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RACE DM training session:
Immunusuppressive treatment for aplastic anemia

Antonio M. Risitano, M.D., Ph.D.
Head of Bone Marrow Transplantation Unit
Federico II University of Naples

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Aplastic anemia

Incidence

- Orphan disease.
- Incidence rates present geographic variations.
- 2 to 3-fold higher rates in Asia than Europe and the United States
- Global incidence rates range 0.7-7.4 cases per million inhabitants.

Aplastic anemia: AA

- **AA: what does it mean?**
- **How we do the diagnosis?**
- **When should we treat?**
- **How we treat?**

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Aplastic anemia: AA

- **AA: what does it mean?**
- **How we do the diagnosis?**
- **When should we treat?**
- **How we treat?**

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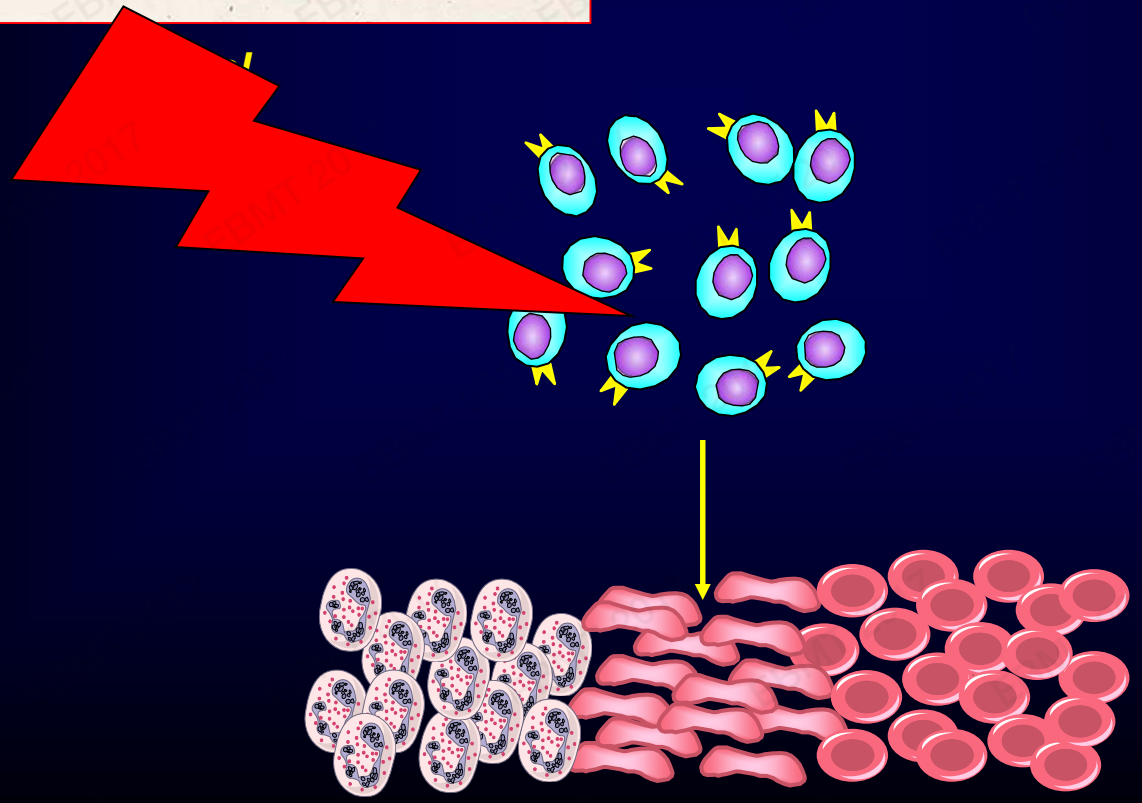
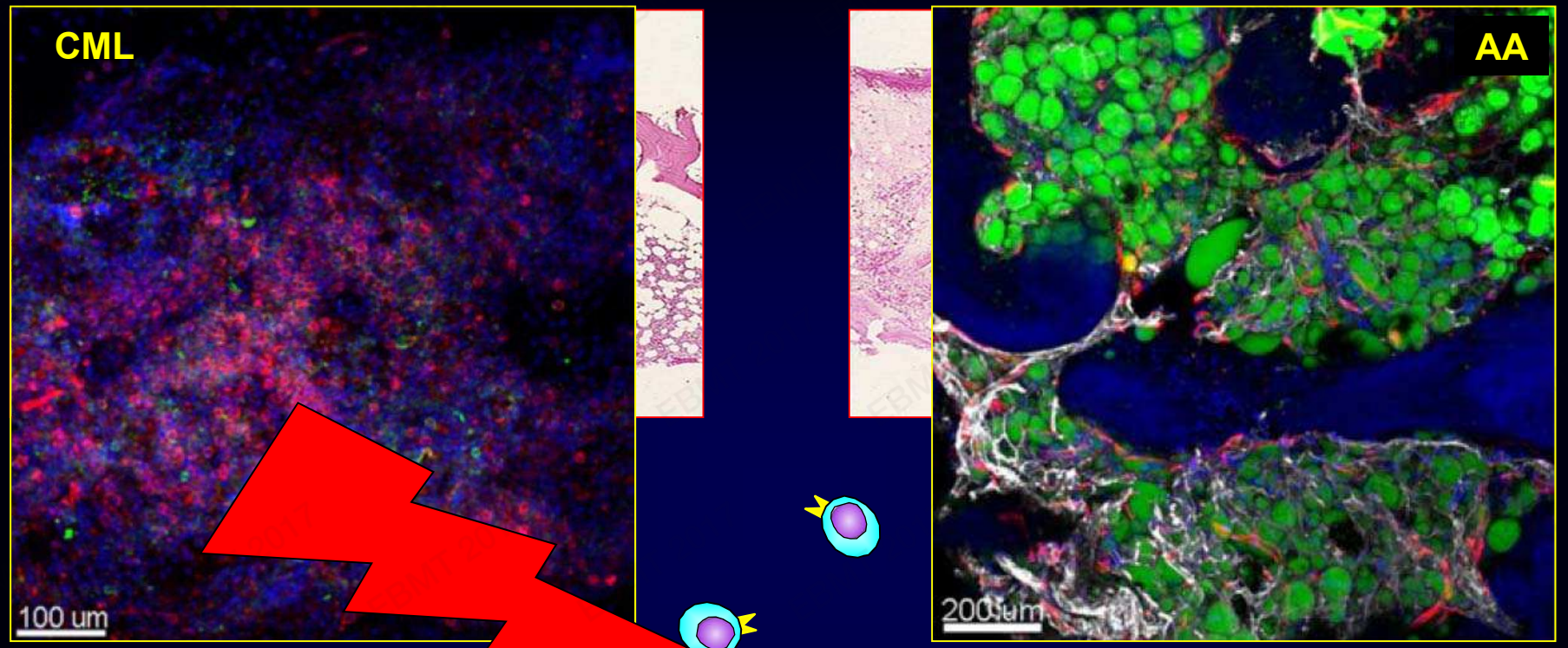
Aplastic anemia



Aplastic anemia



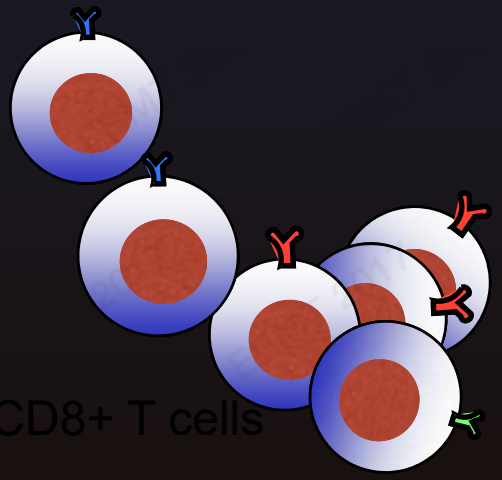
Takaku et al, Blood 2010

Takaku et al, Blood 2010

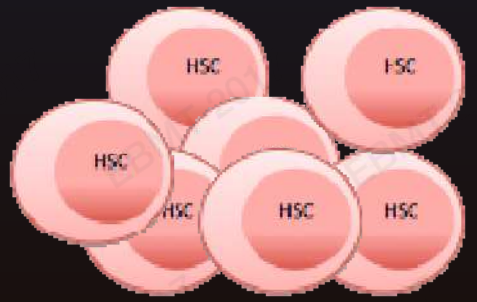
Contraction of stem cell pool

Cytopenia

AA: what does it mean?

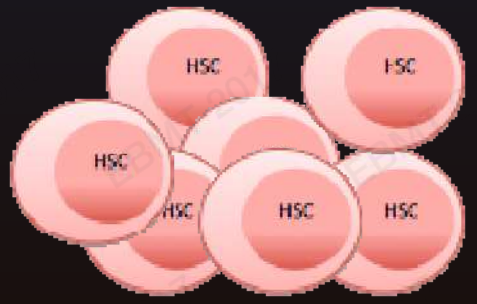


(Oligo) clonal CD8+ T cells



Auto-immunity = immune disorder =
idiopathic AA

AA: what does it mean?



Constitutionnal = inherited disorder
(FA, dyskeratosis congenita)

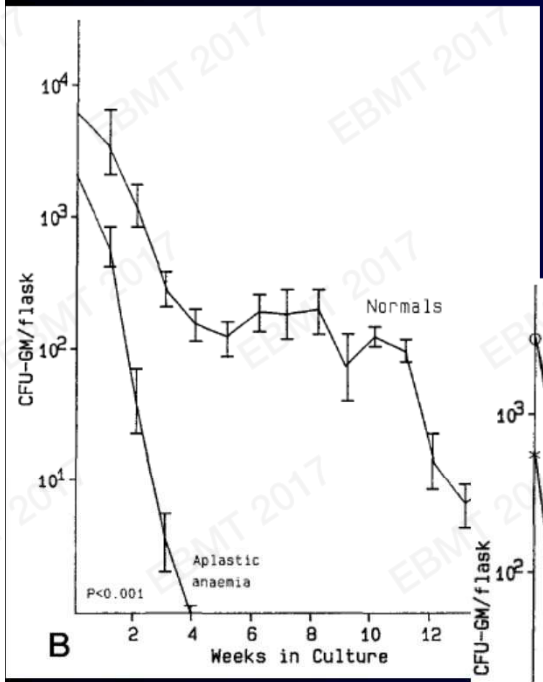
Hematopoietic stem cells in AA

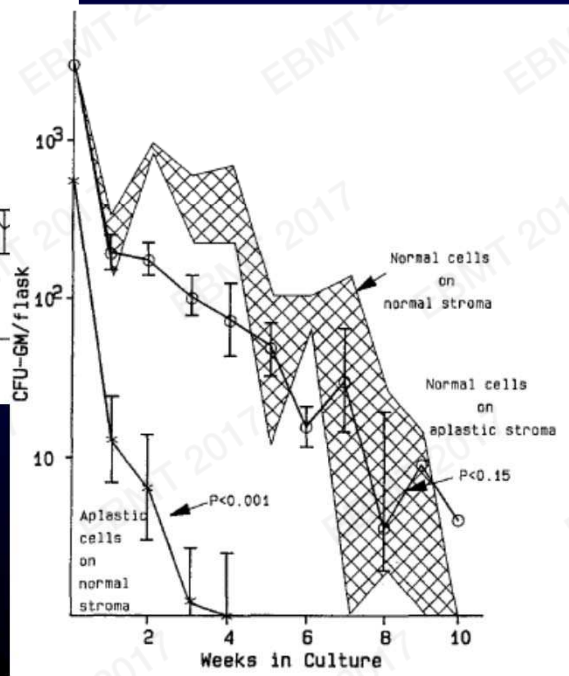
Hematopoietic progenitor cultures

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

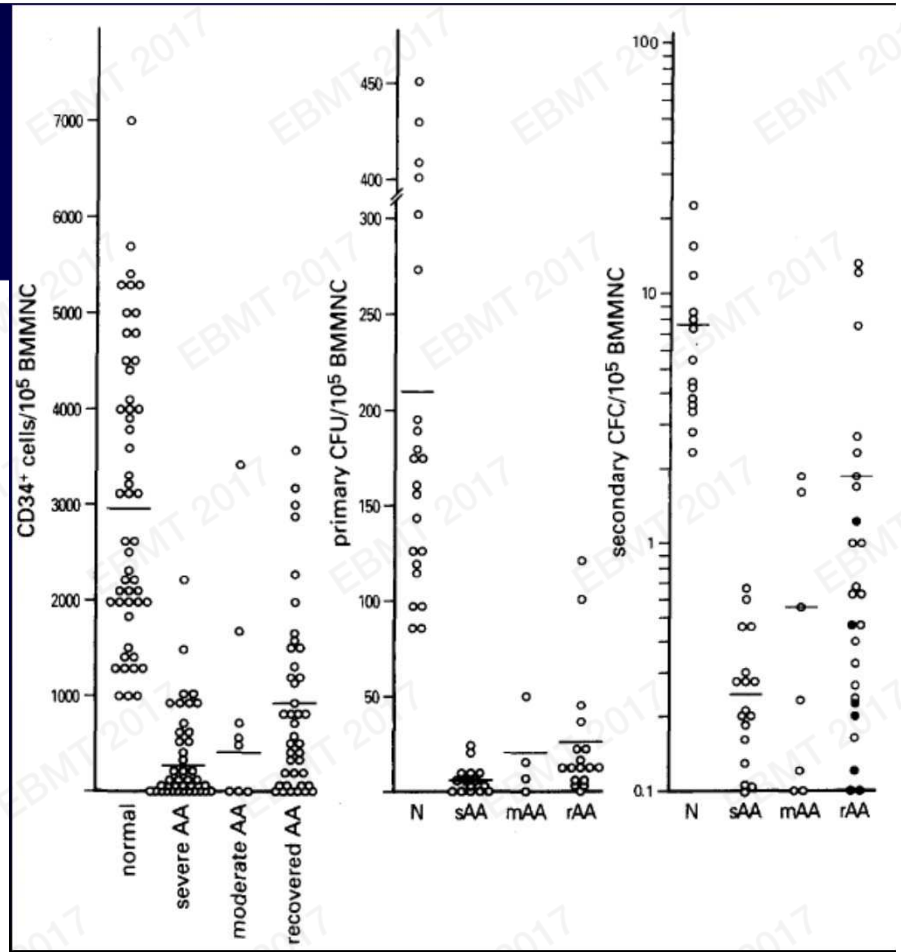




blood 1996 88: 1983-1991

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



T-cell clonality in aplastic anemia

A surrogate marker for Ag-driven immune response

Clonal Analysis of CD4⁺/CD8⁺ T Cells in a Patient with Aplastic Anemia

Ulrich Moebius,* Friedhelm Herrmann,‡ Thierry Hercend,§ and Stefan C. Meuer*
**Abteilung Angewandte Immunologie, Institut für Radiologie und Pathophysiologie, Deutsches Krebsforschungszentrum, 6900 Heidelberg, FRG, ‡Innere Medizin I, Albert Ludwig Universität, Freiburg, FRG, §Unité Biologie Cellulaire, Institute Gustave Roussy, 94800 Villejuif, France*

J. Clin. Invest. Volume 87, May 1991, 1567–1574

ELSEVIER

EXPERIMENTAL HEMATOLOGY

Experimental Hematology 23 (1995): 433

Establishment of a CD4+ T cell clone recognizing autologous hematopoietic progenitor cells from a patient with immune-mediated aplastic anemia.

Nakao S, Takamatsu H, Yachie A, Itoh T, Yamaguchi M, Ueda M, Shiobara S, Matsuda T.

Blood, Vol 89, No 10 (May 15), 1997: pp 3691-3699

Isolation of a T-Cell Clone Showing HLA-DRB1*0405-Restricted Cytotoxicity for Hematopoietic Cells in a Patient With Aplastic Anemia

By Shinji Nakao, Akiyoshi Takami, Hideyuki Takamatsu, Weihua Zeng, Naomi Sugimori, Hiroto Yamazaki, Yuji Miura, Mikio Ueda, Shintaro Shiobara, Takeshi Yoshioka, Toshihiko Kaneshige, Masaki Yasukawa, and Tamotsu Matsuda

Changes in T-cell receptor VB repertoire in aplastic anemia: effects of different immunosuppressive regimens

Hoon Kook, Antonio M. Risitano, Weihua Zeng, Marcin Wlodarski, Craig Lottemann, Ryotaro Nakamura, John Barrett, Neal S. Young, and Jaroslaw P. Maciejewski

BLOOD, 15 MAY 2002 • VOLUME 99, NUMBER 10

Oligoclonal and polyclonal CD4 and CD8 lymphocytes in aplastic anemia and paroxysmal nocturnal hemoglobinuria measured by Vβ CDR3 spectratyping and flow cytometry

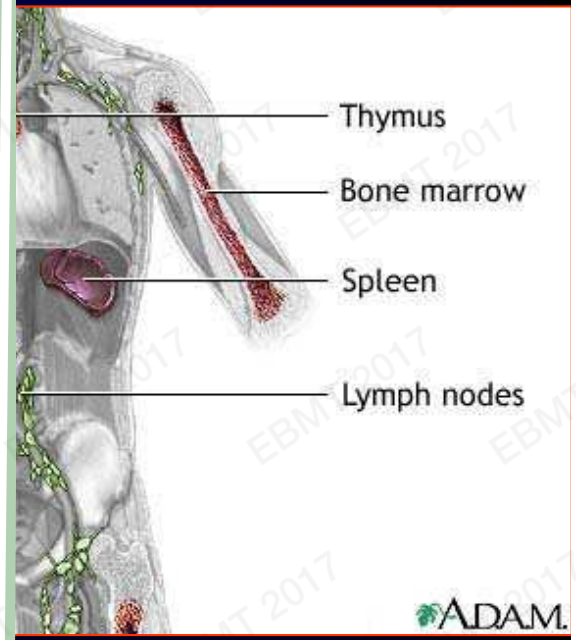
BLOOD, 1 JULY 2002 • VOLUME 100, NUMBER 1

Antonio M. Risitano, Hoon Kook, Weihua Zeng, Guibin Chen, Neal S. Young, and Jaroslaw P. Maciejewski

Pathophysiology of aplastic anemia

Hematopoietic stem cell

The immune system



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Aplastic anemia: AA

- AA: what does it mean?
- How we do the diagnosis?
- When should we treat?
- How we treat?

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How we do the diagnosis

To eliminate something else
(leukemia, lymphoma etc)

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Aplastic anemia

Diagnosis

Full blood counts:

- Pancytopenia
- At least 2 cellular lines are decreased

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How we do the diagnosis: peripheral blood

Full blood counts:

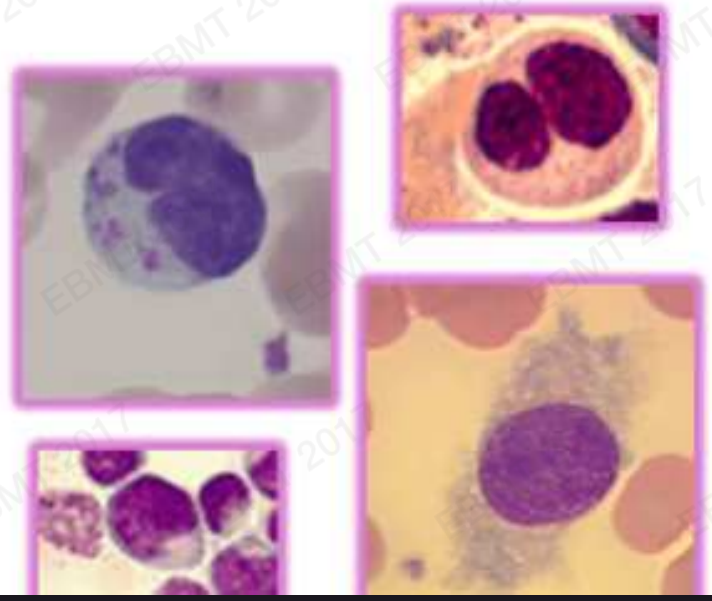
- **Pancytopenia**

- **Anemia** is accompanied, by reticulocytopenia
- Macrocytosis is common
  - No impact on rate of response and OS.
    - Li et al. Zhonghua Xue Ye Xue Za Zhi. 2013 Feb;34(2):117-21.

- **Lymphocyte** count is usually preserved

- Early stages isolated cytopenia, particularly **thrombocytopenia**

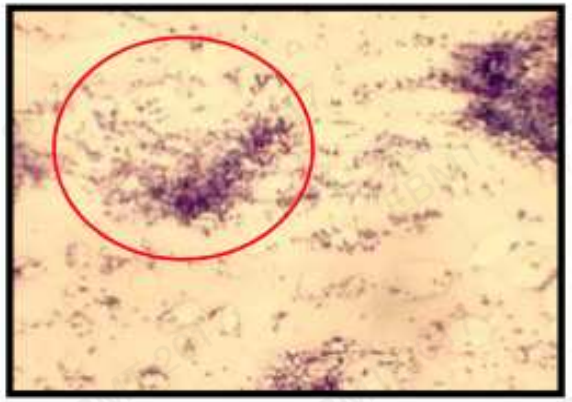
- Careful examination of the blood film to exclude:
  - dysplastic neutrophils
  - abnormal platelets
  - blasts and other abnormal cells, such as hairy cells, LGL

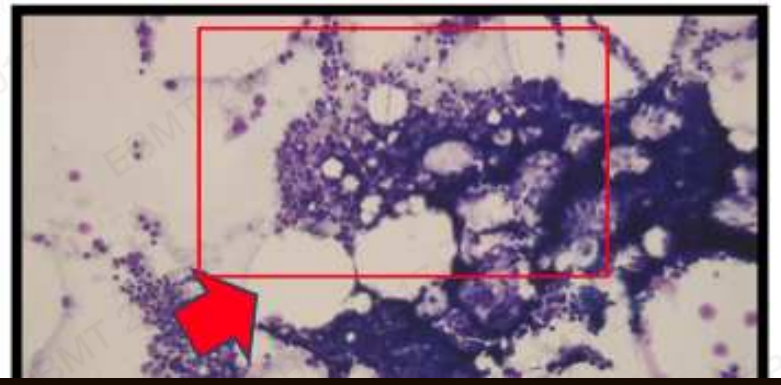


How we do the diagnosis: marrow sampling

- **bone marrow aspirate**
  - dry-tap: suspicion of a diagnosis other than aplastic anemia

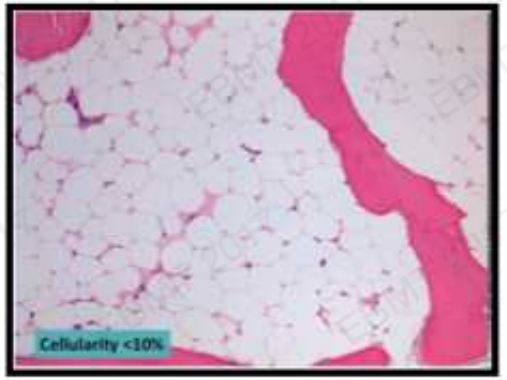
- fragments and trails are **hypocellular**
- prominent **fat spaces**
- variable amounts of residual hemopoietic cells
- megakaryocytes and granulocytic cells are:
  - reduced or absent
  - without dysplasia

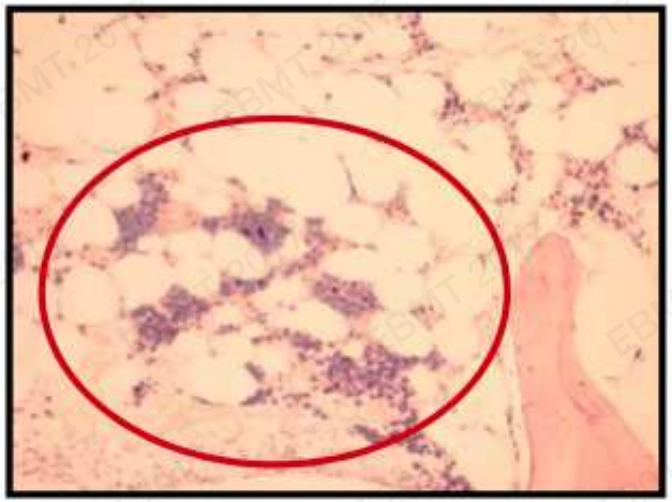




How we do the diagnosis: marrow biopsy

- Bone marrow
  - hypocellularity (<25%) (rather than aplastic)
    - "hot spots" with dominating erythropoiesis
    - *dyserythropoiesis*
  - few or no megakaryocytes
  - mast cells
  - lymphoid hyperplasia
  - plasma cells
  - macrophages

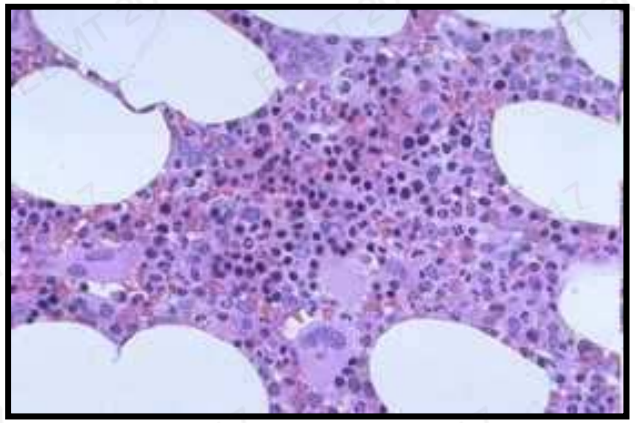


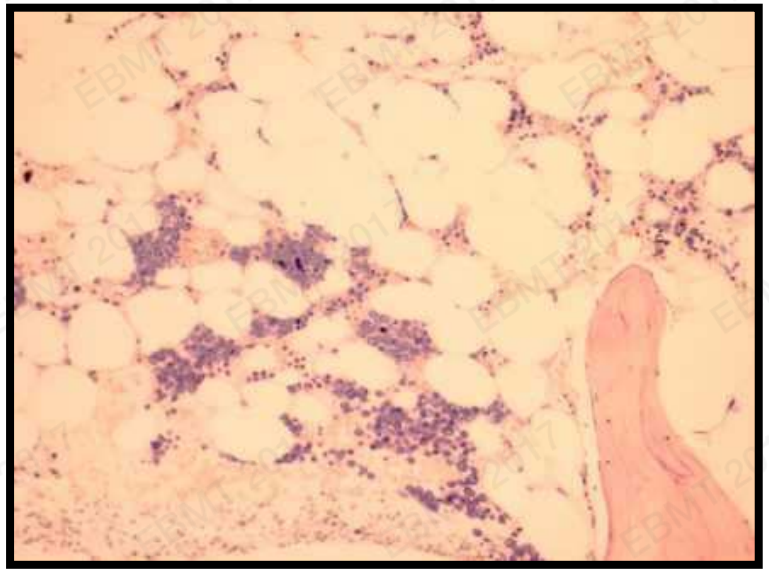


Aplastic anemia

Summary

- Pancytopenia
- Persistent, unexplained marrow aplasia
  - Hematopoiesis replaced by fat cells
- No specific marker
  - Diagnosis by exclusion
- Severity need to be defined





Aplastic anemia

Cytogenetics and flow cytometry

- Due to hypocellular bone marrow frequently insufficient metaphases
- FISH for chromosomes 5 and 7 should be considered
- isolated del(13q) favorable long-term outcome
- An abnormal cytogenetic clone does not imply the diagnosis of MDS or AML
- Cytogenetic abnormalities can be present in up to 12% of typical AA patients
- Detection of small PNH clones has implications for defining the disease.
  - About 50% are ‘aplastic’ with small clones and no hemolysis.
- PNH clone size measurements:
  - at presentation
  - serial monitoring should be performed at least yearly

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Aplastic anemia

Differential diagnosis

Characteristics	AA	hypoplastic MDS
dyserythropoiesis	sometimes	yes
abnormal neutrophil	no	yes
dysplastic megakaryocytes	no	yes
fibrosis	no	occasional
increased blasts	no	Sometimes (ALIPS)
CD34+ cells in BM	< 1.0%	sometimes increased
clonality	possible	sometimes
splenomegaly	absent	occasional

Bennett et al. Sem Hemato 2000;37:15-29

Bennett & Orazi. Haematologica 2009 Feb; 94(2):264-843-70

Hama A et al. Rinsho Ketsueki 2011 Aug ;52(8) :653-8

Aplastic anemia

Differential diagnosis

- **Fanconi anemia:**

- Positive chromosomal breakage test (MMC or DEB) that still represents the diagnostic gold standard.

- **Screening: telomere length**

- **Dyskeratosis congenita**

- Asymptomatic:
  - Frequent association with TERC, TERT mutation
    - (10% all idiopathic forms)
  - Rarely, with TINF2 gene mutation
- Recognizable phenotype of DC:
  - TINF2, NHP2, NOP10, DKC1 mutation

Aplastic anemia
Severity

Based on **peripheral values** and **bone marrow** findings

Severe AA (SAA)

At least two of the following three criteria have to be fulfilled:

- Reticulocytes <60x10^9/L (using an automated analyzer) or < 20 x 10^9/l (manual count)*
- Platelets < 20x10^9/L
- Neutrophil count <0.5 x10^9/L

Very severe AA (vSAA)

Same criteria of SAA have to be fulfilled; but the neutrophil count has to be < 0.2 x10^9/l

Non- severe AA

Patients not fulfilling the criteria for SAA and vSAA.

* The different values are because automated count may over-estimate the counting at low level of reticulocyte counts, i.e. it reads 50x10^9/L but in reality they are less

Aplastic anemia: AA

- AA: what does it mean?
- How we do the diagnosis?
- When should we treat?
- How we treat?

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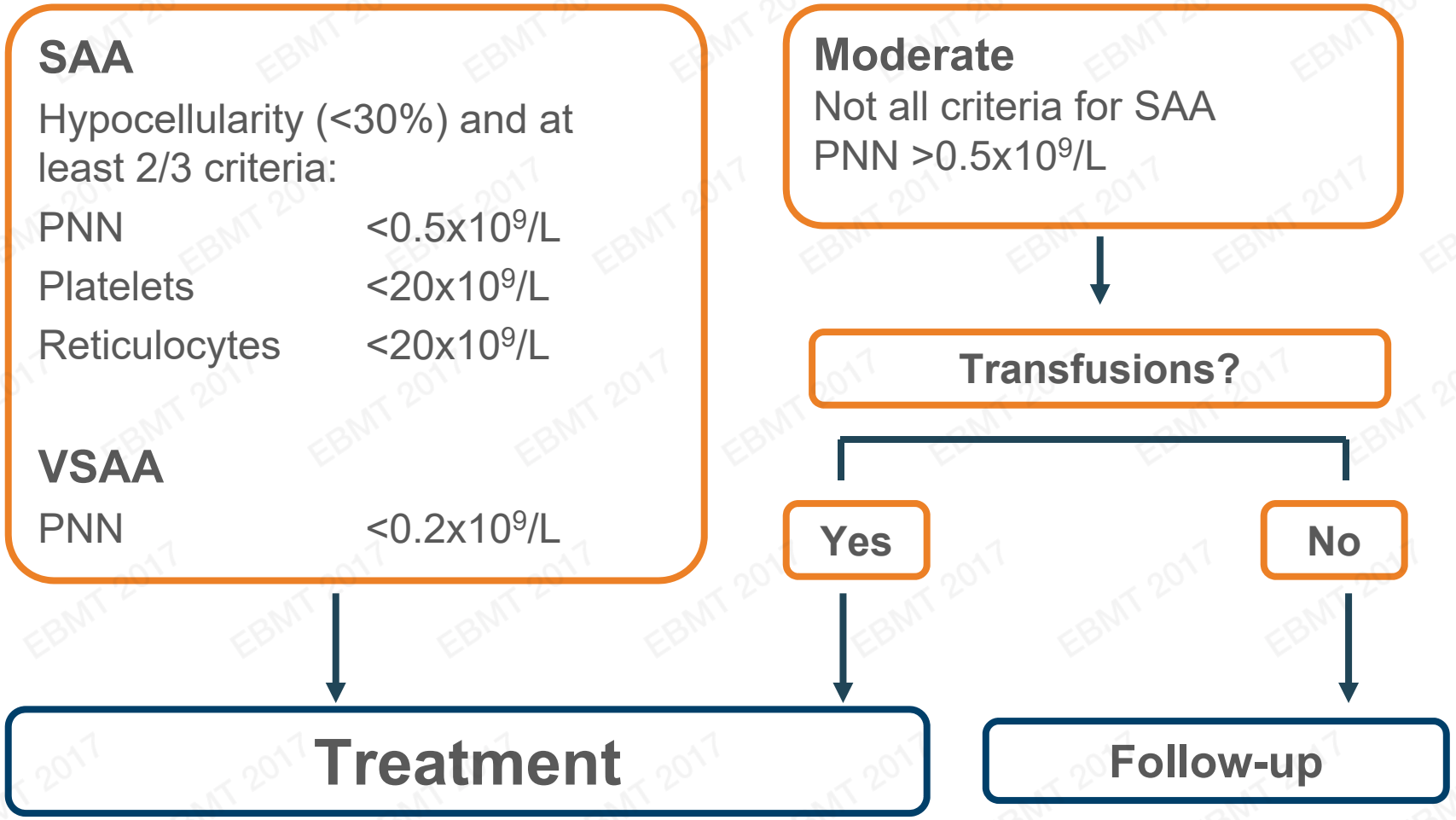
When should we treat?



Camitta BM *et al. Blood* 1976;48:63–70
SAA, severe AA; VSAA, very severe AA

Aplastic anemia: AA

- AA: what does it mean?
- How we do the diagnosis?
- When should we treat?
- How we treat?

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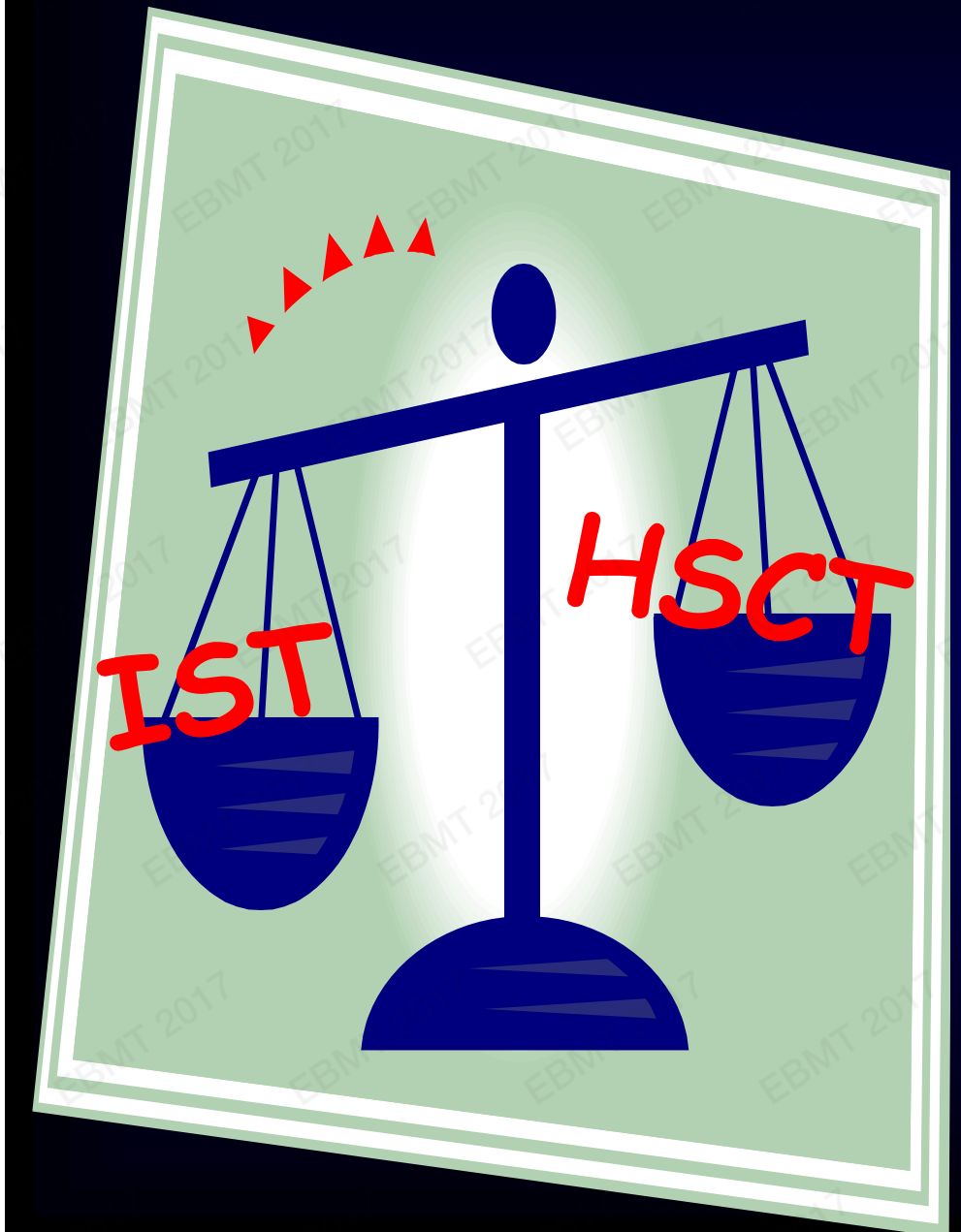
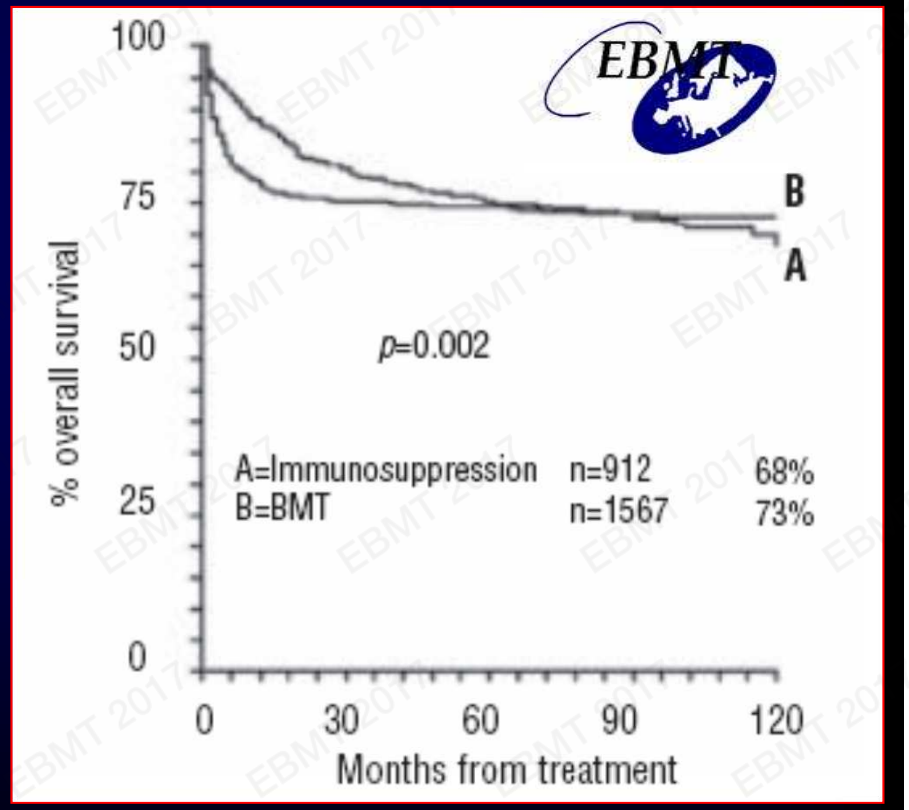
Treatment options for aplastic anemia



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

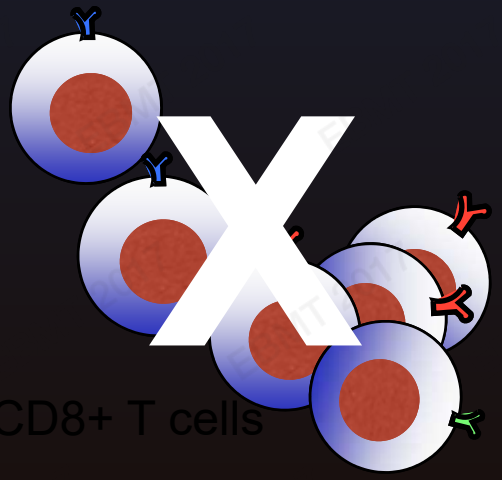
Anna Locasciulli, Rosi Oneto, Andrea Bacigalupo, Gerard Socié, Elisabeth Korthof, Albert Bekassy, Hubert Schrezenmeier, Jakob Passweg, Monika Führer
on the Behalf of the Severe Aplastic Anemia Working Party of the European Blood and Marrow Transplant Group (SAA-WP, BMT).



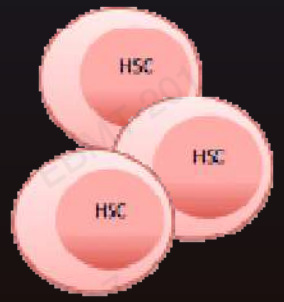
Locasciulli et al, Haematologica 2007

Idiopathic AA: how we treat?

1. Immunosuppressive treatment



(Oligo) clonal CD8+ T cells

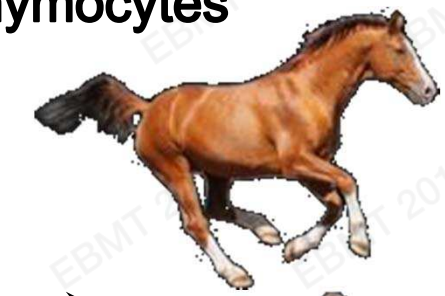


Auto-immunity = immune disorder =
idiopathic AA

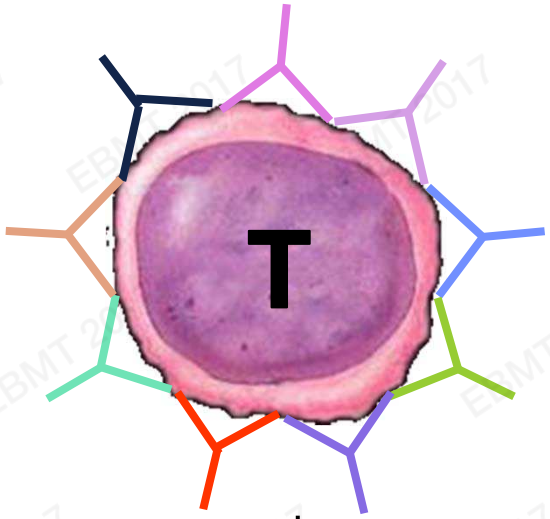
Idiopathic AA: how we treat?

Immunization with human thymocytes

Thymus



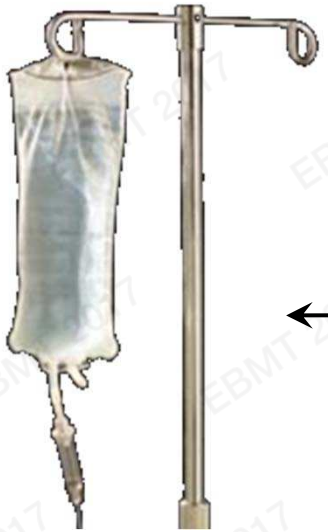
Xenogeneic polyclonal antibodies



Purification of sera

Cytotoxicity assay

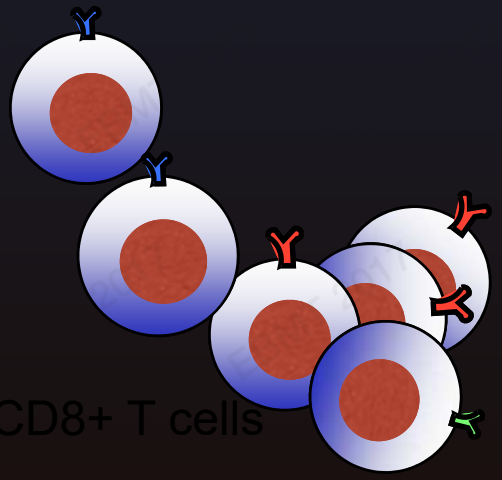
IgG



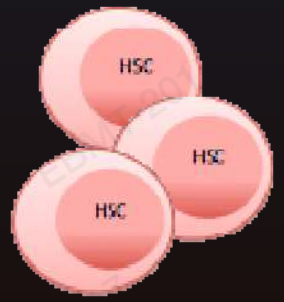
ATG

Idiopathic AA: how we treat?

2. Bone marrow transplantation

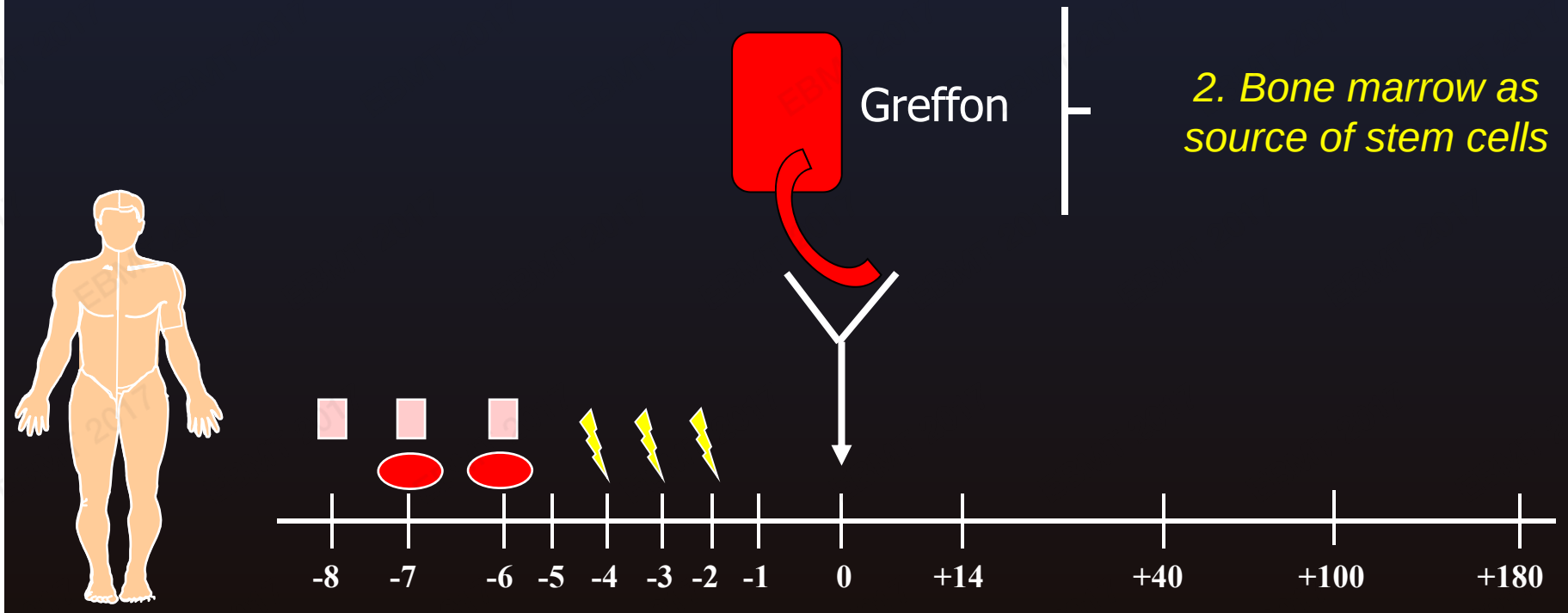


(Oligo) clonal CD8+ T cells



Auto-immunity = immune disorder =
idiopathic AA

Idiopathic AA: how we treat?



2. Bone marrow as source of stem cells

Conditionnement

1. Reduced intensity conditioning regimen

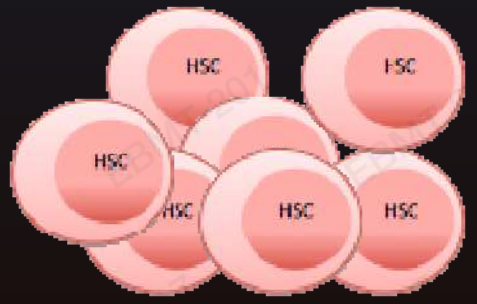
3. No need for GvHD

4. infections

Idiopathic AA: how we treat?

Inherited AA: how we treat?

Bone marrow transplantation



Constitutionnal = inherited disorder
(FA, dyskeratosis congenita)

Conclusion: AA

- **AA: marrow empty, nothing else**
- **Diagnosis is very important**
- **Treatment if SAA or trasnfusions**
- **Immunosuppressive therapy (acquired) or BMT (acquired and inherited)**

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AA and…

… supportive care

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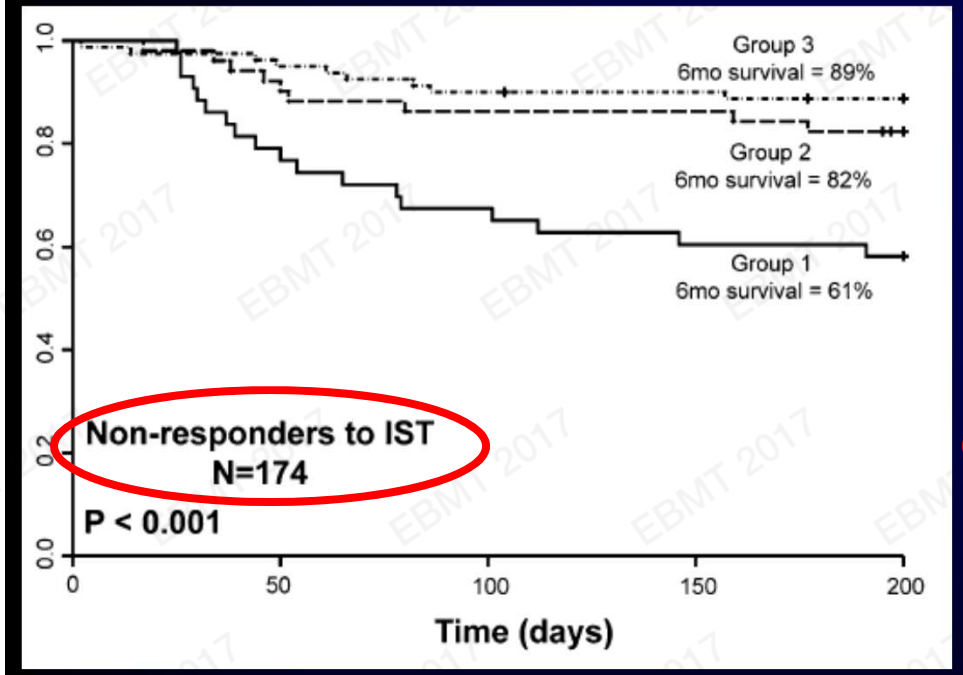
Supportive care

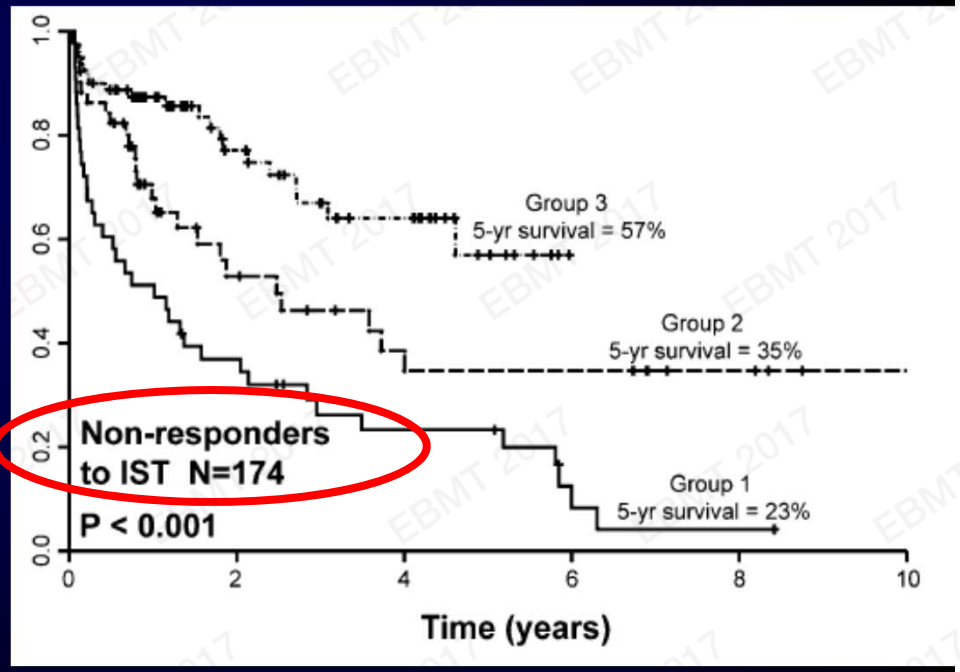
The improvement in anti-infectious management

CID 2011

- ✓n=420 (174 non-responders)
- ✓Infection-related mortality from 37% to 11%
- ✓Incidence of IFIs from 49% to 8%

Group 1: 12/1989-10/1986
Group 2: 11/1986-10/2002
Group 3: 11/2002-04/2008





The most relevant breakthrough in AA treatment was the anti-infectious supportive care: keeping AA patients alive until they recover (IST or SCT)

Supportive care

The role of steroids

- ✓ Steroids are broadly used as ancillary therapy of SAA
  - ✓ Based on old data on potential therapeutic efficacy (Bacigalupo et al NEJM 1982)
  - ✓ Drawn from empirical use (and possible efficacy) of steroids in other immune-mediated cytopenias (Ab-mediated)

BUT

- ✓ No clinical evidence of efficacy
- ✓ Increased risk of severe infectious complications (mostly IFI)
- ✓ May mask ongoing/overt infections (including sepsis)
- ✓ Short-term toxicity (cumulative with CsA): hypertension, diabetes, fluid retention
- ✓ Long-term toxicity: avascular necrosis, cataracts, etc

In the context of SAA, steroids should be used only as prophylaxis of serum sickness during ATG treatment, using the lowest effective dose and the faster tapering

- ✓ Start with 1 mg/kg/day, eventually doubled in case of serum sickness or other allergic manifestations*; then taper by 25% every 2-4 days

**ATG-related allergic infusion reactions should rather considered manifestations of Complement Activation Related Pseudo-Allergy (CARPA), which eventually derive from massive activation of the classical pathway due to the exogenous antibodies and their immune-complexes*

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AA and…

… immunosuppressive treatment

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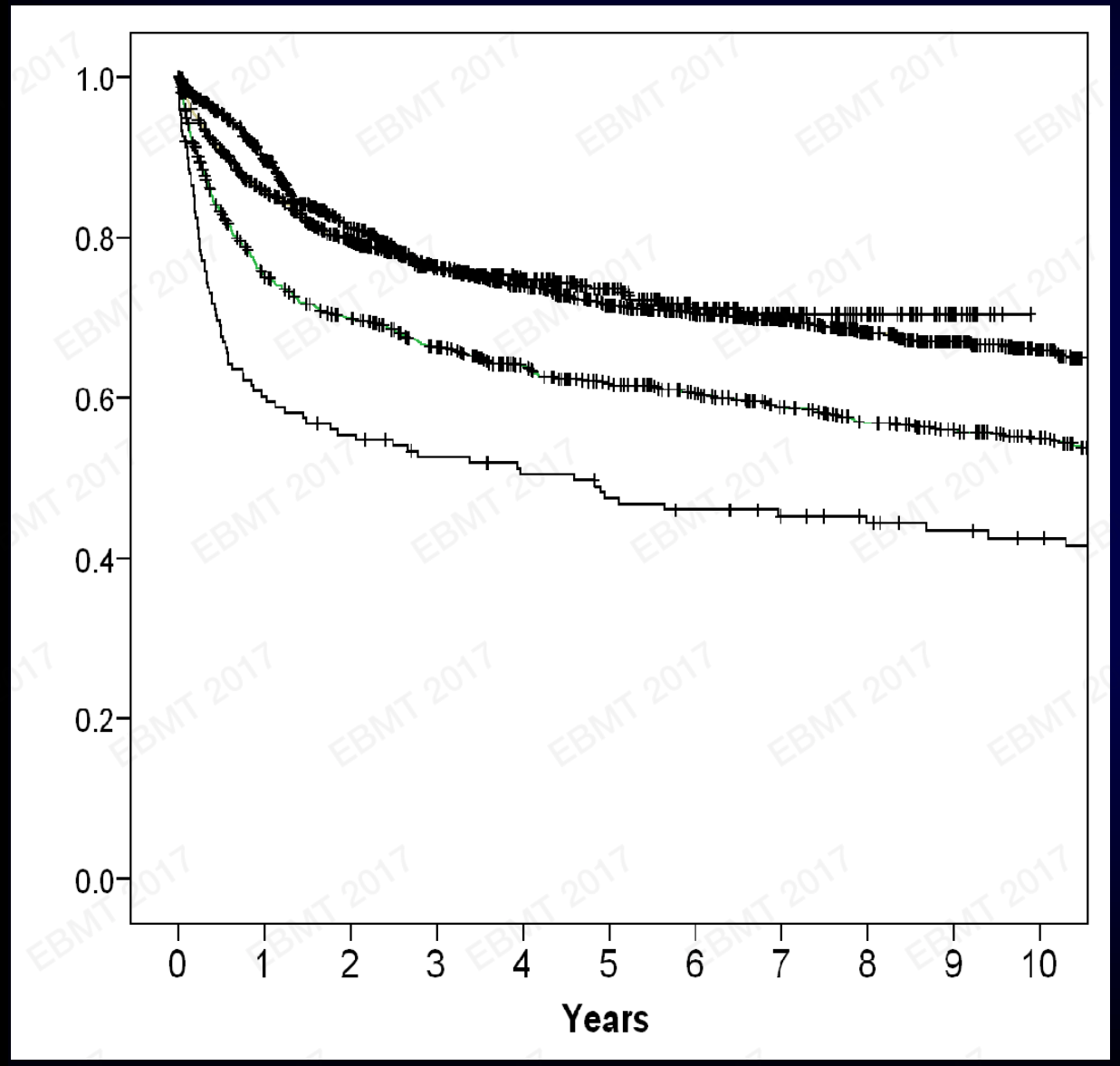
OUTCOME OF IMMUNOSUPPRESSION FOR SAA

Improvement over the years



EBMT Database

N=3202

2000-10
1990-00

1980-90

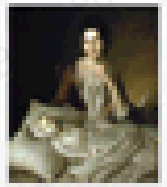
1975-80

Survival improved with years, mostly due to:

- ✓*Better supportive therapy*
- ✓*Better salvage treatment (SCT)*

Courtesy of Jakob Passweg

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

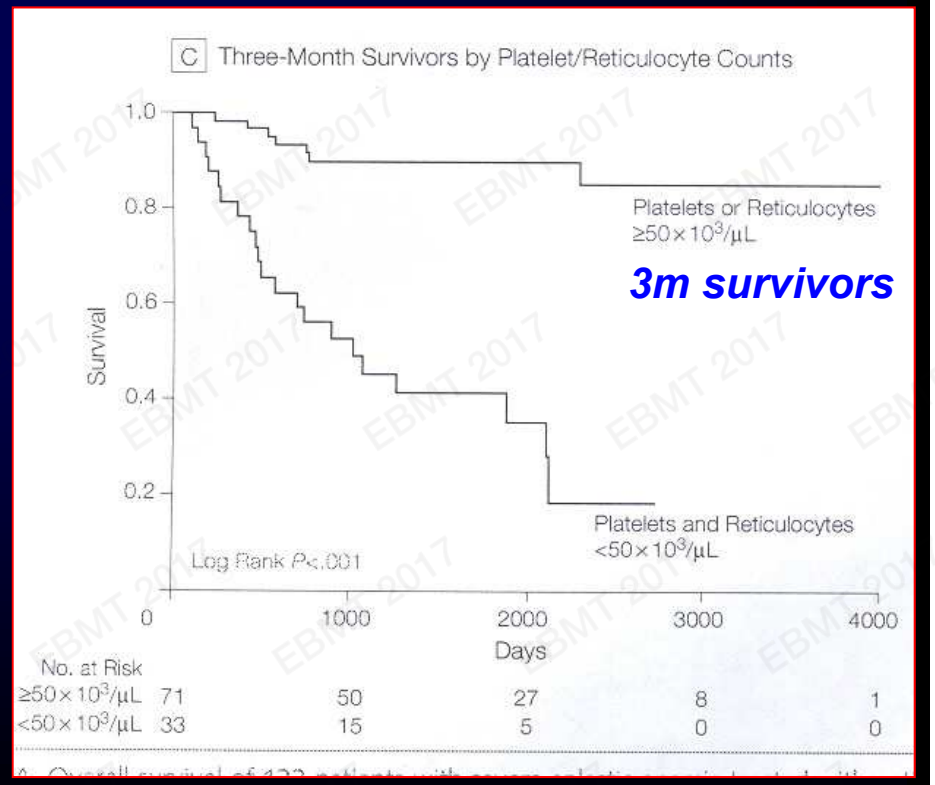
n=112

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

OS 55% @7y;

OR 60% @ 3m, 61% @ 6m, 58% @ 1y

3m survivors



3m survivors

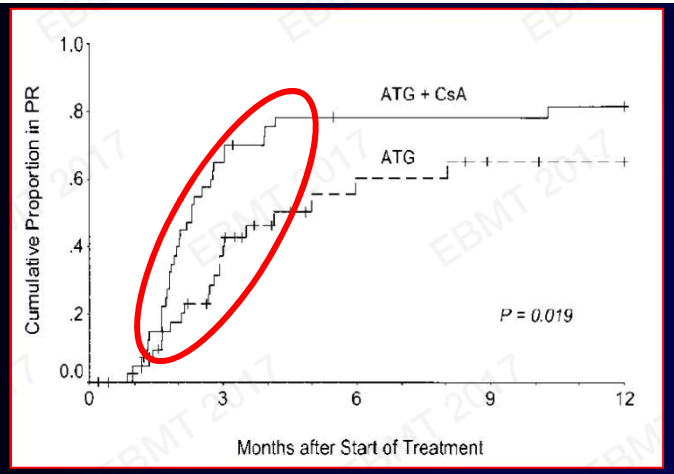
Hematological response is the main predictor for outcome

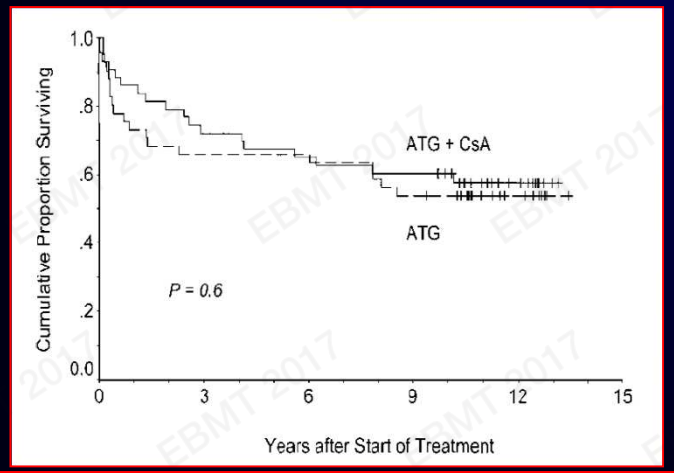
IMPROVING ATG-BASED IMMUNOSUPPRESSION

The benefit of combining ATG and cyclosporine A

Treatment of aplastic anemia with antilymphocyte globulin and methylprednisolone with or without cyclosporine. The German Aplastic Anemia Study Group ***NEJM 1991***

N Frickhofen, JP Kaltwasser, H Schrezenmeier, A Raghavachar, HG Vogt, F Herrmann, M Freund, P Meusers, A Salama, and H Heimpel

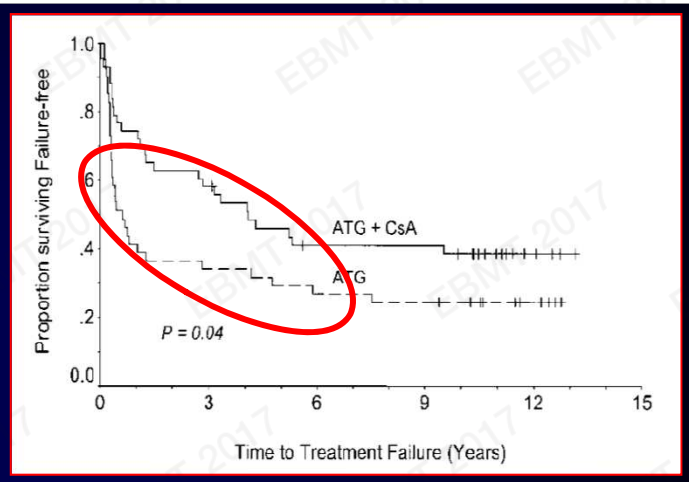


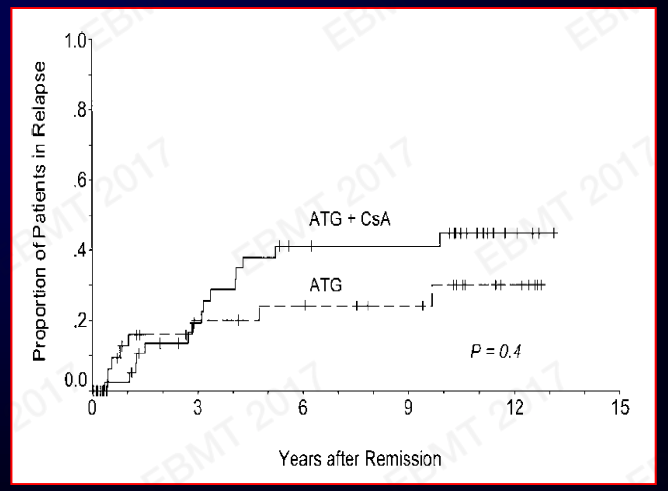


✓**CyA speed hematological response without affecting survival**

Antithymocyte globulin with or without cyclosporin A: 11-year follow-up of a randomized trial comparing treatments of aplastic anemia

Norbert Frickhofen, Hermann Heimpel, Joachim P. Kaltwasser, and Hubert Schrezenmeier, for the German Aplastic Anemia Study Group ***Blood 2003***

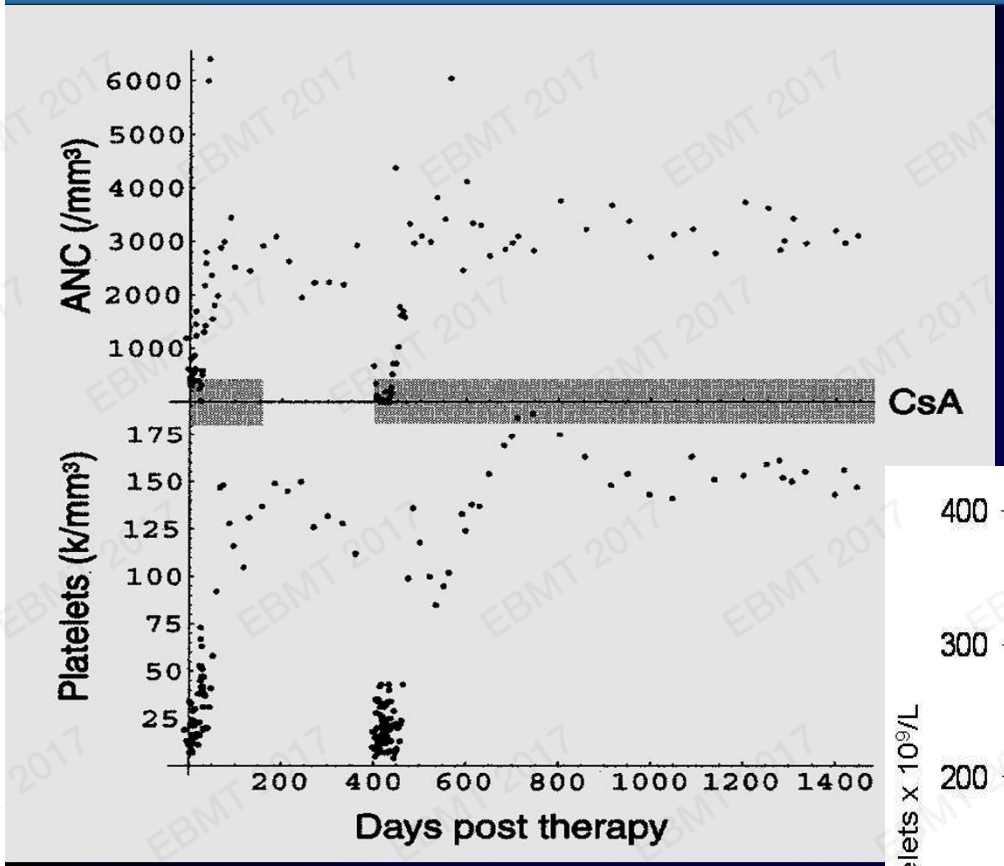




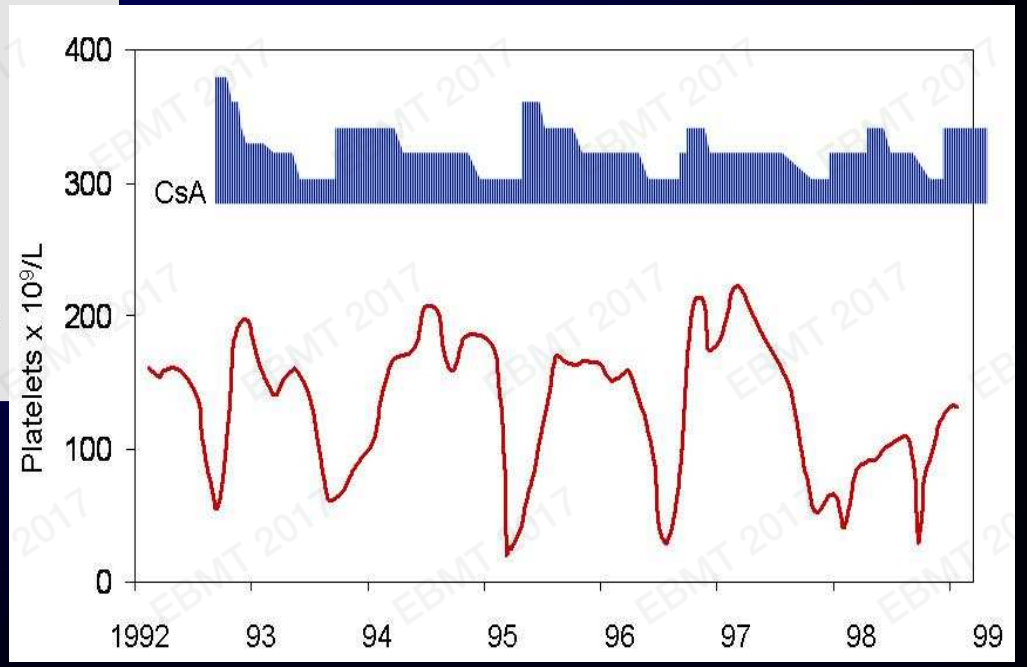
✓**CyA reduces early treatment failure but not long-term relapse rate**

RELAPSES AFTER IST

The role of maintenance CyA therapy



Maintenance CyA is required to sustain blood counts after initial response to IST



Frickhofen N. Blood. 2003 (101). 1236-1242

Aplastic Anemia: Management of Adult Patients

Jaroslaw P. Maciejewski and Antonio M. Risitano

REASONS FOR TREATMENT FAILURE

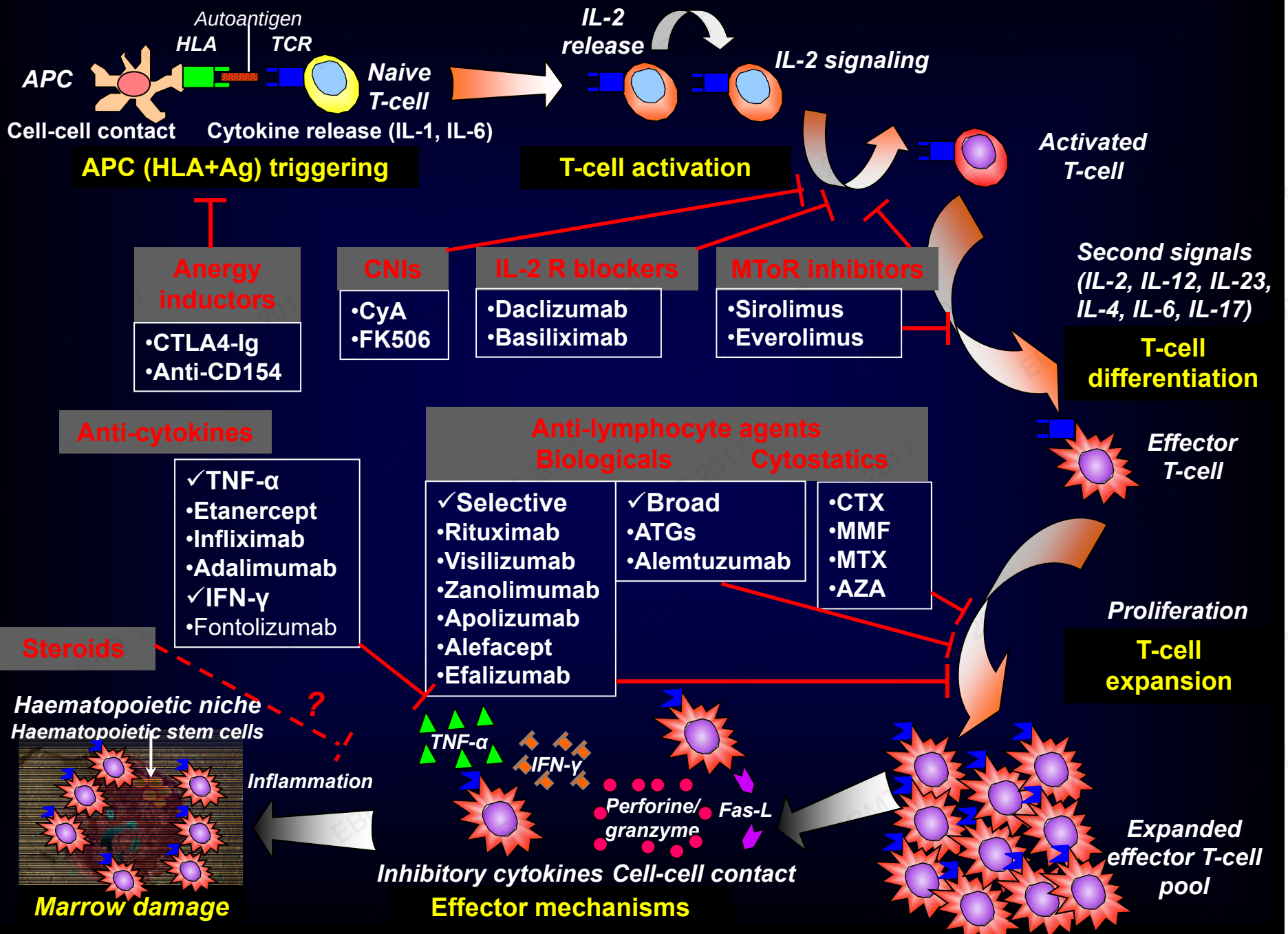
- Pathophysiology other than immune-mediated
- Irreversible stem cell deficit
- Insufficient immunosuppression

Improve front line immunosuppressive therapies

Improving IST for AA: chronicle of a failure

EBMT 2017

STRATEGIES OF IMMUNOSUPPRESSION *(Risitano, BJH 2010)*



IMPROVING IMMUNOSUPPRSSIVE TREATMENT FOR AA

The history of a failure

1. **No benefit from the addition of a third drug over the hATG-CsA platform**
   - ✓ Mycophenolate mofetil (randomized NIH trial)
   - ✓ Rapamicine (open-label NIH trial)
2. **No benefit from using non-hATG based regimens**
   - ✓ Rabbit ATG (NIH, EBMT, etc)
   - ✓ Alemtuzumab (NIH, Naples)
   - ✓ Cyclophosphamide (John Hopkins, NIH)
3. **Novel immunosuppressive strategies**
   - ✓ Anti-cytokine mAbs (TNF, IFN, IL2/IL23, etc)
   - ✓ Daclizumab (anti-IL2R), alefacept (anti-LFA-3), efalizumab (anti-LFA-1)
   - ✓ Mesenchimal stem cells
   - ✓ Anti-CD26 (Begedina®): in development for aGvHD

Scheinberg et al BJH 2006; Scheinberg et al Haematologica 2009; Risitano et al BJH 2009; Scheinberg et al NEJM 2011; Marsh et al Blood 2013; Scheinberg et al Blood 2012

EBMT 2017

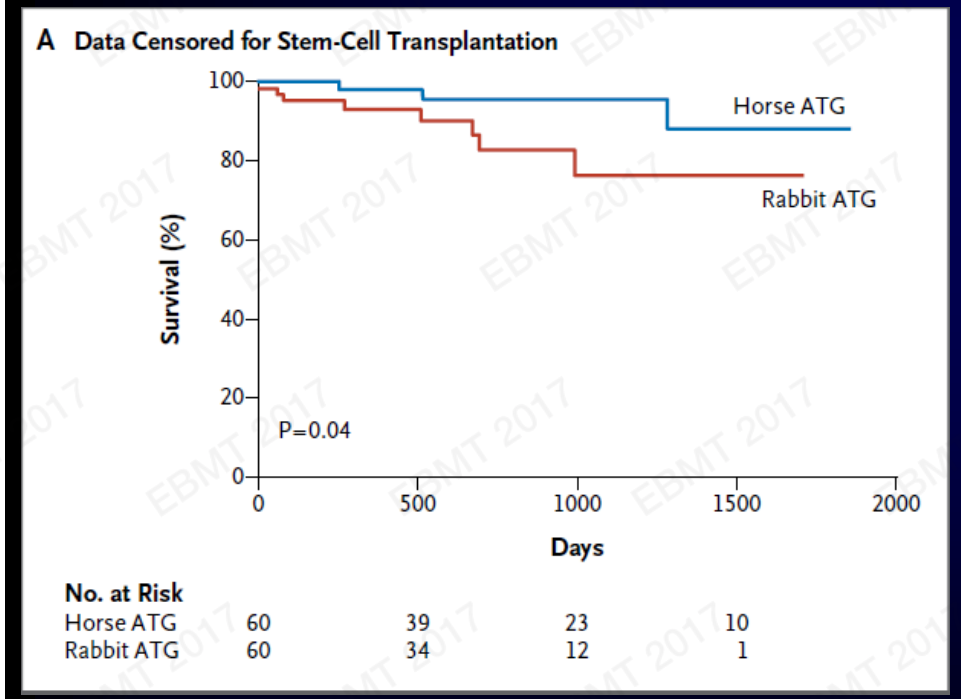
NEJM

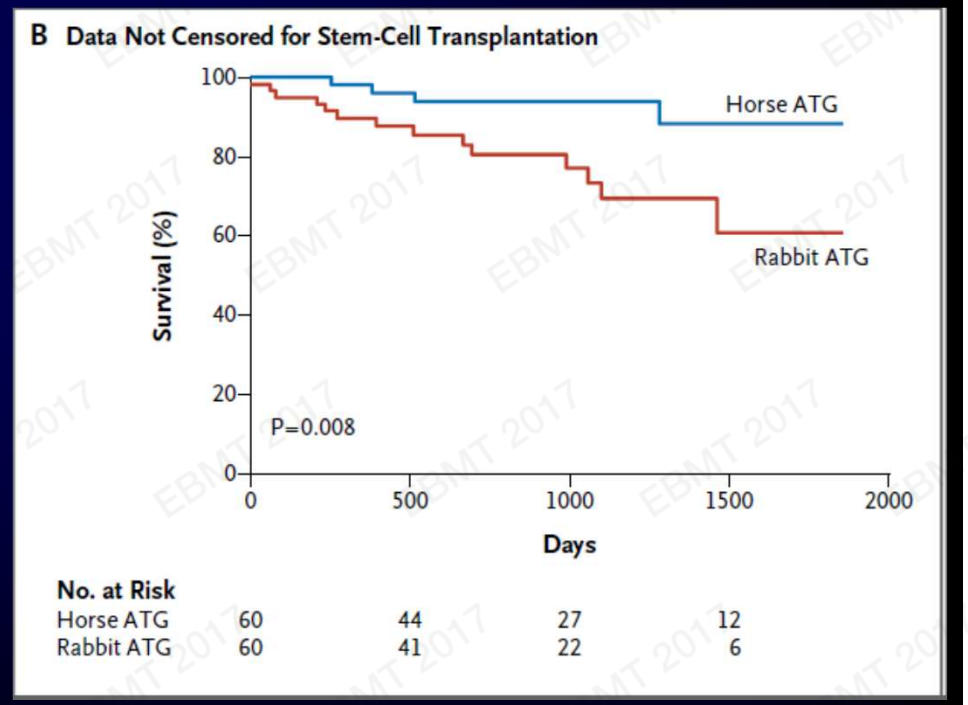
Horse versus Rabbit Antithymocyte Globulin in Acquired Aplastic Anemia

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)***





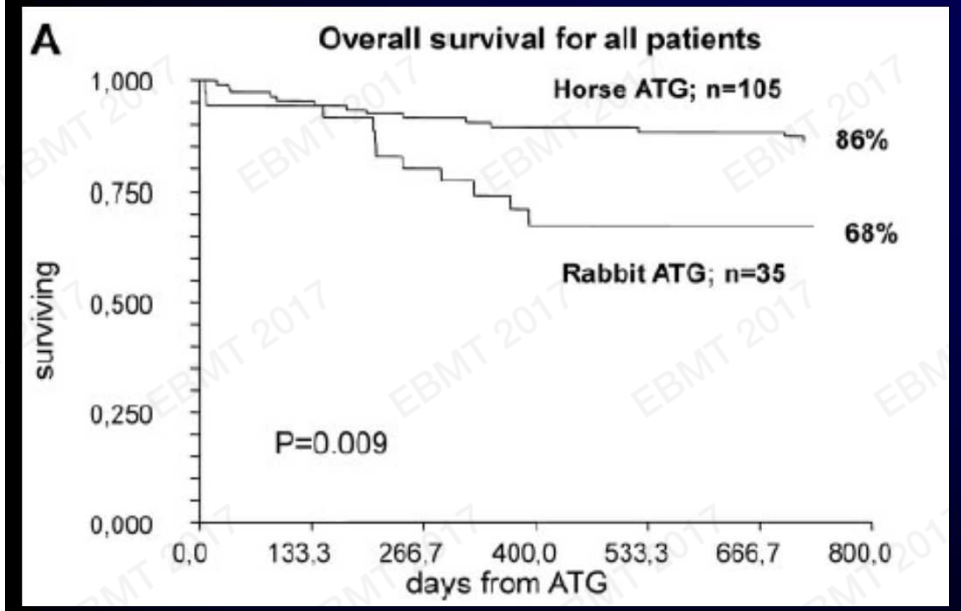
rATG is inferior to hATG in first line treatment of SAA, as indicated by hematological response and survival

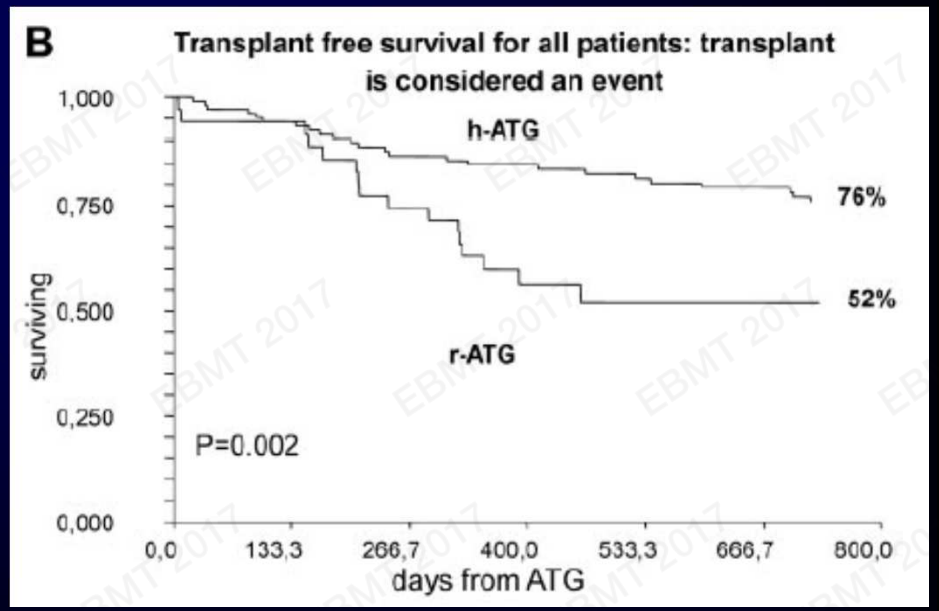
Prospective study of rabbit antithymocyte globulin and cyclosporine for aplastic anemia from the EBMT Severe Aplastic Anaemia Working Party

Judith C. Marsh,[1] Andrea Bacigalupo,[2] Hubert Schrezenmeier,[3] Andre Tichelli,[4] Antonio M. Risitano,[5] Jakob R. Passweg,[4] Sally B. Killick,[6] Alan J. Warren,[7] Theodora Foukaneli,[7] Mahmoud Aljurf,[8] H. A. Al-Zahrani,[8] Philip Schafhausen,[9] Alexander Roth,[10] Anke Franzke,[11] Tim H. Brummendorf,[12] Carlo Dufour,[13] Rosi Oneto,[14] Philip Sedgwick,[15] Alain Barrois,[16] Shahram Kordasti,[1] Modupe O. Elebute,[1] Ghulam J. Mufti,[1] and Gerard Socie,[17] on behalf of the European Blood and Marrow Transplant Group Severe Aplastic Anaemia Working Party

Blood 2012

- ✓ *Phase II pilot study rATG + CyA (n=35)*
- ✓ *Retrospective matched comparison (pair-matched) with hATG + CyA (n=105)*
- ✓ *Pilot rATG + CyA study: OR 40% @ 6m (CR 3%, PR 37%)*





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

Aplastic Anemia: Management of Adult Patients

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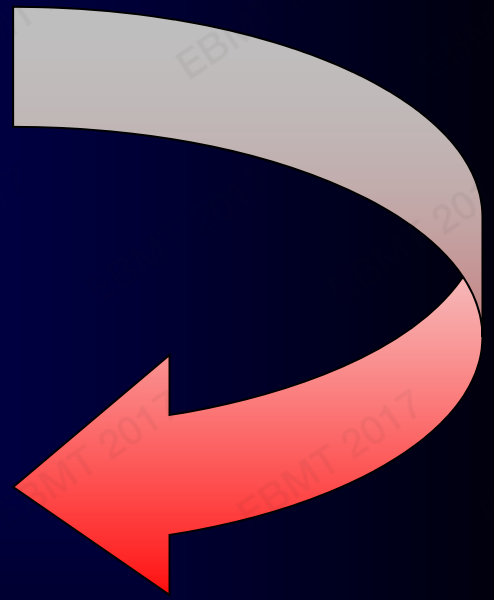
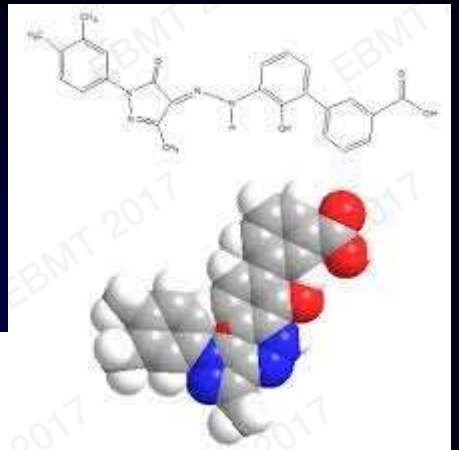
- Pathophysiology other than immune-mediated
- **Irreversible stem cell deficit**
- Insufficient immunosuppression

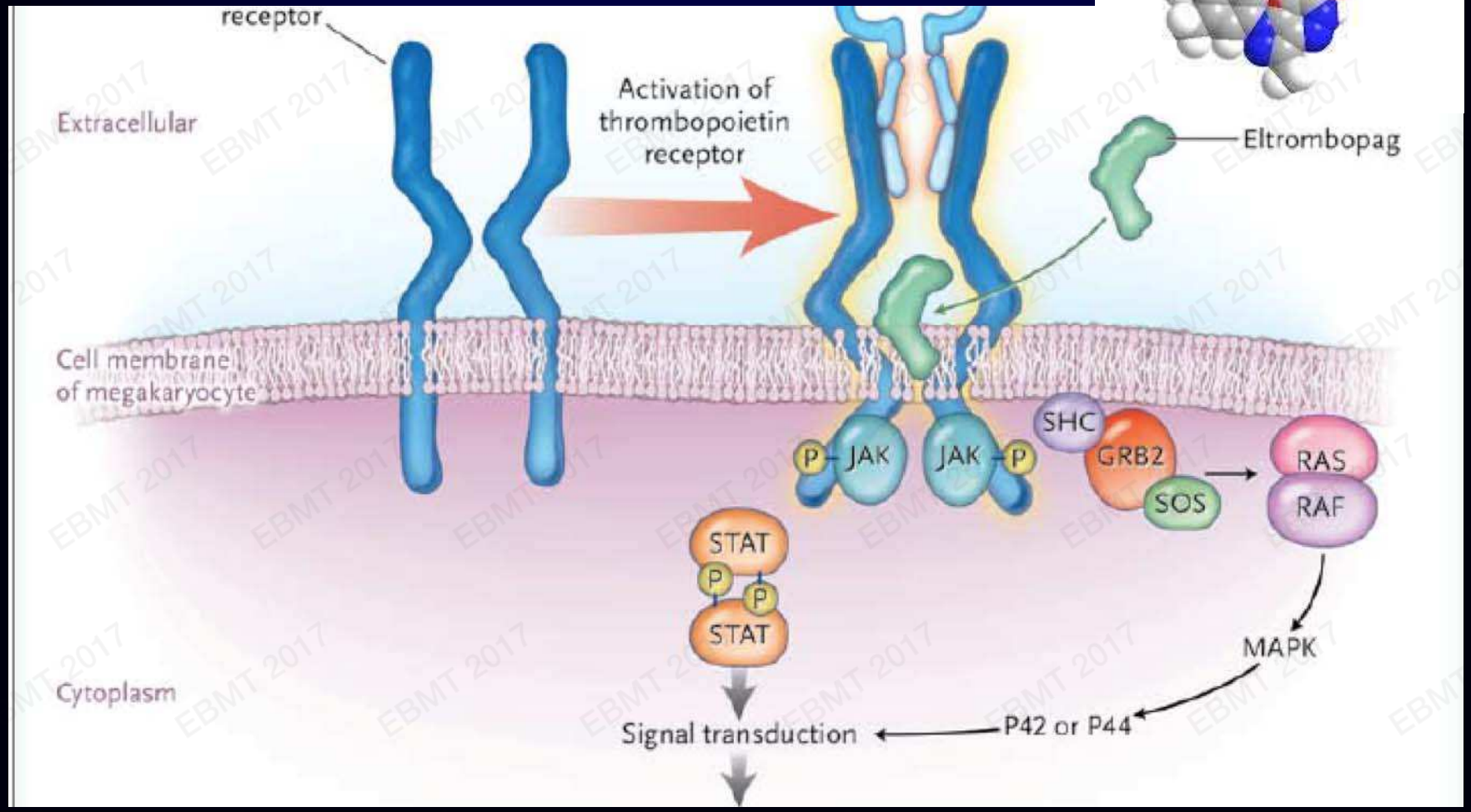


Eltrombopag???

ELTROMBOPAG

A Tpo-mimetic agent





ELTROMBOPAG IN REFRACTORY SAA

The status of art

NEJM

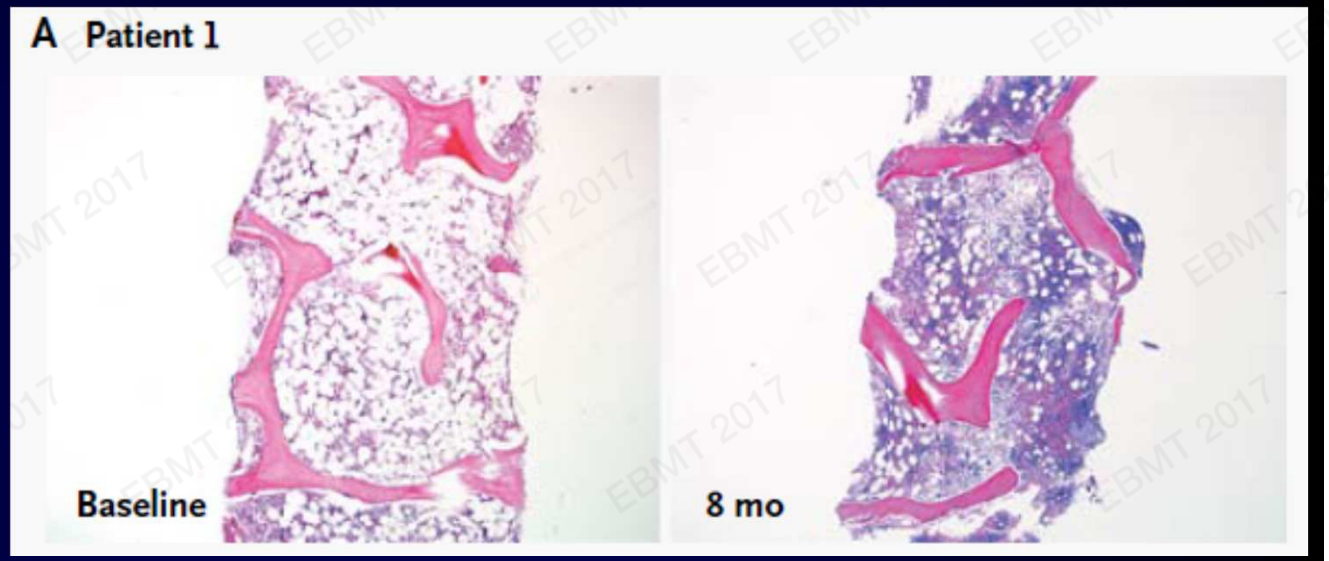
Eltrombopag and Improved Hematopoiesis in Refractory Aplastic Anemia

Phase II study

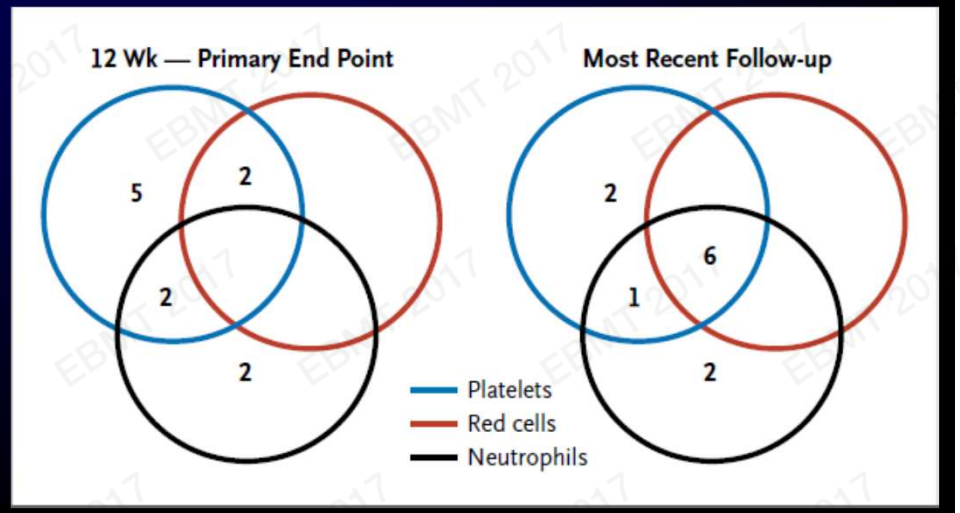
n=25

Refractory SAA

Eltrombopag 50-150 mg, orally, for 12 weeks



- ✓44% hematological response (at least 1 lineage)
  - ✓ Plt response 36%
  - ✓ Hb response 24%
  - ✓ ANC response 36%
- ✓Increased marrow cellularity (resp.)
- ✓Minimal toxicity (liver?), no fibrosis

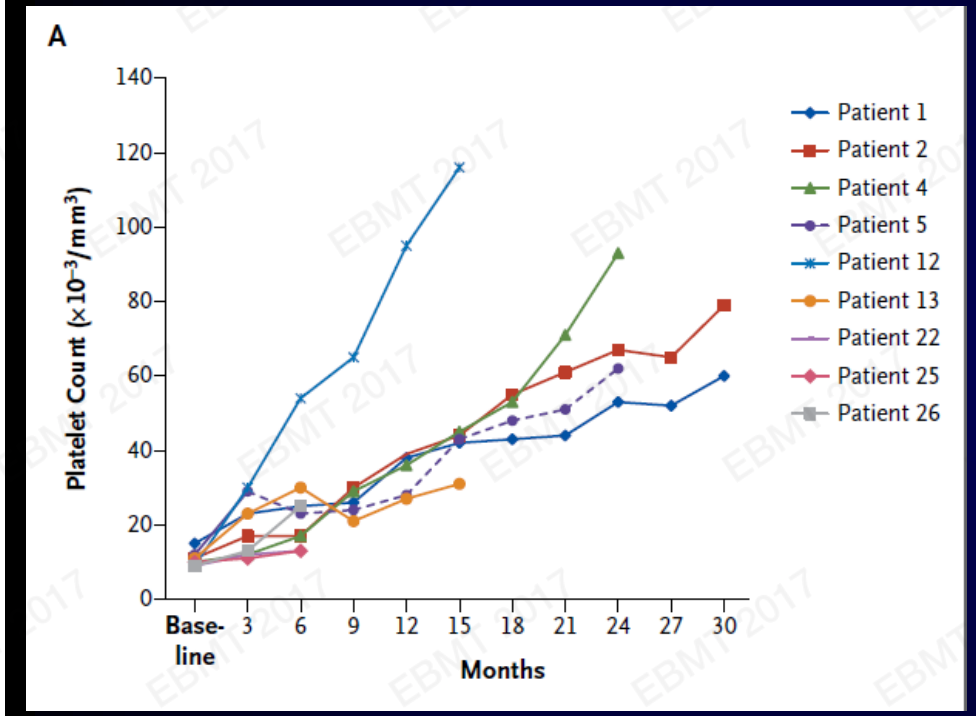


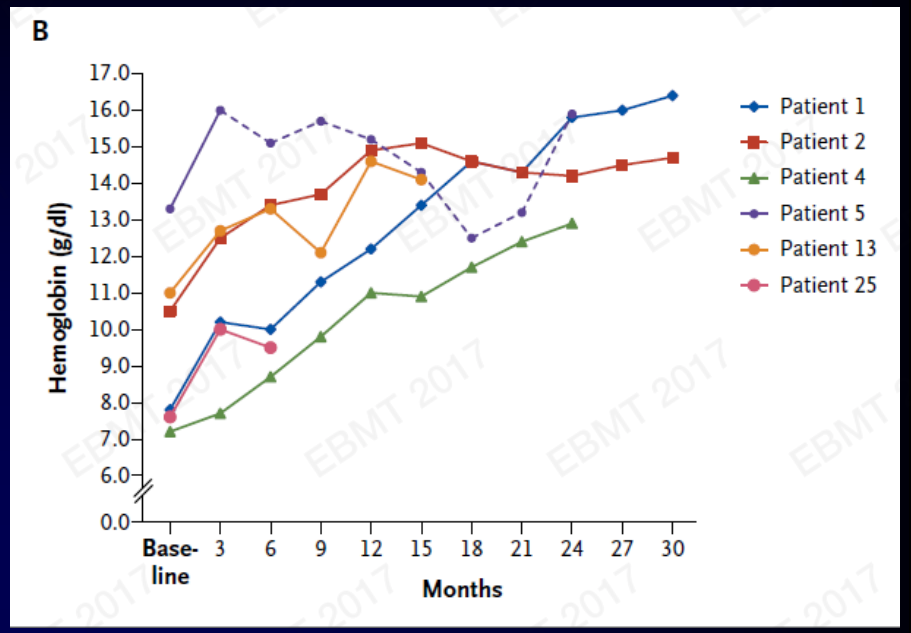
ELTROMBOPAG IN REFRACTORY SAA

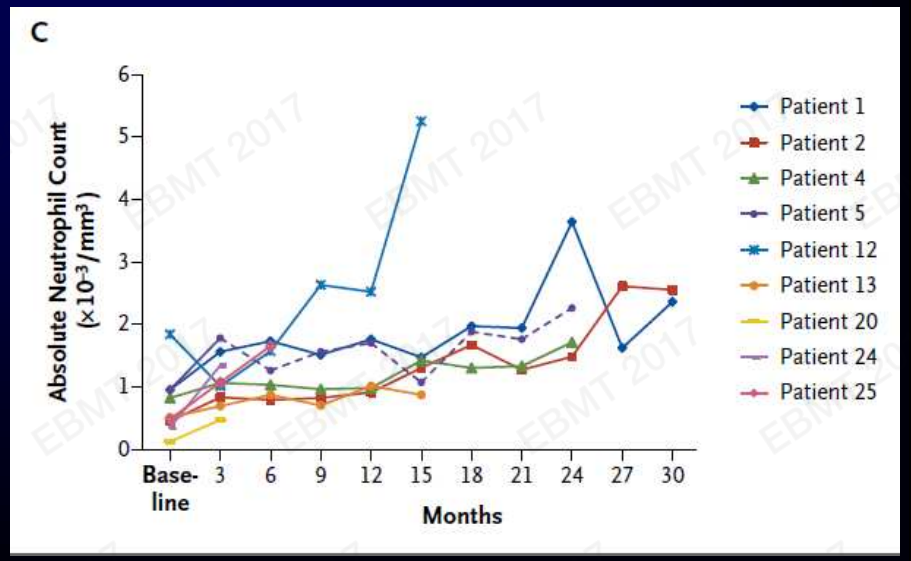
The status of art

NEJM

Eltrombopag and Improved Hematopoiesis in Refractory Aplastic Anemia







- ✓Out 11 responders
  - ✓ 7 still on eltrombopag, showing further improvement
  - ✓ 4 discontinued (2 ANC responders and 2 toxicities)

ELTROMBOPAG IN REFRACTORY SAA

The risk of clonal evolution

BLOOD, 20 MARCH 2014 •

VOLUME 123, NUMBER 12

Regular Article

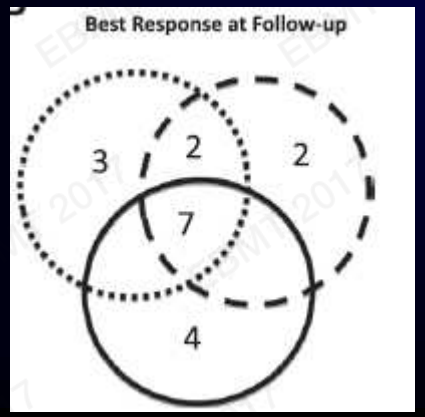
CLINICAL TRIALS AND OBSERVATIONS

CME Article

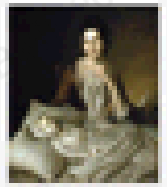
Eltrombopag restores trilineage hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug

Ronan Desmond,[1] Danielle M. Townsley,[1] Bogdan Dumitriu,[1] Matthew J. Olnes,[2] Phillip Scheinberg,[3] Margaret Bevans,[4] Ankur R. Parikh,[1] Kinneret Broder,[1] Katherine R. Calvo,[5] Colin O. Wu,[6] Neal S. Young,[1] and Cynthia E. Dunbar[1]

- ✓Additional 18 patients (n=43), OR 17/43 (40%)
- ✓Long-term follow up
  - ✓ Eltrombopag discontinued in 5 robust VGPR, with sustained response
- ✓Clonal evolution in 8/43 (18%), mostly in non-responders (6/8); no RAEB/AML
  - *NR: 7-/del(7) [n=5], +8 [n=1]*
  - *R: del(13) [n=2]*



Age (y)	Response	CGH (SNP-based) Baseline	At evolution	Time on eltrombopag (mo)	Dysplasia	Outcome
60	NR	46XY[20]	−7[20]	3	N	Died of progressive cytopenias
18	NR	46XX[6]	+8[9]/46XX[11]	3	N	Transplanted successfully
20	NR	46XY[20]	−7[5]t(1;16) [3]/46XY[12]	3	N	Transplanted successfully
67	R	46XY[20]	del(13)[19]/46XY[1]	13	Mild dyserythropoeisis	Transplanted
41	NR	46XY[20]	+21[3]/46XY[17] −7[2]/46XY[19]	3 6	Mild dyserythropoeisis	Awaiting transplant
66	R	46XY[20]	46XYdel13q[2]/46XY[18]	9	N	Under observation
23	NR	46XY[20]	−7[5],XY[15]	3	N	Transplanted successfully
17	NR	No metaphases	+1,der(1;7) [4]/46XY[16]	3	N	Transplanted successfully



2003

Antithymocyte Globulin and Cyclosporine for Severe Aplastic Anemia

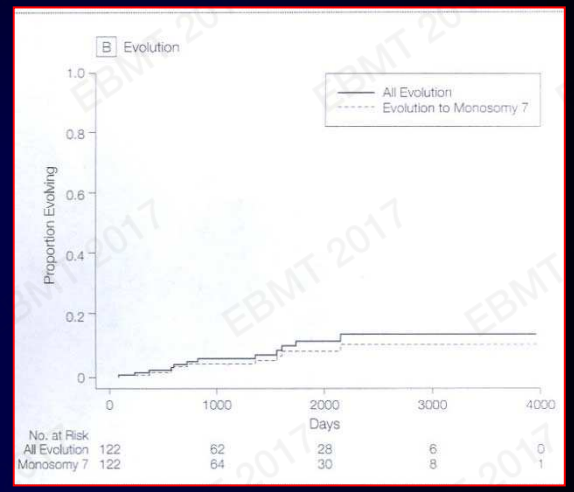
Association Between Hematologic Response and Long-term Outcome

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

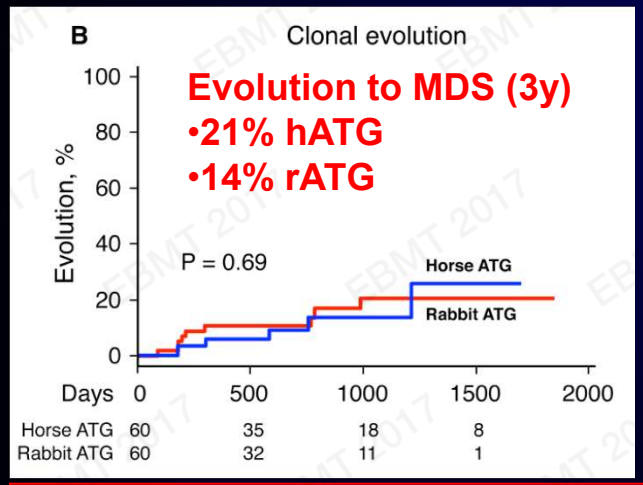
n=112

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

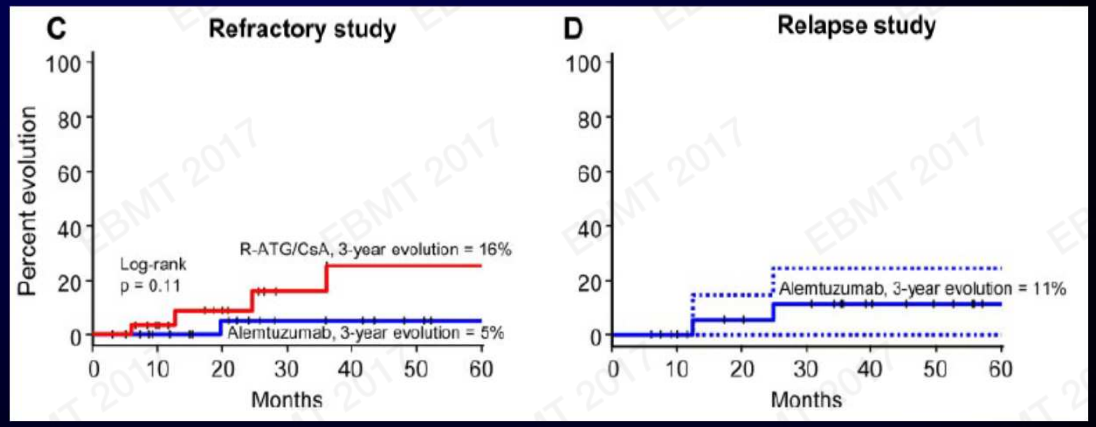
Clonal evolution (3y)
- 11% MDS (especially 7-)
- 10% PNH



NEJM 2011



Blood 2012



In all recent studies, the incidence of clonal evolution is about 10-15%, regardless the specific treatment

ELTROMBOPAG IN SAA

The status of art

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

FDA Approvals > Medscape Medical News

FDA OKs Eltrombopag (Promacta) for Severe Aplastic Anemia

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PROMACTA safely and effectively. See full prescribing information for PROMACTA.

PROMACTA (eltrombopag) tablets, for oral use
Initial U.S. Approval: 2008

WARNING: RISK FOR HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C

See full prescribing information for complete boxed warning

In patients with chronic hepatitis C, PROMACTA in combination with interferon and ribavirin may increase the risk of hepatic decompensation. (5.1)

- **Chronic ITP:** Initiate PROMACTA at 50 mg once daily for most patients. Reduce initial dose in patients with hepatic impairment and/or patients of East Asian ancestry. Adjust to maintain platelet count greater than or equal to 50 x 10^9/L. Do not exceed 75 mg per day. (2.1)
- **Chronic Hepatitis C-associated Thrombocytopenia:** Initiate PROMACTA at 25 mg once daily for all patients. Adjust to achieve target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 100 mg. (2.2)
- **Severe Aplastic Anemia:** Initiate PROMACTA at 50 mg once daily for most patients. Reduce initial dose in patients with hepatic impairment or patients of East Asian ancestry. Adjust to maintain platelet count greater than 50 x 10^9/L. Do not exceed 150 mg per day. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

12.5-mg, 25-mg, 50-mg, 75-mg, and 100-mg tablets. (3)

ELTROMBOPAG ADDED TO STANDARD IMMUNOSUPPRESSION AS FIRST TREATMENT IN APLASTIC ANEMIA

Courtesy of Danielle Townsley

Danielle Townsley, MD

Bogdan Dumitriu, MD, Phillip Scheinberg, MD, Ronan Desmond, MD, FRCPath, Xingmin Feng, PhD, Olga Rios, RN, Barbara Weinstein, RN, Janet Valdez, PA-C, Thomas Winkler, MD, Marie Desierto, BS, Harshraj Leuva, MBBS, Colin Wu, PhD, Katherine R. Calvo, MD, PhD, Andre Larochelle, MD, PhD, Cynthia E. Dunbar, MD and Neal S. Young, MD

National Heart, Lung, and Blood Institute

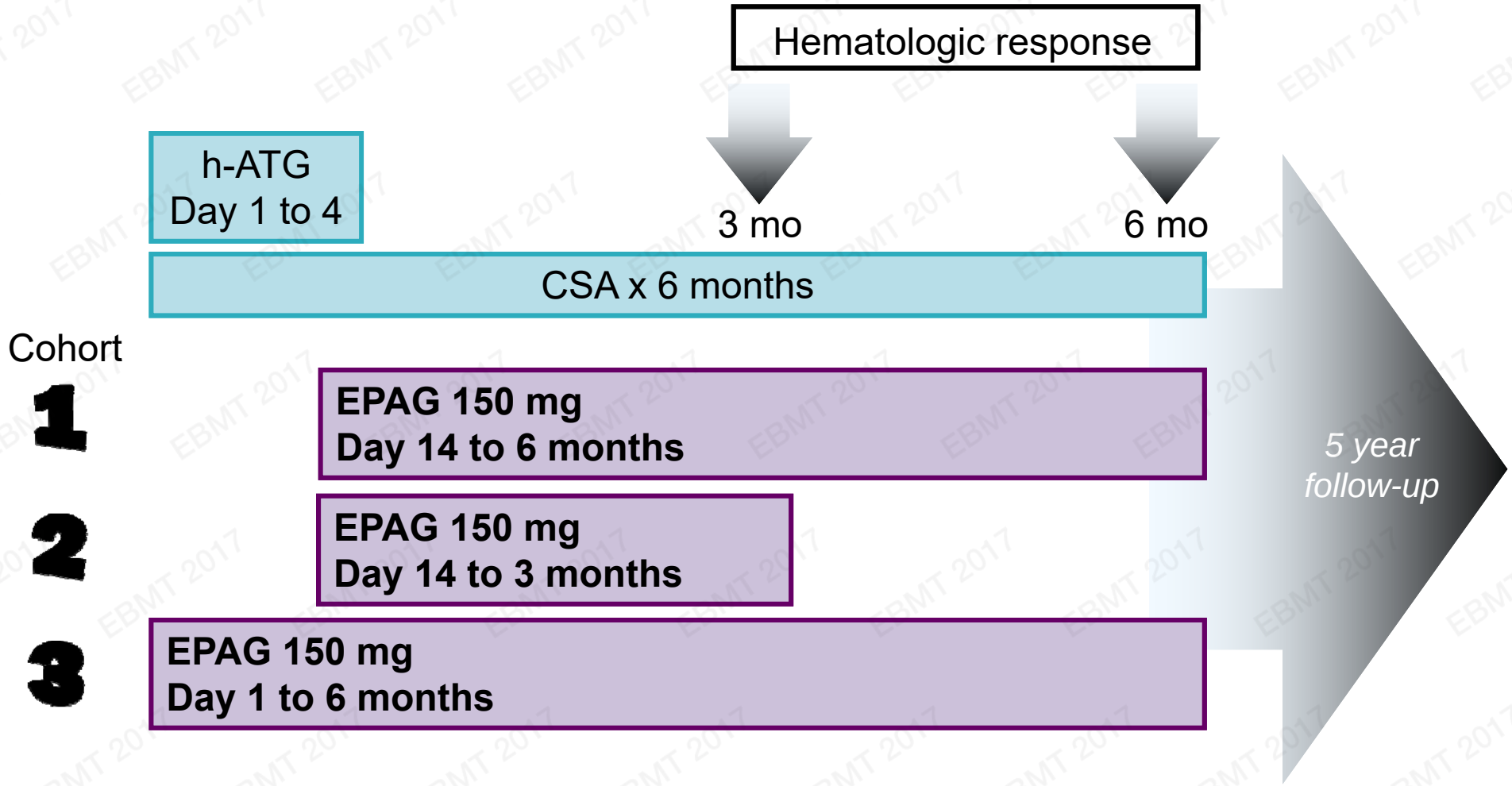
American Society for Hematology 2015 Annual Meeting

December 8, 2015

NIH National Heart, Lung, and Blood Institute

STUDY DESIGN
ELTROMBOPAG ADDED TO IST

Courtesy of Danielle Townsley



clinicaltrials.gov NCT01623167

NIH National Heart, Lung, and Blood Institute

EBMT studies for AA

	moderate AA (EMAA)	vSAA / SAA (RACE)
Primary objective	PR + CR at 6 months	CR at 3 months
Inclusion criteria	- age ≥ 18 years - Treatment requiring MAA (transfusion dependency or ANC < 1G/l or Thrombo < 30G/l or Hb < 8,5g/dl & Reti < 60G/l)	- age ≥ 15 years - SAA/ vSAA - No primary allo-SCT
Treatment	**CsA + Eltrombopag** versus CsA + Placebo	**hATG (ATGAM) + CsA + Eltrombopag** versus h ATG + CsA
Eltrombopag Dosage	150 mg (225 mg)	150 mg
Design	Placebo controlled	Open lable
Patient number	2 x 58	2 x 100
Sponsor	University hospital Ulm	EBMT

THE RACE trial

A prospective Randomized multicenter study comparing horse Antithymocyte globuline (hATG) + Cyclosporine A (CsA) ± Eltrombopag as front-line therapy for severe aplastic anemia patients.

PRINCIPAL INVESTIGATORS

Regis Peffault de Latour (Paris)

Antonio M Risitano (Naples)

A prospective Randomized multicenter study comparing horse Antithymocyte globuline (hATG) + Cyclosporine A (CsA) with or without Eltrombopag as front-line therapy for severe aplastic anemia patients – RACE STUDY(1)

RACE Trial

11 March 2016

Working party	Principal investigators	Trial Coordinator
SAA-WP	**Antonio M Risitano / Regis Peffault de Latour**	**Marleen van Os**
	To investigate whether **Eltrombopag** (Revolade, GSK) added to standard immune-suppressive treatment, CsA + hATG (ATGAM, Pfizer) increases the rate of early complete response in untreated AA patients* * Patients will be stratified by age and disease severity	
Participating countries		

THE EBMT RACE STUDY

Study design

- ✓An **EBMT Severe Aplastic Anemia Working Party study** (approved by the CTO), entirely funded by Novartis and Pfizer
- ✓Aim of the study: to improve the current standard treatment for SAA
  - ✓ To improve the **robustness of hematological response** of SAA patients receiving IST
- ✓Prospective, open label, phase III randomized study
  - ✓ Control arm: horse ATG (40 mg/kg x 4dd, iv) + cyclosporine (5 mg/kg, os)
  - ✓ Investigational arm: horse ATG + cyclosporine + eltrombopag (150 mg/die, os)
- ✓Type B trial, because eltrombopag may theoretically result in a somewhat higher risk (mostly clonal evolution) in comparison to standard medical care
- ✓Participating centers: 30 sites from 7 EU Countries (France, Italy, UK, Germany, Spain, Netherlands, Switzerland)

THE EBMT RACE STUDY

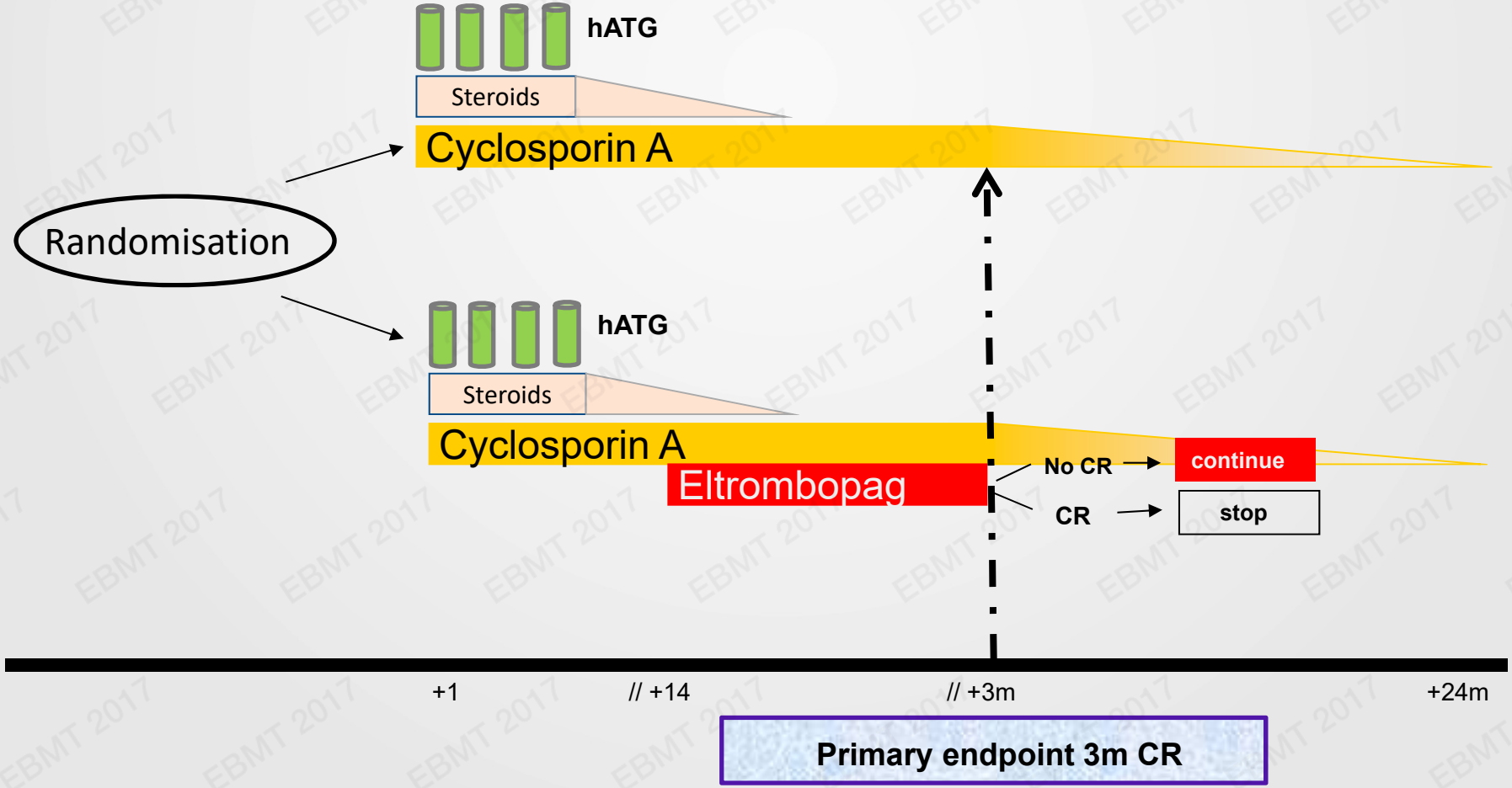
Statistical design

- ✓**Superiority study**
- ✓**Sample size calculation**
  - ✓ Aiming to increase the 3m CR rate from 7% *(Scheinberg, Haematologica 2010)* to 21% *(current NIH data)*
  - ✓ Sample size to reject the null hypothesis at 5% significance level (alpha-error) and with 80% power (two-sided test) is n=96 patients for treatment arm
  - ✓ Sample size increased by 4% to compensate for possibly not evaluable patients: **total number of 200 patients (100 each arm)**
- ✓**Randomization**
  - ✓ **1:1 randomization, including a stratified block design**
  - ✓ Stratification according to:
    - **Disease severity:**
      - Severe aplastic anemia (SAA)
      - Very severe aplastic anemia (VSAA: SAA plus ANC <200/μL)
    - **Age:**
      - >=15 and <40 year old
      - >=40 year old
- ✓**No stopping rules (study continuation led to discretion of the DMSB)**
- ✓**No interim analysis**

RACE STUDY (2)

SAA-WP

TREATMENT Scheme



THE EBMT RACE STUDY

Study flow-chart

Initial treatment

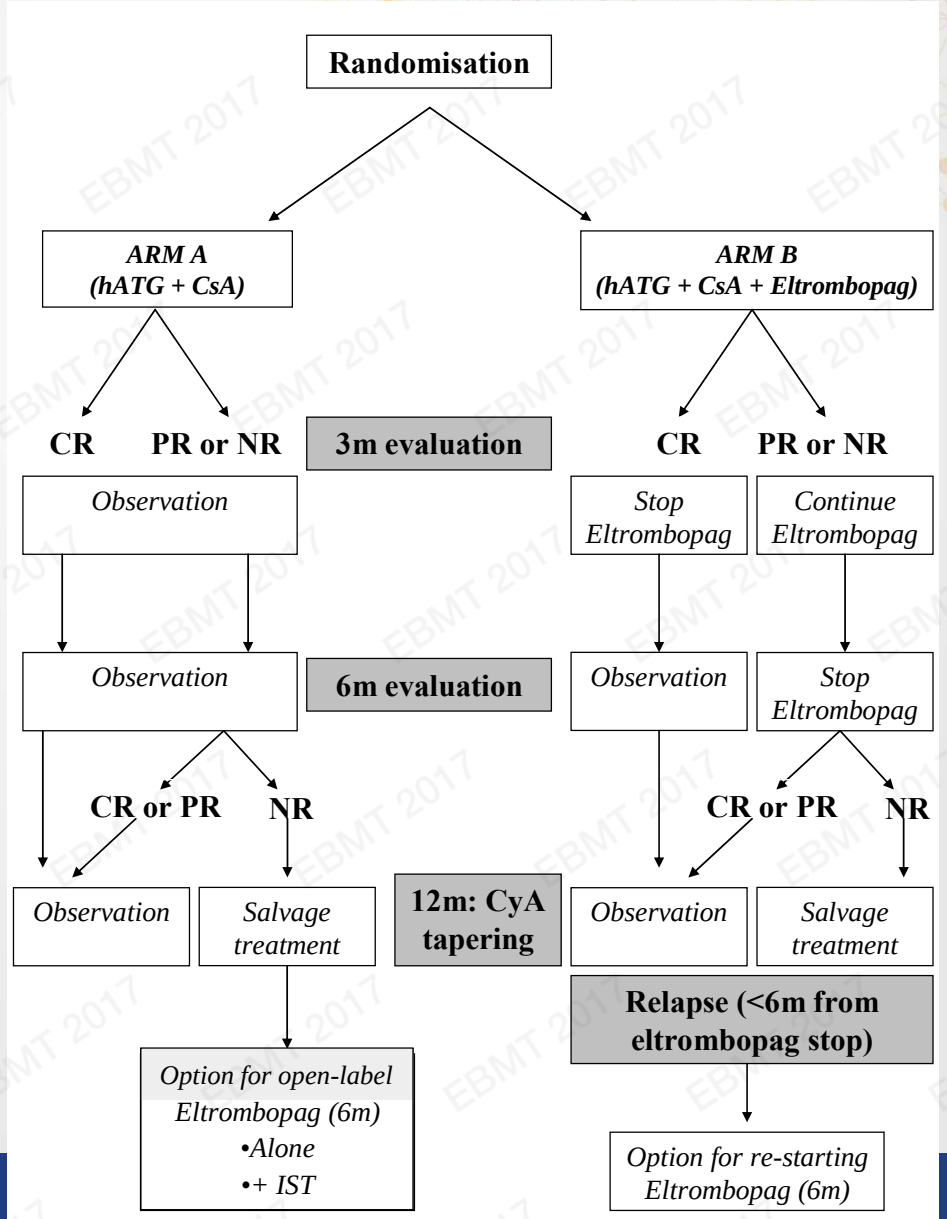
3 month evaluation:
primary endpoint

6 month evaluation:
stop eltrombopag
Possible cross-over (standard arm only)

12 month evaluation:

Relapse: possible eltrombopag re-starting (investigational arm only)

24 month evaluation: end of the study

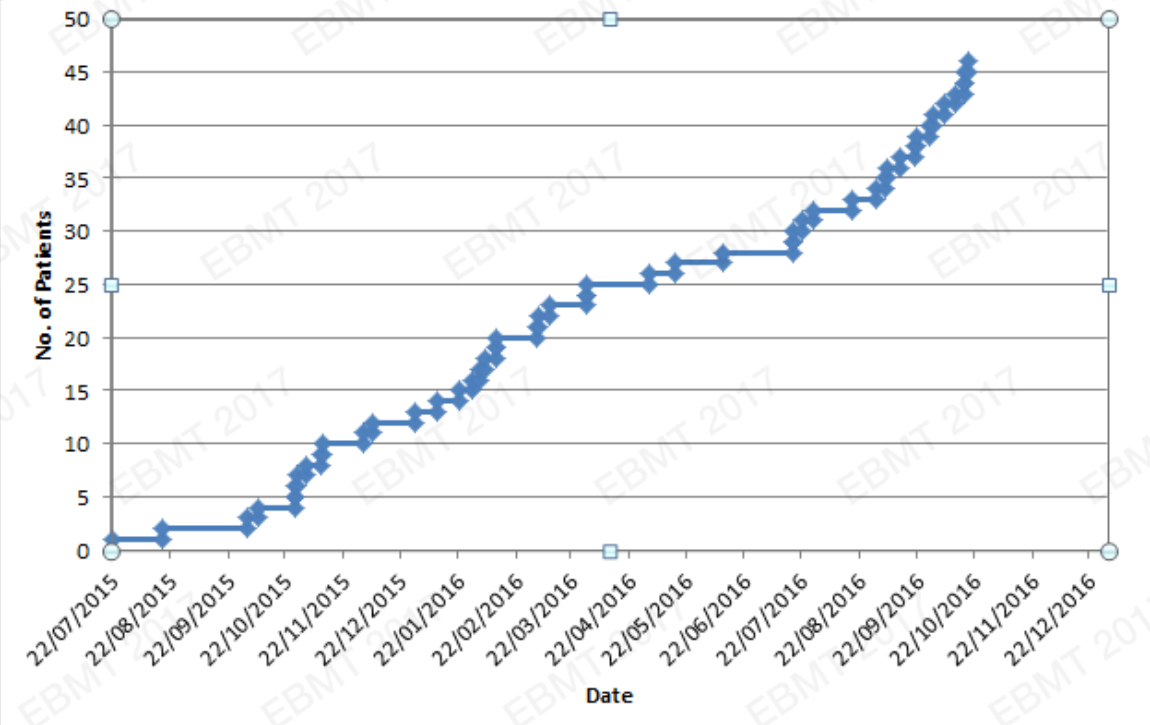


RACE trial – **participating sites**

Country	# sites
France	6 (6 open) +2
Germany	5 (on hold)
Italy	6 (2 open) +3
Netherlands	4 (3 open)
Spain	5 (1 open)
Switzerland	1 (0 open) +1
United Kingdom	5
Total	32 (up to 40)

Brazil	Back up site?

Patient recruitment *(October 10, 2016)*



Patient recruitment is excellent for the number of sites

Delays are in site opening (contracts and regulatory hurdles) – improving

RACE trial – **ancillary biological study (King's College)**

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Regular Article

MYELOID NEOPLASIA

Somatic mutations identify a subgroup of aplastic anemia patients who progress to myelodysplastic syndrome

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Table 3. Details of all the somatic mutations in the study

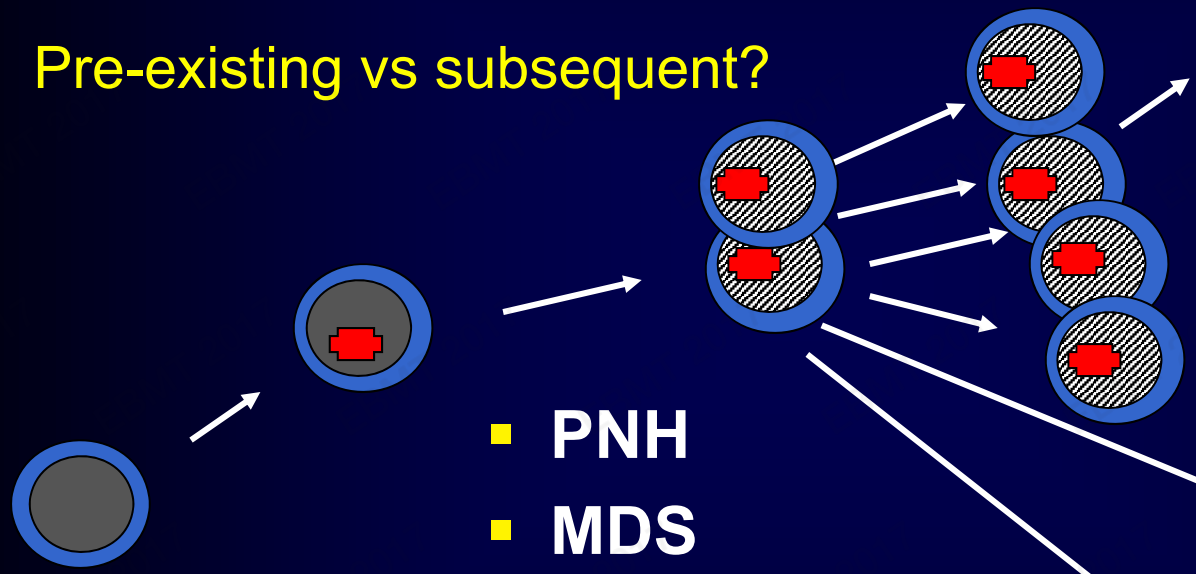
UPN	Gene	Mutant allele burden (%)	Variant class	Nucleotide and protein change	Constitutional DNA
2*	*ASXL1*	30	Frameshift insertion	c.1927_1928insG:p.G643fs	Skin
2*	*DNMT3A*	42	Nonsynonymous SNV	c.C1540G:p.L514V	Skin
2*	*ERBB2*	44	Nonsynonymous SNV	c.G922A:p.V308M	Skin
5*	*TET2*	5	Stopgain SNV	c.C3100T:p.Q1034X	Skin
6*	*ASXL1*	38	Stopgain SNV	c.C2242T:p.Q748X	Buccal
10*	*SRSF2*	43	Nonsynonymous SNV	c.C284T:p.P95L	Buccal
16*	*ASXL1*	23	Frameshift insertion	c.2469_2470insAG:p.L823fs	Skin
18*	*DNMT3A*	31	Nonsynonymous SNV	c.C2644T:p.R882C	Skin
19*	*IKZF1*	14	Nonsynonymous SNV	c.C640G:p.H214D	Skin
21*	*BCOR*	5	Stopgain SNV	c.C526T:p.Q176X	Buccal
29*	*ASXL1*	41	Stopgain SNV	c.G4068A:p.W1356X	Skin
33*	*BCOR*	68	Stopgain SNV	c.G4832A:p.W1611X	Skin
40*	*ASXL1*	31	Nonframeshift deletion	c.2894_2896del:p.965_966del	Buccal
46*	*MPL*	10	Nonsynonymous SNV	c.G1544T:p.W515L	Buccal
64	*DNMT3A*	47	Nonsynonymous SNV	c.C2644T:p.R882C	Skin
66	*ASXL1*	37	Frameshift deletion	c.2433delT:p.N811fs	Skin
67	*U2AF1*	19	Nonsynonymous SNV	c.C101A:p.S34Y	Skin
69	*ASXL1*	34	Stopgain SNV	c.C2077T:p.R693X	Buccal
70	*ASXL1*	2	Stopgain SNV	c.G2026T:p.E676X	Buccal
70	*BCOR*	14	Stopgain SNV	c.T912G:p.Y304X	Buccal
73	*BCOR*	6	Frameshift insertion	c.4834_4835insC:p.L1612fs	Skin
79	*ASXL1*	36	Stopgain SNV	c.G2026T:p.E676X	Buccal
81	*ASXL1*	3	Stopgain SNV	c.T2324G:p.L775X	Skin
88	*ASXL1*	7	Frameshift deletion	c.2126delC:p.A709fs	Skin
93	*DNMT3A*	8	Stopgain SNV	C2311T:p.R771X	Skin
94	*BCOR*	30	Splice site	splice site c.3052-2A>G	Skin
97	*DNMT3A*	7	Nonsynonymous SNV	c.C2644T:p.R882C	Buccal
107	*ASXL1*	30	Stopgain SNV	c.T2468G:p.L823X	Buccal
129	*DNMT3A*	5	Nonsynonymous SNV	c.G2207A:p.R736H	Skin
130	*DNMT3A*	5	Nonsynonymous SNV	c.G2645A:p.R882H	Skin
140	*BCOR*	5	Frameshift deletion	c.4760delC:p.P1587fs	Buccal
142	*DNMT3A*	1.5	Nonsynonymous SNV	c.C2644T:p.R882C	Buccal

CLONAL EVOLUTION

A matter of definition

Consider **oligoclonal** hematopoiesis in AA due to HSC reduction

Pre-existing vs subsequent?



- **PNH**
- **MDS**
- **AML**

7 8

Fixation of neutral mutation (founder effect) vs true clonal complication

The actual meaning of somatic mutations in hematology

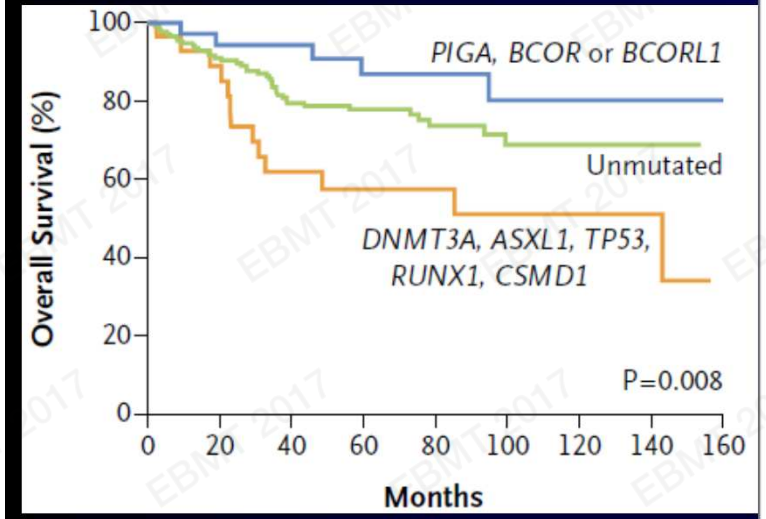
Do all mutations imply cancer (especially in marrow failure)?

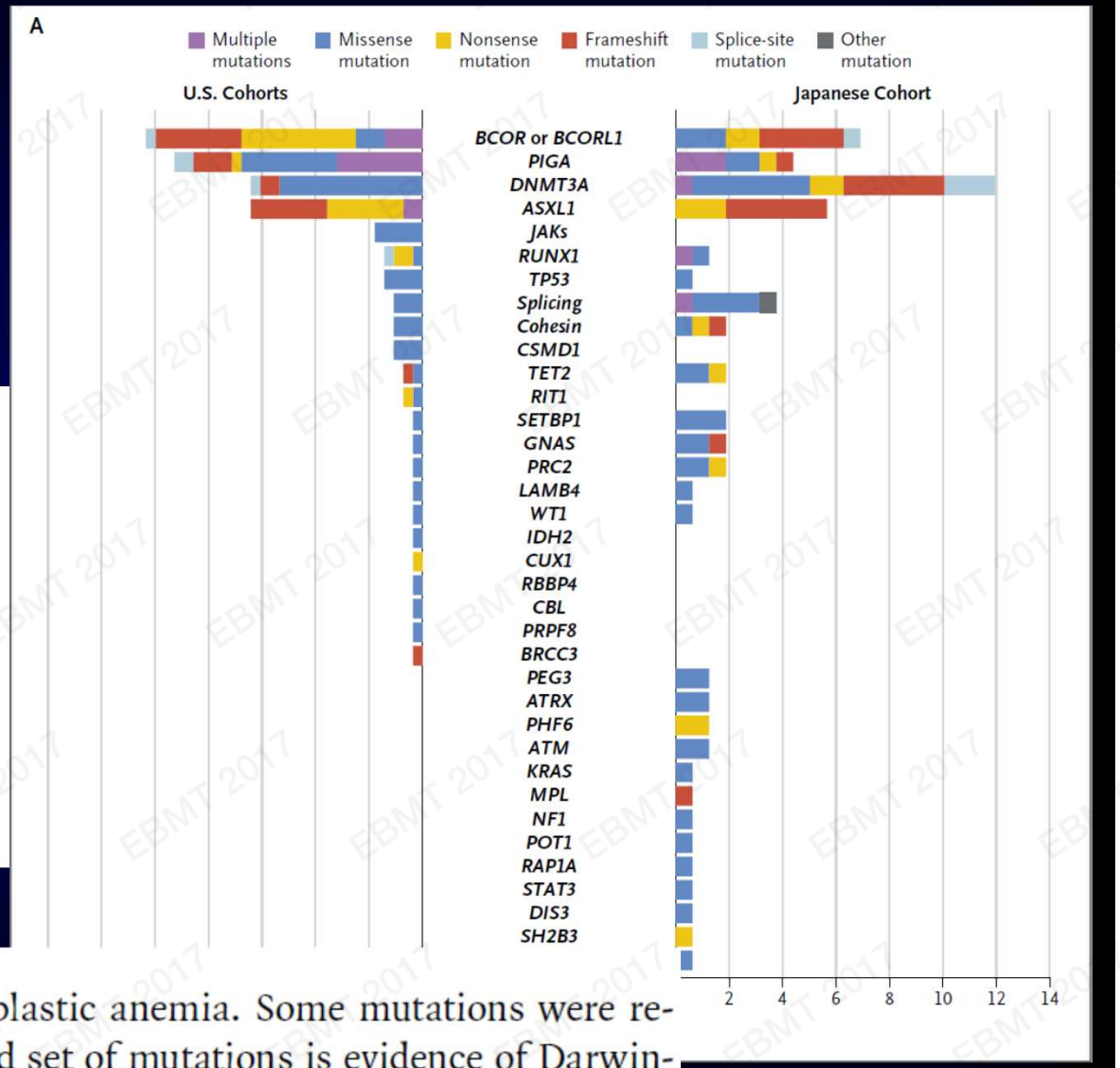
The NEW ENGLAND JOURNAL of MEDICINE

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.

SOMATIC MUTATION IN HSC

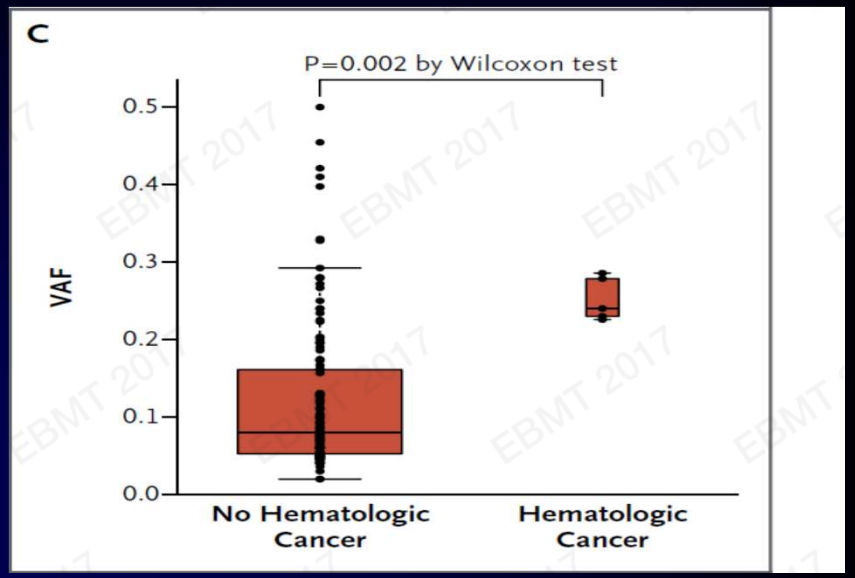
The lesson from ageing

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes

- ✓ **17,182 individuals unselected for hematologic phenotypes**
- ✓ **detectable mutations in 746 persons (4.3%)**
- ✓ **Most common variants in three genes: DNMT3A, TET2, and ASXL1**
- ✓ **The presence of a somatic mutation was associated with increased risk:**
  - hematologic cancer (hazard ratio, 11.1; 95% CI 3.9-32.6)
  - all-cause mortality (HR 1.4; 95% CI 1.1-1.8)
  - incident coronary heart disease (HR 2.0; 95% CI 1.2-3.4)
  - ischemic stroke (HR 2.6; 95% CI 1.4-4.8)



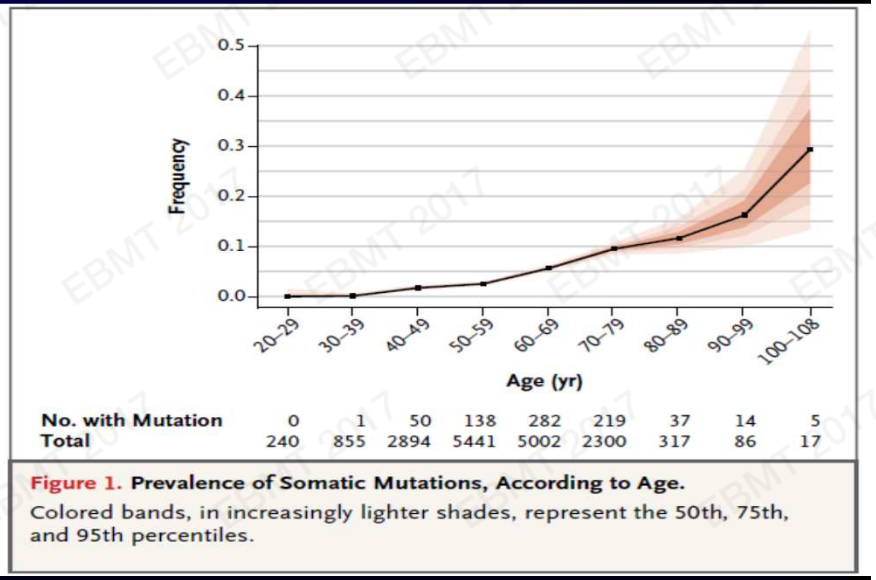


Figure 1. Prevalence of Somatic Mutations, According to Age.
Colored bands, in increasingly lighter shades, represent the 50th, 75th, and 95th percentiles.

Siddhartha Jaiswal *et al*, Dec 2014

ACKNOWLEDGEMENTS

The EBMT RACE team