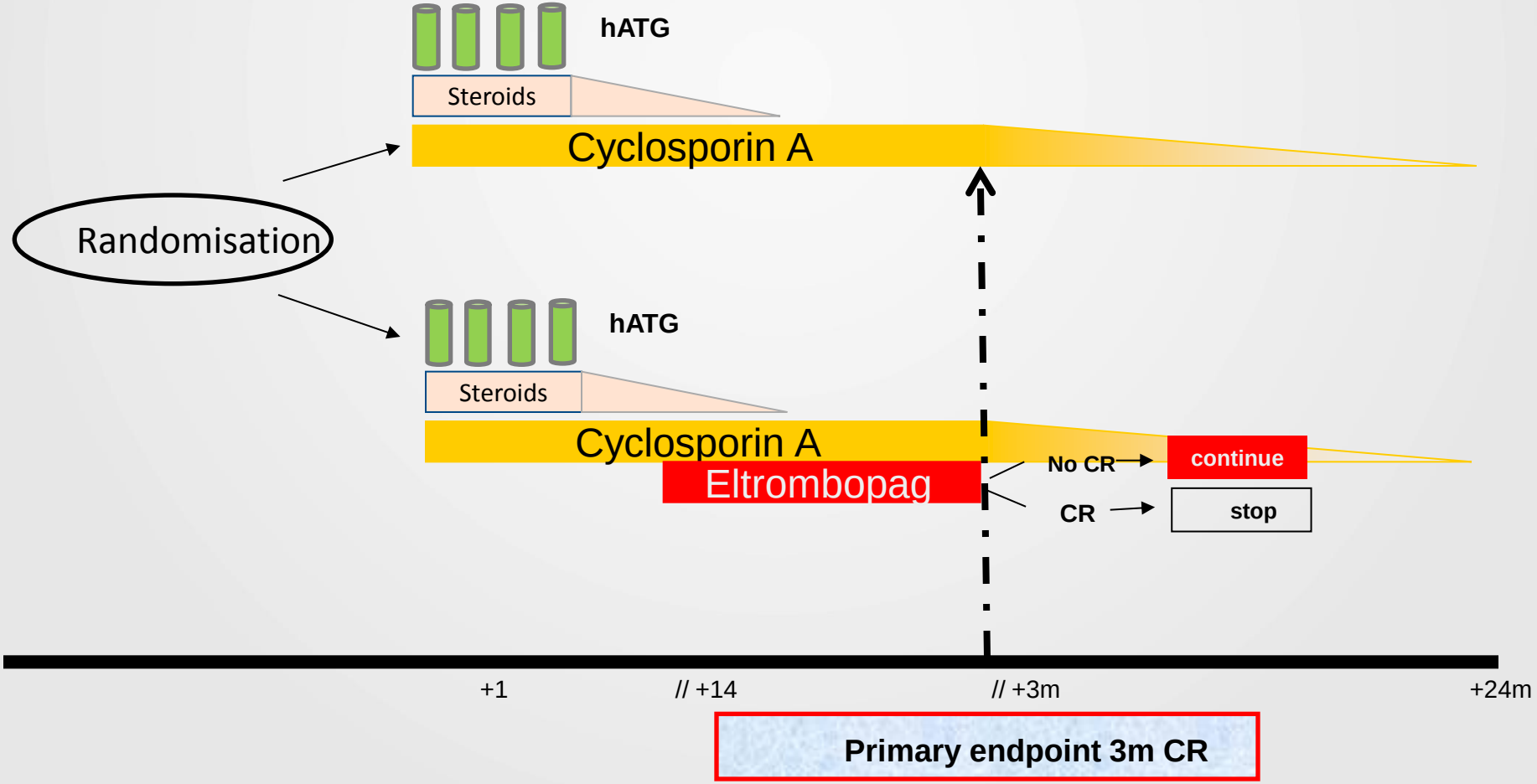
Table 2. Hematologic Response in Patients Treated with Immunosuppression and Eltrombopag.*

Cohort and Response	Rate at 3 Mo	Rate at 6 Mo	P Value
Cohort 1			
No. of patients	30	30	
Response — no. (% [95% CI])			
Overall response	23 (77 [61–93])	24 (80 [65–95])	
Partial response	18 (60 [41–79])	14 (47 [28–66])	
Complete response	5 (17 [3–31])	10 (33 [15–31])	0.01
Cohort 2			
No. of patients	31	31	
Response — no. (% [95% CI])			
Overall response	24 (77 [62–93])	27 (87 [75–100])	
Partial response	16 (52 [33–70])	19 (61 [43–79])	
Complete response	8 (26 [9–42])	8 (26 [9–42])	0.06
Cohort 3			
No. of patients	31	31	
Response — no. (% [95% CI])			
Overall response	27 (87 [75–100])	29 (94 [84–103])	
Partial response	12 (39 [21–57])	11 (35 [18–53])	
Complete response	15 (48 [30–67])	18 (58 [40–76])	<0.001
All cohorts			
No. of patients	92	92	
Response — no. (% [95% CI])			
Overall response	74 (80 [72–89])	80 (87 [80–94])	<0.001†
Partial response	46 (50 [40–60])	44 (48 [37–58])	
Complete response	28 (30 [21–40])	36 (39 [29–49])	<0.001

RACE STUDY (2)

SAA-WP

TREATMENT Scheme



Toward a cure for aplastic anemia

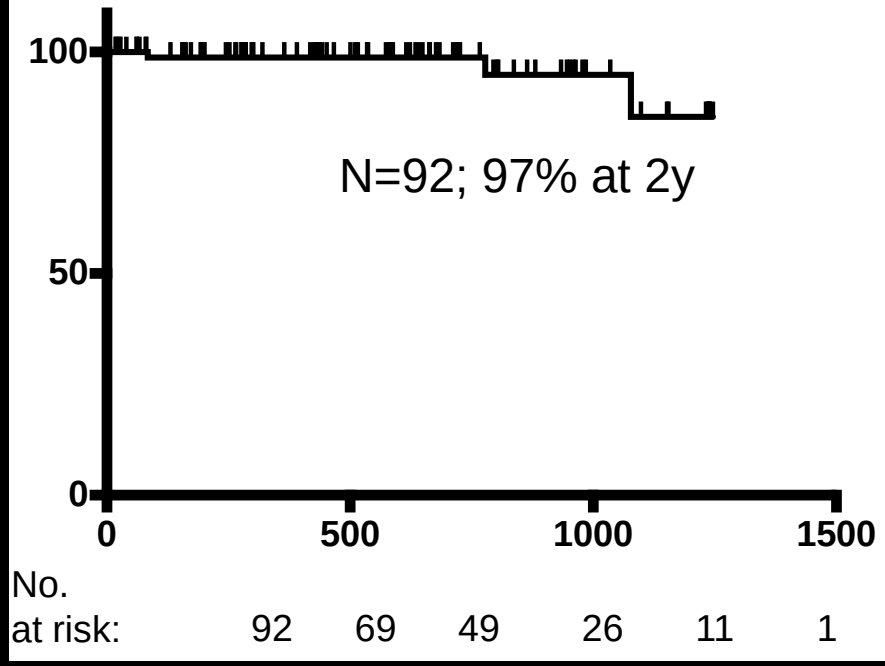
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia

Danielle M. Townsley, M.D., Phillip Scheinberg, M.D., Thomas Winkler, M.D., Ronan Desmond, M.D., Bogdan Dumitriu, M.D., Olga Rios, R.N., Barbara Weinstein, B.S.N., Janet Valdez, P.A., Jennifer Lotter, P.A., Xingmin Feng, Ph.D., Marie Desierto, B.S., Harshraj Leuva, M.B., B.S., Margaret Bevans, Ph.D., Colin Wu, Ph.D., Andre Larochelle, M.D., Ph.D., Katherine R. Calvo, M.D., Cynthia E. Dunbar, M.D., and Neal S. Young, M.D.

OS - Not censored for HSCT



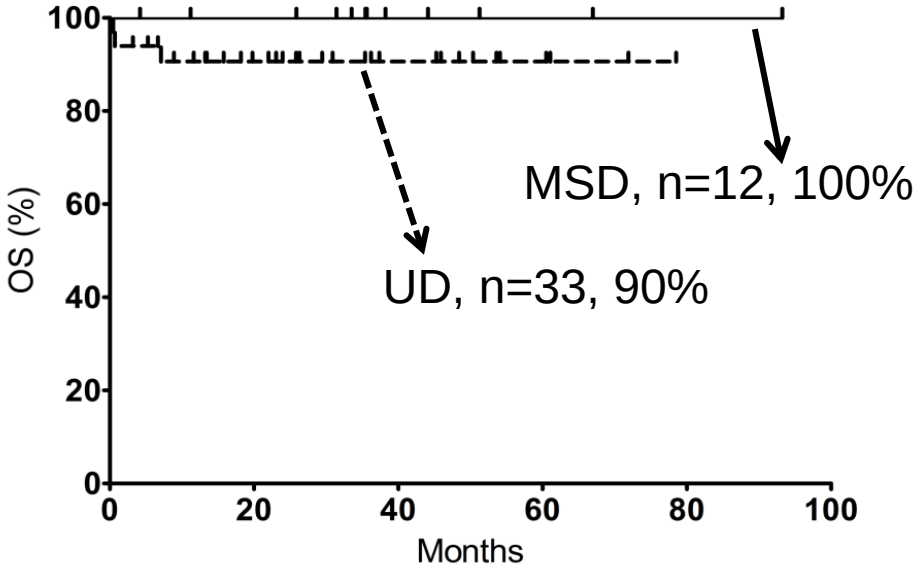
ELSEVIER
Biology of Blood and Marrow Transplantation
journal homepage: www.bbmt.org
ASBMT American Society for Blood and Marrow Transplantation

Mixed T Cell Chimerism After Allogeneic Hematopoietic Stem Cell Transplantation for Severe Aplastic Anemia Using an Alemtuzumab-Containing Regimen Is Shaped by Persistence of Recipient CD8 T Cells

Francesco Grimaldi [1,2], Victoria Potter [1], Pilar Perez-Abellan [3], John P. Veluchamy [3], Muhammad Atif [3], Rosemary Grain [3], Monica Sen [3], Steven Best [1], Nicholas Lea [1], Carmel Rice [1], Antonio Pagliuca [1], Ghulam J. Mufti [1,3], Judith C. W. Marsh [1,3,*], Linda D. Barber [3,†]

[1] Department of Haematology, King's College Hospital NHS Foundation Trust, London, United Kingdom
[2] Department of Clinical Medicine, Haematology Division, AOU Federico II, Naples, Italy
[3] Division of Cancer Studies, King's College London, London, United Kingdom

OS – MSD vs UD



IST vs BMT as first-line therapy for SAA

Pros and cons

IST

Pros

- ✓ Low treatment-related morbidity and mortality
- ✓ Off the shelf therapy
- ✓ Minimal impact on QoL
- ✓ BMT still an option as 2nd line therapy
- ✓ Improved results with eltrombopag?

Cons

- ✓ Longer interval to hematological recovery
- ✓ Risk of clonal evolution
- ✓ Risk of relapse
- ✓ Low rate of cure

BMT

Pros

- ✓ High rate of cure
- ✓ Shorter intervals to hematological recovery
- ✓ Low risk of relapse (or clonal evolution)
- ✓ Outcome significantly improved with latest strategies (e.g., FCC)

Cons

- ✓ High transplant-related morbidity and mortality
- ✓ Risk of GvHD
- ✓ Possible impact on QoL
- ✓ Time to procedure (e.g., donor recruitment)

To transplant or not to transplant?

1. In whom?
2. When?
3. How?
4. Why (not)?

IST HSCT

To cure or not to cure?

1. In whom?
2. When?
3. How?
4. Why (not)?

IST HSCT

What is the goal of future therapies of AA?

Surrogate endpoints of cure

- ✓ **EFS rather than OS**
  - GvHD after HSCT (dynamic?)
  - Clonal evolution after IST
  - Secondary cancers? AVN? QOL?
- ✓ **Prospective comparison**
- ✓ **Randomized trials?**
  - Ethicality?
  - Feasibility?

IST HSCT Eltrombopag

ACKNOWLEDGEMENTS

Regis Peffault De Latour

Carlo Dufour

Neal S. Young

EBMT SAAWP

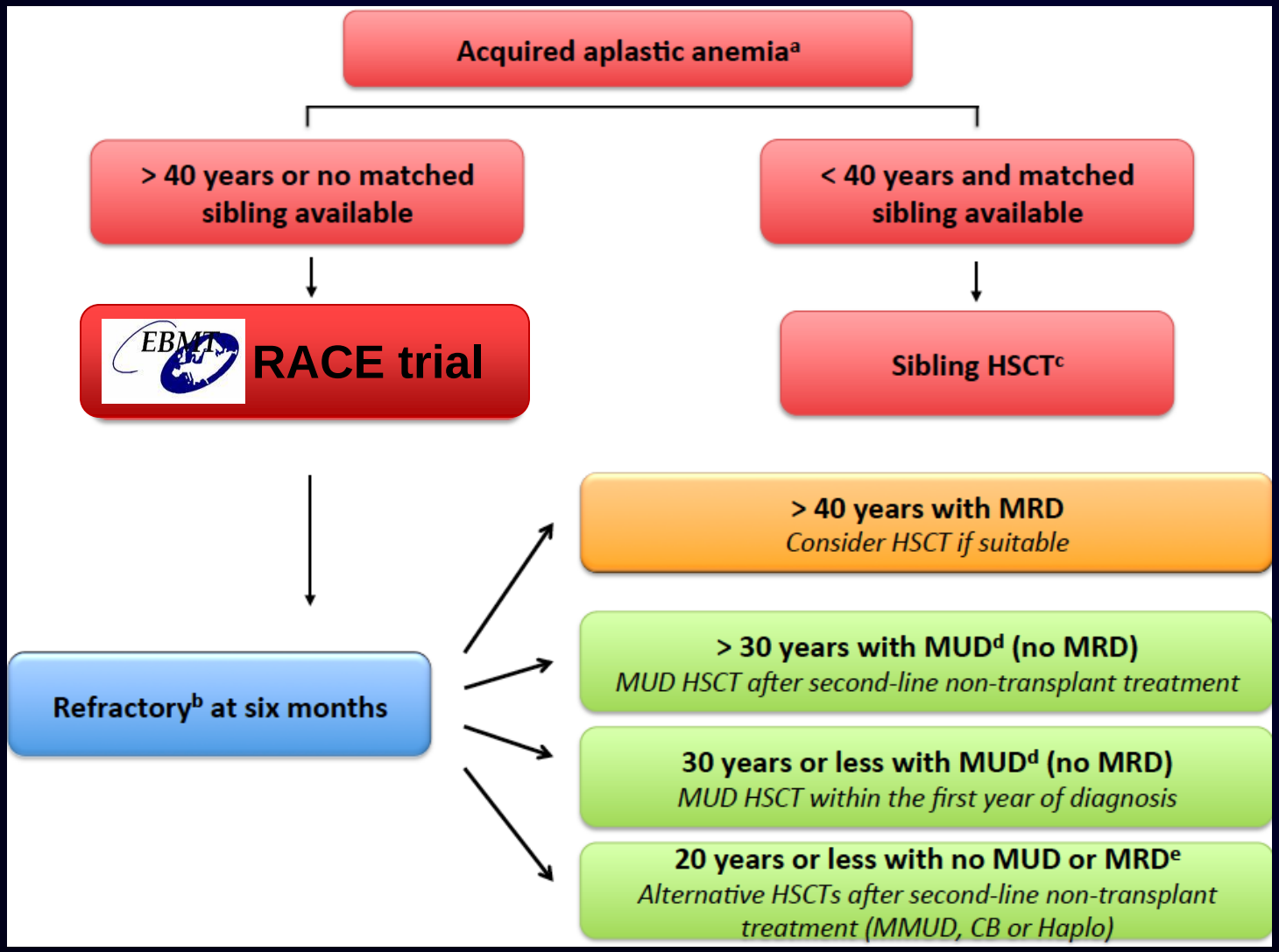
Andrea Bacigalupo
Judith Marsh
Jakob Passweg
Sujith Samarasinghe
Hubert Schrezenmeier
Gerard Sociè
Andrè Tichelli

International AA experts

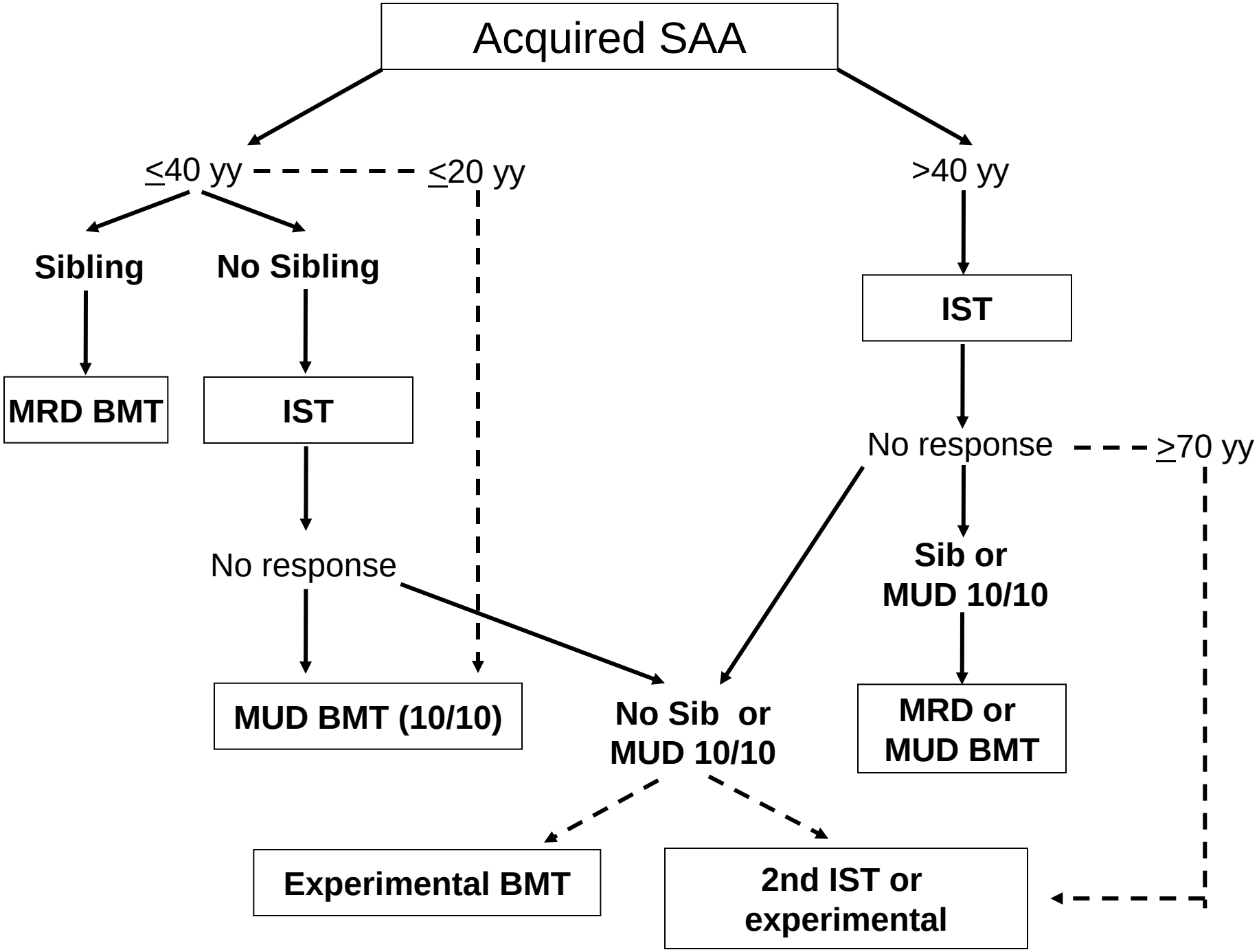
Rodrigo Calado
Jarek Maciejewski
Shinji Nakao
Rosario Notaro
Lucio Luzzatto
Phillip Scheinberg
Danielle Townsley

Treatment algorithm of aplastic anemia

Updated to 2017



Peffault De Latour, ASH Educational 2016


Acquired SAA
≤40 yy
≤20 yy
>40 yy
Sibling
No Sibling
MRD BMT
IST
IST
No response
≥70 yy
No response
Sib or
MUD 10/10
MUD BMT (10/10)
No Sib or
MUD 10/10
MRD or
MUD BMT
Experimental BMT
2nd IST or
experimental

HSCT for AA

The impact of age – revised in 2017

All HSCT (MRD and MUD) in AA patients >40yy

- ✓ **EBMT registry: N=768**

C039

TRANSPLANT OUTCOME FOR PATIENTS WITH ACQUIRED APLASTIC ANEMIA OVER THE AGE OF 40: MORTALITY HAS NOT BEEN REDUCED IN 2015

S. Giammarco[1], S. Sica[1], C. Dufour[2], R. Peffault de Latour[3], G. Socie[3], J. Passweg[4], A. Bacigalupo[1], for the EBMT Severe Aplastic Anemia Working Party

	2001-2009 (n=329)	2010-2015 (n=439)	p
Age (median)	50y	52y	<0,01
MUD	28%		<0,01
BM source	42%		<0,01
Flu-based Cond		%	<0,01
ATG or Campath		87%	<0,001
Graft failure		12%	0,02
Acute GvHD	15%	11%	0,1
Chronic GvHD	32%	26%	0,04
5y OS	**61%**	**58%**	**0,9**
Infectious mortality	18%	22%	
GvHD mortality	5%	4%	

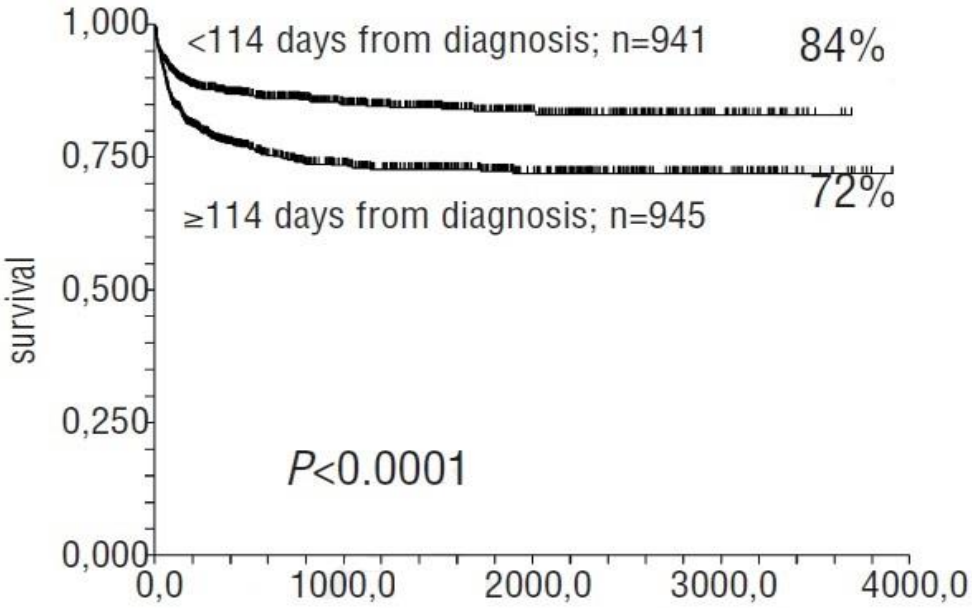
Strong age effect in multivariate analysis: 66%, 57% and 40% according to age decade

Matched related HSCT for SAA

The role of interval between diagnosis and HSCT

Bone marrow *versus* peripheral blood as the stem cell source for sibling transplants in acquired aplastic anemia: survival advantage for bone marrow in all age groups

Andrea Bacigalupo,[1] Gérard Socié,[2] Hubert Schrezenmeier,[3] Andre Tichelli,[4] Anna Locasciulli,[5] Monika Fuehrer,[6] Antonio M. Risitano,[7] Carlo Dufour,[8] Jakob R. Passweg,[4] Rosi Oneto,[1] Mahmoud Aljurf,[9] Catherine Flynn,[10] Valerie Mialou,[11] Rose Marie Hamladji,[12] and Judith C. W. Marsh[13] for the Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (WPSAA-EBMT)

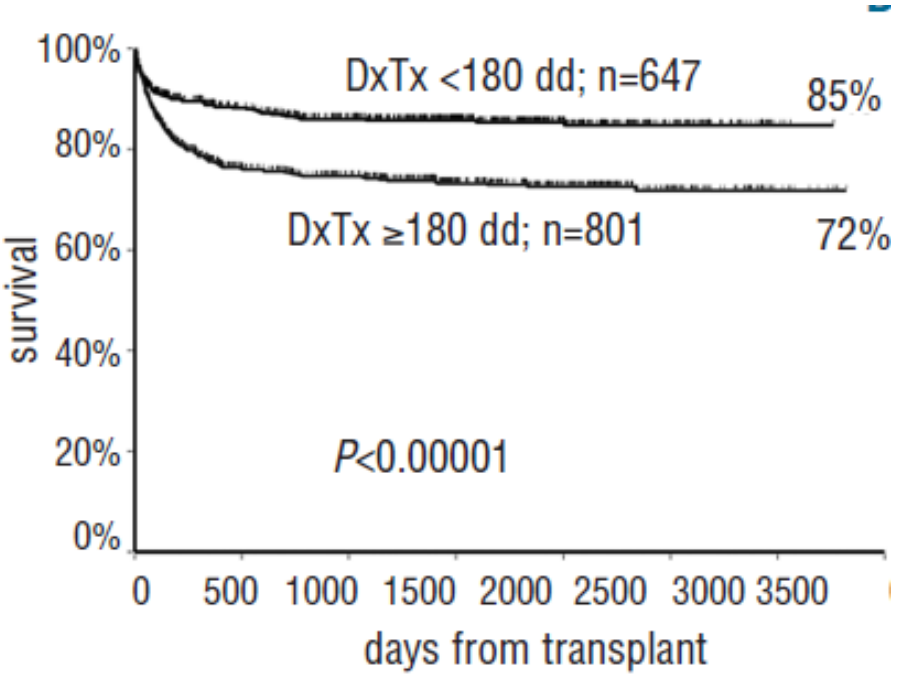


- **Siblings only**
- Graft failure 5-7%
- Late graft rejection 1.3-1.4%

Bacigalupo A et al. Haematologica. 2012;97:1142-1148

Current outcome of HLA identical sibling versus unrelated donor transplants in severe aplastic anemia: an EBMT analysis

Andrea Bacigalupo,[1] Gerard Socié,[2] Rose Marie Hamladji,[3] Mahmoud Aljurf,[4] Alexei Maschan,[5] Slawomira Kyrcz-Krzemien,[6] Alicja Cybicka,[7] Henrik Sengelov,[8] Ali Unal,[9] Dietrich Beelen,[10] Anna Locasciulli,[11] Carlo Dufour,[12] Jakob R. Passweg,[13] Rosi Oneto,[1] Alessio Signori[14] and Judith C.W. Marsh;[15] for the Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (WPSAA-EBMT)



- **Siblings and MUD**
- Graft failure 9%
- Late graft rejection 1.5-2%

Bacigalupo A et al. Haematologica. 2015;100:696-702

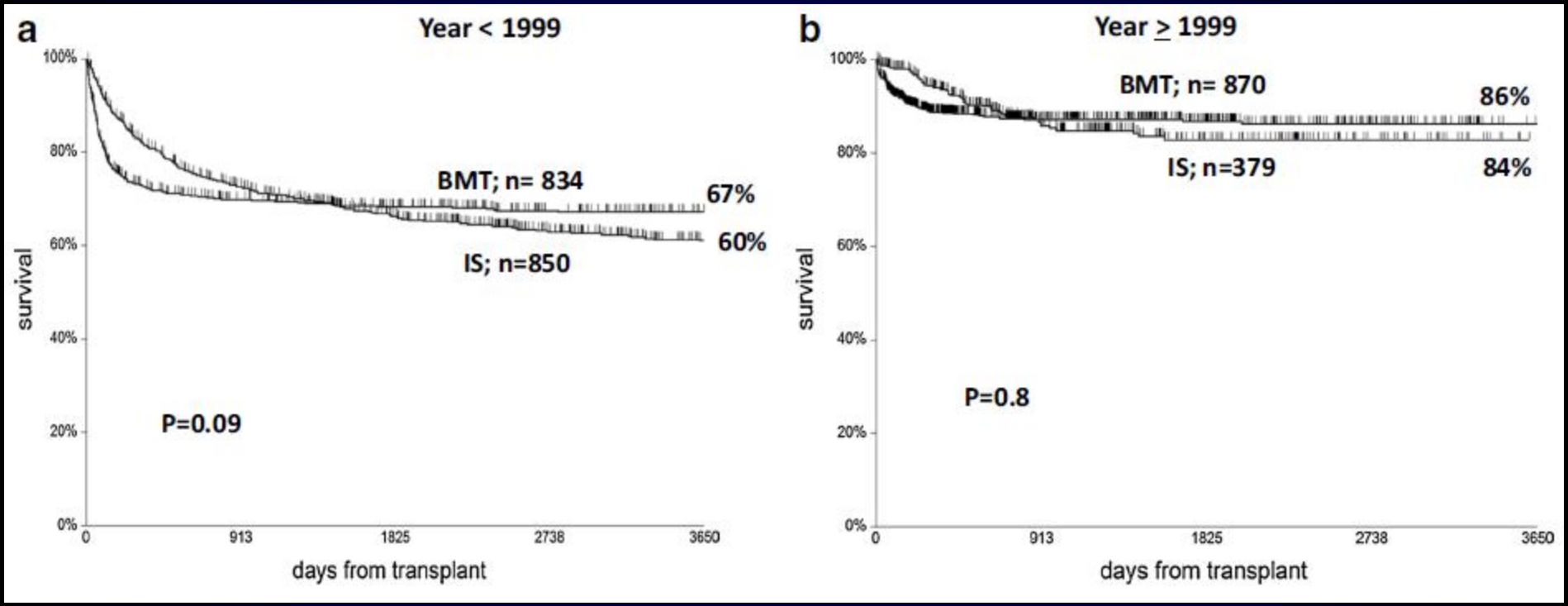
The choice between HSCT and IST as 1st line therapy
Age 0-20

Bone marrow transplantation versus immunosuppressive therapy in patients with acquired severe aplastic anemia

Andrea Bacigalupo[1] · Sabrina Giammarco[1] · Simona Sica[1]

Int J Hematol (2016) 104:168–174
DOI 10.1007/s12185-016-2037-8

PROGRESS IN HEMATOLOGY



- ✓ **Outcome of both treatment improved over decades**
- ✓ **Comparable OS**
- ✓ **EFS much better with HSCT**

Bacigalupo et al, Int J Hematol 2016

The choice between HSCT and IST as 1st line therapy
Age 21-40

Bone marrow transplantation versus immunosuppressive therapy in patients with acquired severe aplastic anemia

Andrea Bacigalupo[1] · Sabrina Giammarco[1] · Simona Sica[1]

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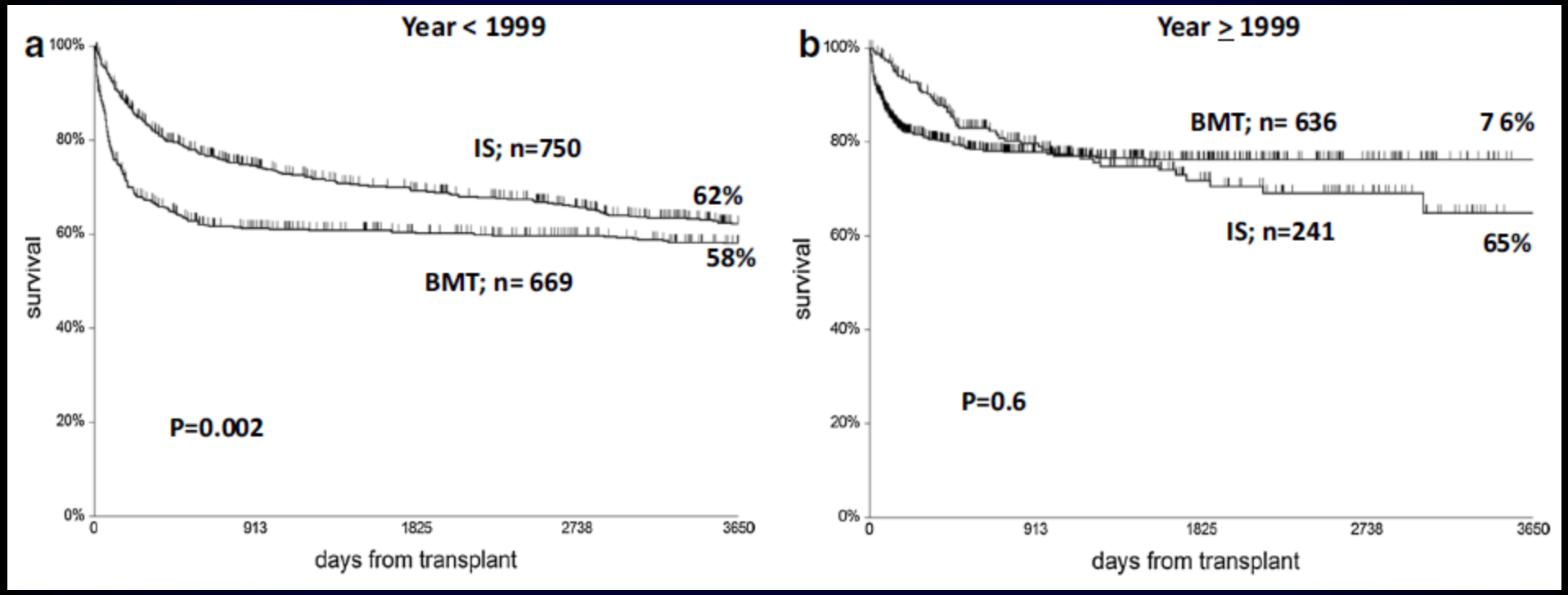

- ✓ **Time-dependent improvement more consistent for HSCT**
- ✓ **Now comparable OS**
- ✓ **EFS much better with HSCT**

Bacigalupo et al, Int J Hematol 2016

The choice between HSCT and IST as 1st line therapy

Age >40

Bone marrow transplantation versus immunosuppressive therapy in patients with acquired severe aplastic anemia

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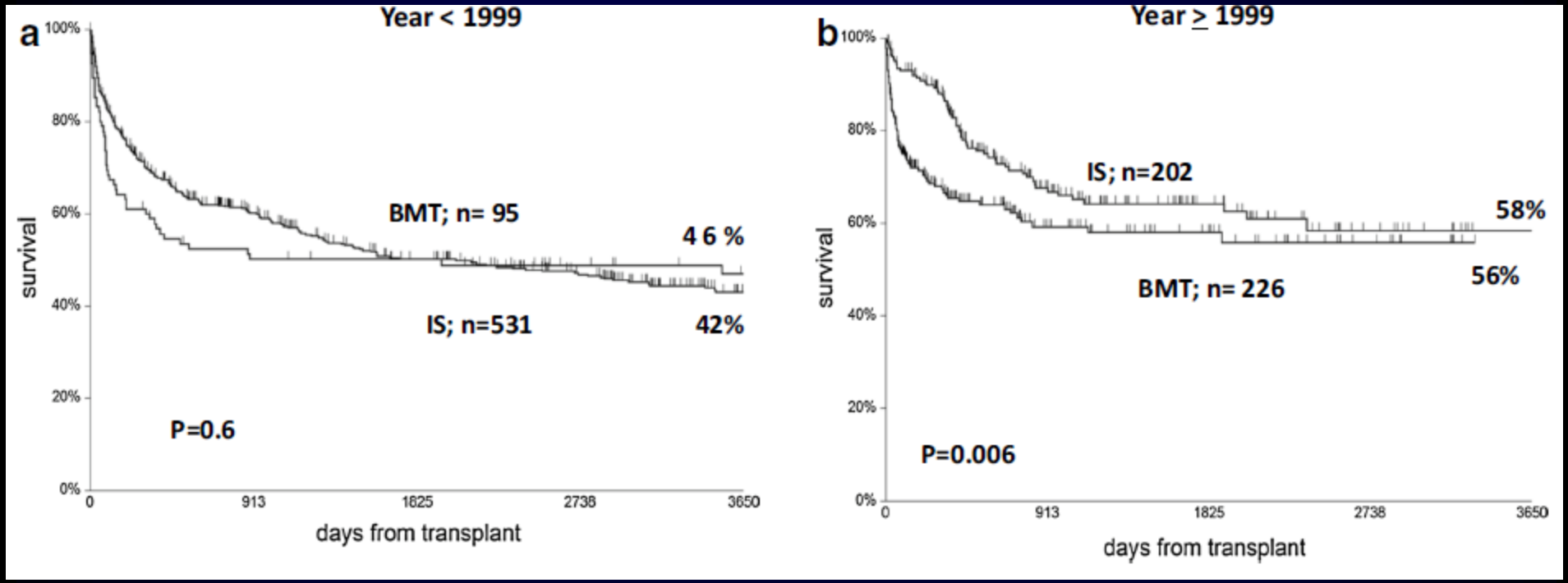
PROGRESS IN HEMATOLOGY



- ✓ **Limited improvement over the past decades**
- ✓ **OS significant better with IST**

Bacigalupo et al, Int J Hematol 2016

Matched related and unrelated HSCT for SAA

The effect of HSC source

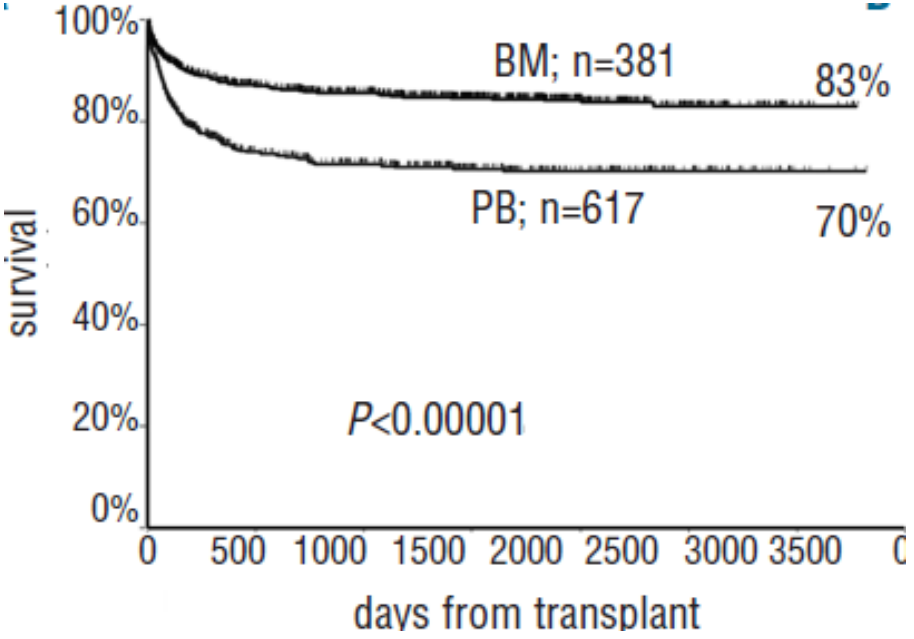
Current outcome of HLA identical sibling versus unrelated donor transplants in severe aplastic anemia: an EBMT analysis

Andrea Bacigalupo,[1] Gerard Socié,[2] Rose Marie Hamladji,[3] Mahmoud Aljurf,[4] Alexei Maschan,[5] Slawomira Kyrcz-Krzemien,[6] Alicja Cybicka,[7] Henrik Sengelov,[8] Ali Unal,[9] Dietrich Beelen,[10] Anna Locasciulli,[11] Carlo Dufour,[12] Jakob R. Passweg,[13] Rosi Oneto,[1] Alessio Signori[14] and Judith C.W. Marsh;[15] for the Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (WPSAA-EBMT)

Retrospective analysis of the SAA-WP

- 1448 patients
- First transplant either MRD or MUD
- 2005-2009
- Acquired aplastic anemia

Source N.	Sibling 940	Unrelated 508	*P*
Causes of death*			
GvHD	37 (3.9%)	34 (6.7%)	
Interstitial pneumonia	1 (0.1%)	7 (0,4%)	
Other lung complications	13 (1.4%)	4 (0.8%)	
Infections	85 (9%)	58 (11.4%)	
Rejection	14 (1.5%)	11 (2.2%)	
Hemorrhage	12 (1.3%)	11 (2.2%)	
VOD	8 (0.9%)	3 (0.6%)	



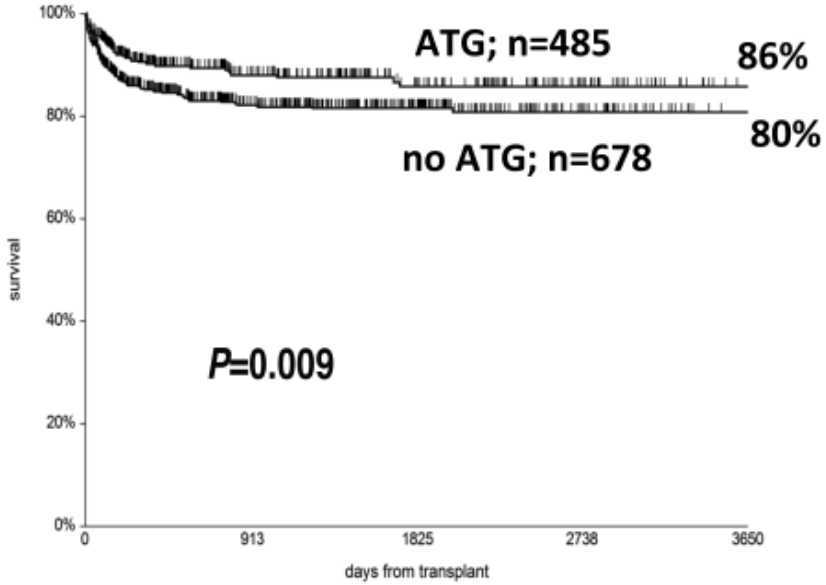
Bacigalupo A et al. Haematologica. 2015;100:696-702

Matched related HSCT for AA

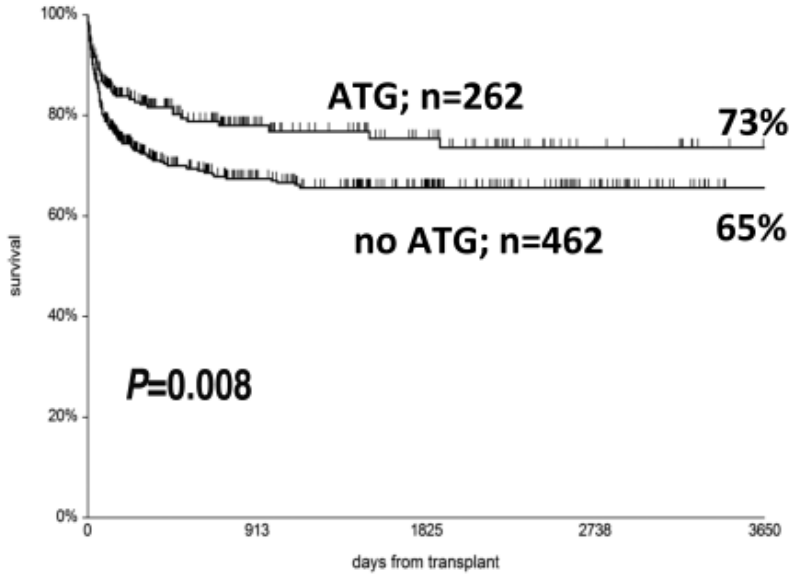
The impact of ATG in the conditioning regimen

HLA id SIB transplants for SAA- EBMT 1999-2009

Bone Marrow grafts



Peripheral Blood grafts



	ATG no	yes	*P*		ATG no	yes	*P*
aGvHD II-IV	13%	8%	0.005		21%	10%	0.0003
Ext cGvHD	4%	2%	0.1		9%	2%	0.001

Bacigalupo, Haematologica 2017

Experimental transplantation for AA

The emerging options

1. **Mismatched Unrelated Donors (MMUD)**
   - 4 x 10^7 frozen TNC /Kg with no more than 2 of 6 HLA mismatches
   - APCORD protocol (NCT 01343953)
2. **Cord Blood Units**
   - BMT CTN study (NCT00326417) or UK guidelines (FCC)
3. **Haploidentical donors**
   - Baltimore protocol (PT-Cy) vs T cell depleted (e.g., ab TCD)

Study - Source of stem cell	year	Number of patients	Median age	OS at 3 years
MMUD 9/10 (JMDP)	2011	169	17	57%
MMUD 7/8 (CIBMTR)	2012	75	10	57%
Cord Blood (EBMT)	2010	71	13	38%
Haplo (EBMT)	2016	73	12	37%

Complications
Graft failure / GvHD / Infection

Only in experienced centers, possibly within prospective trials!!!

Courtesy of Regis Peffault de Latour, ASH Educational 2016