

Algoritmo decisionale nell'Anemia Aplastica Severa nel nuovo scenario terapeutico

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AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

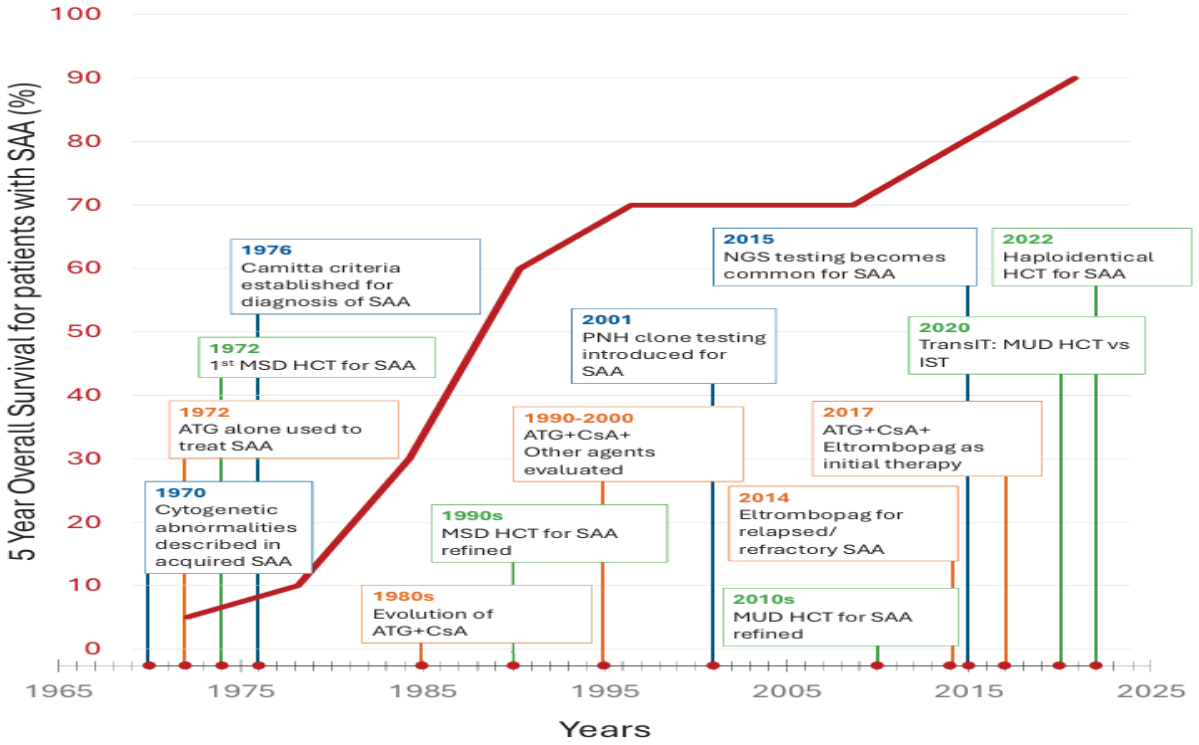
Severe Aplastic Anemia

- The term AA defines a disease characterized by peripheral blood (PB) pancytopenia due to a reduced or absent production of hematopoietic cells by the BM, without intrinsic or extrinsic atypical cell infiltration and without increase in reticulin fibers
- The incidence of AA in the western world is 2 new cases/year/ million inhabitants, while it is two to three times higher in East Asia
- The male-female ratio is 1:1 and there are two incidence peaks, one in young adults and the other one in the elderly . The median age at diagnosis in the pediatric group is 8–9 years
- Most cases (70–80 %) are idiopathic (that is without a detectable cause) but, in some cases, drugs, chemical or infectious agents can be identified as a possible precipitating or triggering cause of bone marrow failure (BMF)

Moderate or non-severe (NSAA)	Severe	Very severe
• Hypocellular bone marrow with peripheral blood cytopenias not fulfilling criteria for severe or very severe aplastic anemia	• Markedly hypoplastic marrow (<25 % of normal cellularity) or • Moderately hypoplastic marrow (25 %–50 % of normal cellularity with <30 % of remaining cells being hematopoietic) • At least two of the following conditions: a) Neutrophils <500/µl b) Platelets <20.000/µl c) Reticulocytes <20.000/µl[a]	• Like severe but with neutrophils <200/µl

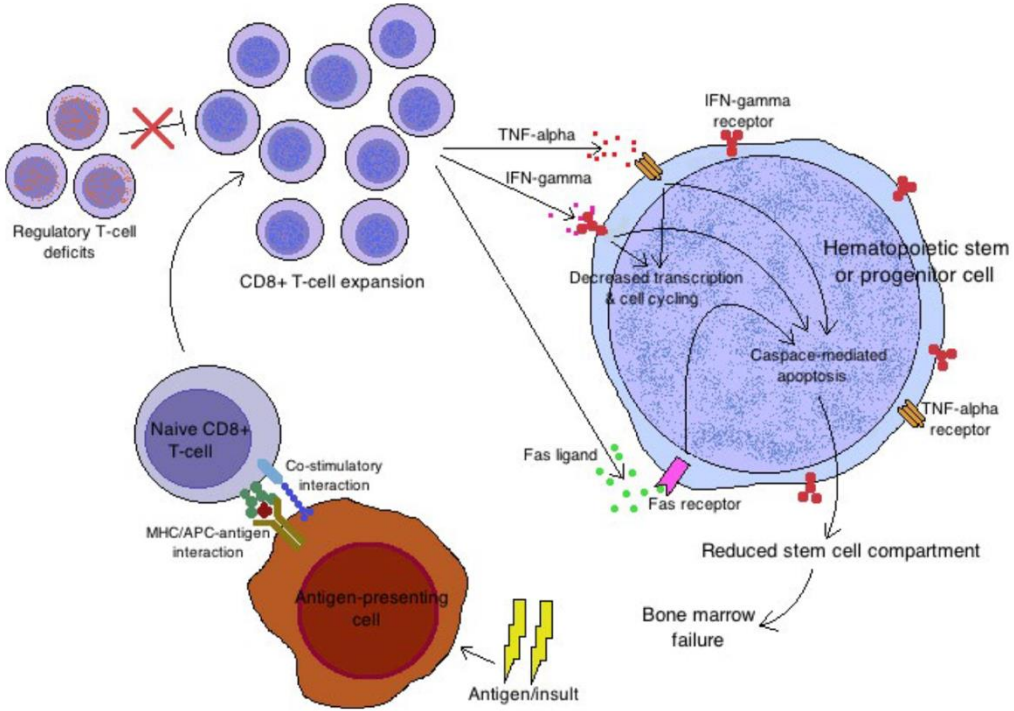
Guarina A et al, Blood Cells, Molecules and Diseases 108 (2024) 102860

A timeline of major advances in the diagnosis and treatment of SAA along with survival trends



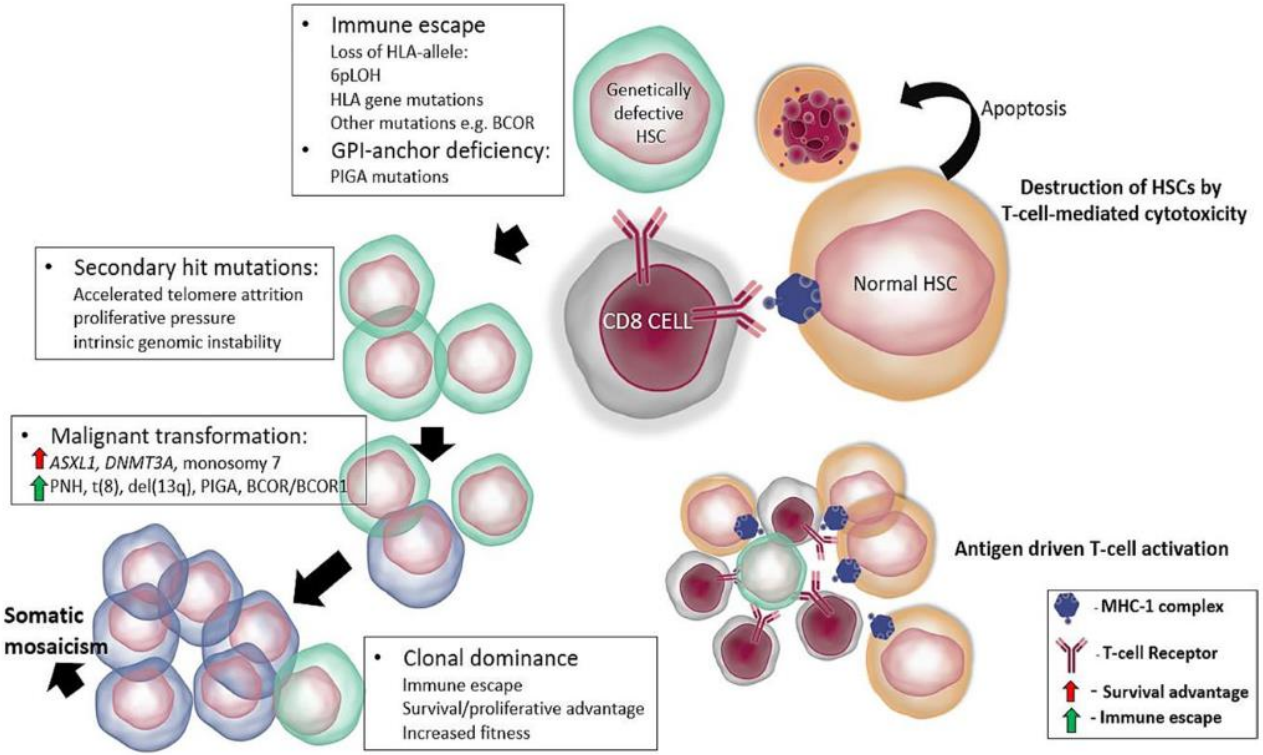
Akshay Sharma - Hematology Am Soc Hematol Educ Program 2025 Dec 5;2025(1):691-698

Immunopathogenic mechanism of hematopoietic stem or progenitor cell apoptosis in the aplastic anemia bone marrow



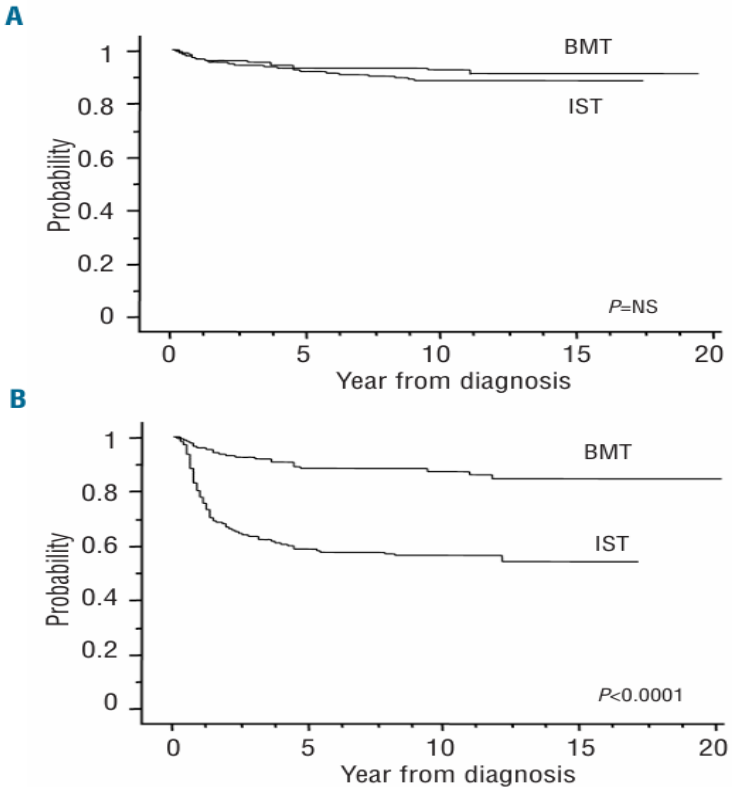
Shallis et al. Eur J Haematol. 2018;101:711–720

Immune escape and clonal evolution mechanisms in acquired aplastic anemia



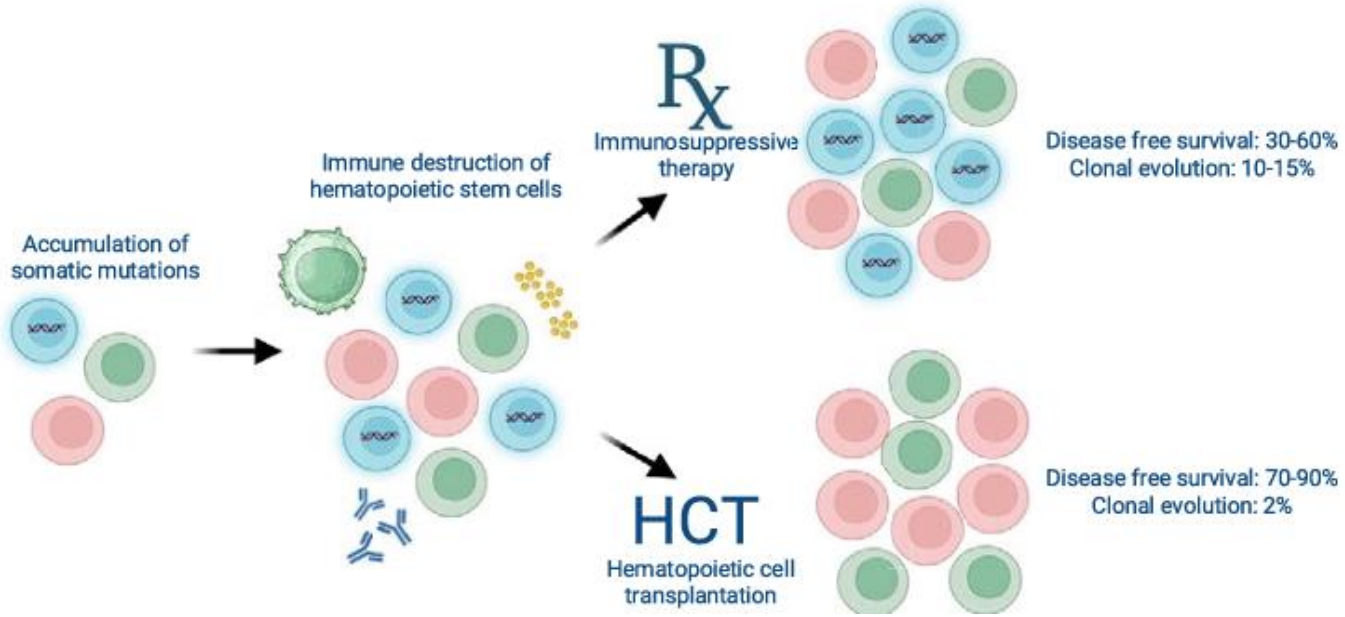
Prajwal C Boddu Tapan M Kadia Eur J Haematol 2019 Feb;102(2):103-110

First-line treatment for SAA in children: bone marrow transplantation from a matched family donor versus IST



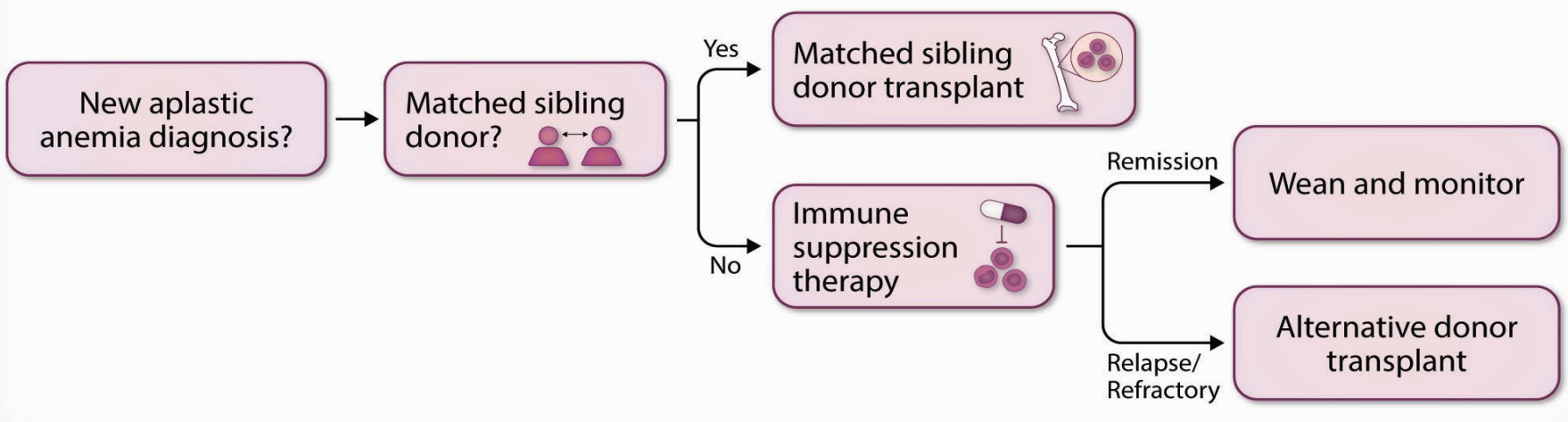
Overall survival	Hazard ratio	95% CI	P
First-line treatment: BMT	1.619	0.881-2.977	NS
Treatment period: 2000-2009	1.536	0.556-2.753	NS
Age: <10 years	2.207	1.240-3.927	0.007
Failure-free survival	**Hazard ratio**	**95% CI**	**P**
First-line treatment: BMT	4.497	2.935-6.891	<0.0001
Treatment period: 2000-2009	1.090	0.812-1.464	NS
Age: <10 years	1.113	0.833-1.488	NS

Yoshida N, et al. Haematologica. 2014;99(12):1784-1791.



Akshay Sharma - Hematology Am Soc Hematol Educ Program 2025 Dec 5;2025(1):691-698

Historical treatment algorithm for SAA



J.H. Oved *et al.* Haematologica | 110 August 2025

The NEW ENGLAND JOURNAL of MEDICINE

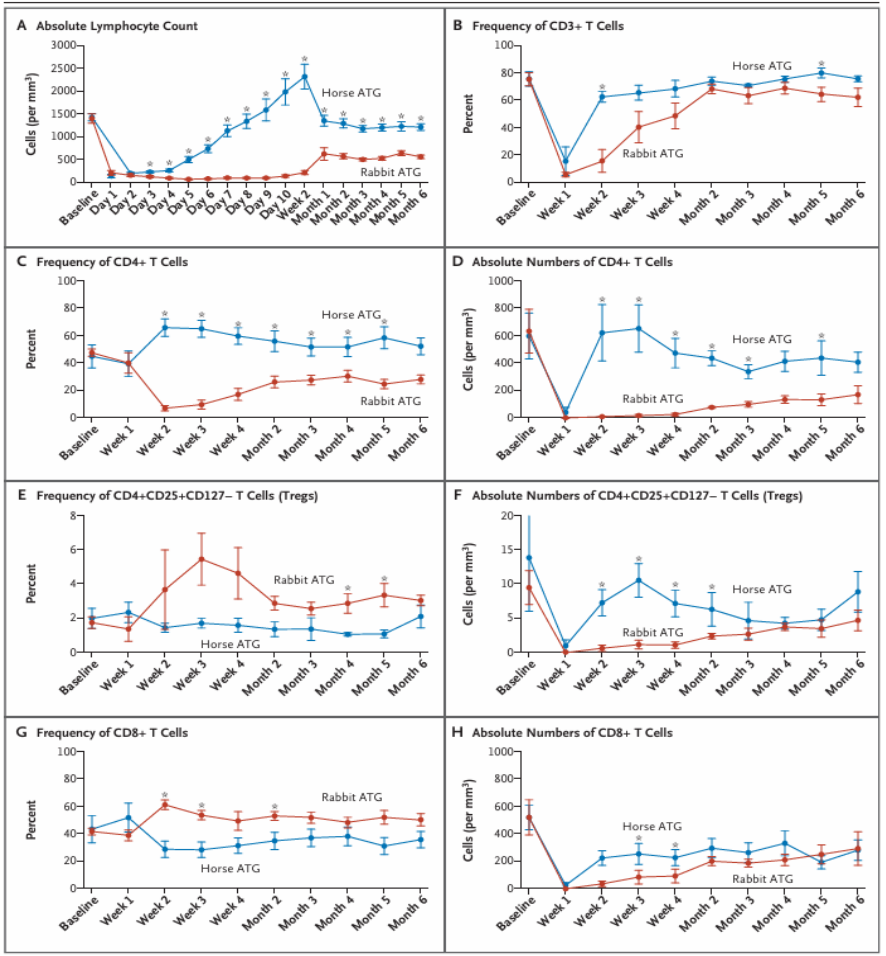
ORIGINAL ARTICLE

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.

Response	Horse ATG	95% CI	Rabbit ATG	95% CI	P-value
3 months	37/60 (62%)	49, 74	20/60 (33%)	21, 46	0.002
6 months	41/60 (68%)	56, 80	22/60 (37%)	24, 49	< 0.001

N Engl J Med. 2011 August 4; 365(5): 430–438



Ferrata Storti Foundation

Immunosuppressive therapy for pediatric aplastic anemia: a North American Pediatric Aplastic Anemia Consortium study

Zora R. Rogers,[1] Taizo A. Nakano,[2] Timothy S. Olson,[3] Alison A. Bertuch,[4] Winfred Wang,[5] Alfred Gillio,[6] Thomas D. Coates,[7] Anjulika Chawla,[8] Paul Castillo,[9] Peter Kurre,[10] Christopher Gamper,[11] Carolyn M. Bennett,[12] Sarita Joshi,[13] Amy E. Geddis,[14] Jessica Boklan,[15] Grzegorz Nalepa,[16] Jennifer A. Rothman,[17] James N. Huang,[18] Gary M. Kupfer,[19] Michaela Cada,[20] Bertil Glader,[21] Kelly J. Walkovich,[22] Alexis A. Thompson,[23] Rabi Hanna,[24] Adrianna Vlachos,[25] Maggie Malsch,[26] Edie A. Weller,[27] David A. Williams[28] and Akiko Shimamura[28]

Haematologica 2019
Volume 104(10):1974-1983

Study overview

Multicenter retrospective cohort study

North American Pediatric Aplastic Anemia Consortium (NAPAAC)

↓

314	25	2002–14
Children with SAA	Institutions	Treatment period

↓

First-line immunosuppressive therapy (IST)

264 patients (84.1%)

Horse ATG + cyclosporine

↓

Assessment of hematologic response, survival, relapse, clonal evolution and second-line therapy

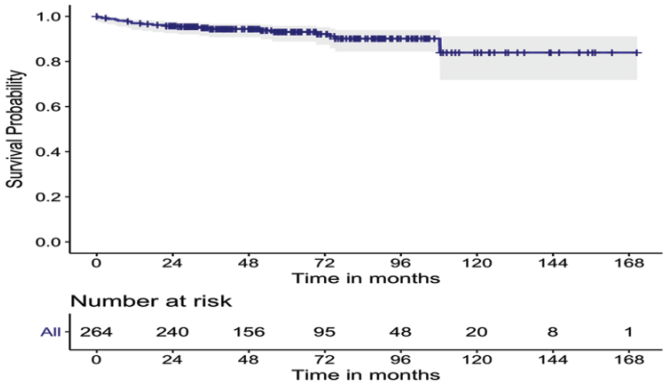
Response Outcome	Treatment	Number of responses	Response Rate (%)	95% CI*
Objective Response (CR+VGPR+PR)	All	222	70.7	65.3, 75.7
	hATG/CyA	188	71.2	65.3, 76.6
Deep Response (CR+VGPR)	All	212	67.5	62.0, 72.7
	hATG/CyA	180	68.2	62.2, 73.8
Complete Response (CR)	All	189	60.2	54.5, 65.7
	hATG/CyA	158	59.8	53.7, 65.8

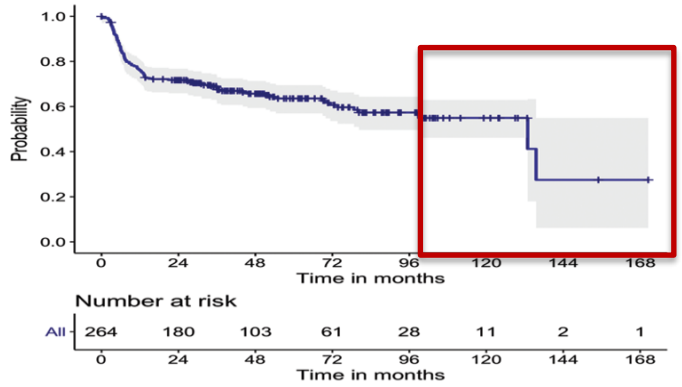
CR: Hb ≥10 g/dL and ANC ≥1x10^9/L and Plts ≥100x10^9/L
VGPR: Hb ≥8 g/dL and ANC ≥0.5x10^9/L and Plts ≥50x10^9/L
PR: Hb ≥8 g/dL and ANC ≥0.5x10^9/L and Plts ≥20x10^9/L
NR: Hb <8 g/dL or ANC <0.5x10^9/L or Plts <20x10^9/L

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CR: Hb ≥10 g/dL and ANC ≥1x10^9/L and Plts ≥100x10^9/L
VGPR: Hb ≥8 g/dL and ANC ≥0.5x10^9/L and Plts ≥50x10^9/L
PR: Hb ≥8 g/dL and ANC ≥0.5x10^9/L and Plts ≥20x10^9/L
NR: Hb <8 g/dL or ANC <0.5x10^9/L or Plts <20x10^9/L

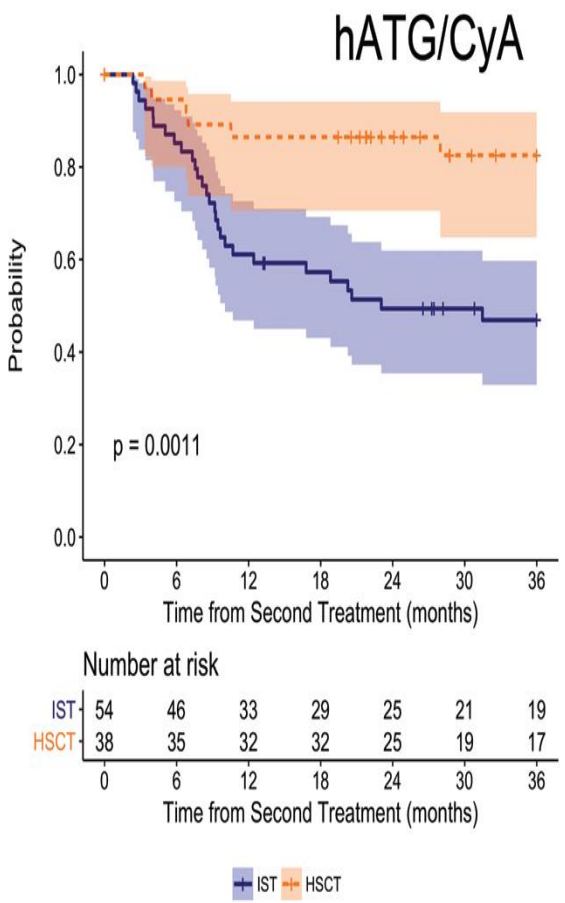
Post-treatment acquisition of chromosomal abnormalities				
Abnormality	Time from diagnosis to first detection (months)	Best response to initial therapy	Second therapy	Outcome
del(13q)(q14q22)*	4.6	CR by 6 months	None	Alive
i(X)(p10)*	5.5	CR by 3 years	None	Alive
der(5)t(1;5)(q11;q11.2)*	66.5	NR by 12 months	IST	Alive
-7*	37.1	VGPR by 2 years	None	Alive
+14,-18*	4.5	CR by 12 months	None	Alive
-7	20	NR by 2 years	BMT	Death, PNA
-5,-7,del(7q),del(20p)*	4.3	NR by 6 months	BMT	Alive
8*	71	VGPR by 5 years	None	Alive
i(2q)*	67.7	Relapse at 2 years	IST	Alive
-7,del(7q)*	30.3	NR by 12 months	IST	Death, ALL
del(7q22)*	67	Relapse at 2 years	IST	Death, AML
-7*	8	NR by 6 months	IST	Alive

*hATG/CyA subjects

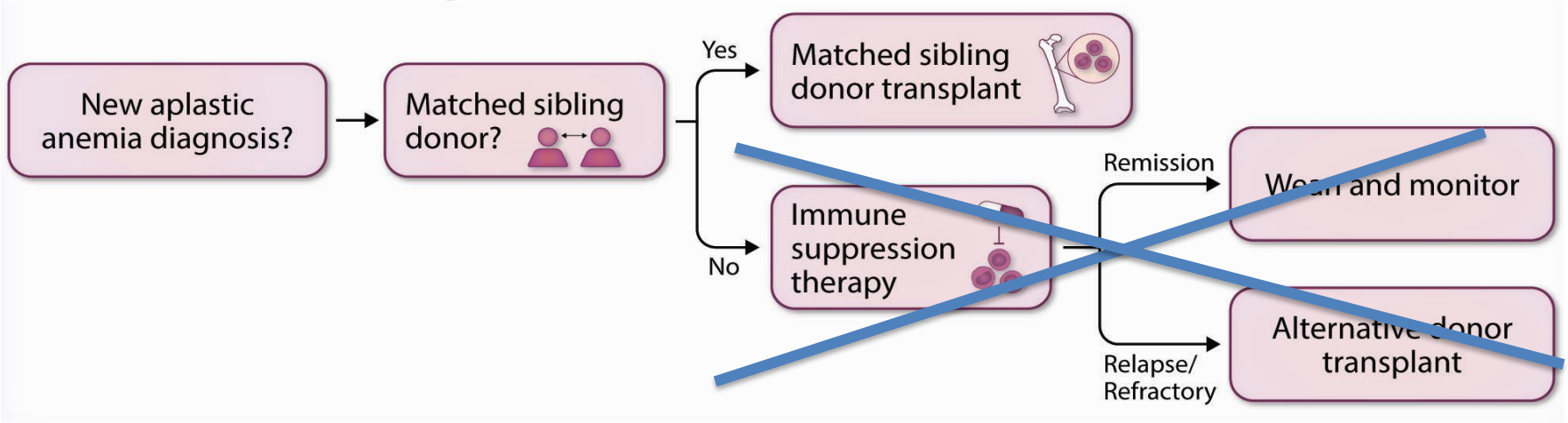
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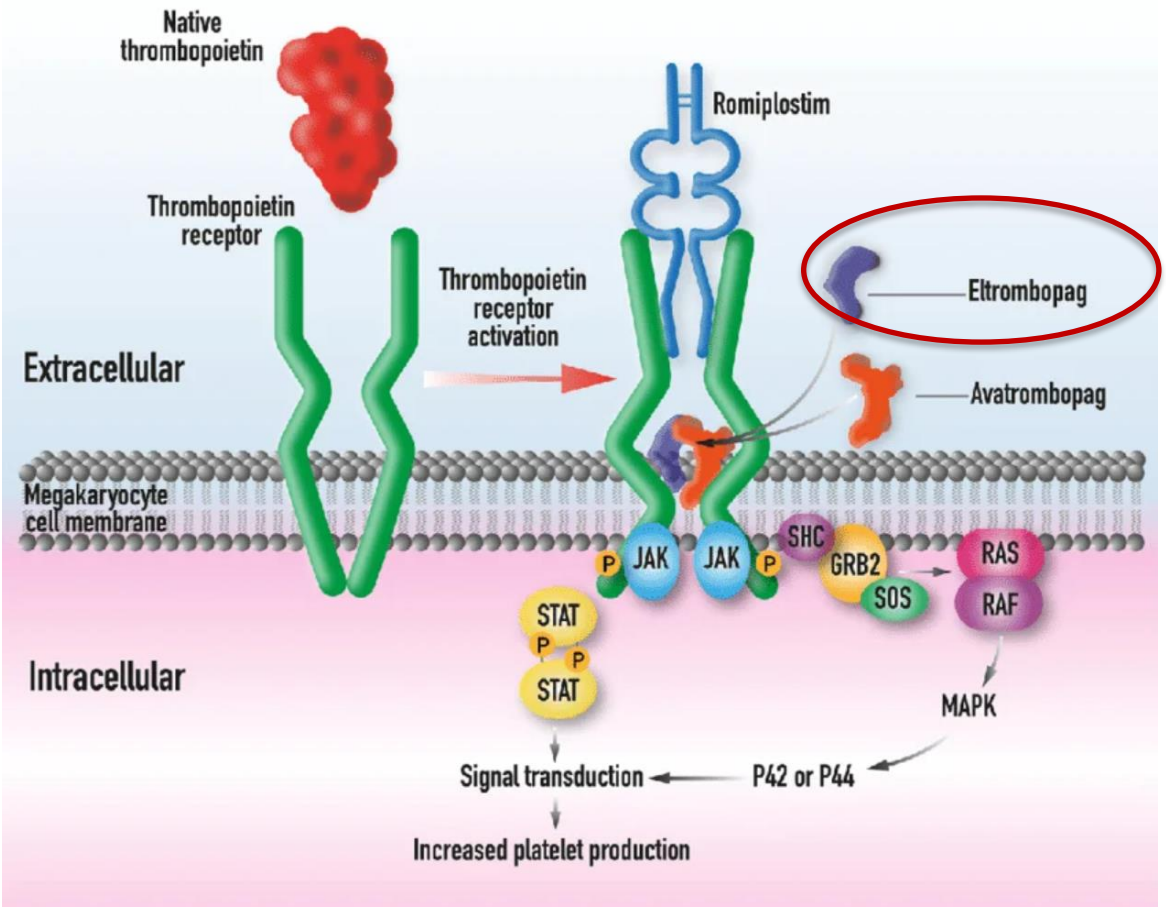
Subsequent Treatment	All patients (N=314)		hATG/CyA (N=264)	
	N	%	N	%
2nd therapy	110	35	92	35
3rd therapy	35	11	33	13
4th therapy	3	1	3	1



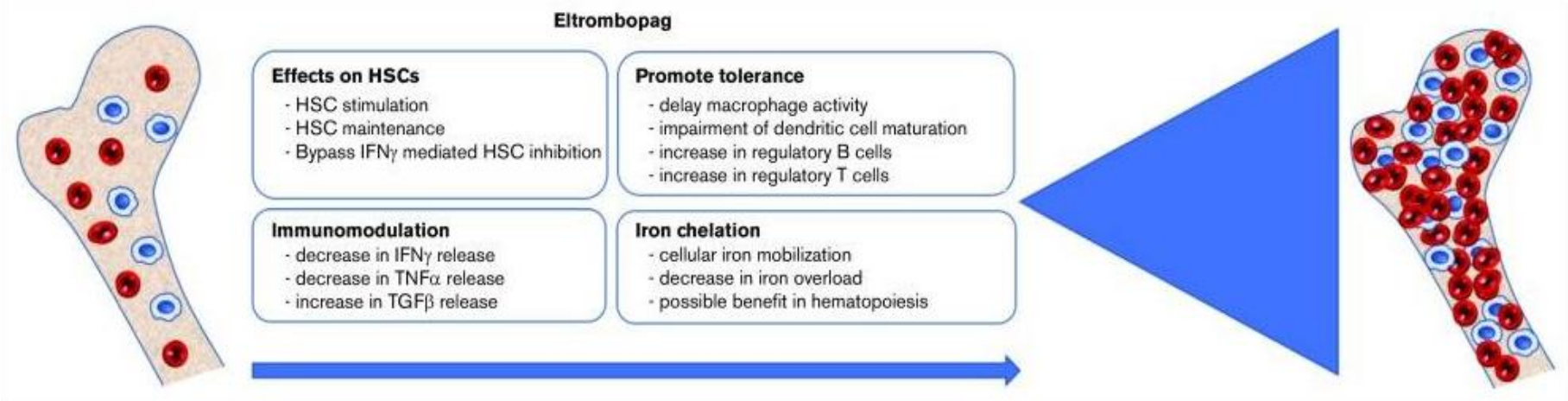
Historical treatment algorithm for SAA



J.H. Oved *et al.* Haematologica | 110 August 2025

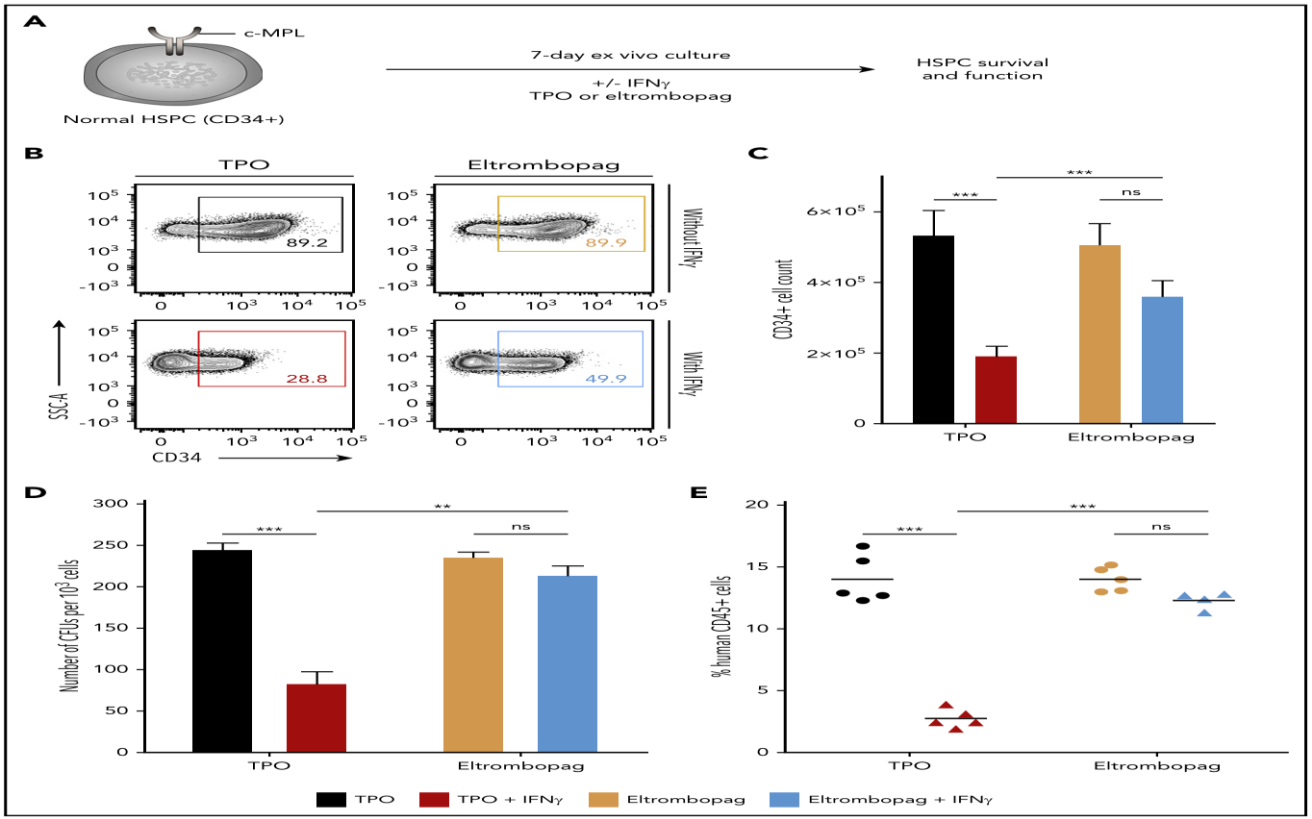

Native thrombopoietin
Romiplostim
Thrombopoietin receptor
Thrombopoietin receptor activation
Eltrombopag
Avatrombopag
Extracellular
Megakaryocyte cell membrane
JAK
JAK
P
P
SHC
GRB2
SOS
RAS
RAF
STAT
P
P
STAT
Intracellular
MAPK
Signal transduction
P42 or P44
Increased platelet production

How eltrombopag is acting in SAA



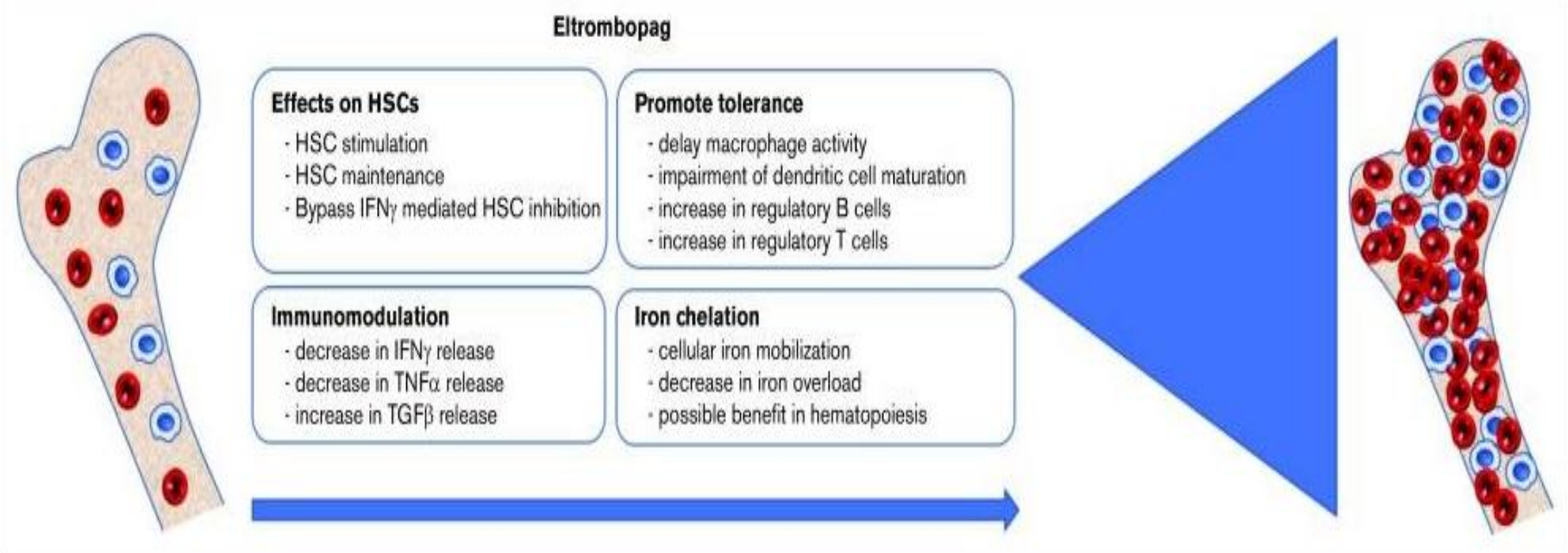
Phillip Scheinberg. Hematology Am Soc Hematol Educ Program 2018 Nov 30;2018(1):450–456.

Elt maintains human hematopoietic stem and progenitor cells under inflammatory conditions mediated by IFN-γ



Alvarado et al. Blood 9 MAY 2019 | VOLUME 133, NUMBER 19

How eltrombopag is acting in SAA



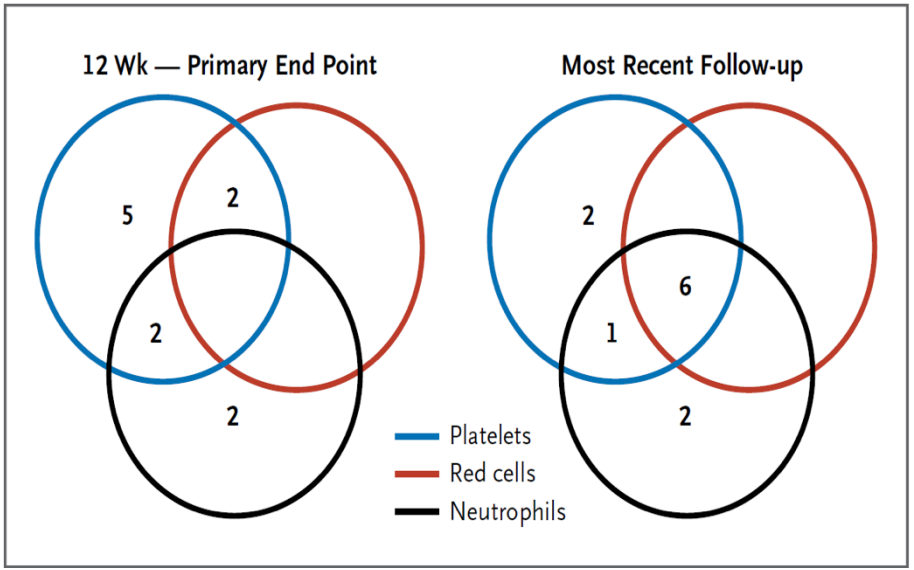
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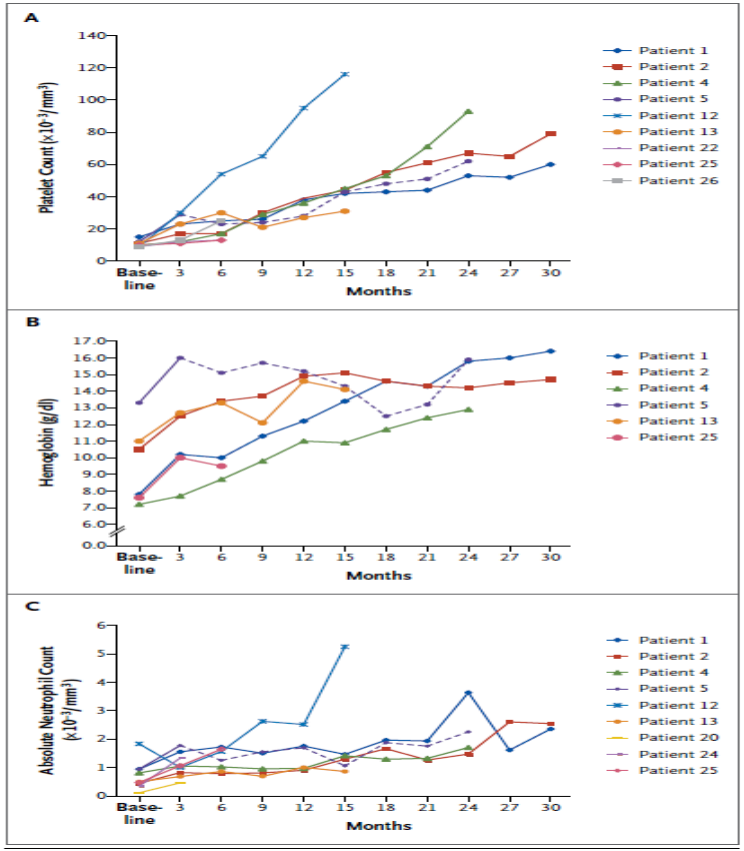
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 5, 2012 VOL. 367 NO. 1

Eltrombopag and Improved Hematopoiesis in Refractory Aplastic Anemia

Matthew J. Olnes, M.D., Ph.D., Phillip Scheinberg, M.D., Katherine R. Calvo, M.D., Ronan Desmond, M.D., Yong Tang, M.D., Ph.D., Bogdan Dumitriu, M.D., Ankur R. Parikh, M.D., Susan Soto, B.S.N., Angelique Biancotto, Ph.D., Xingmin Feng, M.D., Ph.D., Jay Lozier, M.D., Ph.D., Colin O. Wu, Ph.D., Neal S. Young, M.D., and Cynthia E. Dunbar, M.D.

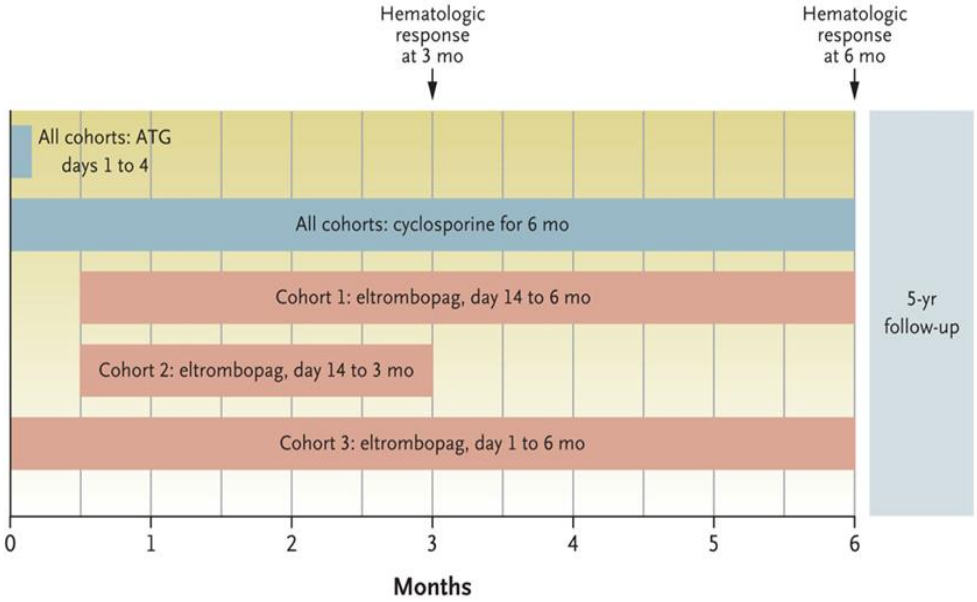




ORIGINAL ARTICLE

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.



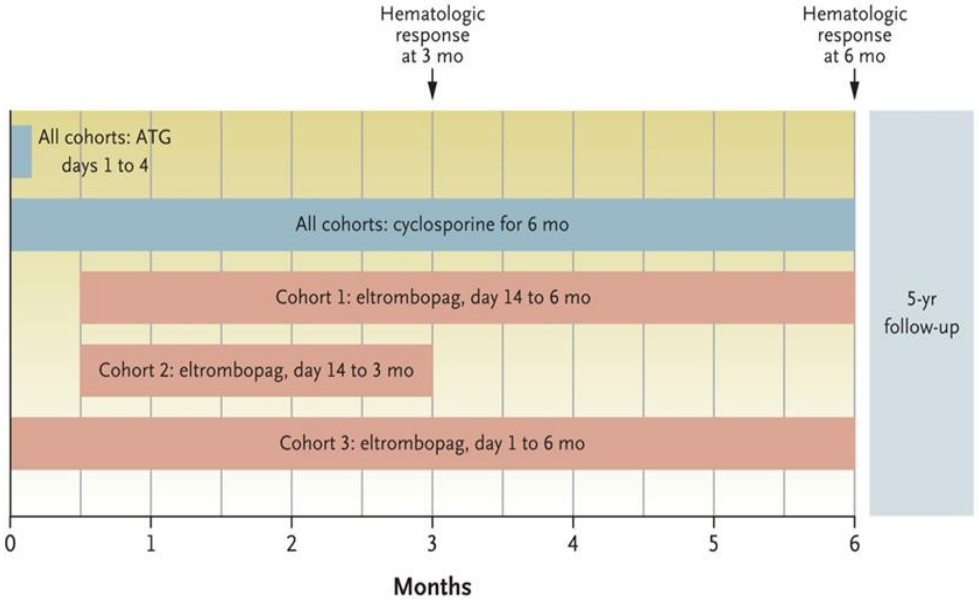
Cohort and Response	Rate at 3 Mo	Rate at 6 Mo	P Value
Cohort 1			
No. of patients	30	30	
Response — no. (% [95% CI])			
Overall response	23 (77 [61–93])	24 (80 [65–95])	
Partial response	18 (60 [41–79])	14 (47 [28–66])	
Complete response	5 (17 [3–31])	10 (33 [15–31])	0.01
Cohort 2			
No. of patients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

Townsley et al. N Engl J Med. 2017 April 20; 376(16): 1540–1550.

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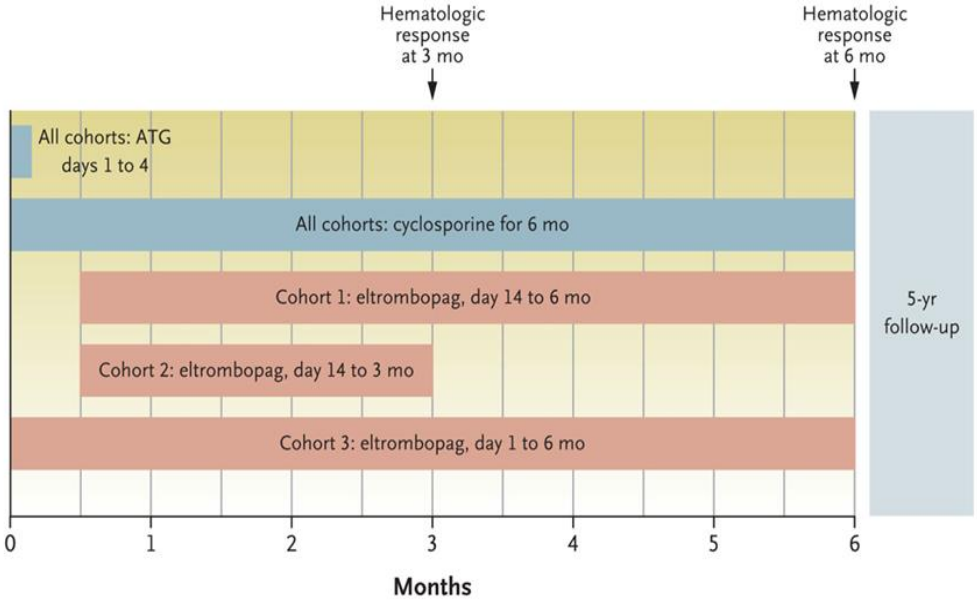
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Townsley et al. N Engl J Med. 2017 April 20; 376(16): 1540–1550.

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Eltrombopag Added to Immunosuppression in Severe Aplastic Anemia

R. Peffault de Latour, A. Kulasekararaj, S. Iacobelli, S.R. Terwel, R. Cook, M. Griffin, C.J.M. Halkes, C. Recher, F. Barraco, E. Forcade, J.-C. Vallejo, B. Drexler, J.-B. Mear, A.E. Smith, E. Angelucci, R.A.P. Raymakers, M.R. de Groot, E. Daguindau, E. Nur, W. Barcellini, N.H. Russell, L. Terriou, A.-P. Iori, U. La Rocca, A. Sureda, I. Sánchez-Ortega, B. Xicoy, I. Jarque, J. Cavenagh, F. Sicre de Fontbrune, S. Marotta, T. Munir, J.M.L. Tjon, S. Tavitian, A. Praire, L. Clement, F. Rabian, L. Marano, A. Hill, E. Palmisani, P. Muus, F. Cacace, C. Frieri, M.-T. van Lint, J.R. Passweg, J.C.W. Marsh, G. Socié, G.J. Mufti, C. Dufour, and A.M. Risitano, for the Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation*

Cohort and Response	Response at 3 Mo				Response at 6 Mo	
	Group A: Horse ATG–Cyclosporine (N=101)	Group B: Horse ATG–Cyclosporine–Eltrombopag (N=96)	Odds Ratio (95% CI)*	P Value	Group A: Horse ATG–Cyclosporine (N=101)	Group B: Horse ATG–Cyclosporine–Eltrombopag (N=95)†
All patients — no. (%)						
Complete response‡	10 (10)	21 (22)	3.2 (1.3–7.8)	0.01	20 (20)	30 (32)
Partial response	21 (21)	36 (38)			21 (21)	35 (37)
No response	70 (69)	39 (41)			60 (59)	30 (32)
Overall response§	31 (31)	57 (59)			41 (41)	65 (68)
Patients with severe aplastic anemia — no./total no. (%)						
Complete response	10/67 (15)	17/62 (27)			15/67 (22)	20/62 (32)
Partial response	17/67 (25)	27/62 (44)			16/67 (24)	26/62 (42)
No response	40/67 (60)	18/62 (29)			36/67 (54)	16/62 (26)
Patients with very severe aplastic anemia — no./total no. (%)						
Complete response	0/34	4/34 (12)			5/34 (15)	10/33 (30)
Partial response	4/34 (12)	9/34 (26)			5/34 (15)	9/33 (27)
No response	30/34 (88)	21/34 (62)			24/34 (71)	14/33 (42)
Patients ≥15 to <40 yr — no./total no. (%)						
Complete response	6/36 (17)	6/29 (21)			11/36 (31)	15/29 (52)
Partial response	6/36 (17)	14/29 (48)			7/36 (19)	8/29 (28)
No response	24/36 (67)	9/29 (31)			18/36 (50)	6/29 (21)
Patients ≥40 yr — no./total no. (%)						
Complete response	4/65 (6)	15/67 (22)			9/65 (14)	15/66 (23)
Partial response	15/65 (23)	22/67 (33)			14/65 (22)	27/66 (41)
No response	46/65 (71)	30/67 (45)			42/65 (65)	24/66 (36)

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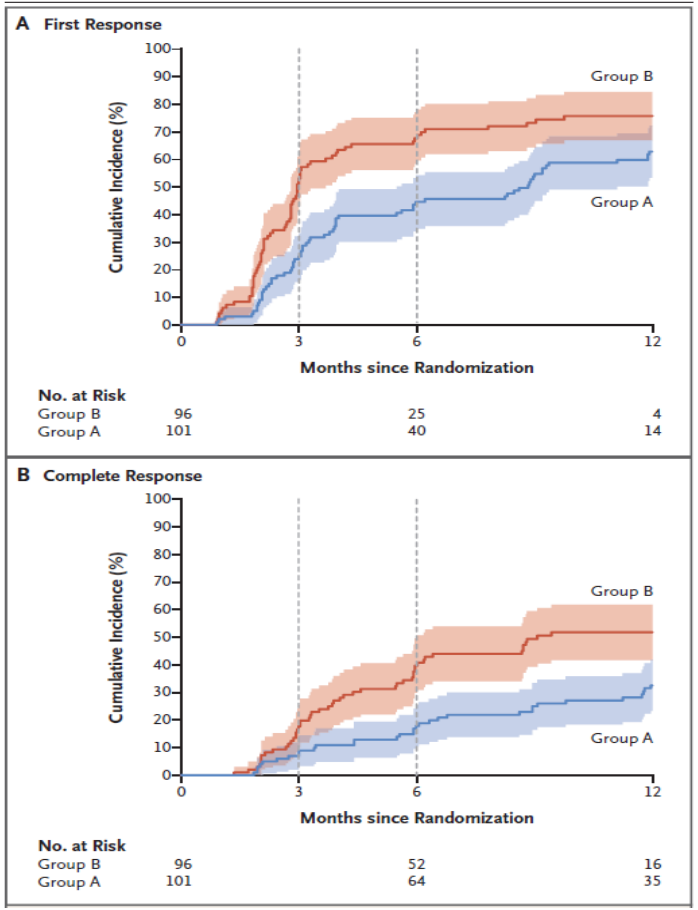
Peffault de Latour et al., *N Engl J Med* 2022;386:11-23)

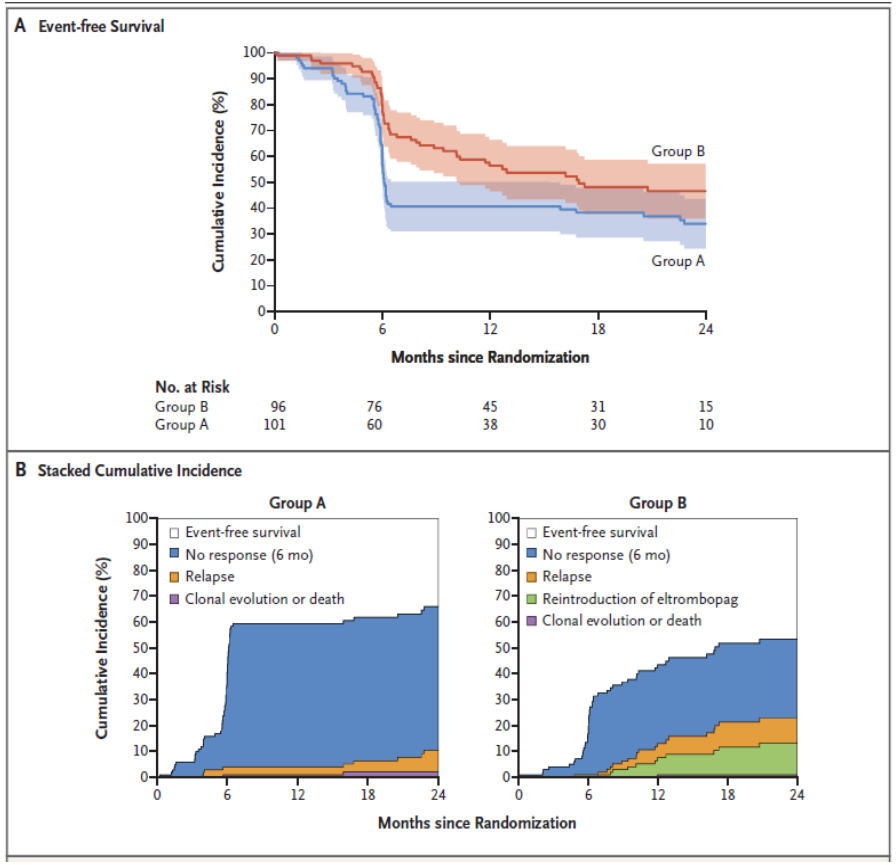
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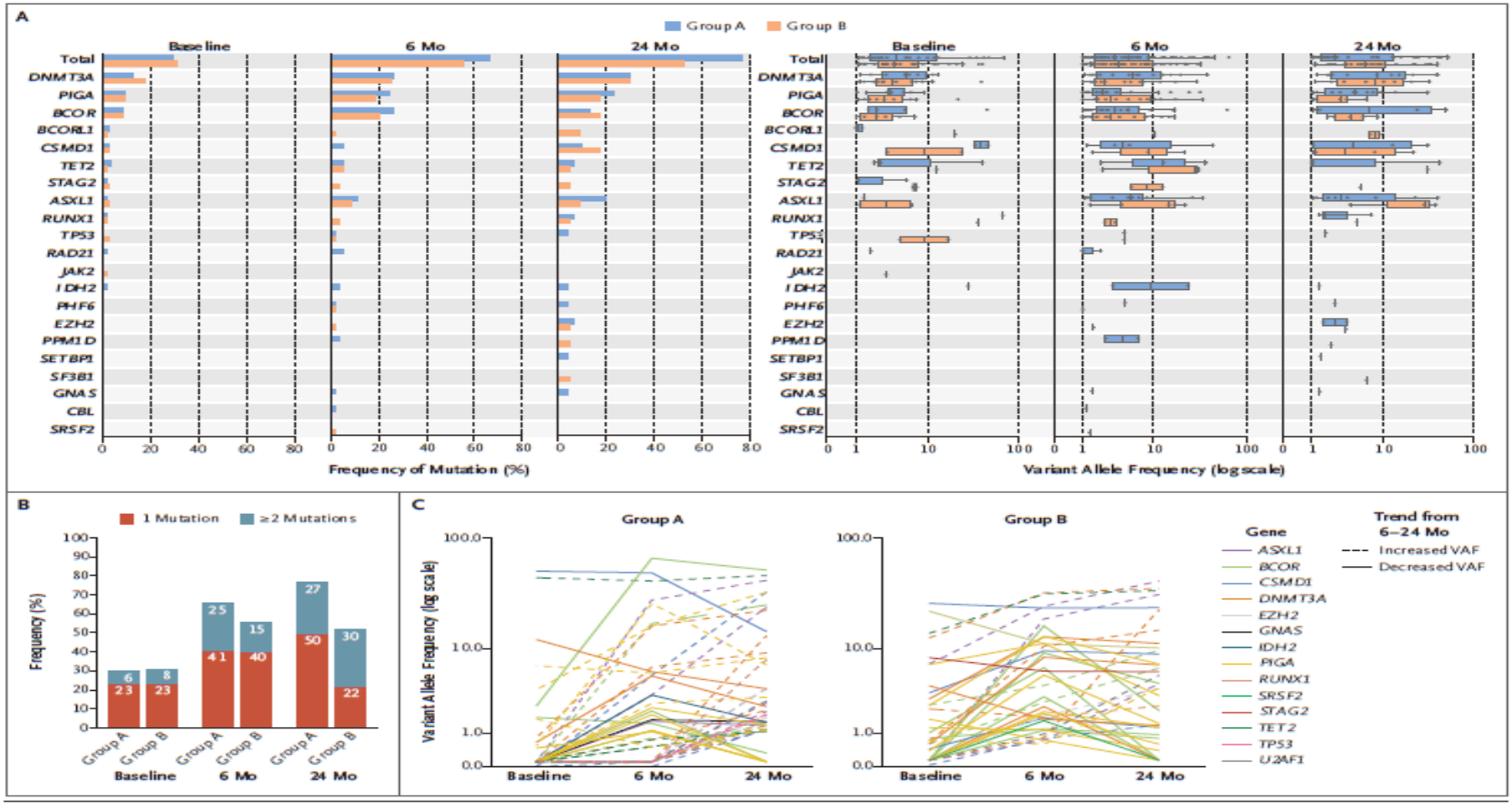
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Peffault de Latour et al., *N Engl J Med* 2022;386:11-23)





Peffault de Latour et al., *N Engl J Med* 2022;386:11-23)



Peffault de Latour et al., *N Engl J Med* 2022;386:11-23)

Eltrombopag Added to Standard Immunosuppressive Treatment as Front-Line Therapy for Severe Aplastic Anemia: Long-Term Outcomes of the Phase-3 Randomized Superiority EBMT-SAAWP RACE Study

Endpoint	Arm A	Arm B	Statistics
Cumulative incidence of complete response	35.3%	62.4%	p<0.001
Complete response at 24 months	30.3%	41.9%	OR 1.94, p=0.037
Overall survival	86.0%	91.4%	p=0.081; adj. HR 0.54 (0.28-1.04), p=0.064
Disease-free survival	36.6%	54.7%	adj. HR 0.50, p<0.001
Event-free survival	32.7%	48.4%	adj. HR 0.54, p<0.001
Relapse (cumulative incidence)	18.0%	22.7%	p=0.82
Clinical PNH	8.1%	1.1%	p=0.039; adj. HR 0.12
Any additional treatment	50.5%	38.5%	-

Risitano AM et al. Am J Hematol 2026;101:2520-2532. doi: 10.1002/ajh.70445

The efficacy and the safety of eltrombopag in pediatric patients with severe aplastic anemia: a systematic review

Study	Design	Patients	Age (years)	IST dose	Eltrombopag (ELT) dose
Fang 2021	Retrospective observational	18 IST+ELT 39 IST	16 years or younger (1.3-13.5)	Porcine ATG 30 mg/kg/day CsA 3-5 mg/kg/day	1 mg/kg/day (max 50 mg/day)
Jie 2021	Retrospective observational	14 IST+ELT	Under 18	Rabbit ATG 3.3-3.5 mg/kg/day CsA 5 mg/kg/day	75 mg/day if over 6 years 2.5 mg/kg/day at 2-5 years
Lesmana 2021	Retrospective observational	9 IST+ELT 16 IST	Under 18	Horse ATG 40 mg/kg/day CsA 5 mg/kg/day	25 mg/day under 6 years 50 mg/day at 6-8 years max 150 mg/day
Filippidou 2020	Case series	11 IST+ELT	Under 18 (2.7-15.5)	Not reported	From 25 to 150 mg/day
Su 2021	Case series	8 IST+ELT	Under 16 (3-16)	Not reported	From 25 mg/day
Groarke 2020 (publ. 2021)	Clinical trial, historical control	40 IST+ELT 87 IST	Under 18	Horse ATG 40 mg/kg CsA 3 mg/kg	150 mg/day from 12 years 75 mg/day at 6-11 years 2.5 mg/kg at 2-5 years
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Goronkova 2022	Randomised trial	49 IST 49 IST+ELT	2-18	Horse ATG 40 mg/kg/day CsA 5 mg/kg/day	2 mg/kg/day

Marrapodi et al., *Front Pediatr* 2023;11:1149718

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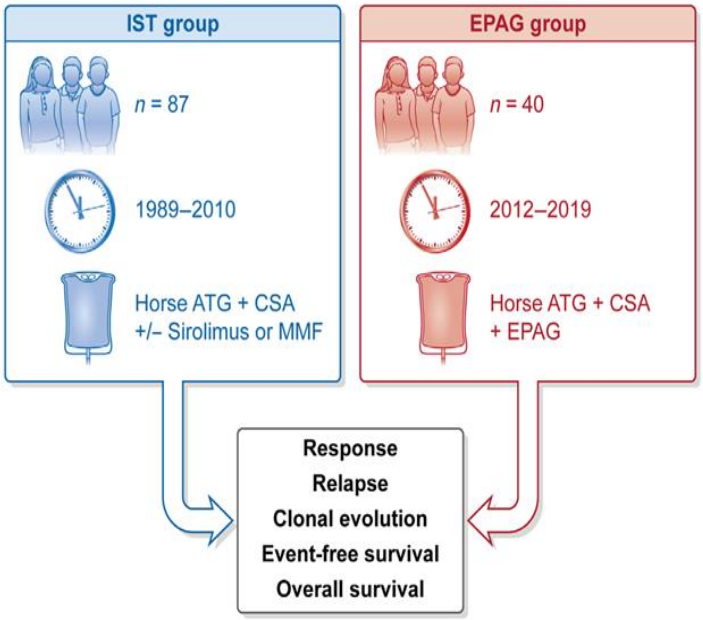
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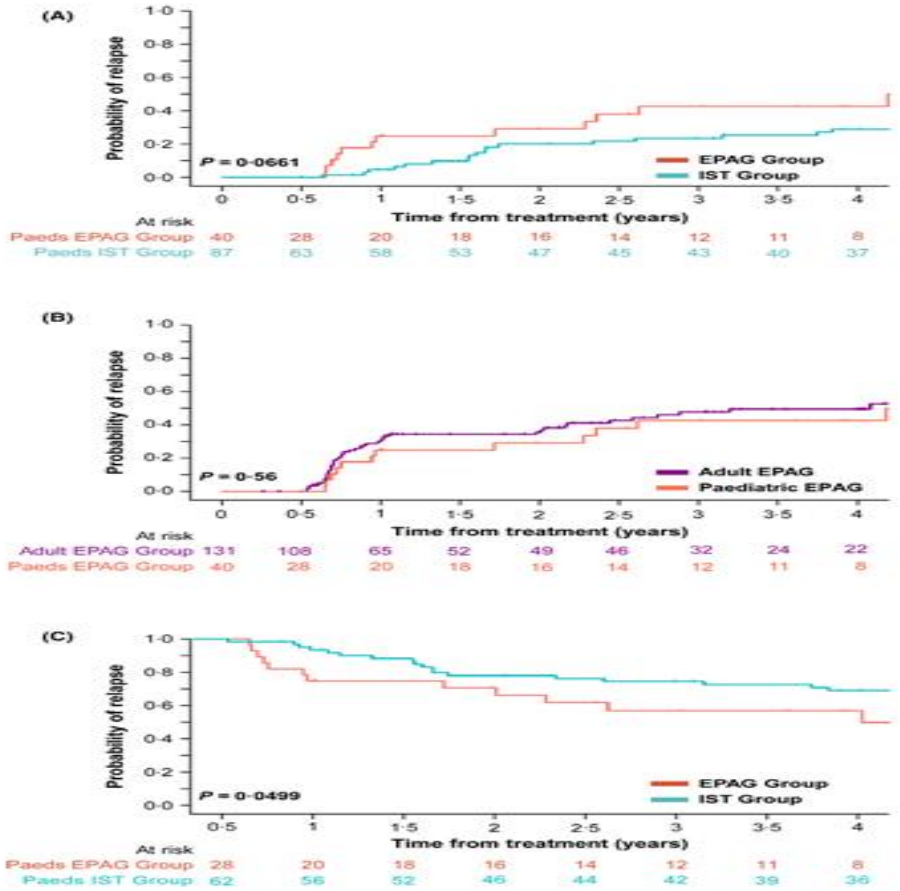
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Marrapodi et al., *Front Pediatr* 2023;11:1149718





Emma M. Groarke ET AL. Br J Haematol. 2021 February ; 192(3): 605–614.

Haematological response in paediatric IST group *versus* EPAG group.

	IST group (n = 87)	EPAG group (n = 40)	P
3-month response			
Response, n (%)			
Overall response	55 (63)	27 (68)	0·64
CR	12 (14)	9 (23)	0·26
PR	43 (49)	18 (45)	
NR	29 (33)	9 (23)	
Off study	3 (3)	4 (10)	
6-month response			
Response, n (%)			
Overall response	63 (72)	28 (70)	0·78
CR	20 (23)	12 (30)	0·42
PR	43 (49)	16 (40)	
NR	19 (22)	4 (10)	
Off study	5 (6)	8 (20)	
1-year response			
Response, n (%)			
Overall response	52 (60)	20 (50)	0·38
CR	31 (36)	16 (40)	0·57
PR	21 (24)	4 (10)	
NR	0 (0)	0 (0)	
Relapsed	5 (6)	7 (18)	
Off study	30 (34)	12 (30)	
Not reached	0 (0)	1 (3	

	IST group	EPAG group	P
Younger children aged <12 years			
Response, n (%)	n = 45	n = 16	
Overall response	35 (78)	10 (63)	0·29
CR	11 (24)	1 (6)	0·049 *
PR	24 (53)	9 (56)	
NR	9 (20)	2 (13)	
Off study	1 (2)	4 (25)	
Adolescents aged >12 years			
Response, n (%)	n = 42	n = 24	
Overall response	28 (67)	18 (75)	0·48
CR	9 (21)	11 (46)	0·052
PR	19 (45)	7 (29)	
NR	10 (24)	2 (8)	
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Clonal evolution in paediatric patients.

Patient	Time to clonal evolution, days	Clonal evolution	Karyotype	Risk category	*SAMD9/SAMD9L*
Paediatric EPAG group					
EPAG2	1470	Del 5q	46,XX,del(5)(q15q31)[2]/46,XX[19]	Low	Not assessed
EPAG9	733	Translocation (5;12)	46,XY,t(5;12)(p10;p10)[2]/46,XY[18]	Low	Not assessed
EPAG15	88	Monosomy 7	45,XY,−7[6]/46,XY[14]	High	Not assessed
EPAG28	1049	AML with Monosomy 7	45,XX,−7[7]/46,XX[13]	High	No
EPAG40	97	Monosomy 7	45,XY,−7[12]/46,XY[8]	High	No
Paediatric IST group					
IST46	2528	AML	46,XY[20]	High	
IST57	990	13q del	46,XX,del(13)(q12q14)[5]	Low	
IST20	185	Trisomy 8	47,XX,+8[2]/46,XX[19]	Low	
IST29	2715	MDS-MLD	Unavailable	High	
IST78	193	13q del	46,XY,del(13)(q12q14)[3]/46,XY[1]	Low	
IST92	955	Translocation (6;14)	46,XY,t(6;14)(q24;q24)[3] 46,XY[17]	Low	
IST97	359	Monosomy 7	45,XY,−7[4/20]	High	
			45,XY,−7,inv(12)(q15q24.1)[1/20]		
			46,XY,inv (12)(q15q24.1)[2/20]		
			46,XY[13/20]		
IST135	1853	Monosomy 7	Unavailable	High	

Emma M. Groarke ET AL. Br J Haematol. 2021 February ; 192(3): 605–614.

Table 2. Hematological response to first-line treatment by treatment group

	ELTR + IST (n = 49), n (%)	IST (n = 49), n (%)	Difference in % (95% CI)*	*P* value
4 mo				
OR	32 (65)	26 (53)	12 (–7 to 32)	.218
CR	15 (31)	6 (12)	18 (3 to 34)	.027
PR	17 (35)	20 (41)	–	–
NR	16 (33)	23 (47)	–14 (–33 to 5)	.149
Death	1 (2)	0 (0)	–	–
6 mo				
OR	27 (55)	25 (51)	4 (–16 to 24)	.686
CR	17 (35)	9 (18)	16 (–1 to 34)	.067
PR	10 (20)	16 (33)	–	–
Relapse	5 (10)	1 (2)	–	–
NR	16 (33)	22 (45)	–	–
Second-line therapy	12 (24)	14 (29)	–	–
HSCT	2 (4)	2 (4)	–	–
Death	1 (2)	1 (2)	–	–
1 y				
OR	25 (51)	22 (45)	6 (–14 to 26)	.544
CR	16 (33)	16 (33)	0 (–19 to 19)	1.0
PR	9 (18)	6 (12)	–	–
Relapse	7 (14)	4 (8)	–	–
NR	14 (29)	21 (43)	–	–
Second-line therapy	8 (16)	14 (29)	–	–
HSCT	2 (4)	3 (6)	–	–
Second-line therapy + HSCT	4 (8)	4 (8)	–	–
Death	1 (2)	1 (2)	–	–
Not reached	2 (4)	1 (2)	–	–

NR, no response; CI, confidence interval.

Efficacy of combined immunosuppression with or without eltrombopag in children with newly diagnosed aplastic anemia

Olga Goronkova,[1] Galina Novichkova,[1] Tatiana Salimova,[1] Irina Kalinina,[1] Dina Baidildina,[1] Ulyana Petrova,[1] Kristina Antonova,[1] Maria Sadovskaya,[1] Elena Suntsova,[1] Dmitry Evseev,[1] Victor Matveev,[1] Dmitry Venyov,[1] Lili Khachatryan,[1] Dmitry Litvinov,[1] Alexey Pshonkin,[1] Galina Ovsyannikova,[1] Natalia Kotskaya,[1] Darina Gobadze,[1] Yulia Olshanskaya,[1] Alexander Popov,[1] Elena Raykina,[1] Olga Mironenko,[1] Kirill Voronin,[1] Bazarma Purbueva,[2] Elmira Boichenko,[3] Yulia Dinikina,[4] Evgeniya Guseynova,[5] Dmitry Sherstnev,[6] Elena Kalinina,[7] Sergey Mezentsev,[8] Olga Streneva,[9] Natalia Yudina,[10] Olga Plaksina,[11] Elena Erega,[12] Michael Maschan,[1] and Alexey Maschan[1]



Table 3. Four-month hematological response to first-line treatment depending on the severity of AA

	SAA (ANC ≥0.2 × 10⁹/L) (n = 39)				vSAA (ANC <0.2 × 10⁹/L) (n = 59)			
	ELTR + IST (n = 18), n (%)	IST (n = 21), n (%)	Difference in % (95% CI)	*P* value	ELTR + IST (n = 31), n (%)	IST (n = 28), n (%)	Difference in % (95% CI)	*P* value
OR	16 (89)	12 (57)	32 (6 to 57)	.028	16 (52)	14 (50)	2 (–24 to 27)	.902
CR	8 (44)	6 (29)	16 (–14 to 46)	.303	7 (23)	0 (0)	23 (8 to 37)	.011
PR	8 (44)	6 (29)	–	–	9 (29)	14 (50)	–	–
NR	2 (11)	9 (43)	–32 (–57 to –6)	.028	14 (45)	14 (50)	–5 (–30 to 21)	.710
Death	0 (0)	0 (0)	–	–	1 (3)	0 (0)	–	–

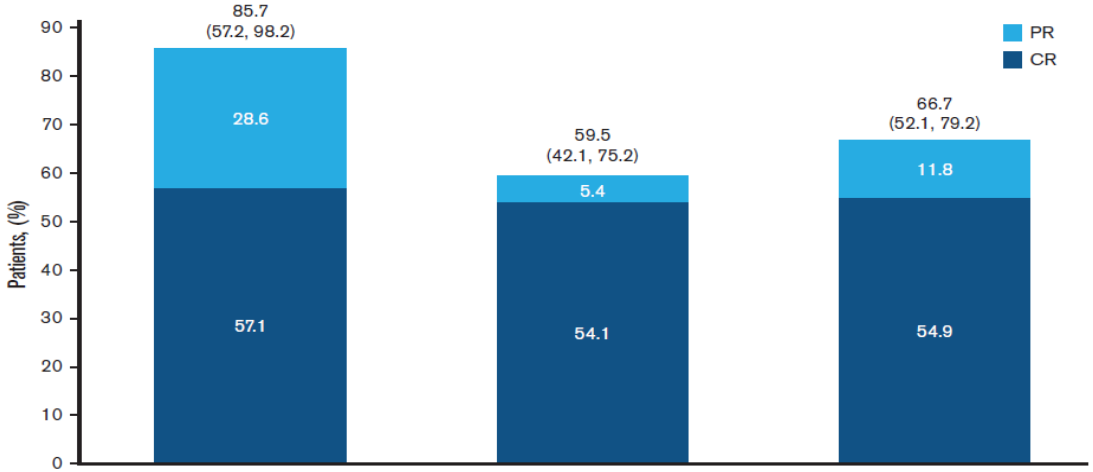
Olga Goronkova et al, Blood Adv 2023 Mar 28;7(6):953-962

REGULAR ARTICLE

blood advances

Eltrombopag in combination with immunosuppressive therapy in pediatric severe aplastic anemia: phase 2 ESCALATE trial

Akiko Shimamura,[1] Alexey Maschan,[2] Carolyn Bennett,[3] Sujith Samarasinghe,[4] Jason E. Farrar,[5] Chi-kong Li,[6] Nongnuch Sirachainan,[7] Bunchoo Pongtanakul,[8] Patcharee Komvilaisak,[9] Ludmila Zubarovskaya,[10] Jennifer A. Rothman,[11] Kelly Walkovich,[12] Taizo A. Nakano,[13] Alison A. Bertuch,[14] Anabela Ferrao,[15] Rukhmi Bhat,[16] Rabi Hanna,[17] Kathleen Overholt,[18] Jessica Boklan,[19] Tze Fang Wong,[20] Qinxia Wang,[21] Patrick Urban,[20] Brigitte Strahm,[22] Winfred Wang,[23] Adrianna Vlachos,[24] and David A. Williams[1]



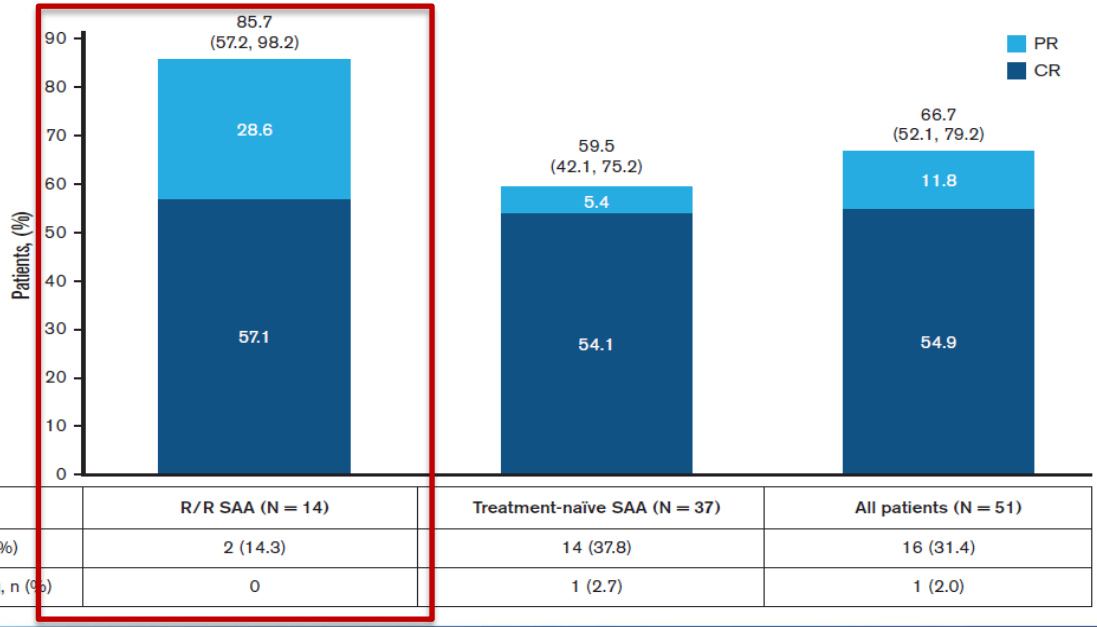
	R/R SAA (N = 14)	Treatment-naïve SAA (N = 37)	All patients (N = 51)
NR, n (%)	2 (14.3)	14 (37.8)	16 (31.4)
Missing, n (%)	0	1 (2.7)	1 (2.0)

REGULAR ARTICLE

blood advances

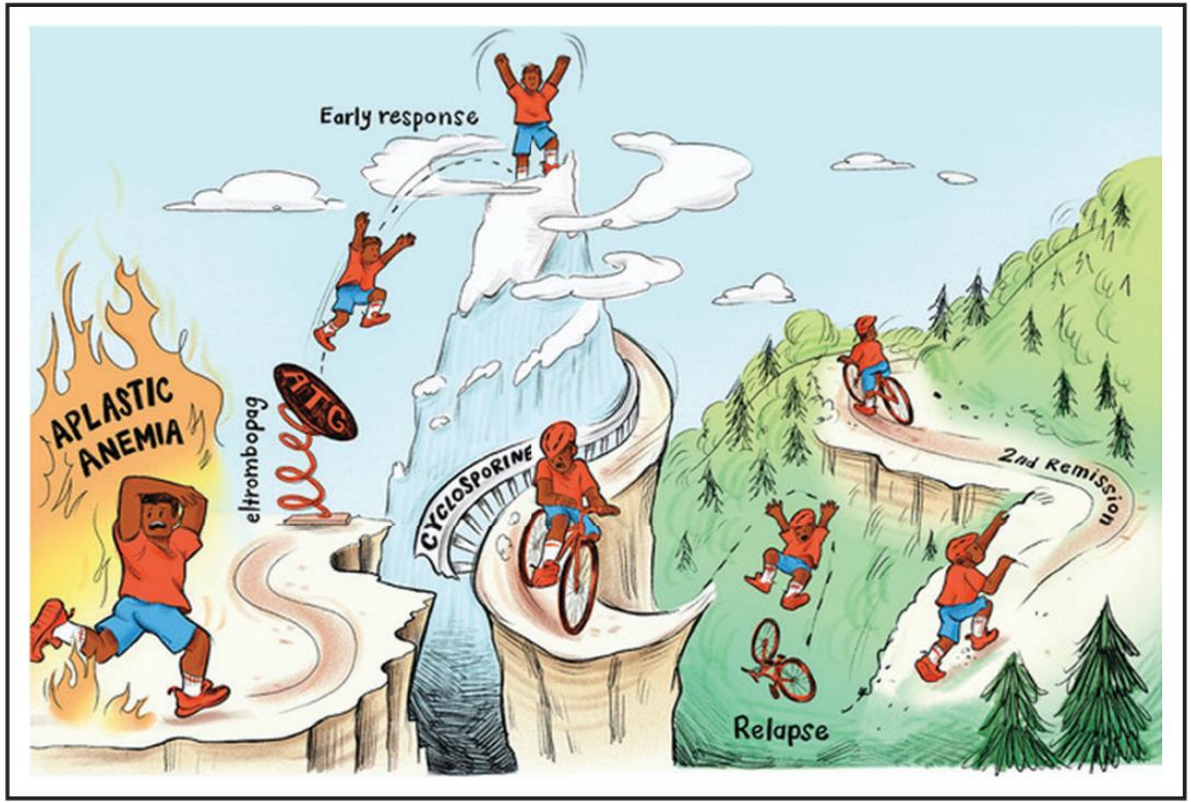
Eltrombopag in combination with immunosuppressive therapy in pediatric severe aplastic anemia: phase 2 ESCALATE trial

Akiko Shimamura,[1] Alexey Maschan,[2] Carolyn Bennett,[3] Sujith Samarasinghe,[4] Jason E. Farrar,[5] Chi-kong Li,[6] Nongnuch Sirachainan,[7] Bunchoo Pongtanakul,[8] Patcharee Komvilaisak,[9] Ludmila Zubarovskaya,[10] Jennifer A. Rothman,[11] Kelly Walkovich,[12] Taizo A. Nakano,[13] Alison A. Bertuch,[14] Anabela Ferrao,[15] Rukhmi Bhat,[16] Rabi Hanna,[17] Kathleen Overholt,[18] Jessica Boklan,[19] Tze Fang Wong,[20] Qinxia Wang,[21] Patrick Urban,[20] Brigitte Strahm,[22] Winfred Wang,[23] Adrianna Vlachos,[24] and David A. Williams[1]



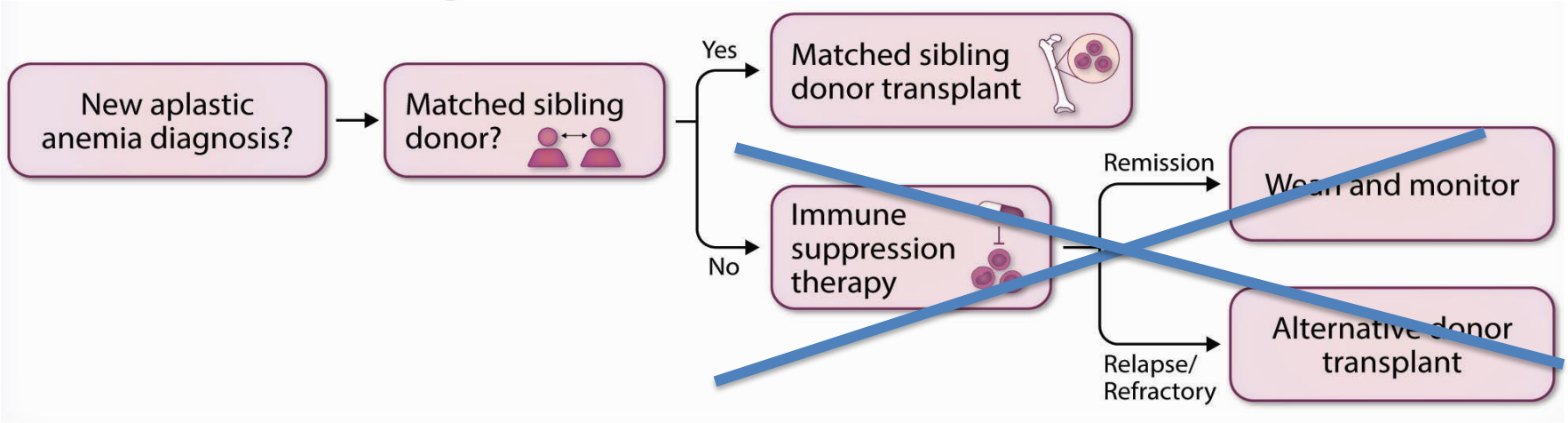
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NR, n (%)	2 (14.3)	14 (37.8)	16 (31.4)
Missing, n (%)	0	1 (2.7)	1 (2.0)

Eltrombopag: a springboard to early responses in SAA

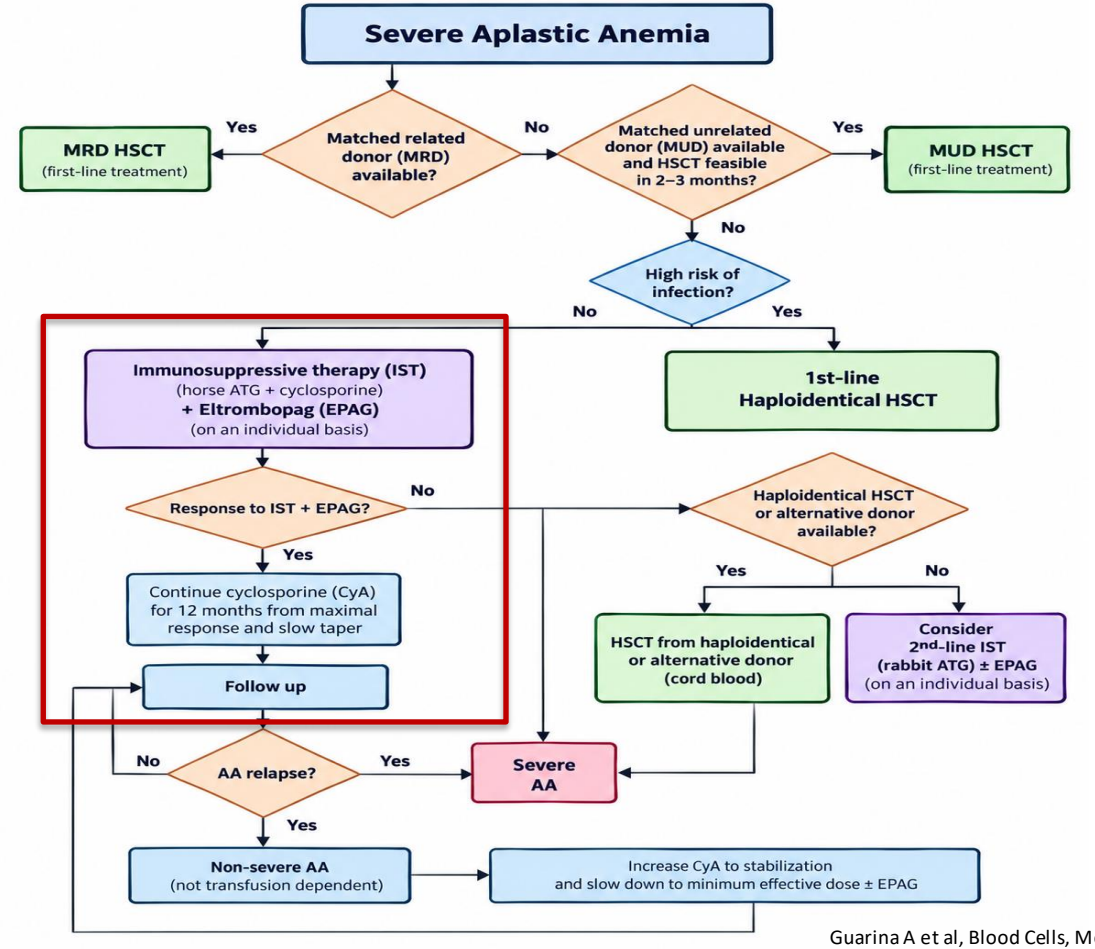


Daria V. Babushok *Blood* (2022) 139 (1): 1–2.

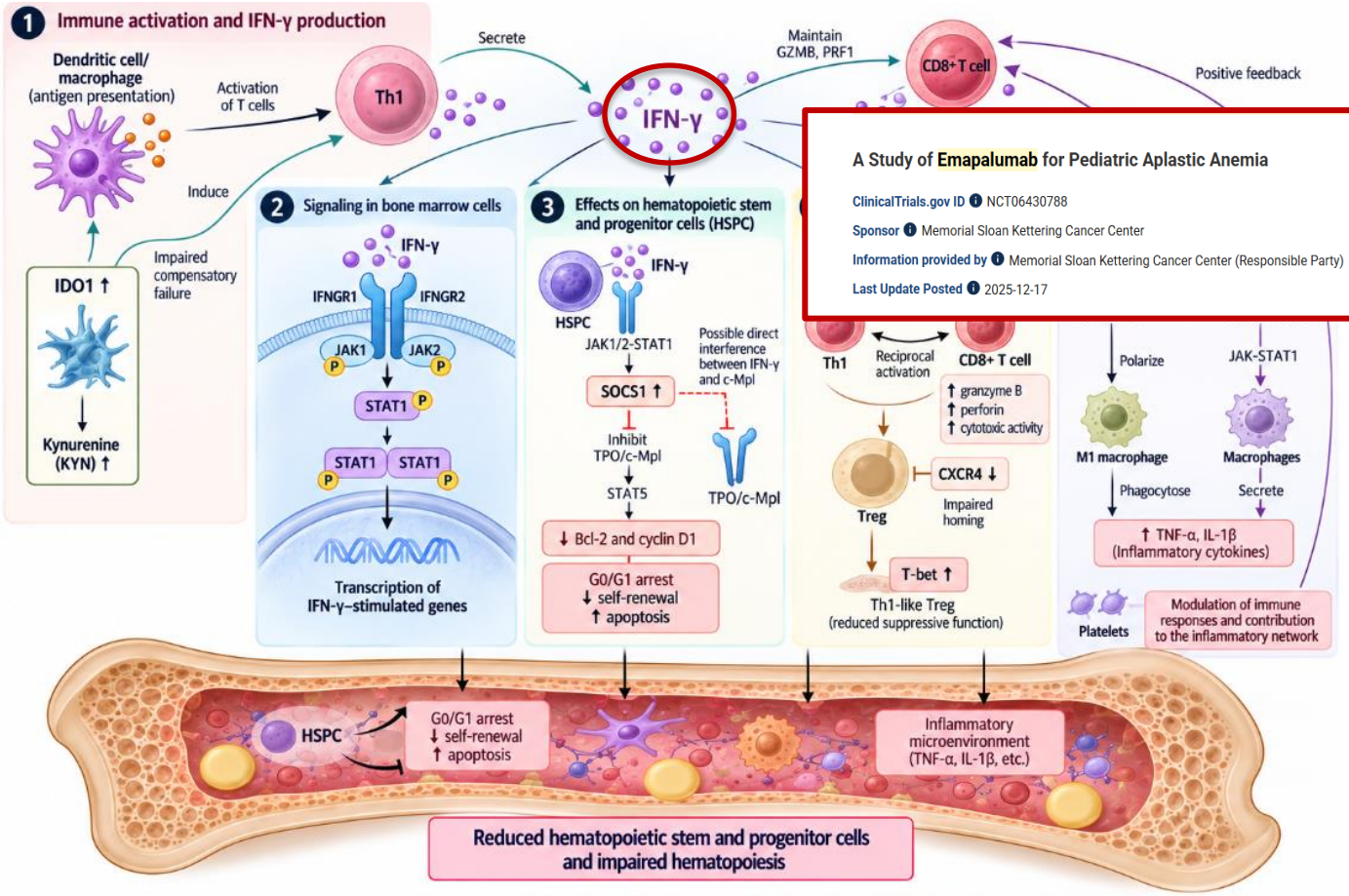
Historical treatment algorithm for SAA



J.H. Oved *et al.* Haematologica | 110 August 2025



Guarina A et al, Blood Cells, Molecules and Diseases 108 (2024) 102860



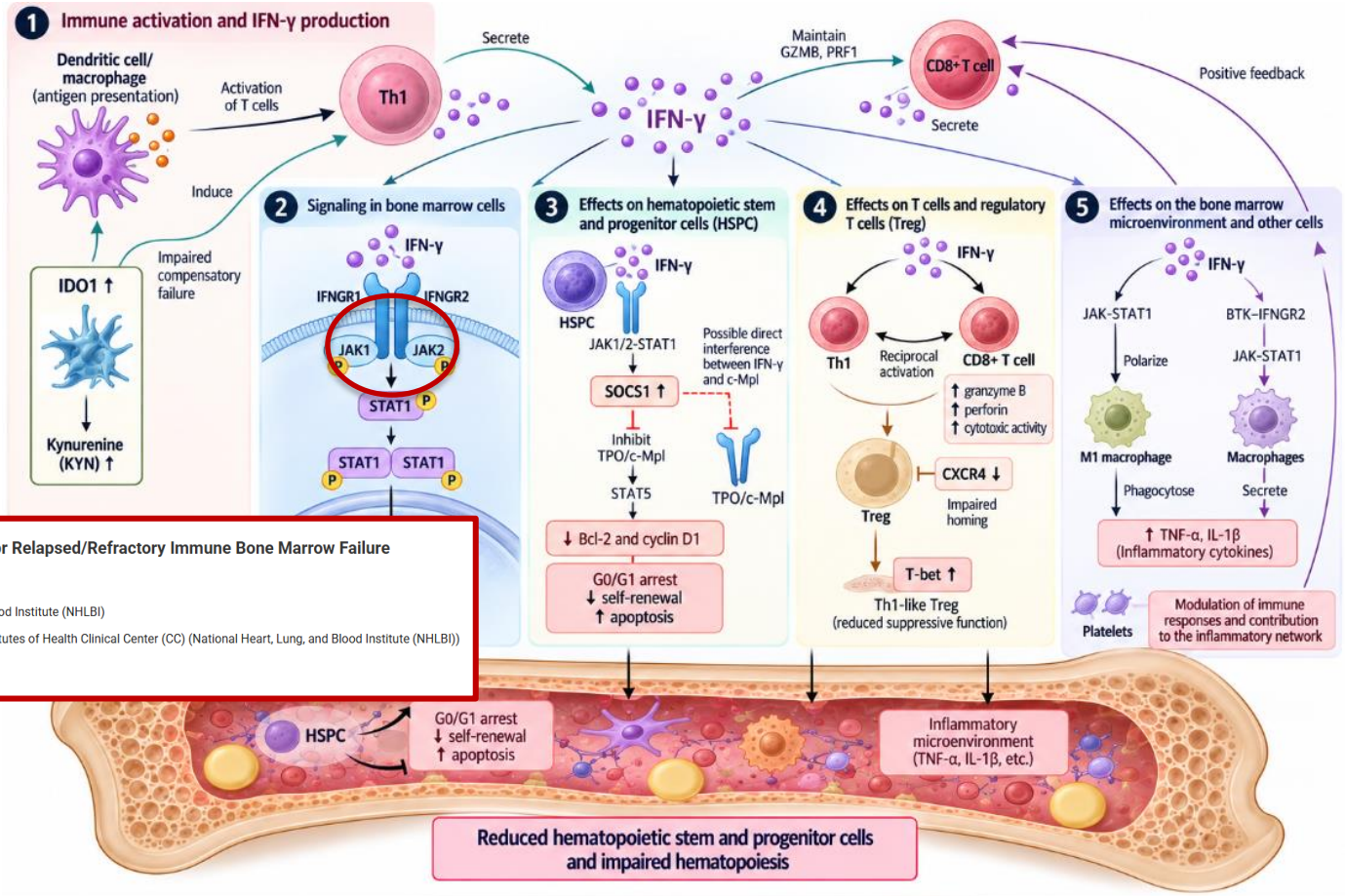
A Study of Emapalumab for Pediatric Aplastic Anemia

ClinicalTrials.gov ID NCT06430788

Sponsor Memorial Sloan Kettering Cancer Center

Information provided by Memorial Sloan Kettering Cancer Center (Responsible Party)

Last Update Posted 2025-12-17



JAK1/2 Inhibitor Ruxolitinib for Relapsed/Refractory Immune Bone Marrow Failure

ClinicalTrials.gov ID NCT05998408

Sponsor National Heart, Lung, and Blood Institute (NHLBI)

Information provided by National Institutes of Health Clinical Center (CC) (National Heart, Lung, and Blood Institute (NHLBI)) (Responsible Party)

Last Update Posted 2026-08-18

Università degli Studi della Campania *Luigi Vanvitelli*



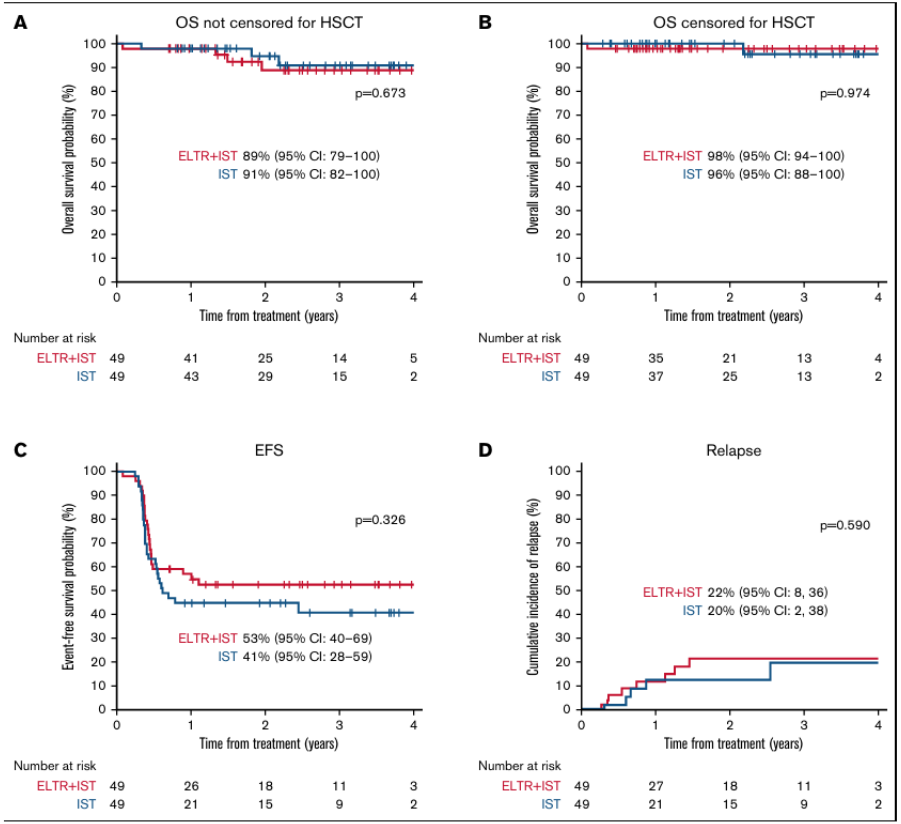
THANKS

HHS Public Access
Author manuscript
Am J Hematol. Author manuscript; available in PMC 2024 June 01.

Published in final edited form as:
Am J Hematol. 2023 June ; 98(6): 932–939. doi:10.1002/ajh.26924.

Alemtuzumab in Relapsed Immune Severe Aplastic Anemia: Long-Term Results of a Phase II Study

Nidhi Aggarwal, BS[1], **Ash Lee Manley, BS**[1], **Ruba Shalhoub, MS**[2], **Jibran Durrani, MD**[1], **Olga Rios, RN**[1], **Jennifer Lotter, PA-C**[1], **Bhavisha A. Patel, MD**[1], **Colin O. Wu, PhD**[2], **Neal S. Young, MD**[1], **Emma M. Groarke, MD**[1]



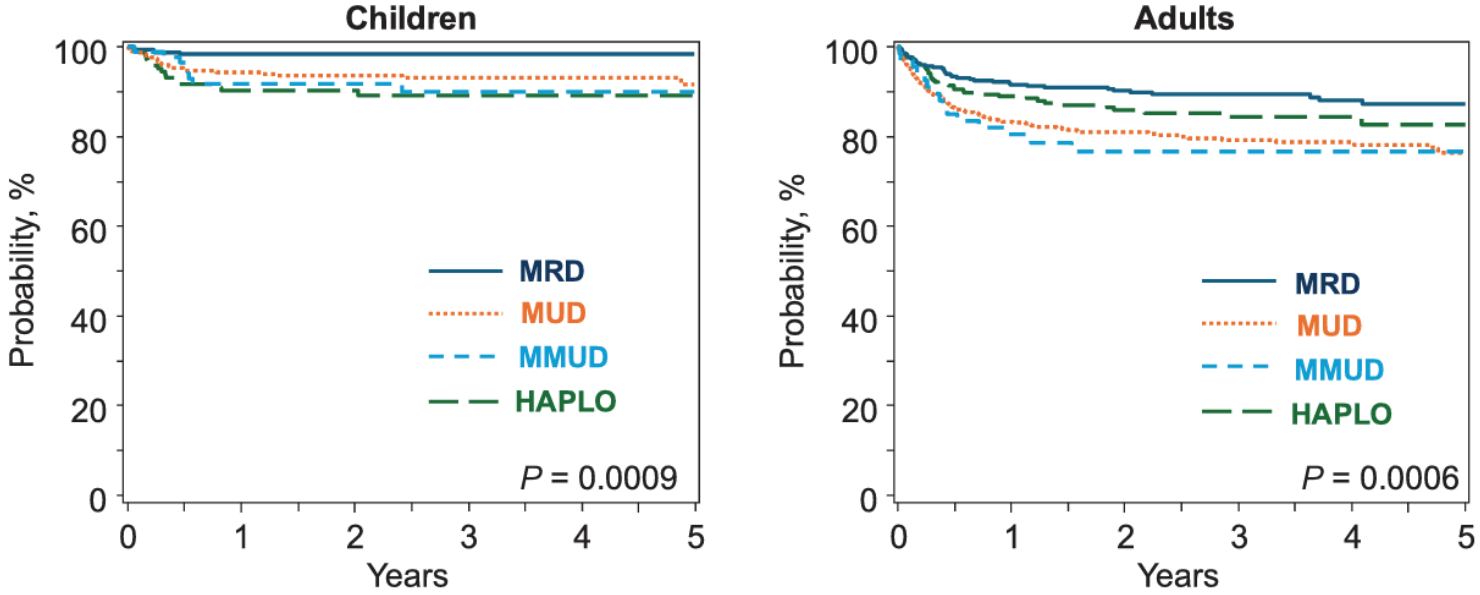
Olga Goronkova et al, Blood Adv 2023 Mar 28;7(6):953-962

Eltrombopag plus cyclosporine A for moderate aplastic anemia (EMAA): a placebo-controlled, double-blind, phase 3 trial

Britta Höchsmann[1,2,3], Philippe Schafhausen[4], Fabian Beier[3,5,6], Michael Heuser[7,8], Jörg Westermann[9], Beatrice Drexler[10], Alexander Röth[11], Regina Herbst[12], Mathias Hänel[12], Michela Schwarz[9], Flore Sicre de Fontbrune[13,14], Regis Peffault de Latour[3,13,14], Astrid Marx-Hofmann[1,2], Antonia Beitzen-Heineke[4], Jens Panse[5,6], Felicitas Thol[7], Sixten Körper[1,2], Tim H. Brümmendorf[5,6], and Hubert Schrezenmeier[1,2,3]

Eltrombopag combined with horse antithymocyte globulin and cyclosporine A (CSA) is the standard of care for patients with severe aplastic anemia who are not eligible for stem cell transplantation. No consensus exists on the optimal treatment of moderate aplastic anemia (MAA). The “Eltrombopag for MAA” (EMAA) trial is an investigator-initiated, prospective, randomized, placebo-controlled, double-blind, multicenter, phase III trial and compared eltrombopag+CSA (n=41) with placebo+CSA (n=44) as a first-line therapy for MAA patients with clinically significant cytopenia. In patients with evaluable response at week 24 (n=75), the overall response rate (ORR), including partial response (PR) and complete response (CR), was significantly higher in the eltrombopag+CSA arm (71.4%; 95% confidence interval [CI], 54.8%-83.8%) than in the placebo+CSA arm (42.5%; 95% CI, 28.5%-57.8%) (p=0.011, Fisher's exact test; primary endpoint). After response assessment at week 24 and unblinding, patients in the placebo arm without CR were switched to receive eltrombopag in addition to continued CSA. This group achieved an ORR of 73.5% by week 48 (p=0.009, McNemar test, comparing response at 24 vs. 48 weeks). Relapse rate and failure-free survival did not differ significantly among the arms. Eltrombopag was well tolerated without new safety concerns. Adding eltrombopag to CSA for first-line treatment of MAA significantly improves trilineage hematologic response at week 24 and addition of eltrombopag in patients without CR after 24 weeks of single-agent CSA treatment also significantly improves the ORR. The trial was

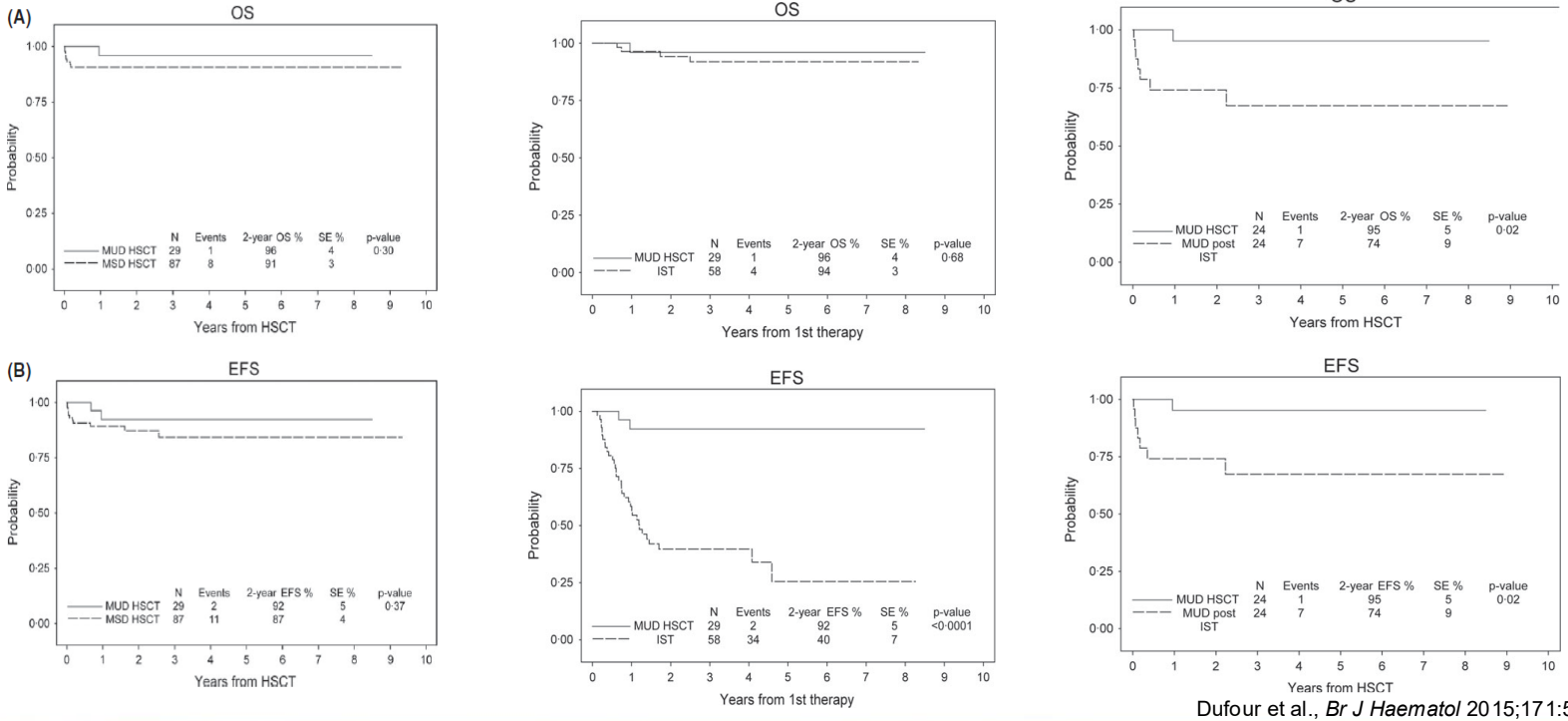
OS after HCT for SAA in the US in the recent era



Akshay Sharma - Hematology Am Soc Hematol Educ Program 2025 Dec 5;2025(1):691-698

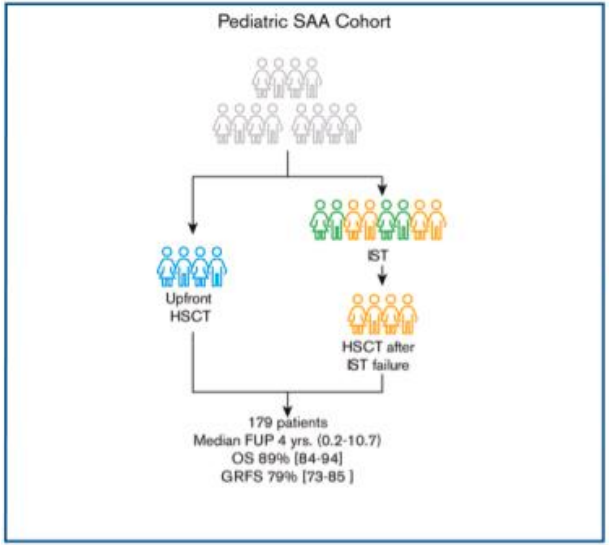
bjh research paper

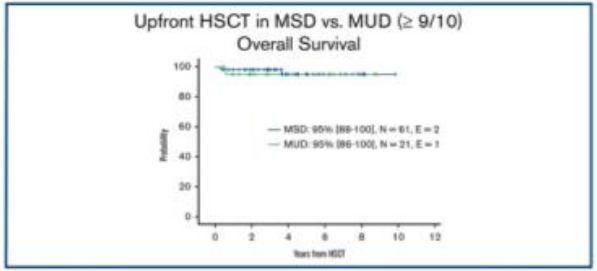
Similar outcome of upfront-unrelated and matched sibling stem cell transplantation in idiopathic paediatric aplastic anaemia. A study on behalf of the UK Paediatric BMT Working Party, Paediatric Diseases Working Party and Severe Aplastic Anaemia Working Party of EBMT

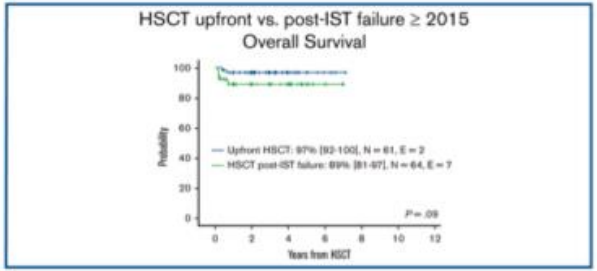


Dufour et al., *Br J Haematol* 2015;171:585-594

Comparable Outcomes of HSCT Upfront and After Failure of IST in Pediatric Aplastic Anemia in Recent Years



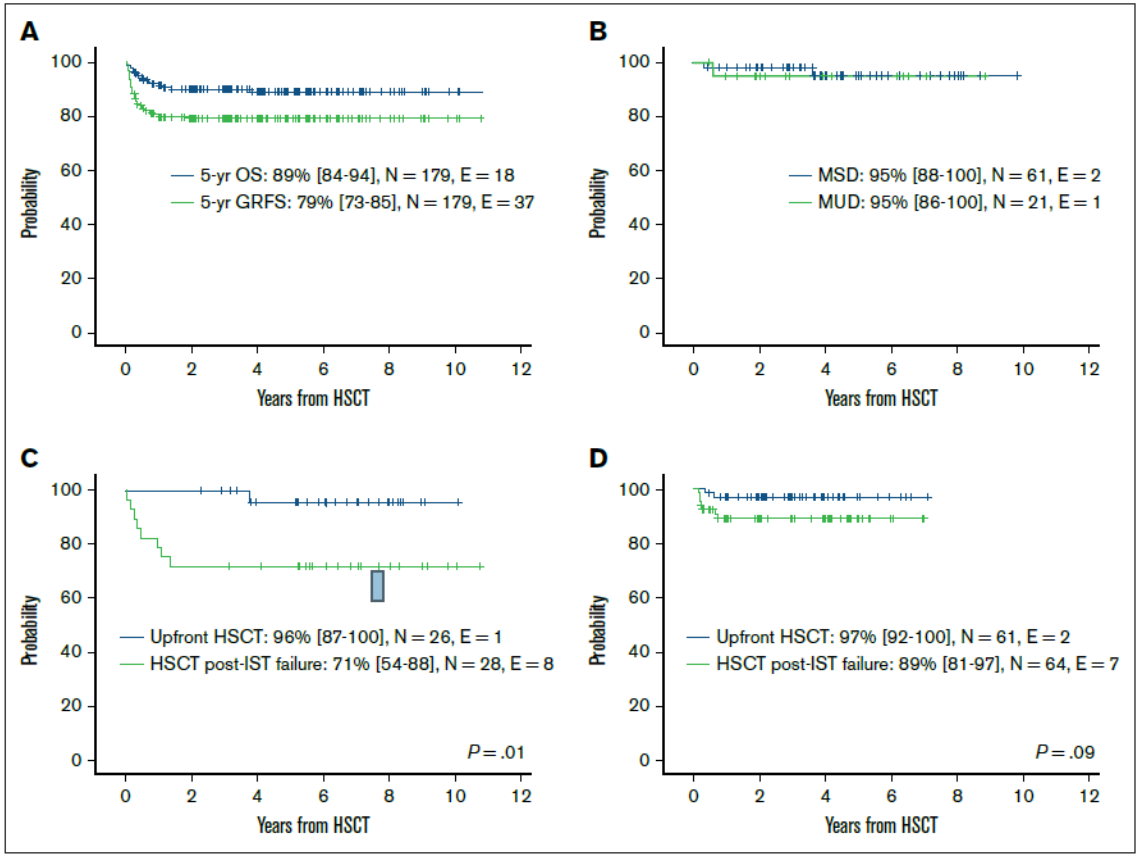




Conclusions: **Upfront HSCT from an MSD or ≥9/10 HLA-matched UD both achieved an OS of 95%. HSCT performed upfront and post-IST failure resulted in a comparable OS from 2015.**

*Andresen et al. DOI: 10.1182/**bloodadvances**.2025018285*

blood advances Visual Abstract



	Relative Risk	95% CI	*P* value
Sex			
Female vs male	1.47	0.64-3.38	ns
Age at HSCT, y			
≥10 vs <10	1.58	0.88-14.60	ns
Year of HSCT			
<2015 vs 2015-2017	0.78	0.28-2.14	ns
<2015 vs ≥2018	3.57	0.88-14.60	.08
2015-2017 vs ≥2018	4.61	1.25-16.96	.02
Type of ATG used in IST			
Thymoglobulin vs Atgam	1.59	0.59-4.30	ns
Conditioning regimen			
Other regimens vs Flu/Cy	2.43	0.98-6.06	.06

ns, not significant.

Andresen et al. Blood Adv 2026 Jan 22;10(6):1992–2005

A Trial Comparing Unrelated Donor BMT With IST for Pediatric and Young Adult Patients With Severe Aplastic Anemia (TransIT, BMT CTN 2202) (TransIT)

ClinicalTrials.gov ID NCT05600426

Sponsor Boston Children's Hospital

Information provided by David Williams, Boston Children's Hospital (Responsible Party)

Last Update Posted 2026-09-25

Up-front MUD versus IST

Study	Patients	Overall survival	Failure-free / event-free survival
Dufour 2015	29 up-front, 58 IST	96% vs 94% at 2 years	92% vs 40% (P=.0001)
Choi	23 vs 19	91.3% vs 71.2%	91.3% vs 30.7% (P<.001)
Cheng	28 vs 24	89.3% vs 73.4% at 10 years	89.3% vs 52.6% (P=.008)
Xu (adults)	76 vs 37	83.7% vs 75.6% at 8 years	83.7% vs 38.5% (P=.001)
Yang	20 vs 29	85.0% vs 79.3% at 3 years	80.0% vs 35.9% (P=.043)
Wu (adults)	114 vs 99	86.5% vs 92.4%	Not reported in the comparison

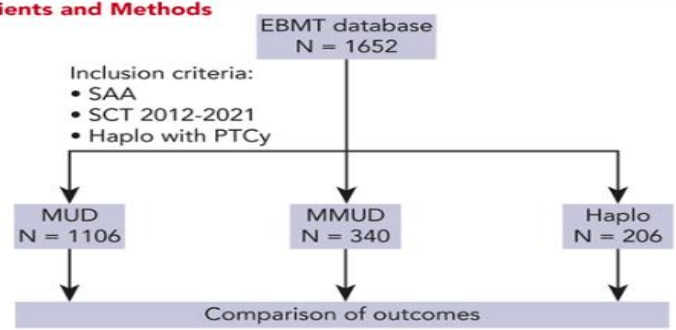
Bhatt NS, et al. Blood Adv 2025;9(17):4448-4457

Alternative Donor Transplantation for Severe Aplastic Anemia (SAA)

Context of Research

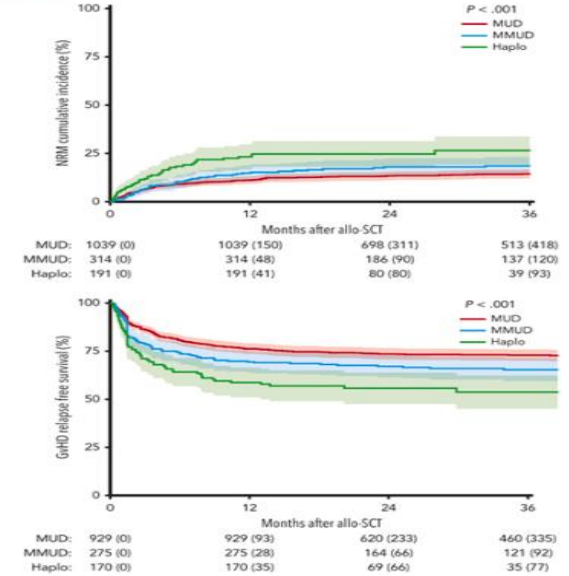
- Stem cell transplantation (SCT) from an HLA-matched sibling donor is the standard of care for younger patients with SAA
- When a sibling donor is not available, selecting the most appropriate alternative donor becomes a challenge

Patients and Methods



MUD, matched unrelated donor; MMUD, mismatched unrelated donor; Haplo, haploidentical donor

Main Findings

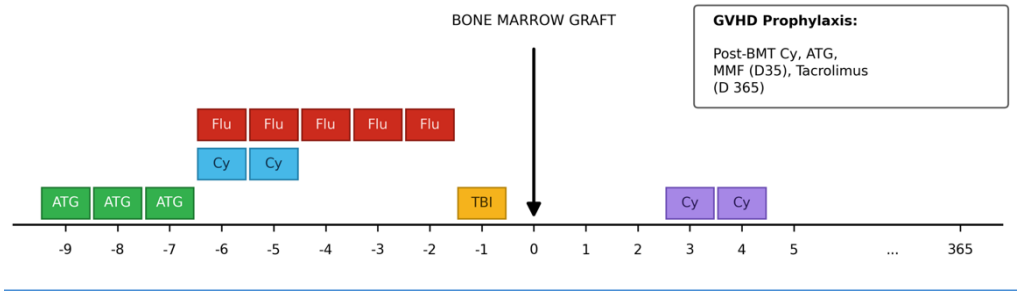


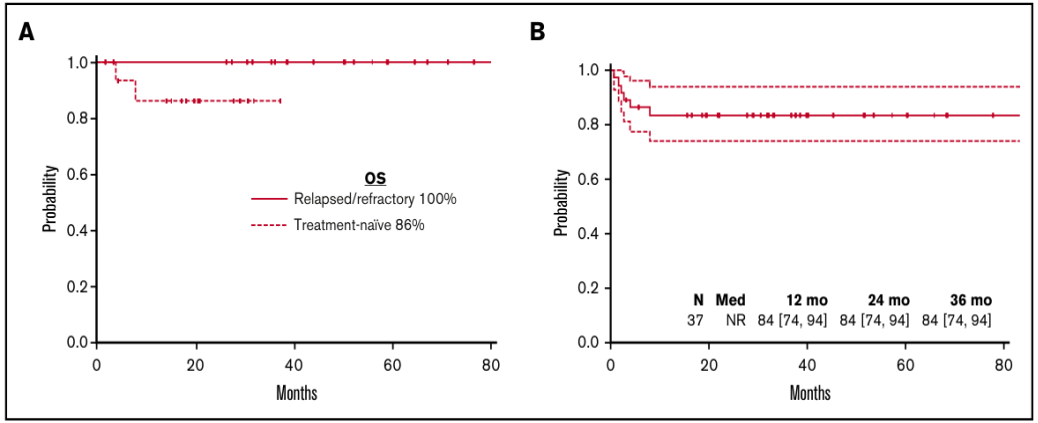
Conclusion: In patients with SAA who do not have a sibling donor, stem cell transplantation from MUD provides superior survival outcomes compared to both MMUD and Haplo.

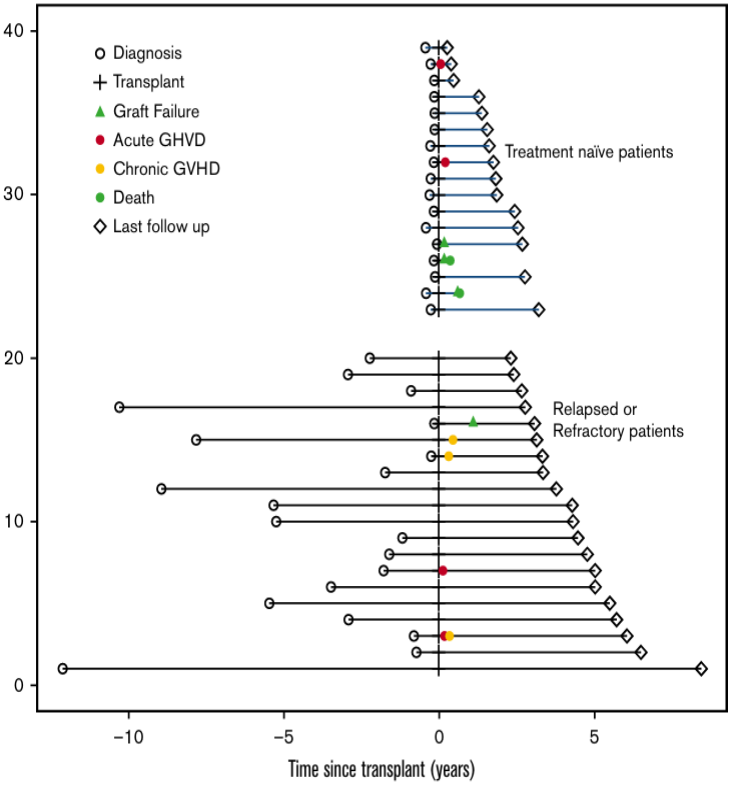
*Montoro et al. DOI: 10.1182/**blood**.2024024173*

blood Visual Abstract

Haploidentical BMT for severe aplastic anemia with intensive GVHD prophylaxis including posttransplant cyclophosphamide







DeZern et al. Blood Adv 2020 Apr 28;4(8):1770-1779

REGULAR ARTICLE

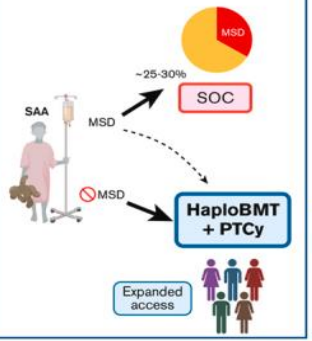
blood advances

PTCy-based allo-BMT platform as a curative, accessible alternative for pediatric and young adult severe aplastic anemia

Margarita Dionysiou,[1,2] Yiouli P. Ktena,[1,2] Challice L. Bonifant,[1,2] Allen R. Chen,[1,2] Nicolas J. Llosa,[1,2] Elias T. Zambidis,[1,2] Amy E. DeZern,[1,3] Richard J. Jones,[1,3] Heather J. Symons,[1,2,*] and Kenneth R. Cooke[1,2,*]

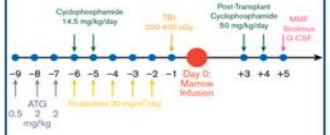
[1]Department of Oncology and [2]Division of Pediatric Oncology, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; and [3]Division of Hematology, Department of Medicine, Johns Hopkins University, Baltimore, MD

Background: AlloBMT is the most definitive curative therapy for SAA, yet only 25–30% of patients have an MSD. RIC haplo-BMT + PTCy provides an accessible curative alternative.



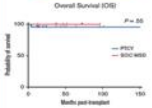
Patients and Methods:

- 31 patients ≤21 yrs with acquired SAA
- Single institution (2014–2024)
- TN + R/R included
- RIC haplo/MSD-BMT + PTCy (n = 23) vs SOC MSD-BMT (n = 8)

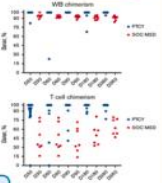


Main findings:

Excellent OS

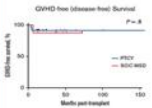


Durable Donor Chimerism



Minimal late effects

High GVHD-free disease-free survival



Conclusions: RIC haploBMT with PTCy achieves excellent survival and near-absence of severe GVHD in pediatric and AYA patients.

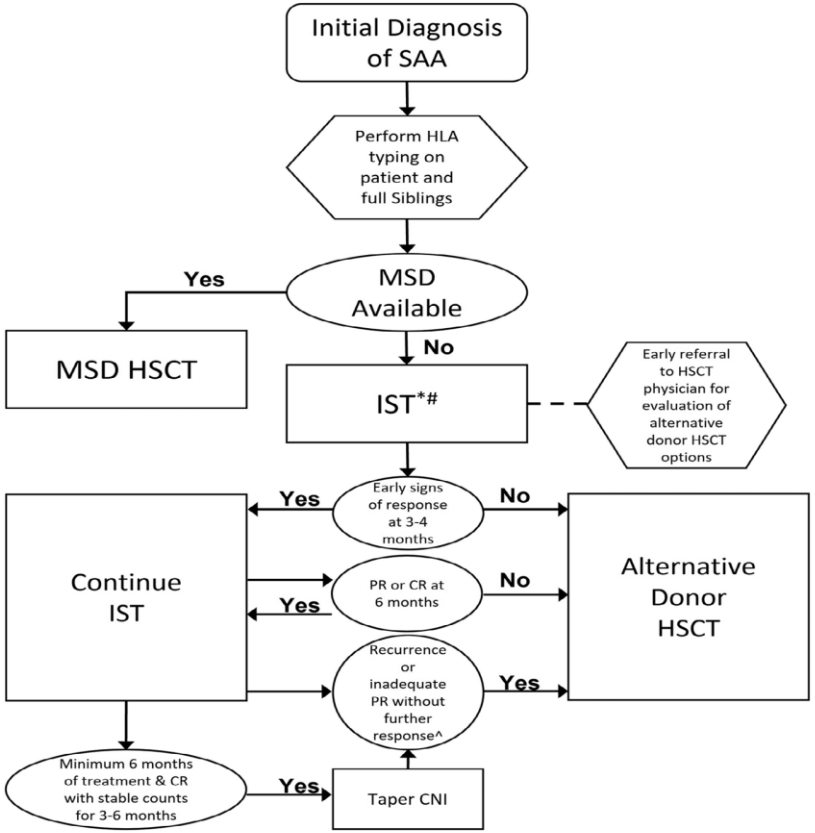
*Dionysiou et al. DOI: 10.1182/**bloodadvances**.2025019581*

blood advances Visual Abstract

Key Points

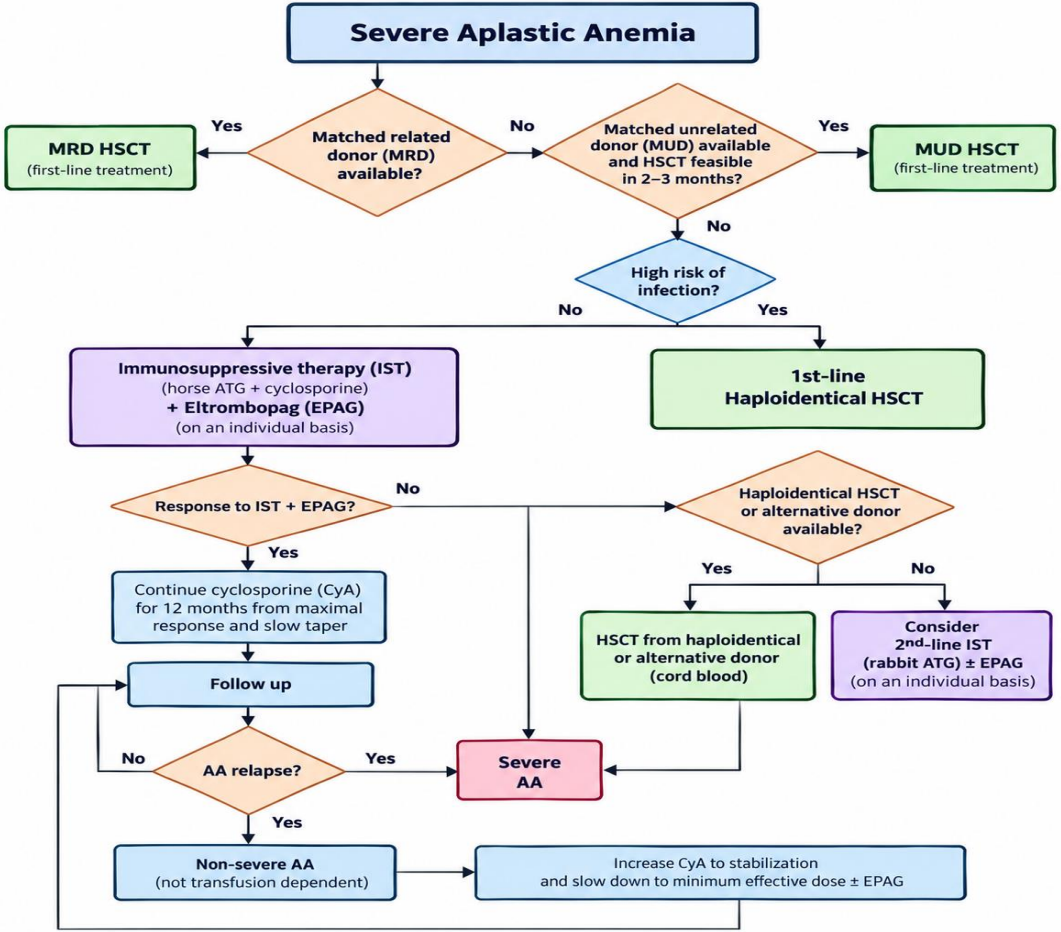
1. Relapsed and refractory SAA carries a grave prognosis if efforts to renew hematopoiesis and avoid clonal evolution are not pursued.
2. Allogeneic bone marrow transplantation addresses both the acute and chronic complications of severe AA, by virtually eliminating the risk of relapse and secondary clonal disease, but introduces the risk of acute and chronic GVHD.
3. High dose cyclophosphamide (50mg/kg/d × 4 days) has a unique history in the context of AA for both transplant and non-transplant therapies.
4. Use of post transplantation cyclophosphamide on Days 3 and 4 posttransplant has allowed for expansion of the donor pool to include haploidentical transplants for patient with relapsed and refractory SAA.
5. Rates of GVHD and other transplant related mortality are low with use of post transplantation cyclophosphamide.

DeZern and Brodsky



*Earlier HSCT may be indicated in certain circumstances
#Consider enrollment on a clinical trial if available
^Treatment should be individualized based on patient factors including complications, quality of life, and donor options

Kristin Shimano et al. *Pediatr Blood Cancer.* 2024;71:e31070


Severe Aplastic Anemia
Matched related donor (MRD) available?
Yes
MRD HSCT (first-line treatment)
No
Matched unrelated donor (MUD) available and HSCT feasible in 2–3 months?
Yes
MUD HSCT (first-line treatment)
No
High risk of infection?
No
Yes
Immunosuppressive therapy (IST) (horse ATG + cyclosporine) + Eltrombopag (EPAG) (on an individual basis)
1st-line Haploidentical HSCT
Response to IST + EPAG?
No
Yes
Haploidentical HSCT or alternative donor available?
Yes
No
Continue cyclosporine (CyA) for 12 months from maximal response and slow taper
HSCT from haploidentical or alternative donor (cord blood)
Consider 2nd-line IST (rabbit ATG) ± EPAG (on an individual basis)
Follow up
No
AA relapse?
Yes
Severe AA
Yes
Non-severe AA (not transfusion dependent)
Increase CyA to stabilization and slow down to minimum effective dose ± EPAG

Changes in Treatment Paradigm for Severe Aplastic Anemia (SAA)

Current Paradigm

Young patient + MSD → HCT

Older patient or No MSD → IST



IST is associated with delayed count recovery, organ toxicity, and risk of infections and clonal expansion



Enablers of Change



Improved GVHD prophylaxis

Reduced toxicity conditioning regimens





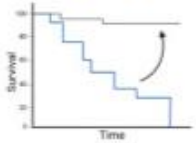
Expanding donor pool

Paradigm Shift in Treatment

HCT from best available donor (MSD/MUD/HAPLO) → First-line treatment



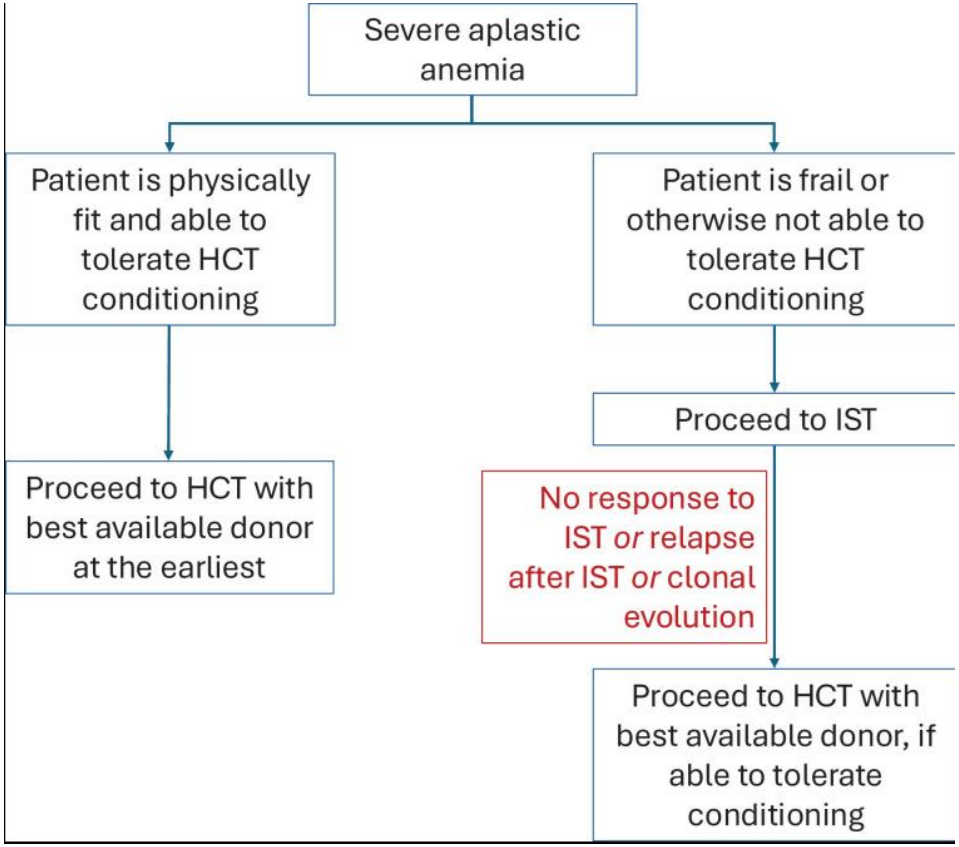
IST reserved for frail/ineligible patients



Improved outcomes

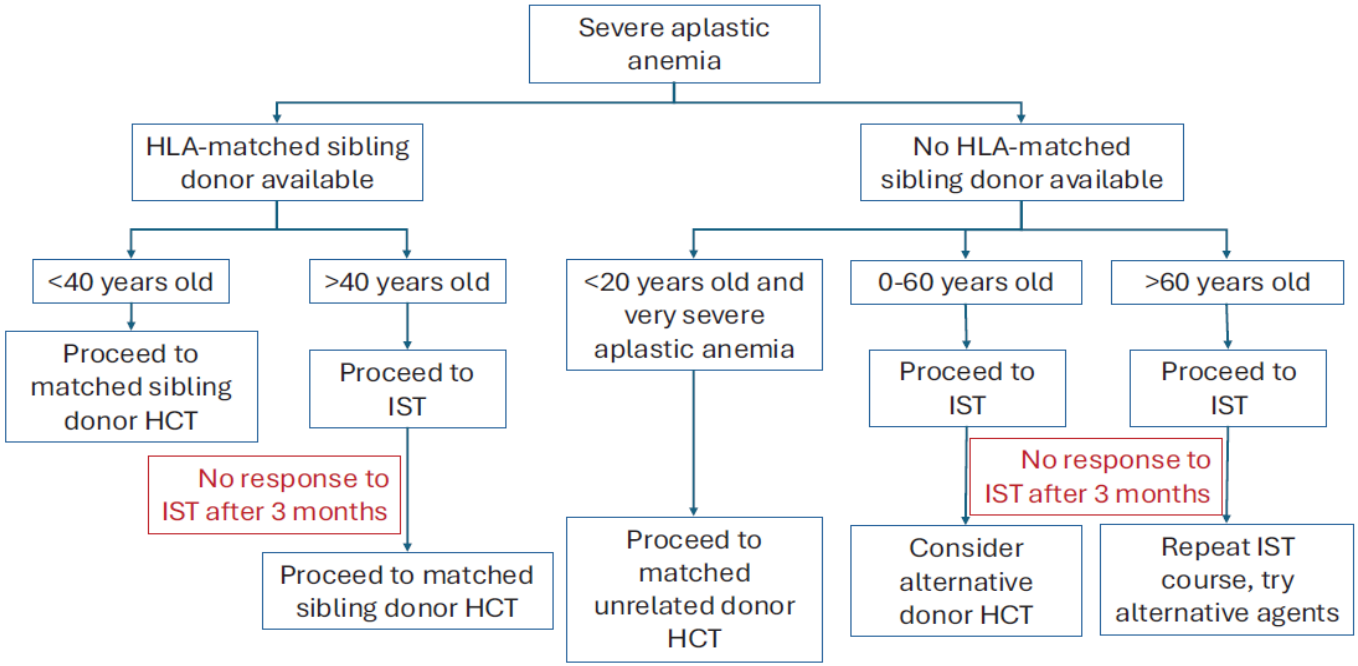
Conclusions: Advances in conditioning regimens, and GVHD prophylaxis as well as expansion of the donor pool are resulting in improved access and a reduction in the morbidity associated with HCT. Therefore, treatment paradigm for SAA treatment is shifting toward early allogeneic transplantation — even in the absence of a matched sibling donor.

Akshay Sharma - Hematology Am Soc Hematol Educ Program 2025 Dec 5;2025(1):691-698



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ASH 2026 guidelines for the diagnosis and management of SAA/VSAA

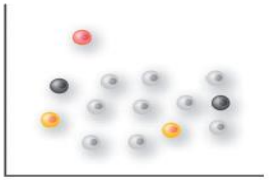


Scheinberg et al. Blood Advances 8 September 2026

Treatment - IST or HCT

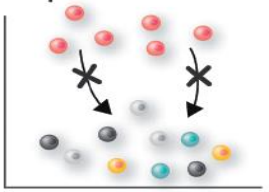
Potential outcomes

1 Complete response after IST



Slightly expanded clonal population within the HSC compartment

2 Relapse after IST



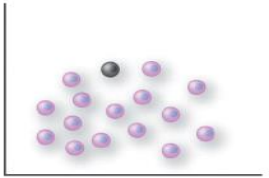
Expansion of clonal populations with survival advantage and resistance to immune attack

3 Clonal progression



Expansion and emergence of new clonal populations may accompany progression to overt malignancy

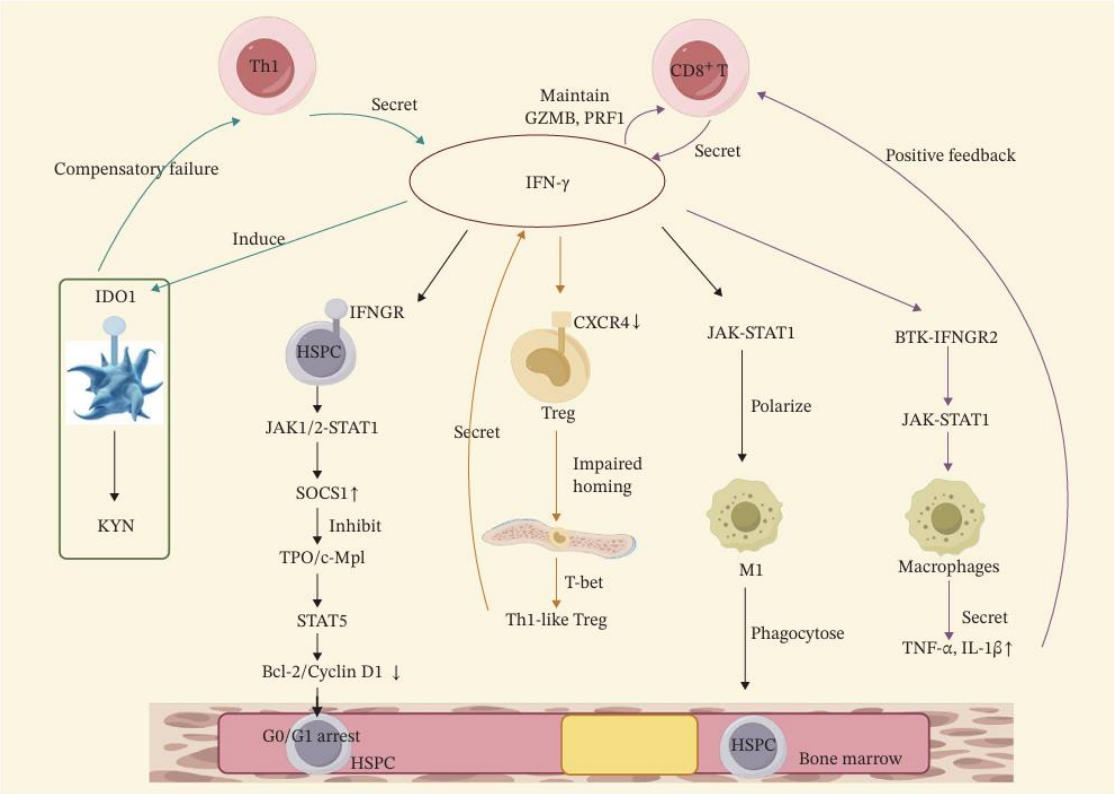
4 Complete response after HCT

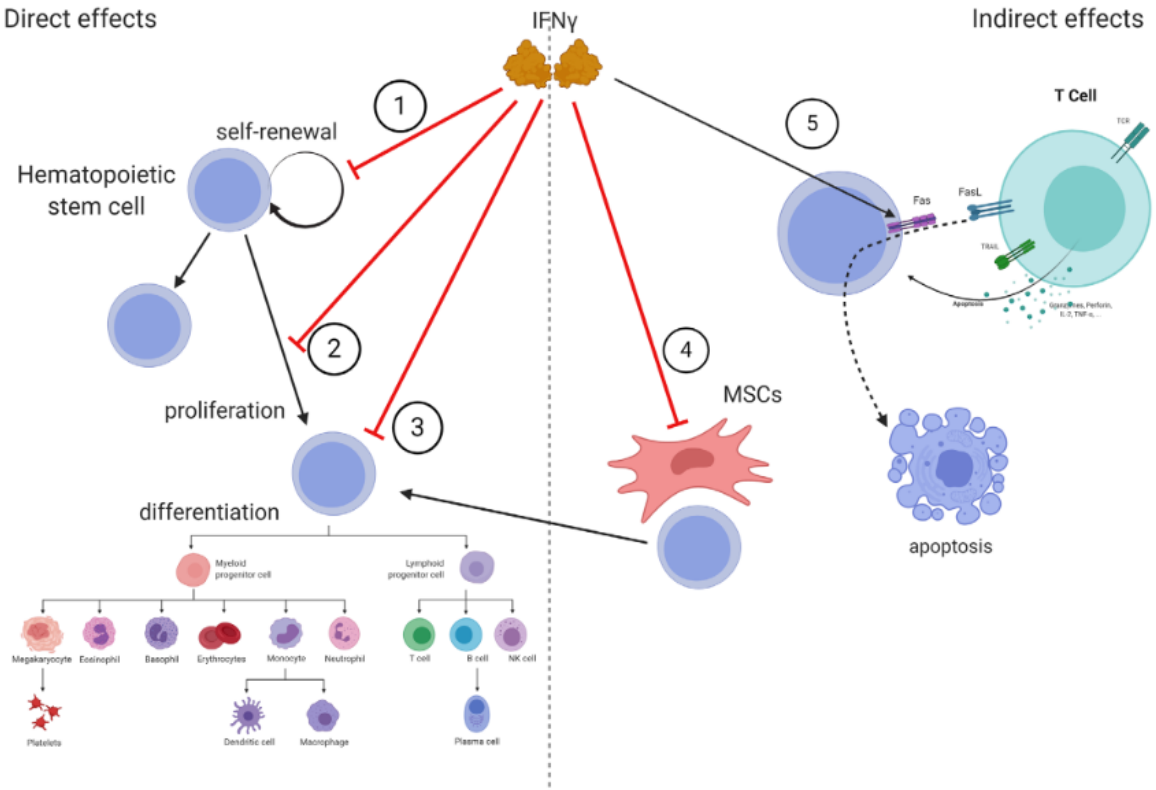


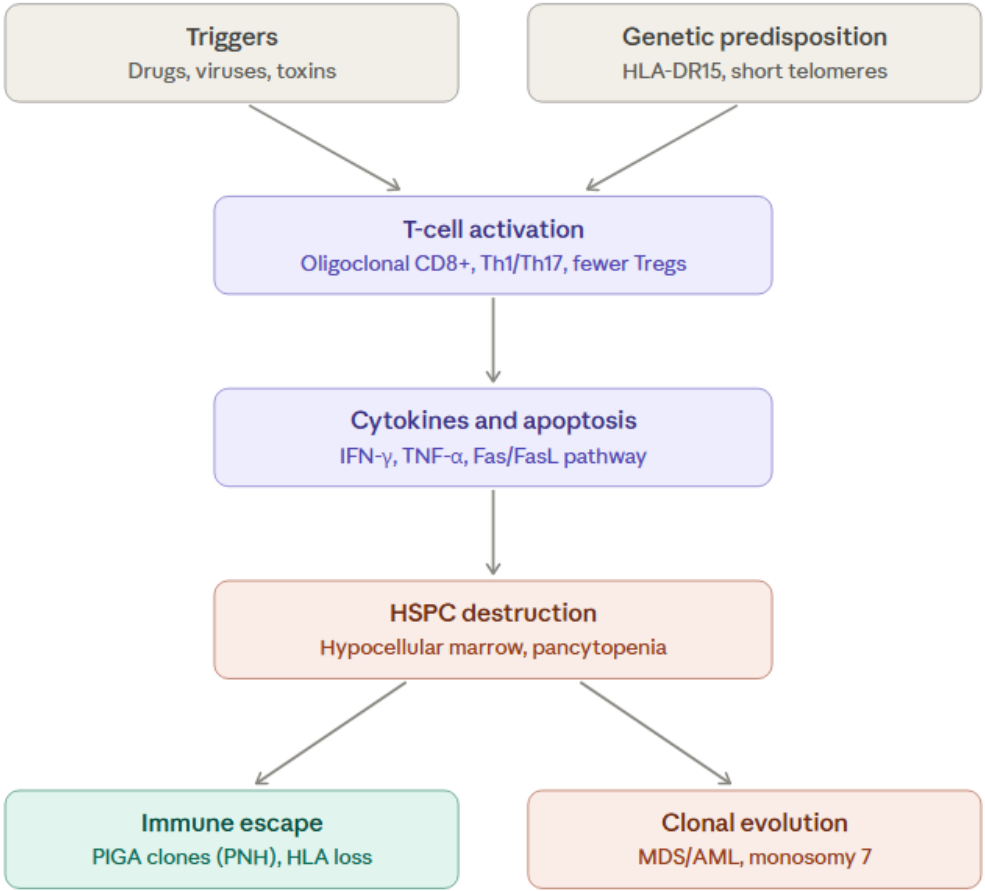
Engrafted donor HSC and quiescent abnormal HSC

- Cytotoxic T lymphocytes
- Abnormal HSC clones
- Normal HSC
- Normal donor HSC

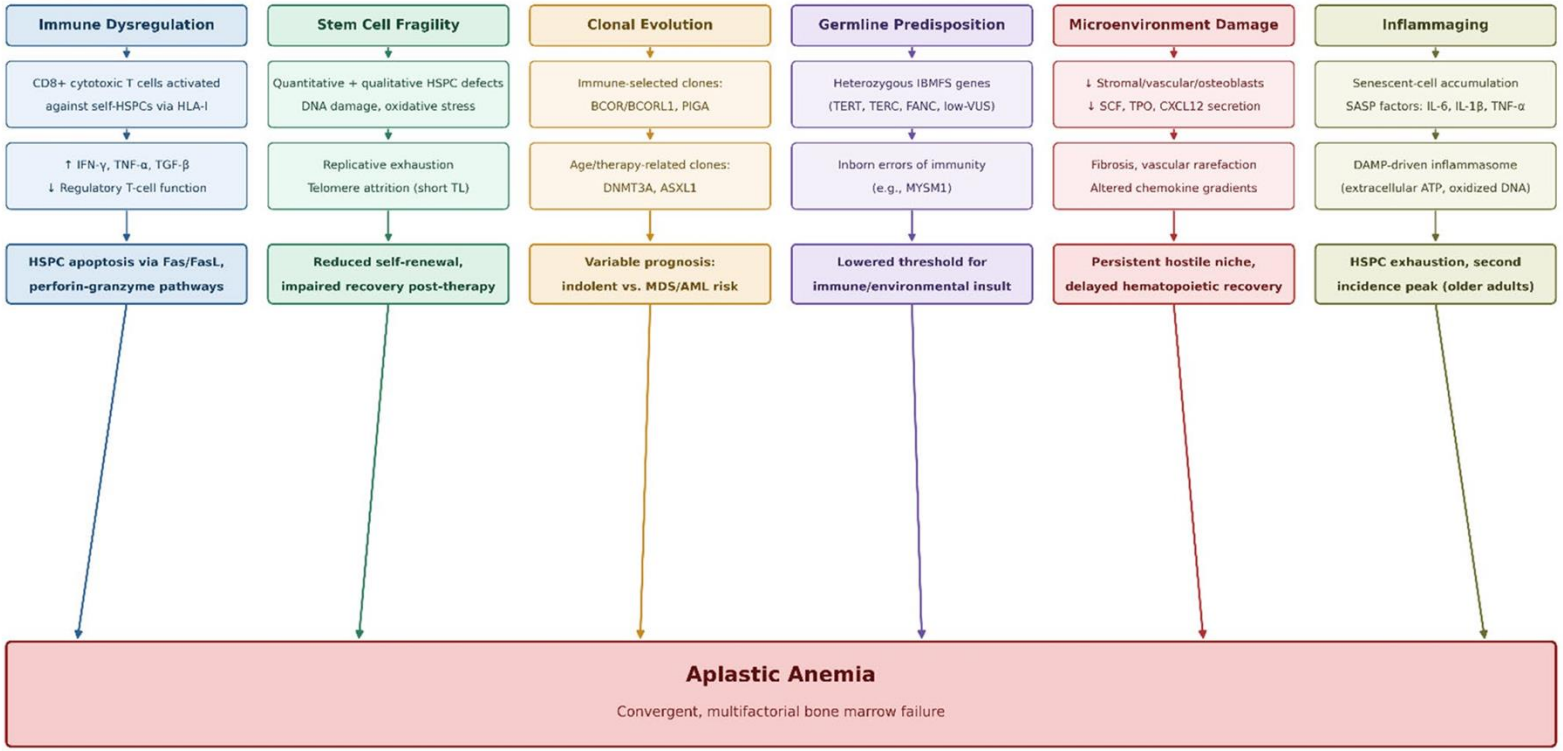
Lucy C. Fox and David S. Ritchie Haematologica 2019 Oct;104(10):1909-1912

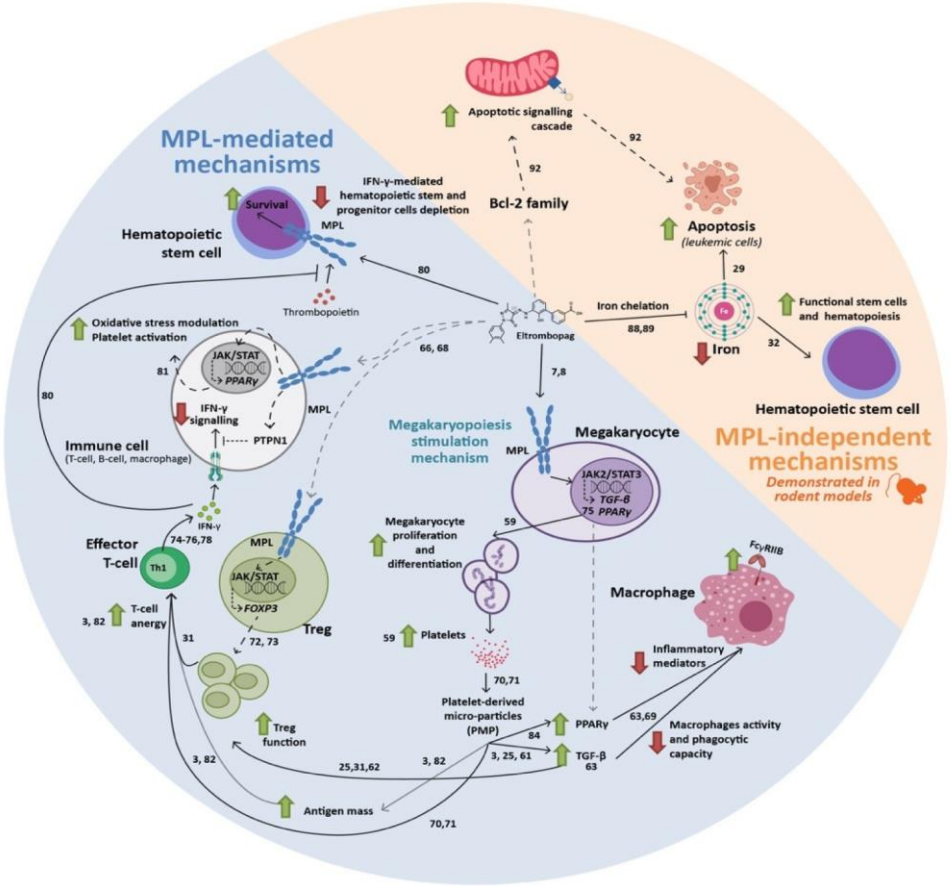

Th1
Secret
CD8+ T
Maintain
GZMB, PRF1
Secret
Positive feedback
Compensatory failure
IFN-γ
Induce
IDO1
KYN
IFNGR
HSPC
JAK1/2-STAT1
SOCS1↑
Inhibit
TPO/c-Mpl
STAT5
Bcl-2/Cyclin D1 ↓
G0/G1 arrest
HSPC
Secret
CXCR4↓
Treg
Impaired
homing
T-bet
Th1-like Treg
JAK-STAT1
Polarize
M1
Phagocytose
BTK-IFNGR2
JAK-STAT1
Macrophages
Secret
TNF-α, IL-1β↑
HSPC
Bone marrow

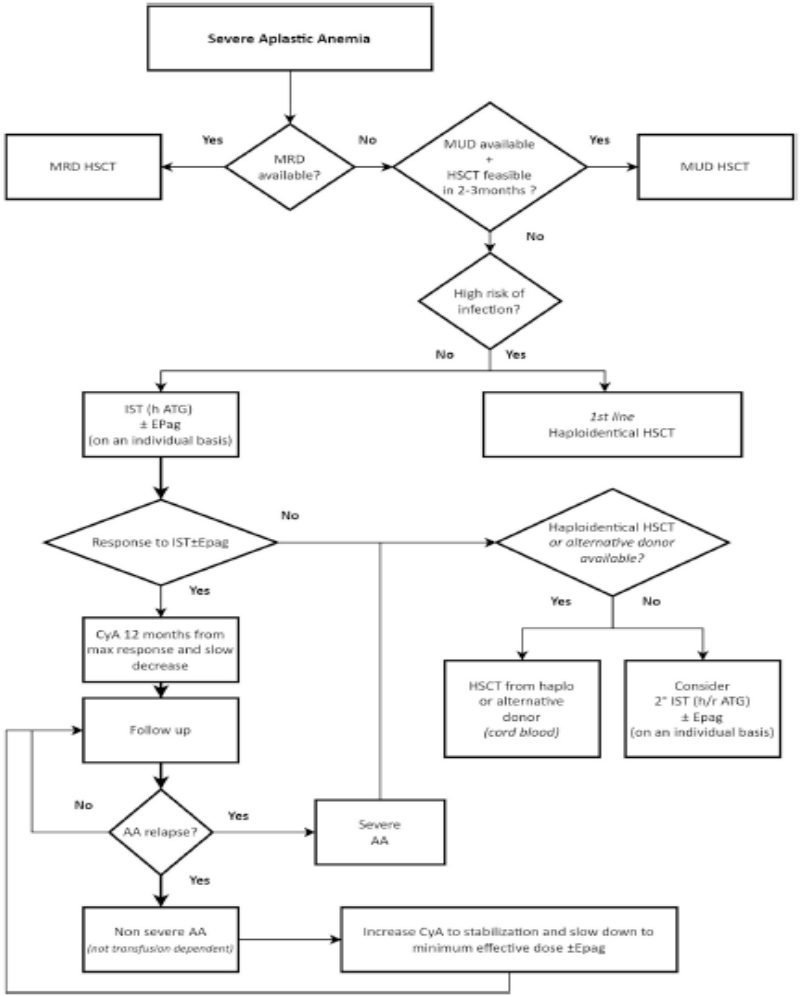

Direct effects
IFNγ
Indirect effects
1
self-renewal
Hematopoietic stem cell
2
proliferation
3
differentiation
4
MSCs
5
T Cell
Fas
FasL
TRAIL
Apoptosis
apoptosis
Myeloid progenitor cell
Lymphoid progenitor cell
Megakaryocyte
Eosinophil
Basophil
Erythrocytes
Monocyte
Neutrophil
T cell
B cell
NK cell
Platelets
Dendritic cell
Macrophage
Plasma cell


Triggers
Drugs, viruses, toxins
Genetic predisposition
HLA-DR15, short telomeres
T-cell activation
Oligoclonal CD8+, Th1/Th17, fewer Tregs
Cytokines and apoptosis
IFN-γ, TNF-α, Fas/FasL pathway
HSPC destruction
Hypocellular marrow, pancytopenia
Immune escape
PIGA clones (PNH), HLA loss
Clonal evolution
MDS/AML, monosomy 7

Pathogenesis of Acquired Aplastic Anemia




MPL-mediated mechanisms
Survival
IFN-γ-mediated hematopoietic stem and progenitor cells depletion
MPL
Hematopoietic stem cell
Thrombopoietin
80
Oxidative stress modulation
Platelet activation
JAK/STAT
PPARγ
81
IFN-γ signalling
PTPN1
Immune cell
(T-cell, B-cell, macrophage)
IFN-γ
Effector T-cell
Th1
74-76,78
T-cell anergy
3, 82
31
MPL
JAK/STAT
FOXP3
Treg
72, 73
Treg function
3, 82
25,31,62
Antigen mass
70,71
Apoptotic signalling cascade
92
Bcl-2 family
92
Apoptosis
(leukemic cells)
29
Iron chelation
88,89
Iron
Functional stem cells and hematopoiesis
32
Hematopoietic stem cell
Eltrombopag
66, 68
7,8
Megakaryopoiesis stimulation mechanism
Megakaryocyte
MPL
JAK2/STAT3
TGF-ß
PPARγ
75
Megakaryocyte proliferation and differentiation
59
59
Platelets
70,71
Platelet-derived micro-particles (PMP)
84
PPARγ
TGF-β
63
3, 25, 61
3, 82
63,69
Macrophage
FcγRIIB
Inflammatory mediators
Macrophages activity and phagocytic capacity
MPL-independent mechanisms
Demonstrated in rodent models

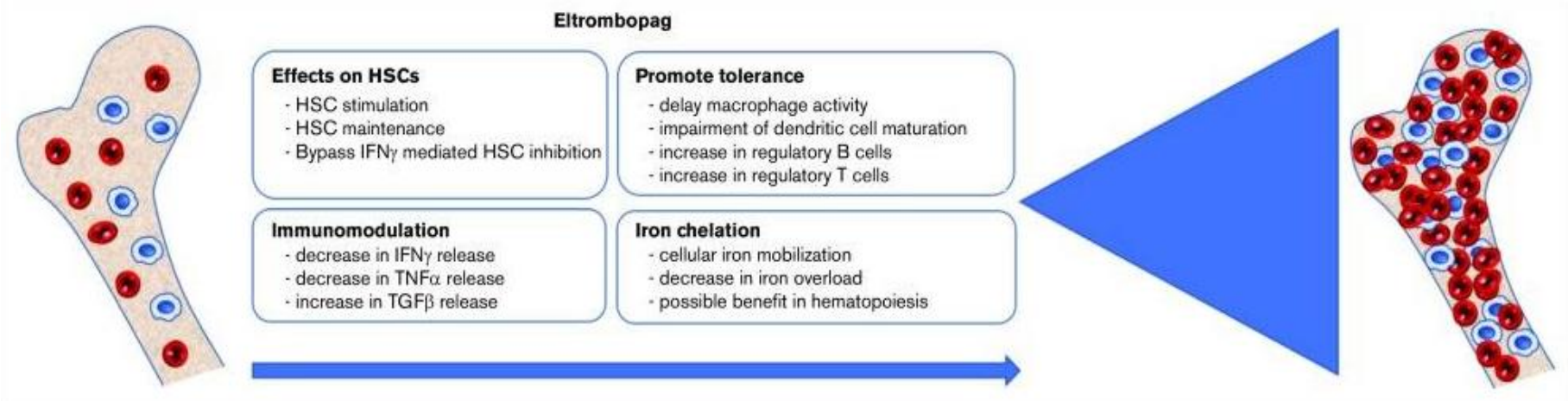

Severe Aplastic Anemia
MRD available?
Yes
No
MRD HSCT
MUD available + HSCT feasible in 2-3months ?
Yes
MUD HSCT
No
High risk of infection?
No
Yes
IST (h ATG) ± EPag (on an individual basis)
1st line Haploidentical HSCT
Response to IST±Epag
No
Yes
Haploidentical HSCT or alternative donor available?
Yes
No
CyA 12 months from max response and slow decrease
HSCT from haplo or alternative donor (cord blood)
Consider 2° IST (h/r ATG) ± Epag (on an individual basis)
Follow up
AA relapse?
No
Yes
Severe AA
Yes
Non severe AA (not transfusion dependent)
Increase CyA to stabilization and slow down to minimum effective dose ±Epag

IST response criteria

	Transfusion status	ANC	Hemoglobin	Platelet count
Complete response (CR)	Independent	$\geq 1 \times 10^9$/L	and ≥ 10 g/dL	and $\geq 100 \times 10^9$/L
Partial response (PR)	Independent	$\geq 0.5 \times 10^9$/L	and ≥ 8 g/dL	and $\geq 20 \times 10^9$/L
Nonresponder (NR) or refractory disease (RD)	Dependent	or $< 0.5 \times 10^9$/L	or < 8 g/dL	or $< 20 \times 10^9$/L

Kristin Shimano et al. *Pediatr Blood Cancer.* 2024;71:e31070

How eltrombopag is acting in SAA



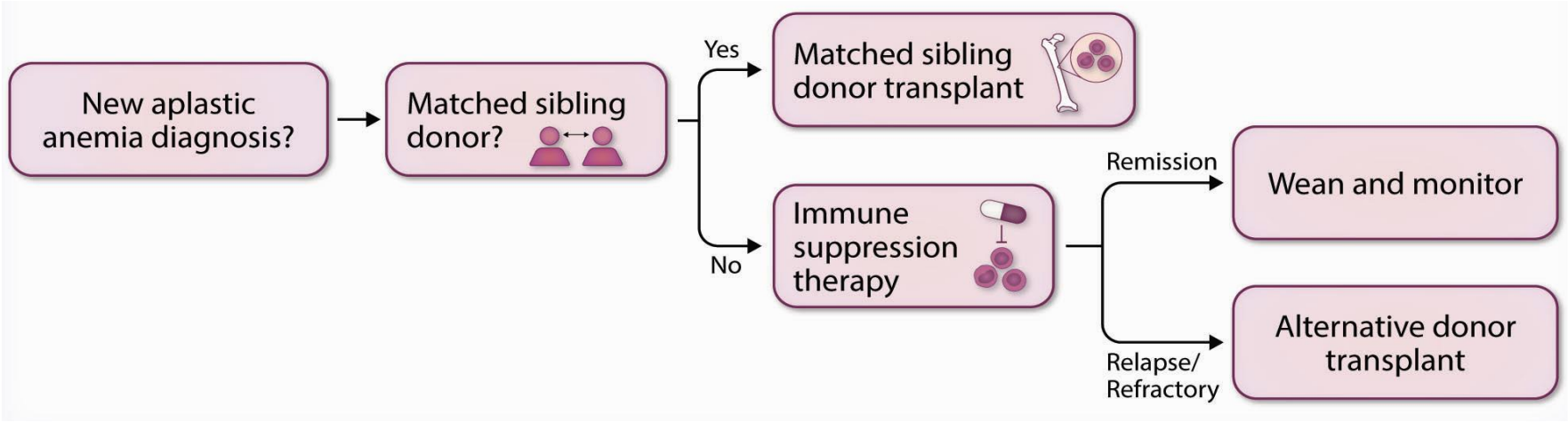
Phillip Scheinberg. Hematology Am Soc Hematol Educ Program 2018 Nov 30;2018(1):450–456.

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Journal of the Ferrata Storti Foundation

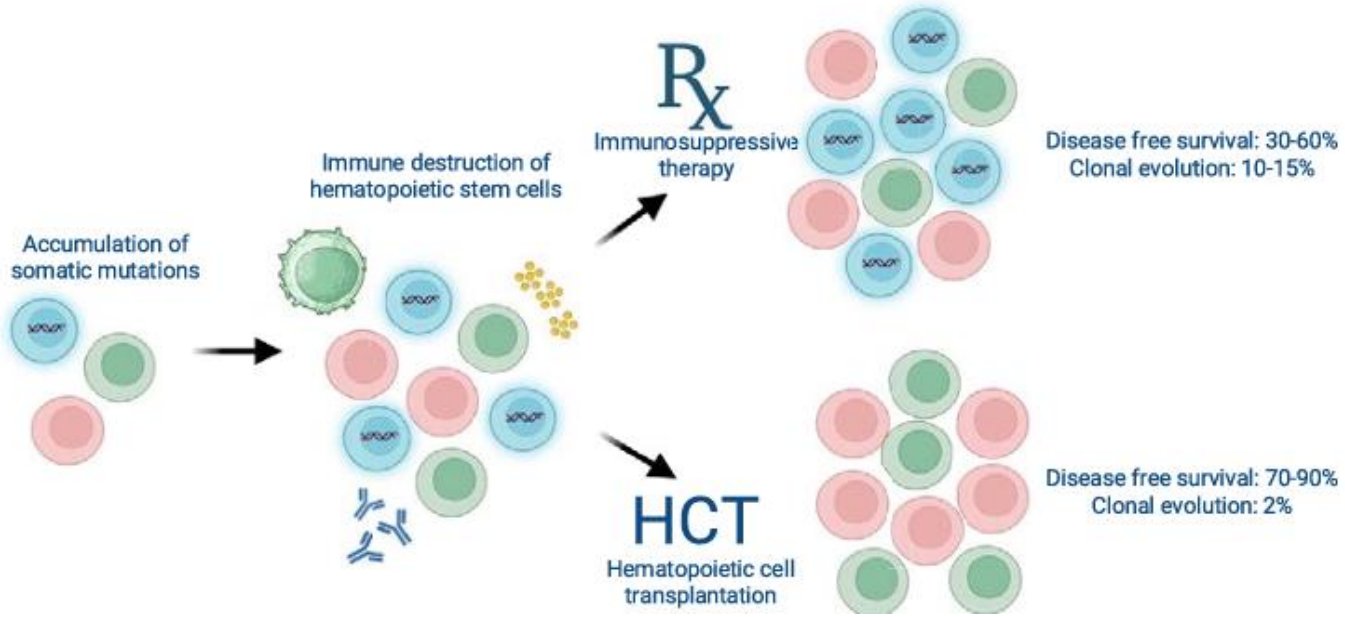
Immunosuppressive therapy for severe aplastic anemia in children under the age of 3 years yields a high response rate: a North American collaborative study

by Talya Wittmann Dayagi, Laura Willis, Staci D. Arnold, Jessica Boklan, Michaela Cada, Thomas D. Coates, Catherine Corriveau-Bourque, Christopher J. Gamper, Amy E. Geddis, Bertil Glader, Gary M. Kupfer, Taizo A. Nakano, Timothy S. Olson, Zora R. Rogers, Akiko Shimamura, Clifford Takemoto, Alexis A. Thompson, David A. Williams and Yigal Dror

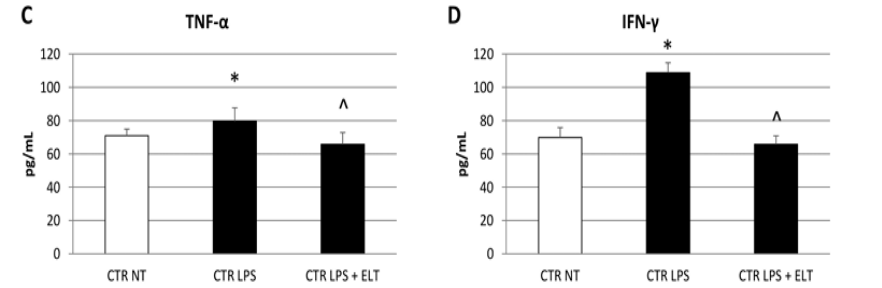
Historical treatment algorithm for SAA

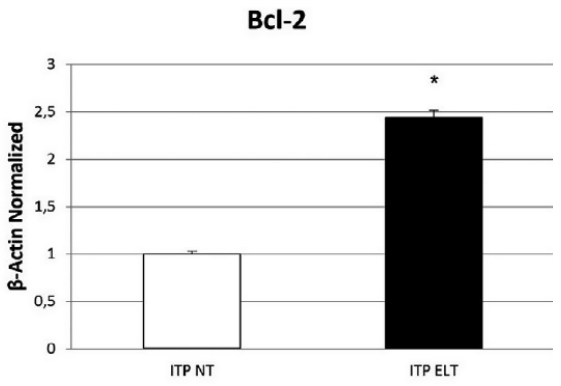


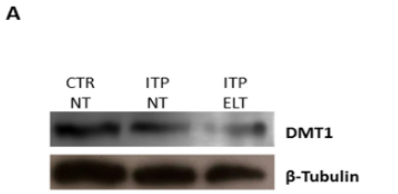
J.H. Oved *et al.* Haematologica | 110 August 2025

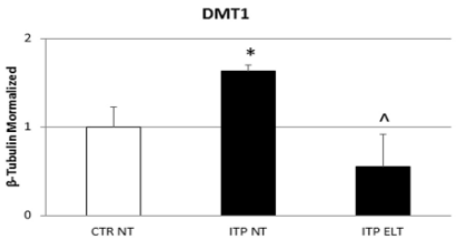


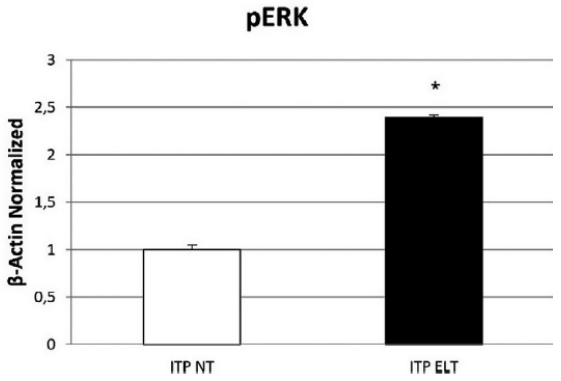
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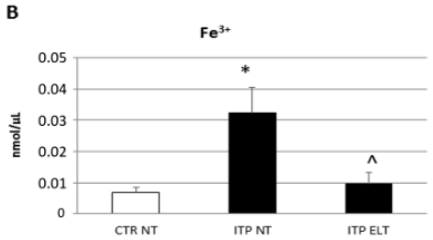


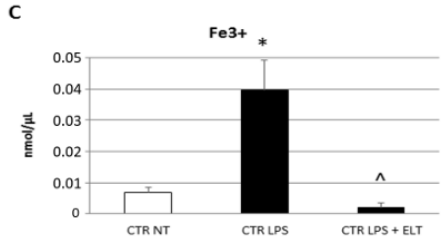






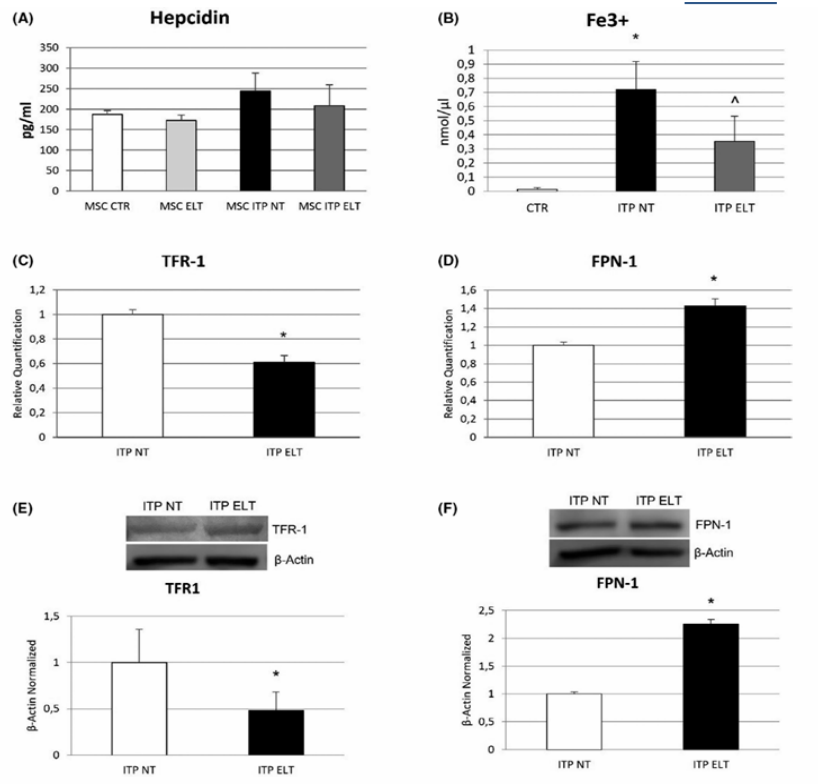


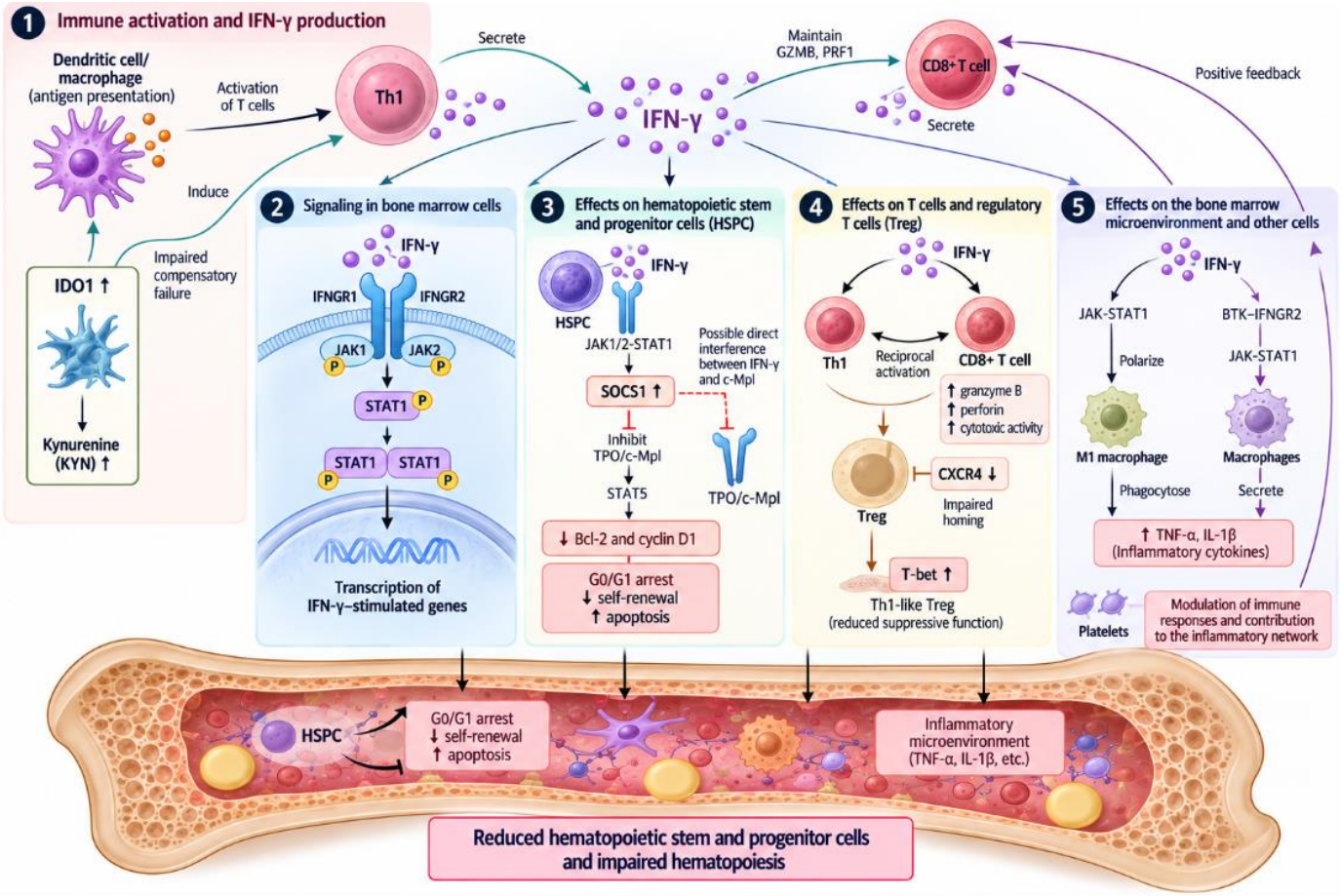




Di Paola A et al. Int. J. Mol. Sci. 2021, 22, 97

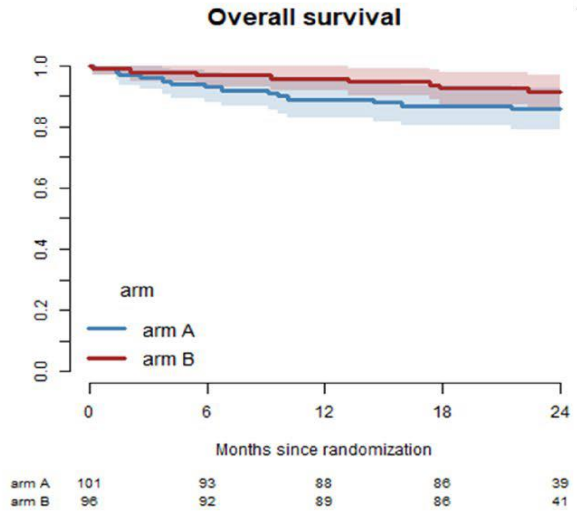
Eltrombopag: Iron metabolism modulation in mesenchymal stromal cells



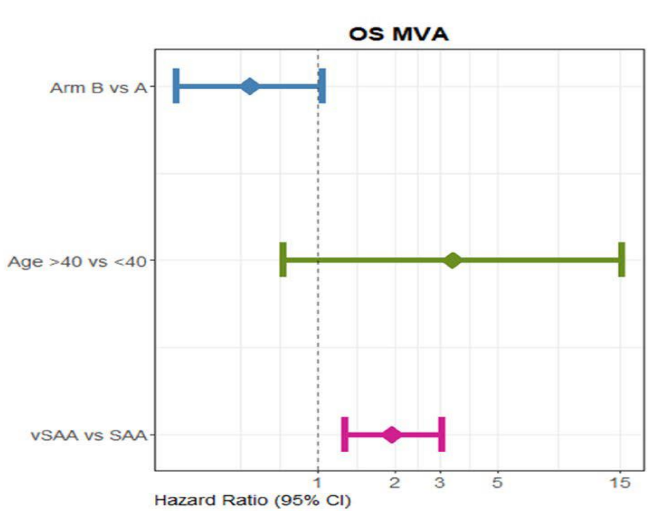

1 Immune activation and IFN-γ production
Dendritic cell/ macrophage (antigen presentation)
Activation of T cells
Th1
Secrete
IFN-γ
Maintain GZMB, PRF1
CD8+ T cell
Secrete
Positive feedback
Induce
Impaired compensatory failure
IDO1 ↑
Kynurenine (KYN) ↑
2 Signaling in bone marrow cells
IFN-γ
IFNGR1
IFNGR2
JAK1
JAK2
STAT1
STAT1
STAT1
Transcription of IFN-γ–stimulated genes
3 Effects on hematopoietic stem and progenitor cells (HSPC)
IFN-γ
HSPC
JAK1/2-STAT1
Possible direct interference between IFN-γ and c-Mpl
SOCS1 ↑
Inhibit TPO/c-Mpl
STAT5
TPO/c-Mpl
↓ Bcl-2 and cyclin D1
G0/G1 arrest
↓ self-renewal
↑ apoptosis
4 Effects on T cells and regulatory T cells (Treg)
IFN-γ
Th1
Reciprocal activation
CD8+ T cell
↑ granzyme B
↑ perforin
↑ cytotoxic activity
CXCR4 ↓
Impaired homing
Treg
T-bet ↑
Th1-like Treg
(reduced suppressive function)
5 Effects on the bone marrow microenvironment and other cells
IFN-γ
JAK-STAT1
BTK–IFNGR2
Polarize
JAK-STAT1
M1 macrophage
Macrophages
Phagocytose
Secrete
↑ TNF-α, IL-1β
(Inflammatory cytokines)
Platelets
Modulation of immune responses and contribution to the inflammatory network
HSPC
G0/G1 arrest
↓ self-renewal
↑ apoptosis
Inflammatory microenvironment
(TNF-α, IL-1β, etc.)
Reduced hematopoietic stem and progenitor cells and impaired hematopoiesis

Eltrombopag Added to Standard Immunosuppressive Treatment as Front-Line Therapy for Severe Aplastic Anemia: Long-Term Outcomes of the Phase-3 Randomized Superiority EBMT-SAAWP RACE Study

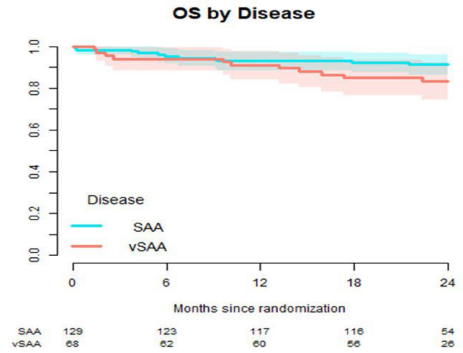
A



B



C



D

