

Management of Refractory Severe Aplastic Anemia: What Are the Options?

Noppacharn Uaprasert, MD

Division of Hematology, Department of Medicine

Faculty of Medicine, Chulalongkorn University

Classification of Aplastic Anemia

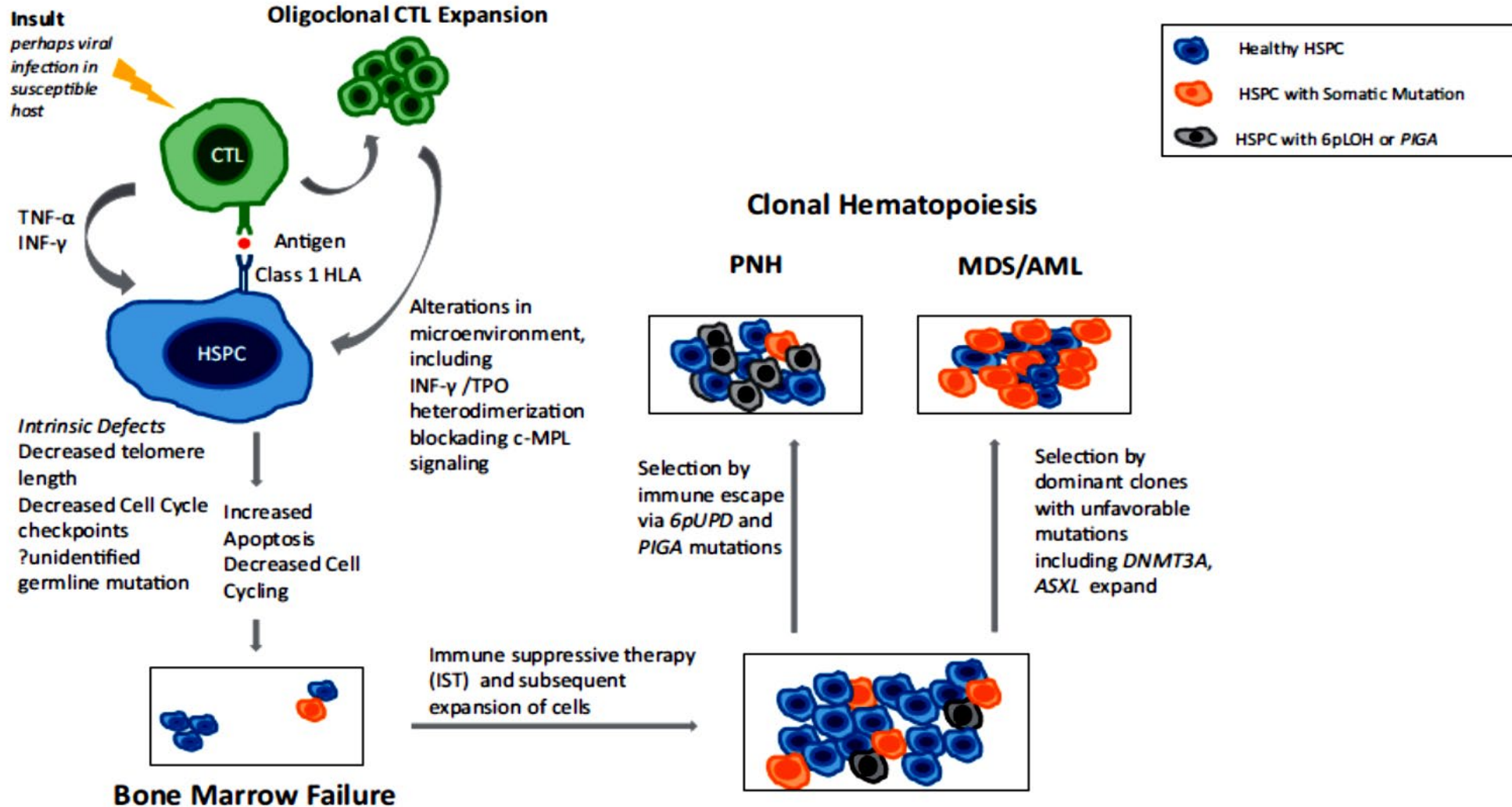
Acquired (immune)
~70%

Inherited
(15–20%)

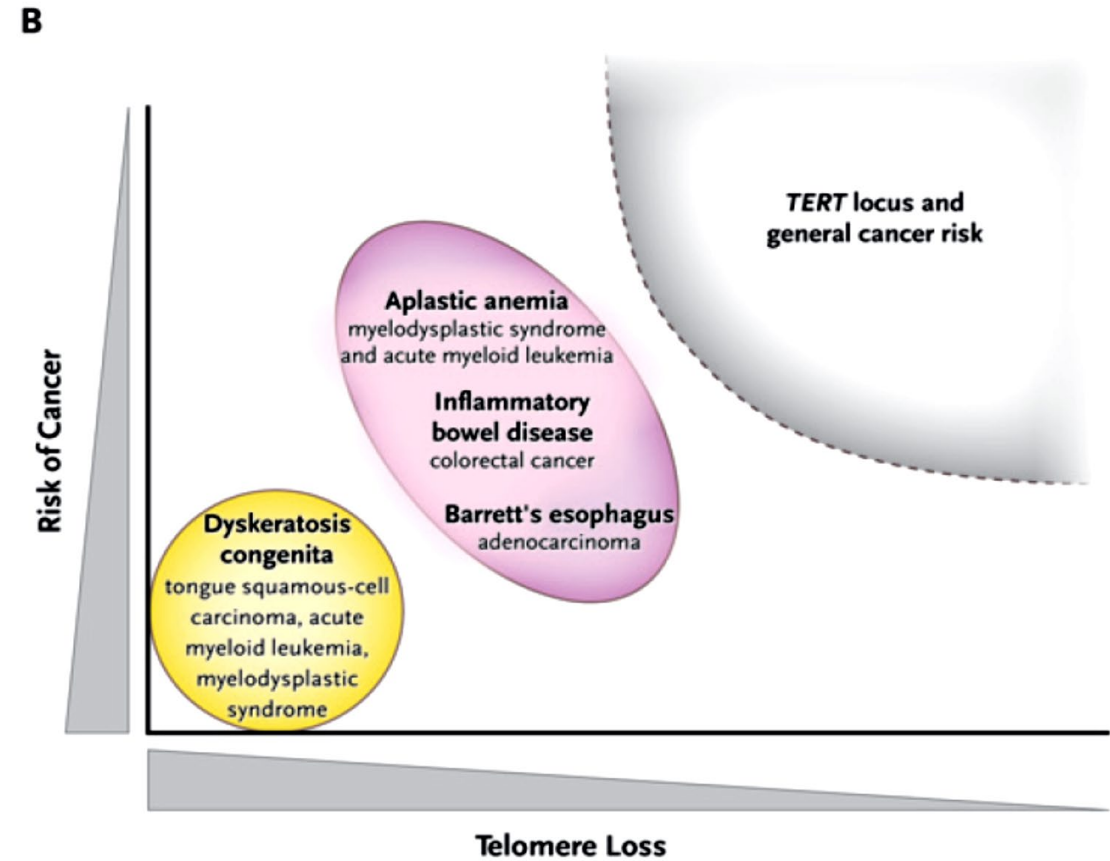
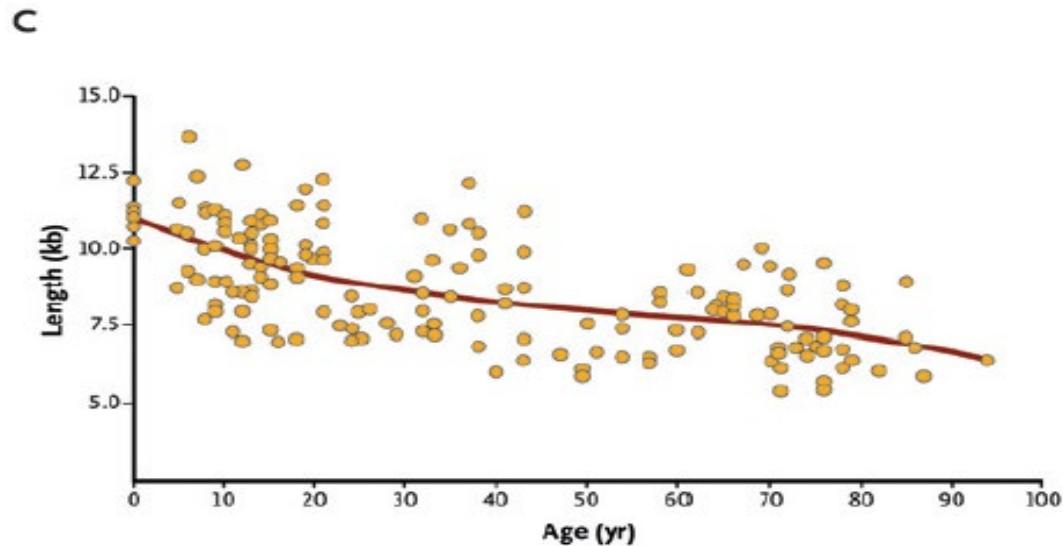
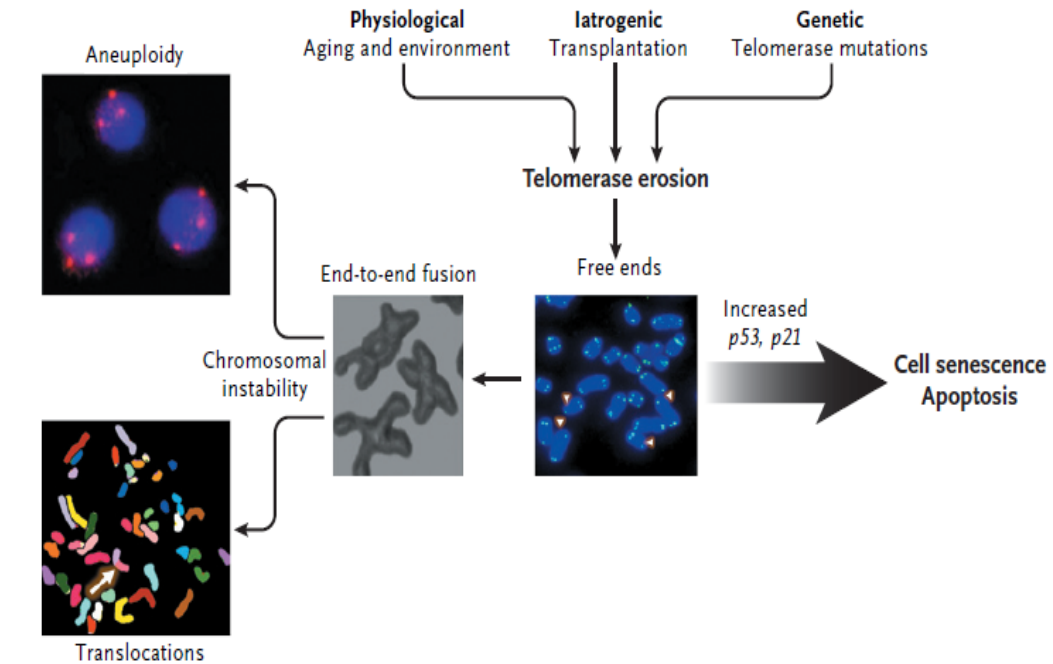
Secondary
(10–15%)

Classification	Criteria
Non-severe	Hypocellular bone marrow with peripheral blood values not meeting the criteria for severe or very severe aplastic anemia
Severe	Bone marrow cellularity equal to 25% of the normal control, or 25-50% of the normal control with <30% residual HSCs AND two of the following peripheral blood criteria: • Neutrophil count: < 500/μL • Platelet count: < 20,000/μL • Reticulocyte count: < 20,000/μL or < 60,000/μL (automated count)
Very severe	Severe aplastic anemia with neutrophil count < 200/ μ L

Pathophysiology of AA



Telomere Disease

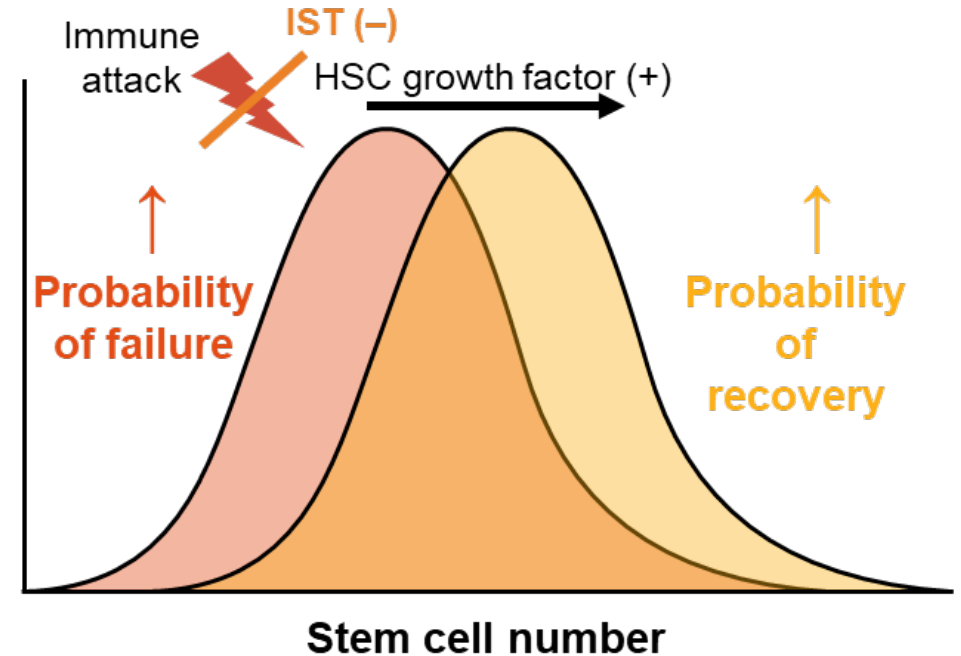


N Engl J Med 2009;361:2353

Stimulation of stem cells may increase probability of recovery in patients receiving IST

- Blood counts may reflect stem cell reserve and predict response to IST
- A lack of response to IST may be due to the limited number of HSCs to maintain hematopoiesis of the bone marrow
- IST in combination with a factor to stimulate stem cell production may overcome the limit of response to IST alone
- G-CSF and ESA have failed to improve outcomes in SAA

Stem Cell Number may be a Limiting Factor in Responsiveness to IST



Adapted from Young NS et al. *Hematology Am Soc Hematol Educ Program*. 2013;76–81.

- Bone marrow aplasia → Allogeneic stem cell transplantation
- Cytotoxic T-cell -mediated HSC injury → ATG and CSA or other T-cell targeted IST
- Telomere disease → Anabolic steroids
- Stem cell exhaustion → Stem cell growth factor → TPO receptor agonist (TPO-RA)

Guidelines in Thailand 2020

บทความพิเศษ

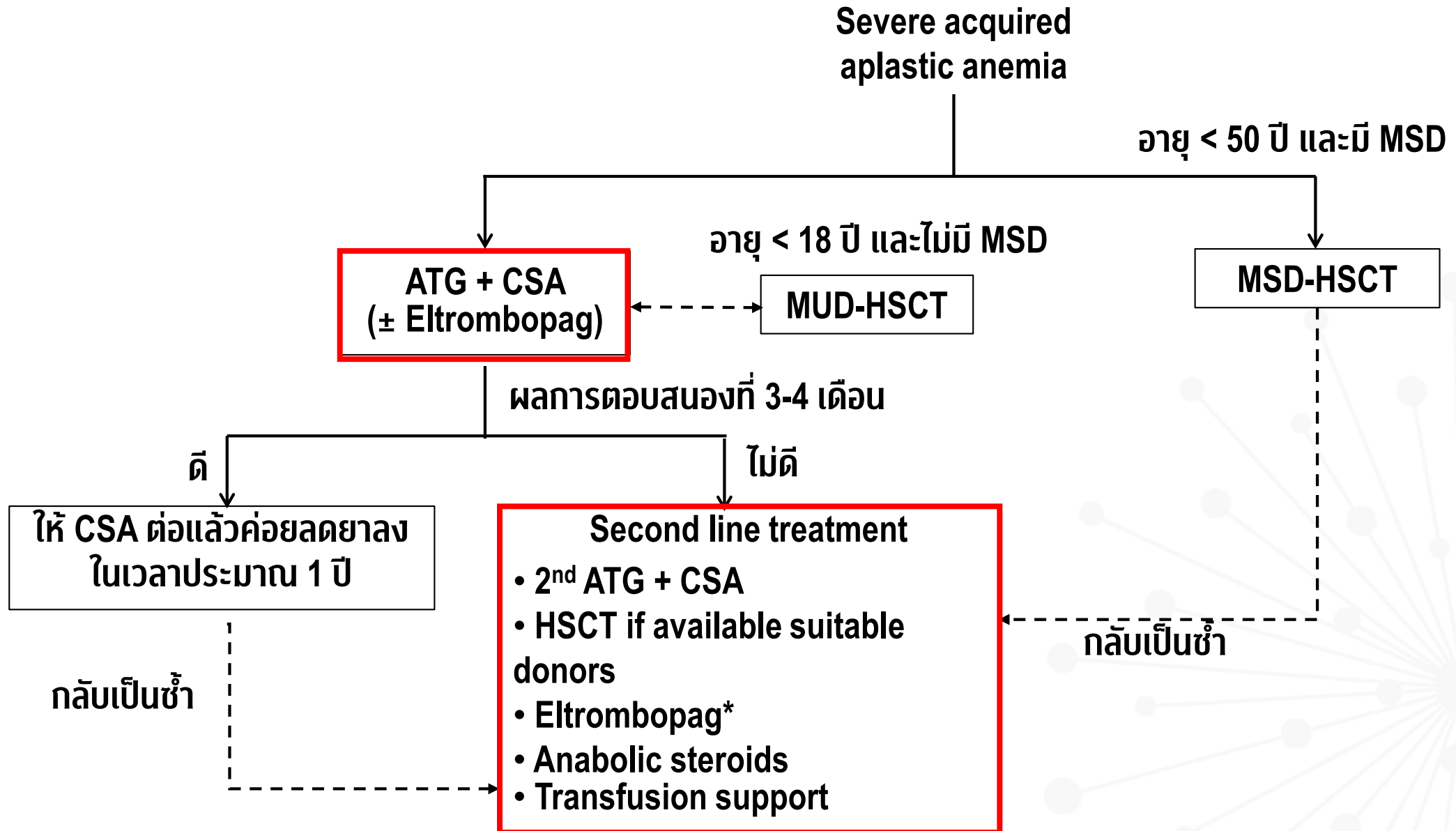
แนวทางการรักษาโรคไขกระดูกฝ่อในประเทศไทยพุทธศักราช 2563

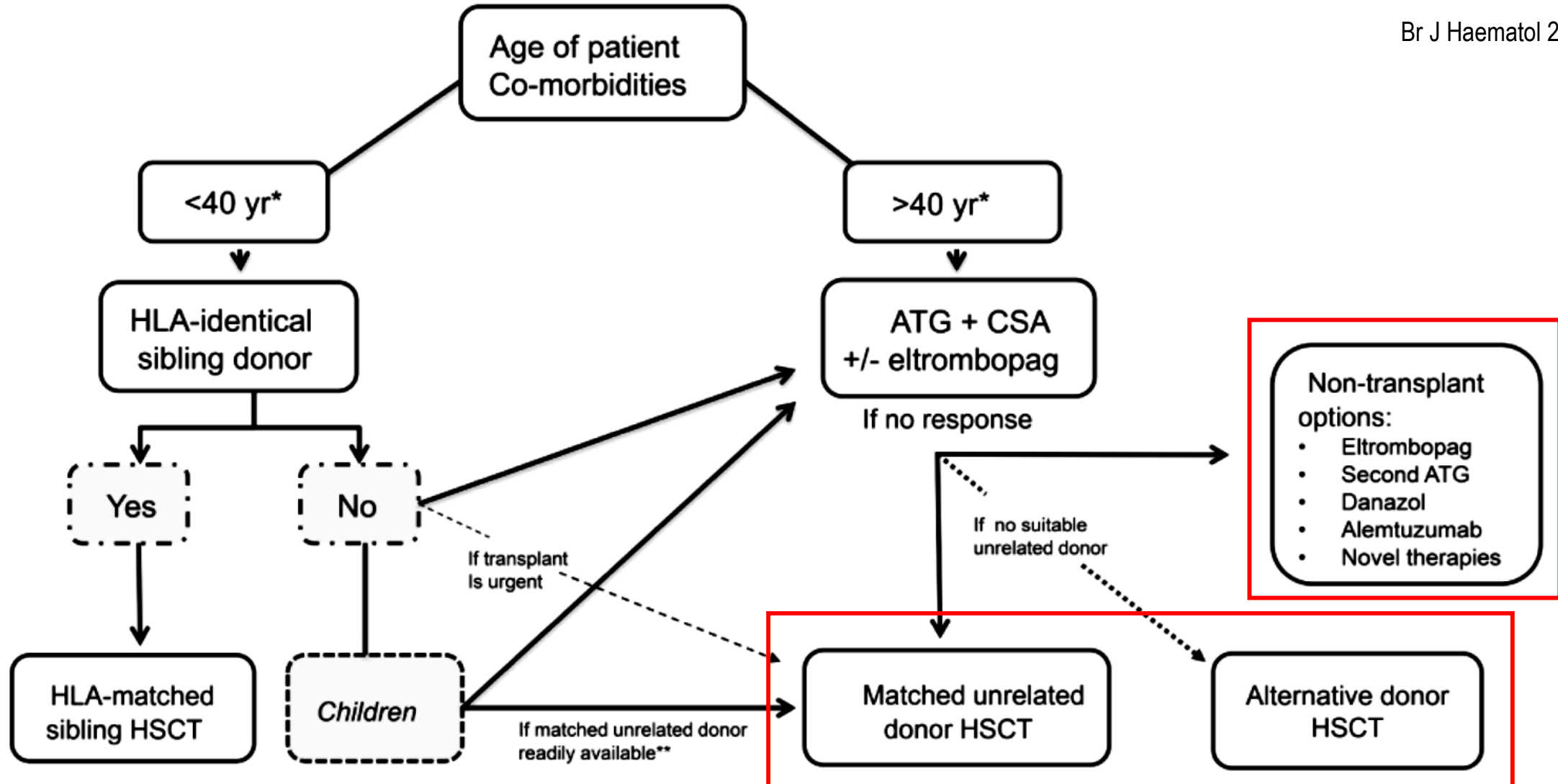
**Guidelines for diagnosis and management of aplastic anemia in
Thailand 2020**

นพชาญ เอื้อประเสริฐ¹ กาญจนา จันทร์สูง² บุญชู พงศ์ธนากุล³ สุภานันท์ เลาสุริโยธิน⁴ นงนุช ลีระชัยนันท์⁵
สนั่น วิสุทธิศักดิ์ชัย⁶ วิชัย ประยูรวิวัฒน์⁷ และ สุรพล อิศรไกรศีล⁸

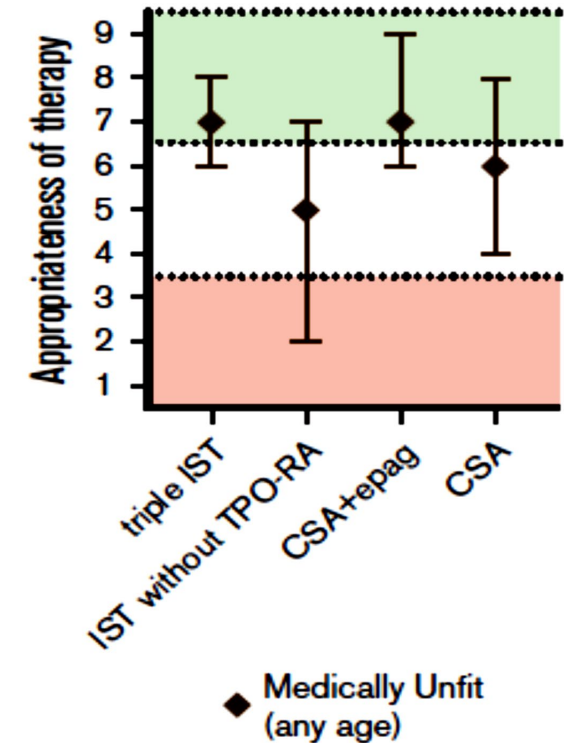
¹ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ²ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น ³ภาควิชากุมารเวชศาสตร์
คณะแพทยศาสตร์ ศิริราชพยาบาล ⁴ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ⁵ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์โรงพยาบาล
รามธิบดี ⁶ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ ศิริราชพยาบาล ⁷กองอายุรกรรม โรงพยาบาลพระมงกุฎเกล้า

Treatment for Acquired AA: SAA and VSAA





Treatment of acquired severe aplastic anemia. *For patients aged between 40 and 50 years, an individual patient assessment based on comorbidities, performance status, expertise of transplant center and rapid availability of sibling donor can be made to help decide whether to treat with first line IST or MSD HSCT. **Within 8 weeks. IST, immunosuppressive therapy; MSD, matched sibling donor



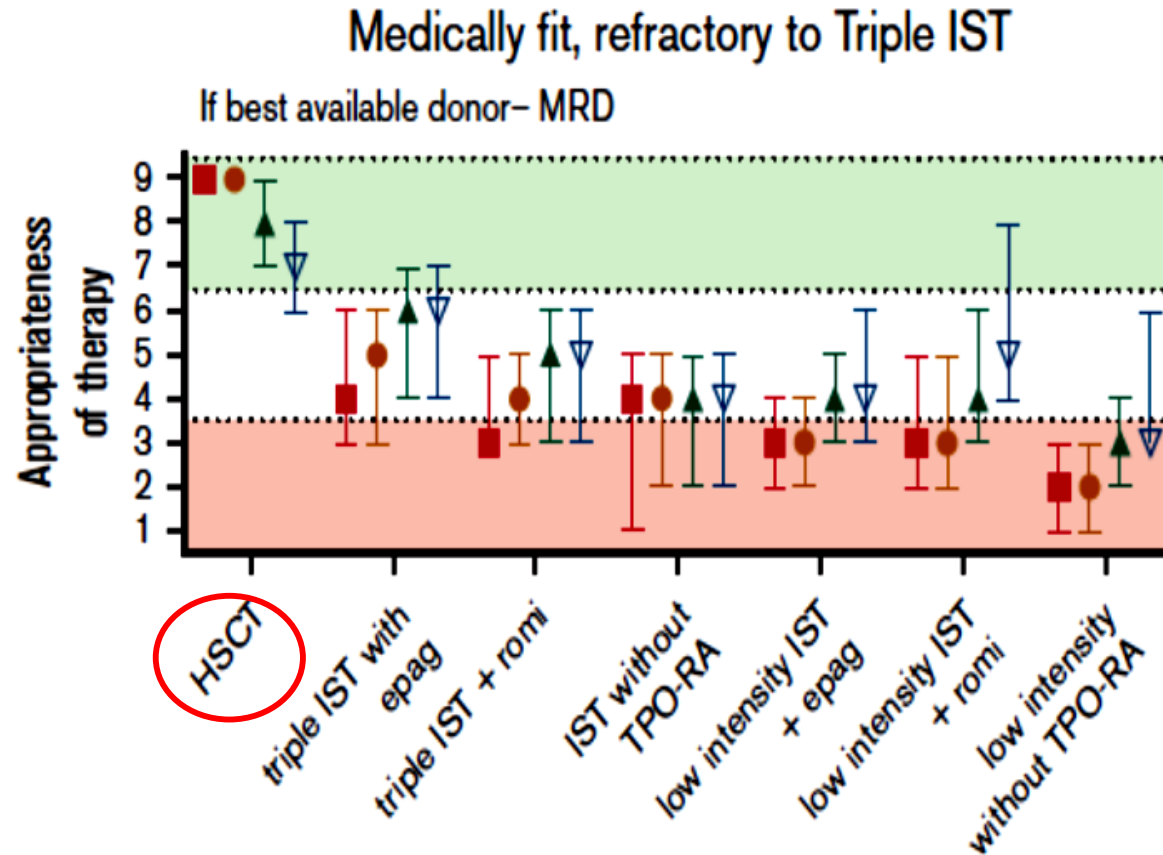
Triple IST = ATG+CSA+TPO-RA

High-intensity therapy	Low-intensity therapy
• Horse or rabbit ATG + CsA w/wo eltrombopag • Horse or rabbit ATG + other non-CsA immunosuppressant (eg, tacrolimus) w/wo eltrombopag • Alemtuzumab • Horse or rabbit ATG + CsA + androgens or growth factors	• CsA w/wo eltrombopag • Other non-CsA immunosuppressant (eg, tacrolimus) • CsA + androgens • Androgens (single agent) • Growth factors (single agent; eg, ESA or G-CSF) • Eltrombopag (single agent)

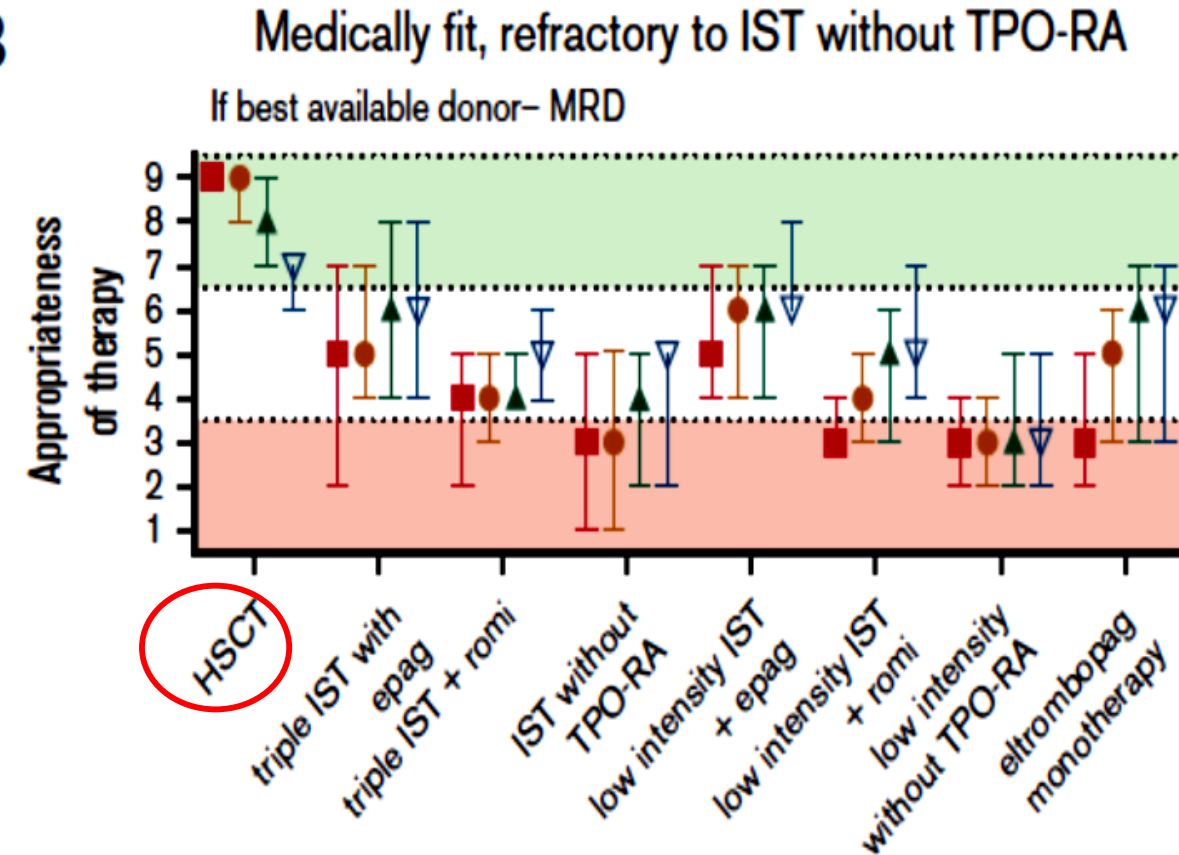
- w/wo, with or without
- These are examples of common therapy combinations. Cyclophosphamide has also shown efficacy for AA but is associated with high levels of toxicity and is no longer routinely recommended.
- Romiplostim can also be combined with horse or rabbit ATG + CsA or non-CsA immunosuppressant or used as a single agent.

ASH 2024: Subsequent therapy in medically fit patients refractory to initial treatment

A

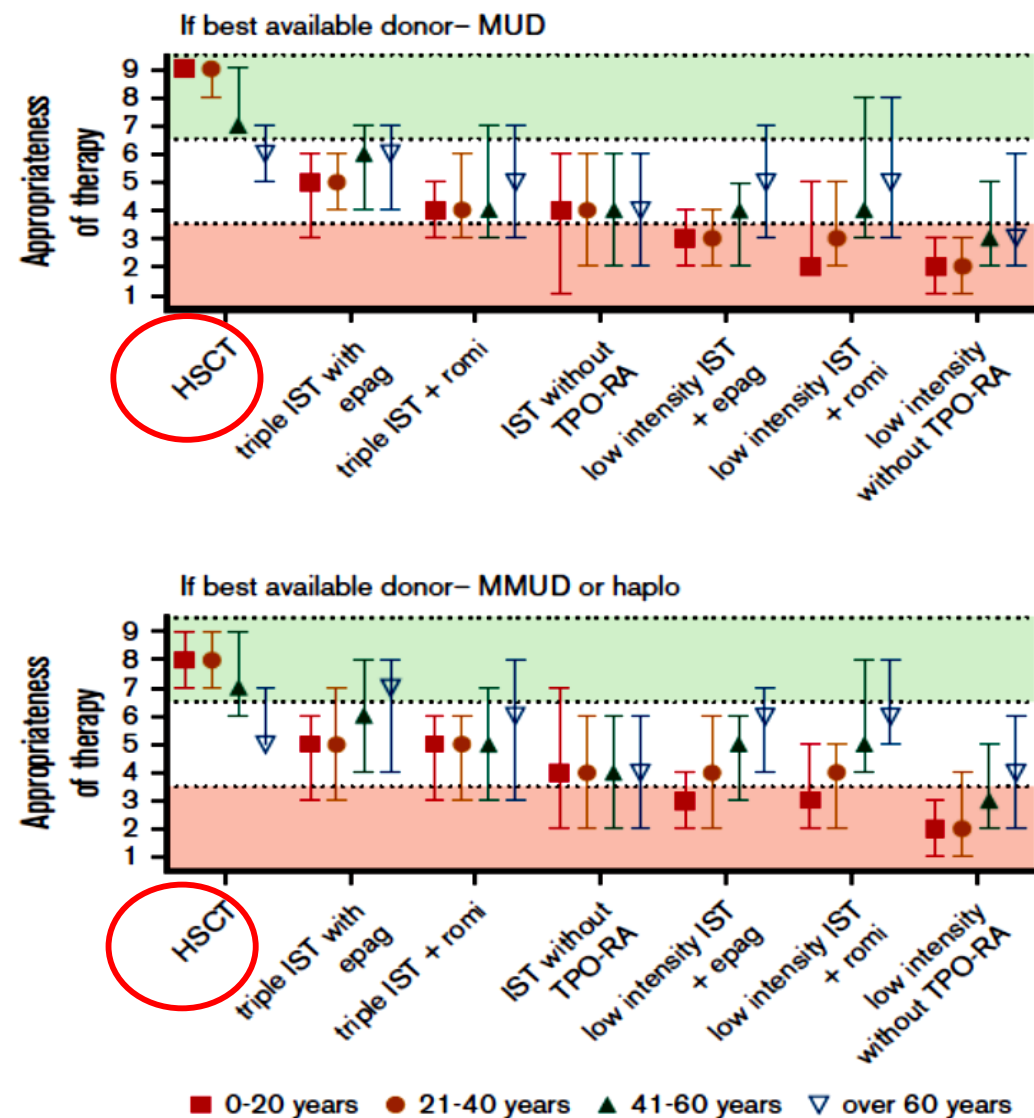


B

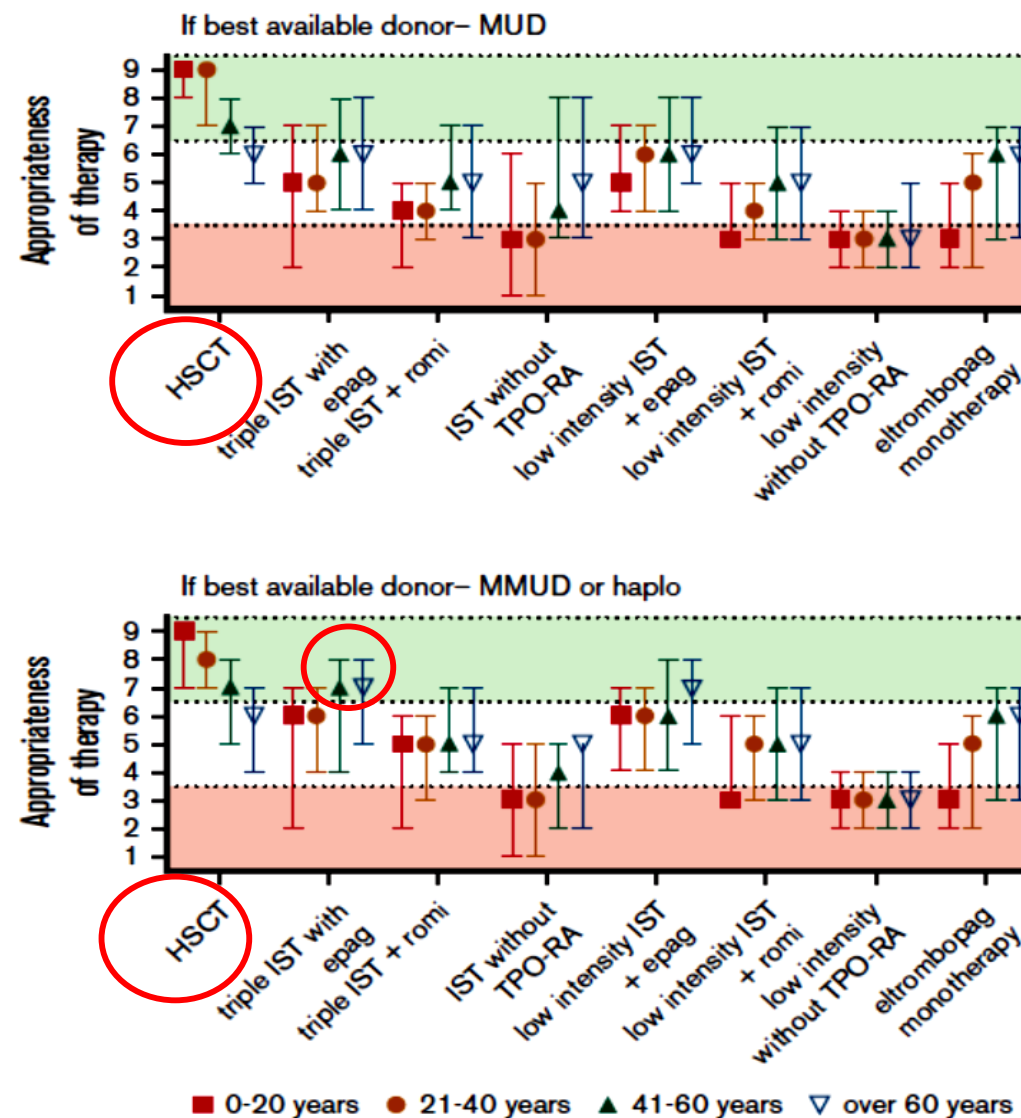


ASH 2024: Subsequent therapy in medically fit patients refractory to initial treatment

Refractory to triple therapy

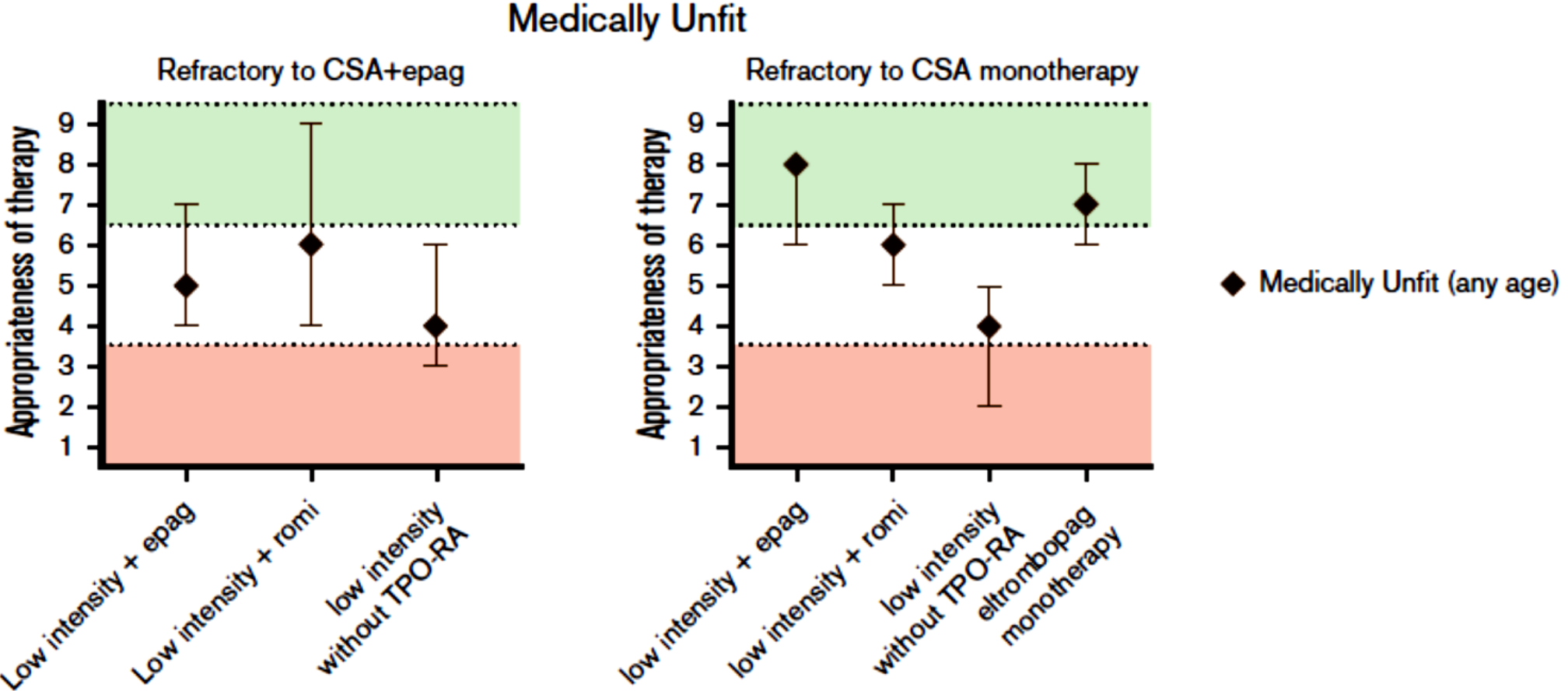


Refractory to IST without TPO-RA

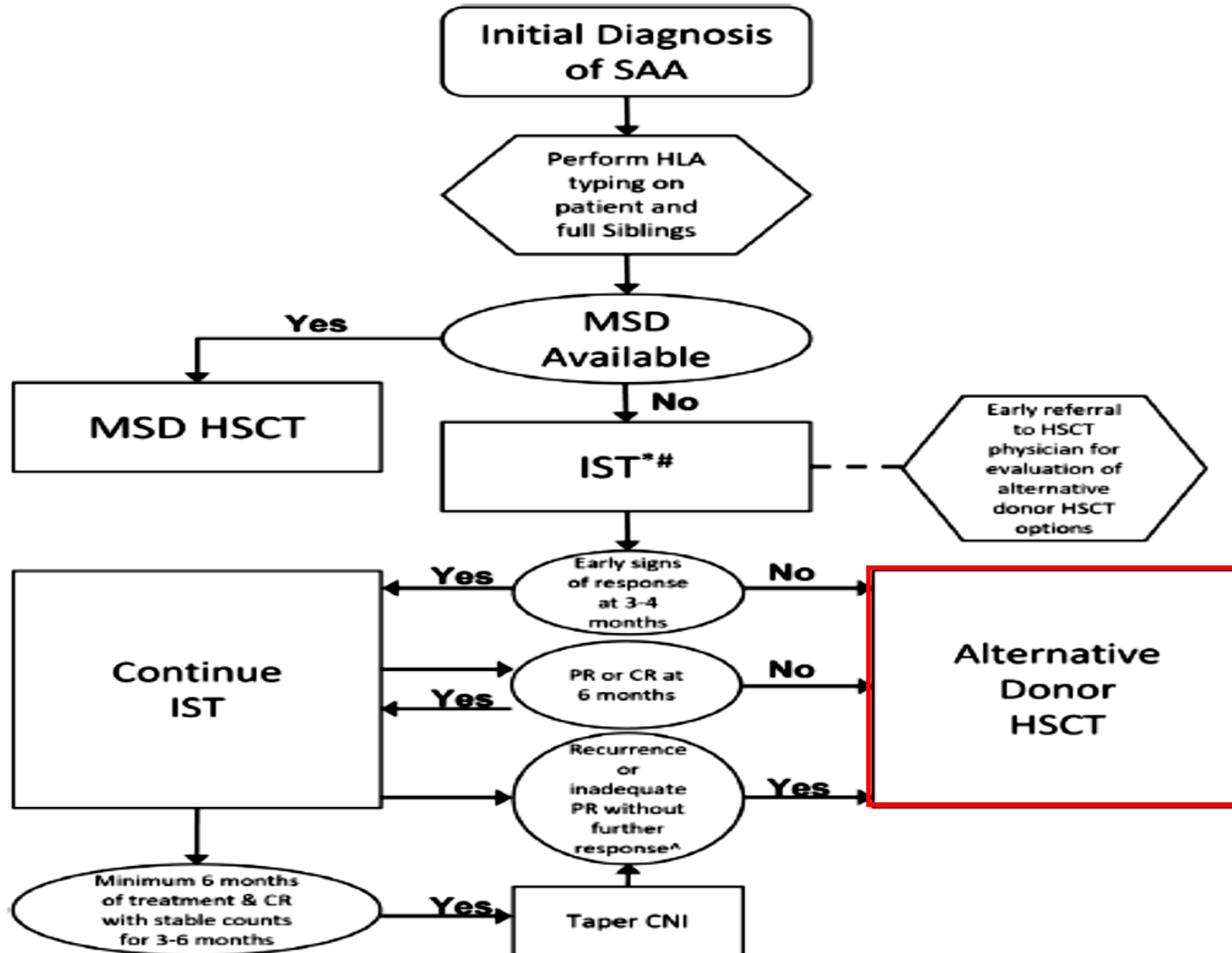


ASH 2024: Subsequent therapy in medically unfit patients refractory to initial treatment

C



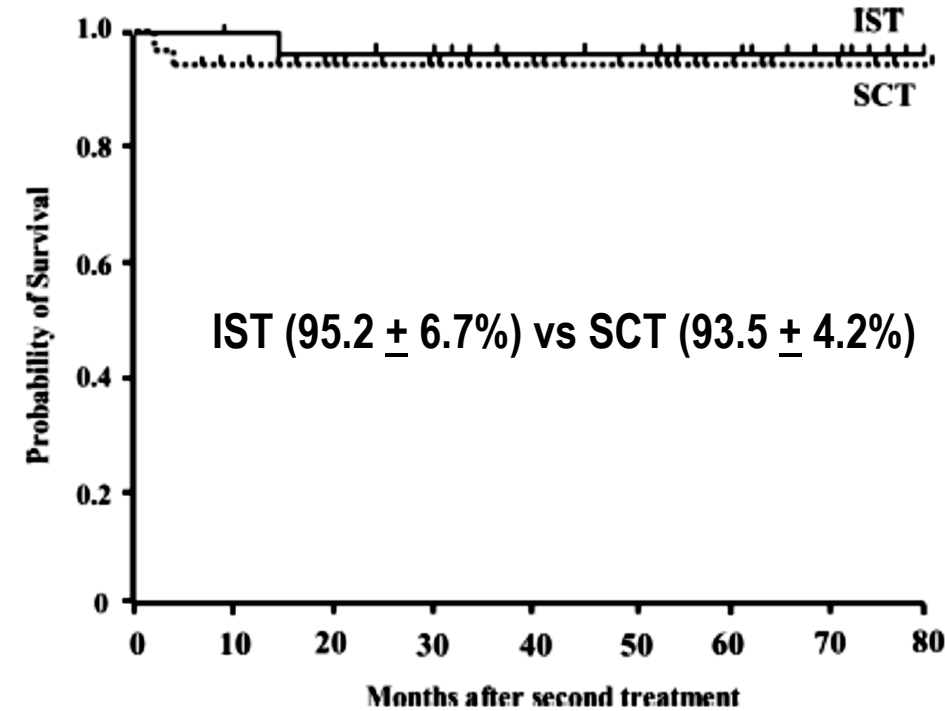
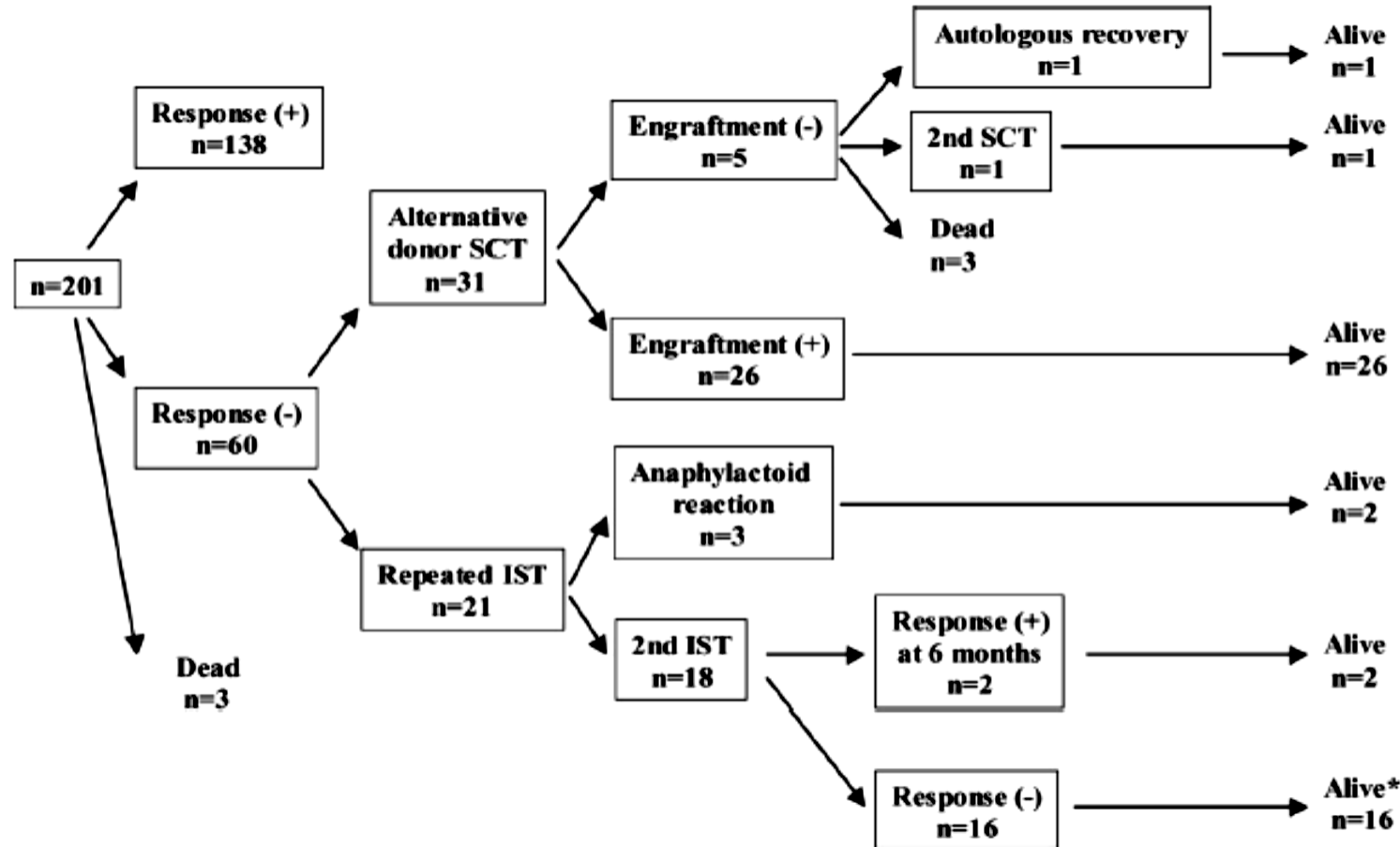
Treatment of relapsed/refractory SAAA in children: Evidence-based recommendations



Treatment options for refractory SAA

- HSCT: MRD > MUD > MMUD/Haploidentical/Cord blood
- Second ATG
- Alternative IST
 - High-intensity: Alemtuzumab
 - Low-intensity: CSA or other T-cell targeted IST (tacrolimus, sirolimus, MMF)
- Thrombopoietin receptor agonists: eltrombopag, romiplostim
- Anabolic steroids: oxymetholone, danazol
- Supportive treatment: transfusion support

Repeat rATG vs alternative donor HSCT in pediatric SAA after failure to IST



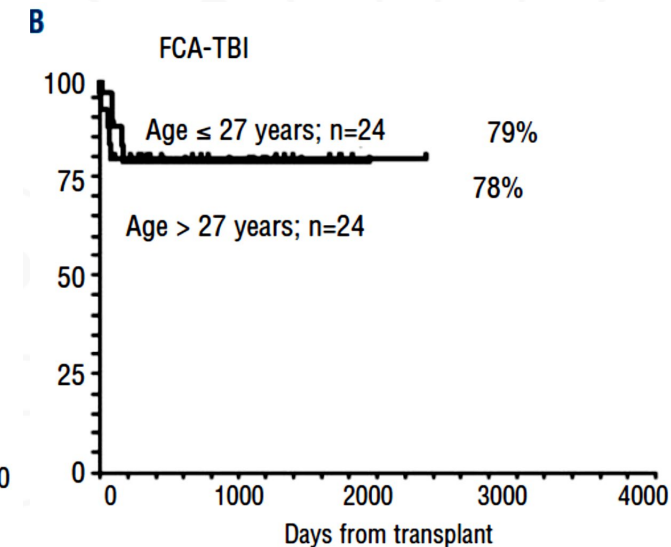
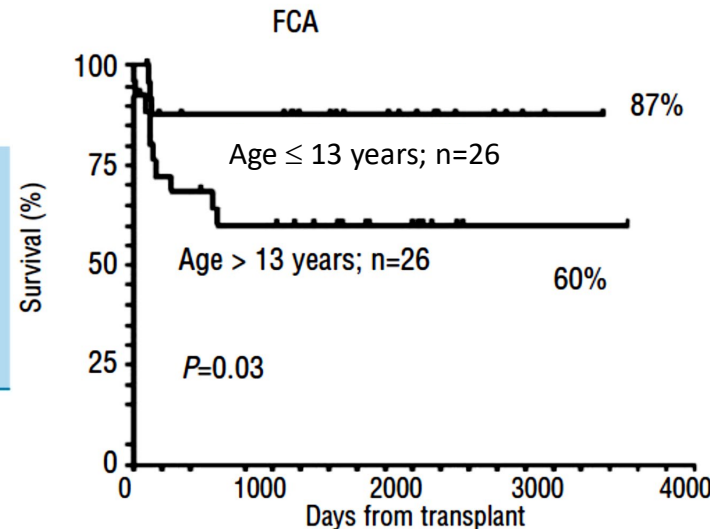
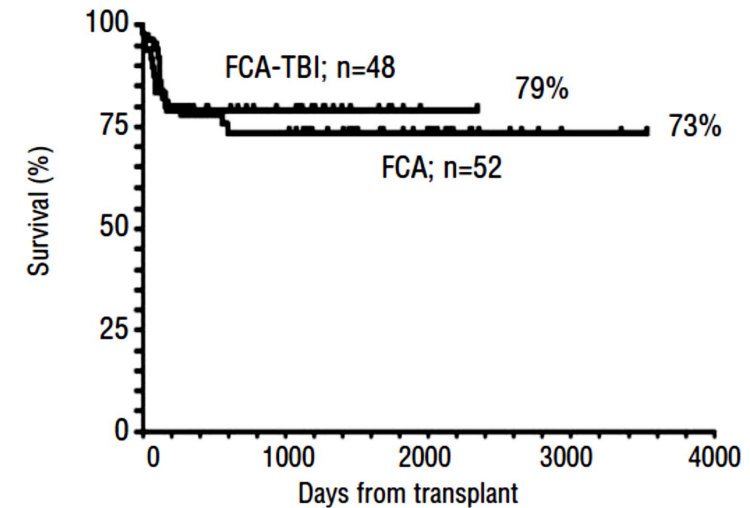
BMT from an HLA-matched unrelated donor (UBMT; n = 25), cord blood transplantation from an unrelated donor (UCBT; n = 2), and BMT from an HLA-mismatched family donor (n = 4)

Estimated failure free survival (FFS), defined as survival with response, was **83.9% (± 16.1%, SD) in the SCT group** compared with **9.5% (± 9.0%) in the IST group** (P = 0.001).

Alternative donor SCT, in SAA after IST: a retrospective study from the EBMT-SAA working party

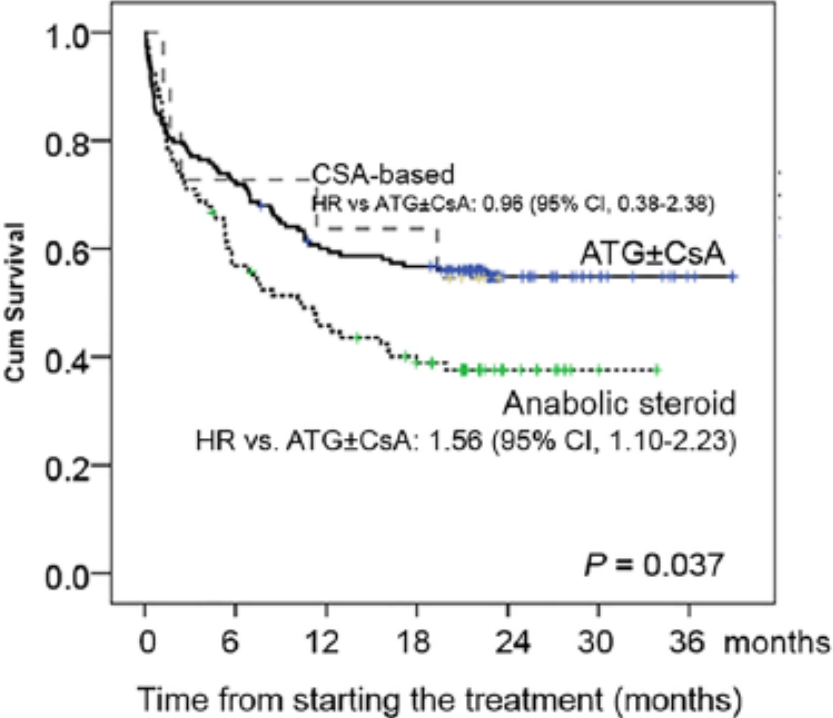
Table 1. Clinical data of the 100 transplanted patients with SAA.

Patients	FCA n=52	FCA-TBI n=48	P value
Sex (male/female)	25/27	29/19	0.15
Median age	13 (3-51)	27 (7-53)	<0.001
Source BM/PB/CB	48/3/1	40/7/1	0.33
Median year Tx	2003 (1998-2009)	2006 (2002-2009)	<0.001
Donor relation			
Unrelated donor	46	41	0.40
HLA matching yes/no*	20/14	26/15	0.68
Family mismatched donor	6	7	
Interval Dx-Tx	530 (92-3919)	461 (158-7437)	0.43
<365 days	16	16	
365-730 days	14	13	
>730 days	20	17	0.87
Unknown	2	2	



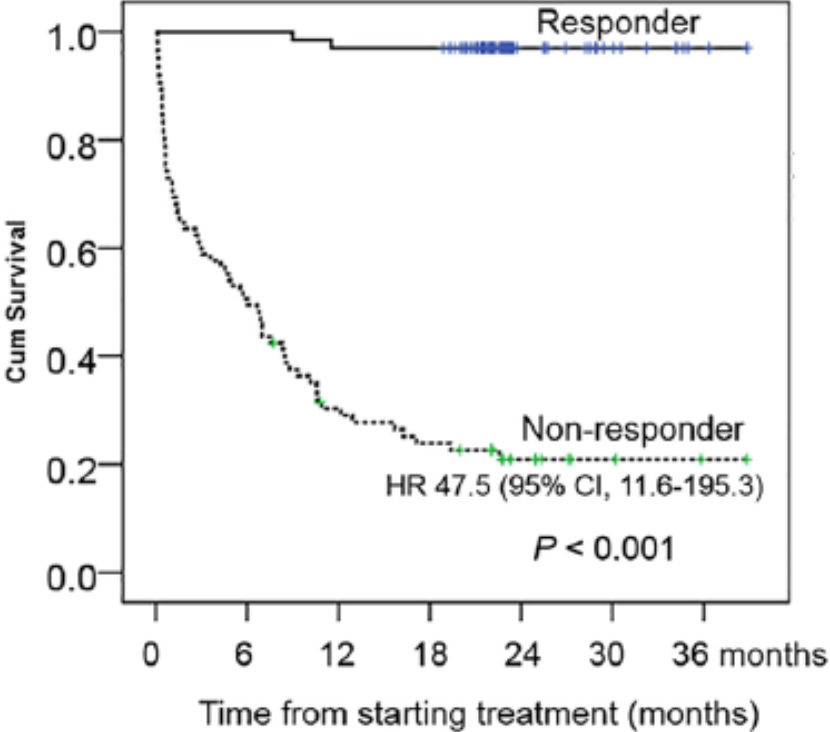
IST for Adult Severe Aplastic Anemia in Thailand

A Patients receiving specific treatment



# at risk	ATG±CsA	153	111	90	85	26	11	3
	CsA	11	8	7	7	0	0	0
	Anabolic S.	93	52	41	33	11	2	0

B Patients receiving ATG



Responder	68	68	66	66	17	8	2
Non-responder	85	43	24	19	9	3	1

ORR in SAA/VSAA treated with rATG ± CSA, CSA and anabolic steroids (44.4% vs 36.4% and 31.2%, $P < 0.001$)

> 60% of SAA/VSAA patients require second-line treatment

IST for Adult Severe Aplastic Anemia in Thailand

Table 2 Treatment modalities according to the frontline and subsequent treatments for patients with SAA and VSAA

<i>n</i> = 280 [‡]	Frontline treatment, <i>n</i> (%)	Subsequent treatment [†] , <i>n</i> (%)	
	rATG ± CsA*	143 (51.1)	rATG ± CsA 20 (14.0) Anabolic steroids 20 (14.0) CsA-based 5 (3.5)
	Anabolic steroids	102 (36.4)	rATG ± CsA 9 (8.8) CsA-based 1 (1.0)
	CsA-based [#]	12 (4.3)	rATG ± CsA 1 (8.3) Anabolic steroids 1 (8.3)
	No specific treatment	23 (8.2)	-

[‡]Did not include 3 patients who underwent HSCT

*rATG ± CsA: rATG with or without CsA; rATG with CsA (*n* = 123); rATG without CsA (*n* = 20)

[#]CsA-based: CsA contained treatment without ATG

[†]Subjects without subsequent treatment were not included
rATG, rabbit anti-thymocyte globulin; CsA, cyclosporin A

ORR in SAA/VSAA treated with rATG ± CsA, CSA and anabolic steroids (44.4% vs 36.4% and 31.2%, *P* < 0.001)

- About 60% of SAA/VSAA patients require second-line treatment

- Only 20% of SAA/VSAA patients received second-line treatment

IST for Adult Aplastic Anemia in Thailand

Table 3 Response rates over time after rATG ± CsA and anabolic steroids treatments in SAA/VSAA

	Month 3	Month 6	Month 12	Month 24
First ATG ± CsA† (N = 153)				
ORR, % (95% CI)	17.6 (12.0–24.6)	30.1 (22.9–38.0)	34.0 (26.5–42.1)	37.9 (30.2–46.1)
CR, n (%)	0 (0)	3 (2.0)	3 (2.0)	8 (5.2)
PR, n (%)	27 (17.6)	43 (28.1)	49 (32.0)	50 (32.7)
Not evaluable* n (%)	40 (26.1)	48 (31.4)	77 (50.3)	88 (57.5)
ORR in evaluable patients** no. (%)	27/113 (23.9)	46/105 (43.8)	52/76 (68.4)	58/65 (89.2)
Second ATG ± CsA (N = 20)				
ORR, % (95% CI)	10.0 (0–8–14)	10.0 (0–8–14)	25 (6.0–44.0)	35 (14.1–55.9)
CR, n (%)	0 (0.0)	0 (0.0)	1 (5.0)	1 (5.0)
PR, n (%)	2 (10.0)	2 (10.0)	4 (20.0)	6 (30.0)
Not evaluable* n (%)	0 (0.0)	3 (15.0)	5 (25.0)	8 (40.0)
Anabolic steroids (N = 93)				
ORR, % (95% CI)	11.8 (6.1–20.2)	18.3 (11.0–27.6)	28.0 (19.1–38.2)	21.5 (13.7–31.2)
CR, n (%)	0 (0.0)	0 (0.0)	5 (5.4)	3 (3.2)
PR, n (%)	11 (11.8)	17 (18.3)	21 (22.6)	17 (18.3)
Not evaluable* n (%)	37 (39.8)	47 (50.5)	52 (55.9)	71 (76.3)

†Including patients receiving first ATG ± CsA as initial (n = 143) and subsequent treatment (n = 10)

*Not evaluable due to lost to follow-up or death

**Excluding non-evaluable patients at each time point

rATG, rabbit anti-thymocyte globulin; CsA, cyclosporin A; ORR, overall response rate; CR, complete response; PR, partial response

Repeat Course of ATG in Severe Aplastic Anemia

Table 1. Summary of response, OS, and clonal evolution in refractory AA patients treated with second-line IST using ATG

Reference	N	ATG first course	ATG second course	Response	OS	Clonal evolution
Scheinberg et al ¹⁸	27	hATG + CSA	rATG + CSA	33%	60% at 3 y	2 with -7, 1 with t(6;14), 1 with trisomy 6
Scheinberg et al ¹⁴	22	hATG + CSA ± MMF or sirolimus	rATG + CSA ± MMF or sirolimus	30%	70% at d +1000	2 (MDS: +6, -7), 2 (AML)
Di Bona et al ¹³	30	hATG + CSA + G-CSF (until d 90)	rATG + CSA + G-CSF d +1-90	77%	93% at d +914	2 (MDS), 1 (MGUS)
Tichelli et al ⁴²	25	hATG + androgens + CSA after 1991	hATG + androgens + CSA after 1991	64%	55% at 10 y	NK
Marsh et al ⁴³	18	hATG + androgens	rATG + androgens	22%	NK	NK

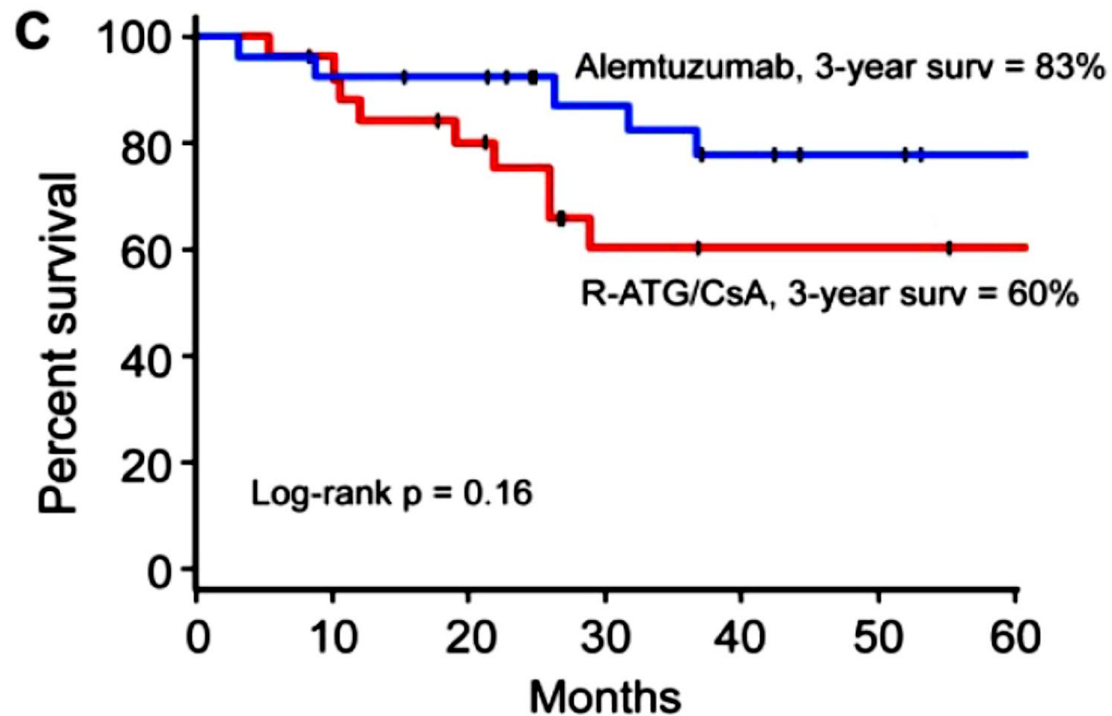
hATG indicates horse ATG; rATG, rabbit ATG; MMF, mycophenolate mofetil; MGUS, monoclonal gammopathy of unknown significance; AML, acute myeloid leukemia; and NK, not known.

ORR of rATG were 22%-77% in refractory cases to hATG

ORR of rATG refractory to rATG was 22% at 6 months

Alemtuzumab for Refractory SAA

RCT: Refractory N = 54



Response rate 37-50% in refractory to ATG patients

Study design	Indication	N	Alemtuzumab regimen	CSA	Response	OS
Prospective randomized	Refractory to hATG + CSA	27	10 mg/kg/d $\times$ 10 IV	None	37%	83% at 3 y
Prospective phase 2	Untreated (n = 6); refractory (n = 5)	11	3, 10, 30, 30 and 30 mg/d SC (total dose 103 mg)	1 mg/kg/d	8/11 (73%) (4/6 untreated)	73%
Retrospective	Refractory	8			3/8 (37%)	
Prospective dose escalating	Untreated (n = 13) Refractory to ATG + CSA/danazol (n = 4)	17	Cohort I: 10, 20, 30 mg IV Cohort II: 30 mg/d $\times$ 3 IV	3 mg/kg/d	4/13 (31%) 2/4 (50%)	81.6% at 2 y

Response rate at 6 months for alemtuzumab was 37% (95%CI, 18%-57%) and for rabbit ATG 33% (95%CI, 14%-52%; $P = 0.78$)

Blood 2012;119:345
Blood 2013;122:3561

Androgenic steroids

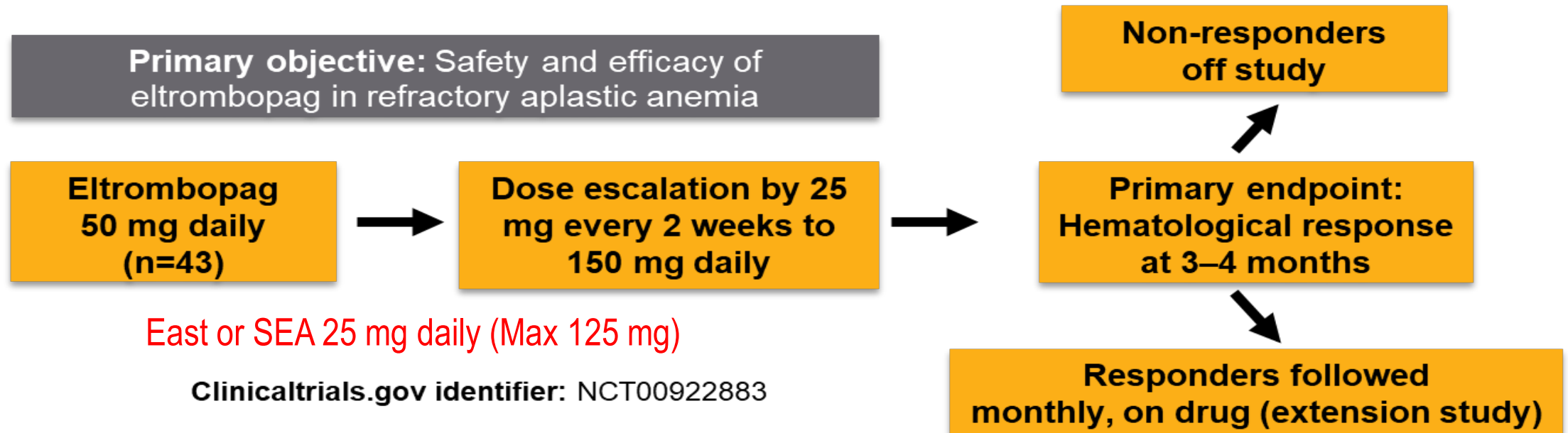
Danazol 300 mg/day, response rate 31.3%, (male 17%, female 75%)

TABLE I. Patient Characteristics

Age	Gender	Immunosuppressive therapy/outcome	Grade of AA at the start of danazol treatment	Cytogenetics
74	Male	ATG+CsA/relapse	moderate	normal
42	Female	CsA/ineffective	moderate	normal
48	Male	CsA/ineffective	severe	normal
28	Male	ATG+CsA/ relapse→ATG/CsA ineffective	severe	normal
22	Male	ATG+CsA/ineffective	severe	normal
28	Male	CsA/ineffective	moderate	normal
69	Male	CsA/ineffective	moderate	45,X
70	Male	ATG+CsA/relapse	moderate	normal
74	Male	ATG+CsA/relapse	moderate	normal
26	Male	ATG+CsA/ineffective	severe	normal
28	Female	CsA/ineffective	moderate	normal
72	Male	CsA/ineffective	moderate	normal
26	Female	ATG+CsA/ineffective	moderate	normal
62	Female	ATG+CsA/ineffective	severe	normal
40	Male	ATG+CsA/ineffective	moderate	normal
62	Male	ATG+CsA/ineffective	severe	normal

ATG, antitymocyte globulin; CsA, cyclosporine.

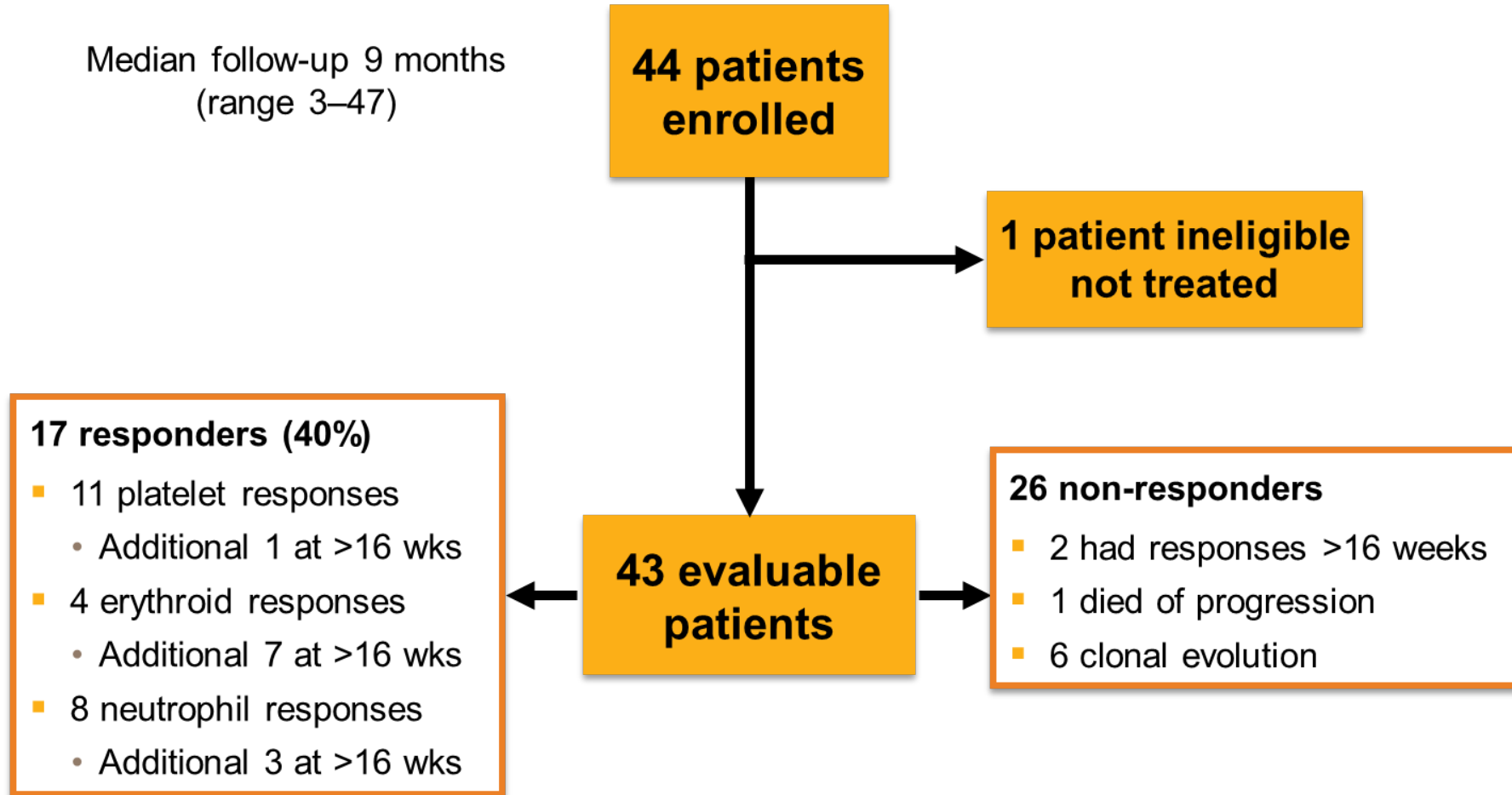
Phase II Study: Eltrombopag for Refractory SAA



1st cohort N = 26 (NEJM 2012), 2nd cohort N = 18
Combined 2 cohorts: N = 43 (Blood 2014)

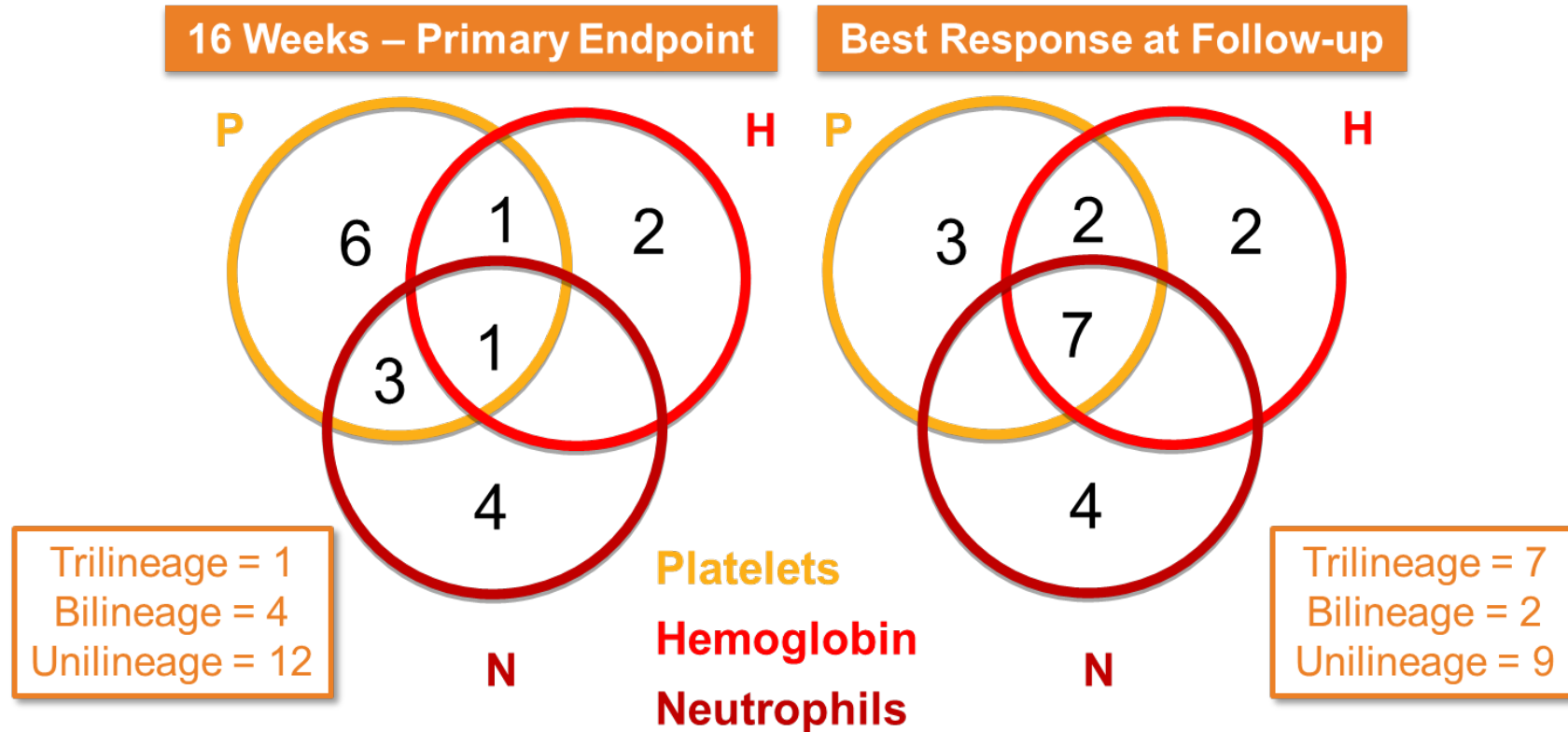
Overall response rate of Eltrombopag in patients with refractory SAA

Median follow-up 9 months
(range 3–47)



SAA, severe aplastic anemia
Desmond R et al. *Blood*. 2014;123:1818–1825.

Eltrombopag can produce multilineage responses over time in refractory SAA



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;123:1818–1825.

**Trilineage response by
>8 weeks, without
transfusion**

- Platelets $>50 \times 10^9/L$
- Hb >10 g/dL
- Neutrophils $>1 \times 10^9/L$



Eltrombopag dose was
tapered



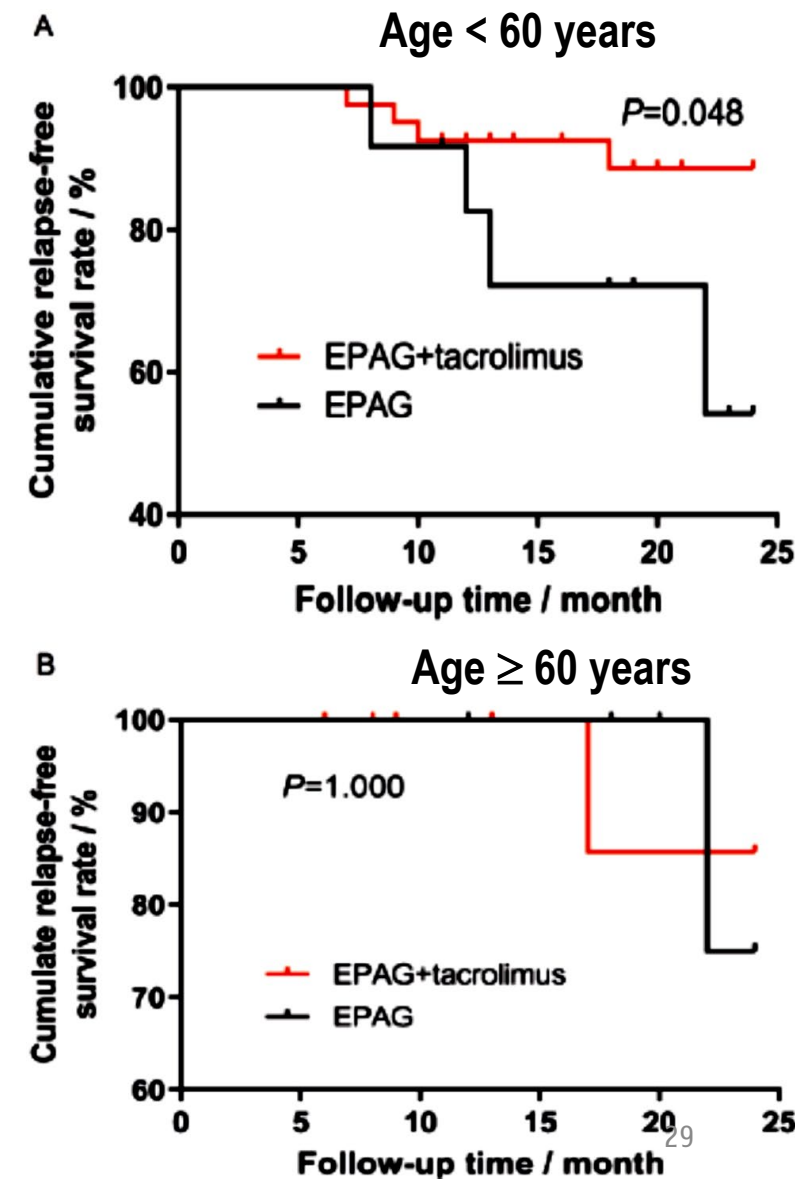
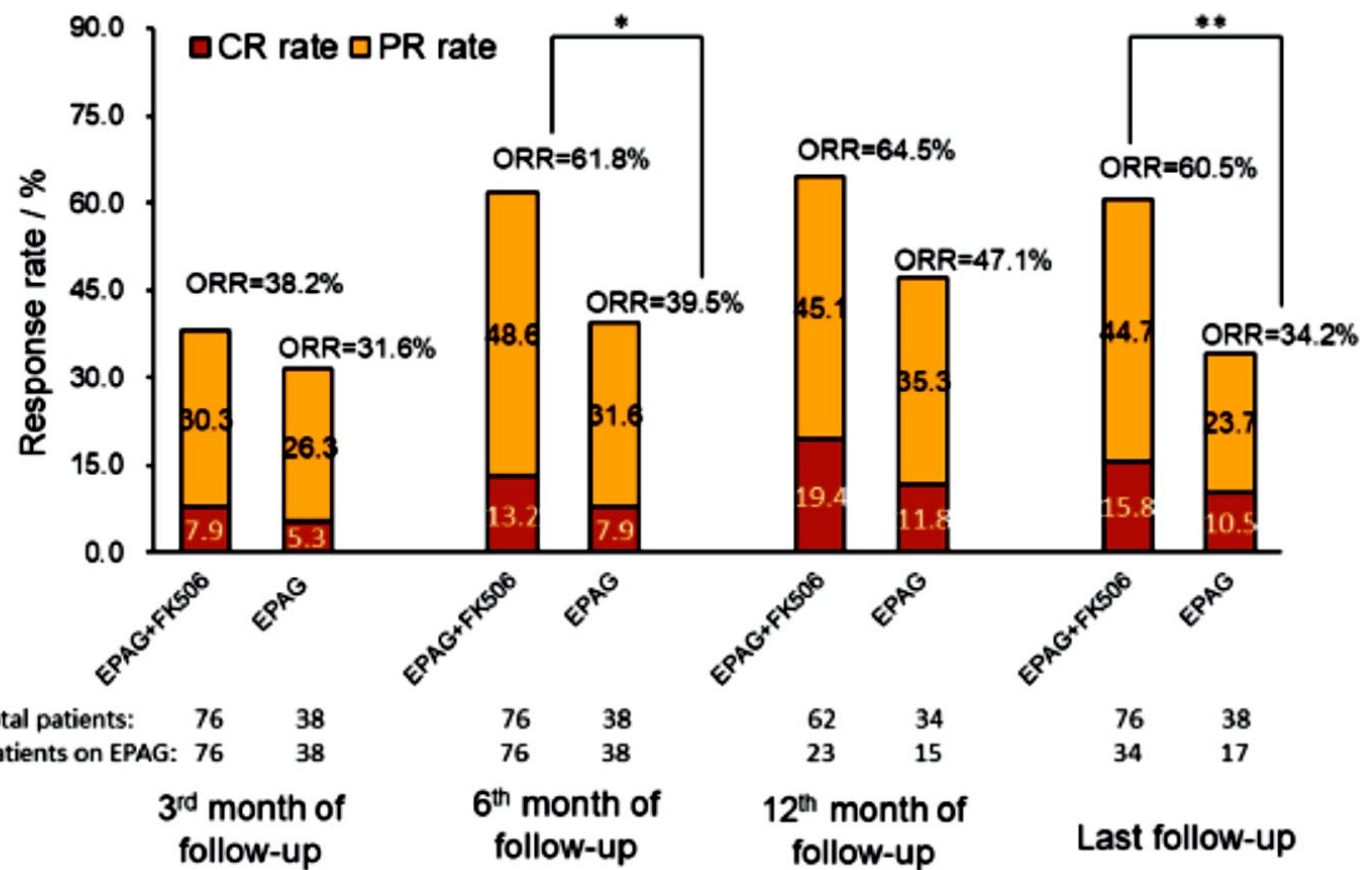
Counts remain above limits for **8 weeks**



Discontinue drug

- 5 fulfilled these criteria
 - 4 after robust response
 - 1 cataract misdiagnosis
- All remain in remission after a median follow-up of 13 months (range, 1–15)

Eltrombopag-tacrolimus vs Eltrombopag in Refractory SAA

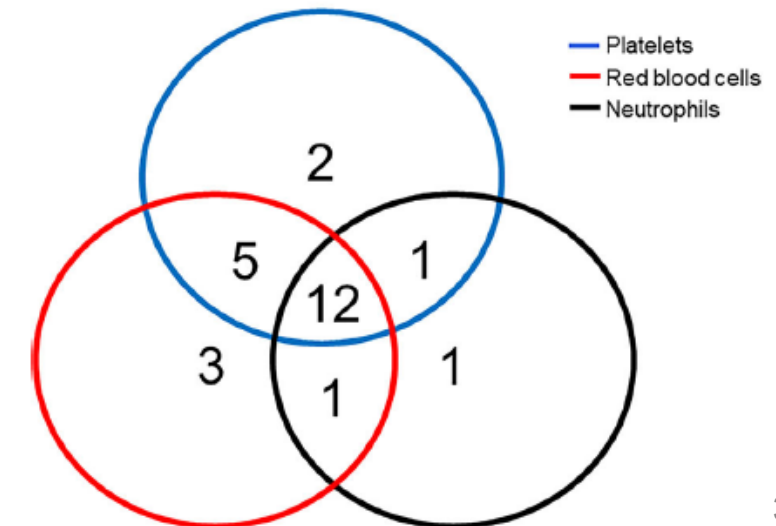
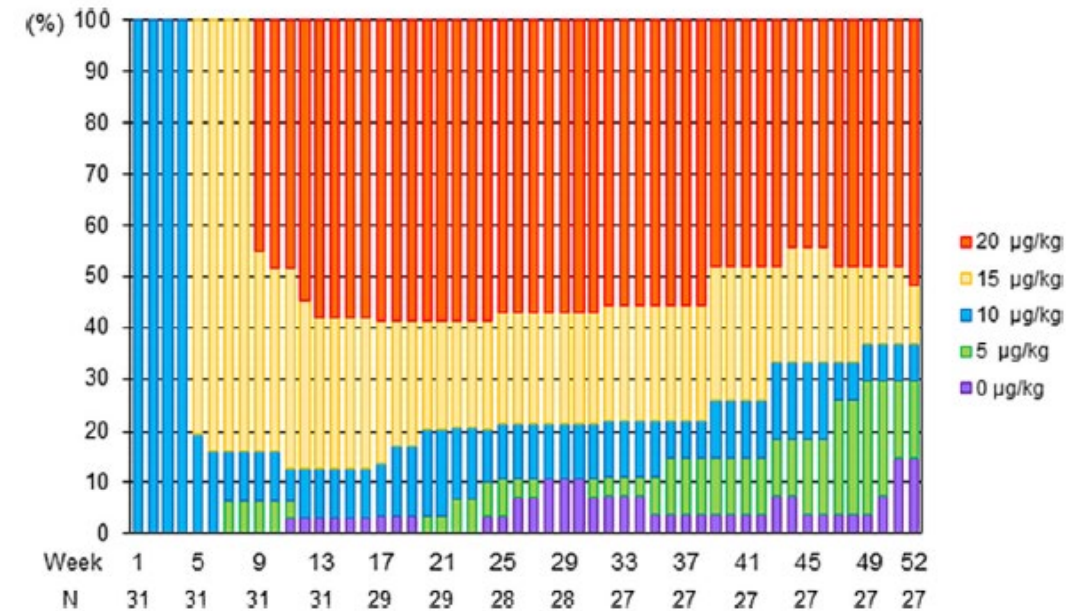


Romiplostim in patients with refractory aplastic anemia previously treated with immunosuppressive therapy

- 35 patients were enrolled and randomly assigned to one of four dose cohorts of romiplostim
 - 1 $\mu\text{g/kg}$ (n=7)
 - 3 $\mu\text{g/kg}$ (n=9)
 - 6 $\mu\text{g/kg}$ (n=9)
 - 10 $\mu\text{g/kg}$ (n=10)
- Dose in second-line treatment of ITP: 1-10 $\mu\text{g/kg}$ SC weekly (median 3 $\mu\text{g/kg}$)
- 10 (30%) of 33 evaluable patients achieved a platelet response at week 9, including 7 (70%) of 10 patients in the 10 $\mu\text{g/kg}$ cohort, 3 (33%) of 9 patients in the 6 $\mu\text{g/kg}$ cohort, and no patients in both the 3 $\mu\text{g/kg}$ and 1 $\mu\text{g/kg}$ cohorts.
- The initial dose of romiplostim in patients with refractory aplastic anemia previously treated with IST should be 10 $\mu\text{g/kg}$

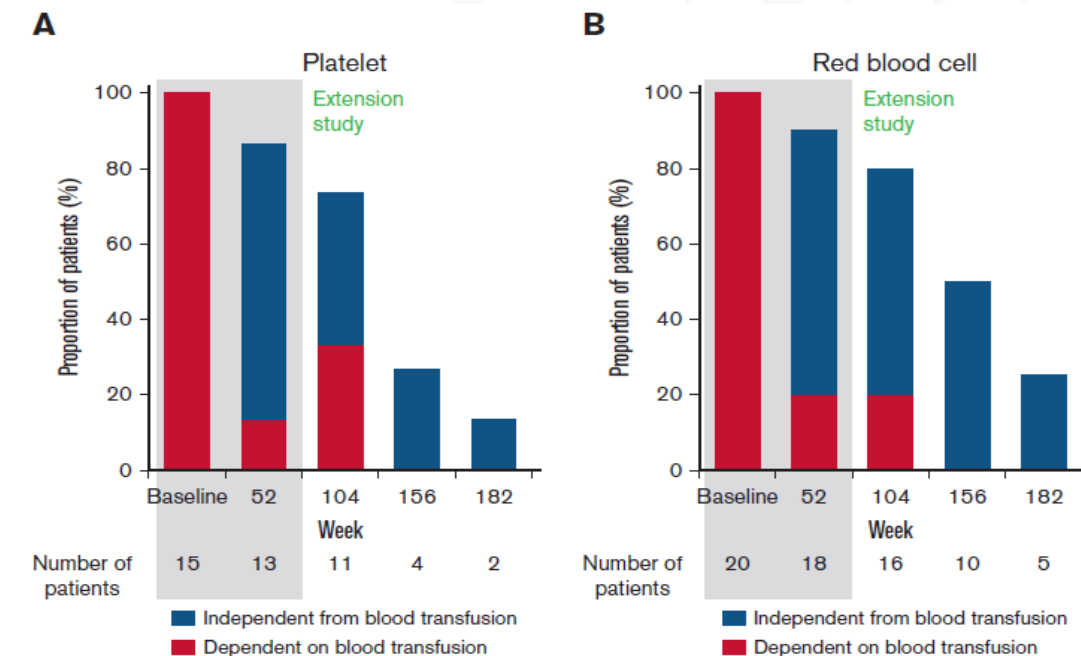
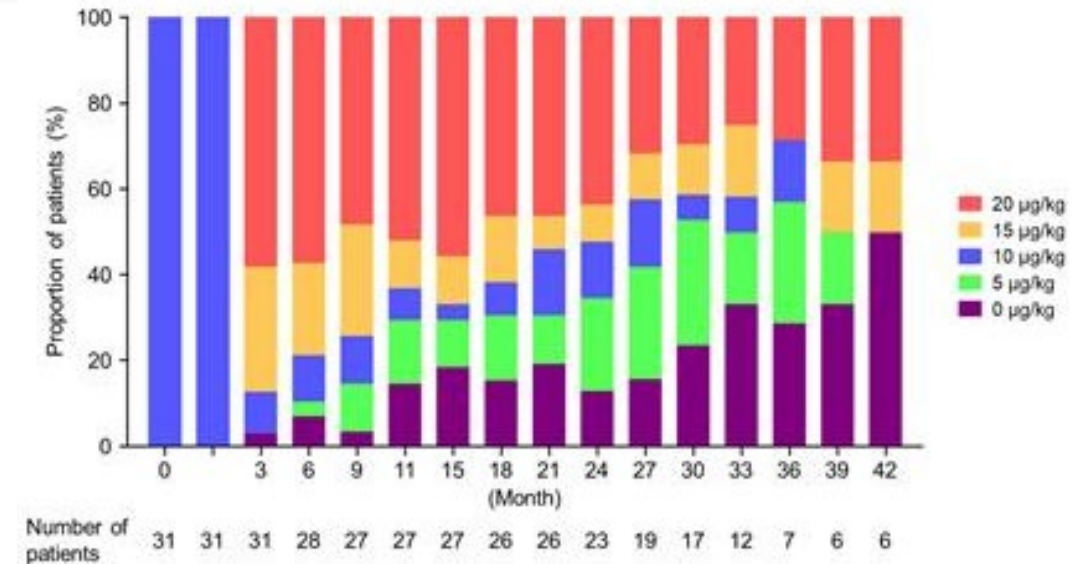
Efficacy and safety of romiplostim in refractory aplastic anaemia: a Phase II/III, multicentre, open-label study

- Romiplostim was administered subcutaneously at a fixed dose of 10 µg/kg once weekly for 4 weeks (weeks 1–4) followed by weekly doses (5, 10, 15 and 20 µg/kg) titrated by platelet response for up to 52 weeks (weeks 5–52).
- A total of 31 patients with AA who were refractory to immunosuppressive therapy (IST) and thrombocytopenia (platelet count of $\leq 30 \times 10^9/l$) were enrolled.
- The primary efficacy endpoint of the proportion of patients achieving any hematological response at week 27 was **84%**.
- No AEs necessitated romiplostim discontinuation.



Efficacy and Safety of Long-Term Romiplostim Use for Refractory Aplastic Anemia

- Of 31 patients, 27 completed the 53-week assessment.
- 25 responders and 2 non-responders entered the extension phase.
- ROMI was administered for 2 years in 23 patients, 3 years in 7 patients, and 3.5 years in 6 patients. The median dose of ROMI was 20 $\mu\text{g}/\text{kg}$ at Week 53, which was reduced to 15 $\mu\text{g}/\text{kg}$ at 2 yrs, and 7.5 $\mu\text{g}/\text{kg}$ at 3.5 yrs.
- Of the 2 non-responders, 1 patient showed platelet response at 2 years, while the other failed to respond.
- Of the patients who failed to achieve the platelet (n=7) and erythrocyte (n=6) responses at 1 year, 3 (43%) and 1 (17%) showed responses at 2 years.
- Cytogenetic abnormality (-7) led to discontinuation of ROMI in 1 case. 2 had unknown significant chromosomal abnormalities: 46,XX,t(11;17) at W108 and 46,XX,add(10) at W134. No transformation to AML or MDS occurred.



Romiplostim is effective for eltrombopag-refractory aplastic anemia: results of a retrospective study

Patient number	Age/Sex	Previous therapy	Before switching		Concomitant therapy	Severity of the disease	ROM		
			Last EPAG dose (mg/kg)	Duration of EPAG, (months)			ROM dose (µg/kg/week)	Duration of ROM (months)	Concomitant therapy
1	84 F	ATG(once) CSA danazole	2.5	22	Danazole	Severe	20	12	Danazole
2	94 M	CSA met-enolone	2	22	CSA	Non severe	20	12	None
3	88 F	CSA danazole	2.4	22	CSA	Non severe	20	7	CSA
4	45 M	CSA	1.4	26	CSA met-enolone	Non severe	20	9	CSA met-enolone
5	53 M	ATG(once) CSA	1.3	22	ATG(once) CSA met-enolone	Non severe	20	12	CSA met-enolone
6	55 M	ATG(once) CSA met-enolone	1.7	22	CSA met-enolone	Non severe	20	12	CSA met-enolone
7	62 F	ATG(twice) CSA met-enolone	2	22	CSA danazole	Non severe	20	11	CSA danazole
8	29 M	ATG(twice) CSA met-enolone	1.8	22	CSA met-enolone	Non severe	20	12	CSA met-enolone
9	32 F	CSA met-enolone	2.2	3	CSA	Non severe	20	8	none
10	77 F	ATG(once) CSA	2	4	metenolone	Severe	20	11	CSA met-enolone

Romiplostim is effective for eltrombopag-refractory aplastic anemia: results of a retrospective study

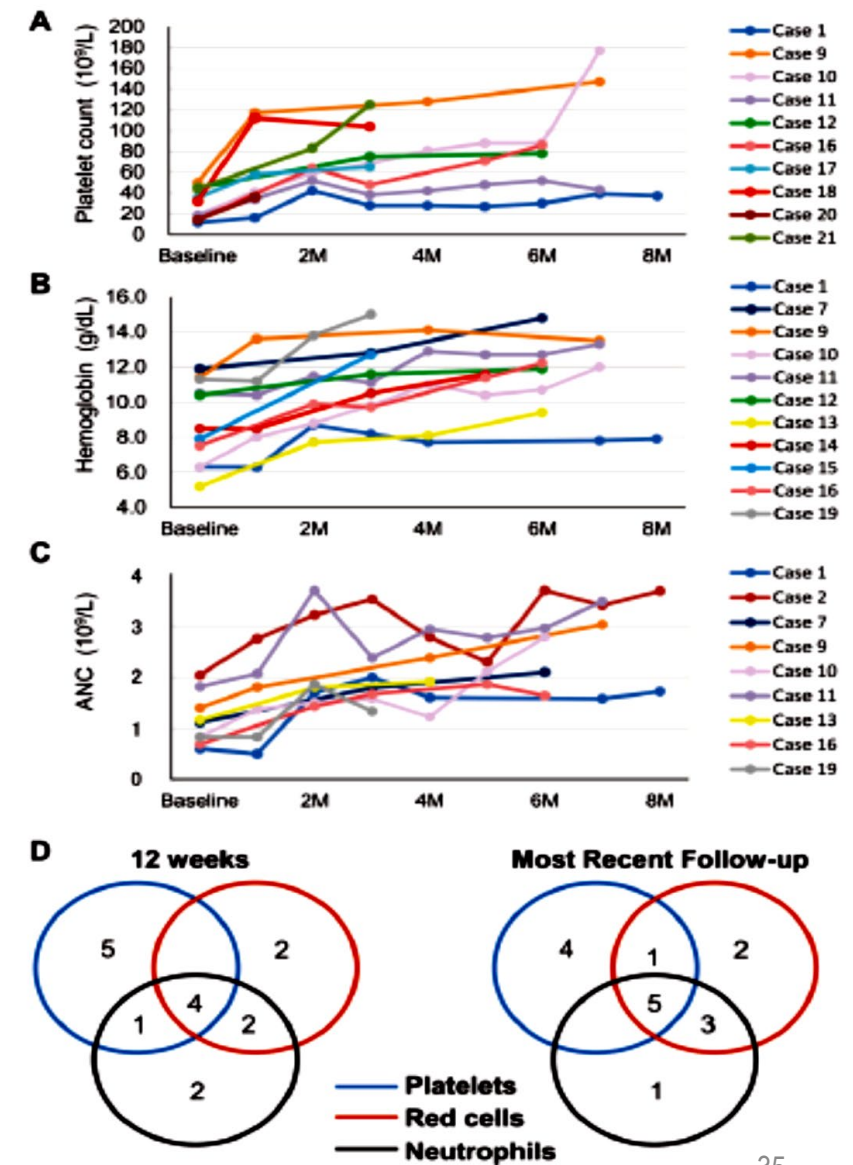
- At a median follow-up of 12 months, 7/10 patients (70%) had achieved either neutrophil, erythroid, or platelet response, including one complete response.
- None of the patients stopped the ROM treatment because of adverse events.

Complete blood counts after ROM (median ROM duration, 12 months)

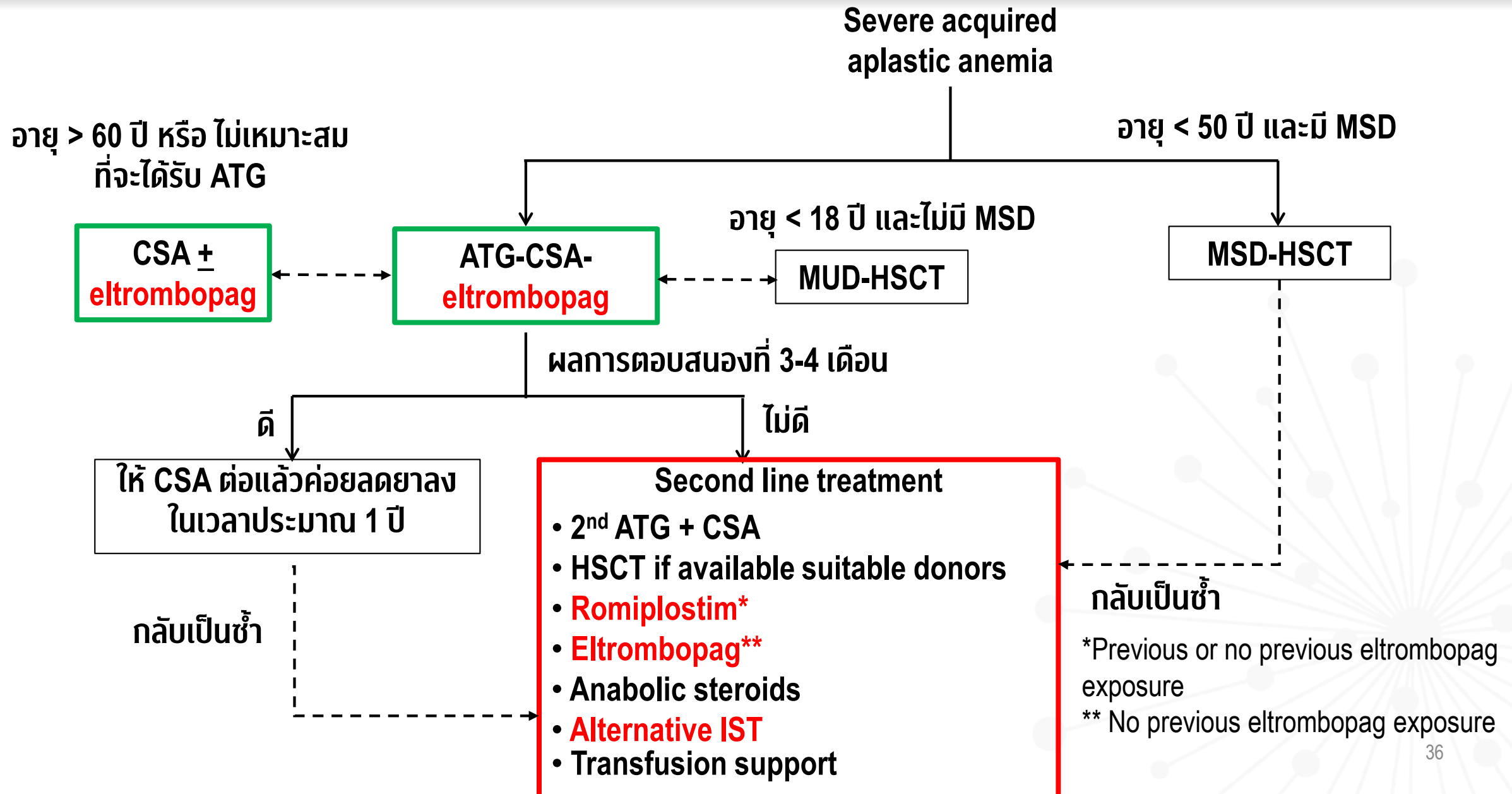
Absolute neutrophil count, $\times 10^9/l$, median (range)	2.066 (1.566–7.436)
Hemoglobin count, x g/dl, median (range)	10.25 (7.0–15.1)
Platelet count, $\times 10^9/l$, median (range)	20.5 (4.0–105.0)
Maximum dose of ROM for responders, x $\mu g/kg/week$	20
Efficacy of the switch on AA ^a , n (%)	
Complete response	1 (10)
Neutrophil response	1 (10)
Erythroid + Platelet response	2 (20)
Erythroid response	1 (10)
Platelet response	2 (20)
No response	3 (30)

High-dose romiplostim in patients with aplastic anemia refractory to eltrombopag

- Retrospective cohort in Japan: romiplostim 20 µg/kg in 21 patients with eltrombopag-refractory AA
- 16 of 21 (76%) achieved a hematologic response in at least one lineage at 3 months.
- 5 of 10 (50%) patients became independent of platelet (n = 2) or red cell (n = 3) transfusions.
- All 21 patients tolerated ROMI and showed no severe treatment-related adverse events that necessitated ROMI discontinuation.



Treatment for Acquired AA: SAA and VSAA in 2025



Treatment for severe aplastic anemia in 2025: Now

- ATG-CSA-Eltrombopag is the standard first-line treatment for transplant-ineligible SAA
- CSA plus eltrombopag is an alternative first-line treatment of ATG-ineligible SAA
- TPRAs are effective as second-line treatment for SAA patients who failed IST
 - High-dose romiplostim 5-10 $\mu\text{g/kg}$: without prior eltrombopag exposure
 - Very high-dose romiplostim 10-20 $\mu\text{g/kg}$: with prior eltrombopag exposure
 - Eltrombopag monotherapy ($\pm$ tacrolimus) without prior eltrombopag exposure
- HSCT may not be a practical second-line treatment for refractory SAA in Thailand
- A second course of rATG has a low response rate and may not be cost-effective as a second-line treatment for adults with refractory SAA in Thailand
- Alternative low-intensity IST and/or anabolic steroids have limited evidence and low response rates but may be considered when no other options are available



Chula
Innovations *for* Society

Thank You for Your Attention

