Mise au point sur l’aplasie médullaire

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MaRIH
Filière de santé Maladies Rares ImmunoHématologiques

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Liens d'intérêt

2017-2018

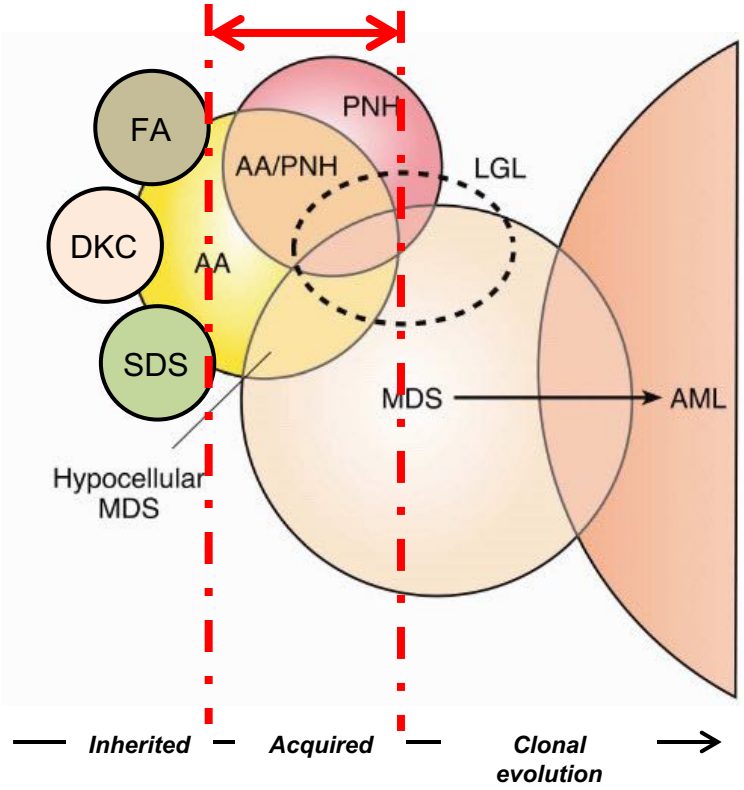
- **Expert consultant / orateur** pour des symposia pour les laboratoires Alexion, Amgen, Gilead, Jazz, Keocyte, MSD, Novartis, Pfizer, Roche, Samsung & Therakos

- **Bourse de recherche** des laboratoires Alexion, Amgen, Jazz pharmaceutical, Novartis, Pfizer

Idiopathic aplastic anemia

Landscape

Bone marrow failure disorders (BMF)



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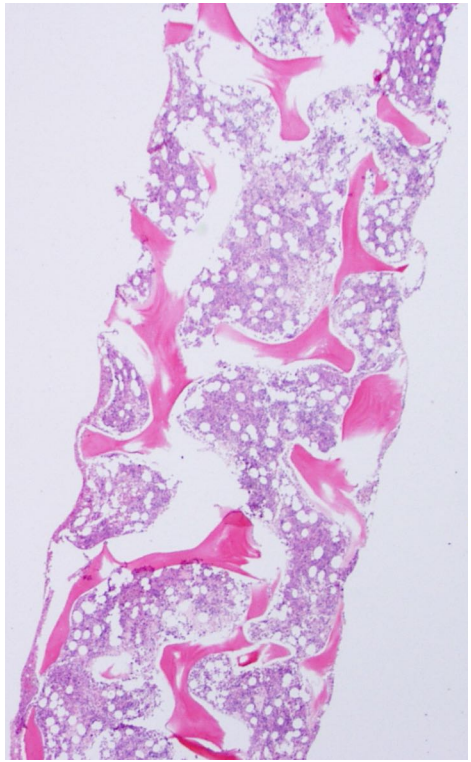
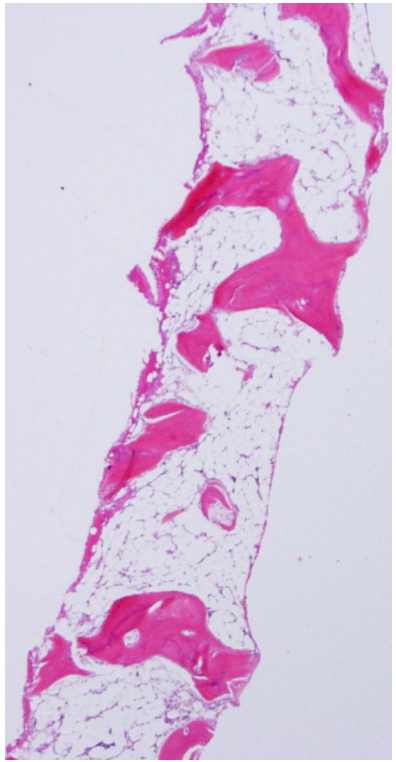
Idiopathic aplastic anemia

Similar presentation





Mise au point sur l'aplasie médullaire

Aims

- **Diagnosis of aplastic anemia?**
- **How make the difference between acquired (idiopathic) and inherited aplastic anemia?**
  - Clinic
  - Biology
- **When should we start a treatment?**
  - Criteria for treatment
- **How to treat?**
  - Immunosuppressive therapy versus transplantation

Diagnosis of aplastic anemia

Juliette F.

- 8-year-old girl presents with severe pancytopenia
- 2 healthy brothers
- A bone marrow was hypocellular (<5%) with no dysplasia
- Cytogenetics showed a normal female karyotype in 20 metaphases
- There were no distinct physicial findings suggestive of IBMFS

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>>>> Aplastic anemia? YES/NO

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Diagnosis of aplastic anemia

Aim #1

- **Pancytopenia**
  - Macrocytosis is common
  - Lymphocytes count is usually preserved
  - Isolated cytopenia at early stage (thrombocytopenia)

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- **Bone marrow aspiration**
  - No abnormal cells

Diagnosis of aplastic anemia

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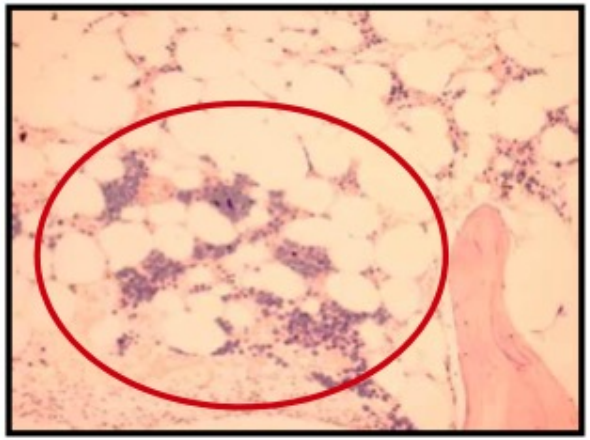

- **Bone marrow aspiration**
  - No abnormal cells

- **Bone marrow biopsy (diagnosis)**
  - Cellularity <30%
  - Dyserythropoiesis (usual)
  - Mast cells, lymphoid hyperplasia, plasma cells, macrophages

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Difference between acquired and inherited aplastic anemia?

Juliette F.

1. This patient has acquired AA, no further testing
2. Sequence telomerase-related genes, looking for mutations
3. Systematic testing for Fanconi Anemia
4. Do whole exome sequencing to rule out inherited forms of AA
5. Send the patient for evaluation by a geneticist

Difference between acquired and inherited aplastic anemia?

Aim #2

> Clinic

- **Disease installation**
  - Progressive versus acute (CBCs history)
- **Personal history**
  - Early development
  - Physical exam
- **Familial history**
  - Hematological disorders
  - Extra hematological disorder (Lung and cirrhosis)

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Difference between acquired and inherited aplastic anemia?

Aim #2

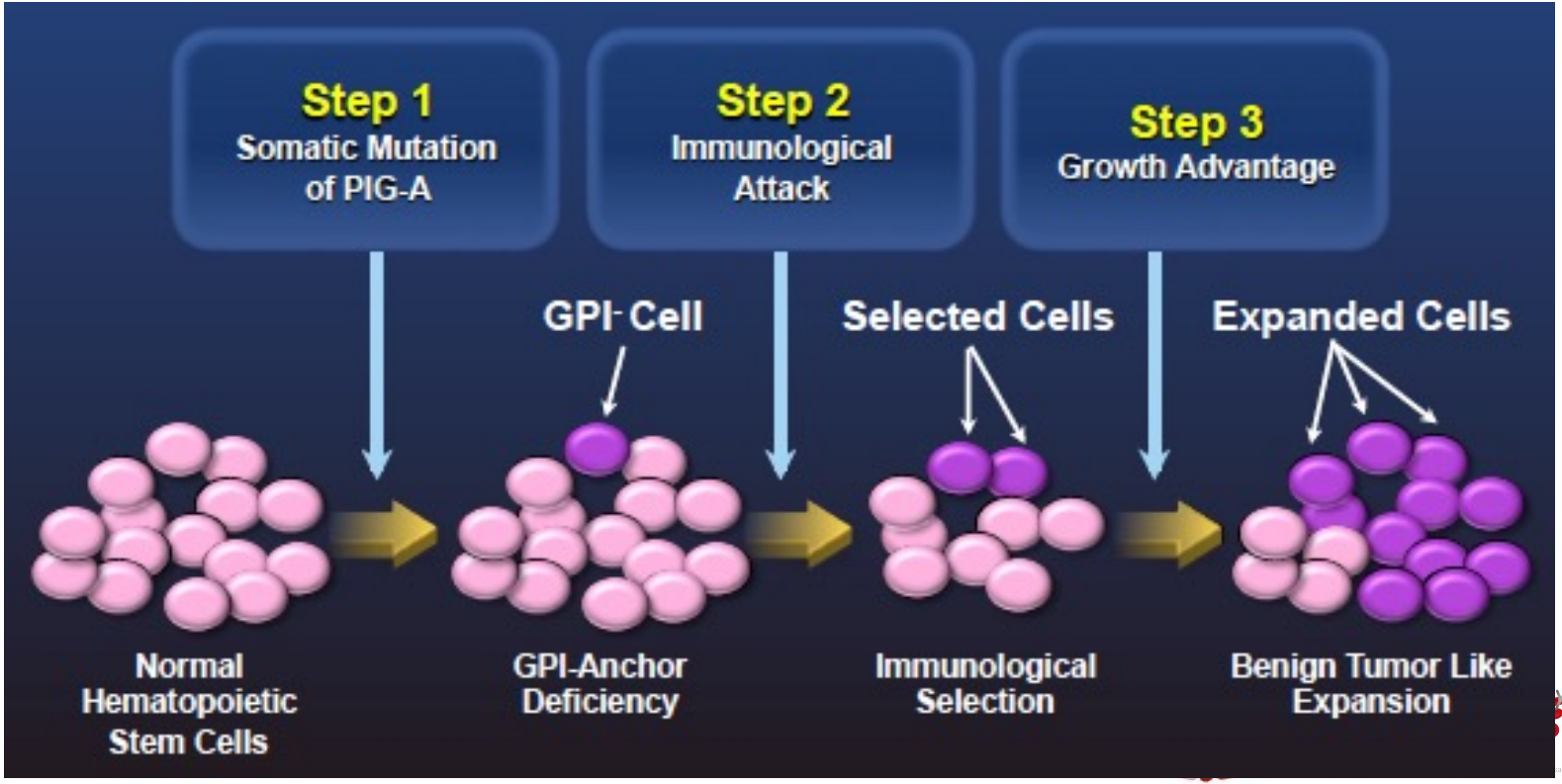
> Biology

- **PNH clone**

Difference between acquired and inherited aplastic anemia?

Idiopathic (80%) – PNH clone

> PNH clone expansion in the context of immune-mediated BMF



Difference between acquired and inherited aplastic anemia?

Aim #2

> Biology

- **PNH clone**
  - In favor of an acquired disorder
- **Immune deficiency & Hemoglobin F / Alpha FP**
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Difference between acquired and inherited aplastic anemia?

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- **PNH clone**
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- **Gene screening**
  - Fanconi anemia
  - Telomeropathies and others

Difference between acquired and inherited aplastic anemia?

Aim #2

OBJECTIVES: in a cohort of patients with an unresolved, likely-Inherited BMF (FA excluded): To identify new IBMF/MDS causes; to draw a broad molecular portrait of this heterogeneous group of patients

N=179 patients from 173 unrelated families

(median age: 8.3 years)

Bluteau O, et al. Blood. 2018

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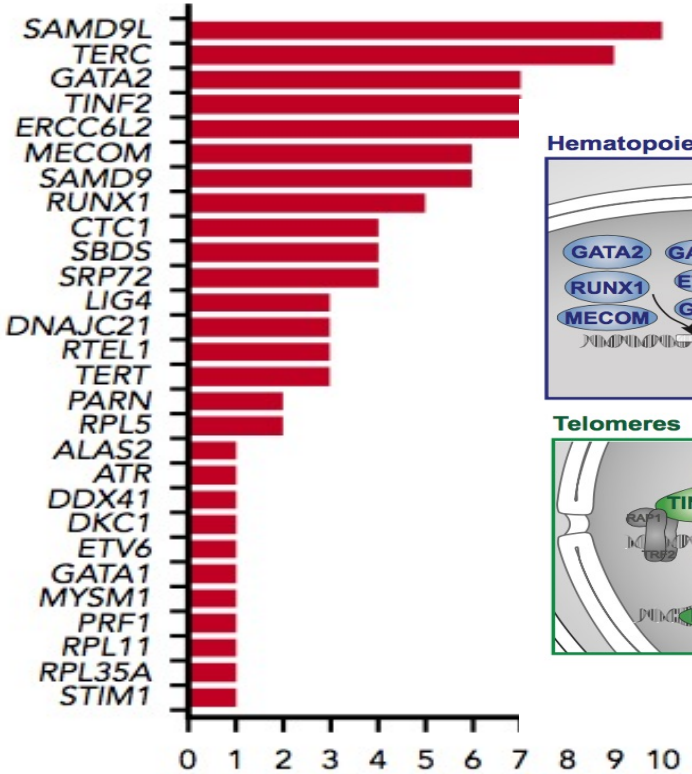
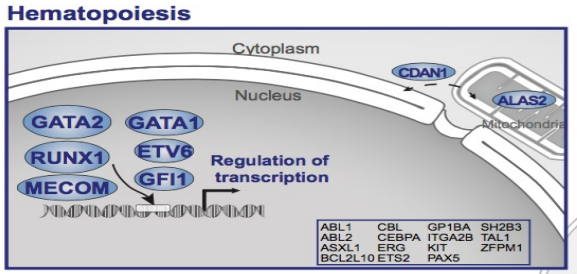
Difference between acquired and inherited aplastic anemia?

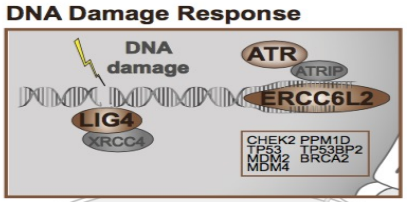
Molecular diagnosis: N=86 patients (almost 50%)

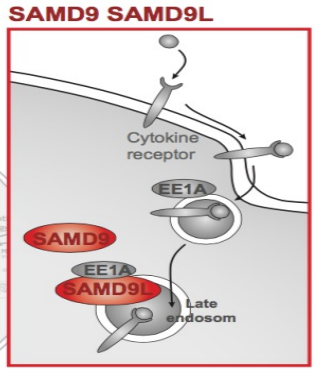


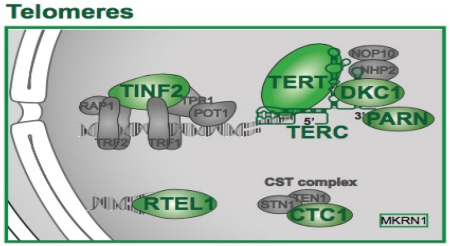
Number of patients with variants

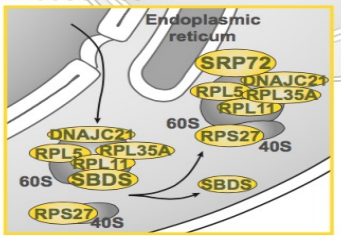
Biological pathways

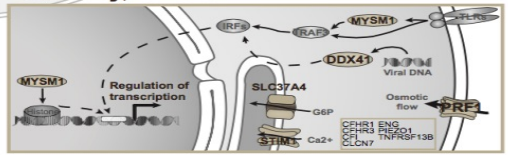






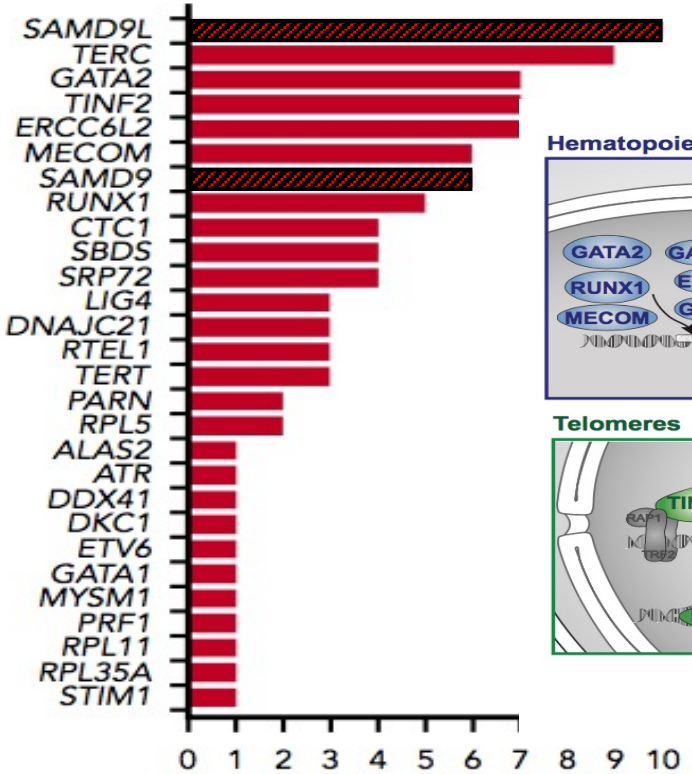






Difference between acquired and inherited aplastic anemia?

***SAMD9L/SAMD9*: N=16 patients (19%)**



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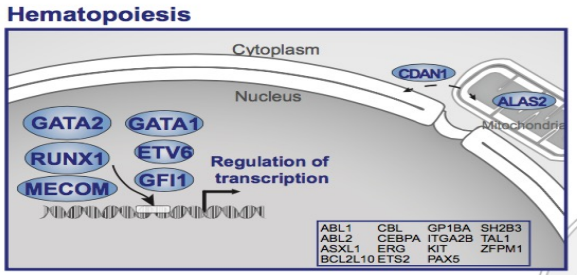
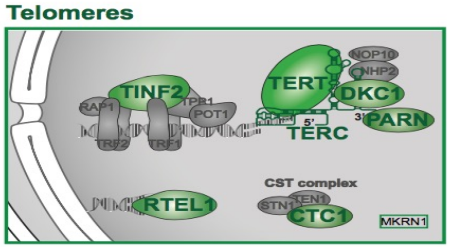
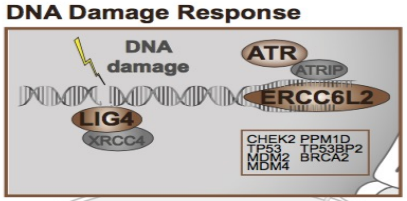
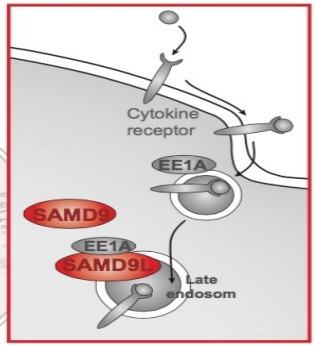
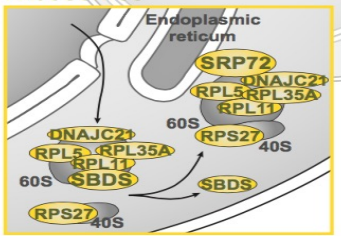
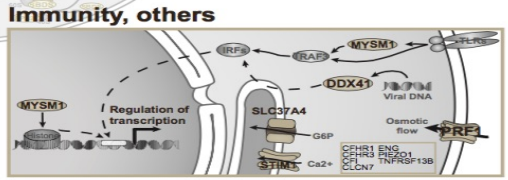






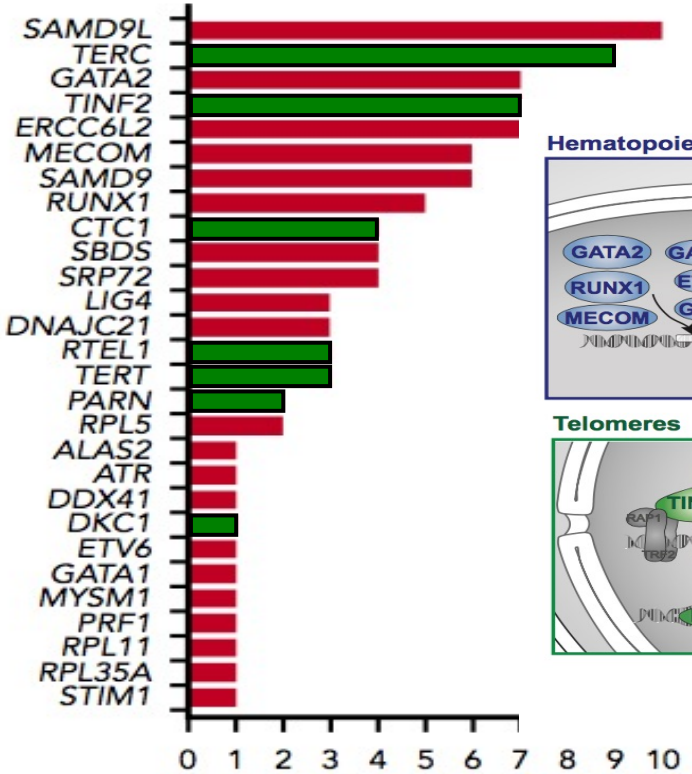






Difference between acquired and inherited aplastic anemia?

Telomeres genes: N=29 patients (34%)



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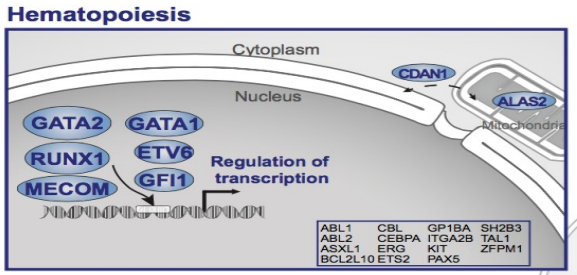
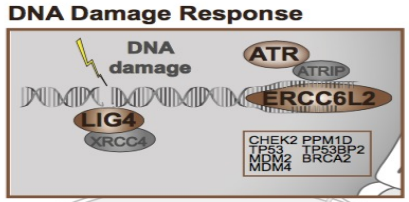
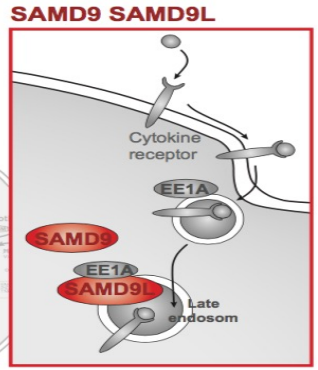
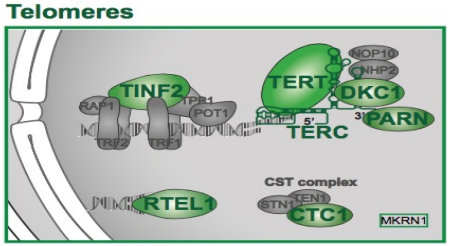
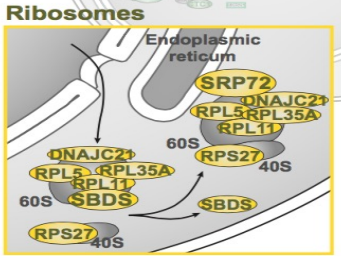
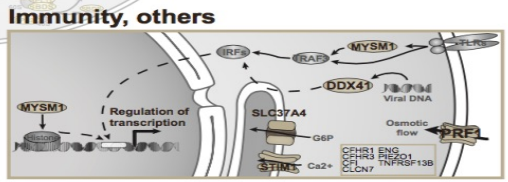






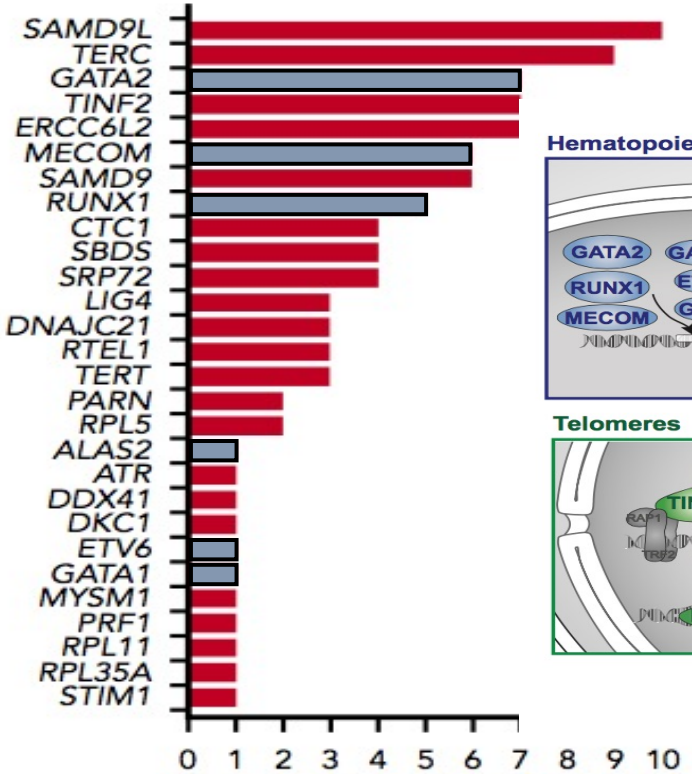




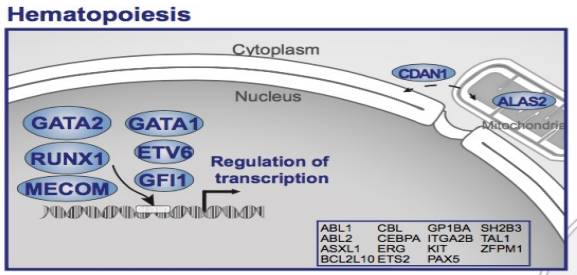


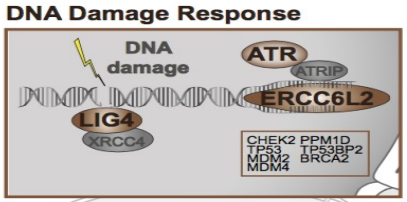
Difference between acquired and inherited aplastic anemia?

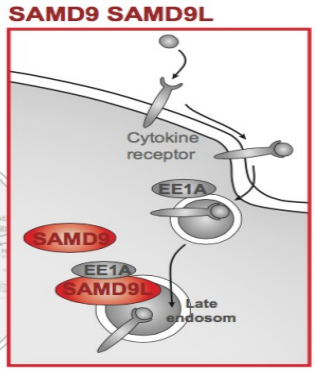
Hematopoietic genes: N=21 patients (24%)

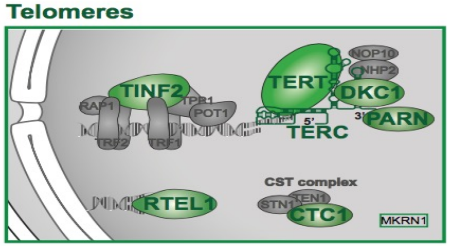


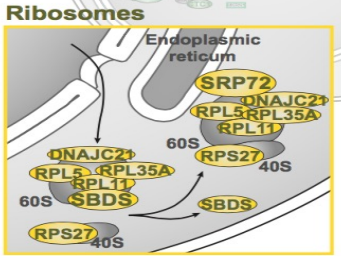
Biological pathways

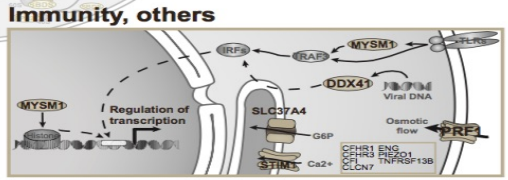






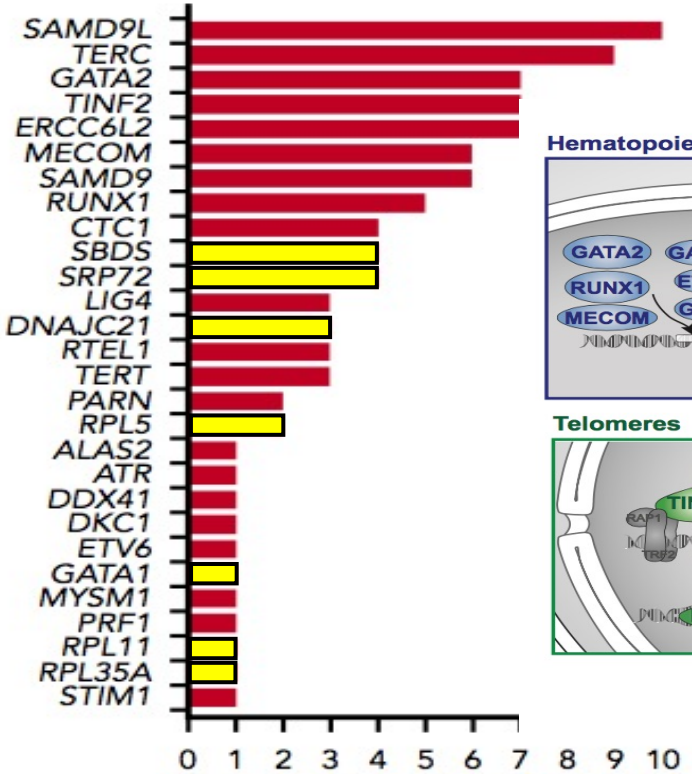




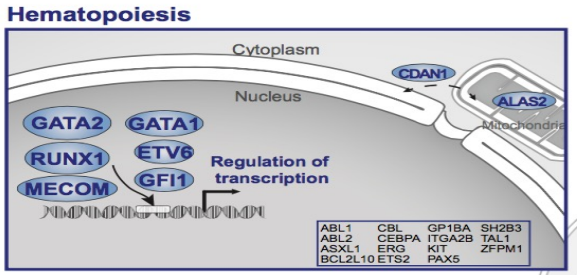


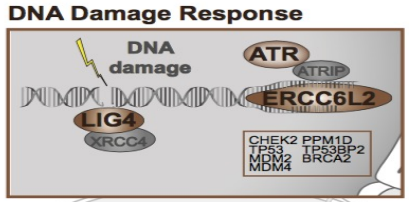
Difference between acquired and inherited aplastic anemia?

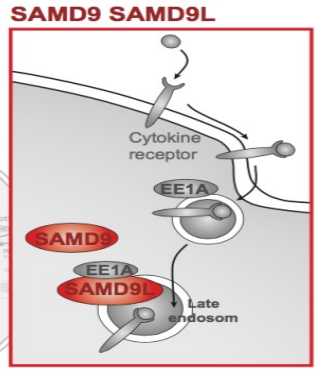
Ribosome biogenesis: N=12 patients (14%)

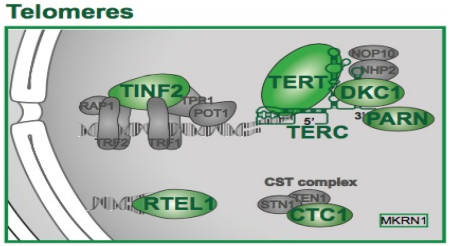


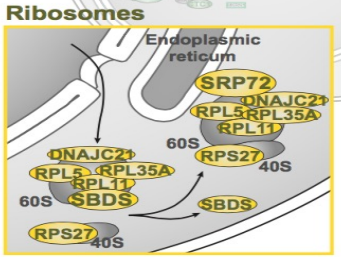
Biological pathways

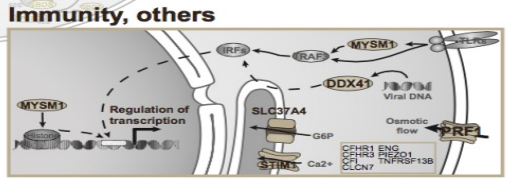






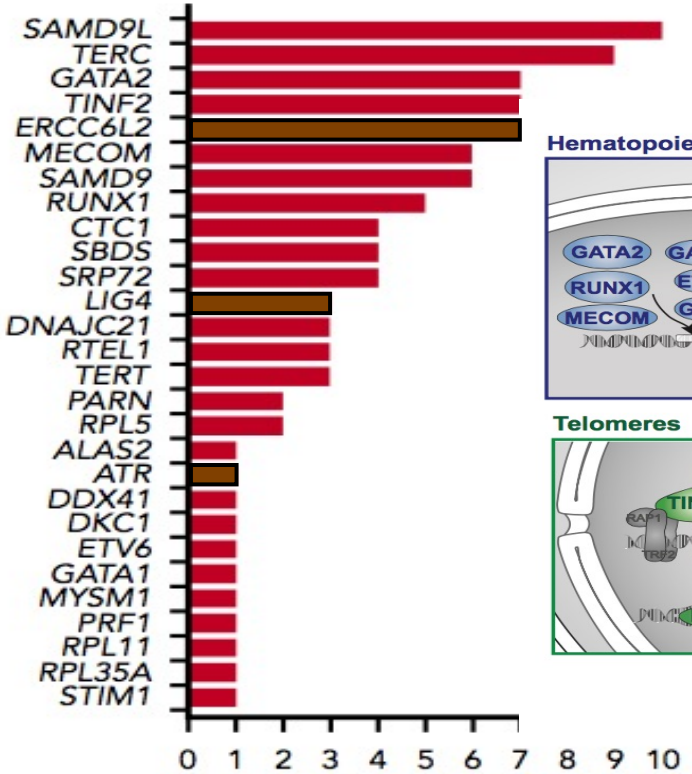




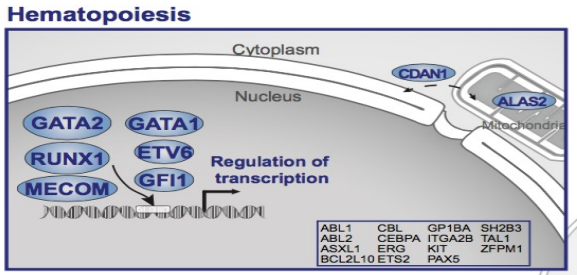


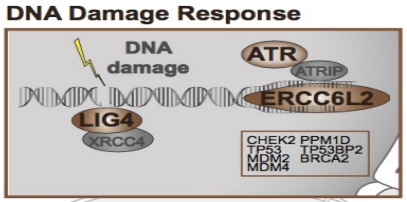
Difference between acquired and inherited aplastic anemia?

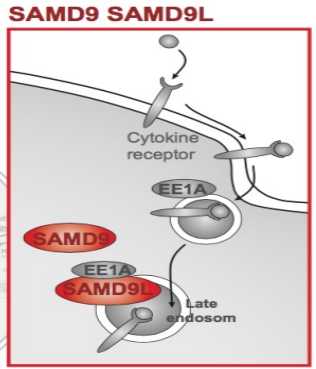
DNA damage: N=11 patients (13%)

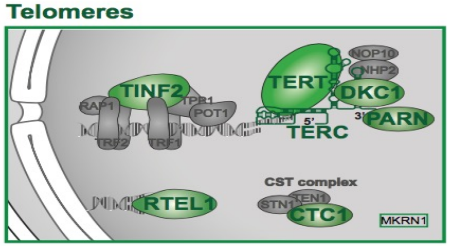


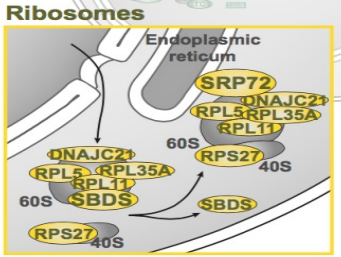
Biological pathways

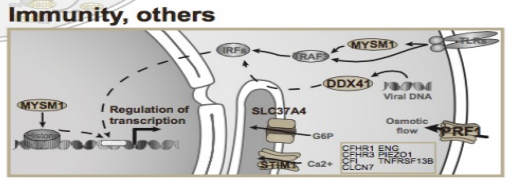












Difference between acquired and inherited aplastic anemia?

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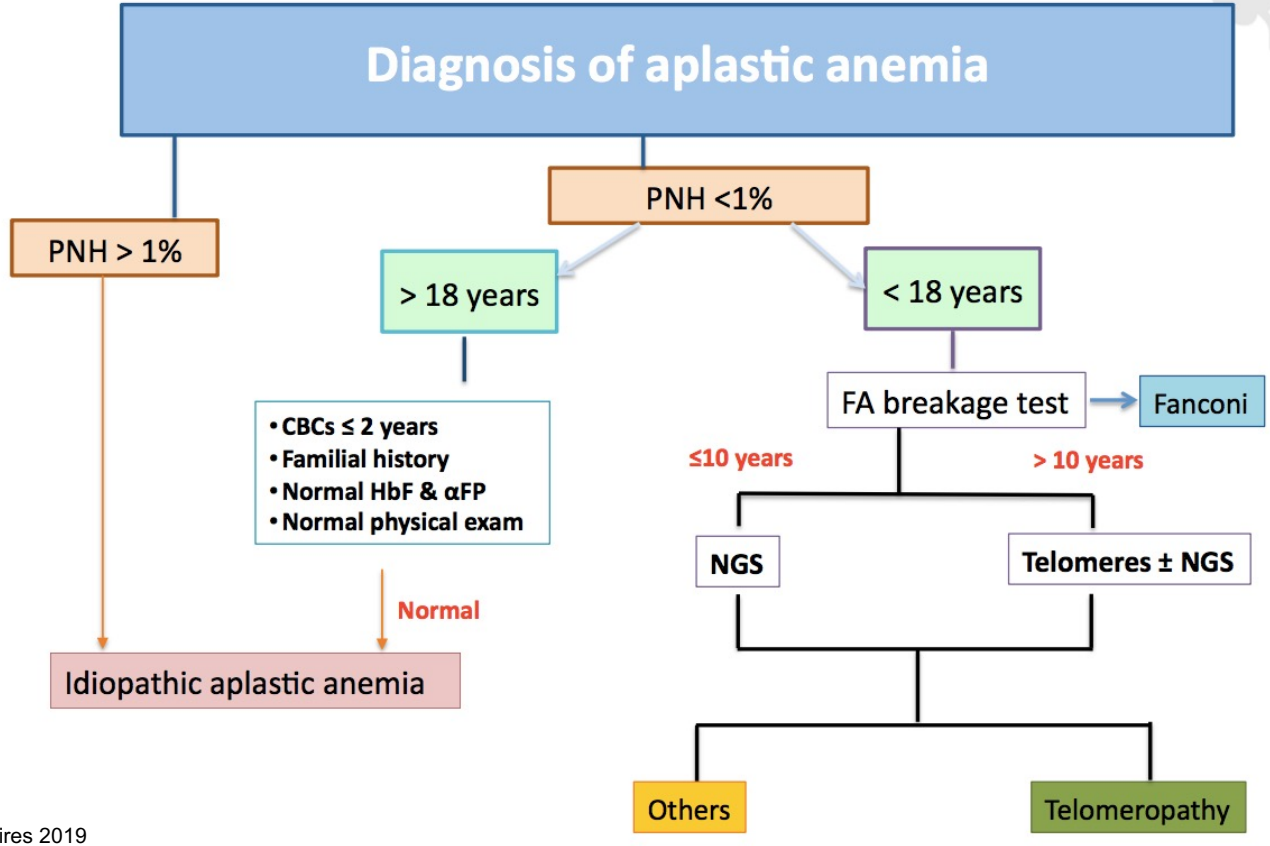

Difference between acquired and inherited aplastic anemia?

Juliette F.

1. This patient has acquired AA, no further testing **False**
2. Sequence telomerase-related genes, looking for mutations **True**
3. Systematic testing for Fanconi Anemia **True**
4. Do whole exome sequencing to rule out inherited forms of AA **+/-**
5. Send the patient for evaluation by a geneticist **False**

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When should we start a treatment?

Juliette F.

Laboratory test	Patient's result	Reference range
Haemoglobin	6.8 g/dL	12–16 g/dL
White blood cell count	0.8×10^9/L	$4.0–10 \times 10^9$/L
Absolute neutrophil count	0.15×10^9/L	$1.4–7.5 \times 10^9$/L
Absolute reticulocyte count	7×10^9/L	$20–80 \times 10^9$/L
Platelet count	7×10^9/L	150–450 x 10^9/L

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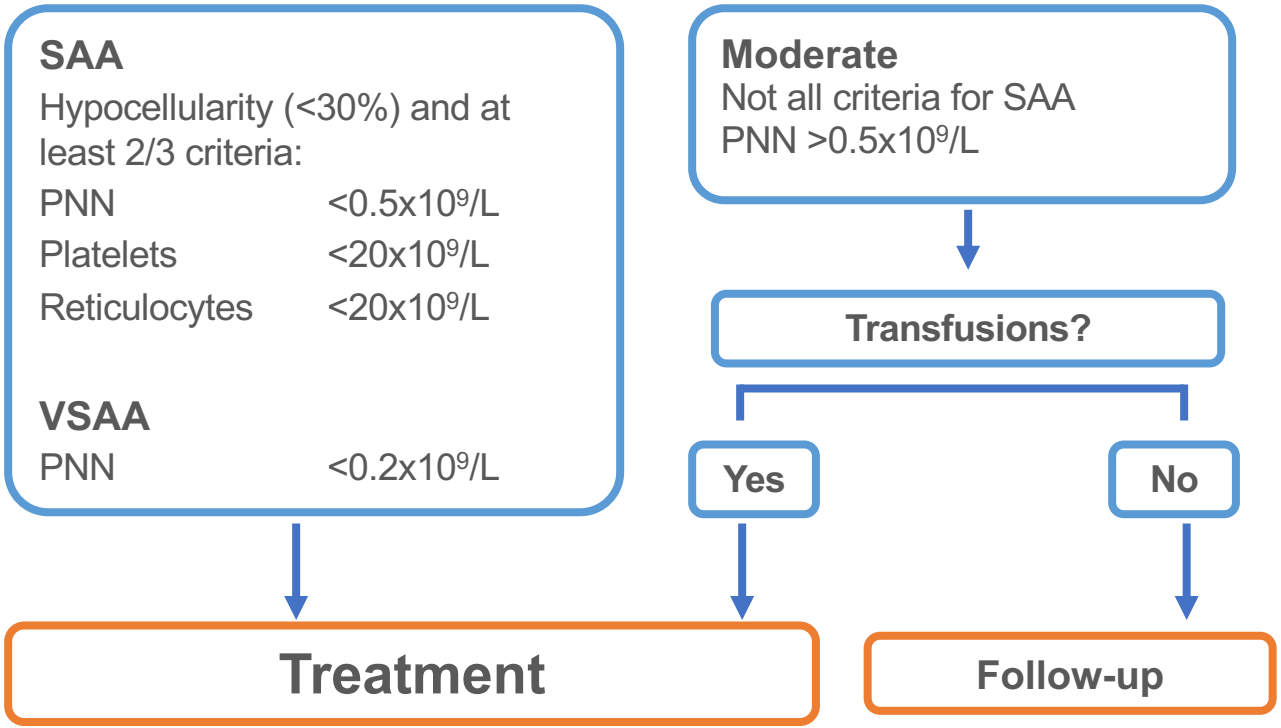
When should we start a treatment?

Aim #3



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

How to treat?

Aim #4

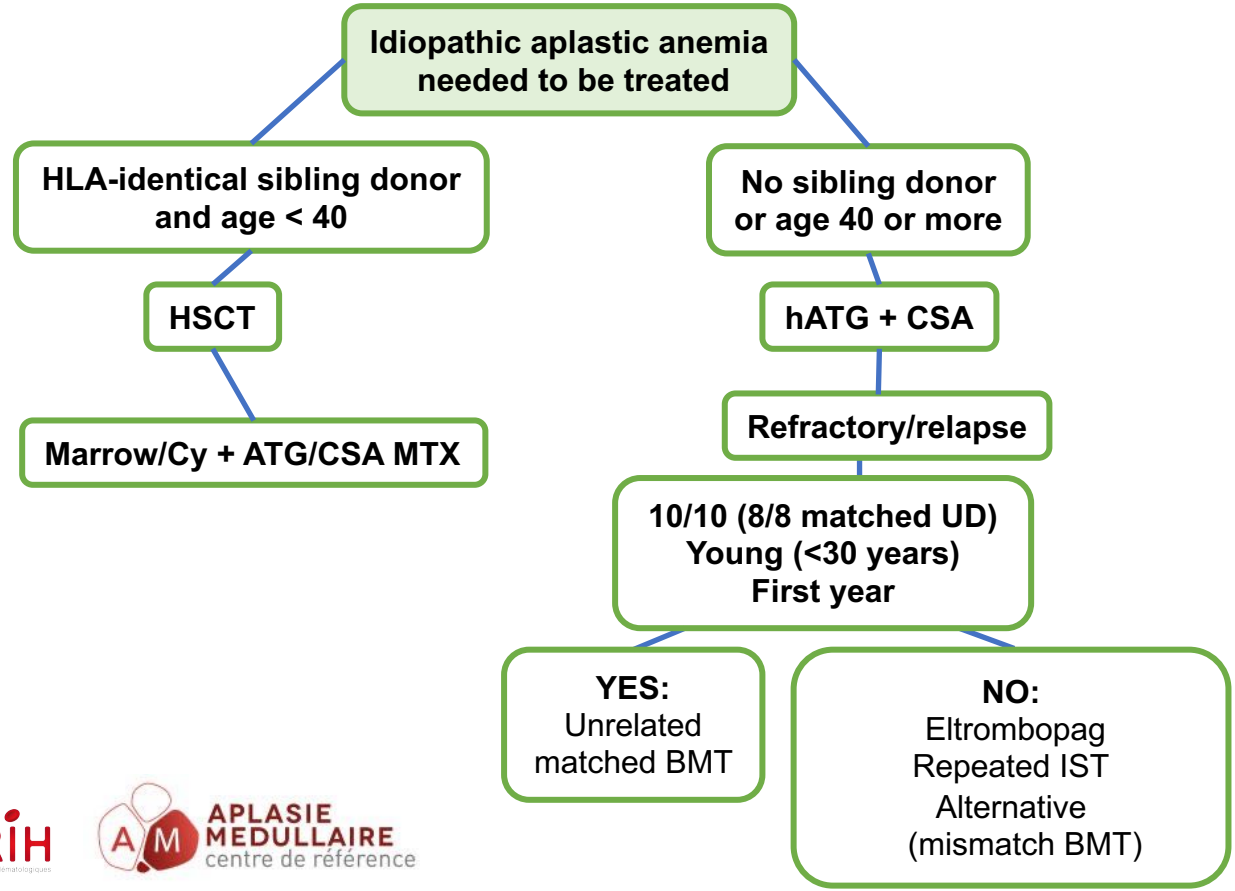
- **Treatment**

  - Idiopathic aplastic anemia: immunosuppressive treatment or transplantation

  - Inherited aplastic anemia: androgens or transplantation

- **Long-term follow-up**
  - Clonal evolution for both causes (MDS, AML)
  - Solid cancer for inherited disorders

Treatment (guidelines)



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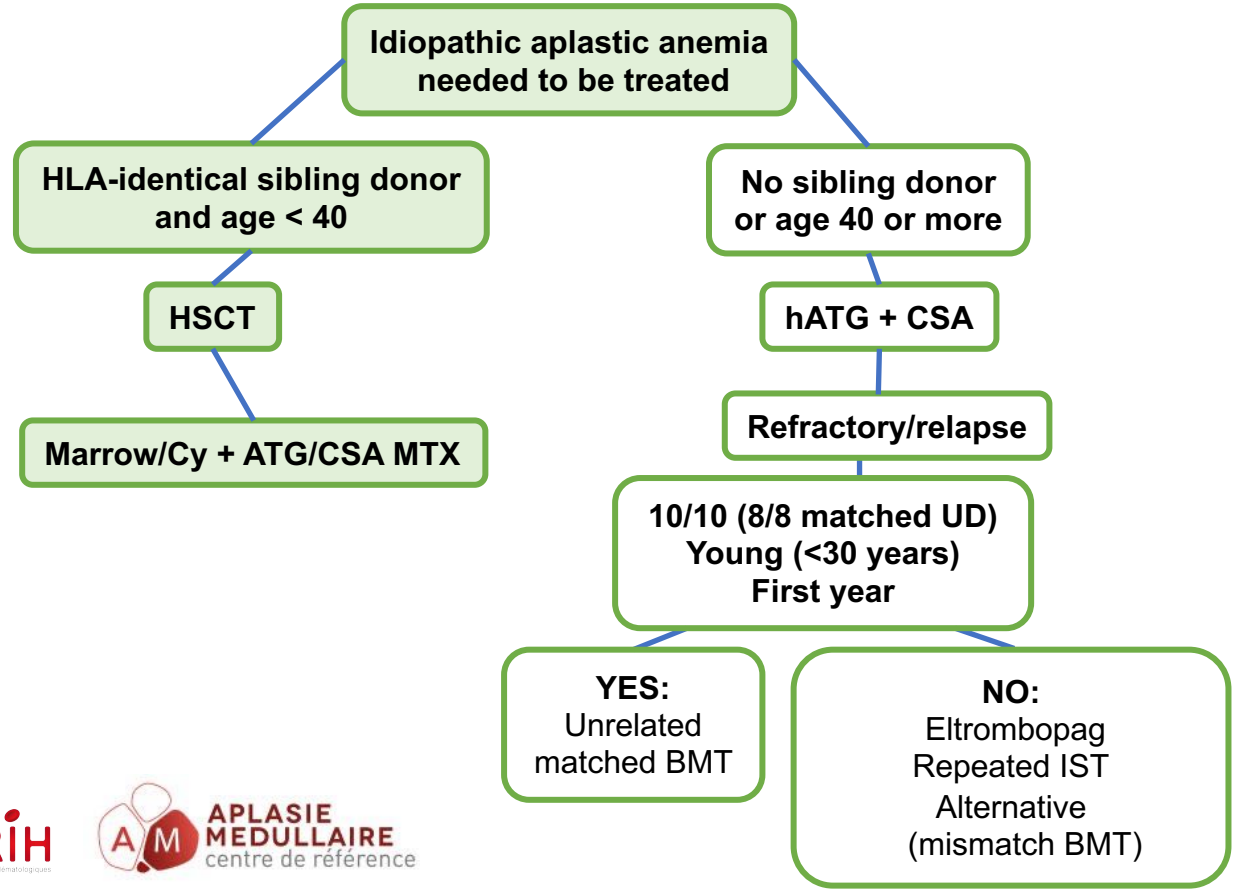
Treatment (guidelines)



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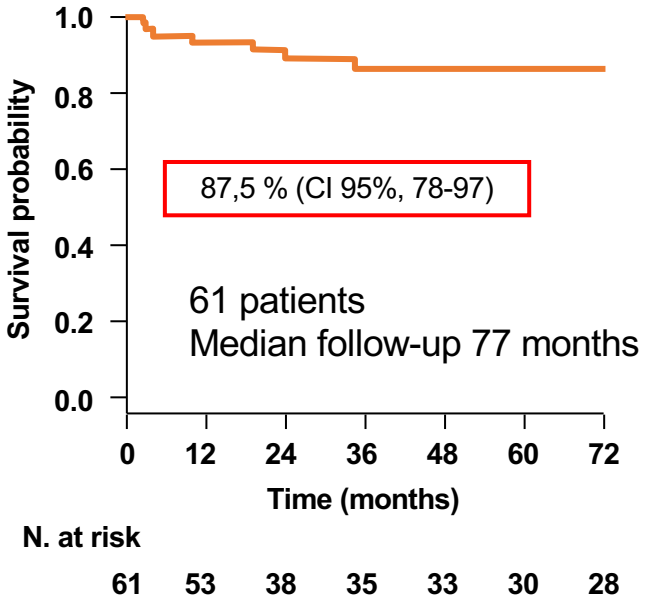
Sibling transplantation

Long-term

Marrow / Cy-ATG / CSA + MTX (standard)
As soon as possible (<100 days)



Event	No of events	6yr-CI (%)
Secondary cancer	1	2 (0-9)
Osteonecrosis	10	21 (10-36)
Cardiovascular complications	1	2 (0-9)
Endocrine dysfunctions	7	19 (9-31)

Saint Louis experience.
Konopacki J, et al. Haematologica. 2012;97:710-6.

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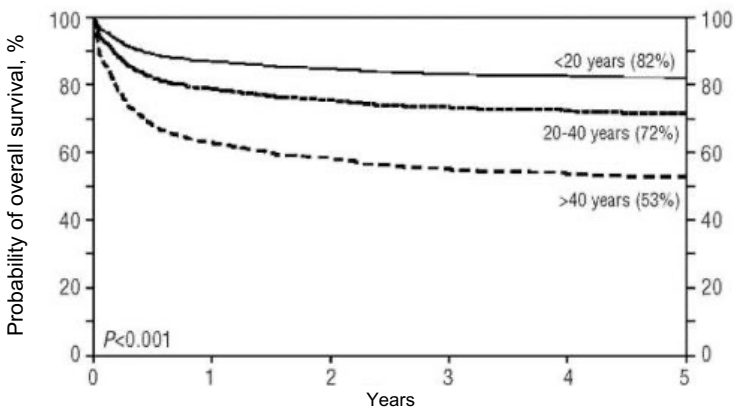
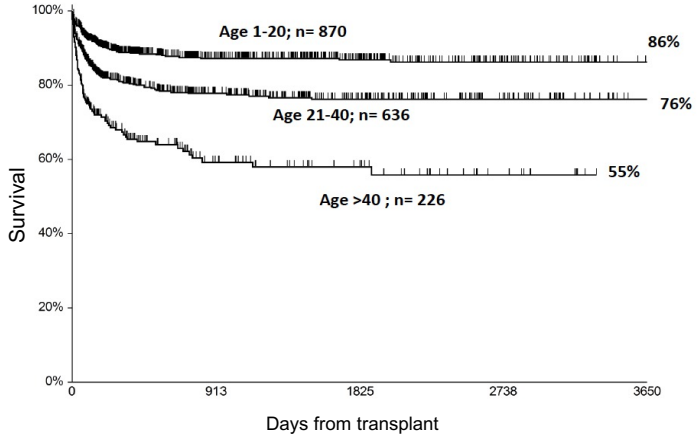
Sibling transplantation

Age

Limitation in 2019





CIBMTR™

2016 EBMT European Society for Blood and Marrow Transplantation

Bacigalupo A. Blood. 2017;129:1428-36. Gupta V, et al. Haematologica. 2010;95:2119-25.

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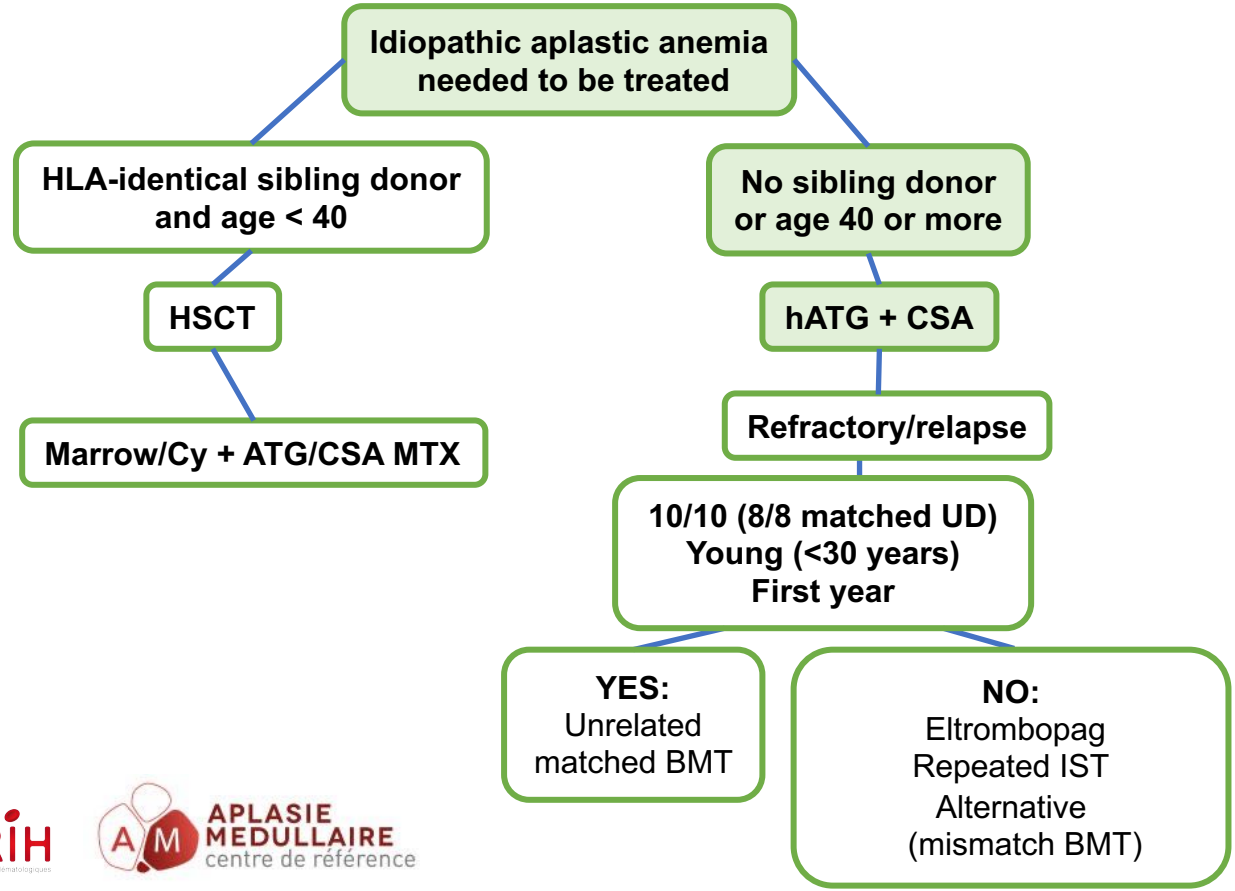
Treatment (guidelines)



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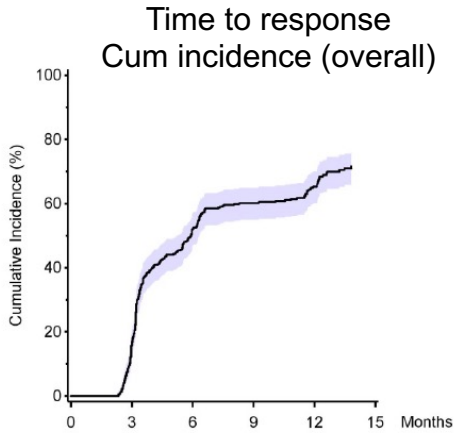
Horse ATG + Cyclosporine

The French experience – response characteristics

- **Response characteristics**
  - **Responders**
    - 40% at months 3 & 60% at months 6



Peffault de Latour R, *et al.* Am J Hematol. 2018;93:635-42.

Horse ATG + Cyclosporine

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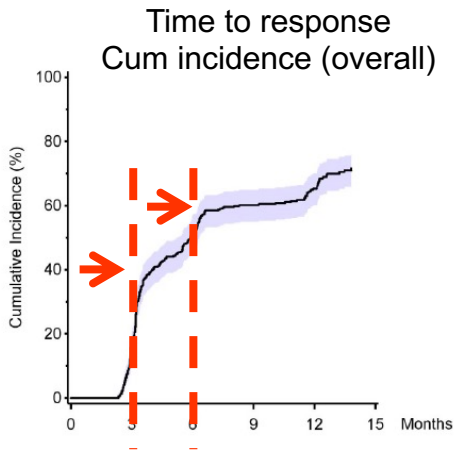

Peffault de Latour R, *et al.* Am J Hematol. 2018;93:635-42.

Horse ATG + Cyclosporine

The French experience – response characteristics

- **Response characteristics**
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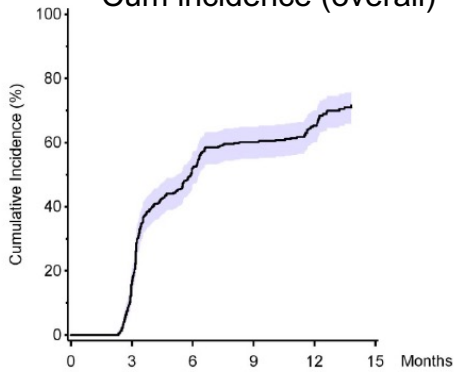
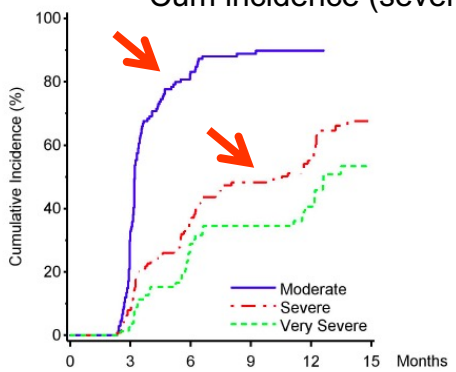
    - 40% at months 3 & 60% at months 6
    - Better & quicker response for patients with moderate aplastic anemia

Time to response
Cum incidence (overall)



Time to response
Cum incidence (severity)



Peffault de Latour R, *et al.* Am J Hematol. 2018;93:635-42.

Horse ATG + Cyclosporine

The French experience – response characteristics

- **Response characteristics**
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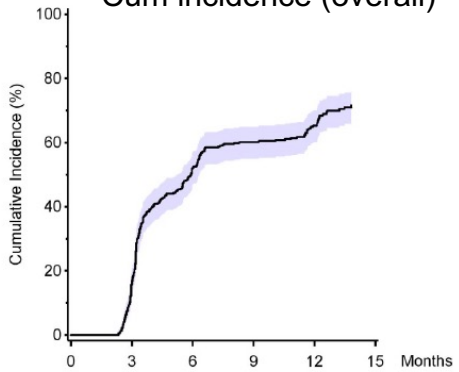
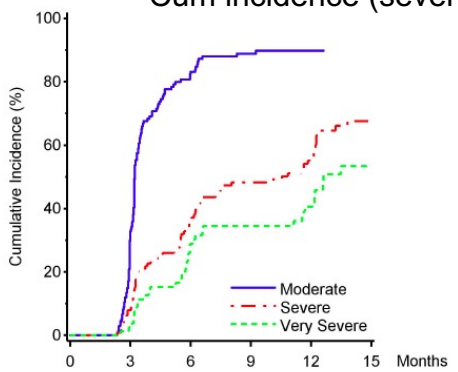
  - **Complete response is exceptional (!)**

Time to response
Cum incidence (overall)



Time to response
Cum incidence (severity)



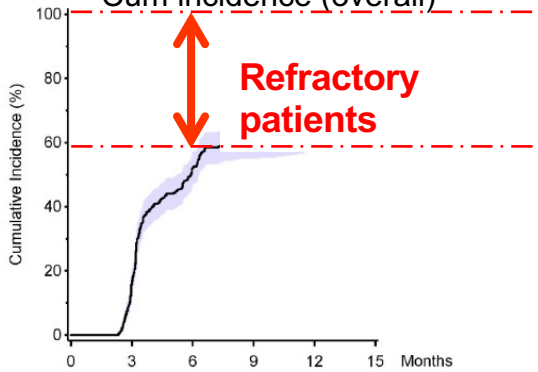
Peffault de Latour R, *et al.* Am J Hematol. 2018;93:635-42.

Horse ATG + Cyclosporine

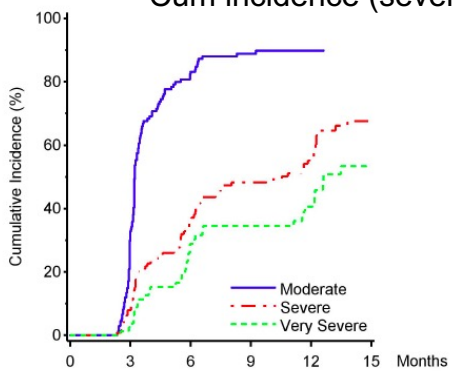
The French experience – response characteristics

- **Response characteristics**
  - **Responders**
    - 40% at months 3 & 60% at months 6
    - Better & quicker response for patients with moderate aplastic anemia
  - **Complete response is exceptional (!)**
  - **Refractory patients (about 30-40%)**

Time to response
Cum incidence (overall)

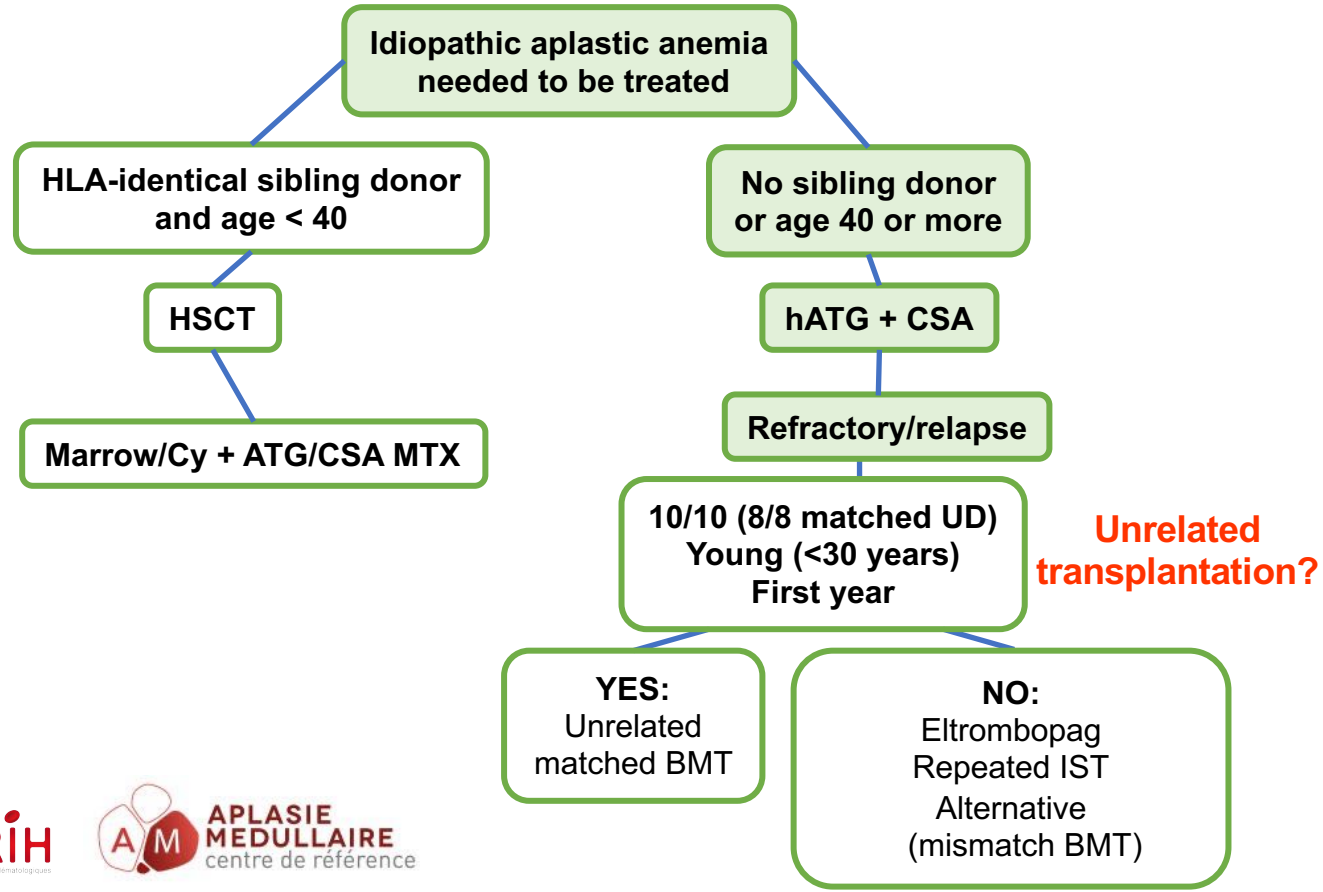


Time to response
Cum incidence (severity)



Peffault de Latour R, *et al.* Am J Hematol. 2018;93:635-42.

Treatment (guidelines)



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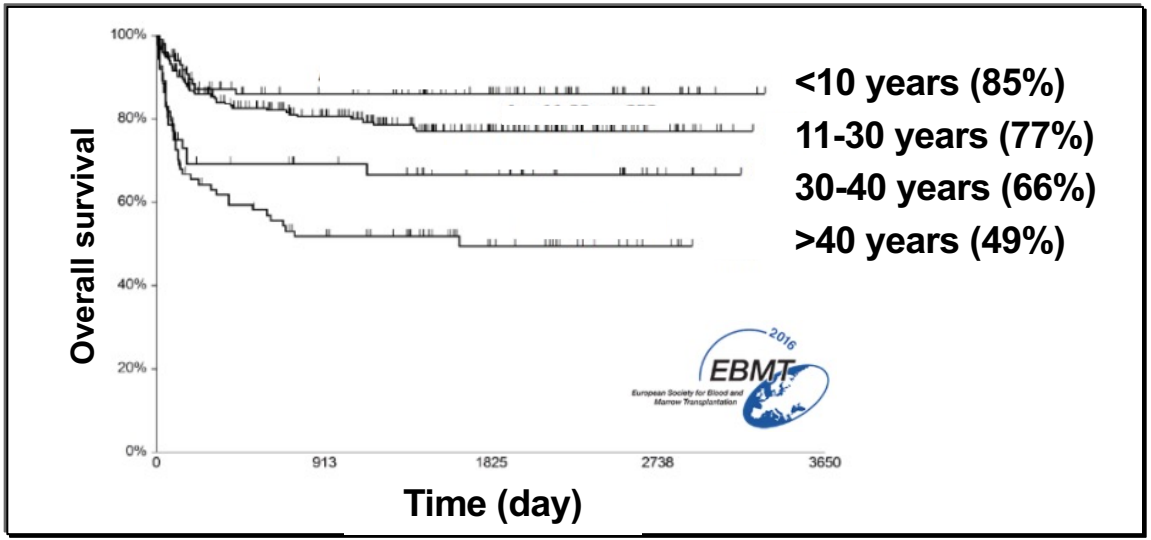
Limitation in 2019

Unrelated transplantation

Guidelines & role of age

Marrow as source of stem cells
In the first year after diagnosis for refractory patients

Flu Cy ATG Low dose TBI (EBMT / BMT CTN / Japan)



Anderlini P *et al*, Lancet Hematol. 2015;2:e367-75. Bacigalupo, Blood 2016 *In press;* Bacigalupo A, *et al.* Haematologica. 2010;95:976-82. Devillier R, *et al.* Haematologica. 2016; 101:884-90. Eapen M, *et al.* Blood. 2011;118:2618-21. Marsh J, *et al.* Blood. 2011;118:2351-7.

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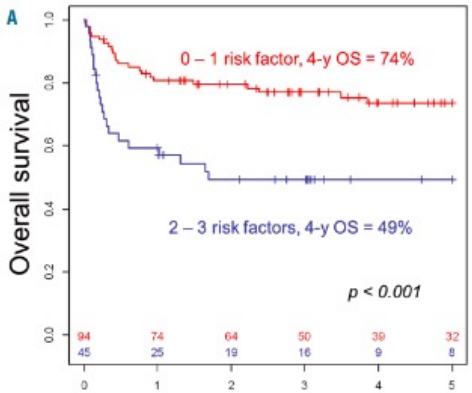
Unrelated transplantation

Decision making process

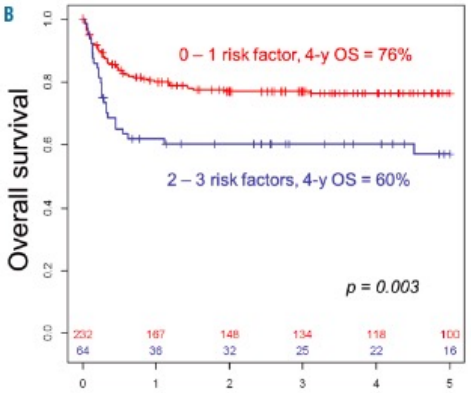
3 Risk factors

- Age (30)
- MUD versus mismatch UD
- BMT in the first year post AA versus after

French cohort (n=131)



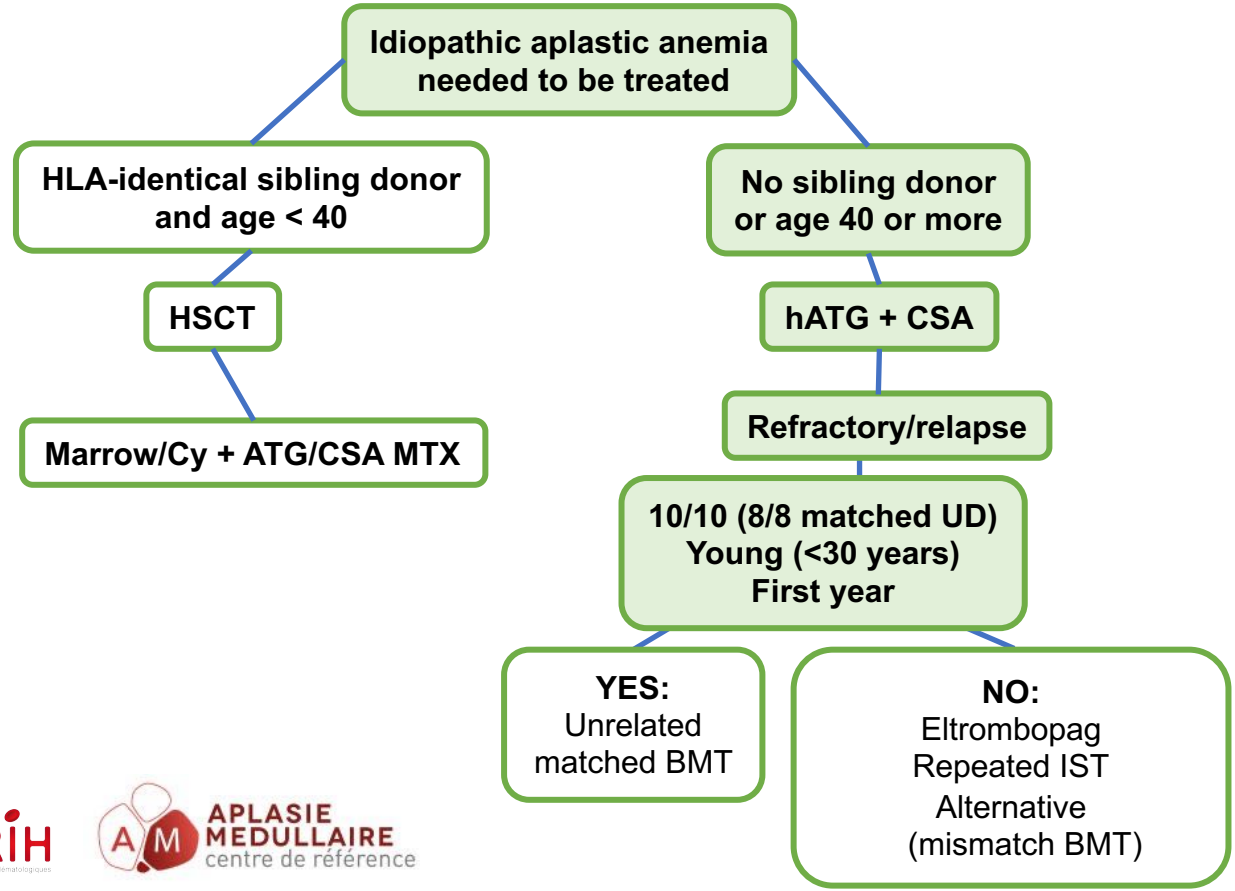
Validation cohort (EBMT) (n=751)



Years post BMT

Bacigalupo, Blood 2016; Devillier R, *et al.* Haematologica. 2016;101:884-90.

Treatment (guidelines)



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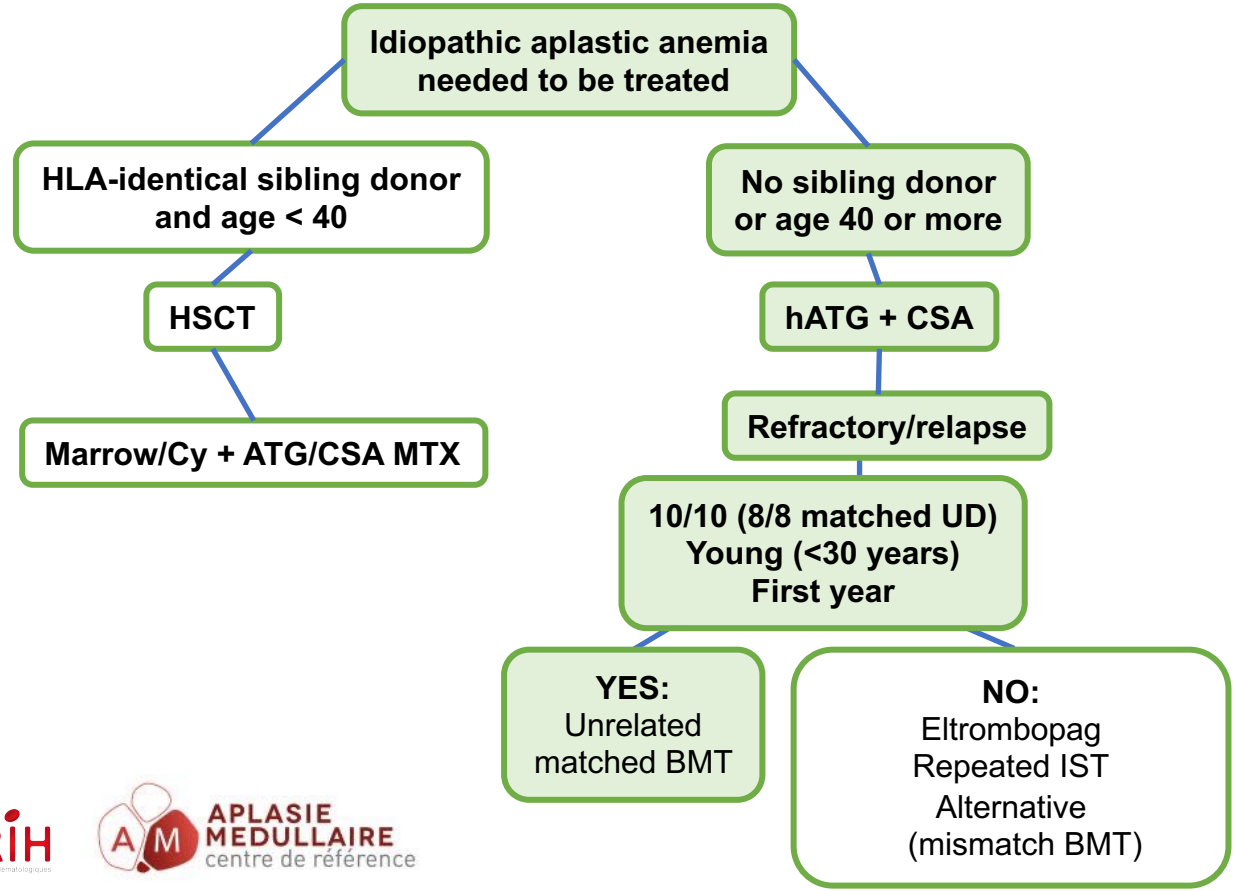
Treatment (guidelines)



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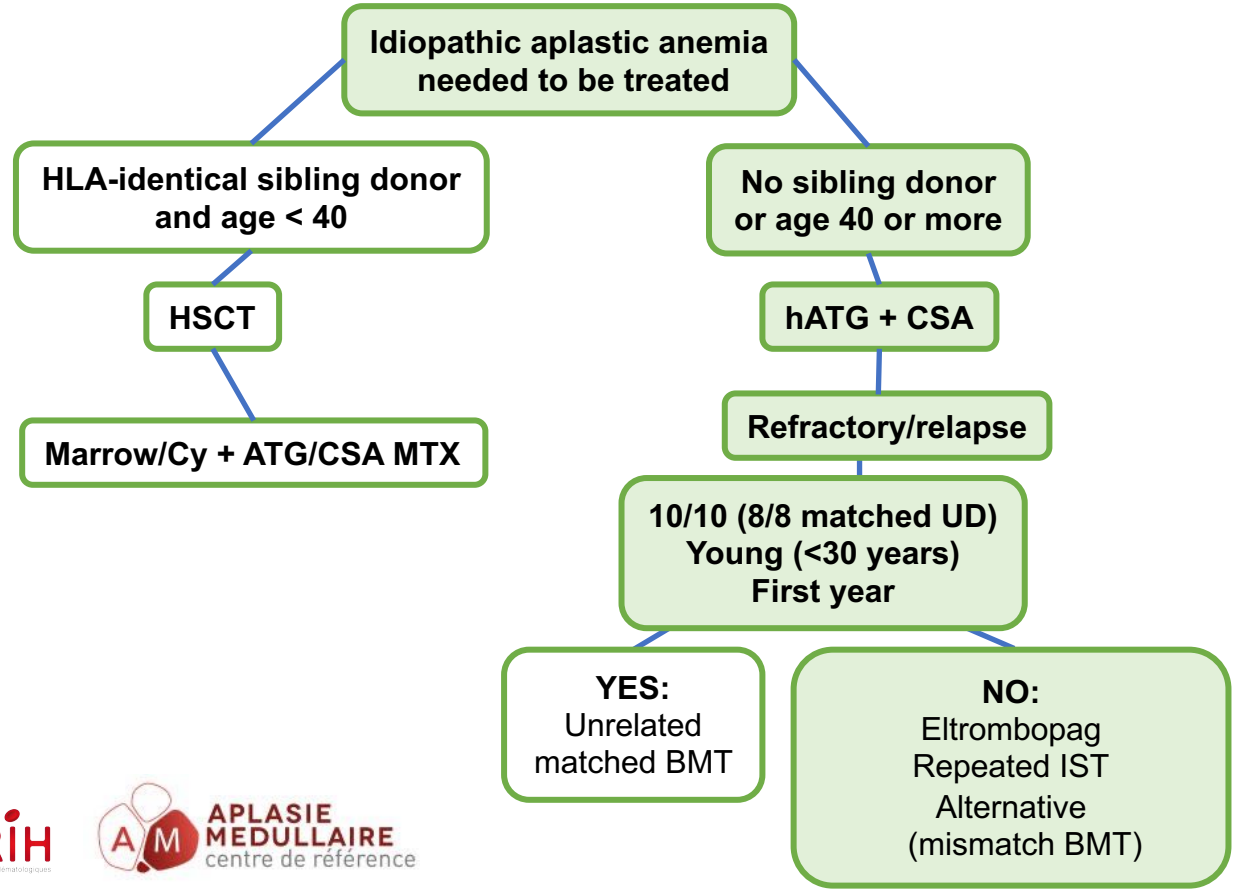
Treatment (guidelines)



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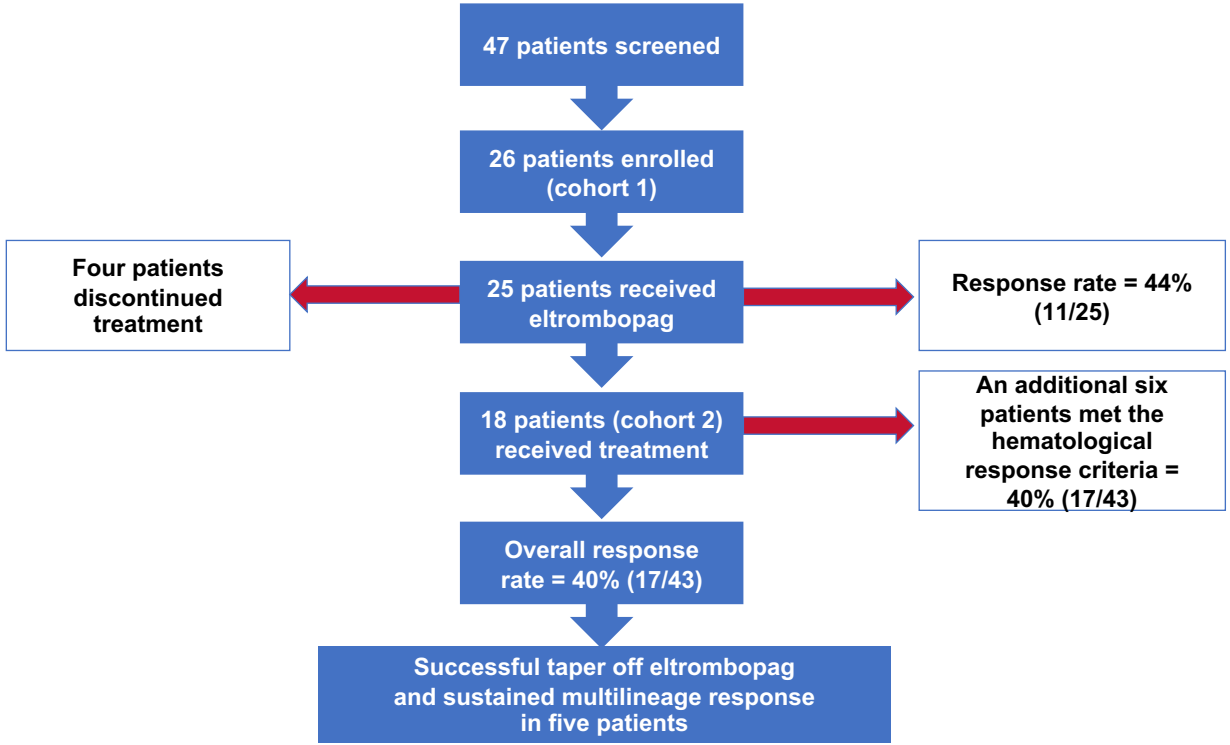
TPO receptor agonist and refractory aplastic anemia

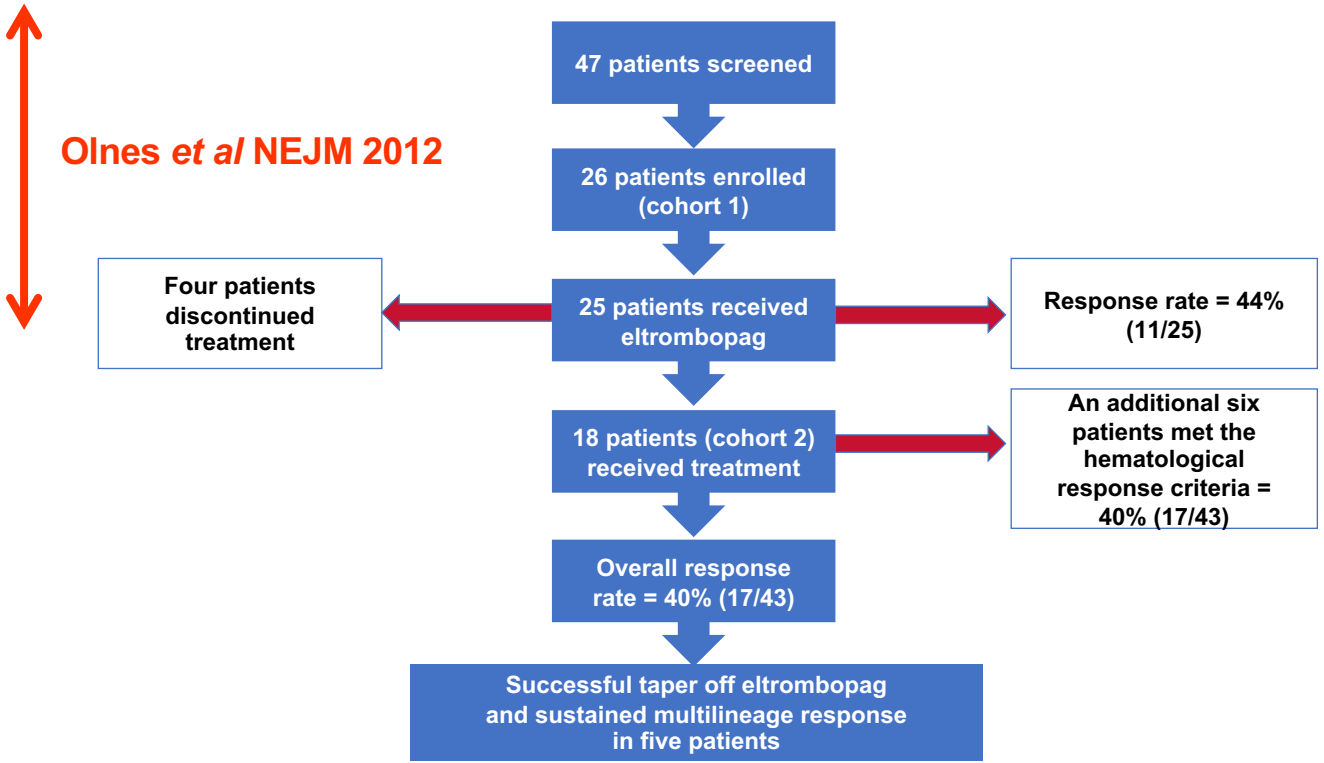
Response rate



Adapted from Olnes M, *et al.* N Engl J Med. 2012;367:11-9. Desmond R, *et al.* Blood. 2014;123:1818-25.

TPO receptor agonist and refractory aplastic anemia

Response rate



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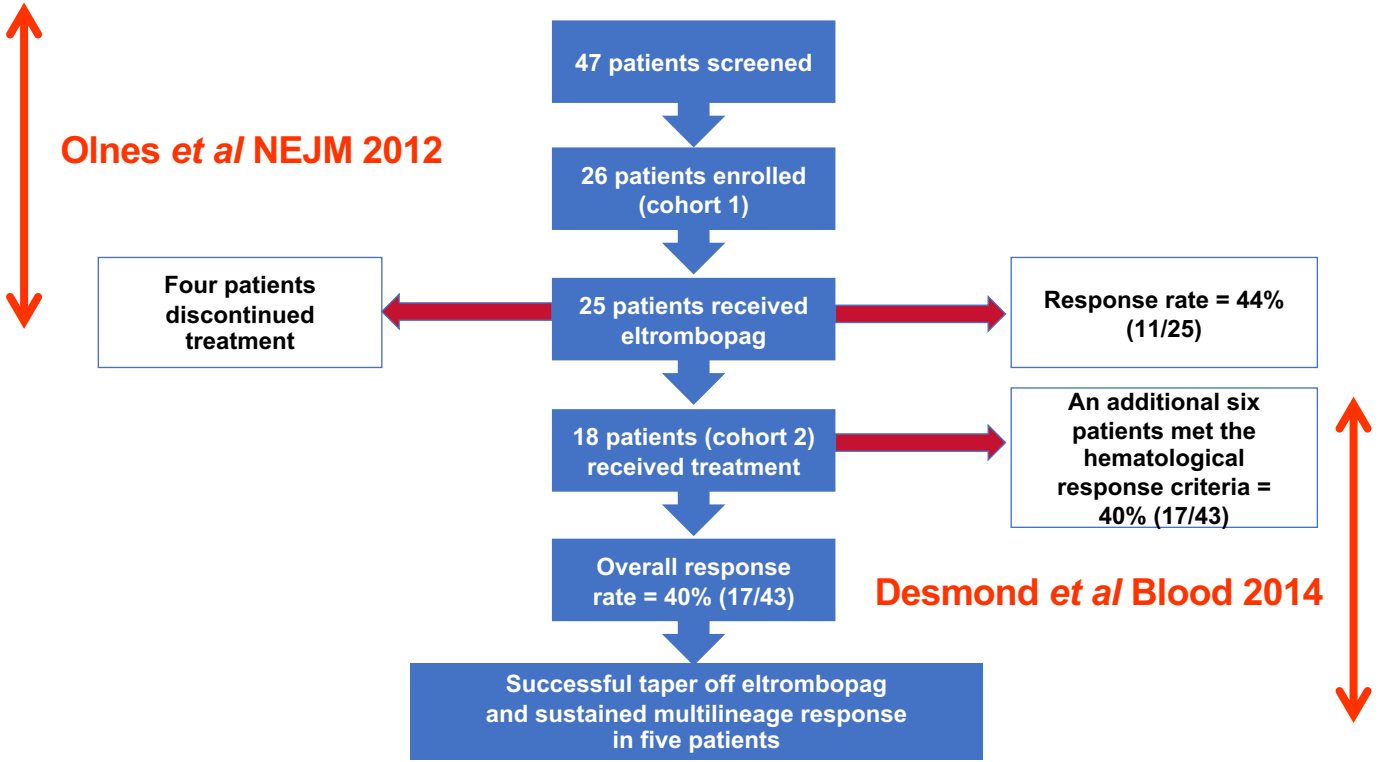
TPO receptor agonist and refractory aplastic anemia

Response rate

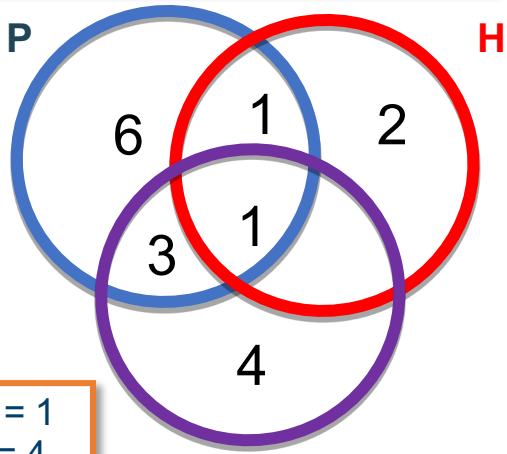


Adapted from Olnes M, *et al.* N Engl J Med. 2012;367:11-9. Desmond R, *et al.* Blood. 2014;123:1818-25.

Phase II study of eltrombopag in refractory AA

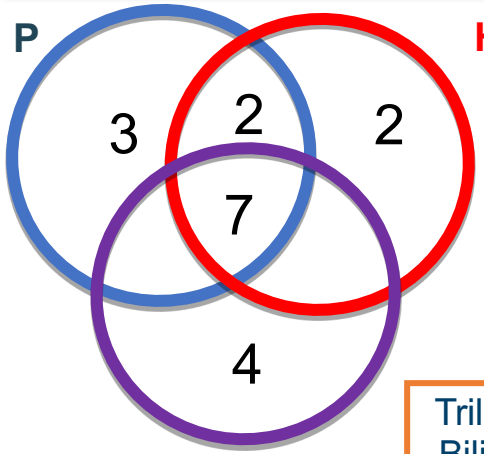
Mutlilineage responses

16 Weeks – primary endpoint



Trilineage = 1
Bilineage = 4
Unilinege = 12

Best response at follow-up



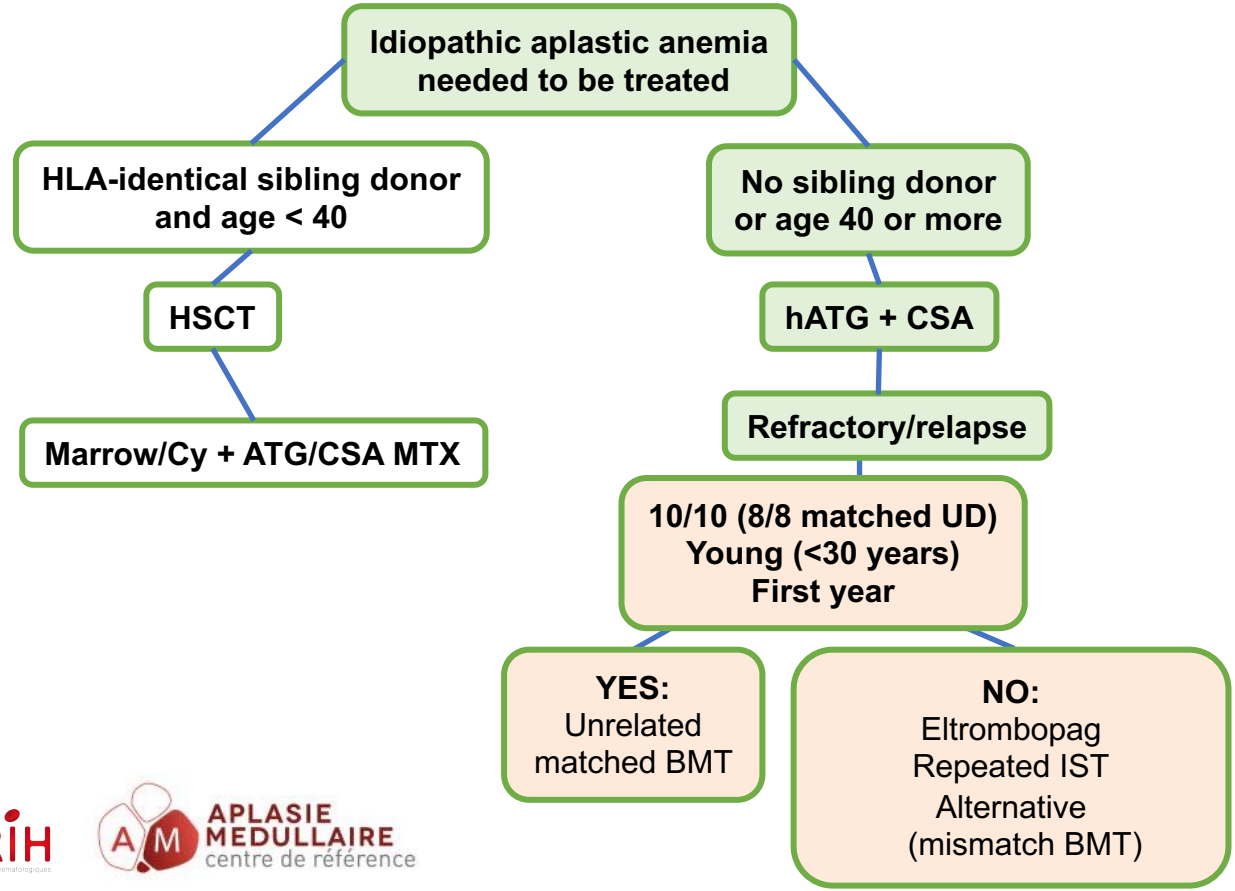
Trilineage = 7
Bilineage = 2
Unilinege = 9

Platelets
Hemoglobin
Neutrophils

Durable multilineage responses are possible after treatment with eltrombopag in refractory AA
Patients can become red blood cell and platelet transfusion independent

AA, aplastic anemia.
Desmond R, *et al.* Blood. 2014;123:1818-25.

Treatment (guidelines)



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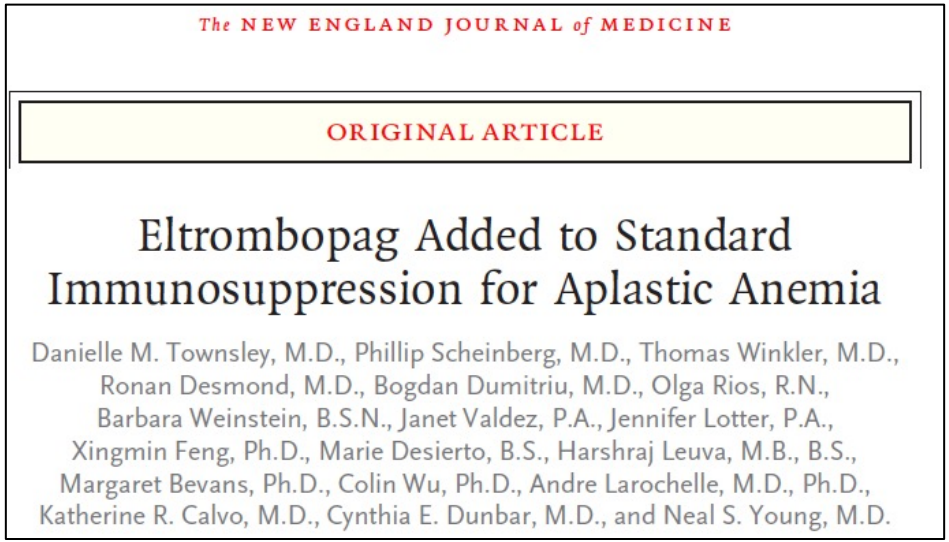
Perspectives – eltrombopag first line

Naive patients *clinicaltrials.gov NCT01623167*

- **Phase II study**
  - Horse ATG + Cyclosporine + eltrombopag
  - Responders 86%; complete response 37% (6 months)



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.

Townsley DM, et al. N Engl J Med. 2017;376:1540-50.

April 2017

Perspectives – eltrombopag first line

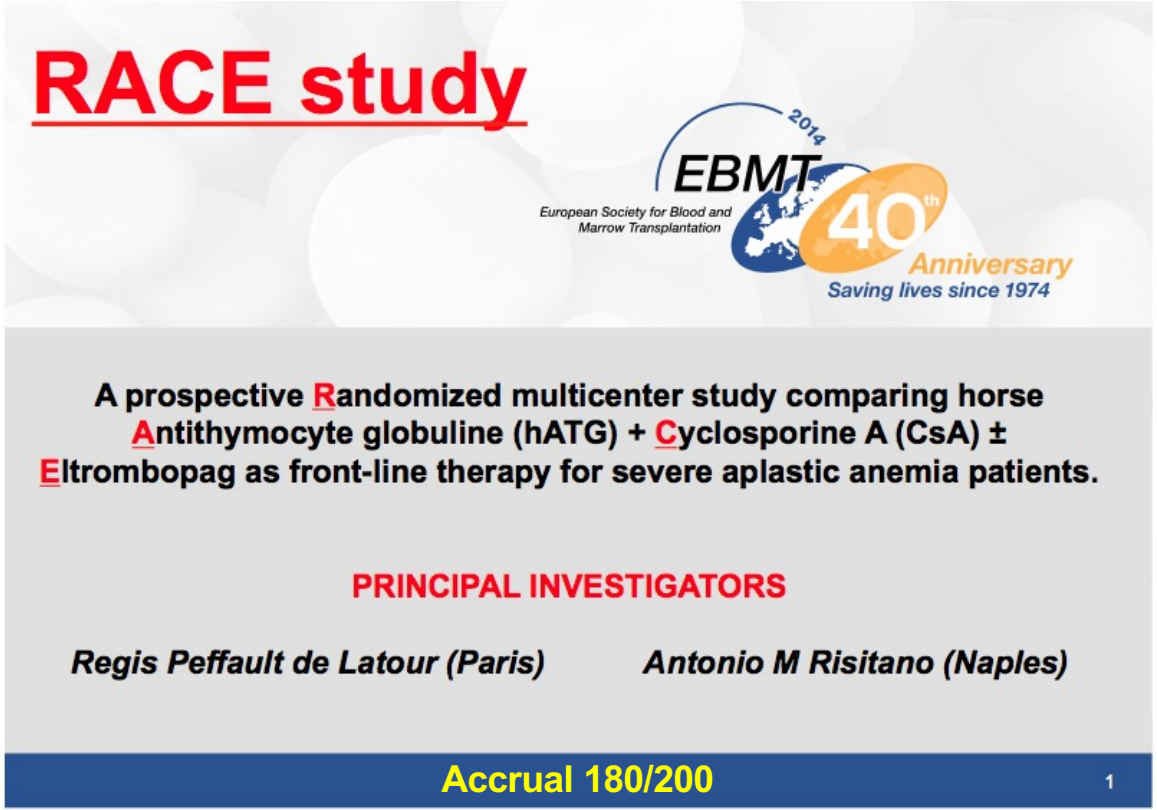
Naive patients *clinicaltrials.gov NCT01623167*

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	All Cohorts N=92
	N (%)	N (%)	N (%)	**N (%)**
3 months				**86/92**
OR	23 (77)	24 (77)	23/25 (92)	**70 (81)**
CR	5 (17)	8 (26)	11/25 (44)	**24 (28)**
6 months				**81/92**
OR	24 (80)	27 (87)	19/20 (95)	**70 (86)**
CR	10 (33)	8 (26)	12/20 (60)	**30 (37)**

April 2017

Perspectives – eltrombopag first line

Naive patients *clinicaltrials.gov NCT02099747*



Mise au point sur l'aplasie médullaire

Conclusion

- **Diagnosis of aplastic anemia? Biopsy**
- **How make the difference between acquired (idiopathic) and inherited aplastic anemia?**
  - Clinic – **personal and familial history**
  - Biology – **PNH – HbF/alpha FP/ Immune deficiency – FA/Telomeres – Gene screening**
- **When should we start a treatment?**
  - Criteria for treatment **SAA or moderate AA with transfusions**
- **How to treat?**
  - Immunosuppressive therapy versus transplantation

Thank you!

The French Reference Center for aplastic anemia and PNH in Paris

Saint-Louis Hospital

Robert Debré Hospital

Institute of Hematology, IUH St-Louis

F Sicre, T Leblanc, A Baruchel, G Socié (clinic)
N Vasquez, W. Cuccuini, J Soulier (Fanconi Team),
C Kannengiesser, E Lainey, L Da Costa (Telomeres team)

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SFGM TC
Société Francophone de GREFFE DE MOELLE et de Thérapie Cellulaire

2016 EBMT
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