Vall d'Hebron
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Thrombopoietin analogues use in thrombocytopenia

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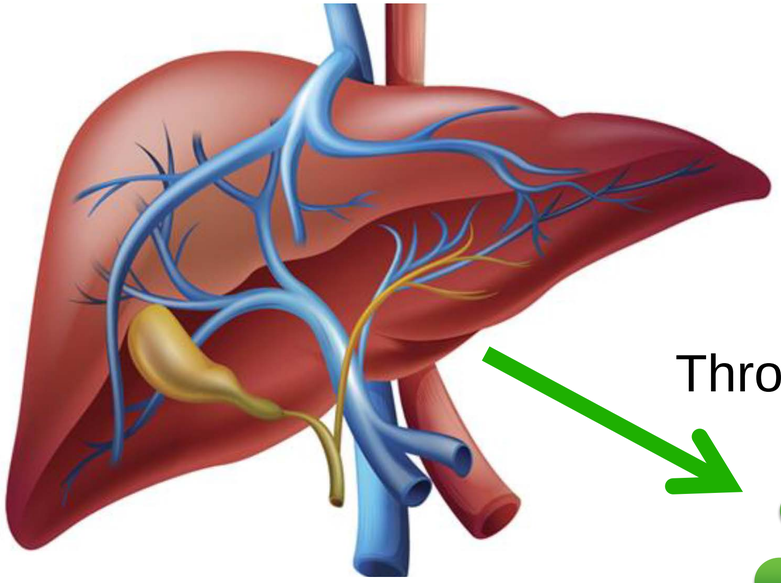
Disclosures

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Celgene	X	X	X					
Novartis	X	X						
Jazz	X	X						
Amgen	X	X						
Pfizzer	X							
Astellas	X	X						
MSD	X							

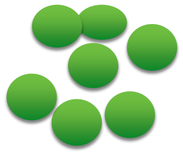
- Introduction
- TPO Analogues in ITP
- TPO Analogues in aplasia
- TPO Analogues in MDS
- TPO Analogues in the post-transplant setting

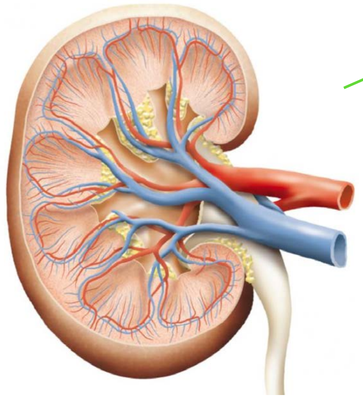
Megacaryocytopoyesis



Thrompoietin

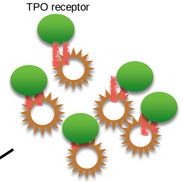
Produced at constitutive rate





Platelet mass regulates the amount of free TPO

TPO receptor



Platelets

After TPO/TPO-R, they are internalized and degrades

Through TPO receptor sigaling

TPO receptor

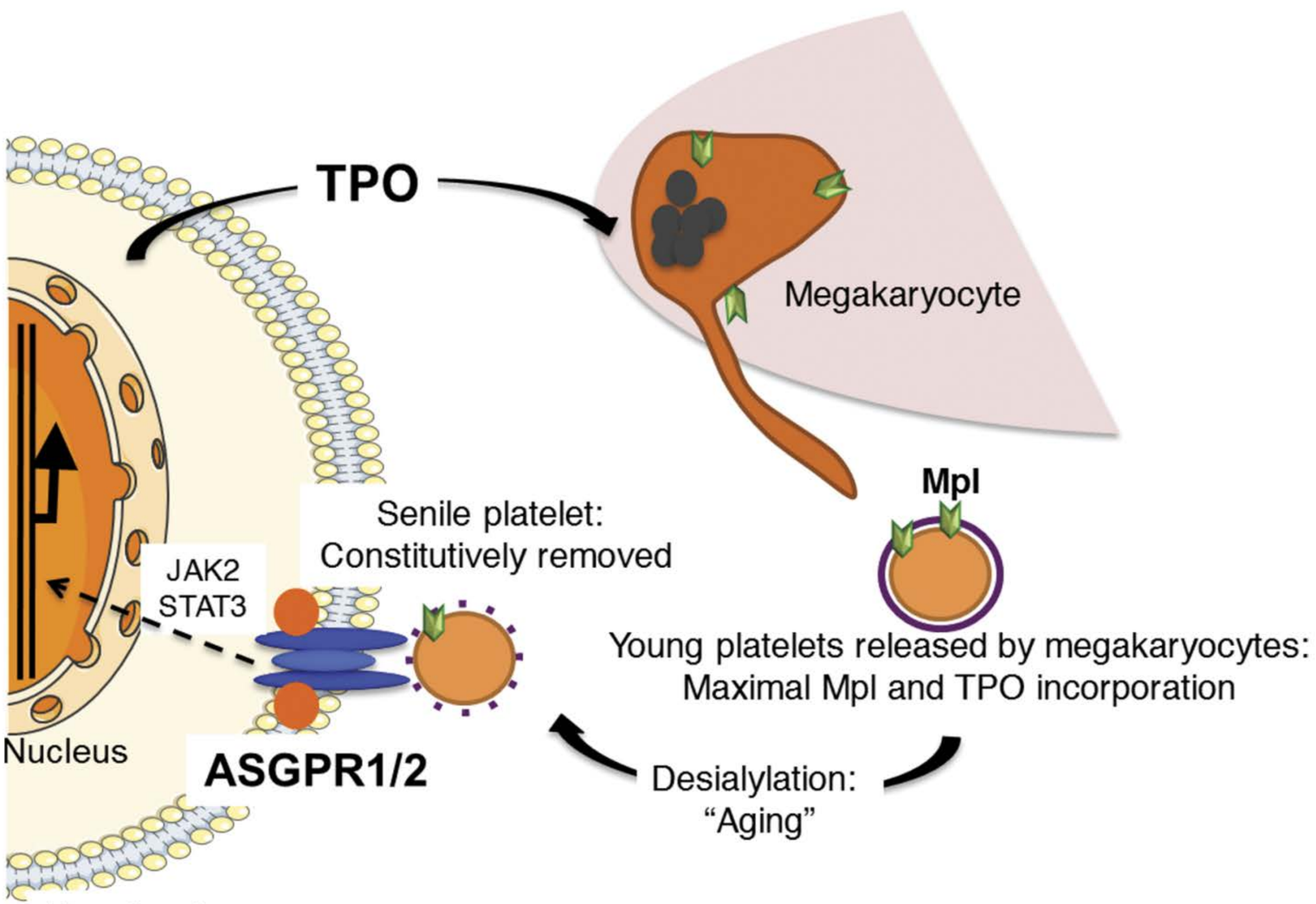
HSC

Proliferating Megakaryocyte

Immature Megakarycoyte

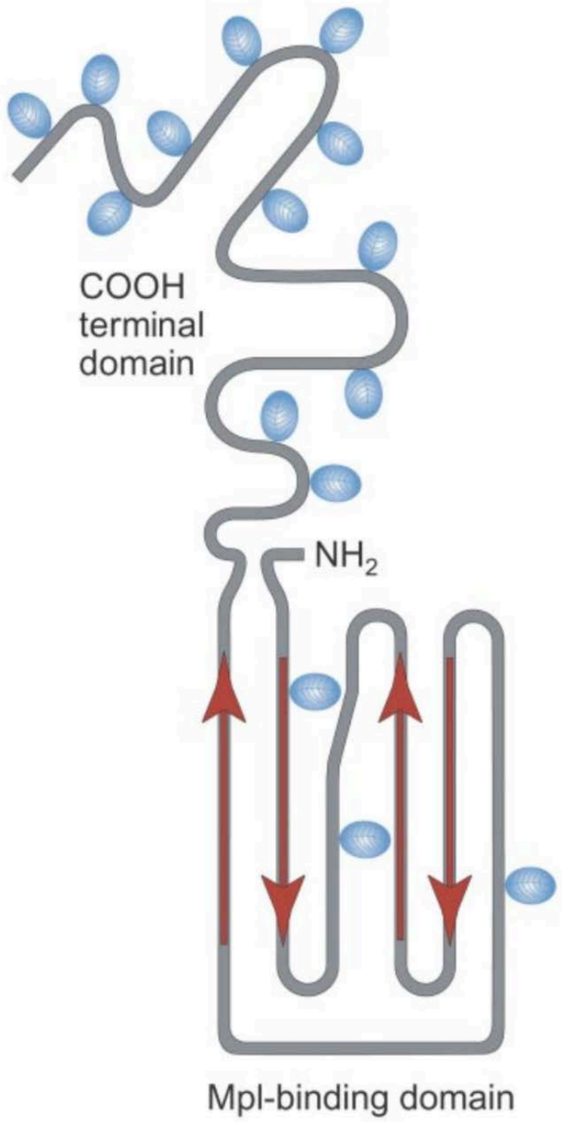
Mature Megakarycoyte

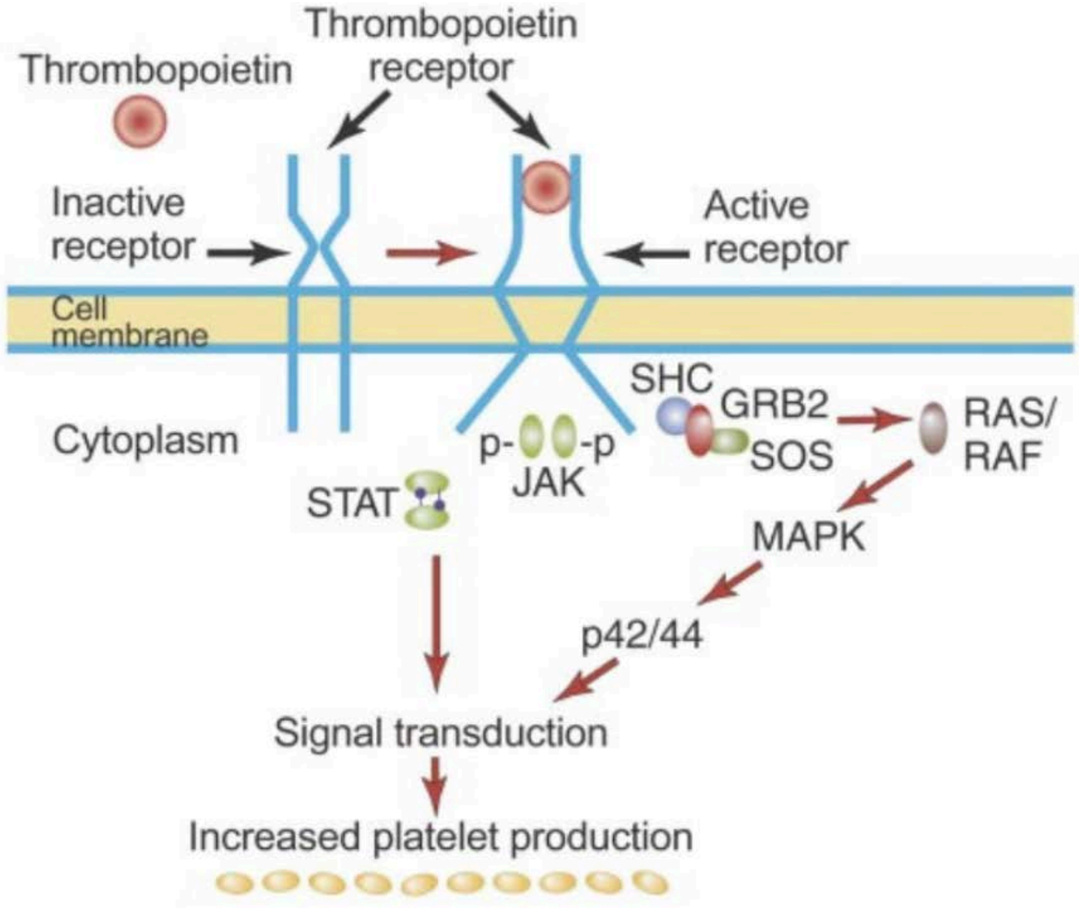
TPO production through Ashwell-Morrell Receptor activation



H. (2016). Platelet clearance by the hepatic Ashwell-Morrell receptor: mechanisms and biological significance. Thrombosis Research, 201

Thrombopoietin, its receptor and the intracellular pathway





Kuter, D. J., & Kuter, D. J. (2007). New thrombopoietic growth factors. Blood, 109(11), 4607–4616.

- Introduction
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TPO Analogues in ITP: Current status

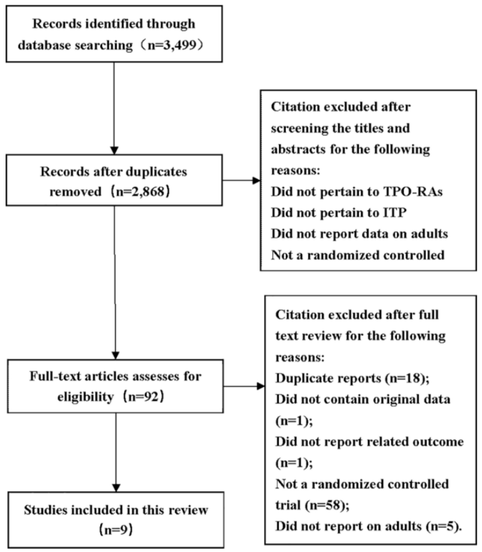
- TPO Analogues are the more efficacious farmacological treatment for ITP
  - Overall response rate around 80%. Usually maintained overtime (with continuous treatment)
  - Reduction in bleeding
  - Reduction of salvage therapy and corticosteroids use

- Favorable safety profile
  - Few treatment related adverse effects, and mostly mild
  - No increase of AEs/SAEs over time
  - Initial concerns are no longer a problem (Malignacies, fibrosis...)
  - The possible higher Risk of thrombosis is still a matter of debate

- Several questions remain unanswered
  - Use in earlier phases
  - Combinations
  - Discontinuation

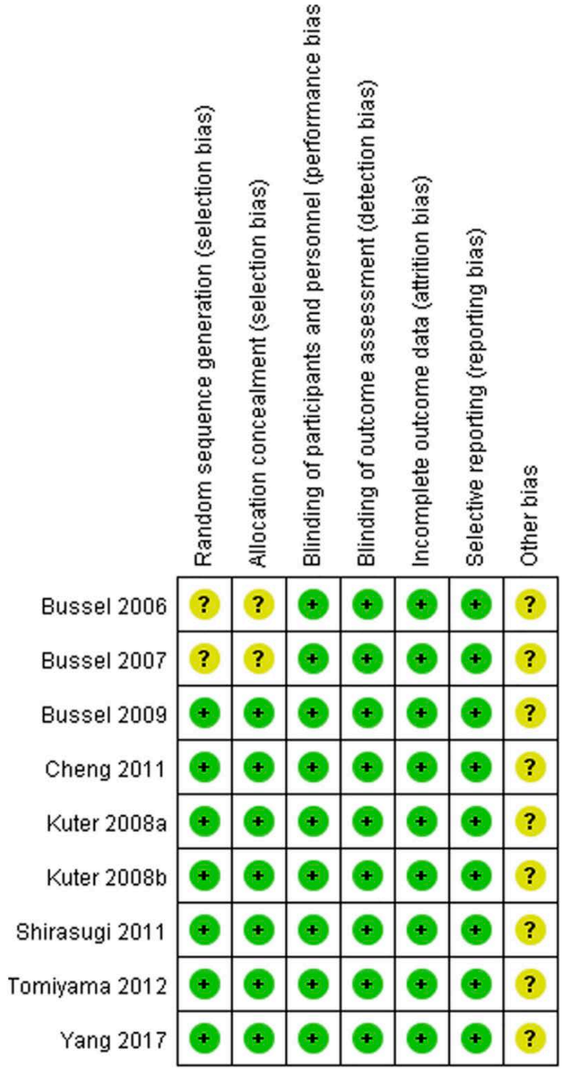
Eltrombopag vs Romiplostim: Meta-analysis

- Adults
- RANDOMIZED
- ELT/ROM vs PLAC
- EFFICACY OR SAFETY
- ENGLISH/CHINESE



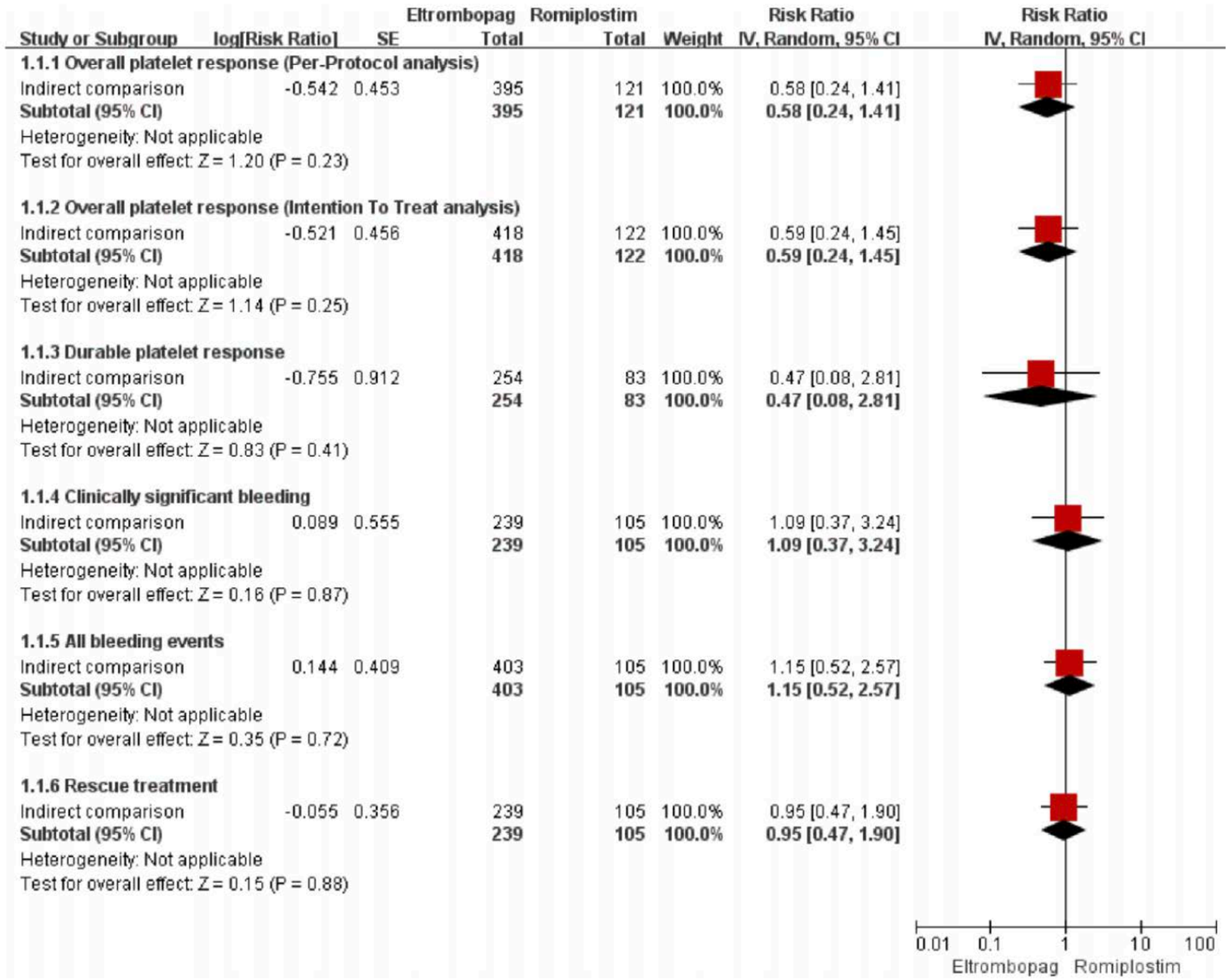
Study ID	Study Design	Population inclusion	Intervention vs Comparison	TPO-RA regimens	Outcomes
Bussel 2007 [16]	Multicenter (44 centers in 14 countries), double-blind, RCT.	Patients≥18 years old, with a diagnosis of ITP (duration of ≥6 months), had received at least one previous treatment for ITP, and had a platelet counts<30×10^9/L.	Eltrombopag vs Placebo	30, 50, or 75mg orally daily for 6 weeks.	①④⑥⑦
Bussel 2009 [17]	Multicenter (63 centers in 23 countries), double-blind, RCT.	Patients≥18 years old, with a diagnosis of ITP (duration of ≥6 months), had received at least one previous treatment for ITP, and had a platelet counts<30×10^9/L.	Eltrombopag vs Placebo	50mg orally daily for 6 weeks; dose was adjusted based on platelet counts.	①④⑥⑦
Cheng 2011 [18]	Multicenter (75 centers in 23 countries), double-blind, RCT.	Patients≥18 years old, with a diagnosis of ITP (duration of ≥6 months), had received at least one previous treatment for ITP, and had a platelet counts<30×10^9/L.	Eltrombopag vs Placebo	50mg orally daily for 24 weeks; dose was adjusted based on platelet counts.	①②③④⑤⑥⑦
Tomiyama 2012 [19]	Multicenter (7 centers in Japan), double-blind, RCT.	Patients≥20 years old, with a diagnosis of ITP (duration of ≥6 months), had received at least one previous treatment for ITP, and had a platelet counts<30×10^9/L.	Eltrombopag vs Placebo	Starting dose of 12.5mg (maximum dose of 50mg) orally daily for 6 weeks; dose was adjusted based on platelet counts.	①②⑥⑦
Yang 2017 [20]	Multicenter (16 centers in China), double-blind, RCT.	Patients≥18 years old, with a diagnosis of ITP (duration of ≥12 months), had received at least one previous treatment for ITP, had a platelet counts<30×10^9/L.	Eltrombopag vs Placebo	25 mg once daily for 8 weeks; dose was adjusted based on platelet counts.	①②③④⑤⑥⑦
Bussel 2006 [21]	Multicenter (9 centers in USA), double-blind, RCT.	Patients(18–65 years old), with a diagnosis of ITP(duration of ≥3 months), had received at least one previous treatment for ITP, and had a platelet counts<30×10^9/L.	Romiplostim vs Placebo	1 or 3ug/kg subcutaneously weekly for 6 weeks, 8 patients with 1ug/kg, 8patients with 3ug/kg, 1 patients with 6ug/kg, no dose adjustments	①⑦
Kuter 2008a [22]	Multicenter (35 centers in the USA and Europe), double-blind, RCT.	Patients≥18 years old, with a diagnosis of ITP (duration of ≥6 months), had received at least one previous treatment for ITP, had a platelet counts<30×10^9/L, and had a splenectomy for the treatment of ITP greater than or equal to 24 weeks prior to study entry.	Romiplostim vs Placebo	Starting dose of 1ug/kg subcutaneously weekly for 24 weeks; dose was adjusted to achieve target platelet counts of 50 to 200×10^9/L.	①②③④⑤⑥⑦
Kuter 2008b [22]	Multicenter (35 centers in the USA and Europe), double-blind, RCT.	Patients≥18 years old, with a diagnosis of ITP (duration of ≥6 months), had received at least one previous treatment for ITP, had a platelet counts<30×10^9/L, and had non-splenectomized status.	Romiplostim vs Placebo	Starting dose of 1ug/kg subcutaneously weekly for 24 weeks; dose was adjusted to achieve target platelet counts of 50 to 200×10^9/L.	①②③④⑤⑥⑦
Shirasugi 2011 [23]	Multicenter (11 centers in Japan), double-blind, RCT.	Patients≥20 years old, with a diagnosis of ITP (duration of ≥6 months), had received at least one previous treatment for ITP, and had a platelet counts<30×10^9/L.	Romiplostim vs Placebo	starting dose of 3ug/kg subcutaneously weekly for 12 weeks; dose was adjusted to achieve target platelet counts of 50 to 200×10^9/L.	③④⑤⑥⑦

①Platelet response
②Durable platelet response
③Clinically significant bleeding
④All bleeding events
⑤Rescue medication
⑥Adverse events
⑦Serious adverse events.



Zhang, J., Liang, Y., Ai, Y., Li, X., Xie, J., Li, Y., et al. (2018). Eltrombopag versus romiplostim in treatment of adult patients with immune thrombocytopenia: A systematic review incorporating an indirect-comparison meta-analysis. Plos One, 13(6), e0198504.

Eltrombopag vs Romiplostim: Meta-analysis, efficacy



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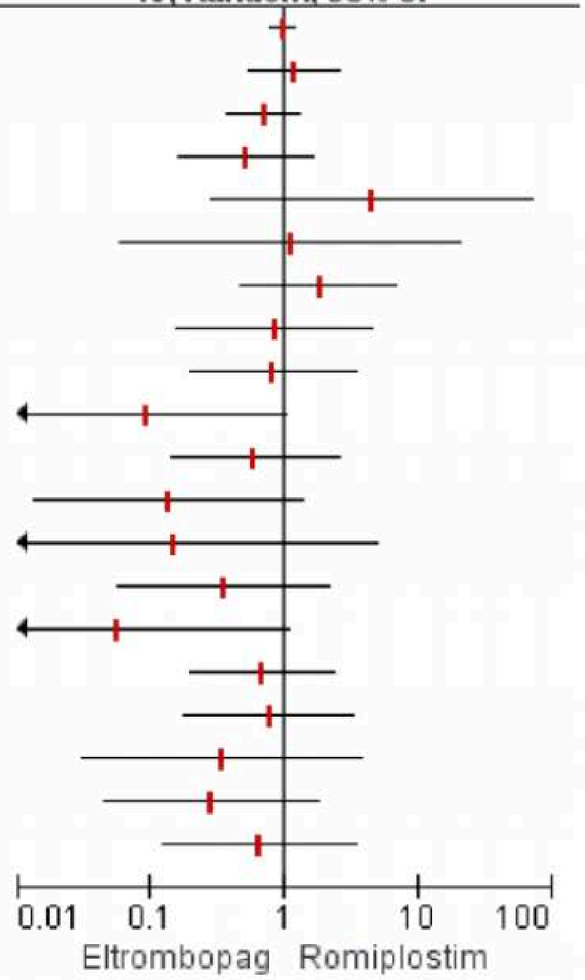
Eltrombopag vs Romiplostim: Meta-analysis, safety

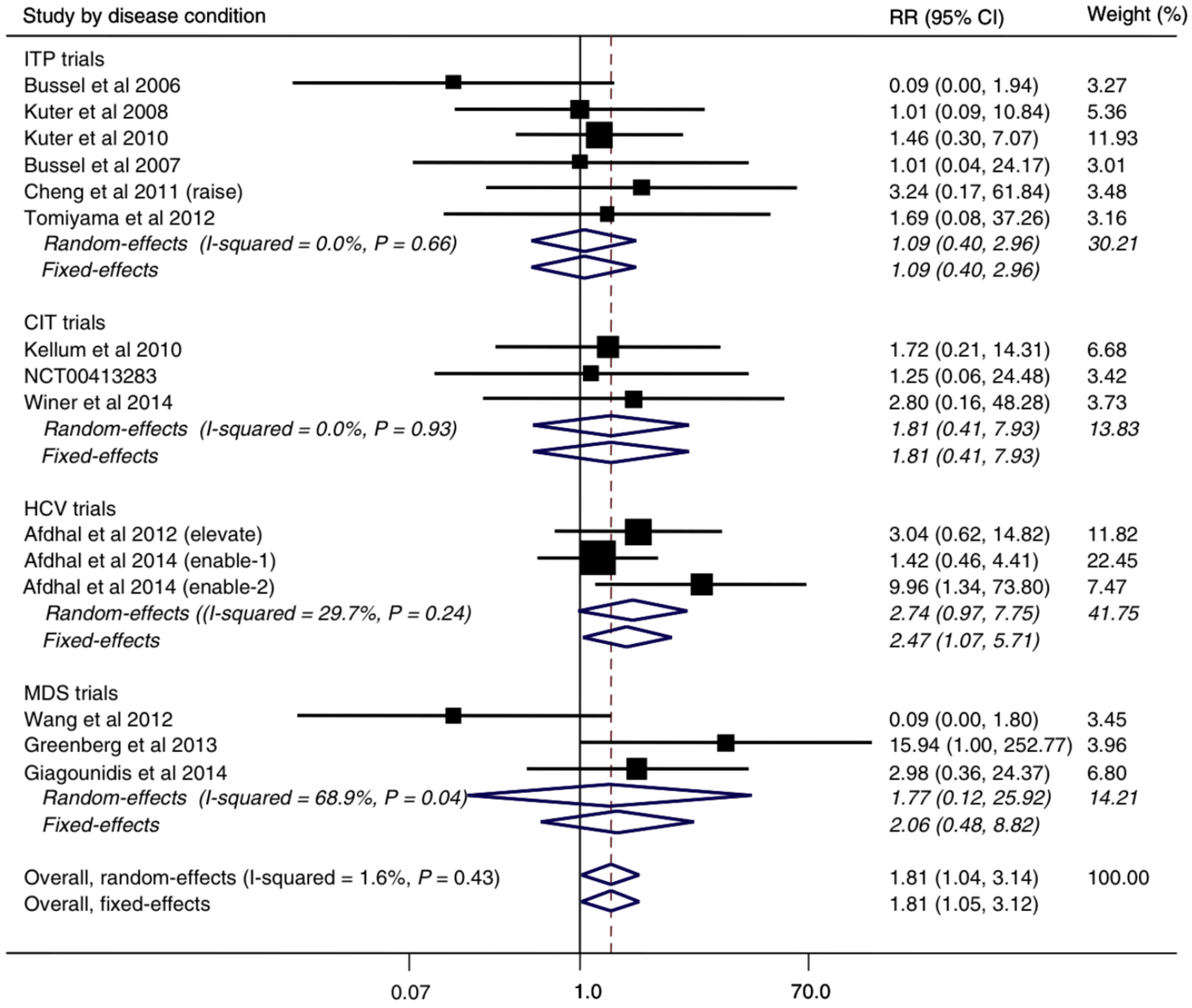
Study or Subgroup	log[Risk Ratio]	SE	Eltrombopag Total	Romiplostim Total	Risk Ratio IV, Random, 95% CI
Overall adverse events	-0.021	0.108	418	106	0.98 [0.79, 1.21]
Serious adverse events	0.185	0.413	418	123	1.20 [0.54, 2.70]
Headache	-0.352	0.314	418	122	0.70 [0.38, 1.30]
Fatigue	-0.665	0.589	314	122	0.51 [0.16, 1.63]
Thrombosis	1.533	1.419	342	100	4.63 [0.29, 74.75]
Arthralgia	0.135	1.499	299	100	1.14 [0.06, 21.61]
Nausea	0.617	0.688	226	100	1.85 [0.48, 7.14]
Nasopharyngitis	-0.148	0.859	226	105	0.86 [0.16, 4.64]
Diarrhea	-0.203	0.733	299	83	0.82 [0.19, 3.43]
Peripheral edema	-2.362	1.228	223	39	0.09 [0.01, 1.05]
Epistaxis	-0.5	0.742	223	100	0.61 [0.14, 2.60]
Pain in extremity	-1.997	1.173	164	105	0.14 [0.01, 1.35]
Dizziness	-1.919	1.807	211	100	0.15 [0.00, 5.07]
Contusion	-1.05	0.939	135	122	0.35 [0.06, 2.20]
Abdominal pain upper	-2.899	1.537	211	83	0.06 [0.00, 1.12]
URT infection	-0.373	0.642	211	83	0.69 [0.20, 2.42]
Cough	-0.245	0.741	211	83	0.78 [0.18, 3.34]
Myalgia	-1.07	1.234	211	83	0.34 [0.03, 3.85]
Anxiety	-1.243	0.946	211	83	0.29 [0.05, 1.84]
Back pain	-0.407	0.848	135	105	0.67 [0.13, 3.51]



Zhang, J., Liang, Y., Ai, Y., Li, X., Xie, J., Li, Y., et al. (2018). Eltrombopag versus romiplostim in treatment of adult patients with immune thrombocytopenia: A systematic review incorporating an indirect-comparison meta-analysis. Plos One, 13(6), e0198504.

TPO safety, the thrombosis issue

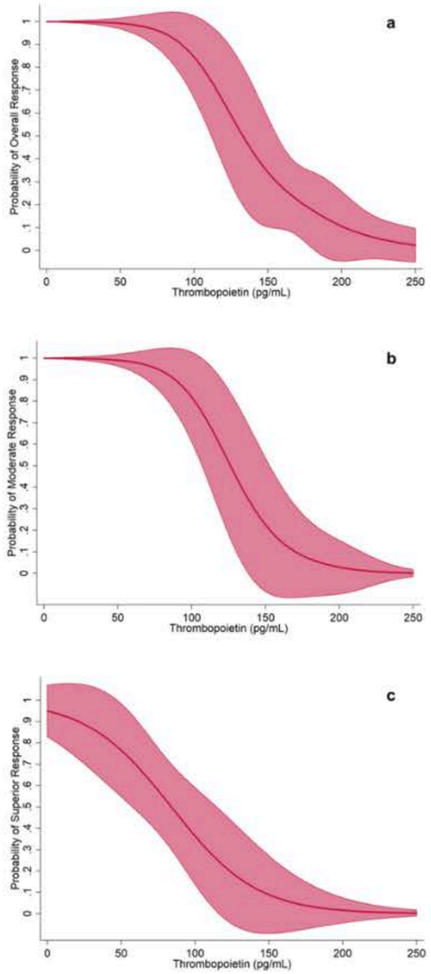
- Initially there were some concerns regarding some safety issues: Possibility of hematological malignacies, development of bone marrow fibrosis, hepatic abnormalities, cataracts, rebound thrombocytopenia, immunogenicity, resistance...
- Nowadays most of these concerns are no longer applicable
- **Thrombosis** is the only safety issue that remain nowadays.



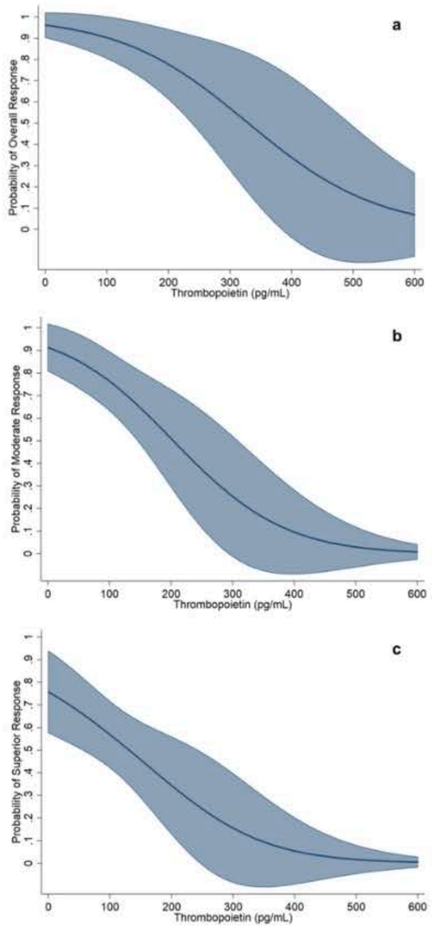
Catalá-López, F., Corrales, I., la Fuente-Honrubia, de, C., González-Bermejo, D., Martín-Serrano, G., Montero, D., & Saint-Gerons, D. M. (2015). Risk of thromboembolism with thrombopoietin receptor agonists in adult patients with thrombocytopenia: Systematic review and meta-analysis of randomized controlled trials. Medicina Clinica, 145(12), 511–519.

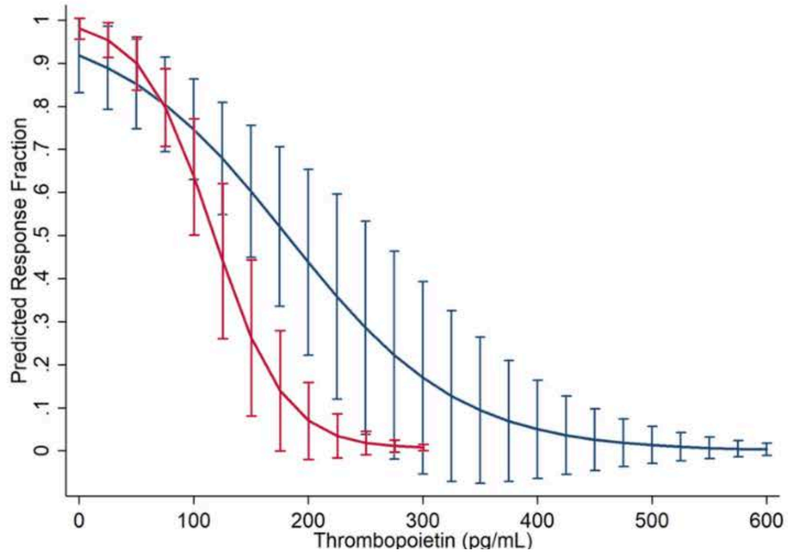
Prediction of response, the highest the endogenous TPO the lower is the probability of response

Eltrombopag



Romiplostim





Optimally discriminating **thresholds**

Eltrombopag ≤136 pg/mL
Romiplostim ≤209 pg/mL

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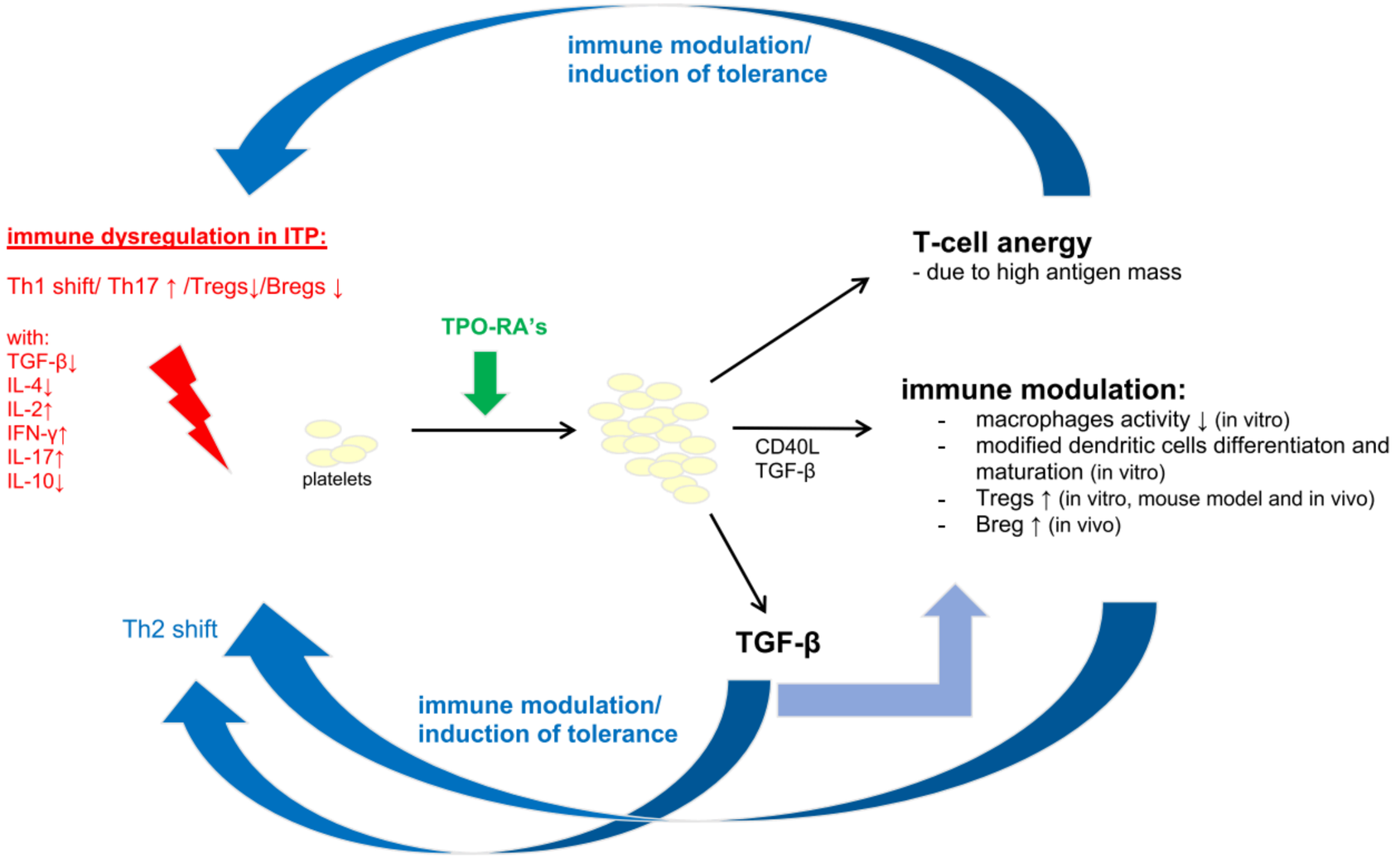
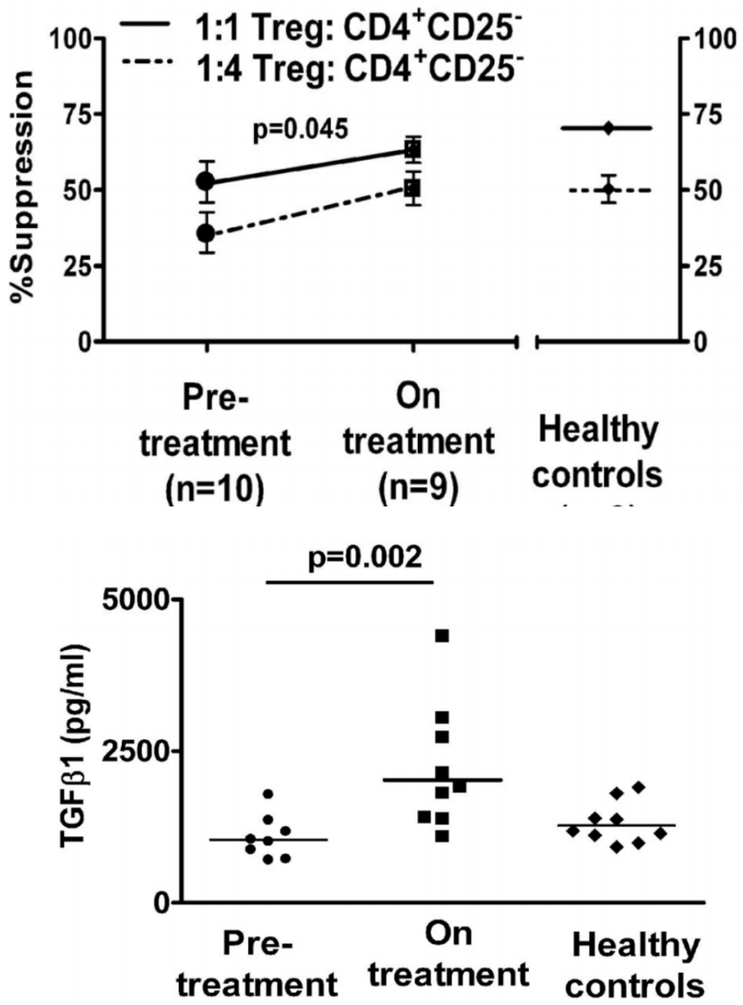
TPO analogues may also induce “immune-modulation”

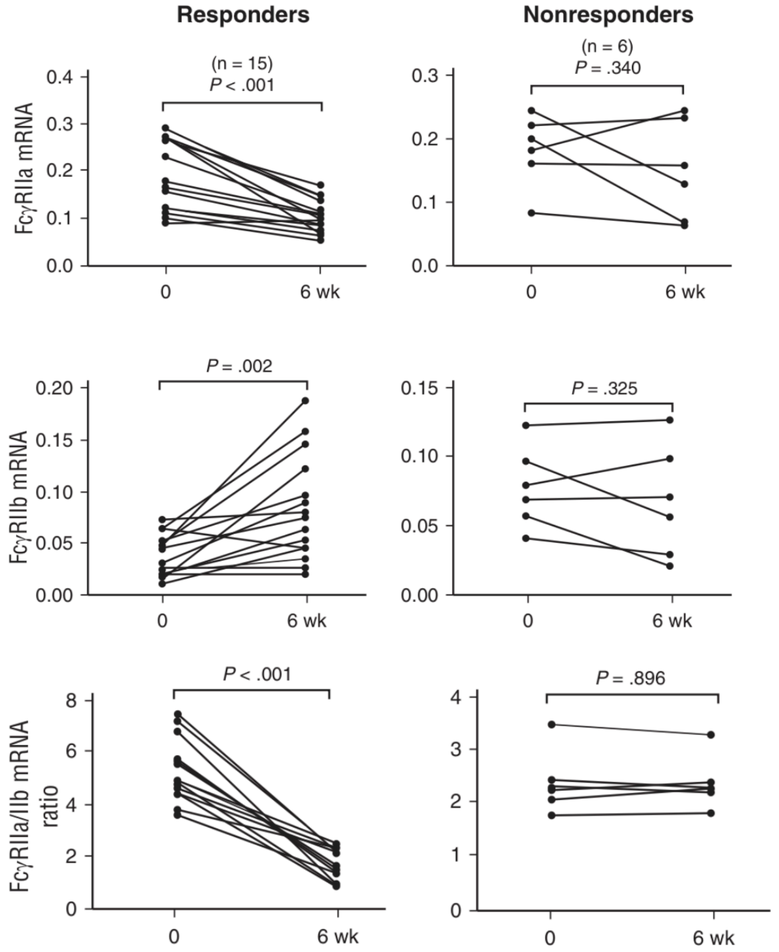


Ref: Schifferli, A., & Kühne, T. (2016). Thrombopoietin receptor agonists: a new immune modulatory strategy in immune thrombocytopenia? Seminars in Hematology, 53 Suppl 1, S31–4.

Immune-regulatory effect of TPO Analogues through Tregs and TGF-B receptor

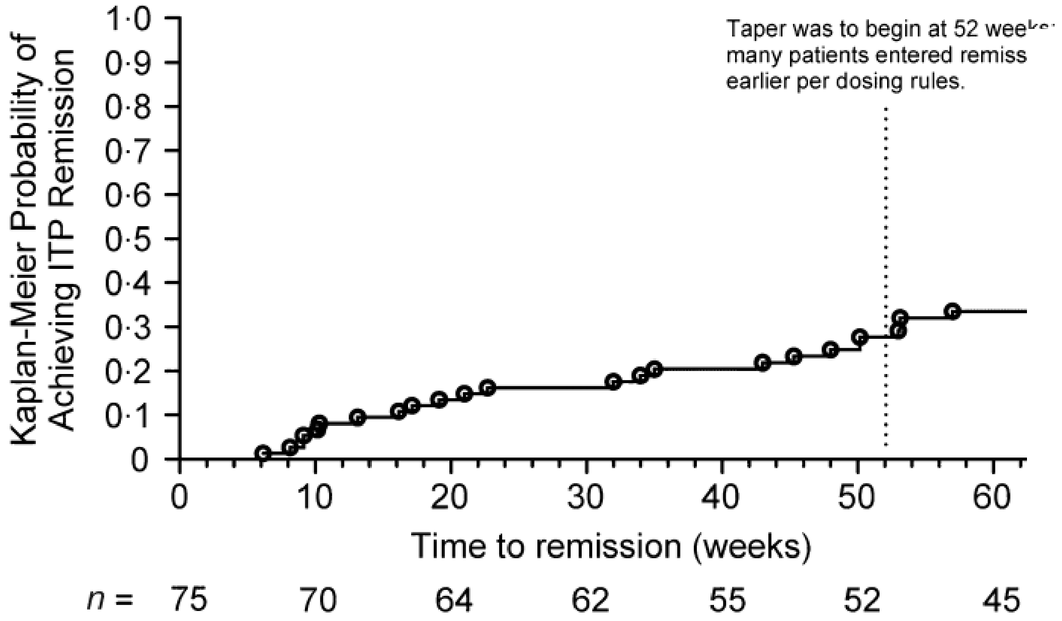


Bao, W., et al, Blood, 2010 116(22), 4639–4645.

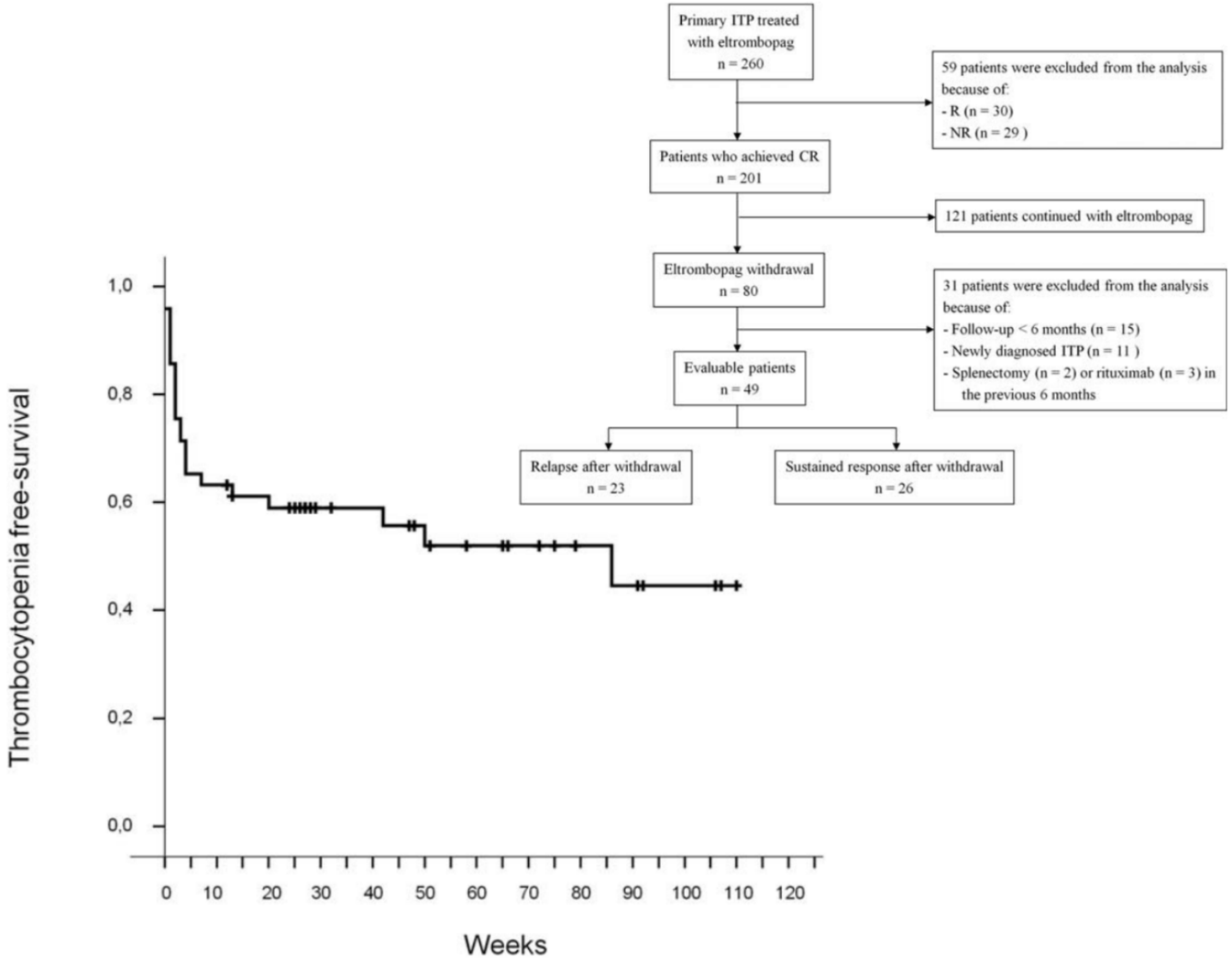


Liu, X.-G., Liu, S., Feng, Q., Liu, X.-N., Li, G.-S., Sheng, Z., et al. (2016). Thrombopoietin receptor agonists shift the balance of Fcγ receptors toward inhibitory receptor IIb on monocytes in ITP. Blood, 128(6), 852–861.

TPO Analogues discontinuation



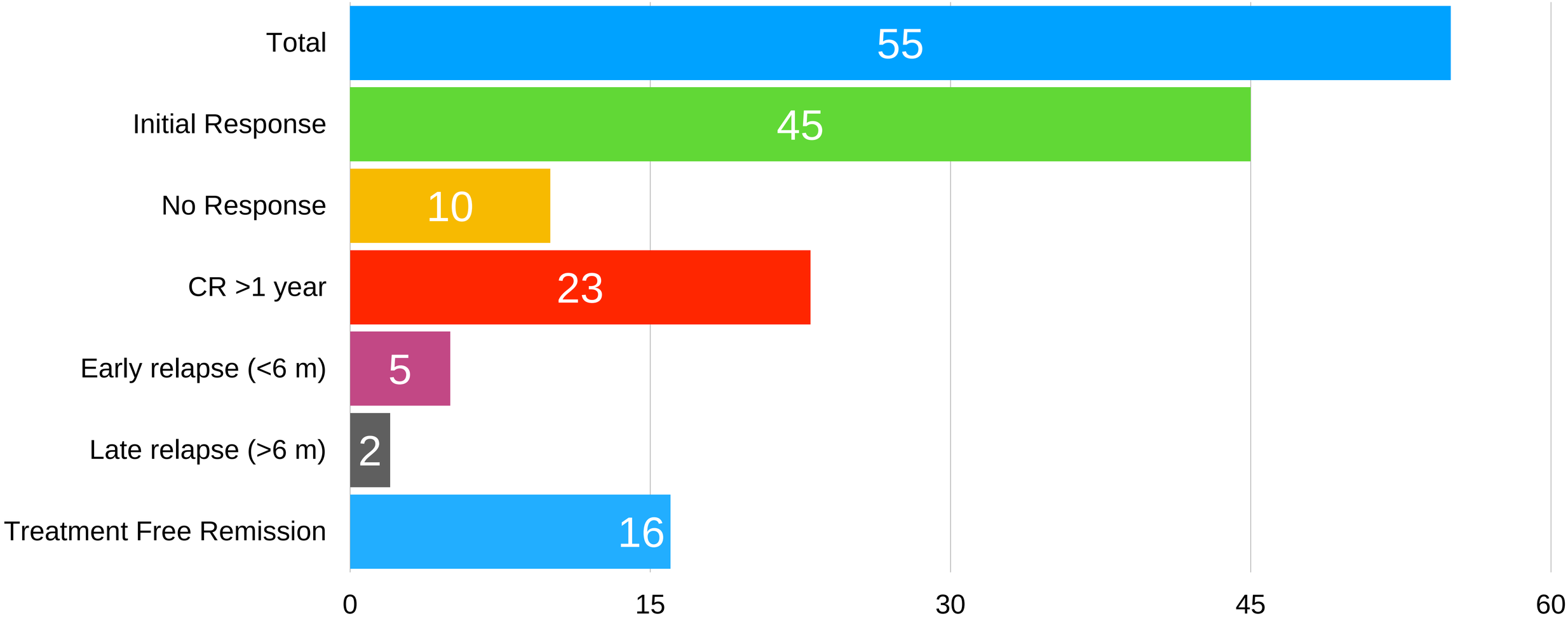
Ref: Newland, A.,Remission and platelet responses with romiplostim in primary immune thrombocytopenia: final results from a phase 2 study. British Journal of Haematology, 2016; 172(2), 262–273 .



González-López, T. J., Pascual, C., Alvarez-Román, M. T., Fernández-Fuertes, F., Sánchez-González, B., Caparrós, I., et al. (2015). Successful discontinuation of eltrombopag after complete remission in patients with primary immune thrombocytopenia. American Journal of Hematology, 90(3), E40–3.

TPO Analogues discontinuation in Vall d'Hebron

After 2 years of median follow-up after discontinuation, the 16 patients who discontinued and remained free of treatment had a median of 202 x10e9/L platelets (54-310)



Rodriguez-Aquino Y, et al, unpublished results from H. Vall d'hebron

Predictors of sustained response after discontinuation with Romiplostim

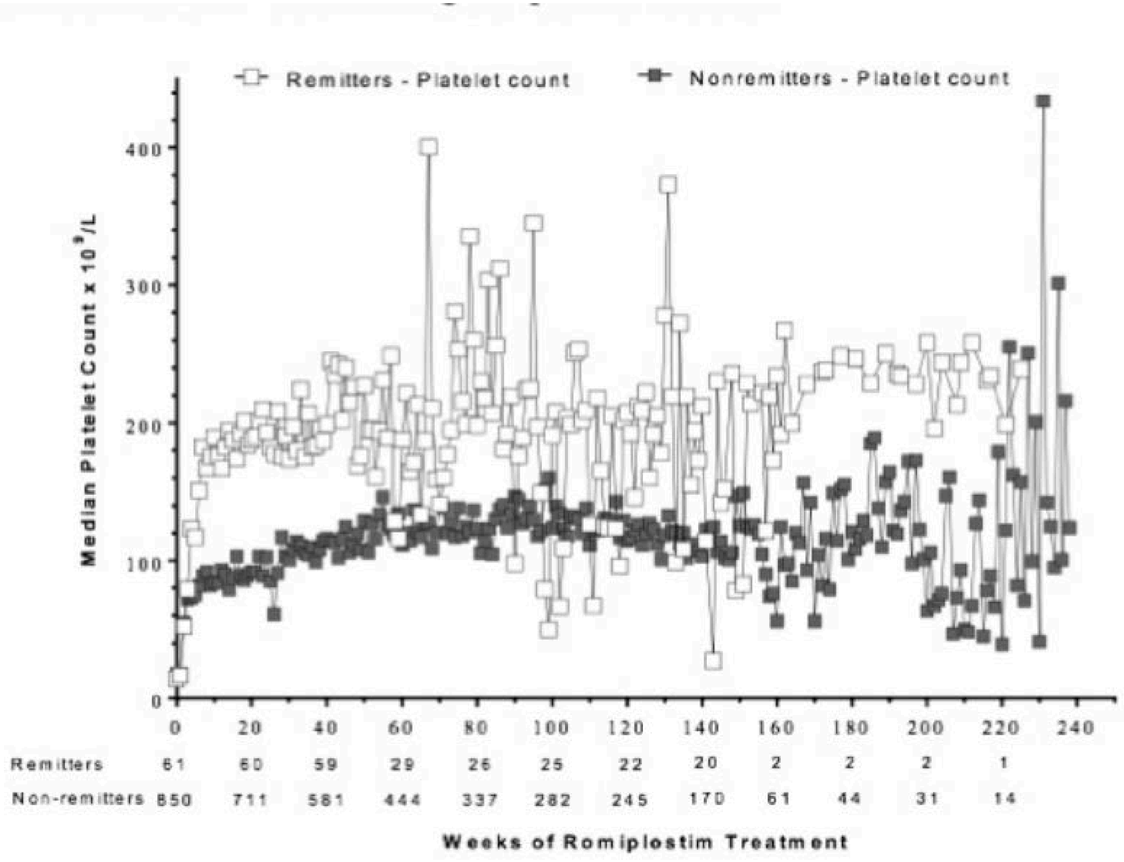


Table 2: Possible predictors of remission—logistic regression results

	OR	95% CI	*P*-value
Univariate model			
Age, continuous	0.995	0.981-1.010	.5167
Age >50 vs ≤50 years	0.939	0.558-1.582	.8141
Sex (female vs male)	0.854	0.505-1.445	.5572
ITP duration, months			
<3 vs >12	4.597	2.536-8.334	<.0001*
3-12 vs >12	2.245	1.103-4.569	.0257*
Prior splenectomy	0.481	0.257-0.903	.0227*
Baseline platelet count, $\times 10^9$/L			
30-50 vs <30	0.749	0.361-1.557	.4395
>50 vs <30	1.499	0.439-5.116	.5182
Any bleeding in the first 6 months	0.548	0.311-0.966	.0377*
Baseline concurrent ITP therapy	0.834	0.473-1.473	.5321
Platelet count >200×10^9/L in the first 4 weeks	1.278	0.706-2.313	.4174
Multivariate model			
ITP duration, months			
<3 vs >12	4.275	2.227-8.206	<.0001*
3-12 vs >12	2.171	1.033-4.564	.0408*
Prior splenectomy	0.860	0.427-1.733	.6734
Any bleeding in the first 6 months	0.565	0.317-1.005	.0522

*Statistically significant values at $P<.05$. CI=confidence interval.

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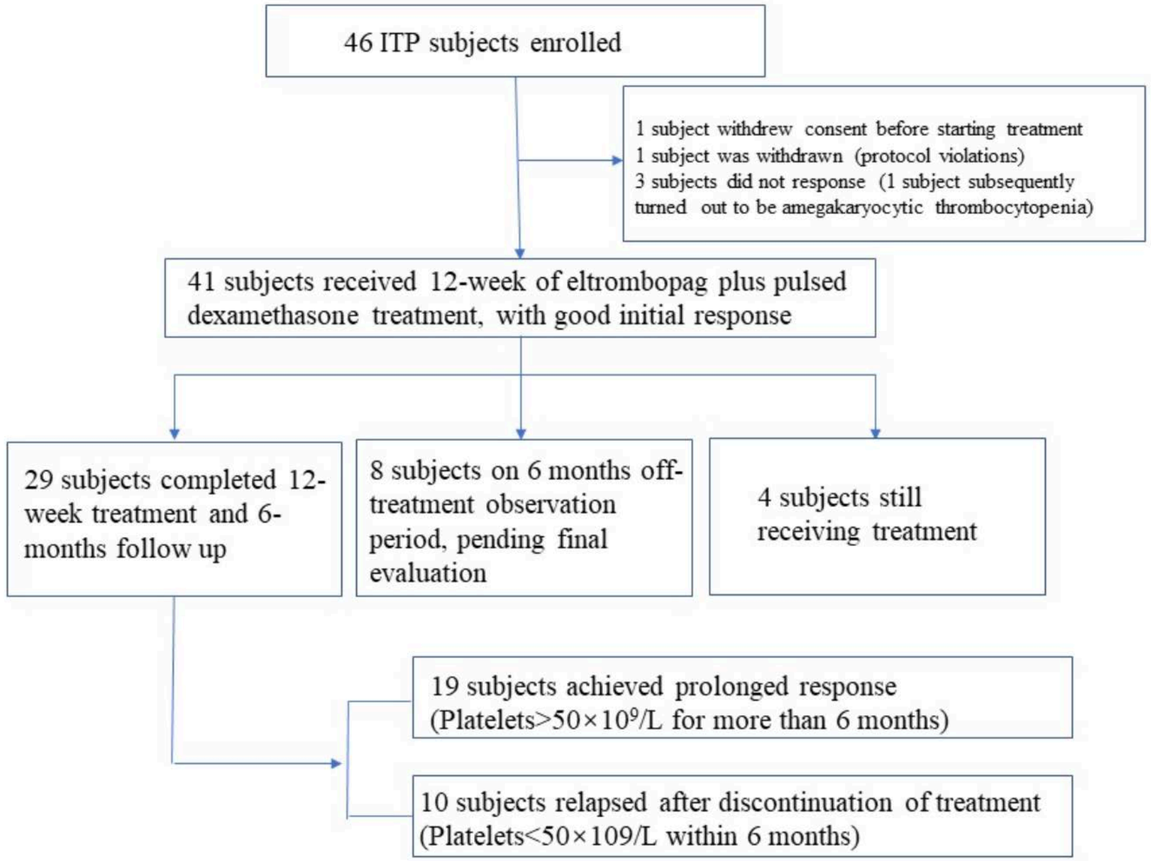
Using TPO Analogues in first line

Dexametasone 40 mg/dx4, (1/3 cycles) **Eltrombopag** 25-75 mg/d 12 weeks



Variable	Prolonged Responders	Relapsed subjects	*P* value
Median Age			
(Years; range)	46 (20-81)	35 (20-54)	0.11
Sex (n, %)			0.23
Male	7 (37)	4 (45)	
Female	12 (63)	6 (55)	
Platelet count (x10^9/L)			
(Median, range)			
Baseline	17 (2-44)	17 (3-30)	0.97
12-week treatment	165 (72-334)	206 (65-383)	0.85
6 months off treatment	135 (78-371)	N/A	N/A
Time to relapse (days)			
(Median, range)	N/A	47.8 (15-148)	N/A
Dose of eltrombopag (mg)			
(Average, range)	36.8 (25-75)	45 (25-75)	0.14
Courses of dexamathesone			
(Average, range)	2.2 (1-3)	2.5 (1-3)	0.3

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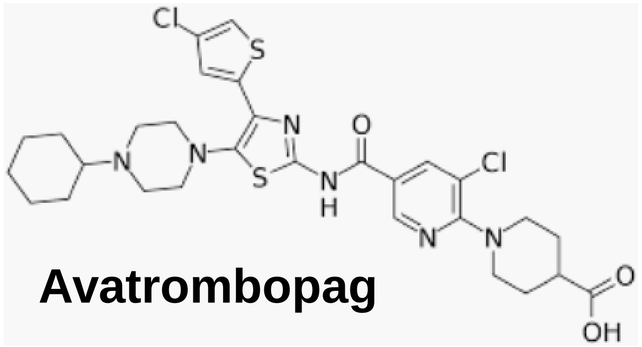
Avatrombopag, the new kind on the block



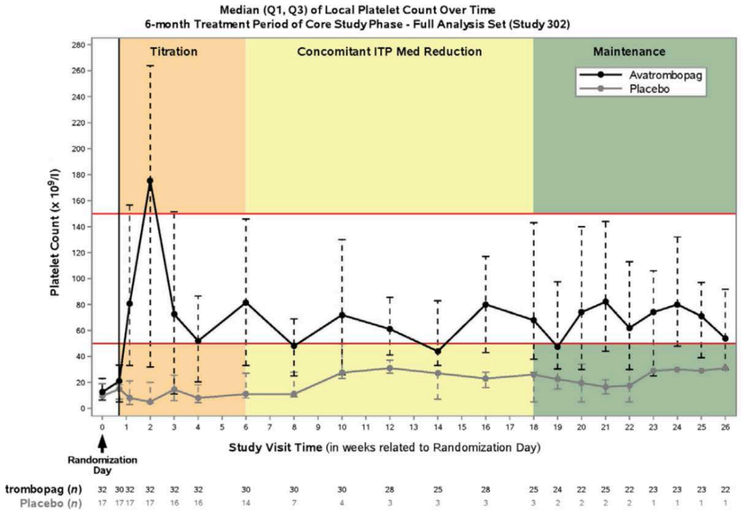
Avatrombopag

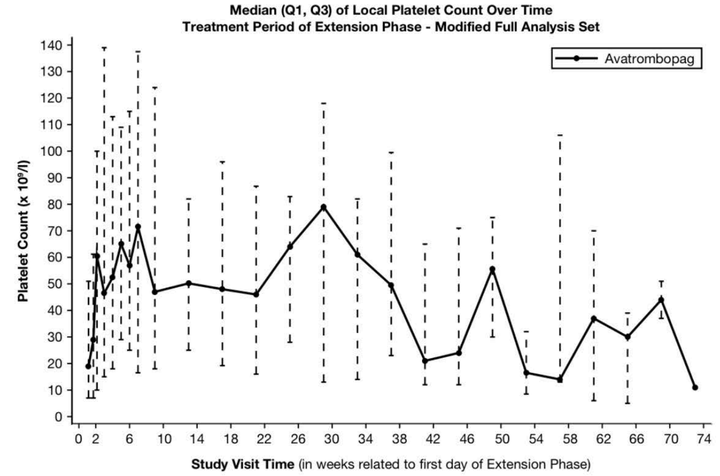
Eltrombopag

Table II. Summary of core study efficacy endpoints (FAS).

	Placebo (N = 17)	Avatrombopag (N = 32)
Cumulative number of weeks of platelet response*		
Mean (SD)	0·1 (0·49)	12·0 (8·75)
Median	0·0	12·4
Min, max	0, 2	0, 25
P-value of Wilcoxon rank sum test		<0·0001
Platelet count ≥50 × 10^9/l at day 8†		
Yes (%, 95% CI)	0·0 (-,-)	65·6 (49·17, 82·08)
No (%)	100·0	34·4
Difference of response rate (95% CI)‡		65·63 (49·17, 82·08)
P-value of Fisher's exact test		<0·0001

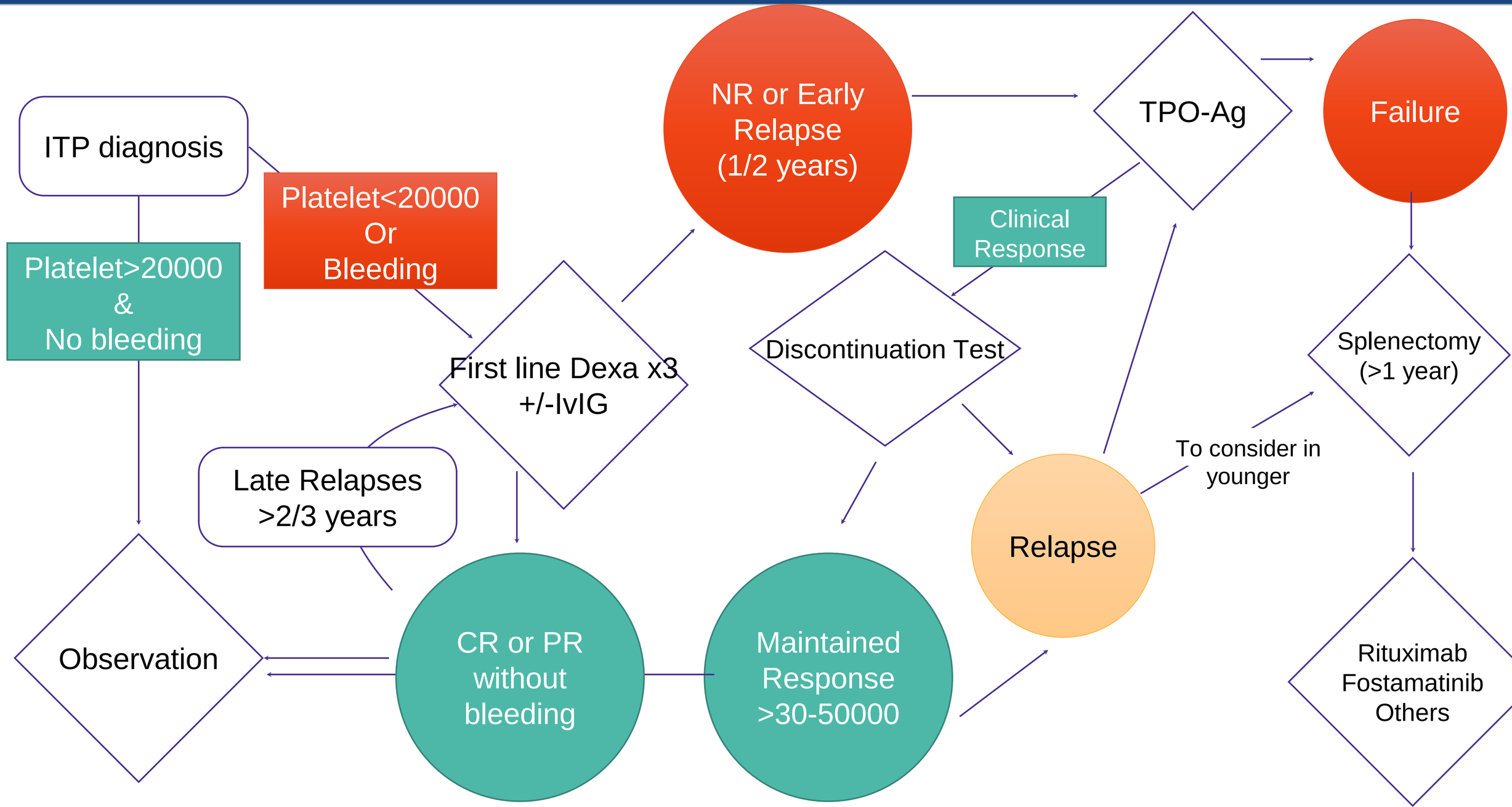
Reduction in use of concomitant ITP medications from baseline§	Placebo (N = 7)	Avatrombopag (N = 15)
Yes (%, 95% CI)	0·0 (-,-)	33·3 (9·48, 57·19)
No (%)	100·0	66·7
Difference of rate of reduction (95% CI)¶		33·33 (9·48, 57·19)
P-value of Fisher's exact test		0·1348





Jurczak, W., Chojnowski, K., Mayer, J., Krawczyk, K., Jamieson, B. D., Tian, W., & Allen, L. F. (2018). Phase 3 randomised study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia. British Journal of Haematology. http://doi.org/10.1111/bjh.15573

Personal approach to ITP treatment



- Introduction
- TPO Analogues in ITP
- **TPO Analogues in aplasia**
- TPO Analogues in MDS
- TPO Analogues in the post-transplant setting

Eltrombopag in aplasia. Results as salvage therapy

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.

ABSTRACT

BACKGROUND

Severe aplastic anemia, which is characterized by immune-mediated bone marrow hypoplasia and pancytopenia, can be treated effectively with immunosuppressive therapy or allogeneic transplantation. One third of patients have disease that is refractory to immunosuppression, with persistent, severe cytopenia and a profound deficit in hematopoietic stem cells and progenitor cells. Thrombopoietin may increase the number of hematopoietic stem cells and progenitor cells.

METHODS

We conducted a phase 2 study involving patients with aplastic anemia that was refractory to immunosuppression to determine whether the oral thrombopoietin mimetic eltrombopag (Promacta) can improve blood counts. Twenty-five patients received eltrombopag at a dose of 50 mg, which could be increased, as needed, to a maximum dose of 150 mg daily, for a total of 12 weeks. Primary end points were clinically significant changes in blood counts or transfusion independence. Patients with a response continued to receive eltrombopag.

RESULTS

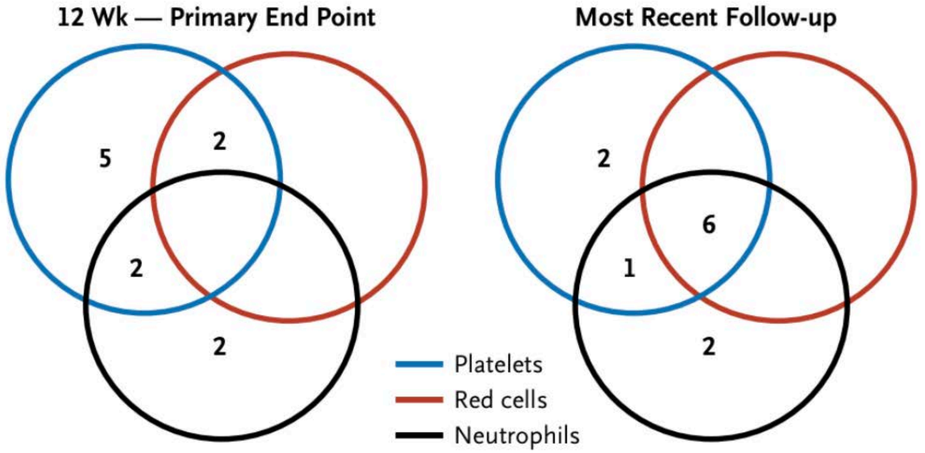
Eleven of 25 patients (44%) had a hematologic response in at least one lineage at 12 weeks, with minimal toxic effects. Nine patients no longer needed platelet transfusions (median increase in platelet count, 44,000 per cubic millimeter). Six patients had improved hemoglobin levels (median increase, 4.4 g per deciliter); 3 of them were previously dependent on red-cell transfusions and no longer needed transfusions. Nine patients had increased neutrophil counts (median increase, 1350 per cubic millimeter). Serial bone marrow biopsies showed normalization of trilineage hematopoiesis in patients who had a response, without increased fibrosis. Monitoring of immune function revealed no consistent changes.

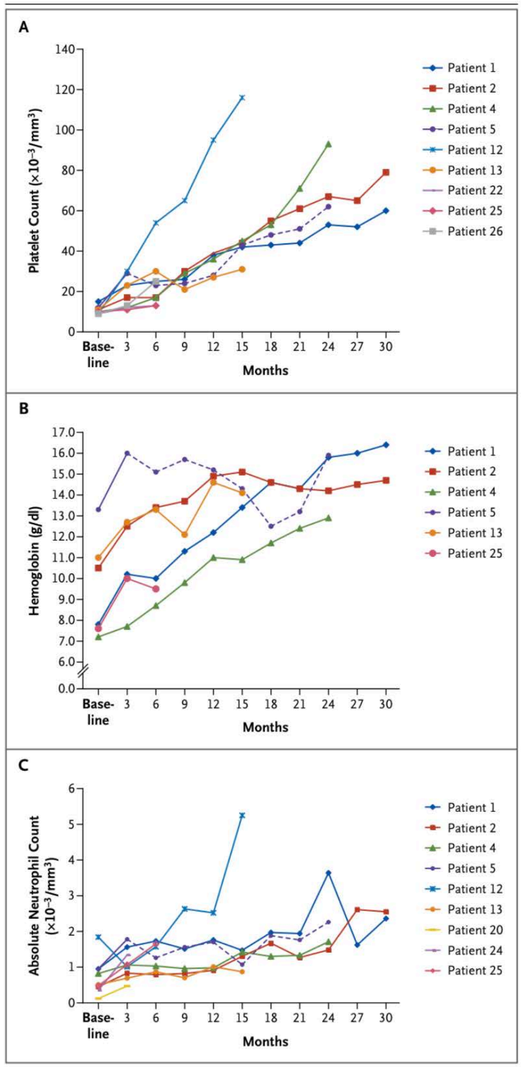
CONCLUSIONS

Treatment with eltrombopag was associated with multilineage clinical responses in some patients with refractory severe aplastic anemia. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT00922883.)

From the Hematology Branch (M.J.O., P.S., R.D., Y.T., B.D., A.R.P., S.S., X.F., N.S.Y., C.E.D.) and the Office of Biostatistics Research (C.O.W.), National Heart, Lung, and Blood Institute; the Hematology Section, Department of Laboratory Medicine, Mark O. Hatfield Clinical Research Center (K.R.C., J.L.); and the Trans-NIH Center for Human Immunology, Autoimmunity, and Inflammation (A.B.); National Institutes of Health, Bethesda, MD. Address reprint requests to Dr. Dunbar at the Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bldg. 10 CRC 4E-5132, Bethesda, MD 20892, or at dunbarc@nhlbi.nih.gov.

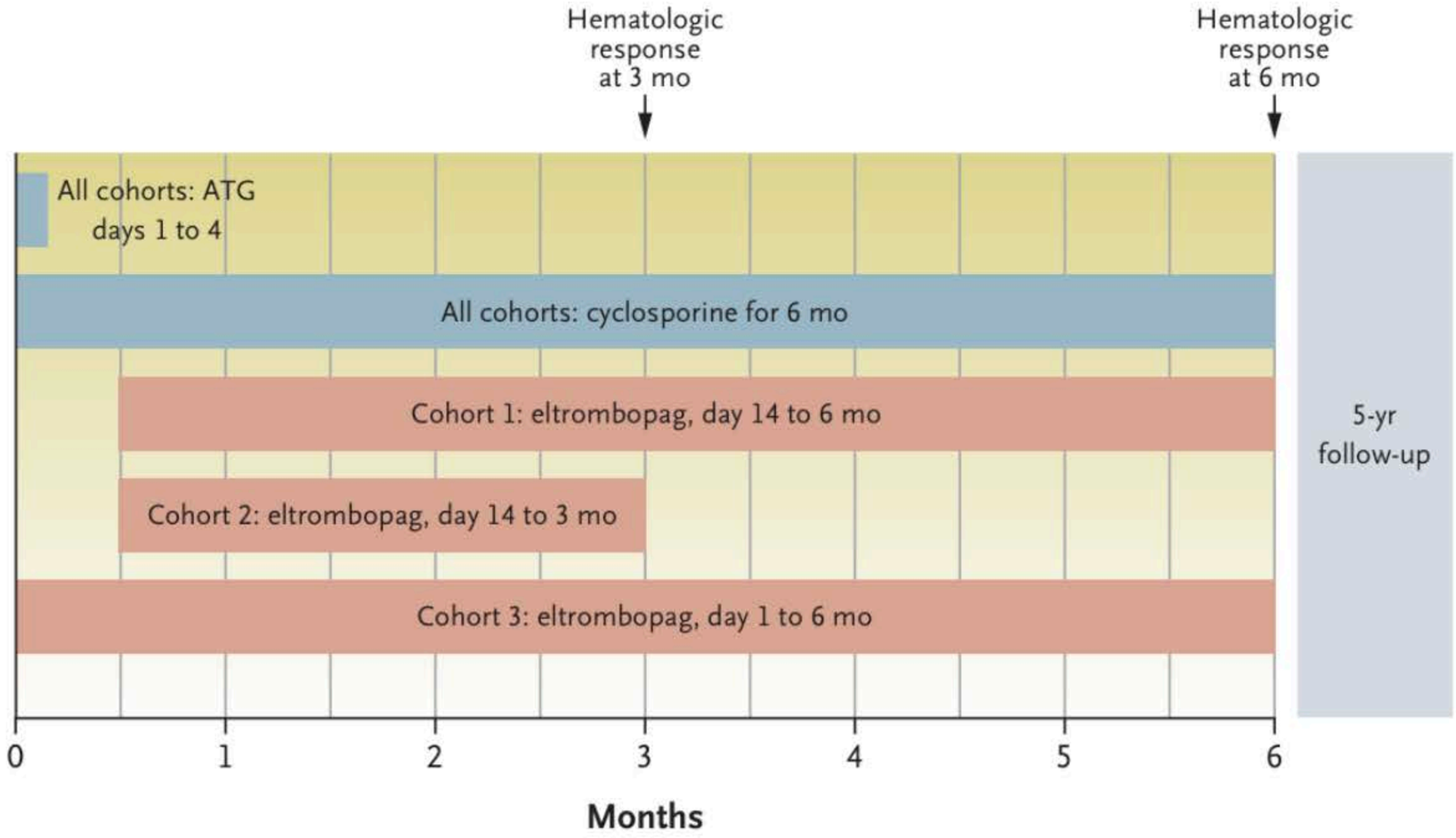
N Engl J Med 2012;367:11-9.
DOI: 10.1056/NEJMoa1200931





Olnes, M. J., et al. New England Journal of Medicine, 2012; 367(1), 11–19.

Eltrombopag in addition to ATG+CsA as frontline therapy in aplasia



Townsley, D. M.et al.. New England Journal of Medicine, 2017: 376(16), 1540–1550.

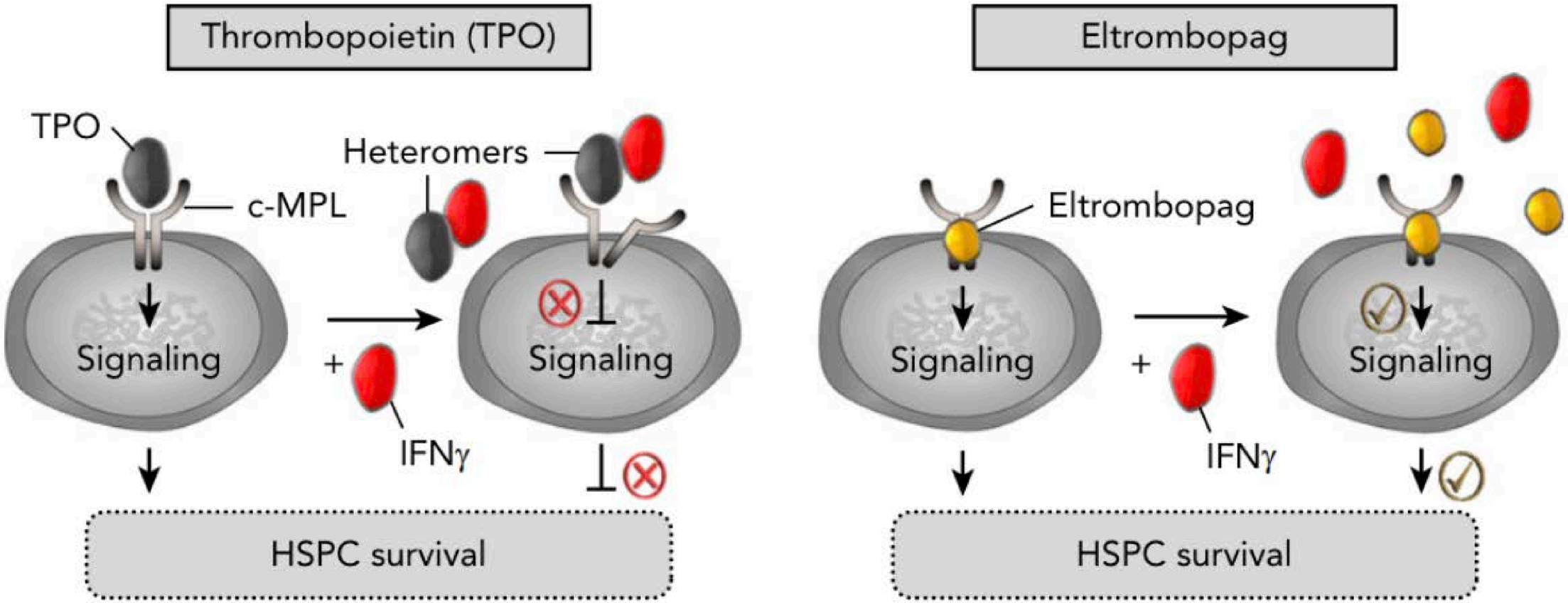
Eltrombopag in addition to ATG+CsA as frontline therapy in aplasia

Table 2. Hematologic Response in Patients Treated with Immunosuppression and Eltrombopag.*

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, D. M.et al.. New England Journal of Medicine, 2017: 376(16), 1540–1550.

Eltrombopag overcomes IFN gamma inhibition of hematopoiesis

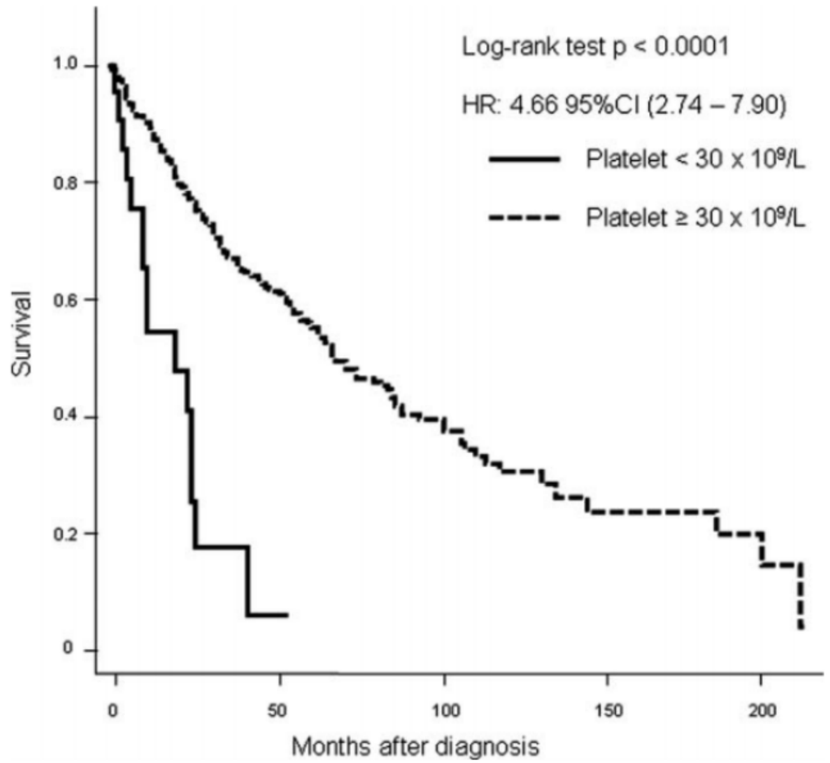


Alvarado, L. J. et al. Blood, 2019; 133(19), 2043–2055.

- Introduction
- TPO Analogues in ITP
- TPO Analogues in aplasia
- TPO Analogues in MDS
- TPO Analogues in the post-transplant setting

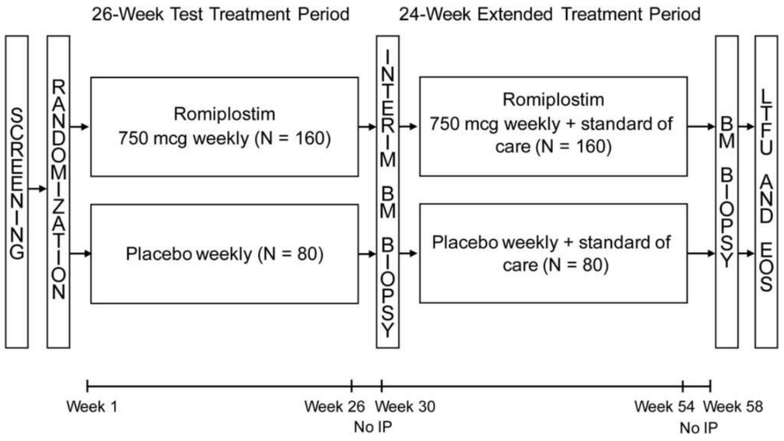
Thrombocytopenia in MDS

Variable	Platelets ≥30 × 10^9/L	Platelets <30 × 10^9/L	Univariate *P*	Multivariate OR [95% CI], *P*
WHO subtype			<.0001	4.12 [1.17-14.65], .0
RAEB-1/RAEB-2, n = 919	804 (34%)	115 (63%)		
RA/RCMD/RS/5q−, n = 1646	1579 (66%)	67 (37%)		
IPSS subtype			<.0001	1.99 [1.01-3.93], .04
Intermediate-2/high, n = 390	333 (19%)	57 (52%)		
Low/intermediate-1, n = 1457	1404 (81%)	53 (48%)		
Blasts in BM			<.0001	2.09 [0.58-7.60], .26
≥5 %, n = 878	771 (32%)	107 (59%)		
<5%, n = 1687	1612 (68%)	75 (41%)		
LDH			.049	1.61 [0.98-2.64], .06
≥340 mg/dL, n = 1030	947 (52%)	83 (61%)		
<340 mg/dL, n = 913	861 (48%)	52 (39%)		
Cytogenetic category			<.0001	1.27 [0.72-2.25], .41
Poor/intermediate, n = 436	389 (22%)	47 (43%)		
Good, n = 1411	1348 (78%)	63 (57%)		
Age			.007	1.29 [0.81-2.07], .28
<70 years, n = 874	795 (33%)	79 (43%)		
≥70 years, n = 1691	1588 (67%)	103 (57%)		
Sex			.024	—
Men, n = 1469	1350 (57%)	119 (65%)		
Women, n = 1096	1033 (43%)	63 (35%)		

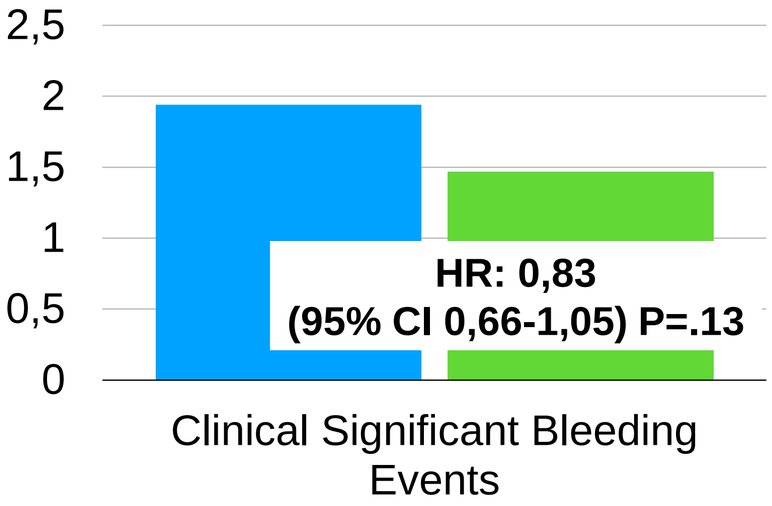


Gonzalez-Porras, J. R. et al. Cancer, 2011; 117(24), 5529–5537.

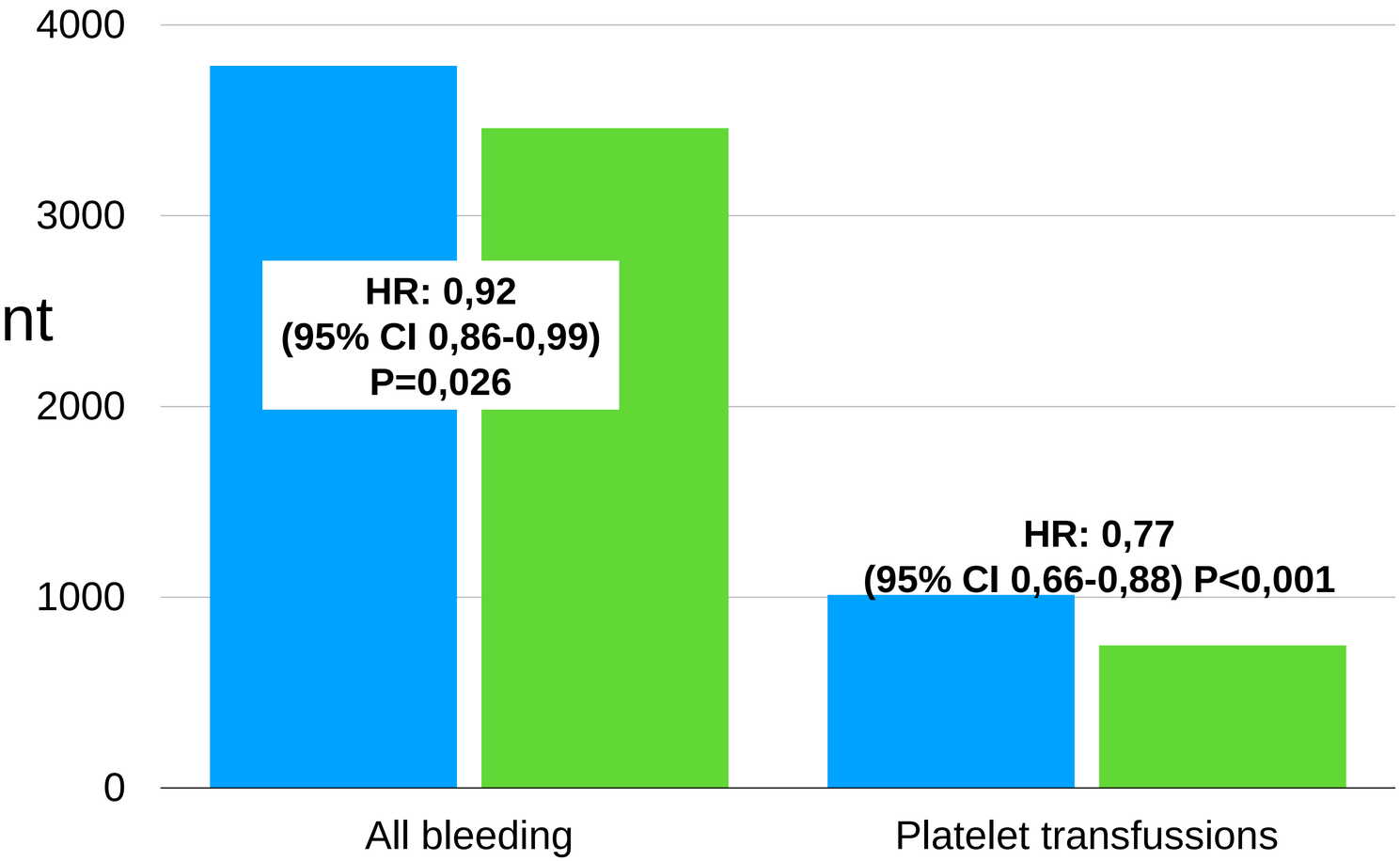
Romiplostim in MDS



Mean number of events per patient at week 26



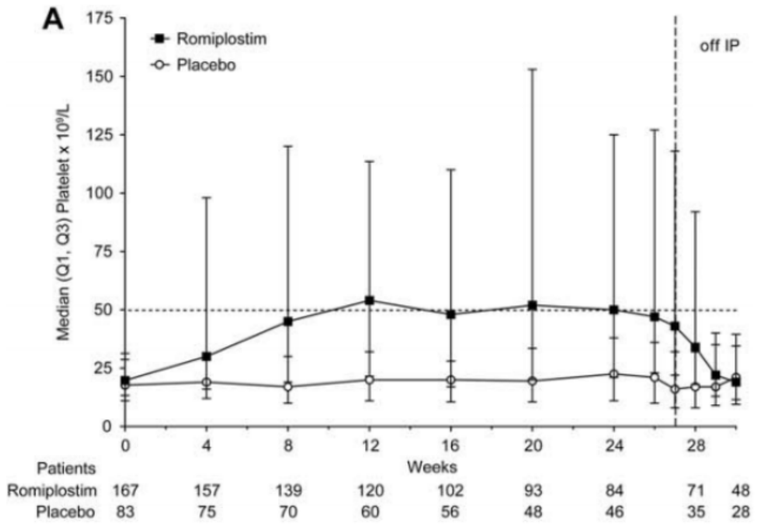
Per 100 patient years

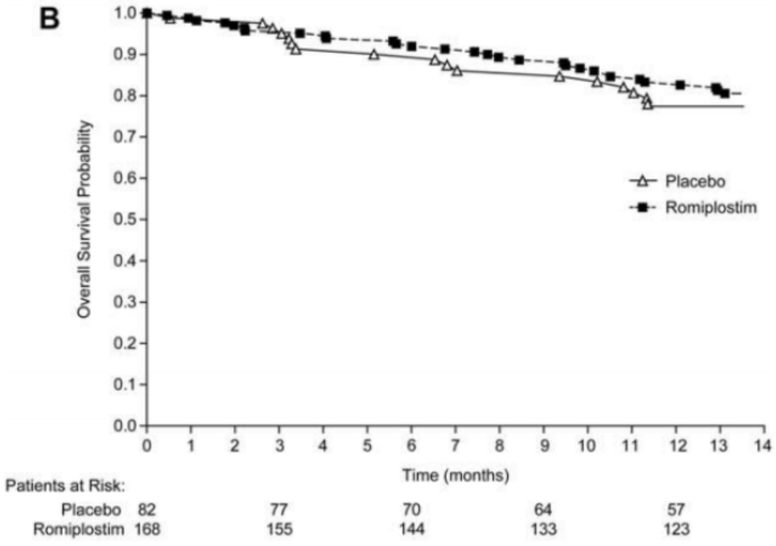


Placebo Romiplostim

Giagounidis, A., et al. Cancer, 2014; 120(12), 1838–1846.

Romiplostim in MDS

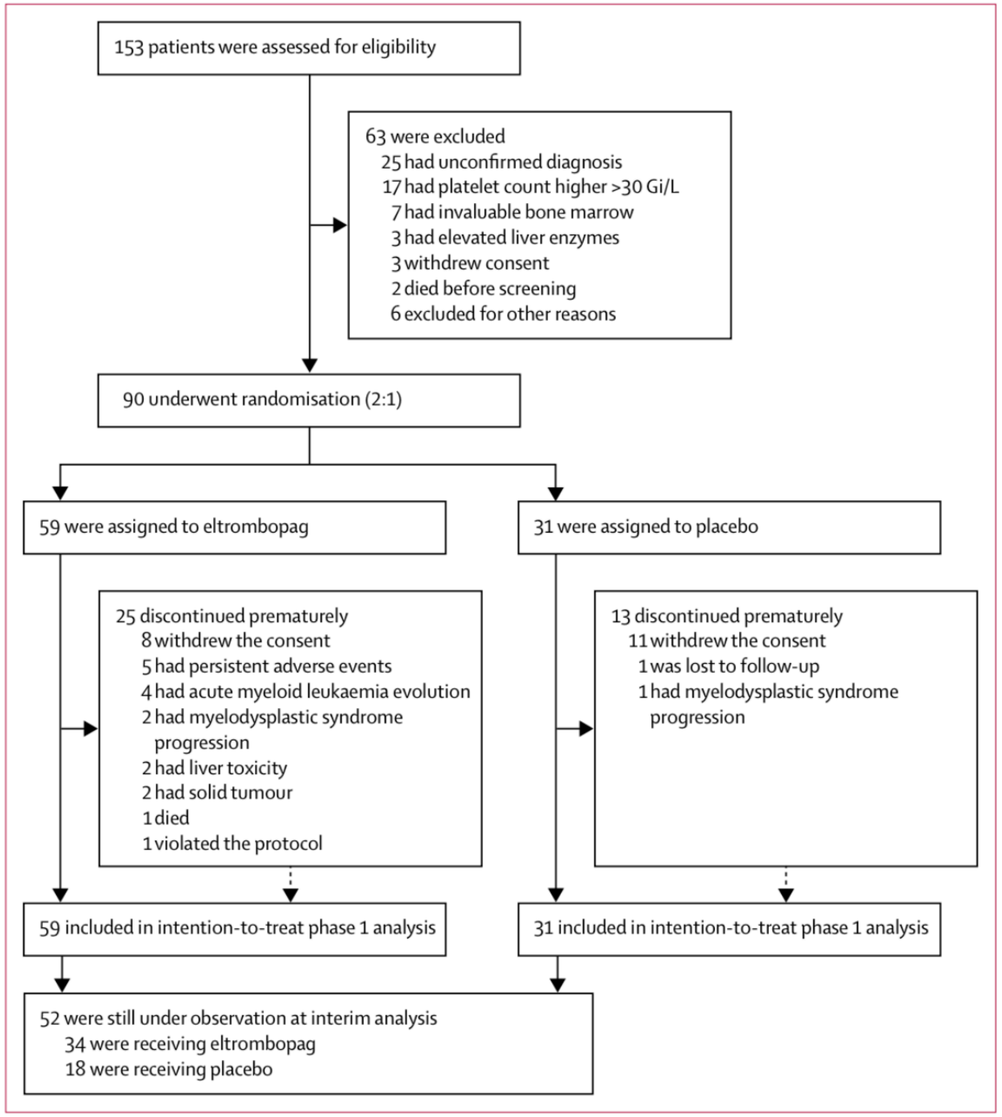




Variable	No. of Patients (%)		
	Placebo, N = 82	Romiplostim, N = 168	Total, N = 250
Total no. with study-defined AML	4	10	14
Baseline WHO classification			
RAEB-1 or RAEB-2	3 (75)	6 (60)	9 (64)
Non-RAEB	1 (25)	4 (40)	5 (36)
AML diagnosis by			
Bone marrow/peripheral blasts ≥20%	2 (50)	7 (70)[a]	9 (64)
Anti-AML therapy alone	2 (50)	3 (30)	5 (36)

Giagounidis, A., et al. Cancer, 2014; 120(12), 1838–1846.

Eltrombopag in lower risk MDS



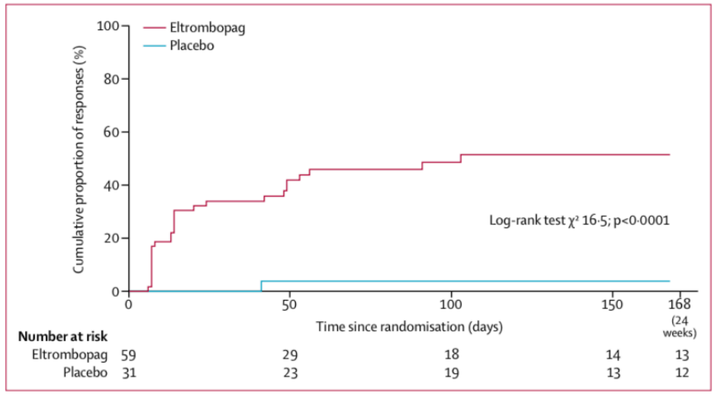
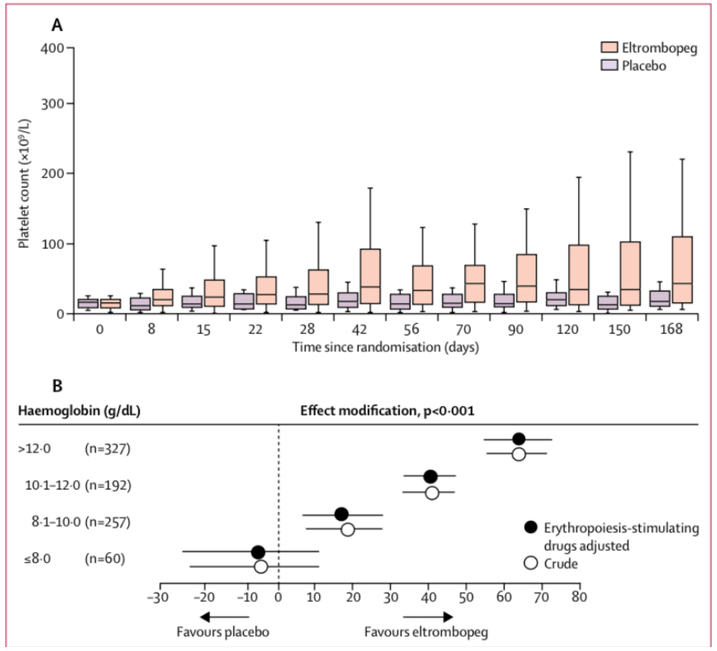


Figure 2: **Incidence of platelet response in both treatment groups**



Oliva, E. N et al. The Lancet Haematology, 2017; 4(3), e127–e136.

- Introduction
- TPO Analogues in ITP
- TPO Analogues in aplasia
- TPO Analogues in MDS
- TPO Analogues in post transplant

Thrombopoietin receptor agonists for severe thrombocytopenia after allogeneic stem cell transplantation: Experience of a multicenter study from GETH

L. Bento, JM. Bastida, I. García-Cadenas, E. García-Torres, D. Rivera, A. Bosch, C. De Miguel, ME. Martínez-Muñoz, F. Fernández-Avilés, E. Roldán, A. Chinea, L. Yáñez, T. Zudaire, C. Pinho Vaz, I. Espigado, J. López, D. Valcárcel, R. Duarte, R. Cabrera, A. Gutiérrez, C. Solano, A. Sampol on behalf of the Grupo Español de Trasplante Hematopoyético (GETH)

San Diego, 1 December 2018

Objective

To analyze the efficacy and safety of TPO-RAs for severe and persistent thrombocytopenia after allo-SCT

<u>Endpoints:</u>

- Efficacy:
  - Platelet recovery to ≥50000/µL without transfusion for 7 consecutive days
  - Time to response
  - Predictors of response
- Safety:
  - Toxicity evaluation was based on CTCAE guidelines
- Overall survival

Patients and methods

- Retrospective multicenter study
- Patients with thrombocytopenia were included:
  - Prolonged isolated thrombocytopenia (PT):
    - Engraftment of all peripheral blood cell lines but platelet count <20000/µL for 7 consecutive days.
    - Requirement of transfusion within the first 60 days after allo-SCT.
  - Secondary failure of platelet recovery (SFPR):
    - Decline of platelet count to <20000/µL for 7 consecutive days.
    - Requirement of transfusion after platelet recovery (platelets ≥50000/µL without transfusion for 7 days post-SCT).
- Exclusion criteria:
  - Primary disease recurrence
  - Thrombotic microangiopathy

Y. Akahoshi et al. Biol Blood Marrow Transplant. 2016; 1678-16

Patients characteristics

	N= 86
Age, years (median, R)	53 (8-74)
Sex (M/F)	50 (58%) / 36 (42%)
Disease:	
- MDS	6 (7%)
- AML	33 (38%)
- ALL	12 (14%)
- NHL	16 (19%)
- HL	4 (5%)
- Aplastic anemia	5 (5%)
- Others	11 (13%)
Donor:	
- HLA-identical sibling	21 (24%)
- Unrelated	28 (33%)
- Haplo	32 (37%)
- CB / Haplo-cord	5 (6%)
Pre-SCT status:	
- CR	55 (64%)
- PR	9 (10%)
- Active disease	22 (26%)

	N= 86
CD34 dose (median, R) (x10^6/kg):	5 (0.6-11.8)
Source:	
- PB	74 (86%)
- BM	6 (7%)
- CB	6 (7%)
Conditioning:	
- Mieloablative	34 (39%)
- Reduced intensity	52 (60%)
GVHD prophylaxis:	
- MTX + CsA o Tacrolimus	13 (15%)
- MMF + CsA o Tacrolimus	10 (12%)
- Tacrolimus + Sirolimus	9 (10%)
- Post-SCT Cyclophosphamide	35 (41%)
- ATG/Alemtuzumab based prophylaxis	19 (22%)

Treatment characteristics

	N=86
Type of thrombocytopenia (SFPR/PT):	70 (82%) / 16 (19%)
Platelet count before starting TPO-RAs (median, R) (µ/L):	14000 (1000-57000)
Type of TPO-RAs: Eltrombopag Romiplostim	 51 (59%) 35 (41%)
Starting dose (median, range): Eltrombopag (mg daily) Romiplostim (µg/kg)	 50 (25-150) 1 (1-7)
Maximum dose (median, range): Eltrombopag (mg daily) Romiplostim (µg/kg)	 75 (25-150) 5 (1-10)
Days from SCT to starting TPO-RAs (median, range):	127 (27-1177)
Days from platelets <20000/µL to starting TPO-RAs (median, range):	32 (0-1016)
Duration of TPO-RAs (median, range) (days):	62 (7-700)
Follow up after starting TPO-RAs (median, range) (months):	10 (1-59)

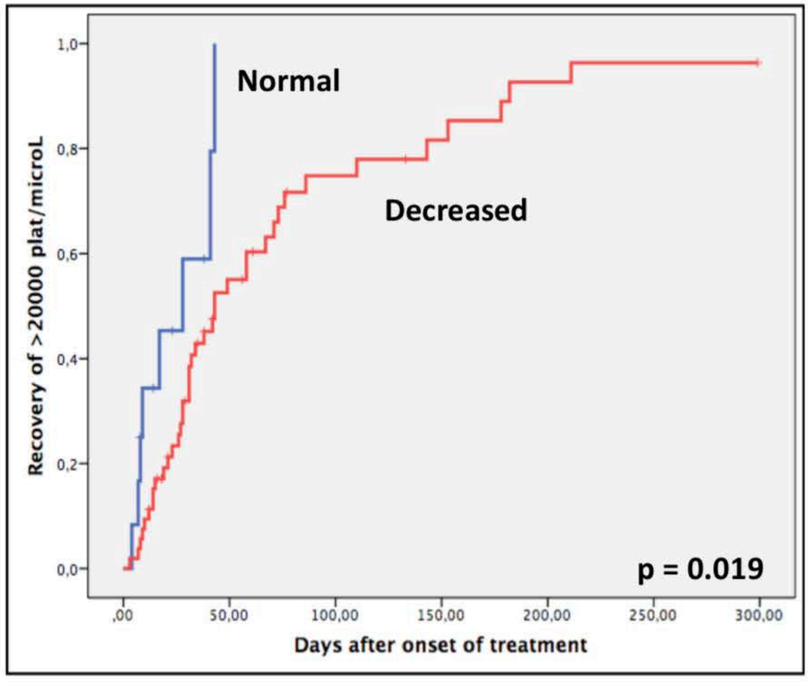
Efficacy: Predictors of response

Characteristics	% Response ≥50000/uL	p
Age:		
- 0-40	73%	0.15
- >40	55%	
Sex:		
- Male	50%	**0.026**
- Female	75%	
Disease:		
- MDS/AML	56%	**0.03**
- ALL	92%	
- NHL/HL	65%	
- Aplastic anemia	75%	
- Others	27%	
Status at allo-SCT:		**0.011**
- CR/PR	69%	
- SD/PD	36%	
Donor:		
- Identical sibling	57%	0.35
- Unrelated	54%	
- Haplo	72%	
- Cord / haplocord	40%	
Type allo-SCT:		
- PB	61%	0.83
- BM	67%	
- Cord/dual	50%	

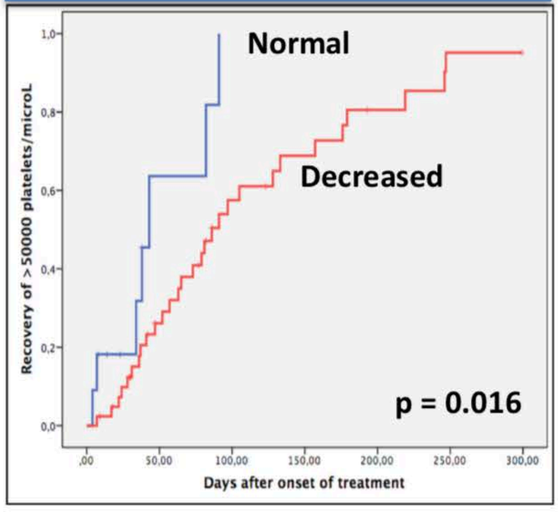
Characteristics	% Response ≥50000/uL	p
Prophylaxis:		
- MTX + CsA o Tacrolimus	54%	0.48
- MMF + CsA o Tacrolimus	50%	
- Tacrolimus + Sirolimus	44%	
- Post-SCT Cyclophosphamide	58%	
- ATG/Alemtuzumab based prophylaxis	71%	
Thrombocytopenia type:		
- SFPR	62%	0.57
- PT	53%	
Response to EPO:		
- Yes	65%	1
- No	64%	
Response to G-CSF:		
- Yes	65%	0.35
- No	50%	

Megacaryocytes

№ megacaryocytes	N	Platelets ≥20000/µL (median, R) (days)	Platelets ≥50000/µL (median, R) (days)
Normal	16 (19%)	28 (3-53)	82 (26-138)
Decreased	70 (81%)	43 (25-61)	91 (70-112)
		p=0.019	p=0.12



Platelets ≥50000/uL in SFPR group



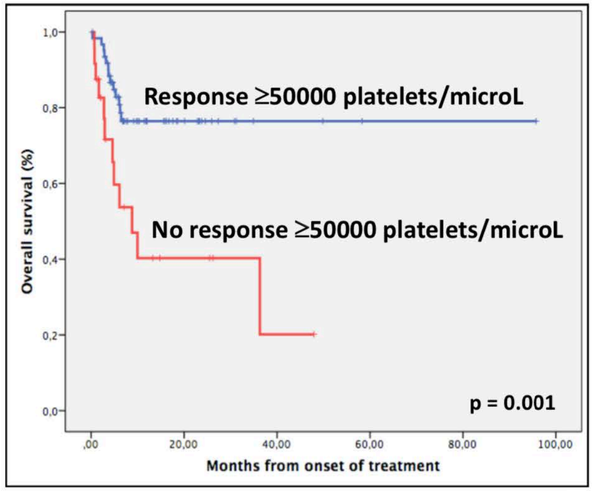
Safety of TPO-RA

- TPO-RAs were well tolerated.
- Only 2 patients showed adverse effects (2%):
  - Grade 3 liver abnormalities
  - Grade 3 fatigue
- No patients discontinued the TPO-RAs because of adverse effects.

Overall survival

Last follow up	
Response platelets ≥50 x10^9/L:	
Yes	63%
No	37%
Responders patients ongoing:	
Yes	19%
No	81%
Status:	
Alive	71%
Dead	29%

Causes of death	
Relapse	28%
Infection	48%
GVHD	16%
Others	8%



Conclusions

- To our knowledge this is the biggest series analyzing the use of TPO-RAs after allo-SCT.
- Our results support the efficacy and safety in this new setting with an overall response rate of 72% and good tolerability.
- PT required more time to response in comparison with SFPR.
- In our series faster responses were observed in patients with a normal number of megacaryocytes.
- Further prospective trials are needed to increase the level of evidence and to identify predictors of response.

Final remarks

- TPO analogues have become a standard in second line therapy in ITP
  - Optimal management including time to begin and discontinuation remain to be fully determined
- The improvement of response in aplasia support its use in front-line therapy
- In MDS patients they can be of help for those patients with thrombocytopenia as the main manifestation
- The safety profile suggest they can be used as support therapy in many other indications as hepatitis, post-transplant, post-chemo, pre-surgery, and many other that will probably come

Gracias

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