Actualités dans la prise en charge de l’aplasie médullaire

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

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Filière de santé Maladies Rares ImmunoHématologiques

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Actualités dans la prise en charge de l'aplasie médullaire idiopathique

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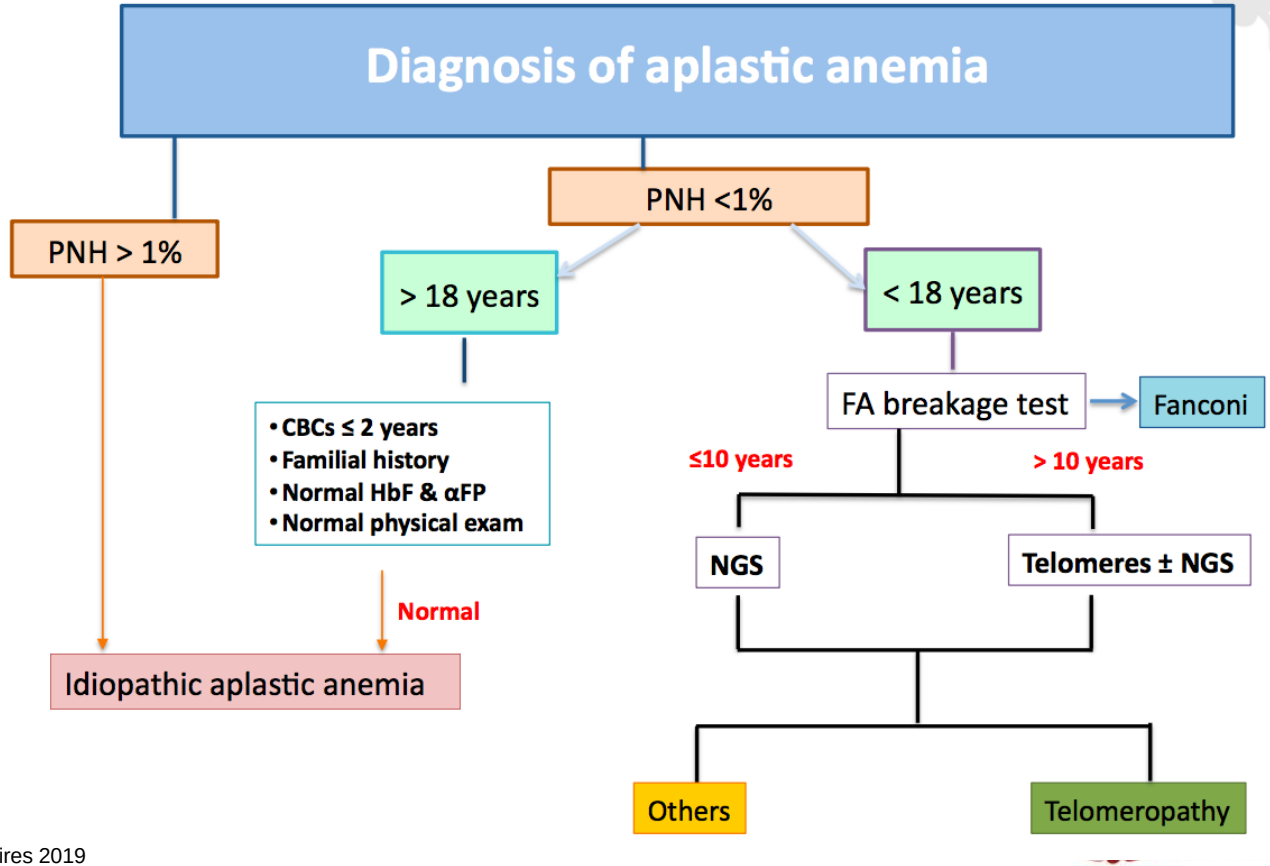
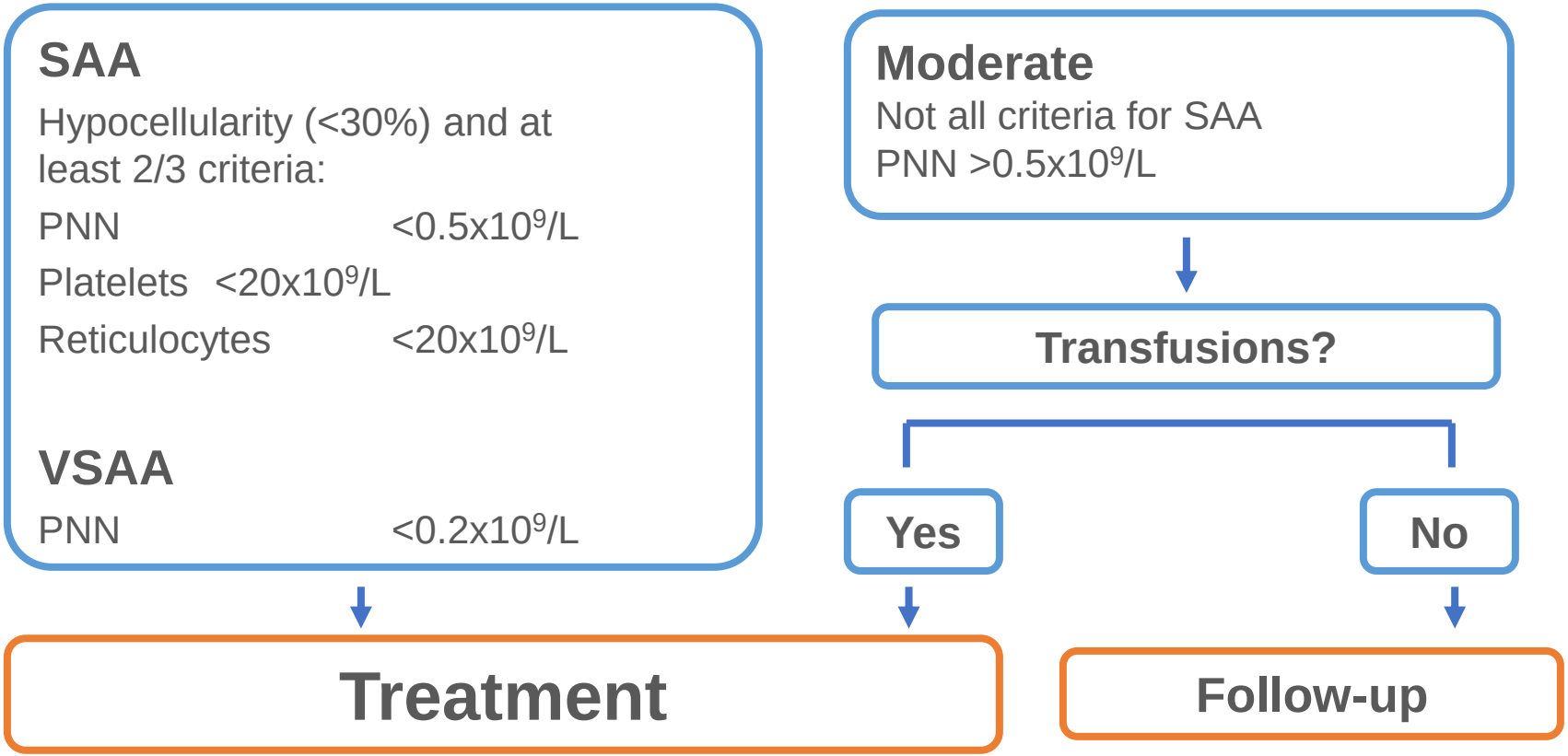
Difference between acquired and inherited aplastic anemia?

Question #1



Difference between acquired and inherited aplastic anemia?

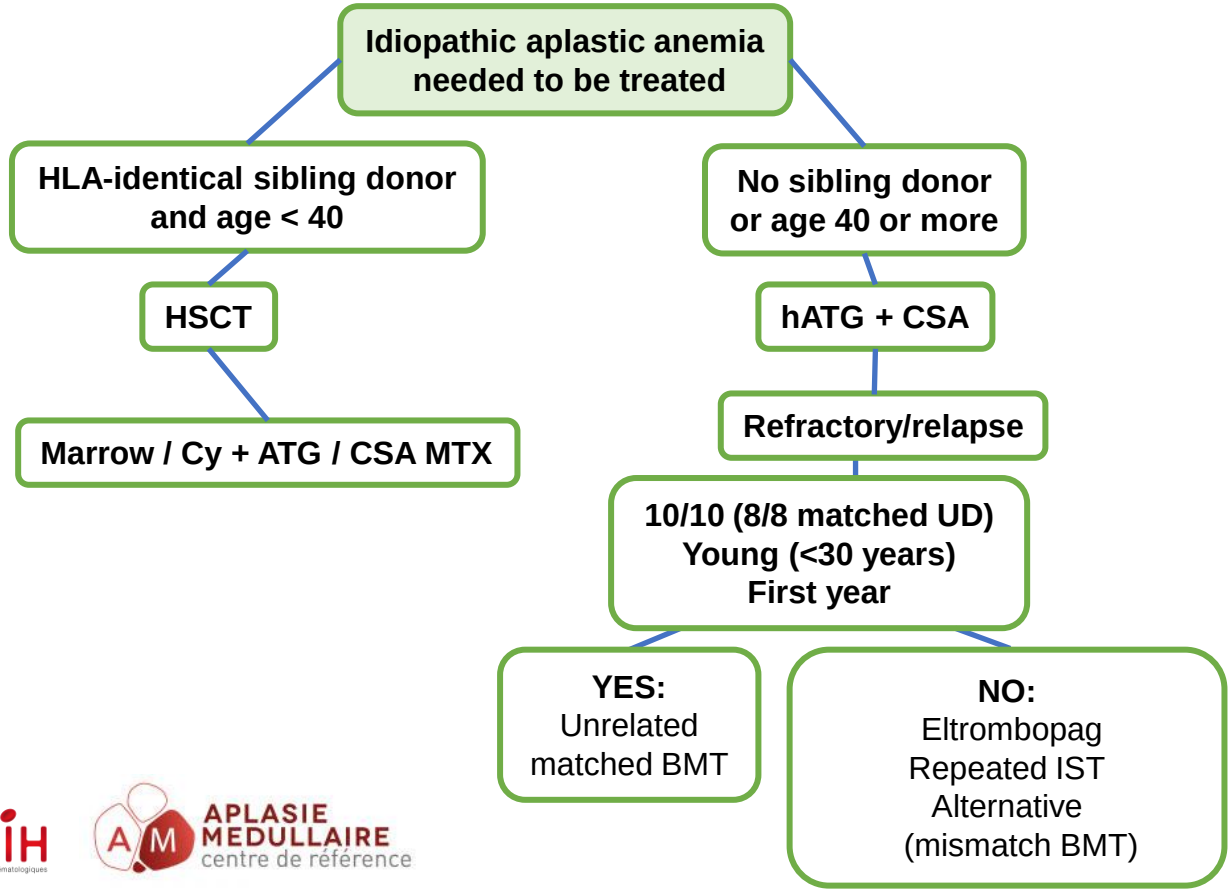
Question #2



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

Treatment (guidelines & update)

Question #3



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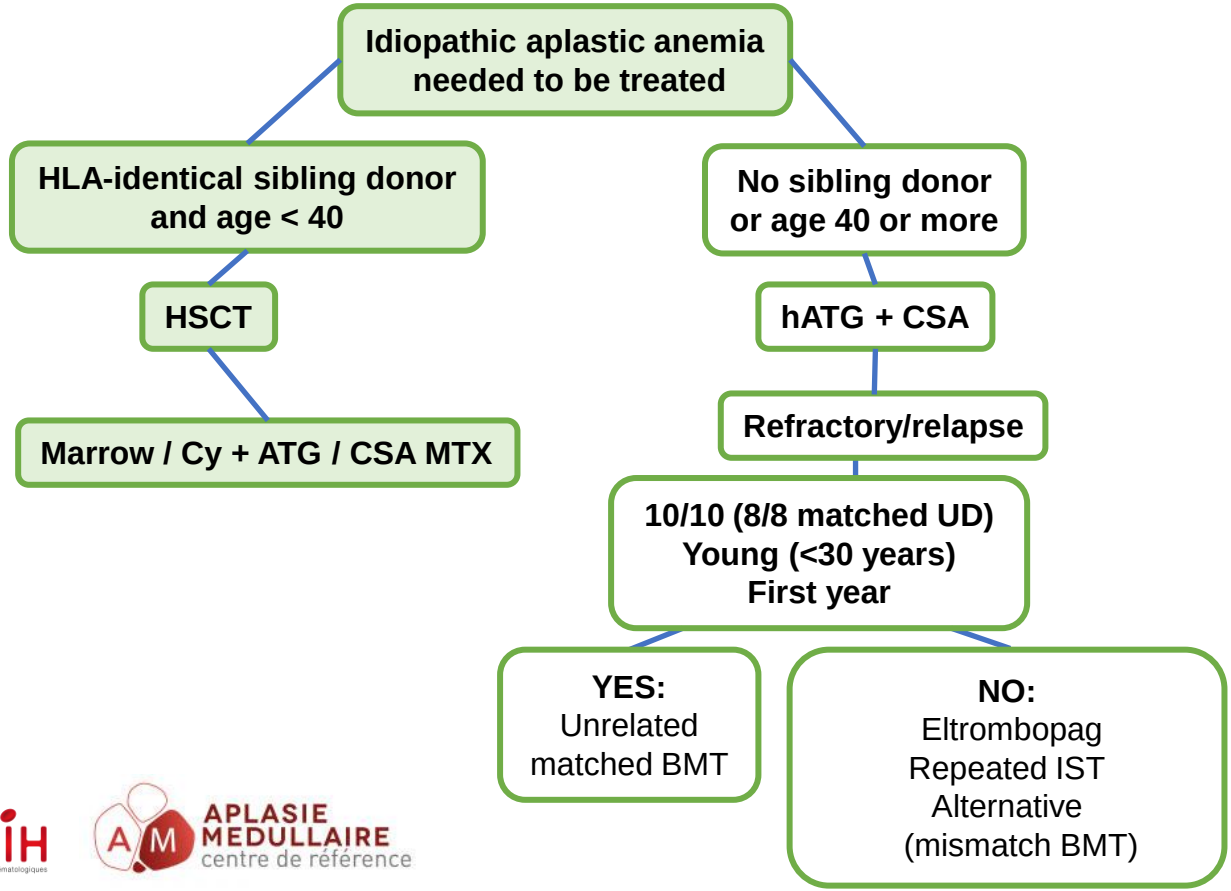
Treatment (guidelines)



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Up-front MUD transplantation

Experimental approach

PHRC National 2019 / PI : JH Dalle (<18 years) & R Peffault de Latour

Essai de phase II évaluant la faisabilité de réaliser une allogreffe à partir après d'un **donneur non apparenté HLA 10/10 en première intention** chez des enfants atteints **d'aplasies médullaires idiopathiques**

> Endpoint primaire et nombre de patients requis:

- Réalisation de l'allogreffe dans les 60 jours après identification du donneur 10/10
- 25 patients (36 mois /24 mois de suivi), <18 ans, analyse intermédiaire 12 pts

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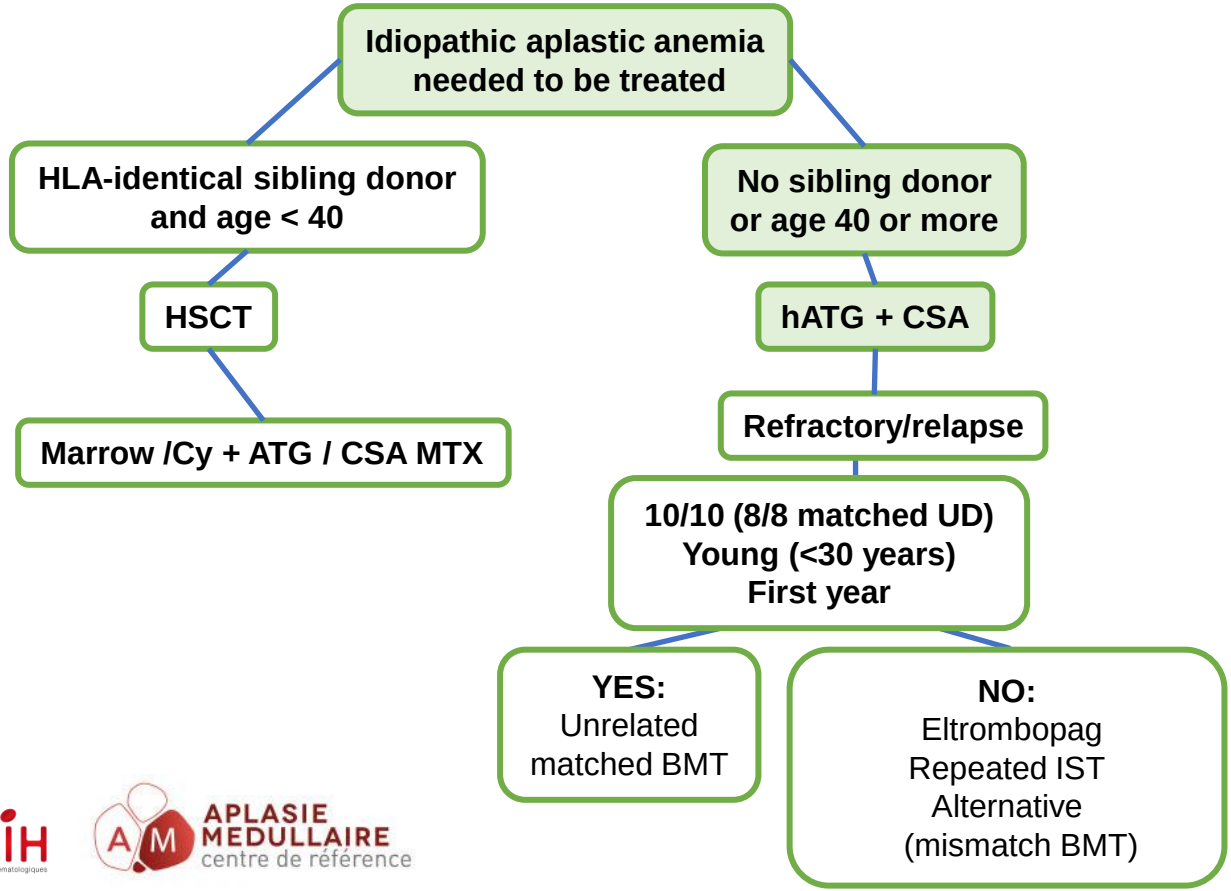
AM APLASIE MEDULLAIRE centre de référence

Treatment (guidelines)



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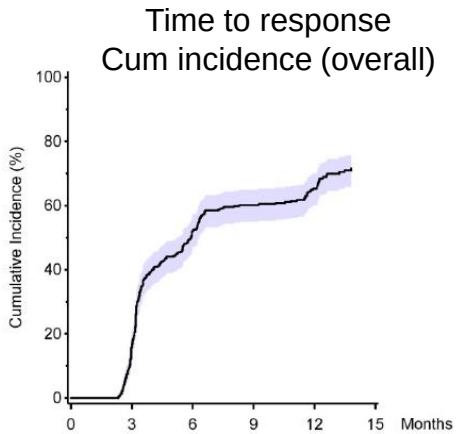
Horse ATG + Cyclosporine

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.

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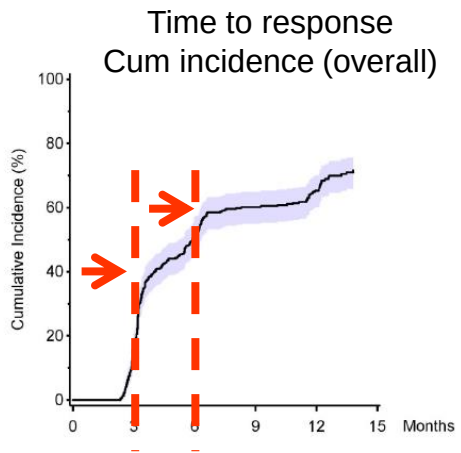

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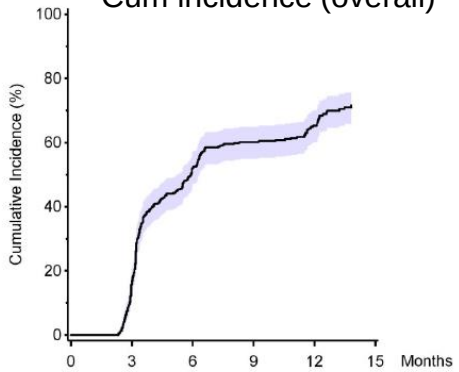
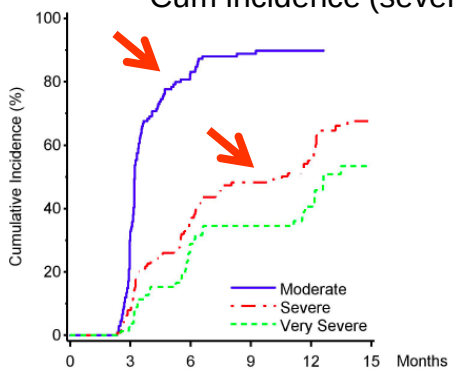
Time to response
Cum incidence (overall)



Time to response
Cum incidence (severity)



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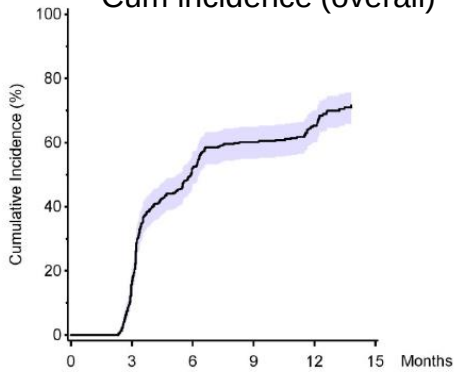

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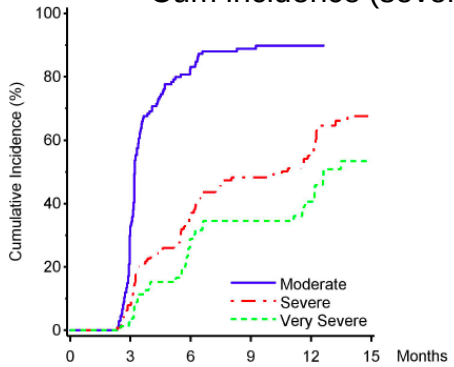

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Horse ATG + Cyclosporine

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

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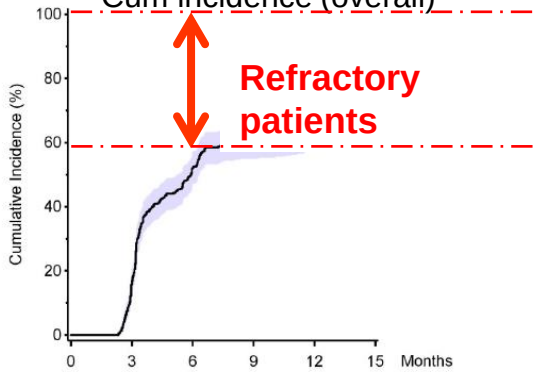
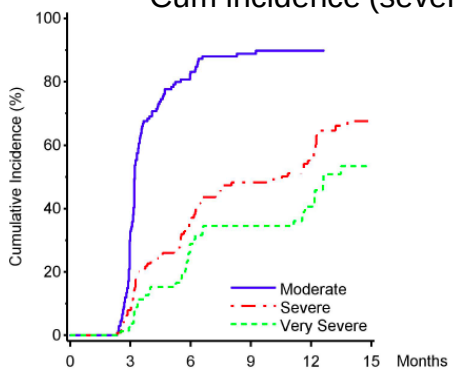


Time to response
Cum incidence (severity)



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

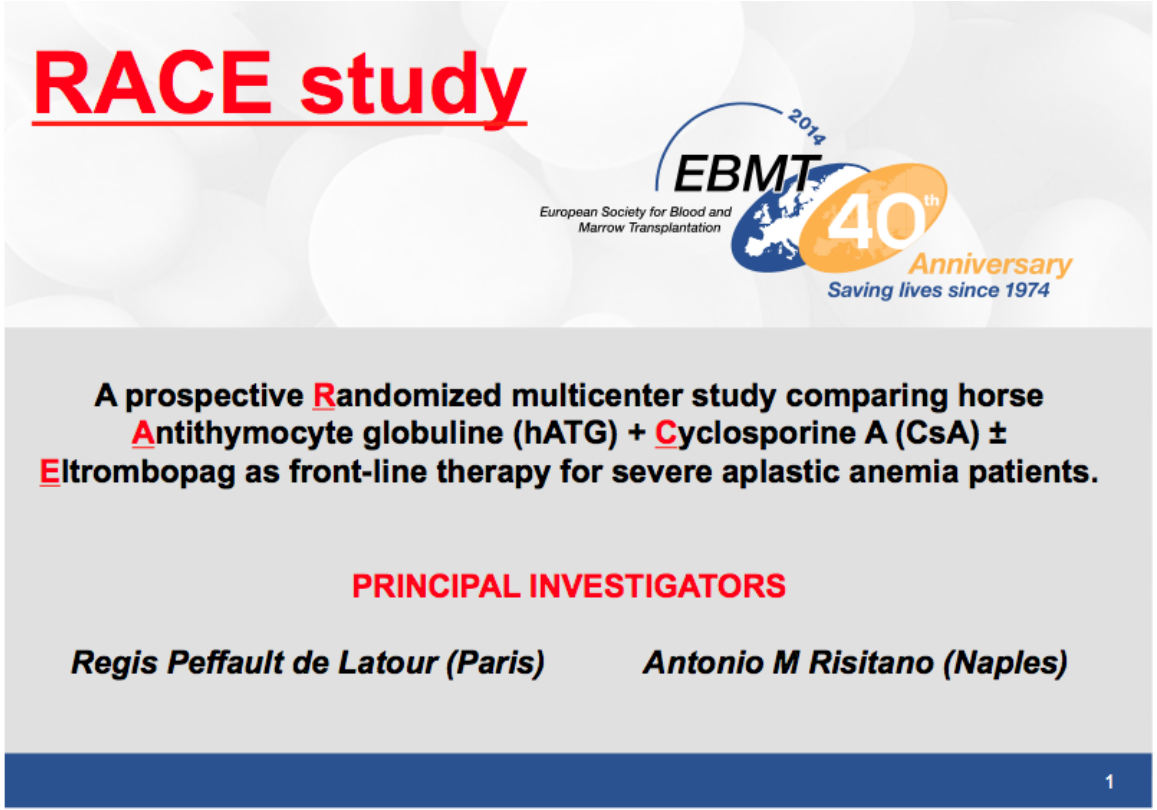
Any progress since 40 years?

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)

Perspectives – eltrombopag first line

Naive patients *clinicaltrials.gov NCT02099747*



Perspectives – eltrombopag first line

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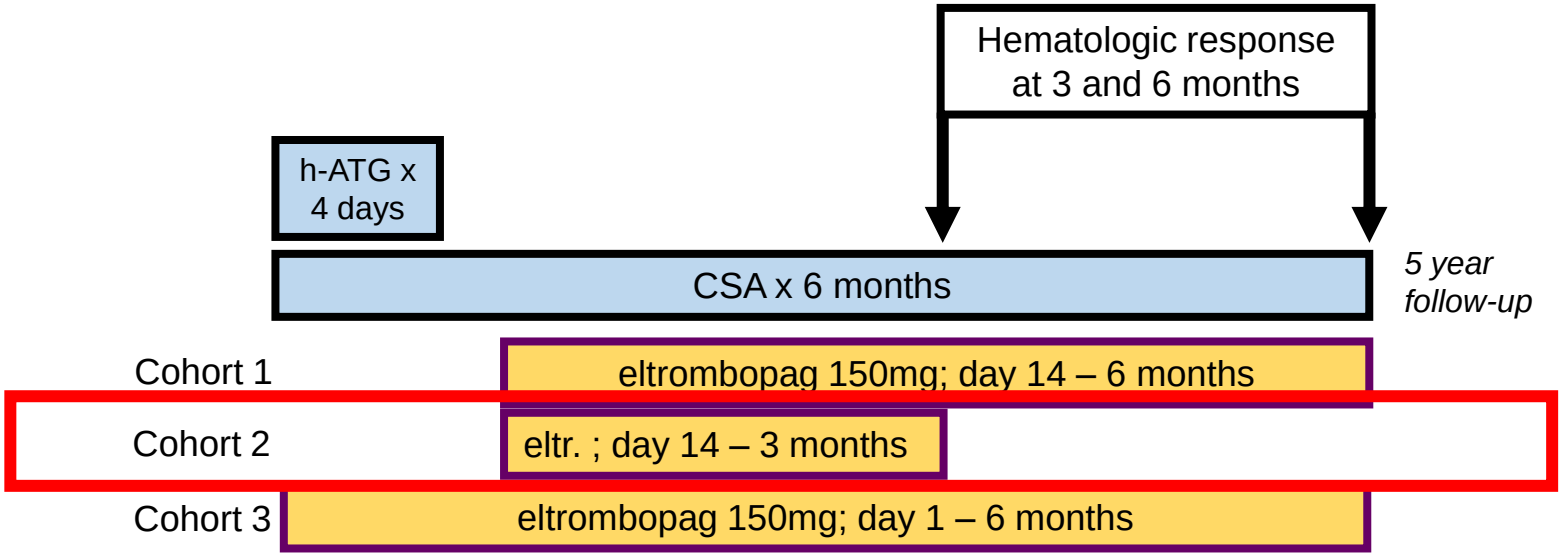

Primary endpoints: CR rate at 3 mo, 7% (standard IST) versus 21% (Experimental arm)

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

Perspectives – eltrombopag first line

Naive patients *clinicaltrials.gov NCT02099747*

Country	# sites	# open sites	# Randomized subjects
FR	8	7	85
IT	9	6	28
NL	4	4	27
ES	6	4	11
CH	3	3	9
UK	5	4	45
DE	5	0	0
Total	40	28	**205**

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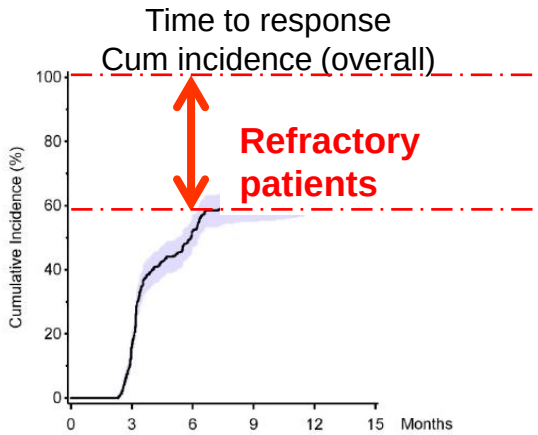
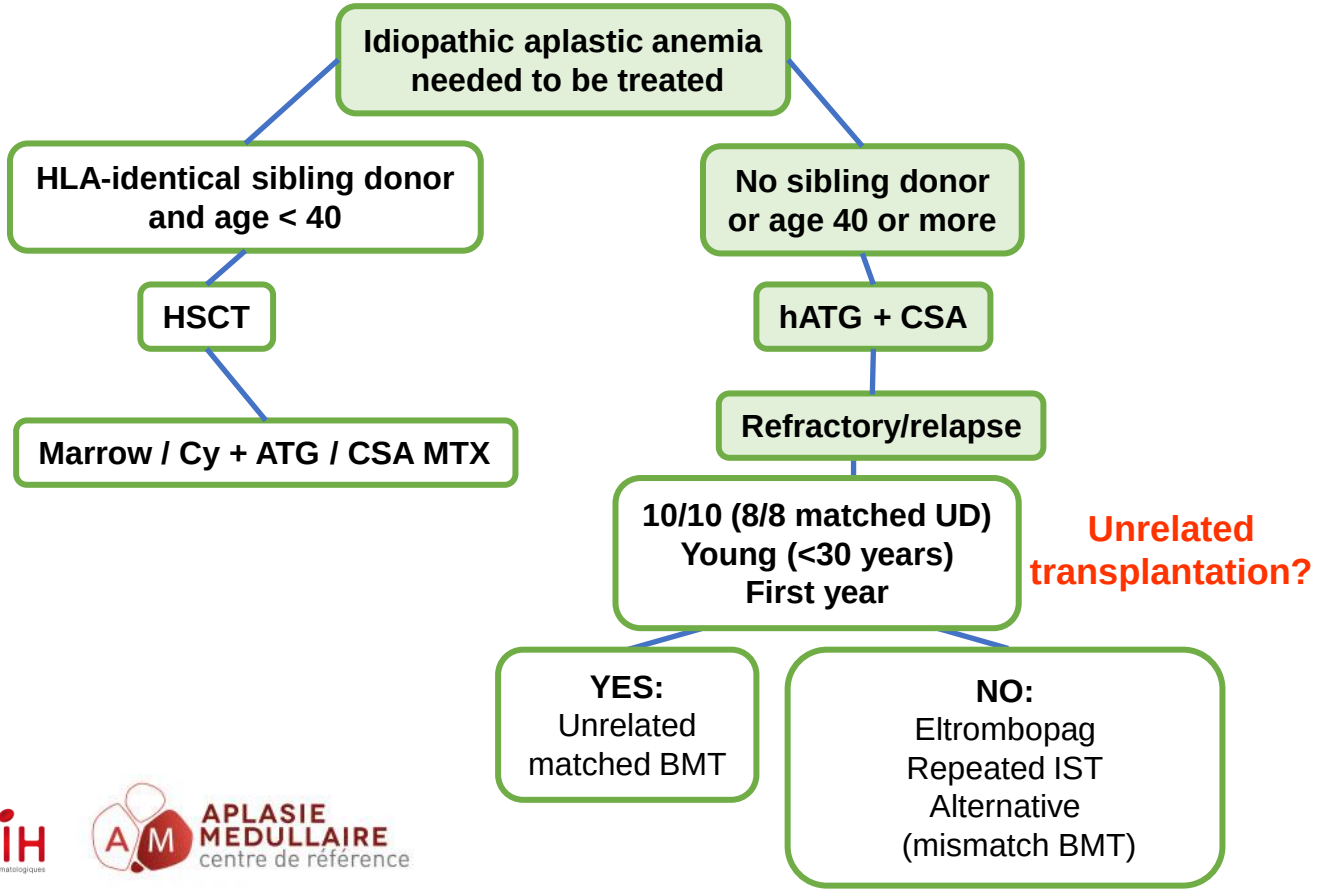


- **Refractory patients = 2 questions:**
  - Is it really acquired?
  - Clonal evolution?

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

Treatment (guidelines)



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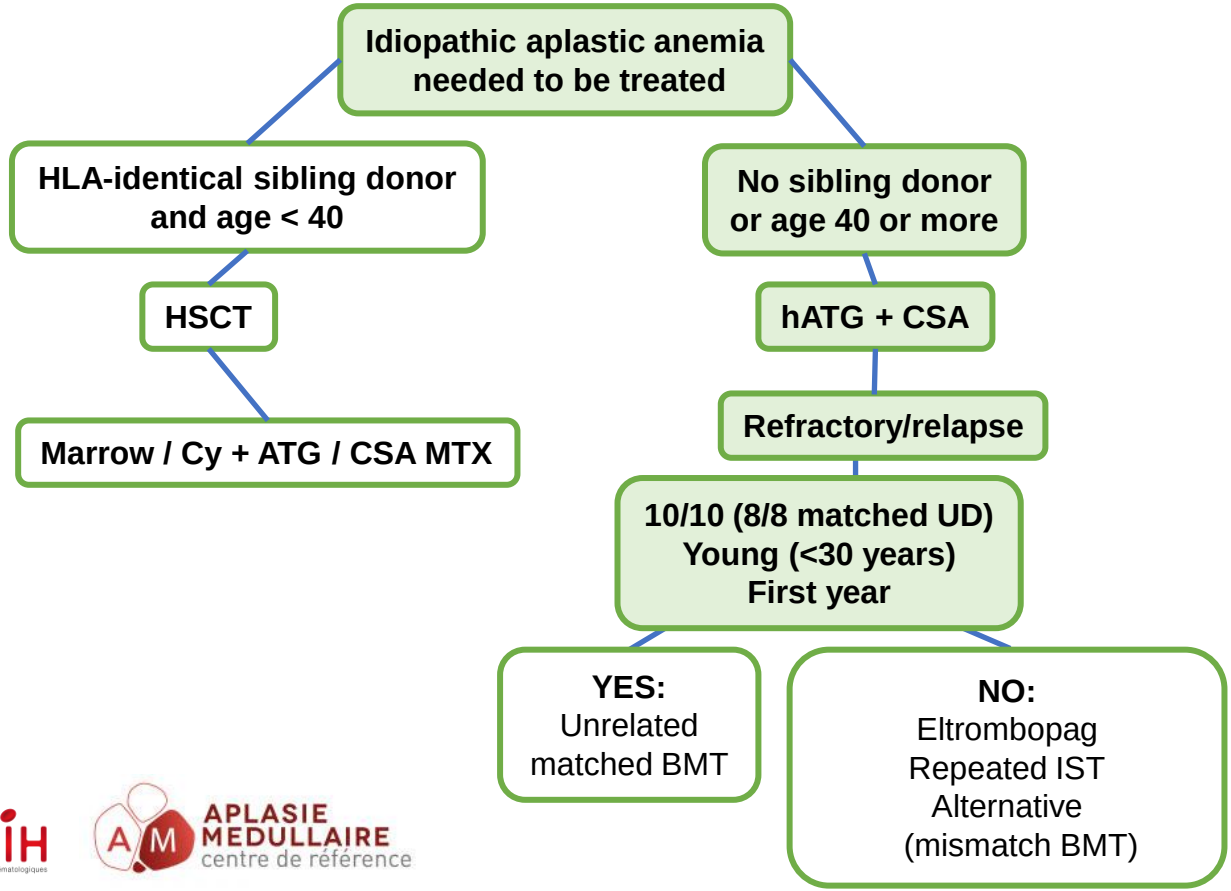

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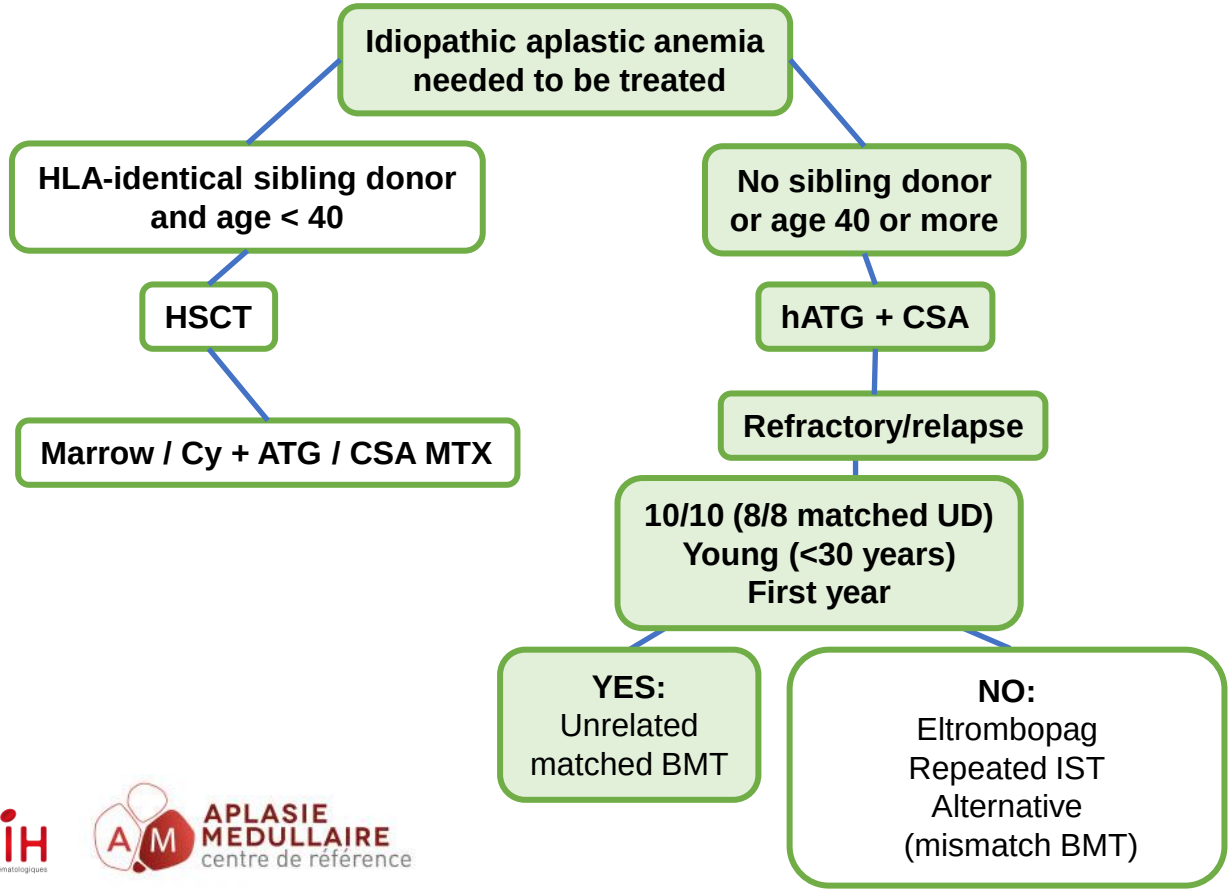

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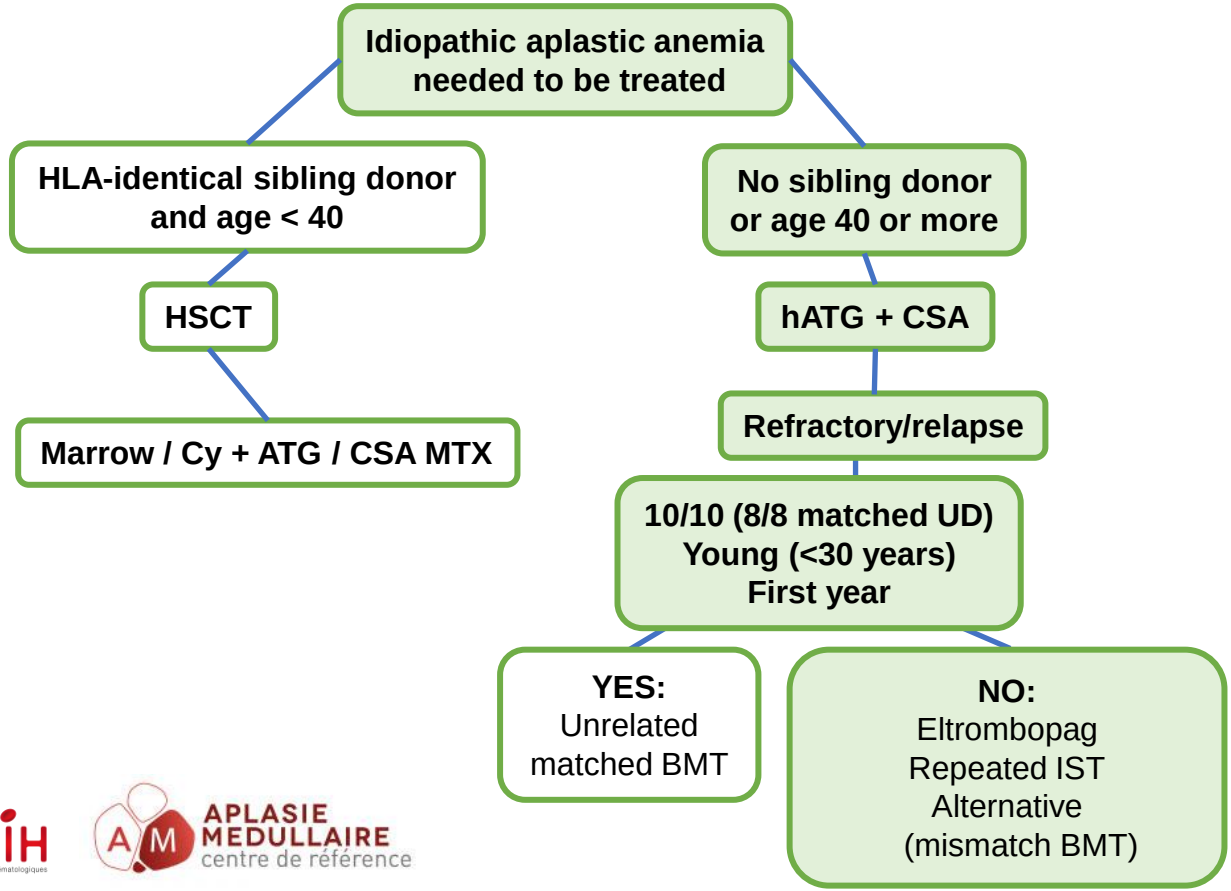

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TPO receptor agonist and refractory aplastic anemia

French experience - patients characteristics

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

- Disease characteristics:

	Cohort A	Cohort B	p-value
no. (%) [IQR]	**11**	**35**	
Demographic characteristics			
Age at diagnosis (y)	73.7 [60.9, 77.5]	53.4 [26.3, 67.3]	0.003
Age at ELT initiation (y)	74.1 [67.4, 78.0]	55.3 [35.9, 68.5]	0.003
Male (%)	4 (36.4)	21 (60.0)	0.298
Aplastic anemia characteristics			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)	

Lengline E, et al. Haematologica. 2018;103:212-220.

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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 …)

Lengline E, et al. Haematologica. 2018;103:212-220.

TPO receptor agonist and refractory aplastic anemia

French experience - main messages

- **Safety**
  - 1 SAE (liver toxicity)
  - Clonal evolution (lack of follow-up …)
- **Response rate = 40%**
  - 3 months for refractory patients
  - 6 months for 1st line
  - Multi-lineage response = 30% among responders

Lengline E, et al. Haematologica. 2018;103:212-220.

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- **Safety**
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- **Response rate = 40%**
  - 3 months for refractory patients
  - 6 months for 1st line
  - Multi-lineage response = 30% among responders
- **Of note**
  - 20% of non responders responded at a higher dose (225 mg)
  - Eltrombopag can be stopped in case of robust response

Lengline E, et al. Haematologica. 2018;103:212-220.

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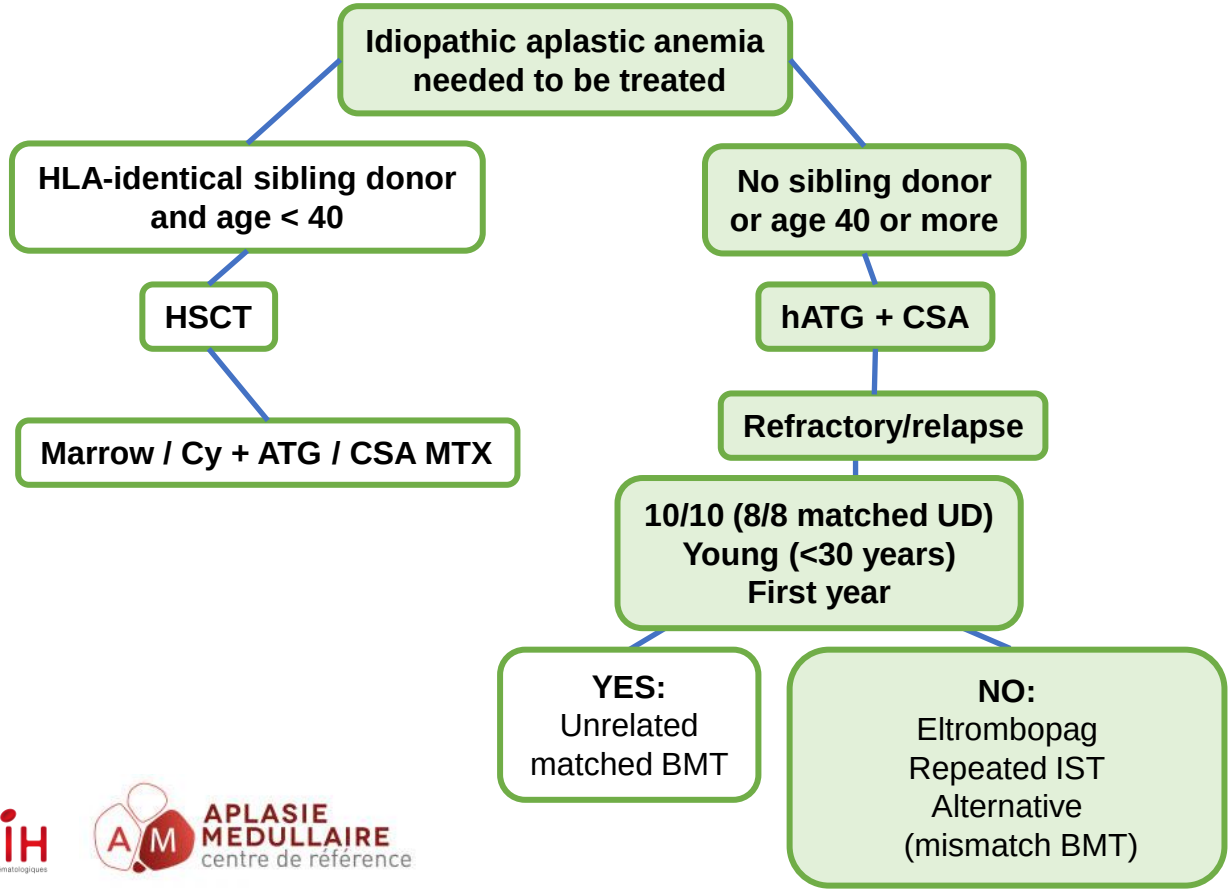
Treatment (guidelines)



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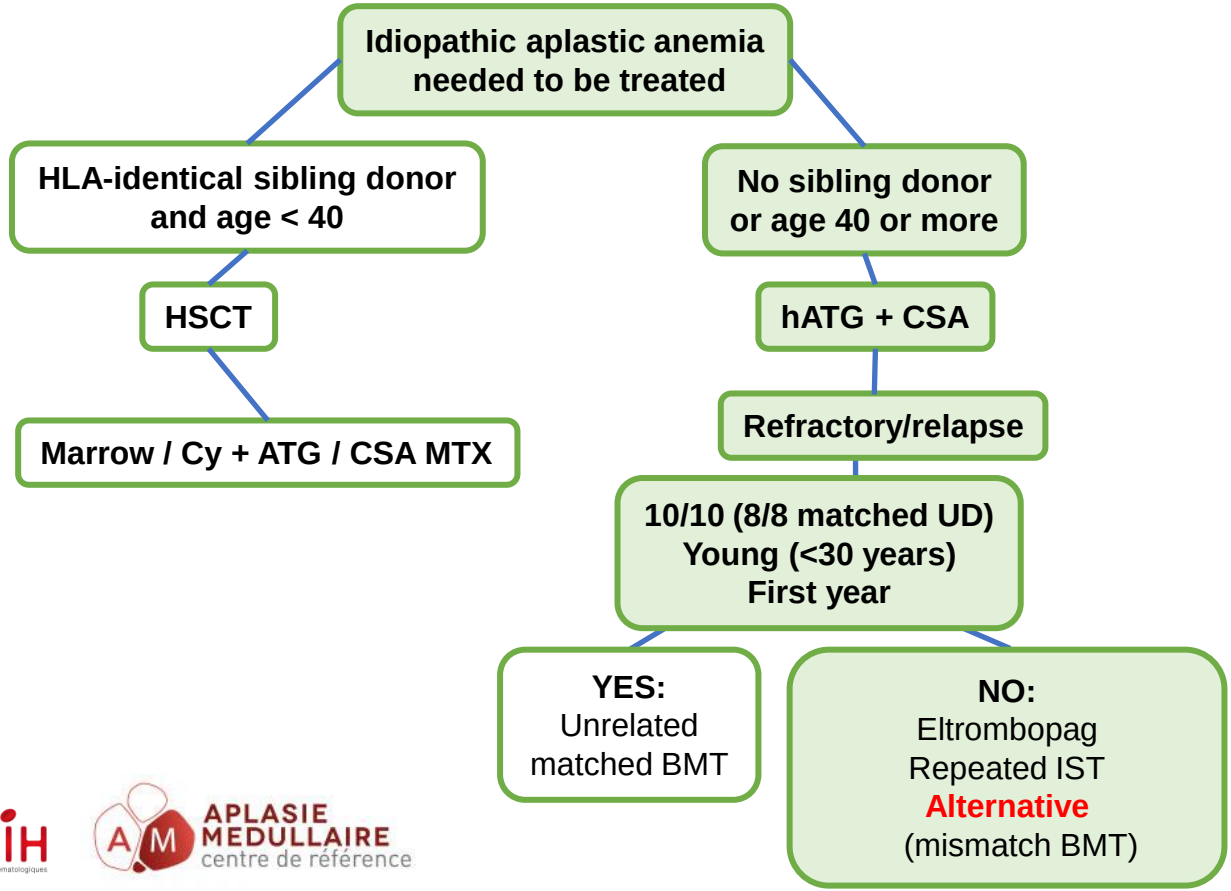

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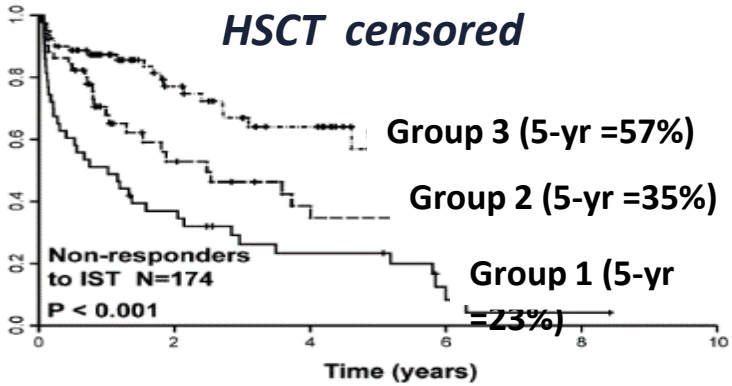
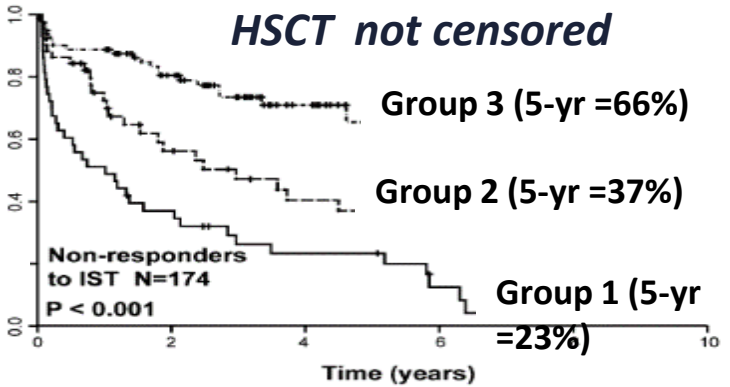
Emerging strategies: experimental transplantation

Experimental = Cord blood, **M**MUD 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)





Valdez *et al*, CID 2011

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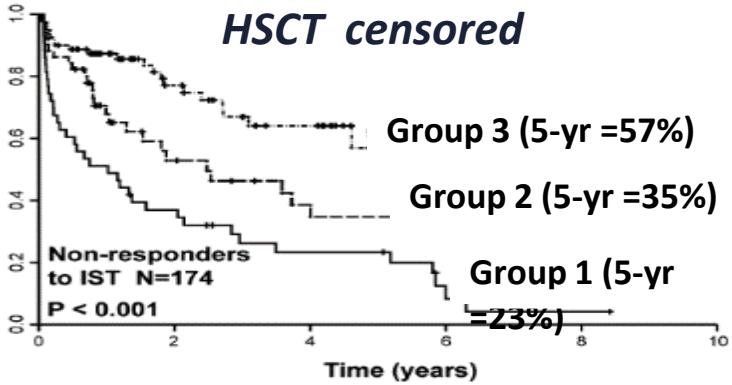

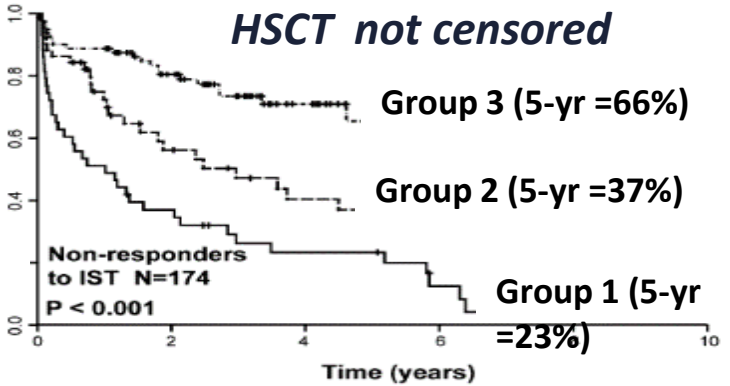

! Before Eltrombopag Era !

Valdez *et al*, CID 2011

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

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

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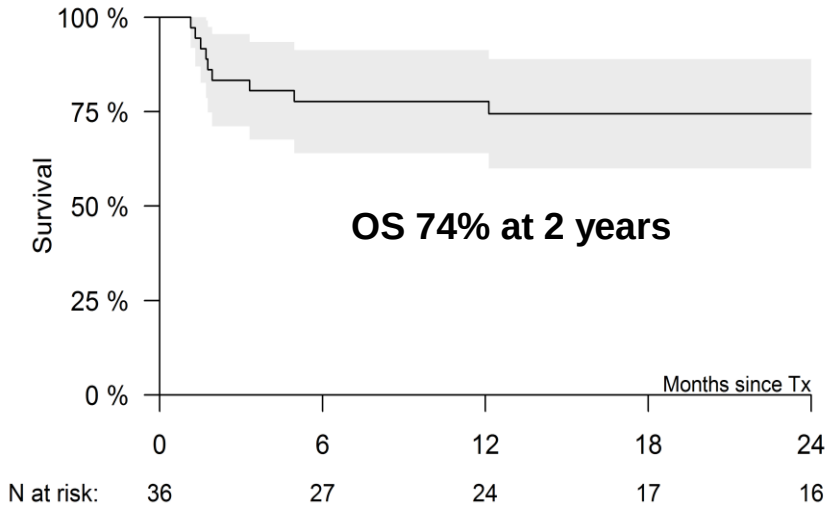
SFGM-TC Société Francophone de GREFFE DE MOELLE et de Thérapie Cellulaire

Peffault de Latour *et al*, Blood 2018

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

- Aquired (7/32):
  - 5 infections
  - 2 other HSCT-related

Prata *et al*, BMT 2019

Haplo-empty

Experimental approach

PHRC National 2019 / Haplo-EMPTY /PI : Régis Peffault de Latour

Allogreffe haplo-identique avec injection de cyclophosphamide post-greffe chez des patients présentant une **aplasie médullaire idiopathique réfractaire** à un traitement immunosuppresseur

> Endpoint primaire et nombre de patients requis:

- Taux de survie globale à 2 ans de 60% à 80% avec haplo-SCT avec PTCy.
- 31 patients (36 mois d'inclusion /24 mois suivi) , de 3-35 ans

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Conclusion

Acquired aplastic anemia in 2020

- **First line treatment in 2020**
  - Sibling transplantation: patients < 40 years
  - Horse ATG + Cyclosporine + EPAG for the others
  - Up-front MUD (experimental)

- **Refractory patients (6 months)**
  - Matched unrelated transplantation: patients < 30 years
  - Experimental transplantation: patients < 20 years (?); CB & Haplo-empty (experimental)
  - Eltrombopag for the others

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)

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

2016 EBMT European Society for Blood and Marrow Transplantation