Key pediatric ITP clinical data

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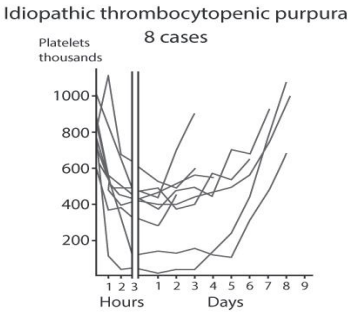
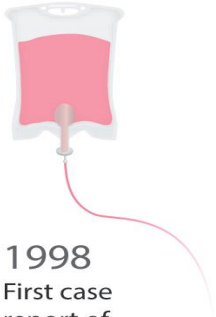
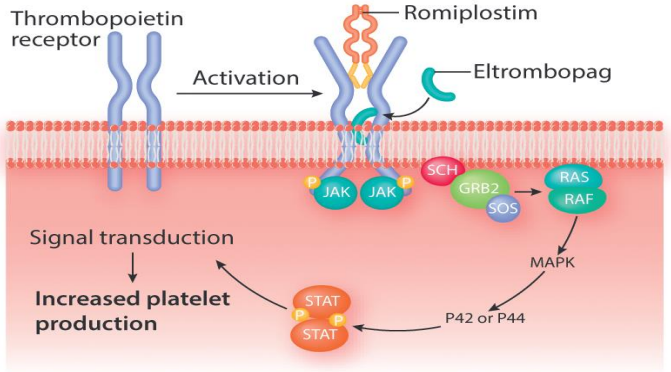
History of discovery and therapies for ITP

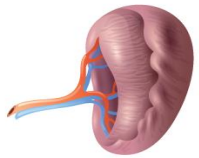






1735
First description of ITP (Werlhof Disease)

1916
First splenectomy conducted



1950
Established ITP as an autoimmune blood disorder

1994
Successful cloning of thrombopoietin

1998
First case report of rituximab

2003-2004
Confirmation of impaired thrombopoiesis related to platelet antibodies

2006
First rituximab trial in pediatrics

2008
Romiplostim FDA approval for adults

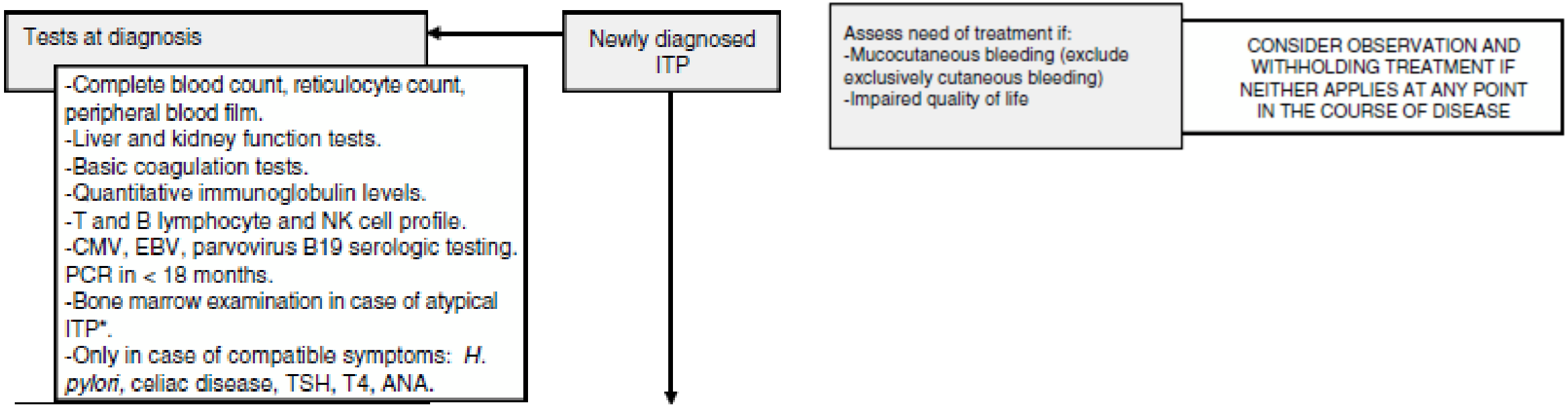
2011
Eltrombopag FDA approval for adults

2016
Eltrombopag extended for children

2018
Romiplostim extended for children

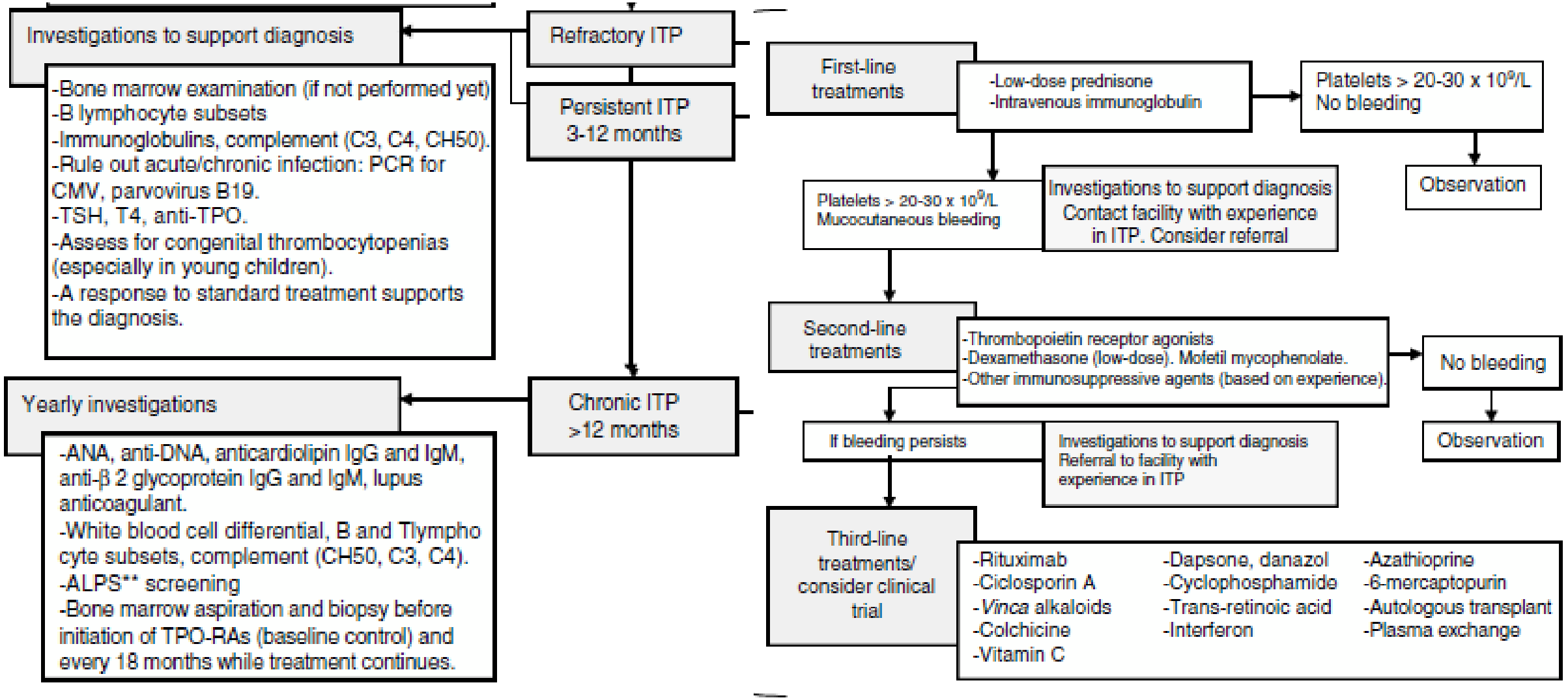
haematologica 2020; 105(11)

Approach to the diagnosis and management of ITP in patients that are not eligible for splenectomy (or did not respond to surgical intervention)



An Pediatr (Barc). 2018;89(3):189.e1---189.e8

Approach to the diagnosis and management of ITP in patients that are not eligible for splenectomy (or did not respond to surgical intervention)



An Pediatr (Barc). 2018;89(3):189.e1---189.e8

Comparison of first-line therapies for pediatric ITP

Medication	Dose	Duration	Time to response	Response rate	Cost*	Common side effects
Prednisone	2–4 mg/kg/day Max 120 mg daily	5–7 days, no taper	2–7 days	50–77%	$786.00	Gastritis, mood changes, weight gain, hypertension, hyperglycemia
IVIG	1 g/kg ×1 2nd dose may be given if needed	Single dose	24–48 hours	>80%	$2,492	Headache, nausea, aseptic meningitis
Anti-D immune globulin	50–75 μg/kg ×1	Single dose	24–48 hours	~75%	$2,035	Headache, chills, fever, hemolysis

*estimated for 20 kg child.

Ann Blood 2021;6:4 | http://dx.doi.org/10.21037/aob-20-96

Main drugs and procedures used in the management of persistent and refractory ITP

Drug/procedure	Dosage	Response rate	Time to response	Adverse effects	Special considerations
Splenectomy	–	70–85% initially, 60–75% at 5 years	Immediate	Risk of infection. Potential risk of thrombosis	Vaccination according to current schedule for splenectomised patients. Antibiotic prophylaxis after surgery.
Rituximab	375 mg/m^2/dose, weekly doses (x4), IV	60–68% initially, 20–25% at 5 years	1–8 weeks	Infusion reaction, serum sickness, HBV reactivation, progressive multifocal leukoencephalopa-thy	Not indicated for this disease in summary of product characteristics

An Pediatr (Barc). 2018;89(3):189.e1---189.e8

Drug/procedure	Dosage	Response rate	Time to response	Adverse effects	Special considerations
Romiplostim	1–10 μg/kg/dose weekly, SC	40–50% sustained response	1–4 weeks	Bone marrow fibrosis, thrombosis	Currently not indicated for use in children. Requires weekly monitoring at the beginning of treatment
Eltrombopag	25–75 mg/day p.o.	40–50% sustained response	1–2 weeks	Bone marrow fibrosis, thrombosis, hepatotoxicity	Indicated for chronic ITP in children
Low-dose prednisone	<5 mg/day p.o.	<10%	N/A*	Weight gain, hyperglycaemia, high blood pressure, osteoporosis, cataracts	Not initiated at a low dose: dose is gradually lowered in patients that respond to intermediate doses

An Pediatr (Barc). 2018;89(3):189.e1---189.e8

Drug/procedure	Dosage	Response rate	Time to response	Adverse effects	Special considerations
Azathioprine	1–2 mg/kg/day p.o. (max 150 mg/day)	40–60%	3–6 months	Hepatotoxicity, neutropenia, infection, pancreatitis	
Mycophenolate mofetil	250–1000 mg p.o. twice a day	11–80% variability in sustained response	4–6 weeks	Headache, diarrhoea, nausea, anorexia, infection	Usually well tolerated
6-Mercaptopurine	50–75 mg/m^2/day	83%	Not reported	Hepatotoxicity, neutropenia, infection, pancreatitis	Evidence from studies in children with immune-mediated cytopenias. Few responses in patients with ITP
Ciclosporin A	5–6 mg/kg/day every 12 h (target level, 100–200 ng/mL)	30–60%	3–4 weeks	Nephrotoxicity, high blood pressure, tremors, paraesthesia, gingival enlargement	One study in children reported one case of fungal infection. Requires monitoring of blood pressure and renal function

An Pediatr (Barc). 2018;89(3):189.e1---189.e8

Drug/procedure	Dosage	Response rate	Time to response	Adverse effects	Special considerations
Danazol	50–800 mg/day p.o. divided in 2–4 doses	10–70%	3–6 months	Hepatotoxicity, virilisation, amenorrhoea	Improved responses with prolonged treatment and durable responses with treatment >1 year
Dapsone	75–100 mg p.o. once a day	40–75%	3 weeks	Haemolysis (in the case of G6PDh deficiency), rash, nausea, methe-moglobinemia, agranulocytosis, aplastic anaemia	No evidence from randomised clinical trials. Rule out G6GPDh deficiency
Cyclophosphamide	0.3–1 g/m^2 IV every 2–4 weeks (1–3 doses), 50–200 mg p.o. once a day	24–85%	1–16 weeks	Neutropenia, nausea, vomiting, infertility, secondary tumours	It is important to emphasise the need of fluid intake to prevent haemorrhagic cystitis. Very few published data. Not recommended if clinician has no experience in its use

An Pediatr (Barc). 2018;89(3):189.e1---189.e8

TPO-RA

- Short-term response in more than 90% of patients
- Variable long-term response (30-90%)
- Effective in patients with and without splenectomy
- The 2 TPO-RAs, eltrombopag and romiplostim, are not cross-resistant; if one TPO-RA fails, the other one can still achieve a response
- Romiplostim seems to be less effective when the serum thrombopoietin levels are high
- Slow tapering over several months

Oncol Res Treat 2018;41(suppl 5):1–30

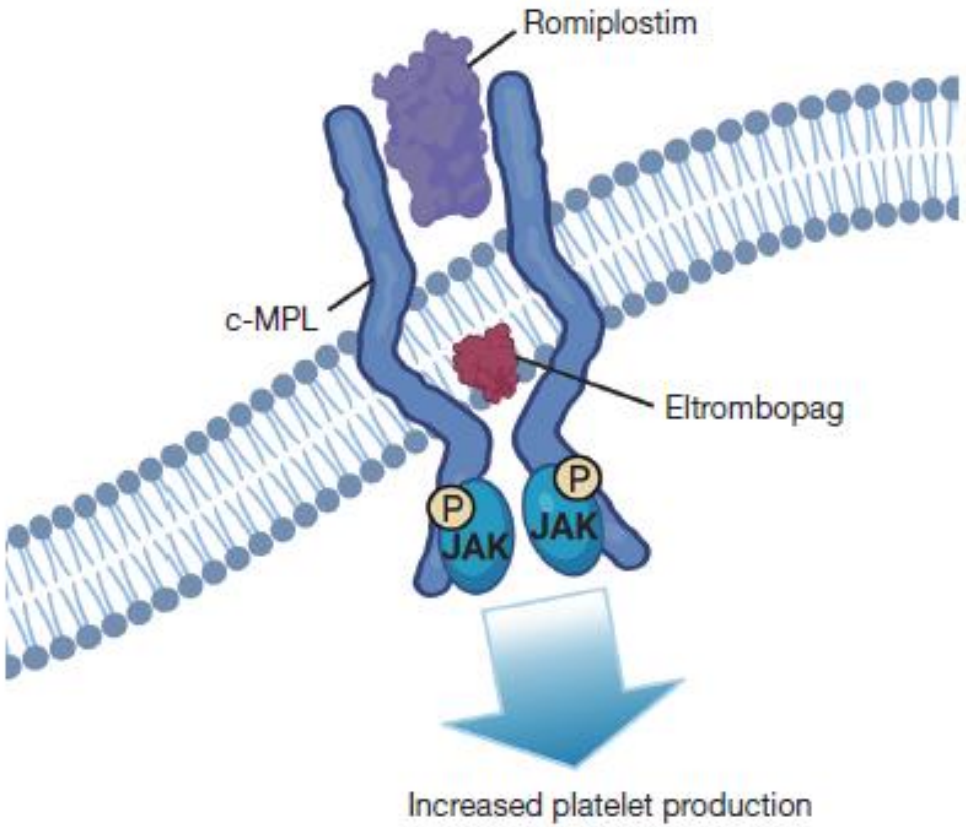


Figure 3 Binding regions of romiplostim and eltrombopag. Both romiplostim and eltrombopag bind and stimulate the thrombopoetin receptor, *c-mpl*. Romiplostim binds at the distal cytokine homology 2 (CRH-2) domain while eltrombopag binds a transmembrane region. Image created with BioRender.com.

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Romiplostim
The starting dose of romiplostim recommended in the prescribing information is 1 μg/kg once weekly based on the actual body weight. The weekly dose should be increased in steps of 1 μg/kg until a stable platelet count (≥50 × 10^9/l) is reached.
The maximum dose should not exceed 10 μg/kg/week.
The target range for the platelet count is 50–150 × 10^9/l, normalization of platelet count is not necessary
With romiplostim the platelet count should not exceed 250 × 10^9/l
Initially the platelet count should be checked weekly, then every 4 weeks Note: if the patient is bleeding a higher starting dose is often used (e.g. 3–5 μg/kg), for severe bleeding, start with the maximum dose to avoid long titrations

Eltrombopag
The recommended starting dose for eltrombopag is 50 mg once daily (25 mg for patients of East Asian descent). The dose should be adjusted until a stable platelet count ($\geq 50 \times 10^9$/l) is reached
The maximum dose should not exceed 75 mg p.o. daily
The target range for the platelet count is $50–150 \times 10^9$/l
With eltrombopag the platelet count should not exceed 250×10^9/l
Initially the platelet count should be checked weekly, then every 4 weeks

Protocol for tapering romiplostim
Patients who maintained platelet counts >50 × 10^9/l for at least 12 months were eligible for dose-tapering. Romiplostim dose was reduced by 1 μg/kg every 2 weeks as long as platelet counts remained >50 × 10^9/l [103]
Protocol for tapering eltrombopag
Patients who maintained platelet counts >50 × 10^9/l for at least 4 months were eligible for dose-tapering. Eltrombopag dose was reduced by 10–20% every 4 weeks as long as platelet count remained >50 × 10^9/l [104]

PETIT and PETIT 2: Treatment with Eltrombopag in 171 Children with Chronic Immune Thrombocytopenia (ITP)

- Subjects aged 1 to <18 years with a confirmed diagnosis of persistent or chronic ITP and a platelet count <30 Gi/L at day 1 were randomized 2:1 to eltrombopag (EPAG) or Placebo (PBO)
- stratified by age: 12–17 years (Cohort 1), 6–11 years (Cohort 2), and 1–5 years (Cohort 3)
- Subjects could continue baseline ITP medications
- After the PBO-controlled randomized phase, subjects were permitted to complete 17 or 24 weeks of treatment with open-label (OL) EPAG
- Dose was adjusted based on platelet counts to a maximum of 75 mg daily.

Blood (2014) 124 (21): 1450.

Results

- A total of 174 subjects were enrolled in both studies; 171 received ≥1 dose of EPAG
- 159 subjects were randomized (intent-to-treat population), and 157 received ≥1 dose of randomized study treatment (safety population)
- Most subjects (93%) were diagnosed with ITP for ≥12 months, and 13% were receiving ITP medications at baseline.
- The majority of subjects (81%) received ≥2 prior ITP therapies.
- Most subjects (59%) had a baseline platelet count <15 Gi/L
- splenectomized subjects were randomized to the EPAG group.

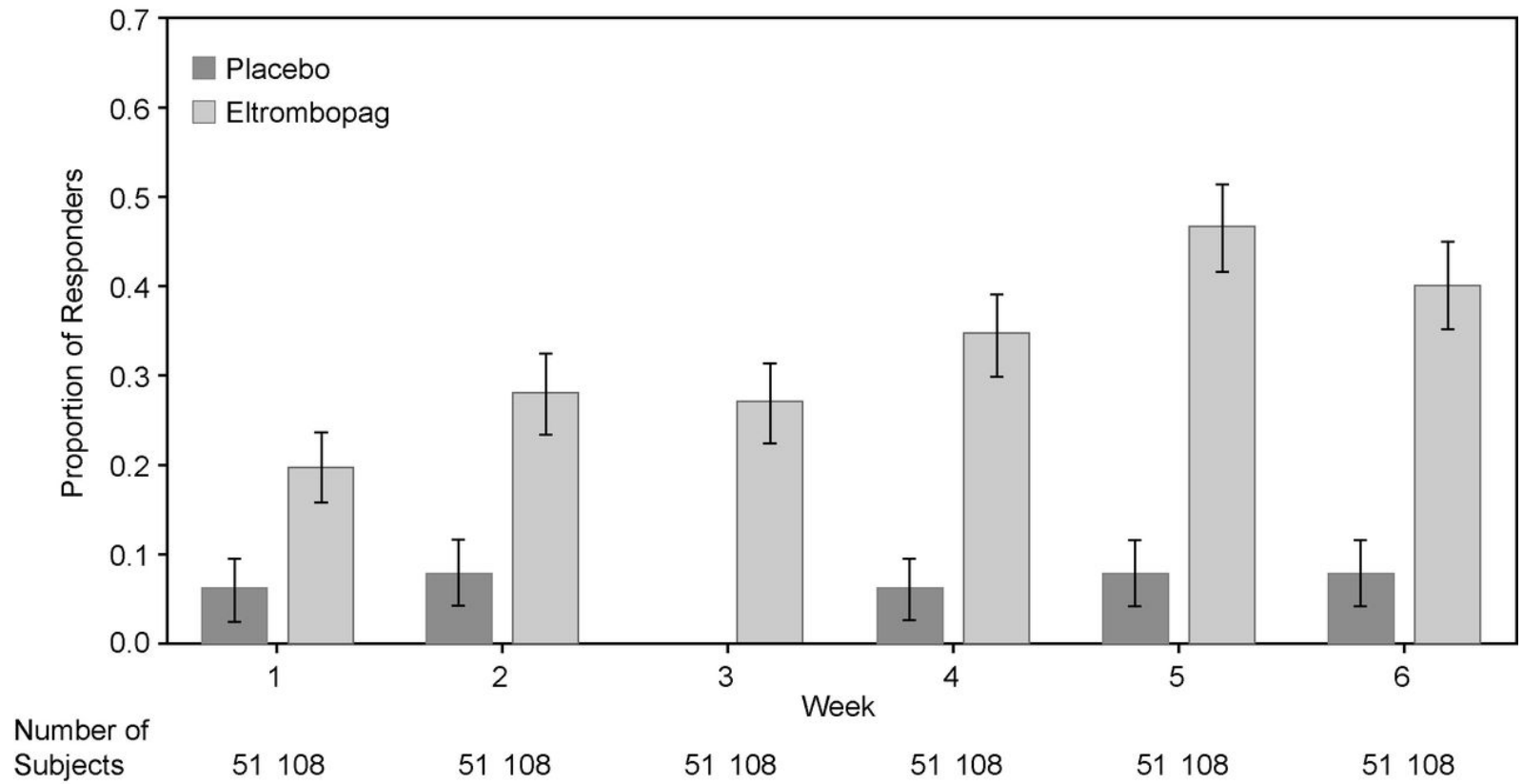
Blood (2014) 124 (21): 1450.

Randomization period

- A higher proportion of EPAG versus PBO subjects (62% vs 24%; *P* < 0.001) achieved a response with platelet counts ≥50 Gi/L at least once between weeks 1–6 (Cohort 1, 64% vs 11%; Cohort 2, 64% vs 27%; Cohort 3, 54% vs 36%, respectively)
- At each week, a higher proportion of EPAG subjects had a response versus PBO
- A lower proportion of EPAG subjects (13%) received rescue treatment compared with PBO subjects (31%; *P* = 0.009)
- The odds of having WHO bleeding grades 1–4 (0.19; *P* = 0.011) and clinically significant (WHO grades 2–4) bleeding (0.29; *P* = 0.007) were lower for EPAG versus PBO subjects.

Blood (2014) 124 (21): 1450.

Figure 1. Platelet Count Responders (± SE) by Week and Treatment (Randomized Period)



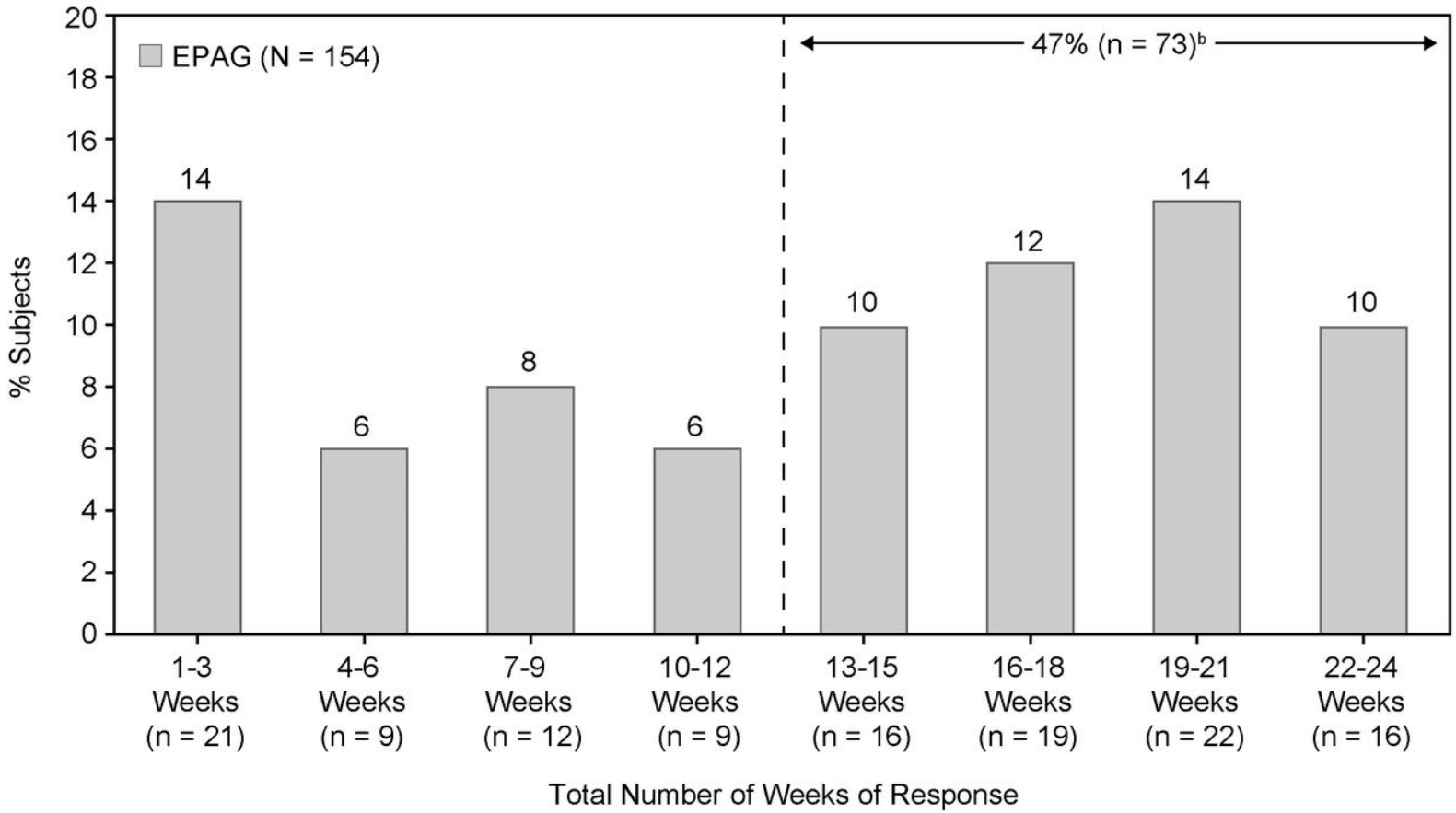
SE, standard error.

EPAG-only period

- Sustained reduction or discontinuation of baseline ITP medications, primarily corticosteroids, was achieved by 50% of subjects
- 81% of subjects had a platelet count response at least once; 52% (n = 80/154) had a platelet count response for ≥50% of assessments; and 38% (n = 58/154) responded for ≥75% of assessments
- For >13 of 24 weeks, 47% of subjects achieved responses
- The median average daily dose for EPAG-exposed patients in Cohorts 1, 2, and 3 were 64.0 mg (0.93 mg/kg), 57.6 mg (1.50 mg/kg), and 37.0 mg (2.02 mg/kg), respectively.

Blood (2014) 124 (21): 1450.

Figure 2. Total Number of Weeks Subjects Achieved a Response During EPAG-Only Period[a]



[a]EPAG-only period includes EPAG exposure in the randomized period of PETIT as well as the EPAG exposure in the open-label periods of PETIT and PETIT2.
[b]Percentages do not add up correctly due to rounding.

Blood (2014) 124 (21): 1450.

Adverse events

- The most common AEs (≥10% of subjects) were headache, upper respiratory tract infection, and nasopharyngitis in the EPAG group
- headache, epistaxis, and vomiting in the PBO group
- Serious AEs (SAEs) were reported in 8% of EPAG subjects versus 12% of PBO subjects
- In the randomized period, a transient ALT elevation of 3 x ULN occurred in 5 (4.7%) subjects in the EPAG group and no subjects in the PBO group
- In the OL period, there were an additional 7 subjects with ALT 3 x ULN
- Fewer EPAG than PBO subjects reported bleeding AEs (17% vs 36%, respectively)
- No thromboembolic events were reported
- Cataract events were experienced by 2 subjects who received EPAG; both had used corticosteroids and 1 had pre-existing cataracts

Efficacy and safety of eltrombopag in the treatment of Chinese children with chronic immune thrombocytopenia

- A retrospective, single-center study included 30 children with cITP treated with eltrombopag at Sun Yat-Sen Memorial Hospital, China, between 1 July 2017 and 1 January 2019
- Patients with at least 12 weeks of eltrombopag treatment and follow-up data were included in the analysis
- The starting dose of eltrombopag was 50 mg per day for children aged 6 years or above, and 1.5 mg/kg/d for those aged 1–6 years or weight<27 kg
- Eltrombopag dosing was adjusted to achieve a platelet count goal of 50×10^{9}/L, not to exceed 150×10^{9}/L

Hematology, 26:1, 31-36, DOI:10.1080/16078454.2020.1856511

- The dose could be escalated every 2 weeks in increments of 12.5 mg to achieve the target platelet range (Max dose 75 mg/day)
- The dose was decreased by 12.5 mg once per day at 2-week intervals with a platelet count increase of more than $150 \times 10^{9}/L$
- In case of platelet count increase of more than $400 \times 10^{9}/L$, treatment was interrupted and resumed at the next lower dose based on 12.5 mg increments once the patient's platelet count had decreased to below $150 \times 10^{9}/L$.

Hematology, 26:1, 31-36, DOI:10.1080/16078454.2020.1856511

Efficacy and safety analysis

- **Complete response (CR):** platelet count >100 × 10^{9}/L
- **Partial response (PR):** platelet count at 30–100 ×10^{9}/L, or baseline count doubling after treatment
- **No response (NR):** platelet count less than 30 × 109/L, baseline count doubling, or bleeding events after administration of an appropriate dose of eltrombopag for 12 weeks
- **Overall response rate (ORR):** defined as CR rate + PR rate
- **Relapse** defined as either 2 consecutive platelet counts<30 × 10^{9}/L or need for additional therapy
- **Initial response**, measured at or around the 12-week mark from the first dose
- **Duration of response (DR):** calculated from the date of initial response to relapse or latest follow-up

Hematology, 26:1, 31-36, DOI:10.1080/16078454.2020.1856511

Results

- Median duration of Eltrombopag administration 6 months (range, 3-8)
- 14/30 patients (46.7%) discontinued eltrombopag treatment
- 8/30 (26.7%) discontinued eltrombopag permanently for a platelet count consistently <30 × 10^9/L within the first 12 weeks of treatment
- 4 showed relapse and 2 still kept an effective level after treatment discontinuation

Table 1. Demographic and baseline clinical data of pediatric patients with cITP.

Variables	Eltrombopag (*N* = 30)
Gender [*N*(%)]	
Male	17 (56.7)
Female	13 (43.3)
Age at onset of ITP, years	
Median (range)	5 (1–12)
ITP duration before the first dose, years	
Median (range)	2 (1.0–3.5)
Age at eltrombopag treatment initiation, years	
Median (range)	7 (2.3–14.0)
Median starting dose, mg/Kg.d	
Median (range)	1.5 (1.1–1.8)
Baseline platelet count, × 10^9/L	
Median (range)	15 (7–26)
Number of previous anti-ITP medications	3 (2–4)
Median (range)	
≥2	30 (100)
≥3	7 (23.3)

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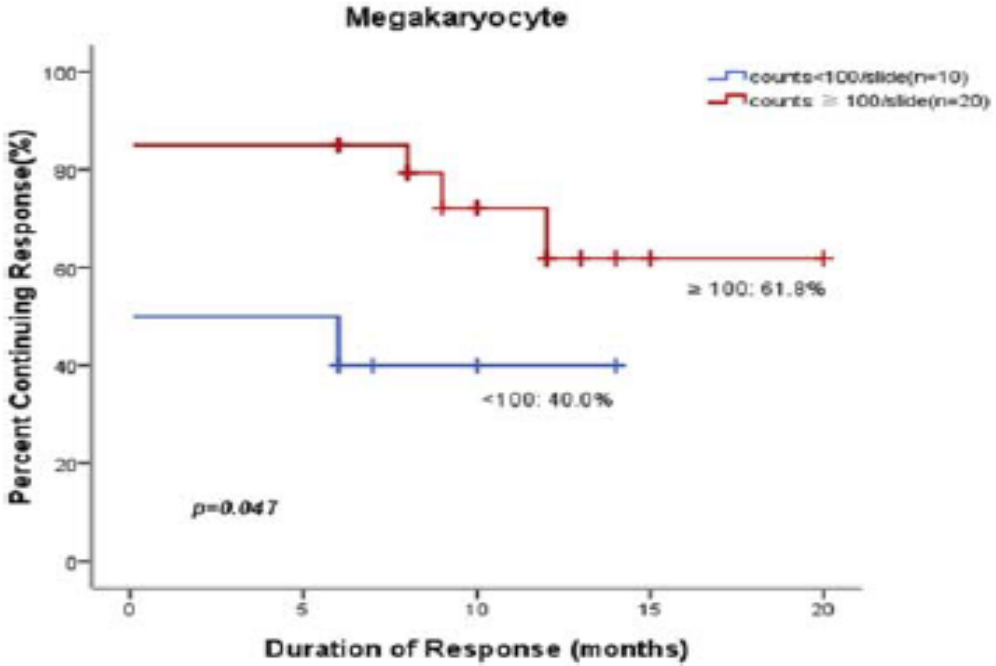

Figure 1. Effects of megakaryocyte count on prognosis after eltrombopag therapy. Patients with megakaryocyte count≥100/slide prior to treatment initiation were more likely to achieve initial response and maintain durable response.

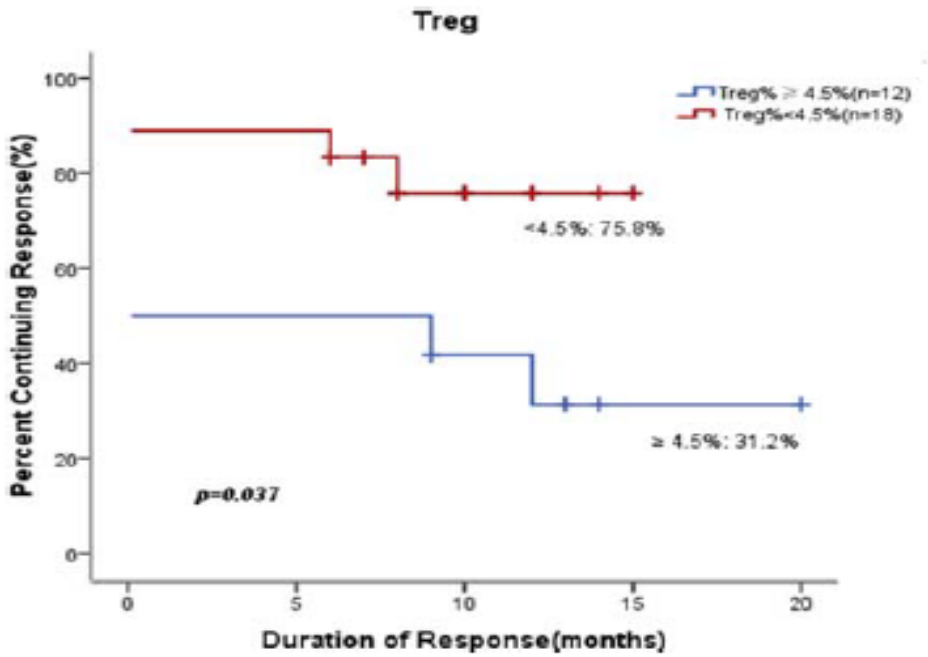

Figure 2. Kaplan-Meier curves of response rates in pediatric patients with cITP based on Treg% at baseline. Treg<4.5% not only predicted higher initial response to the therapy, but also had a significant effect on the likelihood of maintaining remission.

Table 3. Prognostic factors of durable response by multivariable analysis.

	B	SE	Wald	df	Sig	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Megakaryocyte count ≥ 100/slide	1.454	.656	4.921	1	.027	4.281	1.184	15.473
Treg<4.5%	1.471	.651	5.115	1	.024	4.355	1.217	15.589

- 25 (83.3%) of the 30 patients achieved a platelet count of over 50 × 10^9/L at least once in the absence of rescue therapy
- At the end of 12 weeks of treatment, the median platelet count was 78 × 10^9/L (20-310)
- 11/30 patients (36.7%) achieved PR and 11 (36.7%) achieved CR
- The initial response rate (Week 12) was 73.3%
- median follow up time 10 months (6–20 months)
- 18 patients (53.2%) maintained a durable response without additional treatment

Table 2. Initial efficacy data of pediatric patients with cITP treated with eltrombopag.

Variables	Efficacy
Megakaryocyte count ≥ 100/slide, (%)	17/20 (85.0)
Treg<4.5%, (%)	16/18 (88.9)
Male, (%)	12/17 (70.6)
Female, (%)	10/13 (76.9)
Time to first response, median day (range)	14 (7–35)
Platelet count at first response, ×10^9/L, median (range)	70 (40–150)
Maximum platelet count, ×10^9/L, median (range)	110 (60–510)

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Safety

- vomiting (3.3%)
- Mild bleeding (6.7%)
- Transient elevation of transaminases (3.3%)
- No serious adverse events
- No patients withdrew due to adverse events
- No thrombosis or malignancy

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Romiplostim treatment for children with immune thrombocytopenia: Results of an integrated database of five clinical trials

- Pooled analysis combined data from pediatric patients across five clinical trials of romiplostim
- Two completed double-blind, placebo-controlled trials
- two completed open-label extensions
- one ongoing open-label trial

Pediatr Blood Cancer. 2020;67:e28630.

- A double-blind, placebo-controlled phase 1/2 clinical trial
- 22 children with ITP from 10 study centers who were of ages 1-17 years and had ITP for at least 6 months,with an average platelet count of 30 × 109/L or less at screening.
- 8 Patients received romiplostim (n = 17) or placebo (n = 5) weekly for 12 weeks
- Responders (n = 14) received romiplostim weekly for an additional 4 weeks.
- Randomization was stratified by age groups (1-2, 3-11, and 12-17 years).

Pediatr Blood Cancer. 2020;67:e28630.

- A double-blind, placebo-controlled phase 3 clinical trial
- 62 children with ITP from 27 study centers.
- patients ages 1-17 years
- average platelet count of 30 × 10^{9}/L or less.
- Patients entering the phase 3 trial had either received at least one prior therapy for ITP or were ineligible for other ITP therapy.
- Enrolled patients received double-blind romiplostim (n = 42) or placebo (n = 19) weekly for 24 weeks.
- Randomization was stratified by age groups (1 to <6, 6 to <12, 12 to <18 years).

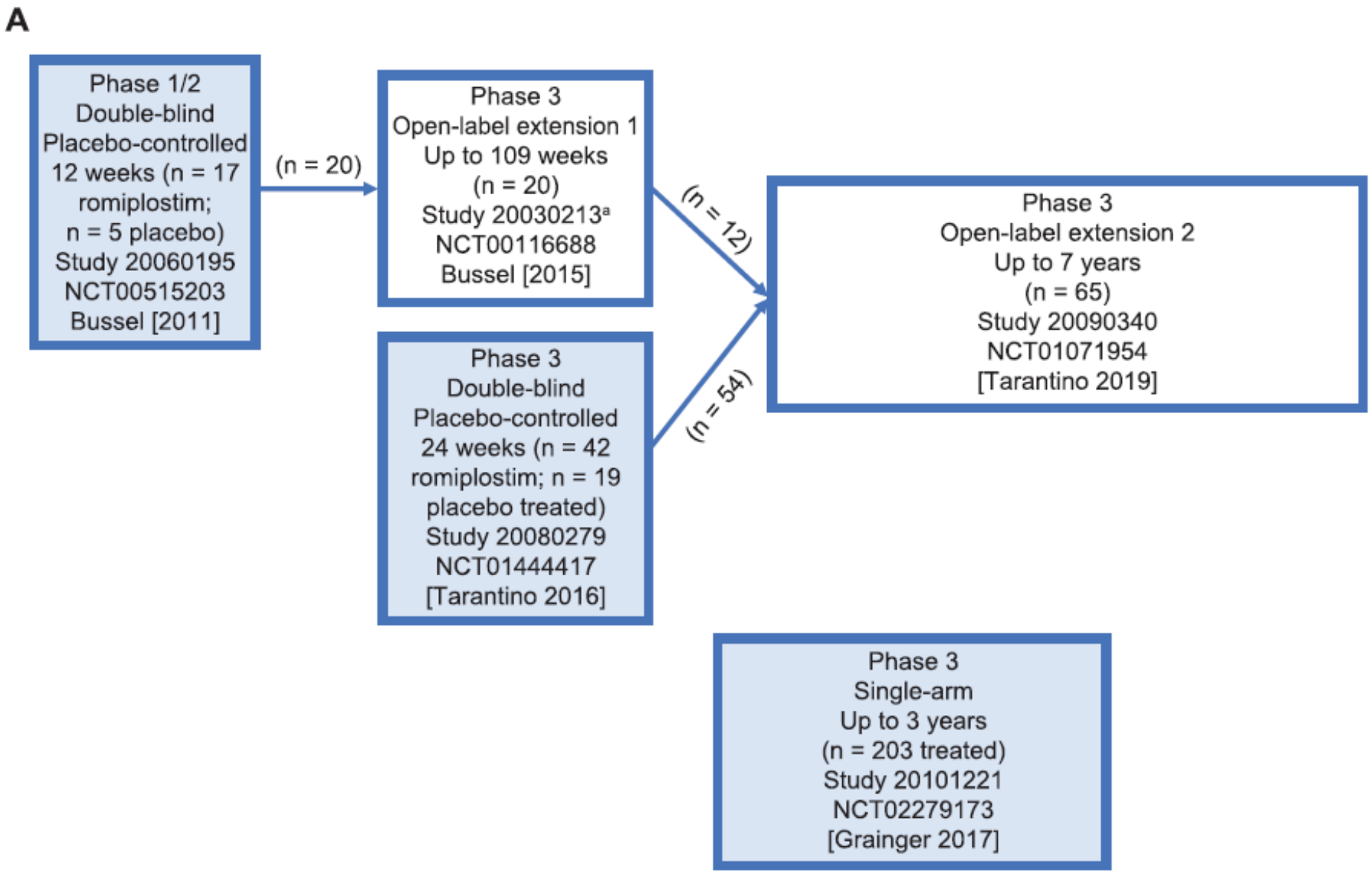
Pediatr Blood Cancer. 2020;67:e28630.

- The first open-label extension enrolled patients (n = 20) who completed the phase 1/2 double-blind clinical trial, regardless of their age at study entry
- The second open-label extension enrolled patients (n = 66) who either rolled over from the first extension (n = 12) or completed the phase 3 double-blind clinical trial (n=54)
- To enter the second extension, patients were required to be 17 years of age upon study entry.
- Patients in each extension received open-label romiplostim: for up to 109 weeks in the first extension, and for up to 7 years in the second extension

Pediatr Blood Cancer. 2020;67:e28630.

- The single-arm open-label trial recruited 204 children in 17 countries who had ITP for at least 6 months, at least one prior ITP therapy, and either a platelet count of 30×10^{9}/L or less at screening or uncontrolled bleeding
- In this ongoing trial, all patients will receive open-label romiplostim for up to 3 years

Pediatr Blood Cancer. 2020;67:e28630.


A
Phase 1/2
Double-blind
Placebo-controlled
12 weeks (n = 17
romiplostim;
n = 5 placebo)
Study 20060195
NCT00515203
Bussel [2011]
(n = 20)
Phase 3
Open-label extension 1
Up to 109 weeks
(n = 20)
Study 20030213[a]
NCT00116688
Bussel [2015]
Phase 3
Double-blind
Placebo-controlled
24 weeks (n = 42
romiplostim; n = 19
placebo treated)
Study 20080279
NCT01444417
[Tarantino 2016]
(n = 12)
(n = 54)
Phase 3
Open-label extension 2
Up to 7 years
(n = 65)
Study 20090340
NCT01071954
[Tarantino 2019]
Phase 3
Single-arm
Up to 3 years
(n = 203 treated)
Study 20101221
NCT02279173
[Grainger 2017]

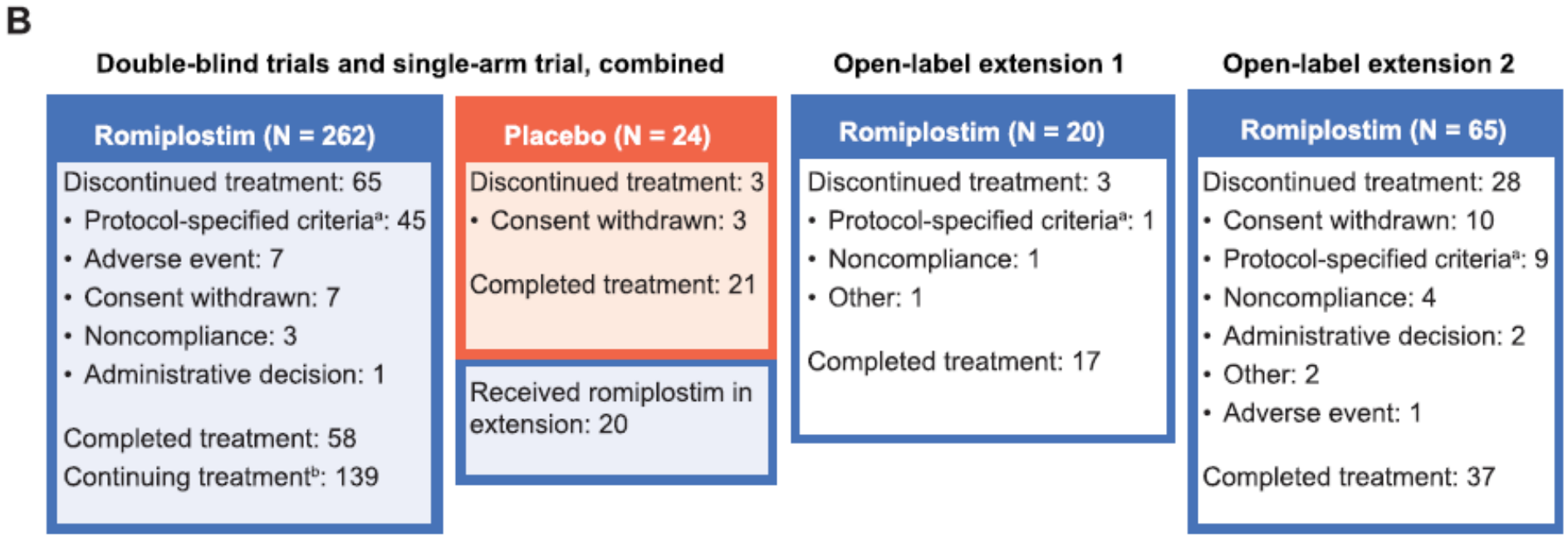


FIGURE 1 A, Romiplostim trials included in pooled analysis; [a]study NCT00116688 also enrolled adults; only pediatric patients from that study were included in this analysis. B, Treatment disposition; [a]included reducing or withholding doses for elevated platelets; [b]the single-arm trial was ongoing at the time of the analysis

Pediatr Blood Cancer. 2020;67:e28630.

TABLE 1 Baseline demographics and disease characteristics

	Any placebo[a] (N = 24)	Any romiplostim[a] (N = 282)	Total (N = 286)
Age group, years, n (%)			
1-5 years	5 (20.8)	65 (23.0)	66 (23.1)
6-11 years	10 (41.7)	114 (40.4)	116 (40.6)
12-17 years	9 (37.5)	103 (36.5)	104 (36.4)
Median [Q1, Q3]	10.5 [6.5, 13.5]	10 [6.0, 13.0]	10.0 [6.0, 13.0]
Sex, n (%)			
Male	11 (45.8)	139 (49.3)	142 (49.7)
Female	13 (54.2)	143 (50.7)	144 (50.3)
Years since ITP diagnosis, median [Q1, Q3]	2.4 [1.5, 4.4]	1.9 [1.0, 4.0]	1.9 [1.0, 4.0]
Age at ITP diagnosis, years, median [Q1, Q3]	6.6 [4.8, 10.2]	6.0 [3.6, 10.2]	6.0 [3.6, 10.2]
Platelet count, $\times 10^9$/L, median [Q1, Q3]	16.2 [8.7, 22.8]	14.3 [7.5, 23.0]	14.3 [7.5, 23.0]
Number of prior ITP treatments, n (%)			
1	5 (20.8)	40 (14.2)	41 (14.3)
2	4 (16.7)	110 (39.0)	111 (38.8)
3	8 (33.3)	64 (22.7)	66 (23.1)
>3	7 (29.2)	67 (23.8)	67 (23.4)

Pediatr Blood Cancer. 2020;67:e28630.

Median [Q1, Q3]	3 [2.0, 4.0]	2 [2.0, 3.0]	2.0 [2.0, 3.0]
Prior ITP treatment(s) received, n (%)			
Corticosteroid	20 (83.3)	249 (88.3)	252 (88.1)
IVIg	22 (91.7)	247 (87.6)	250 (87.4)
Anti-D antibody	10 (41.7)	64 (22.7)	65 (22.7)
Rituximab	11 (45.8)	60 (21.3)	61 (21.3)
Azathioprine	2 (8.3)	23 (8.2)	23 (8.0)
Danazol	1 (4.2)	17 (6.0)	17 (5.9)
Vincristine/vinblastine	1 (4.2)	7 (2.5)	7 (2.4)
Cyclophosphamide	0	1 (0.4)	1 (0.3)
Other	10 (41.7)	93 (33.0)	94 (32.9)
Splenectomized, n (%)	3 (12.5)	20 (7.1)	20 (7.0)
Any bleeding event in prior 30 days, n (%)	18 (75.0)	165 (58.5)	168 (58.7)

Abbreviations: ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin G; Q1, first quartile; Q3, third quartile.

[a]Each treatment group includes 20 patients who received placebo in a double-blind study and then switched to open-label romiplostim in an extension study.

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Results

- The duration of romiplostim treatment ranged from 8 to 471 weeks (median 65 weeks)
- 175/282 patients (62.1%) received romiplostim for more than 48 weeks
- The average weekly dose of romiplostim ranged from 0.1 to 9.7 μg/kg (median 6.6 μg/kg)

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- After starting romiplostim, median platelet counts of the cohort were between 50 × 10^{9}/L and 200 × 10^{9}/L by week 12 and continued through the last assessment
- For romiplostim-treated patients, the first platelet response occurred by a median of 6 weeks (95% CI, 5-6 weeks)
- 252 of 282 patients (89.4%) had a platelet response at least once after starting romiplostim
- two of 24 patients (8.3%) had a platelet response during exposure to placebo

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- The median percentage of months that patients had platelet responses was 75.6% (Q1: 25.0%, Q3: 93.3%)
- For the 47 patients treated with romiplostim for less than 6 months, the median percentage of months that patients had platelet responses was 0% (IQR 16.7%); median follow up 3.68 months
- For patients treated with romiplostim for 6 months to 2 years (n = 167) or greater than 2 years (n = 68), the median percentage of months that patients had platelet responses was 76.5% (IQR 42.9%) and 88.9% (IQR 22.5%), respectively

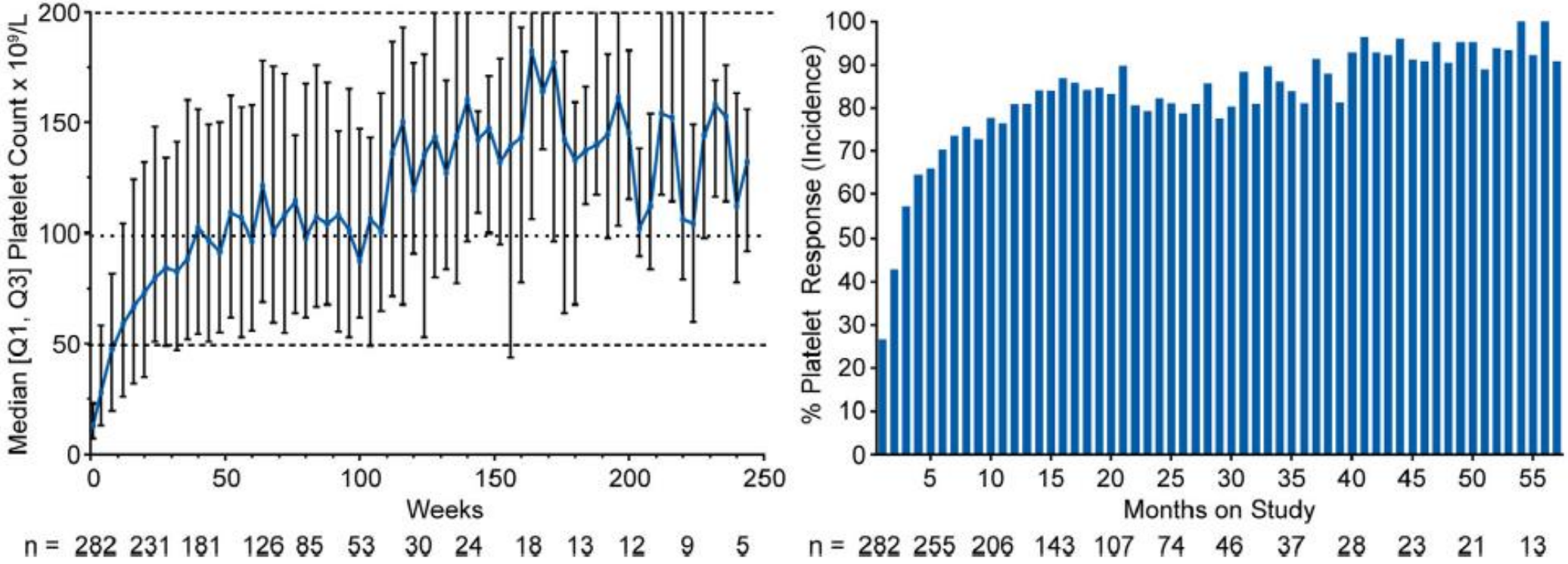

FIGURE 2 Platelet counts and platelet response rates over time after starting romiplostim. Platelet response was defined as a platelet count of at least 50×10^9/L without a rescue medication (intravenous immunoglobulin G, anti-D, platelet transfusion, steroid, or antifibrinolytic) in the prior 4 weeks. Q1, first quartile; Q3, third quartile

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- Nineteen romiplostim-treated patients maintained a treatment-free response for at least 6 months after discontinuation of all ITP therapies, including romiplostim
- The median average weekly dose of romiplostim was lower for patients with a treatment-free response relative to patients without a treatment-free response (4.06 μg/kg [Q1: 1.0, Q3: 4.7] vs 6.57 μg/kg [Q1: 4.4, Q3: 8.1]

TABLE 2 Baseline characteristics of patients with treatment-free response after romiplostim

	Patients with treatment-free response(N = 19)
Age, years, median [Q1, Q3]	7 [3, 12]
Sex, female, n (%)	12 (63.2)
Years since ITP diagnosis, median [Q1, Q3]	1.1 [0.7, 2.9]
Age at ITP diagnosis, years, median [Q1, Q3]	4.6 [1.7, 8.9]
Platelet count, $\times 10^9$/L, median [Q1, Q3]	18 [11, 37.5]
Number of prior ITP treatments, median [Q1, Q3]	3 [1, 4]
>3 Prior ITP treatments, n (%)	7 (36.8)
Prior splenectomy, n (%)	2 (10.5)

Abbreviations: ITP, immune thrombocytopenia; Q1, first quartile; Q3, third quartile.

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Adverse events

	Patient incidence, n (%)		Event rate, # [rate]	
	Placebo (N = 24)	Romiplostim (N = 282)	Placebo10.1 Pt-yr	Romiplostim 467.6 Pt-yr
Overview				
Grade 3 or higher	5 (20.8)	82 (29.1)	12 [119]	255 [55]
Grade 4 or higher	1 (4.2)	19 (6.7)	4 [40]	36 [8]
Any SAE	1 (4.2)	69 (24.5)	2 [20]	150 [32]
Treatment-related SAEs	0	7 (2.5)	0	11 [2]
Any bleeding AE	15 (62.5)	193 (68.4)	115 [1139]	2111 [451]
Led to treatment discontinuation	0	9 (3.2)	0	14 [3]
Fatal AEs	0	0	0	0
Most frequent SAEs (>2%)				
Epistaxis	0	16 (5.7)	0	21 [4.5]
Decreased platelet count	0	7 (2.5)	0	12 [3]
Thrombocytopenia	0	7 (2.5)	0	14 [3]

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Adverse events

Most frequent AEs (>20%)				
Headache	13 (54.2)	114 (40.4)	36 [356]	442 [95]
Epistaxis (bleeding AE)	11 (45.8)	111 (39.4)	20 [198]	394 [84]
Pyrexia	2 (8.3)	89 (31.6)	2 [20]	198 [42]
Nasopharyngitis	3 (12.5)	86 (30.5)	4 [40]	190 [41]
Vomiting	6 (25.0)	81 (28.7)	7 [69]	152 [33]
Contusion (bleeding AE)	8 (33.3)	80 (28.4)	37 [366]	826 [177]
Cough	3 (12.5)	78 (27.7)	4 [40]	180 [39]
Upper respiratory tract infection	6 (25.0)	75 (26.6)	9 [89]	198 [42]
Petechiae (bleeding AE)	7 (29.2)	69 (24.5)	13 [129]	339 [73]
Oropharyngeal pain	1 (4.2)	65 (23.0)	1 [10]	146 [31]
Nausea	7 (29.2)	60 (21.3)	10 [99]	97 [21]
Diarrhea	3 (12.5)	60 (21.3)	3 [30]	120 [26]
Upper abdominal pain	1 (4.2)	58 (20.6)	1 [10]	109 [23]

Note. Exposure-adjusted rates are per 100 patient-years.

Abbreviations: AE, adverse event; ITP, immune thrombocytopenia; Pt-yr, patient-years; SAE, serious adverse event.

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TABLE 4 Antibodies to romiplostim or thrombopoietin

Developed postbaseline antibodies	Placebo (N = 24)n (%)	Romiplostim (N = 282)n (%)
Binding antibody to romiplostim		
Transient	0	9 (3.2)
Persistent	0	11 (3.9)
Neutralizing antibody to romiplostim		
Transient	0 (0.0)	2 (0.7)
Persistent	0 (0.0)	5 (1.8)
Binding antibody to thrombopoietin		
Transient	1 (4.2)	6 (2.2)
Persistent	0 (0.0)	1 (0.4)
Neutralizing antibody to thrombopoietin		
Transient	0 (0.0)	0 (0.0)
Persistent	0 (0.0)	0 (0.0)

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Efficacy and safety of romiplostim in children with chronic and persistent immune thrombocytopenic purpura

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INTRODUCTION

Romiplostim is a thrombopoietin receptor agonist (TPO-RA) which has recently been approved for treatment of immune thrombocytopenic purpura (ITP) in children.

AIM

We tried to investigate the efficacy and safety of romiplostim in a heterogeneous group of children with persistent and chronic ITP and acquired aplastic anemia.

METHOD

We enrolled 14 patients with the following diagnoses: chronic ITP (n=10), persistent ITP (n=3) and acquired aplastic anemia (n=1). Romiplostim dose was adjusted according to the issued treatment guideline (1). The patients were followed for 26 weeks.

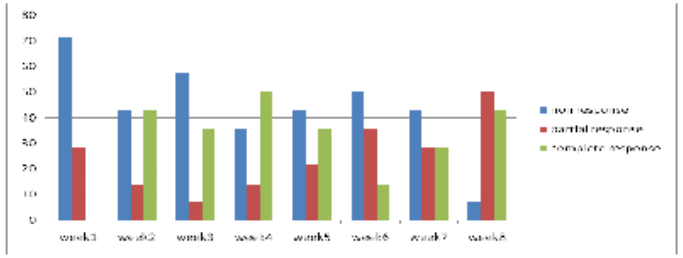
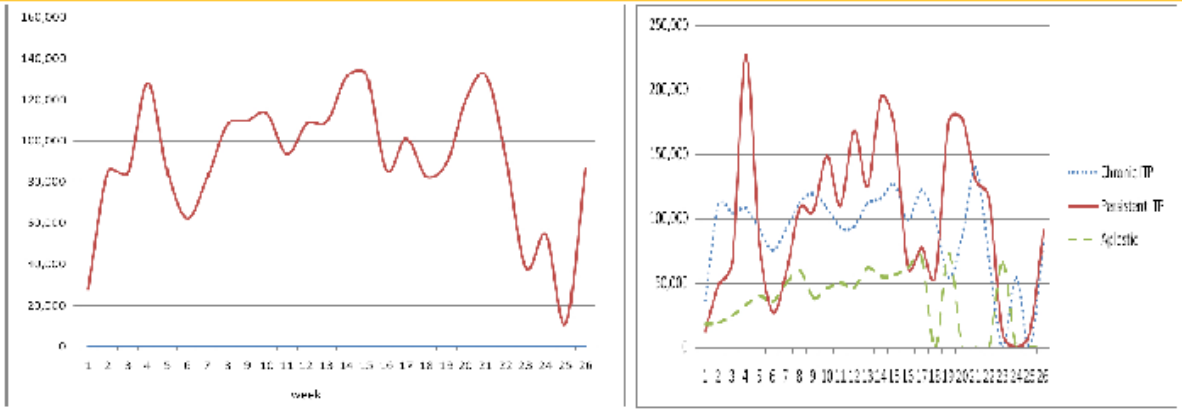


Fig. 1- Treatment response in the first 8 weeks of Romiplostim injection

RESULTS

Mean baseline platelet count was 26714± 15774 (range 6000-49000). The mean treatment duration was 22.2± 5.5 weeks (range 8-26 weeks). Totally, 63% ± 24.7% (range 12.5-95.2%) of the patients showed partial or complete response (Table 1). The overall response was comparable in the 3 treatment categories (P=0.71). Figure-1 demonstrates treatment response in the first 8 weeks of Romiplostim injections. The trend of changes in platelet counts during the 26 weeks of patients' follow up are demonstrated in Figure 2.

There was no severe adverse effects during the intervention period. One patient reported headache and body pain in the first week of treatment, which was treated with oral analgesic.



2a 2b

Fig. 2- The trend of platelet counts in the study population (a) and in the 3 treatment categories (b)

Table 1. platelet response to romiplostim injection in the study population

Diagnosis	Mean (SD)	Range
Chronic ITP (n=10)		
no response	35.3 (28.3)	(4.5-87.5)
partial response	27.8 (14.9)	(0.0-47.9)
complete response	36.9 (25.3)	(0.0-76.2)
overall response	64.7 (28.3)	(12.5-95.2)
Persistent ITP (n=3)		
no response	35.4 (11.8)	(21.8-43.5)
partial response	20.5 (8.9)	(13.0-30.4)
complete response	44.1 (3.5)	(40.9-47.8)
overall response	64.6 (11.8)	(56.5-78.2)

Data are shown as percentages.
Partial response: platelet count 50 100×10^9 µ/L ; Complete response: platelet count more than 100×10^9 µ/L; Overall response: platelet count more than 50×10^9 µ/L

CONCLUSIONS

We observed that about 65% of patients with chronic or persistent ITP responded to romiplostim, which is very close to 73% response rate reported by the Pediatric ITP Consortium of North America (ICON2) study (2). Although Romiplostim has not been approved for treatment of severe aplastic anemia, we observed that our case showed partial response in 42% of observations. A larger longitudinal study is advised to elucidate the durability of response and safety of this drug in patients with ITP and aplastic anemia.

REFERENCES

1. Neunert CE, Rose MJ. Romiplostim for the management of pediatric immune thrombocytopenia: drug development and current practice. Blood advances 2019;3(12):1907-1915.

2. Neunert C, Despotovic J, Haley K, Lambert MP, Nottage K, Shimano K, et al. Thrombopoietin Receptor Agonist Use in Children: Data from the Pediatric ITP Consortium of North America ICON2 Study. Pediatr Blood Cancer. 2016 ; 63(8): 1407–1413

Results

- Mean baseline platelet count was 26714± 15774 (range 6000-49000)
- The mean treatment duration was 22.2± 5.5 weeks (range 8-26 weeks).
- 63± 24.7% (range 12.5-95.2%) of the patients showed partial or complete response
- The overall response was comparable in the 3 treatment category (P=0.71).
- There was no severe adverse effect during the intervention period. One patient reported headache and body pain in the first week of treatment which was treated with oral analgesic.

Table 1. platelet response to romiplostim injection in the study population

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overall response	64.6 (11.8)	(56.5-78.2)

Data are shown as percentages.
Partial response: platelet count 50-100×10^9 µ/L ; Complete response: platelet count more than 100×10^9 µ/L; Overall response: platelet count more than 50×10^9 µ/L

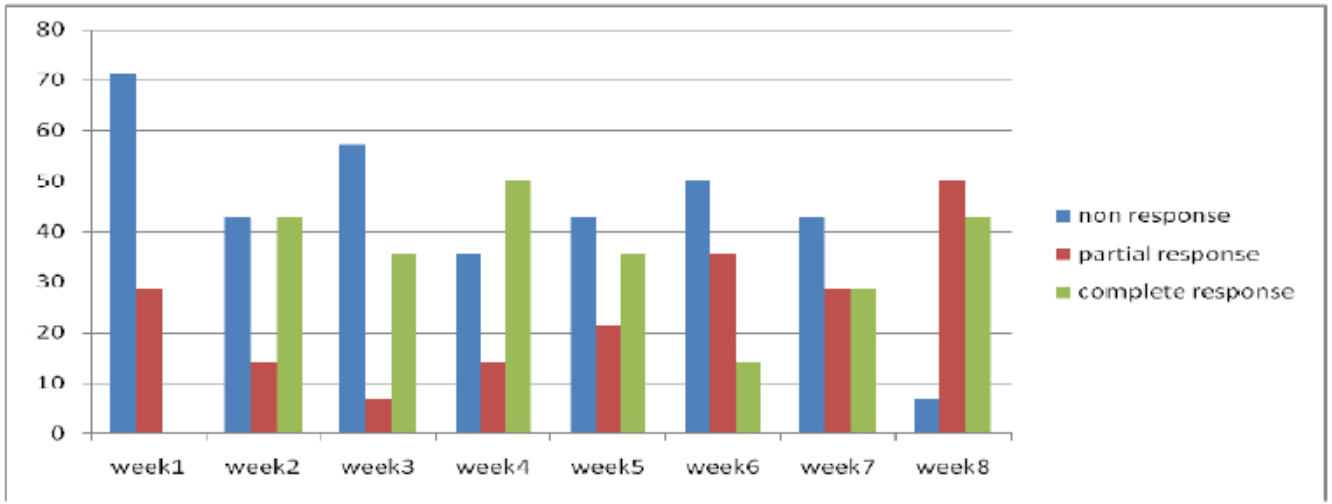
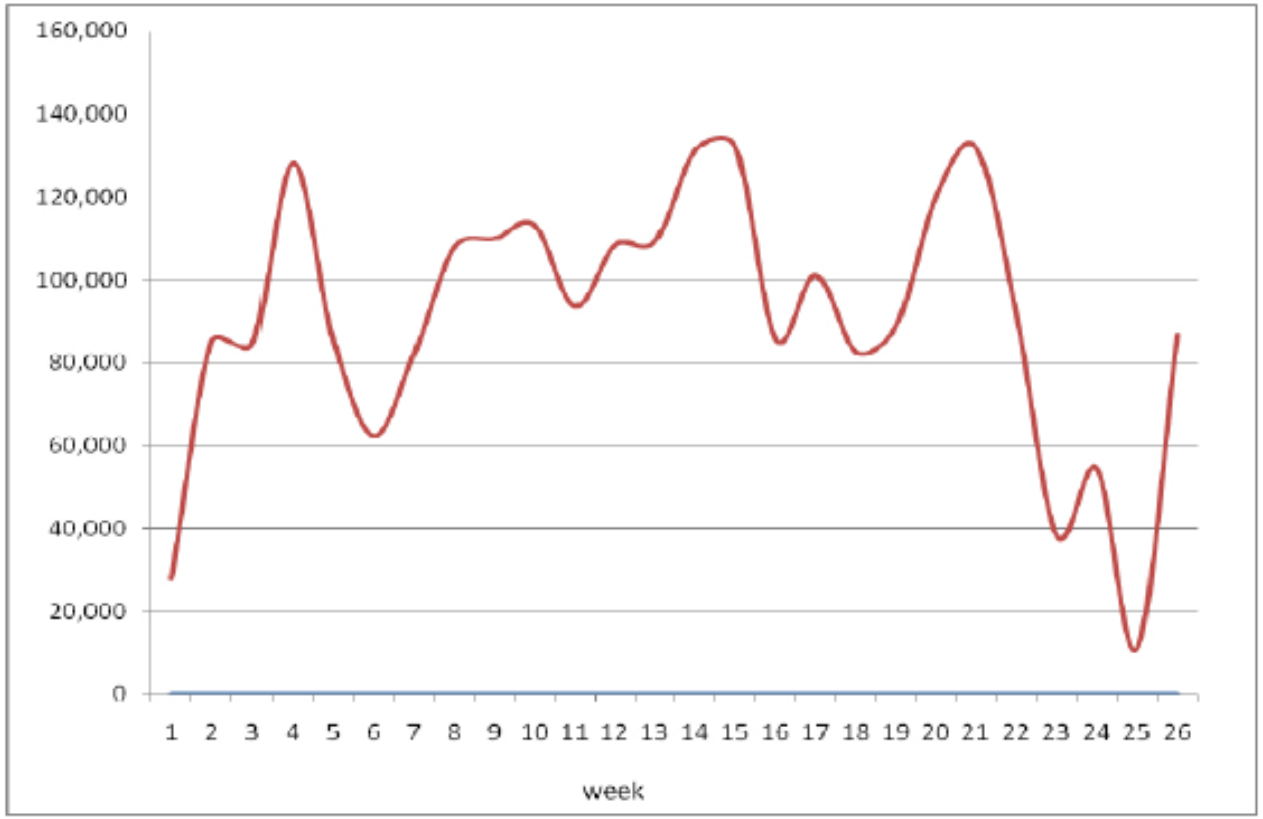
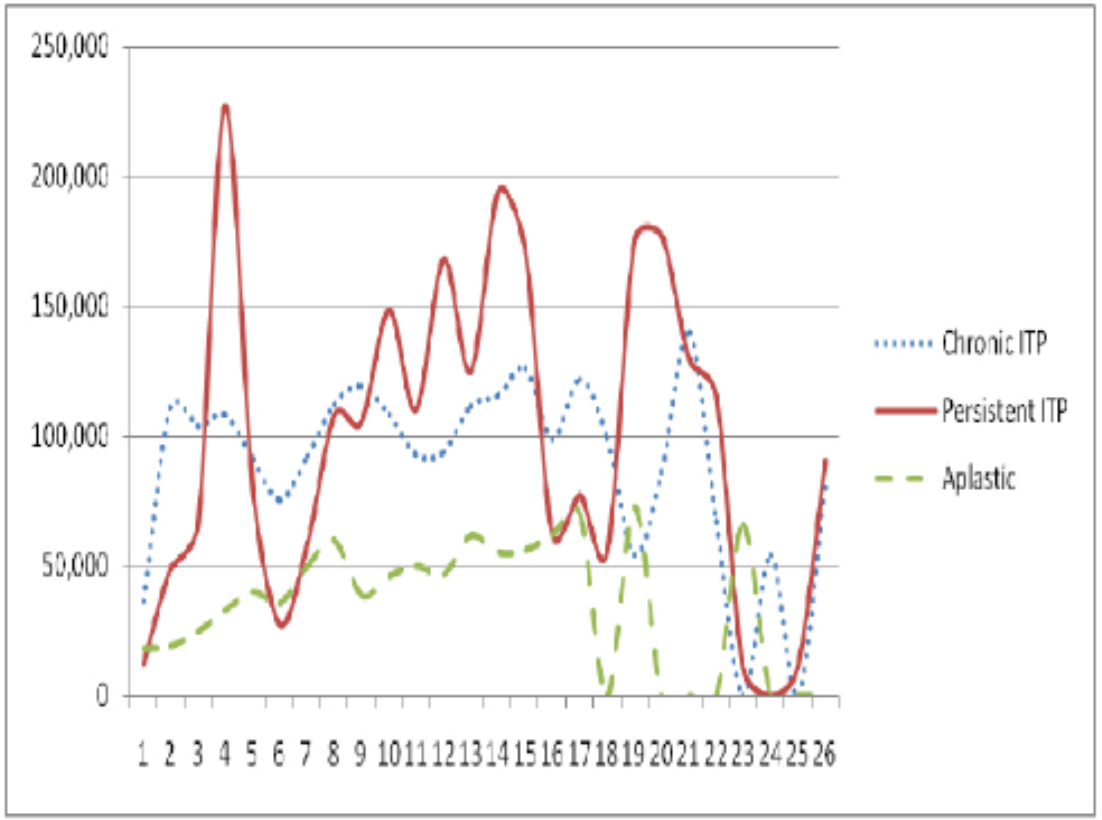


Fig. 1- Treatment response in the first 8 weeks of Romiplostim injection



2a



2b

Fig. 2- The trend of platelet counts in the study population (a) and in the 3 treatment categories (b)

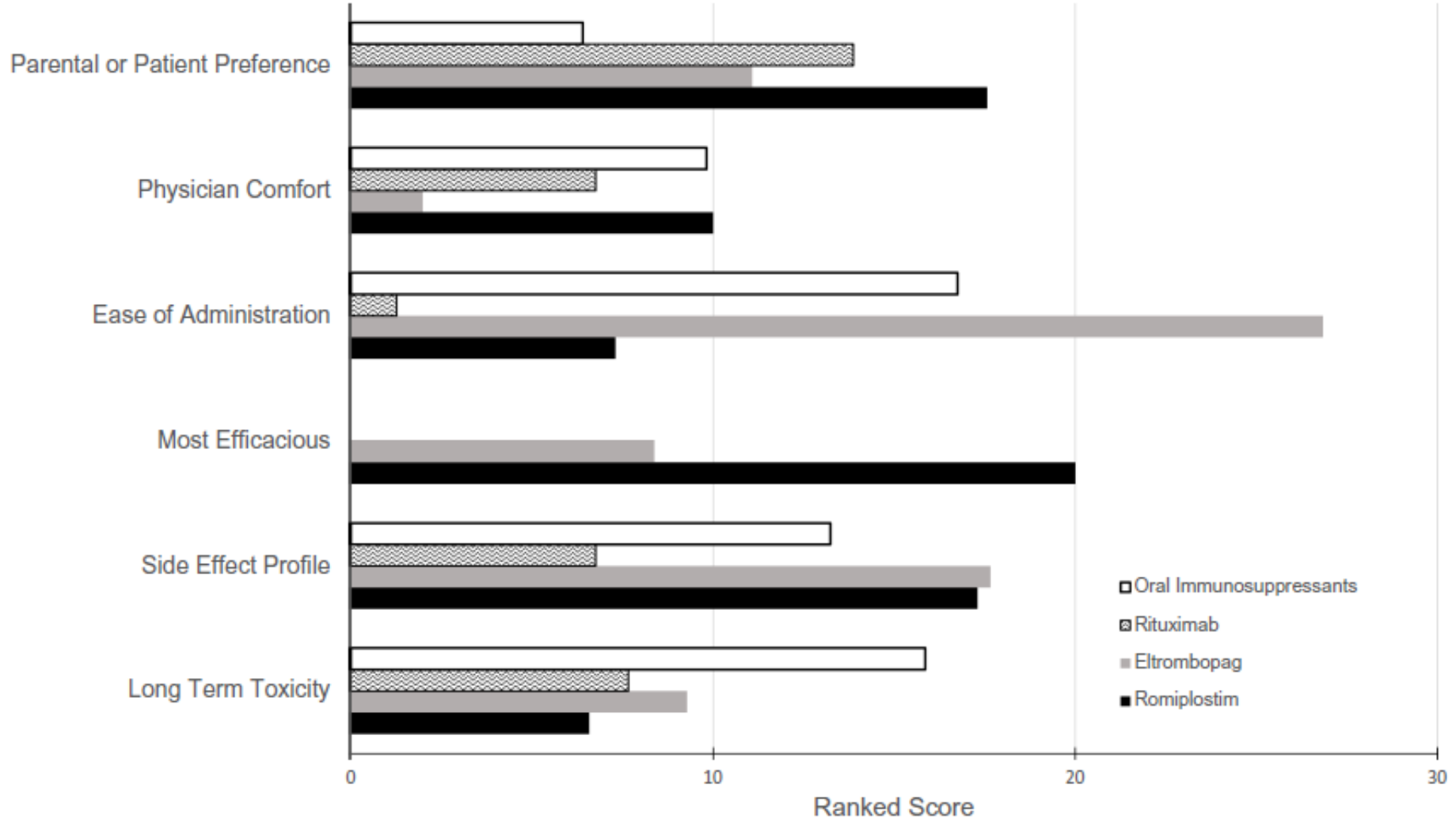


Figure 3 Selected factors affecting physician choice of second-line therapy at ICON treatment sites. Weighted scores were assigned to reasons for physician choice within individual therapies. Equal length bars indicate the reason was equally ranked for each treatment. Adapted with permission from Grace RF, Despotovic JM, Bennett CM, et al. Physician decision making in selection of second-line treatments in immune thrombocytopenia in children. *Am J Hematol*. 2018;93(7):882–888e. © 2018 Wiley Periodicals, Inc.[59]

Table 1 Comparing TPO-RAs

Medication	Route	Frequency	Special Considerations	Average Wholesale Price for 30 Days[a]
Romiplostim	Subcutaneous	Once weekly	• Weekly medical visits for dose titration • Lack of universal availability for home administration	$4460 to $17,840 depending on vial size
Eltrombopag	Oral	Once daily	• Powder preparation for reconstitution recently available • Frequent lab visits during dose titration • Significant dietary restrictions due to interaction with divalent cations • Potential for iron chelation • Hepatotoxicity	$5910 to $32,095 depending on tablet strength
Avatrombopag	Oral	Once daily	• No liquid preparation or powder for reconstitution available • Frequent lab visits during dose titration • No dietary restrictions • No data available in children	$1425 to $21,384 depending on dose and frequency

Note: [a]Average wholesale price (AWP) as reported on Lexicomp.[62]

Targeted therapies

- **CTLA-4 haploinsufficiency and LRBA deficiency:**

➢ Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is constitutively expressed on regulatory T cells and inhibits T cell activation

➢ LPS-responsive beige-like receptor anchor protein (LRBA) is thought to be a regulator of CTLA-4 function

➢ Both CTLA-4 haploinsufficiency and LRBA deficiency lead to abnormal activation and proliferation of T cells resulting in loss of immune tolerance

Ann Blood 2021;6:4 | http://dx.doi.org/10.21037/aob-20-96

- Patients have other features including recurrent infections, hypogammaglobulinemia, and lymphocytic infiltration of multiple organ systems
- chronic ITP patients with additional features of immune dysregulation
- **Abatacept**, a fusion protein comprised of the extracellular domain of CTLA-4 bound to IgG1, restores CTLA-4 and ameliorates symptoms of autoimmunity

1. Ann Blood 2021;6:4 | http://dx.doi.org/10.21037/aob-20-96; 2. J Allergy Clin Immunol 2016;137:327-30

PI3Kδ syndrome

- Gain-of-function mutations in PI3Kδ lead to activation of the mTOR pathway and, though Akt phosphorylation may promote effector T cell development
- children age 1 to 7 years of age
- autoimmune cytopenias, lymphadenopathy, hepatosplenomegaly and immunodeficiency
- Sirolimus (mTOR inhibitor)
- Leniolisib (a selective PI3Kδ inhibitor) is currently in clinical trials

1. J Allergy Clin Immunol 2017;139:597-606.e4.; 2. Blood 2017;130:2307-16.

STAT1 and 3 gain-of-function

- Excess STAT1 signaling results in skewed Th17 differentiation and hyperresponsiveness to IFN-γ
- autoimmunity and chronic mucocutaneous candidiasis
- Janus kinase (JAK) recruit STATs, leading to signal transduction
- **Ruxolitinib** (JAK inhibitor)
- Excess STAT3 activation leads to suppressed apoptosis via cytokine signaling, including IL-6
- **Tocilizumab** (IL-6 inhibitor)
- **ABT-737** targets anti-apoptotic protein Bcl2

1. J Clin Immunol 2018;38:589-601; 2. Clin Immunol 2017;181:32-42

Potential future pediatric therapies

- A transcytosis receptor, the neonatal Fc receptor (FcRn) regulates circulating IgG
- Inhibition of the FcRn, results in increased lysosomal IgG degradation and subsequently decreases serum IgG levels
- **Efgardigomod** and **rozanolixizumab** are both novel FcRn receptor antagonists
- Phase 2 trials of efgardigomod, a weekly intravenous infusion, showed efficacy and favorable side effect profiles in adults with refractory ITP
- Rozanolixizumab, a subcutaneous injection, raised platelet counts and decreased IgG levels with minimal side effects in phase 2 trials of adult ITP patients with multiply refractory disease

1. Am J Hematol 2020;95:178-87; 2. Blood Adv 2020;4:4136-46.

- **Avatrombopag**
- An oral TPO-RA first approved in adults with ITP and chronic liver disease
- Adults with chronic ITP who failed prior therapies (June 2019)
- No dietary restrictions that accompany eltrombopag
- A pediatric clinical trial is running (NCT04516967)

https://www.globenewswire.com/news-release/2019/06/27/1875237/0/en/Dova-Pharmaceuticals-Announces-FDA-Approval-of-Supplemental-New-Drug-Application-for-DOPTELET-avatrombopag-for-Treatment-of-Chronic-Immune-Thrombocytopenia-ITP.

- **Fostamatinib**
- A spleen tyrosine kinase (SYK) inhibitor which inhibits Fc receptor mediated platelet destruction
- Approved in 2018 for use in refractory adult ITP patients.
- A phase III study in multiply refractory adult chronic ITP patients demonstrated 43% of patients achieved a platelet count of ≥50,000/μL at 3 months
- Due to concerns on effects on cartilage in growing children, it has yet to be studied in pediatrics

Am J Hematol 2018;93:921-30

Thanks for your attention