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# Management of idiopathic aplastic anemia in 2018

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**Régis Peffault de Latour, MD, PhD**

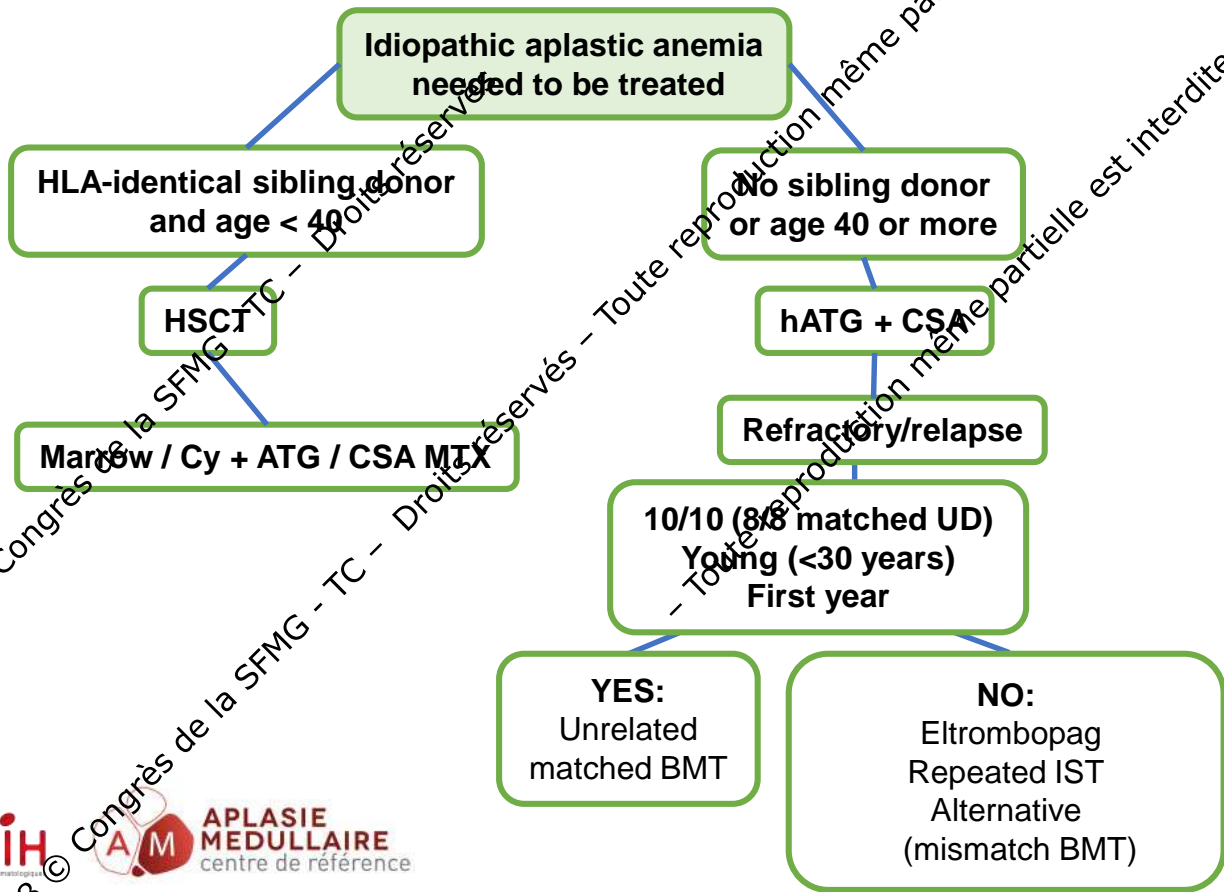
French reference center for aplastic anemia & PNH

French network for rare immunological & hematological disorders (MaRIH)

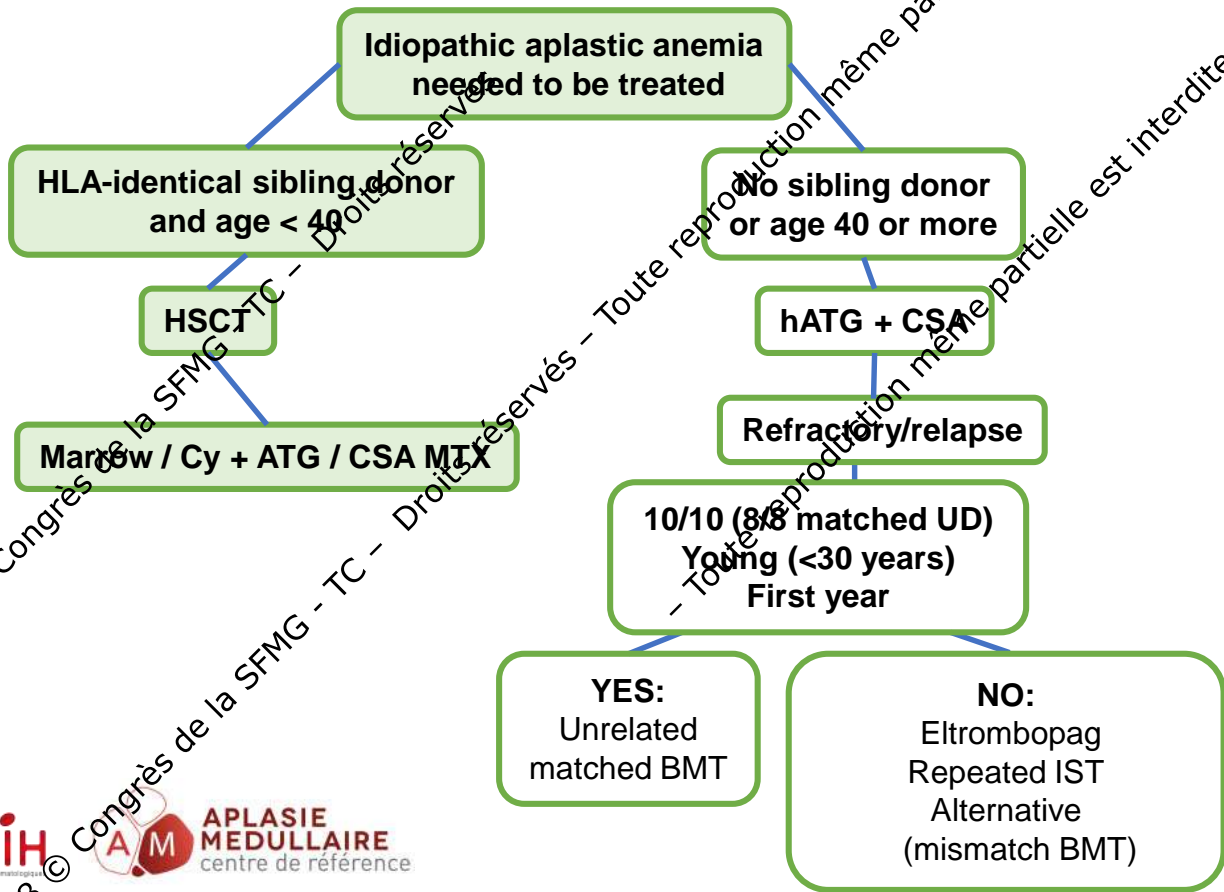
Severe aplastic anemia working party of EBMT (SAAWP EBMT)

Hôpital Saint-Louis, Paris, France

# Treatment (guidelines)



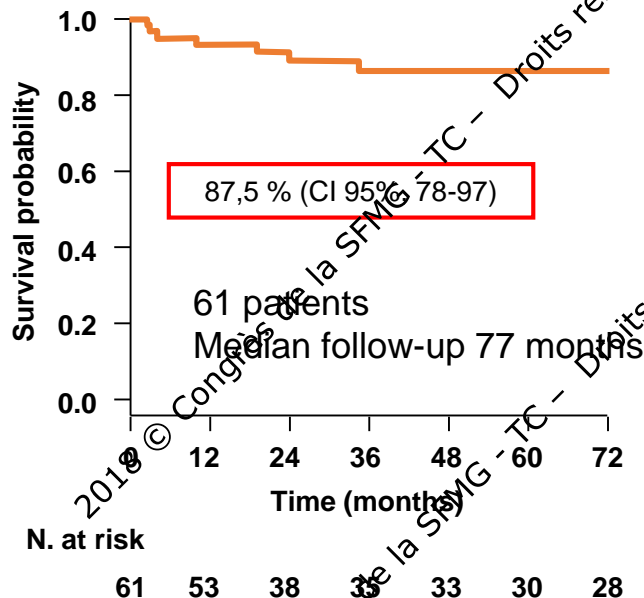
# Treatment (guidelines)



# Sibling transplantation

## Long-term

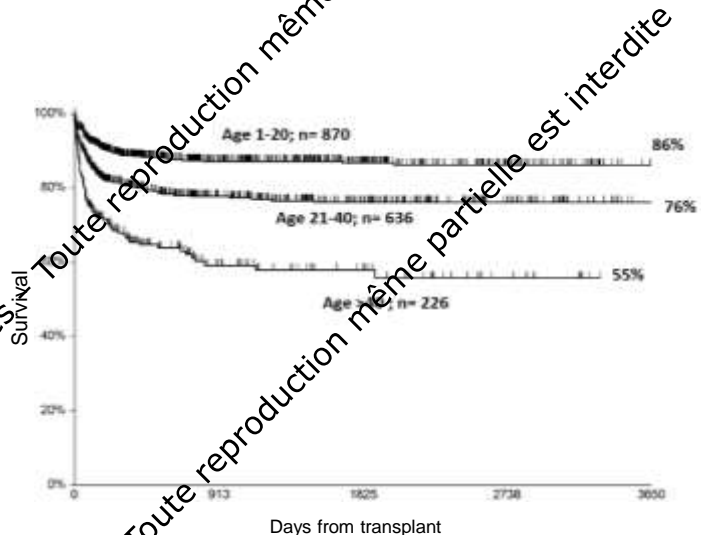
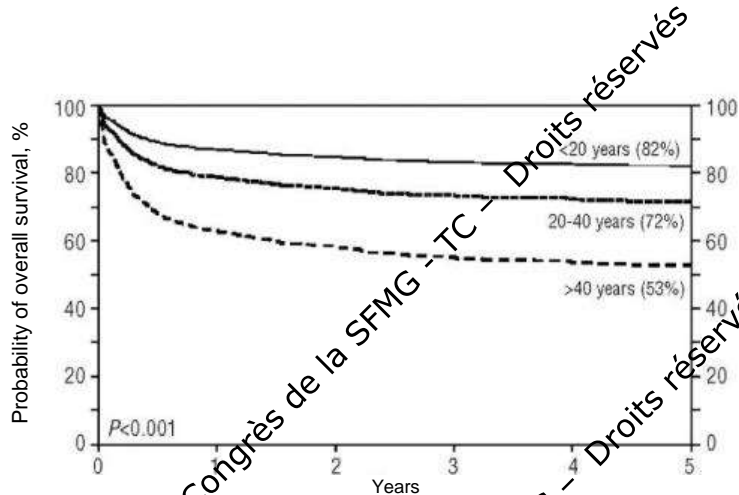
Marrow / Cy-ATG / CSA + MTX (standard)  
As soon as possible (<100 days)



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)

# Sibling transplantation

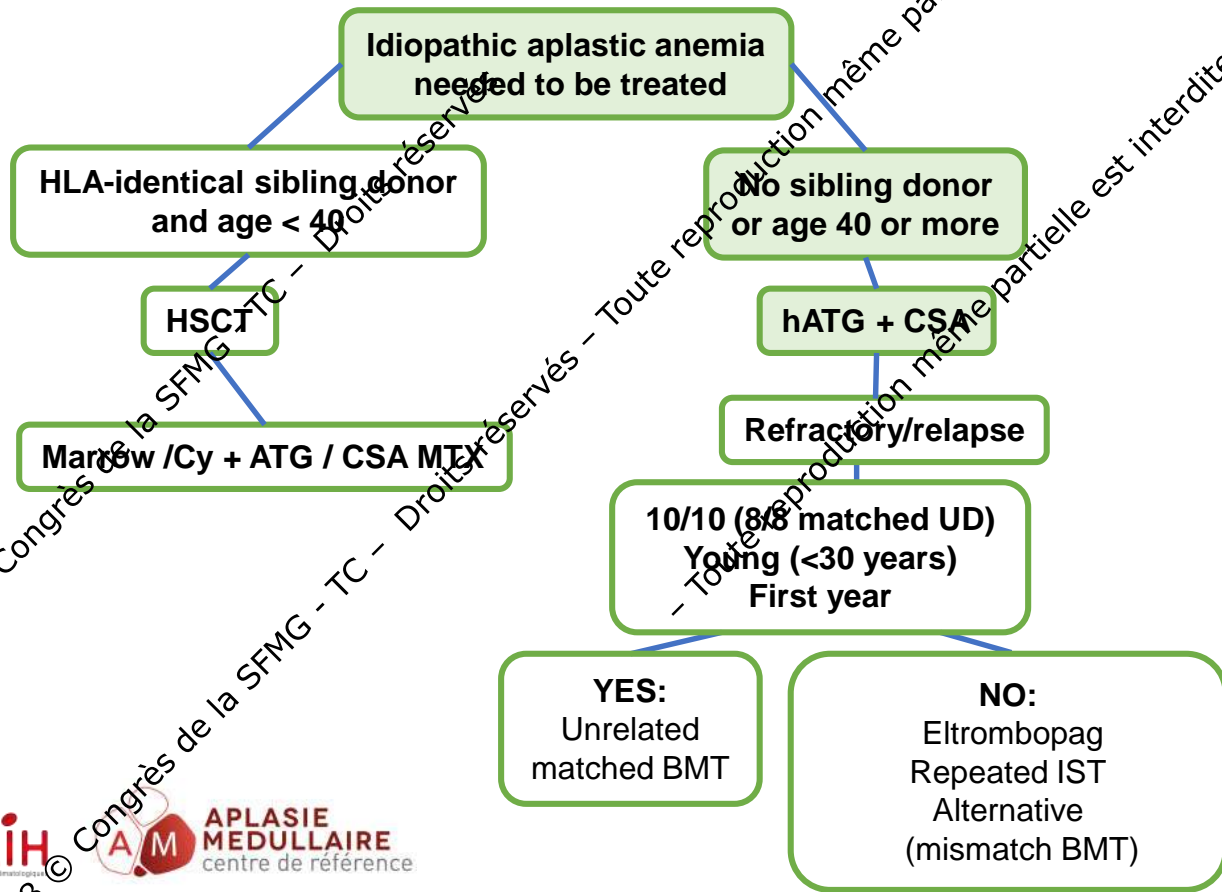
## Age is still a limitation



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- Toute reproduction même partielle est interdite

# Treatment (guidelines)



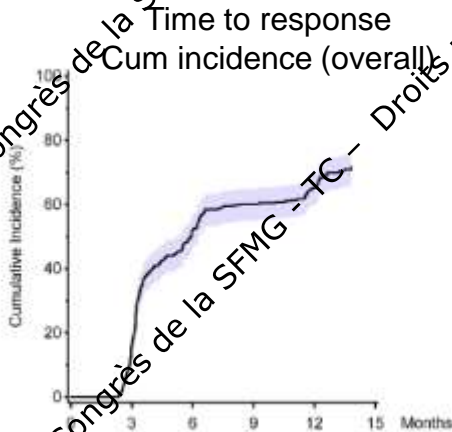
# Horse ATG + Cyclosporine

## The French experience – response characteristics

- **Response characteristics**

- **Responders**

- 40% at months 3 & 60% at months 6



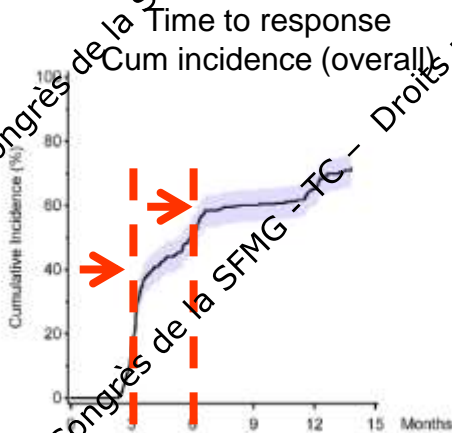
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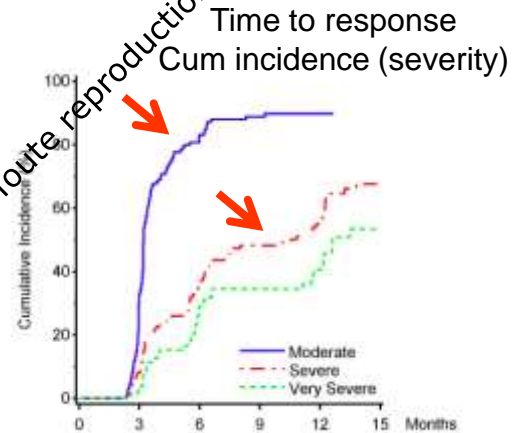
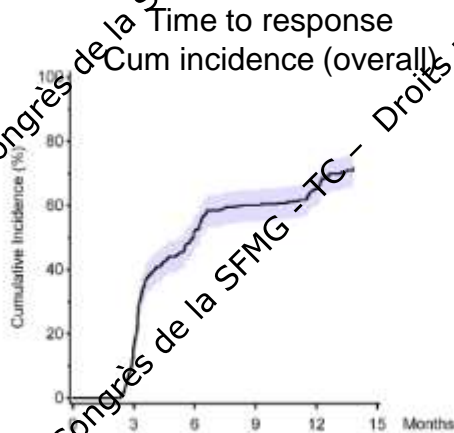
# Horse ATG + Cyclosporine

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    - Better & quicker response for patients with moderate aplastic anemia



# Horse ATG + Cyclosporine

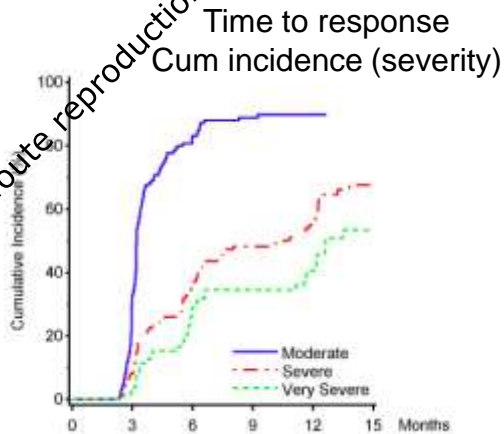
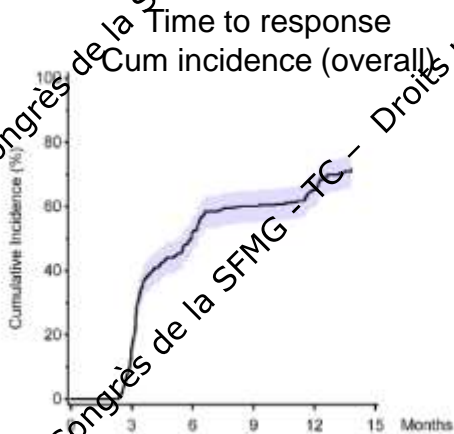
## The French experience – response characteristics

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



# Horse ATG + Cyclosporine

## The French experience – response characteristics

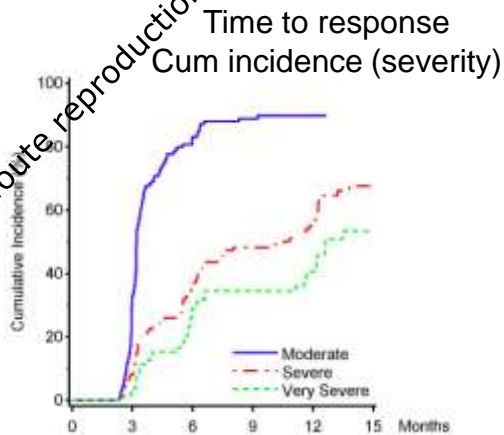
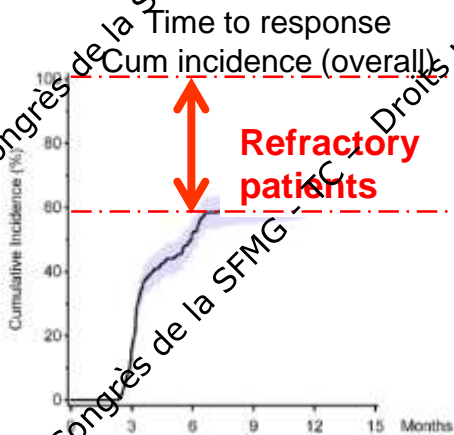
- **Response characteristics**

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

- **Refractory patients (about 30-40%)**



# Any progress since 40 years?

## Anti-thymocyte globuline

- Add androgens to ATG
  - No increase in response rate (Champlin, Blood 1985)
- Add to or replace ATG with megadose corticosteroids
  - No increase in response; high toxicity (Marmontl, Prog Clin Biol Res 1984)
- Replace ATG with high dose cyclophosphamide
  - Toxicity (Tisdale, Lancet 2001; Blood 2002)
- Replace ATG with moderate dose cyclophosphamide
  - Excessive toxicity secondary to neutropenia (Scheinberg, Blood 2014)
- Add mycophenolate mofetil to ATG/CsA
  - No improvement in response/survival (Scheinberg, Br J Haematol 2006)
- Add sirolimus to ATG/CsA
  - No improvement in response/survival (Scheinberg, Haematologica 2009)
- Add G-CSF to ATG/CsA
  - No improvement in response/survival (Locasciulli, Haematologica 2004)
- Prolonged CsA (2 years) to prevent relapse
  - Delayed but ultimately equivalent rate (Scheinberg, Am J Hematol 2014)

# Horse ATG + Cyclosporine

## The French experience – response characteristics

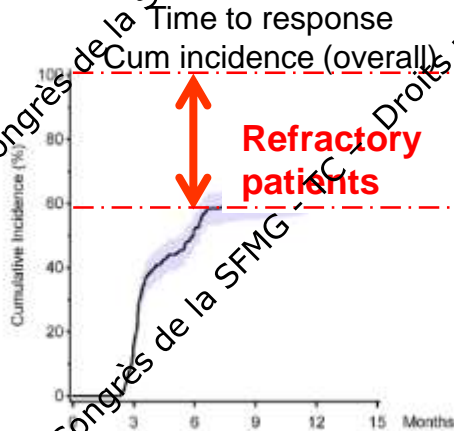
- **Response characteristics**

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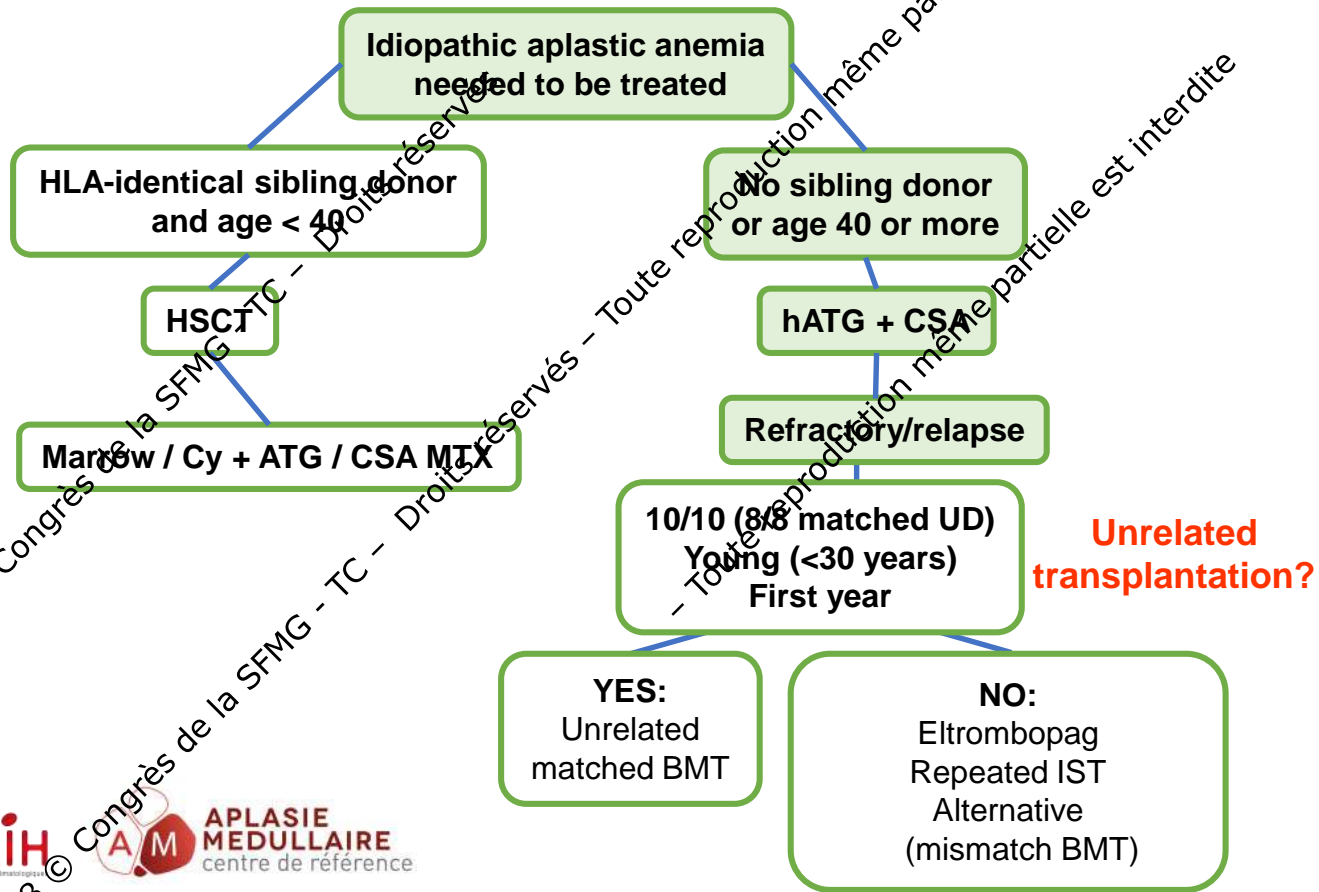
- **Complete response is exceptional (!)**

- **Refractory patients (about 30-40%)**



- **Refractory patients = 2 questions:**
  - Is it really acquired?
  - Clonal evolution?

# Treatment (guidelines)



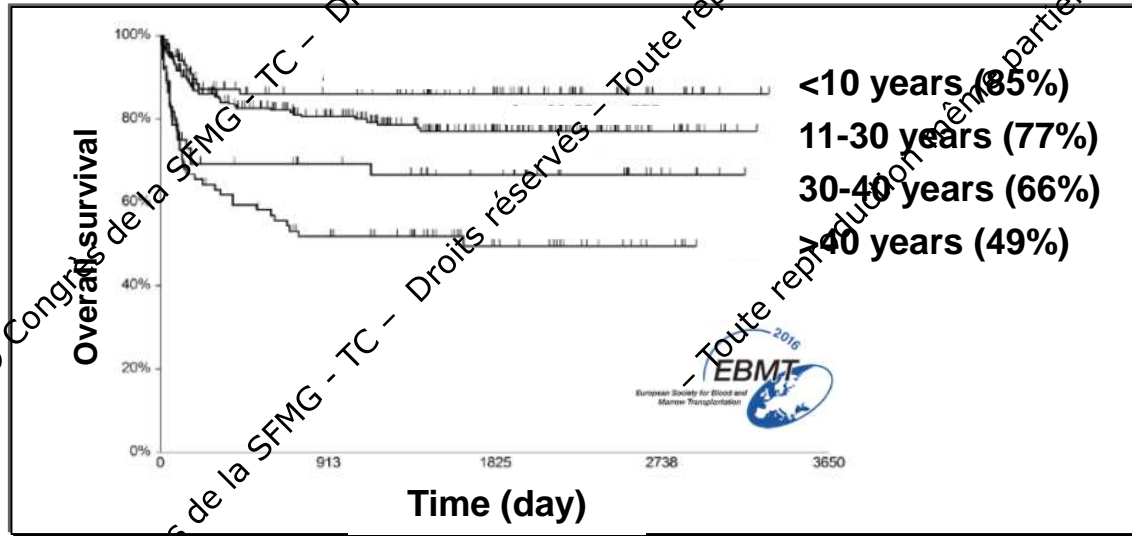
# Unrelated transplantation

## 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)

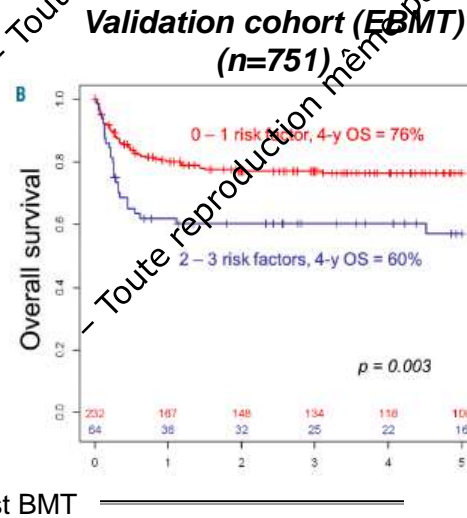
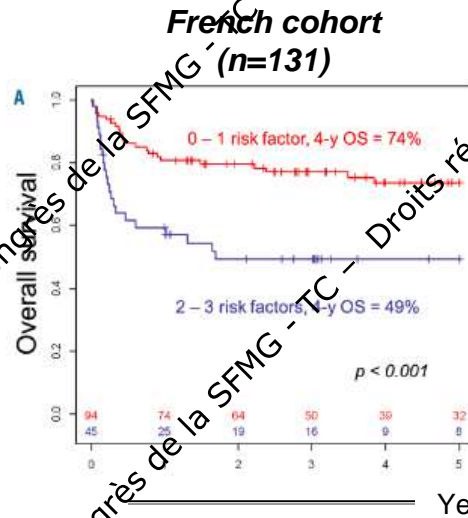


# Unrelated transplantation

## Decision making process

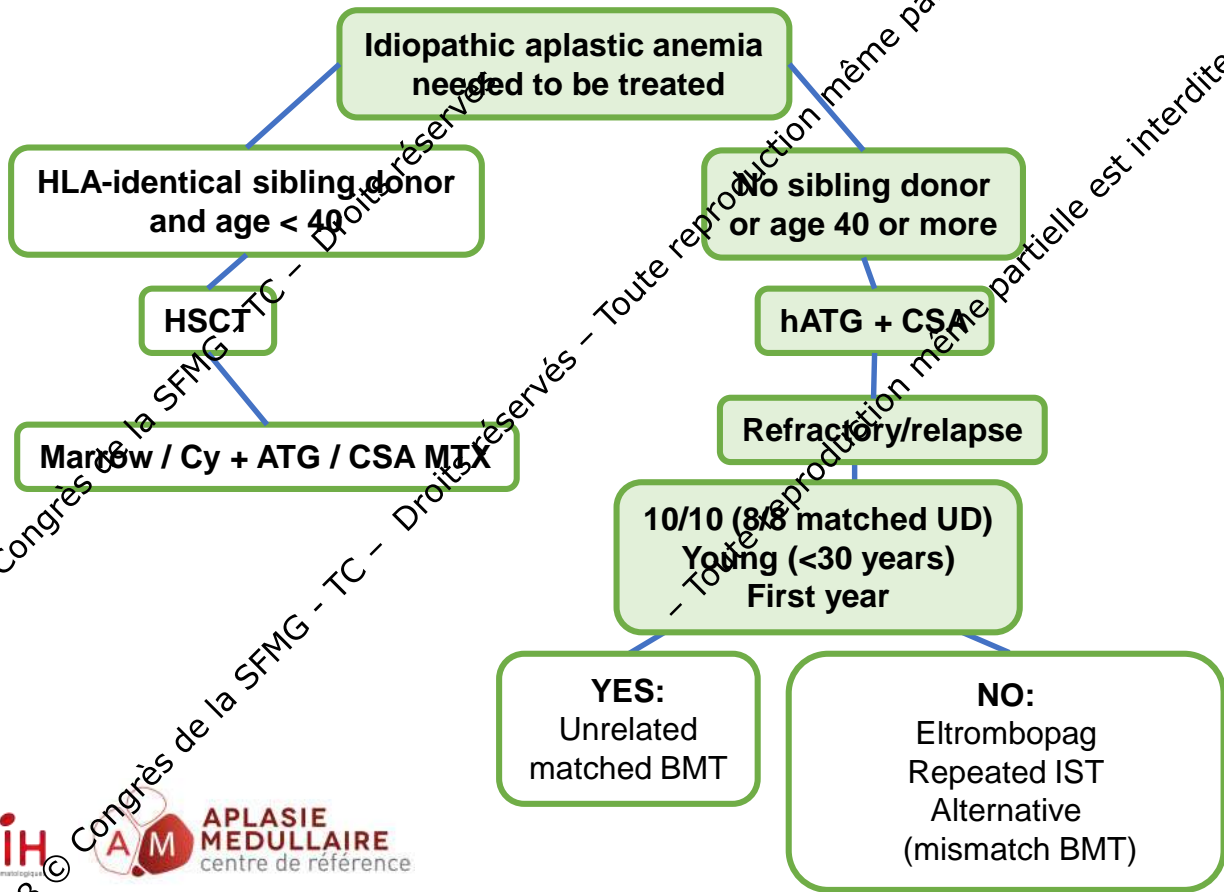
### 3 Risk factors

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

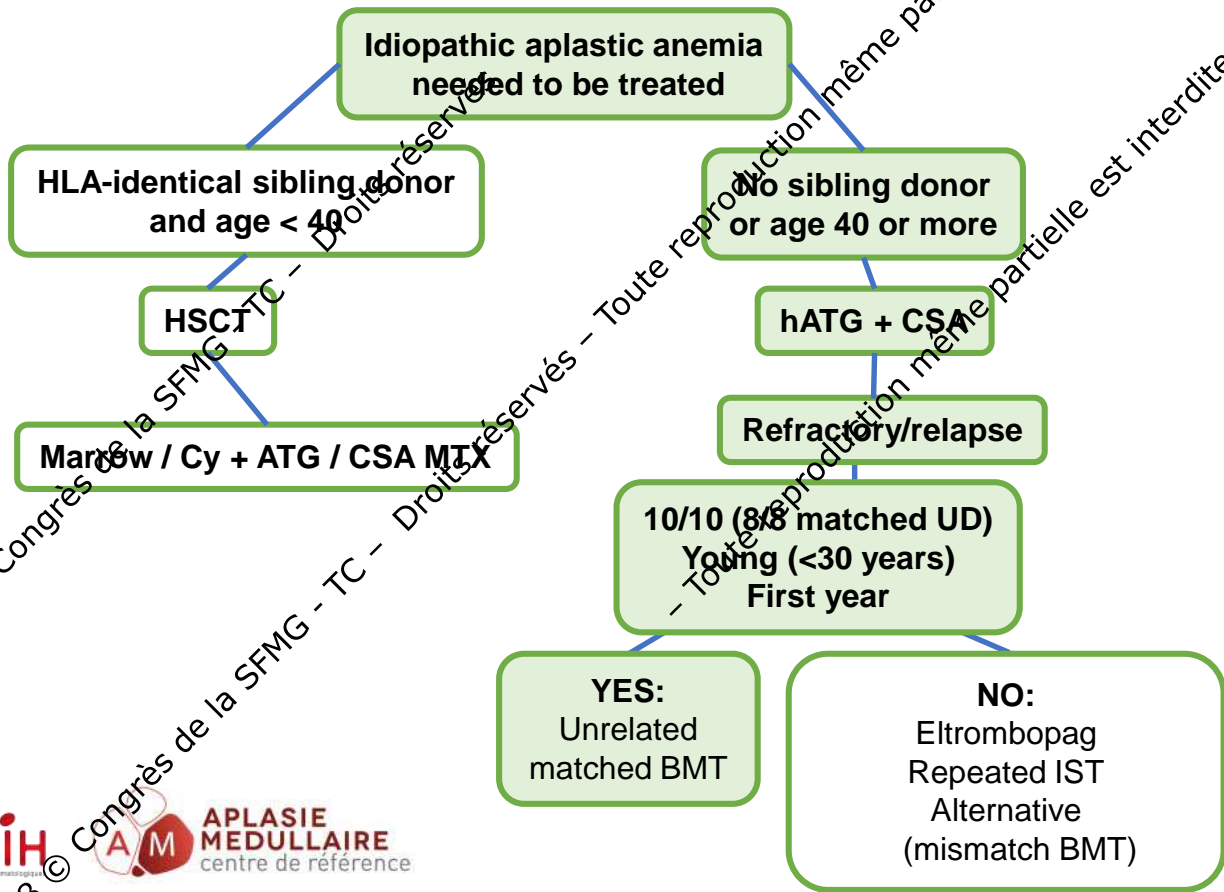




# Treatment (guidelines)

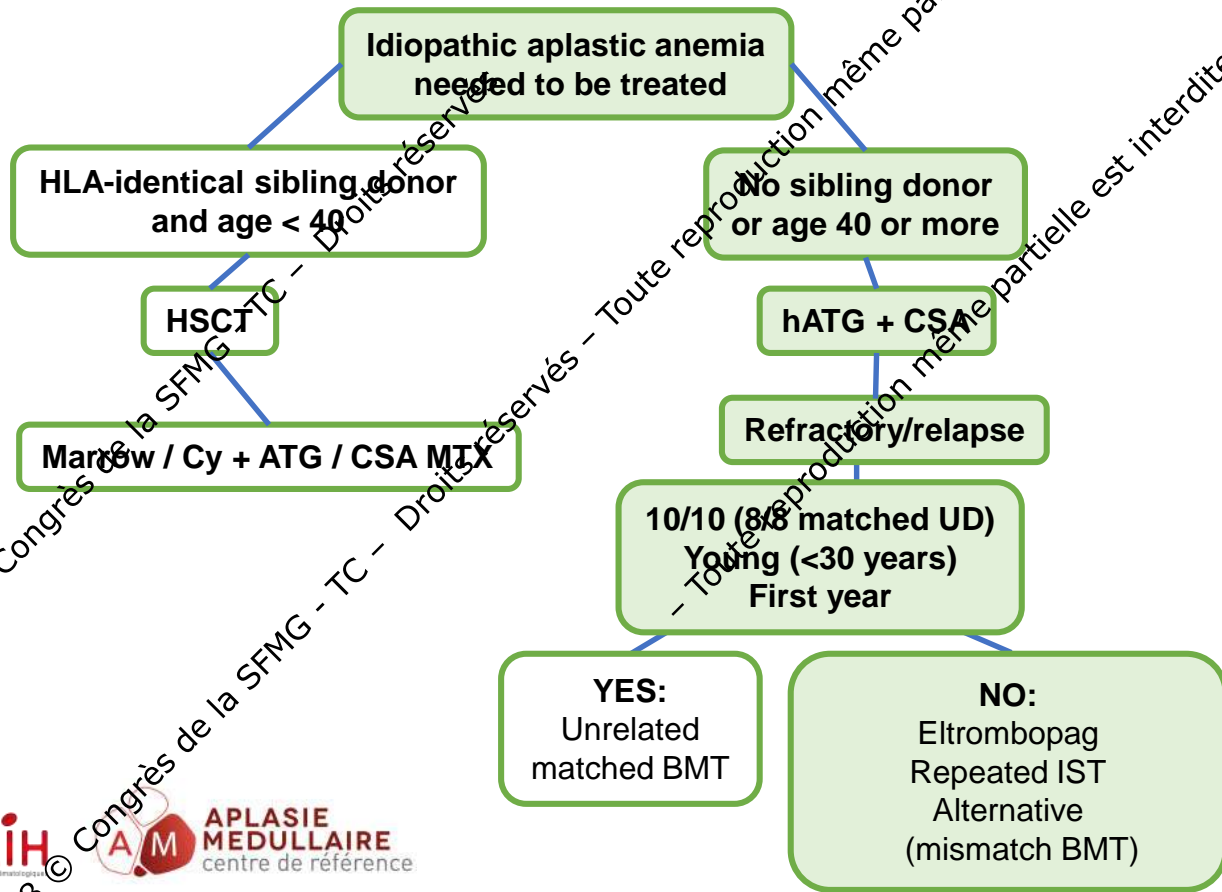


# Treatment (guidelines)



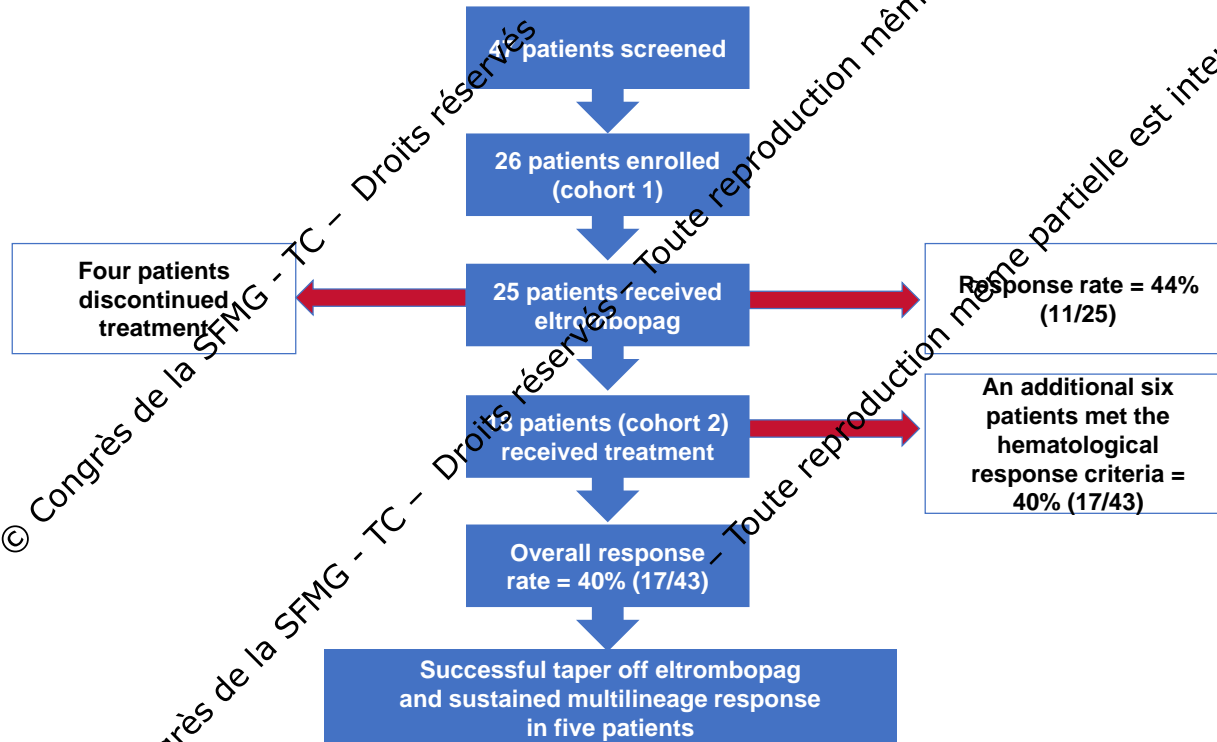
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# Treatment (guidelines)



# TPO receptor agonist and refractory aplastic anemia

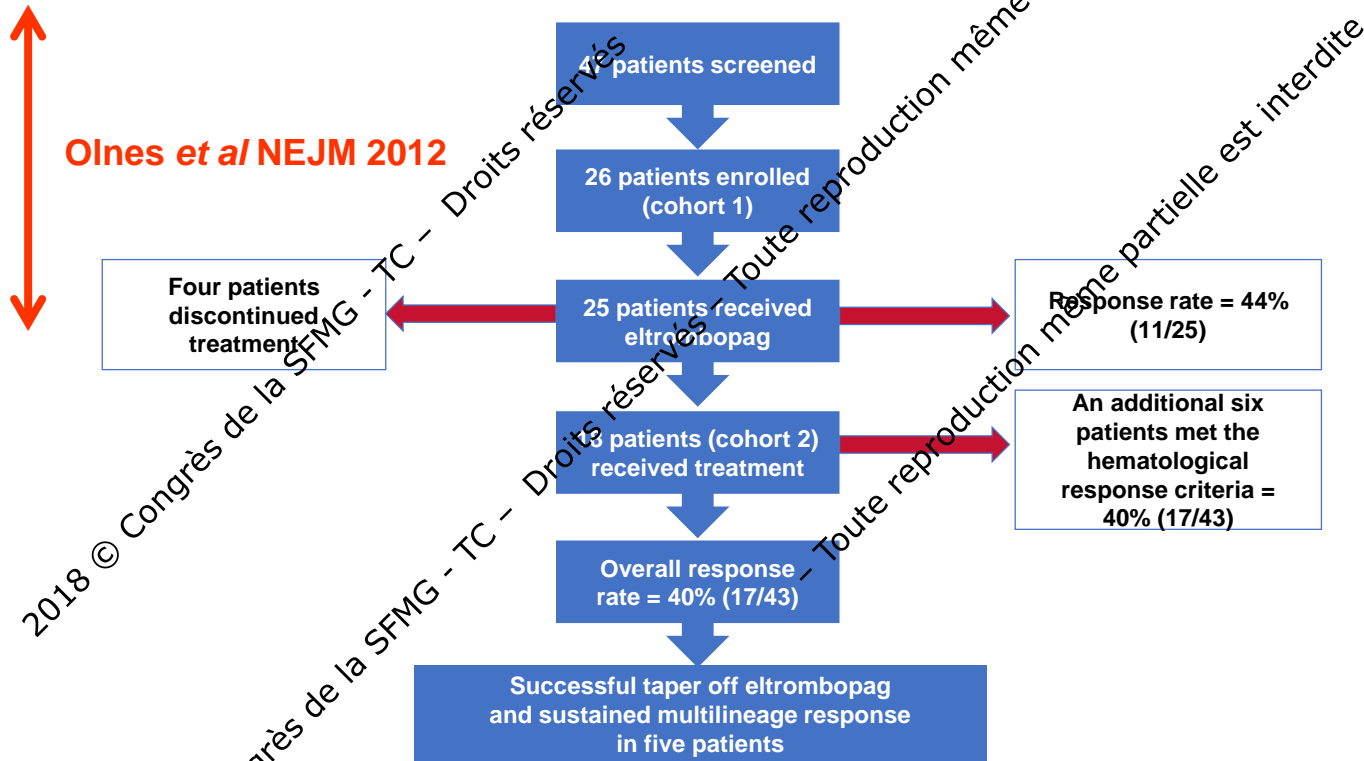
## Response rate



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# TPO receptor agonist and refractory aplastic anemia

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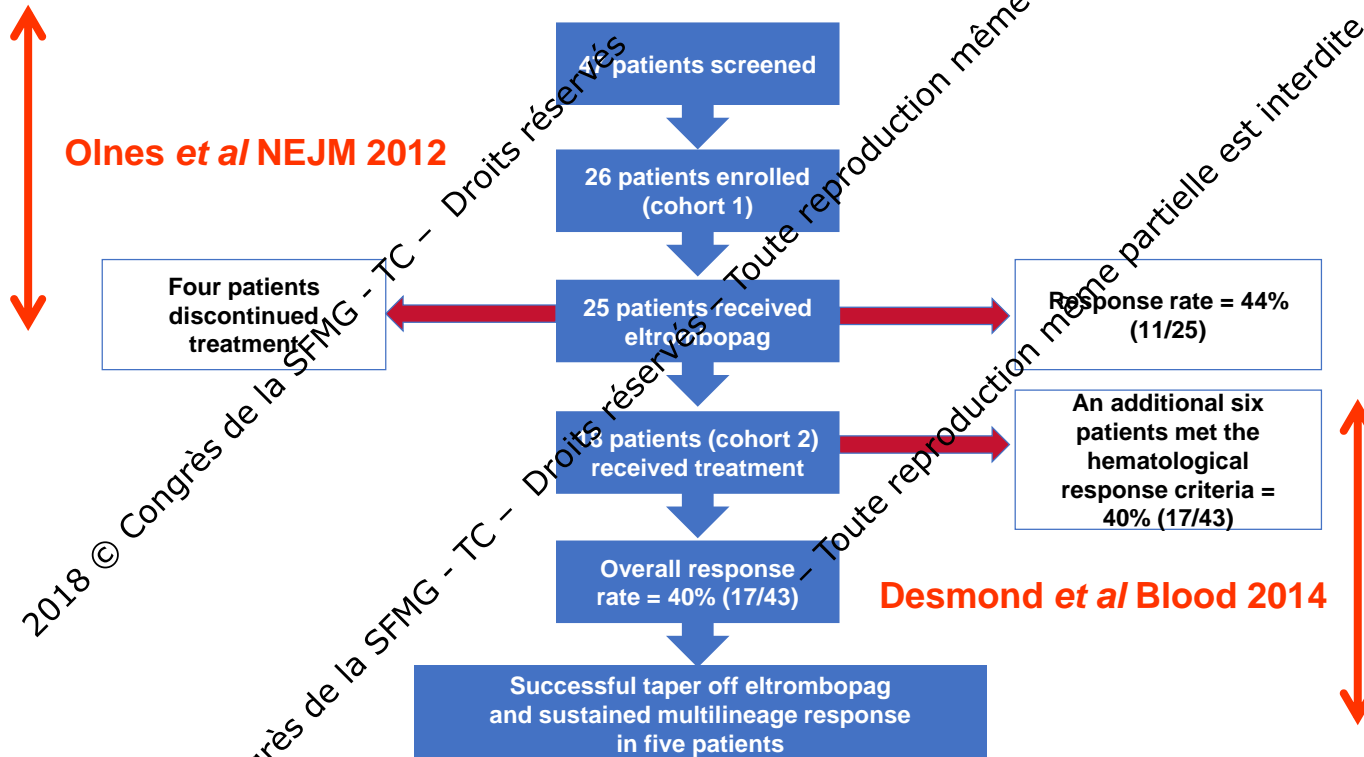


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Adapted from Olnes M, et al. N Engl J Med. 2012;367:11-9. Desmond R, et al. Blood. 2014;123:1818-25.

# TPO receptor agonist and refractory aplastic anemia

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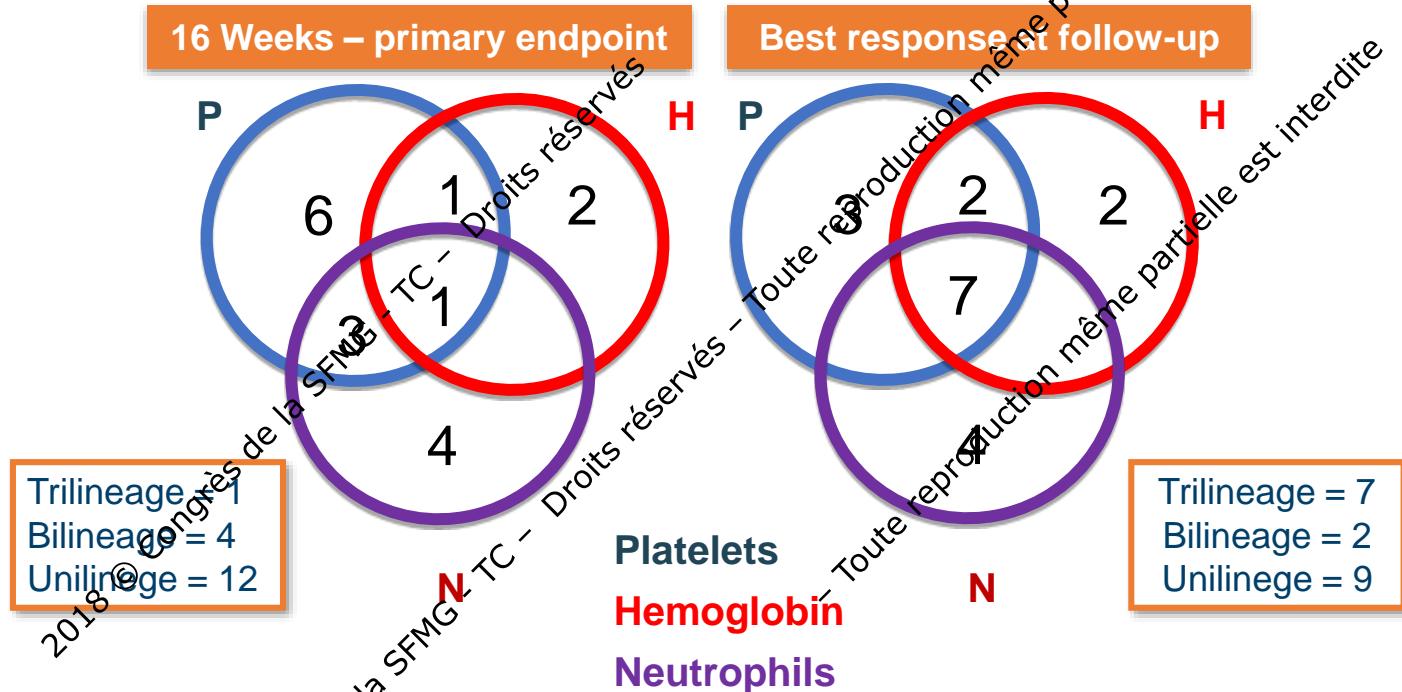


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Adapted from Olnes M, et al. N Engl J Med. 2012;367:11-9. Desmond R, et al. Blood. 2014;123:1818-25.

# Phase II study of eltrombopag in refractory AA

## Multilineage responses



Trilineage = 1  
 Bilineage = 4  
 Unilineage = 12

Trilineage = 7  
 Bilineage = 2  
 Unilineage = 9

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.

# Eltrombopag and refractory aplastic anemia

## Clonal evolution

Subject (age)	Response	Baseline	Abnormality	Time on eltrombopag (months)	Dysplasia	Outcome
7 (60)	NR	46XY[20]	Monosomy 7		N	Died of progressive cytopenias
8 (18)	NR	46XX[6]	Trisomy 8	3	N	HSCT
19 (20)	NR	46XY[20]	Monosomy 7	3	N	HSCT
26 (67)	R	46XY[20]	del(13q)	13	Yes (mild)	HSCT
31 (41)	NR	46XY[20]	Trisomy 21 Monosomy 7	3 6	Yes (mild)	Awaiting HSCT
32 (66)	R	46XY[20]	del(13q)	9	N	Under observation
36 (23)	NR	46XY[20]	Monosomy 7	3	N	HSCT
42 (17)	NR	No metaphases	Chromosome 7	3	N	HSCT

- Eight patients (19%) developed cytogenetic abnormalities during eltrombopag\* treatment
- Advise serial bone marrow biopsies



# TPO receptor agonist and refractory aplastic anemia

## French experience - patients characteristics

- ATG-naïve patients (cohort A, n=11)
- Refractory patients (cohort B, n=35)
- Disease characteristics:

no. (%) [IQR]	Cohort A 11	Cohort B 35	p-value
<b>Demographic characteristics</b>			
- Age at diagnosis (y)	73.7 [60.9, 77.9]	53.4 [26.3, 67.3]	0.003
- Age at ELT initiation (y)	74.1 [67.4, 80.0]	55.3 [35.9, 68.5]	0.003
- Male (%)	4 (36.4)	21 (60.0)	0.298
<b>Aplastic anemia characteristics</b>			0.152
- Idiopathic, no PHN clone	4 (36.4)	23 (65.7)	
- Idiopathic, with PHN clone	6 (54.5)	11 (31.4)	
- Dyskeratosis congenita	1 (9.1)	1 (2.9)	

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# TPO receptor agonist and refractory aplastic anemia

## French experience - main messages

- **Safety**

- 1 SAE (liver toxicity)
- Clonal evolution (lack of follow-up ...)

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- **Response rate = 40%**

- 3 months for refractory patients
- 6 months for 1st line
- Multi-lineage response = 30% among responders

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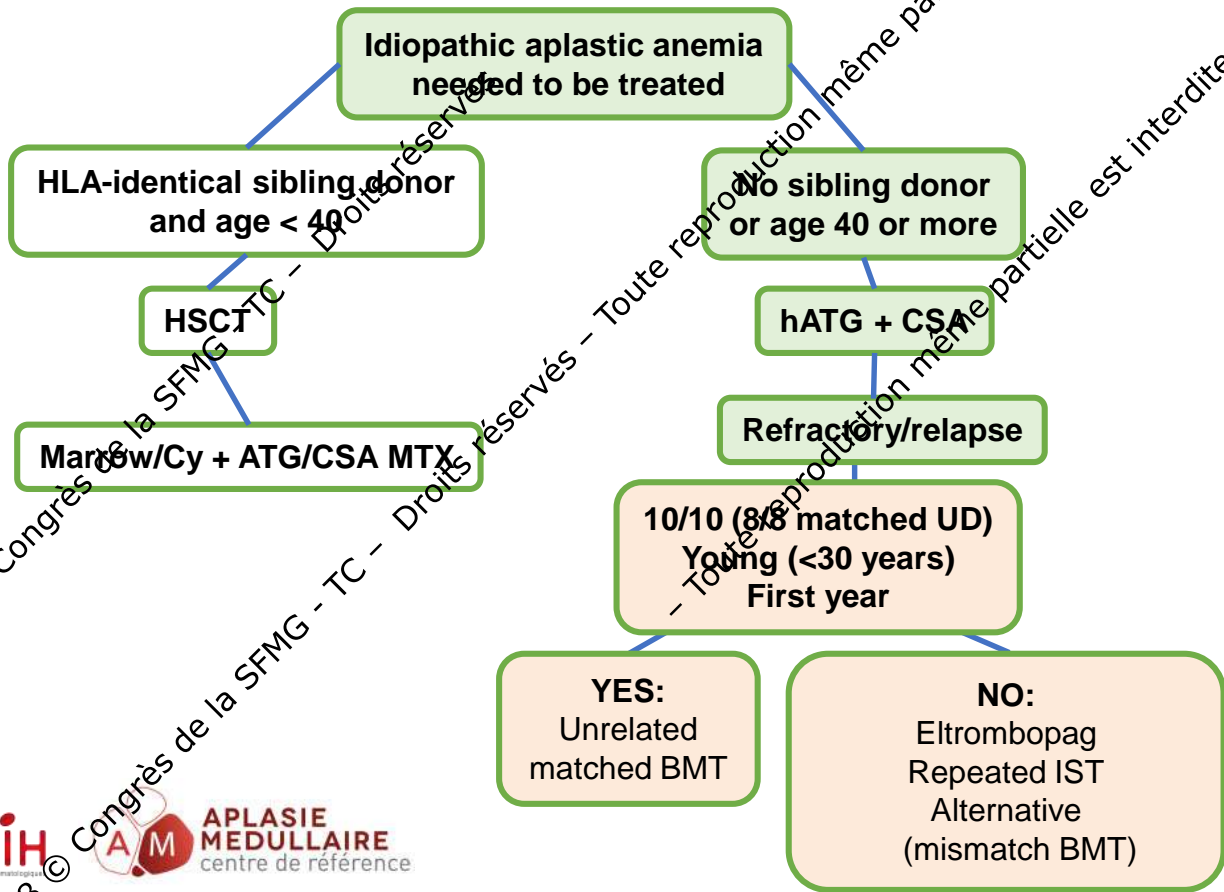
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- **Of note**

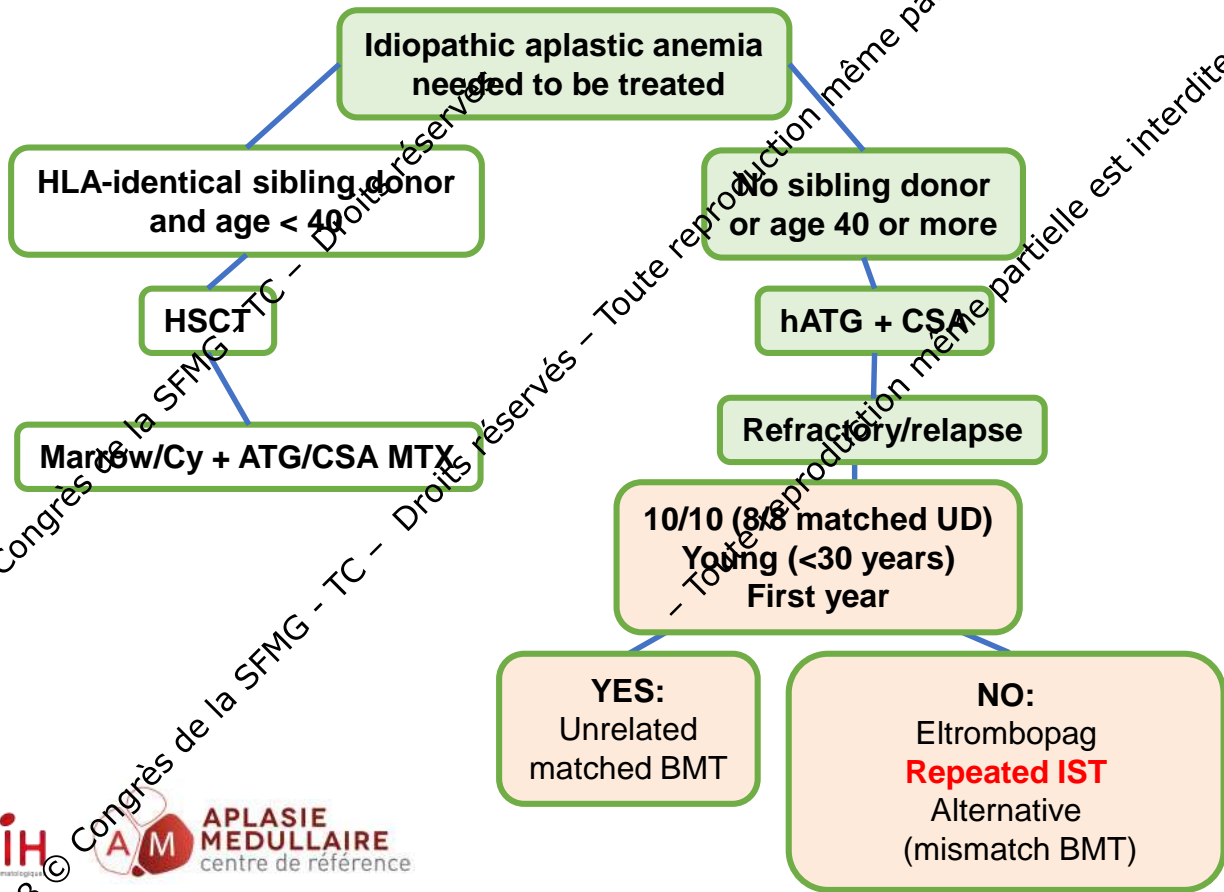
- 20% of non responders responded at a higher dose (225 mg)
- Eltrombopag can be stopped in case of robust response

# Treatment (guidelines)



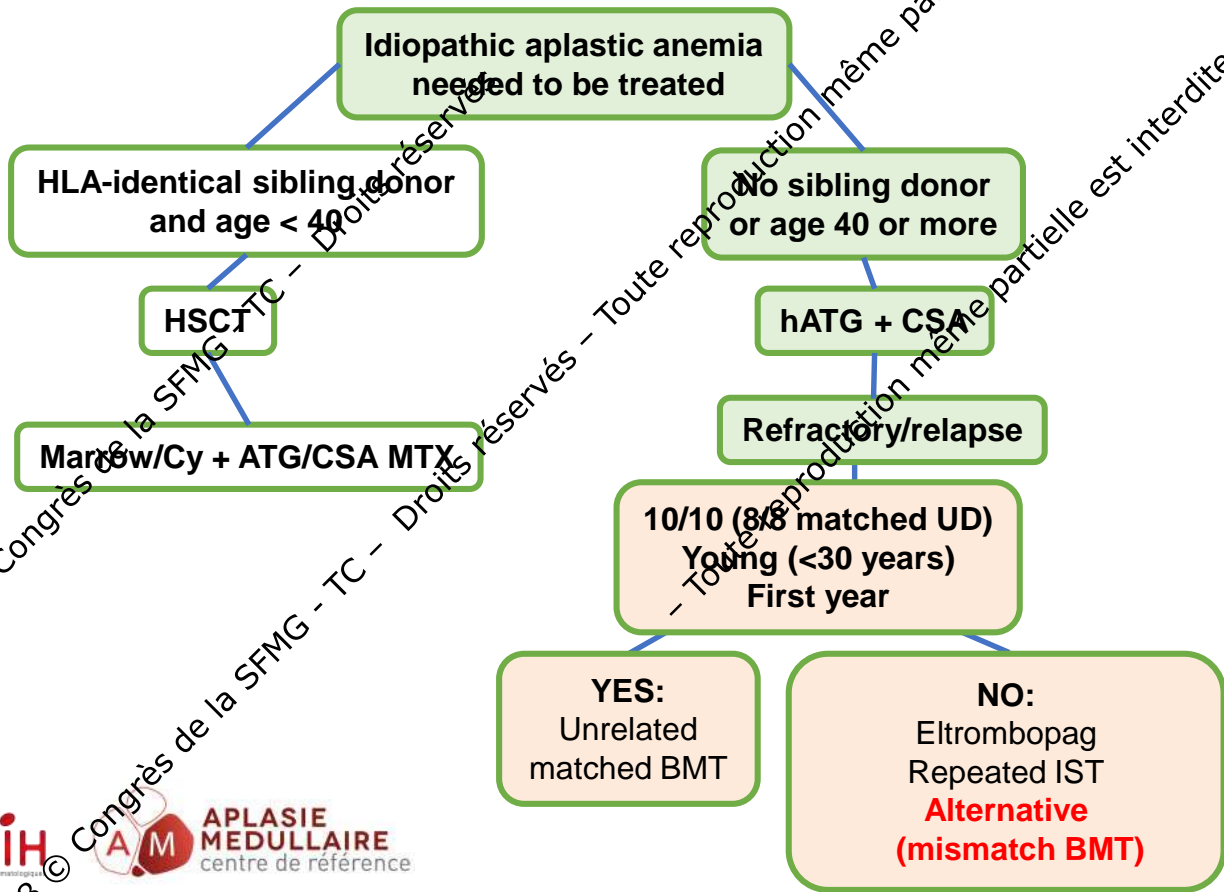
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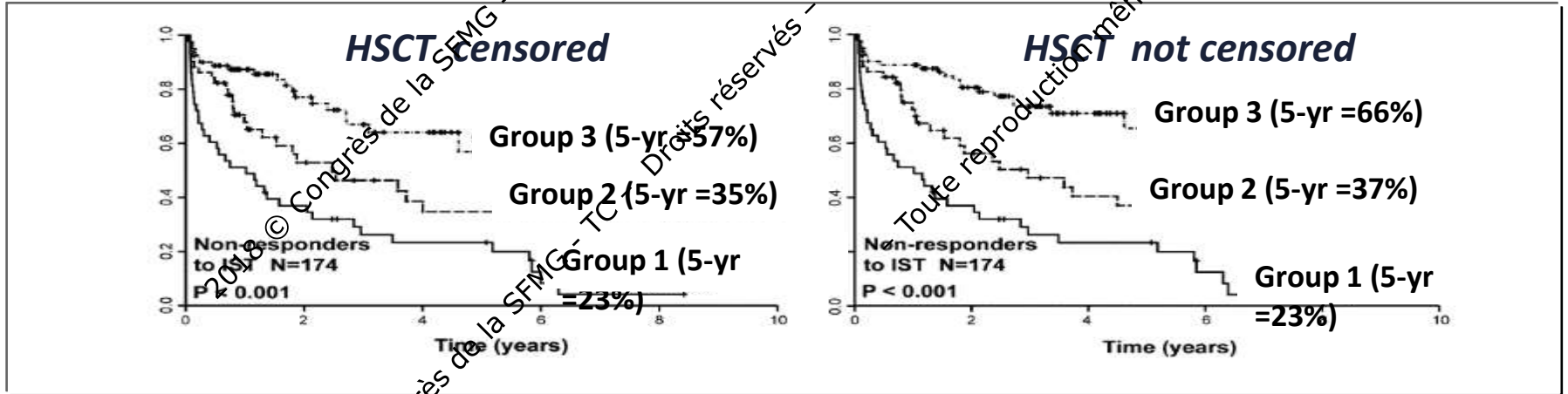
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# Emerging strategies: experimental transplantation

Experimental = Cord blood, MMUD and haplo

Don't forget what supportive care can do with non-responders to IST!

All patients (n=174)	Group 1 (1989-1996)	Group 2 (1996-2002)	Group 3 (2002-2008)
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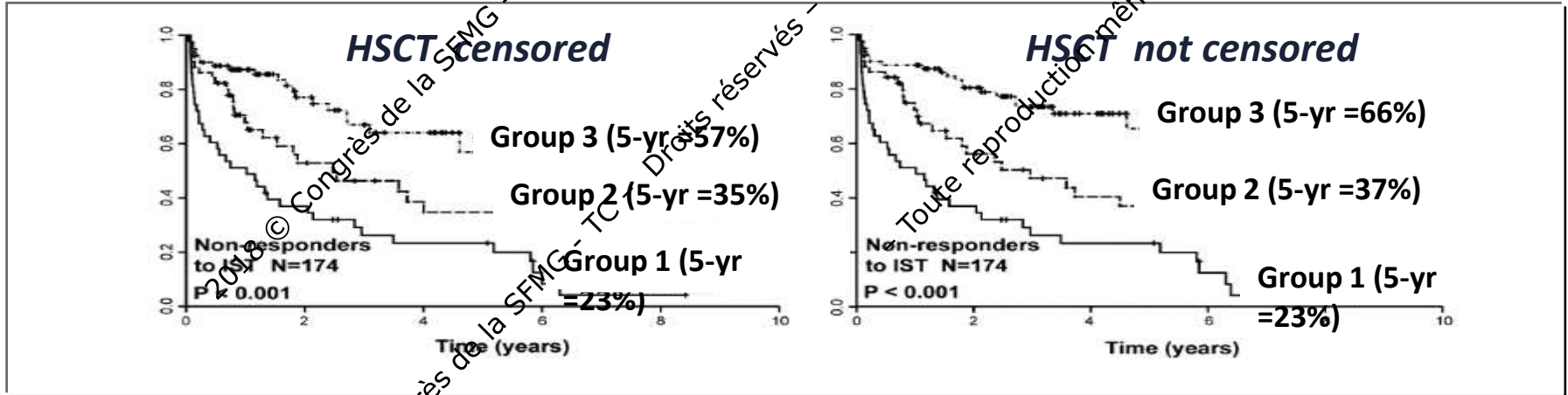


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**! Before Eltrombopag Era !**

# Emerging strategies: experimental transplantation

- Refractory patients & young patients (<20 years)
- TBI 2 Gray-based regimen (risk of rejection)

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# Emerging strategies: Cord Blood transplantation

## TRANSPLANTATION

### CME Article

## Unrelated cord blood transplantation in patients with idiopathic refractory severe aplastic anemia: a nationwide phase 2 study

Regis Peffault de Latour,<sup>1,4</sup> Sylvie Chevret,<sup>5</sup> Charlotte Jubert,<sup>3,6</sup> Anne Sirvent,<sup>7</sup> Claire Galambun,<sup>3,8</sup> Annalisa Ruggeri,<sup>9,10</sup> Virginie Gandemer,<sup>11</sup> Jérôme Comillon,<sup>12</sup> Fanny Rialland,<sup>13</sup> Jean-Hugues Dalle,<sup>3,14</sup> Edouard Forcade,<sup>15</sup> Benedicte Bruno,<sup>3,16</sup> Catherine Paillard,<sup>17</sup> Pierre S. Rorlich,<sup>18</sup> Alexandra Salmon,<sup>17</sup> Sabine Fürst,<sup>3,19</sup> Flore Sicre de Fontbrune,<sup>1,3</sup> Marie Therese Rumi,<sup>20</sup> Jacques-Olivier Bay,<sup>21</sup> Mohamad Mohty,<sup>22,23</sup> Jerome Larghero,<sup>24,25</sup> Eliane Gluckman,<sup>26</sup> and Gerard Socié,<sup>1,3</sup> on behalf of the Francophone Society of Bone Marrow Transplantation and Cellular Therapy

- 60 day-Cuml of **neutrophil engraftment of 88.5%** with full chimerism for all of them (23/26).
- 100 day-Cuml of grade II-IV **acute GVHD was 40%** (95% CI, 20-60) (8 grade II; 0 grade III; 2 grade IV)
- 1-year Cuml of **cGVHD at 26%** (95% CI, 6-46) (severe cGVHD in 2 pts).
- 3-years **overall survival at 82%**

# Emerging strategies: experimental transplantation

- Refractory patients & young patients (<20 years)
- TBI 2 Gray-based regimen (risk of rejection)
  - Cord blood
    - $4 \times 10^7$  frozen TNC /Kg with no more than 2 of 6 HLA mismatches
    - APCORD protocol (NCT 01343953)

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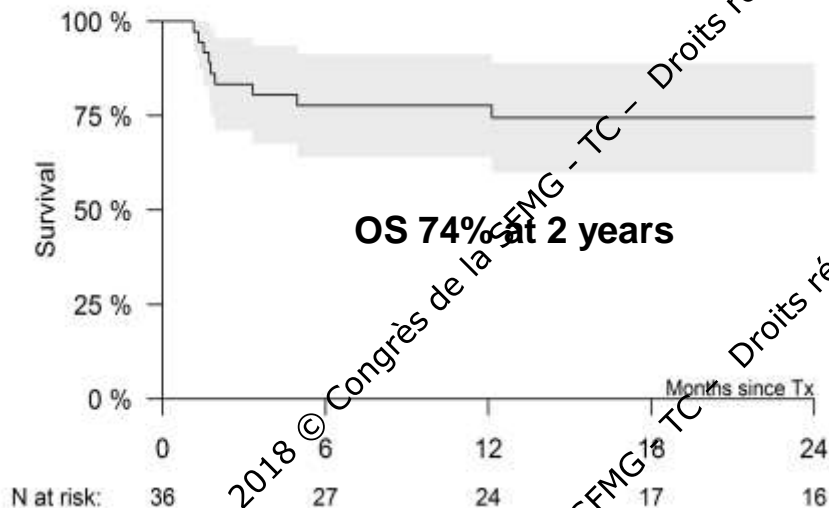
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# Emerging strategies: experimental transplantation

- **Refractory patients & young patients (<20 years)**
- **TBI 2 Gray-based regimen (risk of rejection)**
  - Cord blood
    - 4 x 10<sup>7</sup> frozen TNC /Kg with no more than 2 of 6 HLA mismatches
    - APCORD protocol (NCT 01343953)
  - MMUD
    - BMT CTN study (NCT00326417) or UK guidelines (FCC)

# Emerging strategies: Haplo-identical transplantation (Post-Cy)

- 36 patients (32 with acquired SAA and 4 with IBMF)



## Causes of death:

- IBMF (2/4):
  - 1 infection
  - 1 GvHD
- Acquired (7/32):
  - 5 infections
  - 2 other HSCT-related

:

# Emerging strategies: experimental transplantation

- Refractory patients & young patients (<20 years)
- TBI 2 Gray-based regimen (risk of rejection)
  - Cord blood
    - 4 x 10<sup>7</sup> frozen TNC /Kg with no more than 2 of 6 HLA mismatches
    - APCORD protocol (NCT 01343953) abstract # 2671
  - MMUD
    - BMT CTN study (NCT00326417) or UK guidelines (FCC)
  - Haplo
    - « according to Baltimore protocol »
- Better in experienced center / **Clinical trial+++**

# Conclusion

Acquired aplastic anemia in 2018

- **First line treatment in 2018**
  - Sibling transplantation: patients < 40 years
  - Horse ATG + Cyclosporine for the others
- **Refractory patients (6 months)**
  - Matched unrelated transplantation: patients < 30 years
  - Experimental transplantation: patients < 20 years (?)
  - Eltrombopag for the others

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# Perspectives – eltrombopag first line

Naive patients [clinicaltrials.gov NCT01623167](https://clinicaltrials.gov/ct2/show/study/NCT01623167)

- **Phase II study**

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



April 2017

# Perspectives – eltrombopag first line

Naive patients [clinicaltrials.gov NCT02099747](https://clinicaltrials.gov/ct2/show/study/NCT02099747)

## RACE study



A prospective **R**andomized multicenter study comparing horse  
**A**ntithymocyte globuline (hATG) + **C**yclosporine A (CsA) ±  
**E**ltrombopag as front-line therapy for severe aplastic anemia patients.

### PRINCIPAL INVESTIGATORS

**Regis Piffault de Latour (Paris)**

**Antonio M Risitano (Naples)**

**Accrual 180/200**

# 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, JH Dalle, A Baruchel, G Socié,  
N Vasquez, W. Cuccuini, J Soulier (Fanconi team),  
C Kannengiesser, E Lainey, L Da Costa (Telomeres team)**

