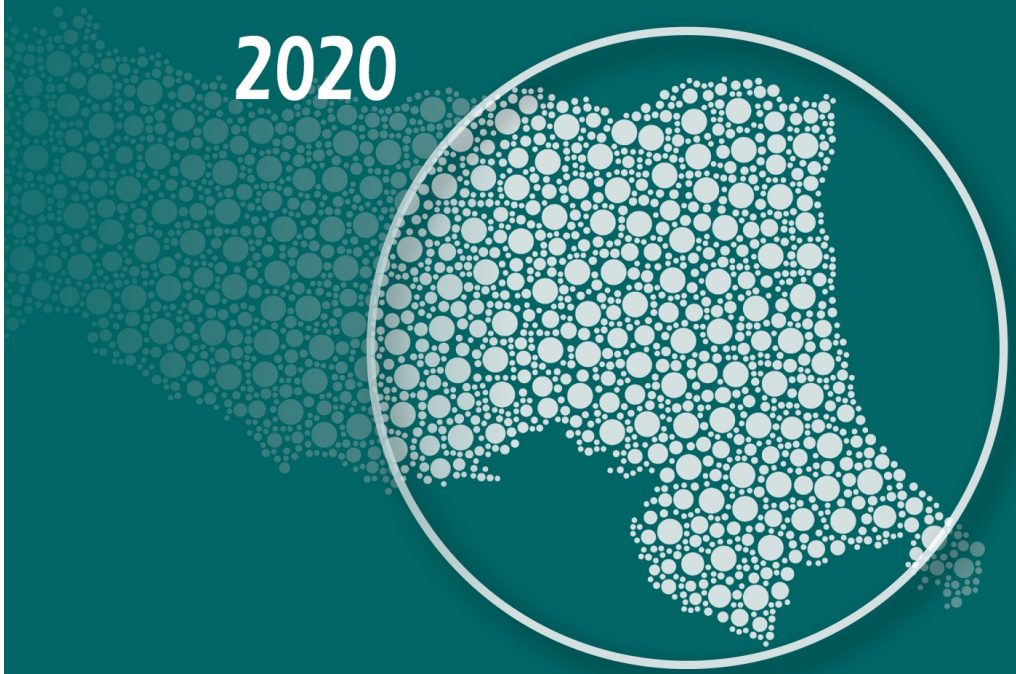


Progetto
Ematologia
Romagna

Piastrinopenia Immune

Marco Ruggeri

Dott. Marco Ruggeri

Non presenti conflitti di interesse

2020 ITP: Immune ThrombocytoPenia

- Autoimmune disease, characterized by a low platelet count (< 100 x 10^9/L)
- It causes bleeding (skin and mucosa) in ~ 2/3 patients
- Prevalence ~10 x 10^5; incidence ~1.5 - 4 x 10^5/year
- Adult present a chronic course (80% > 1 year)
- It is a diagnosis of exclusion (to rule out thrombocytopenia secondary to drug, DIC, vitamins deficit, congenital syndromes, spleen sequestration, bone marrow disorders)

Rodeghiero F et al; Blood. 2009

ITP: Immune ThrombocytoPenia

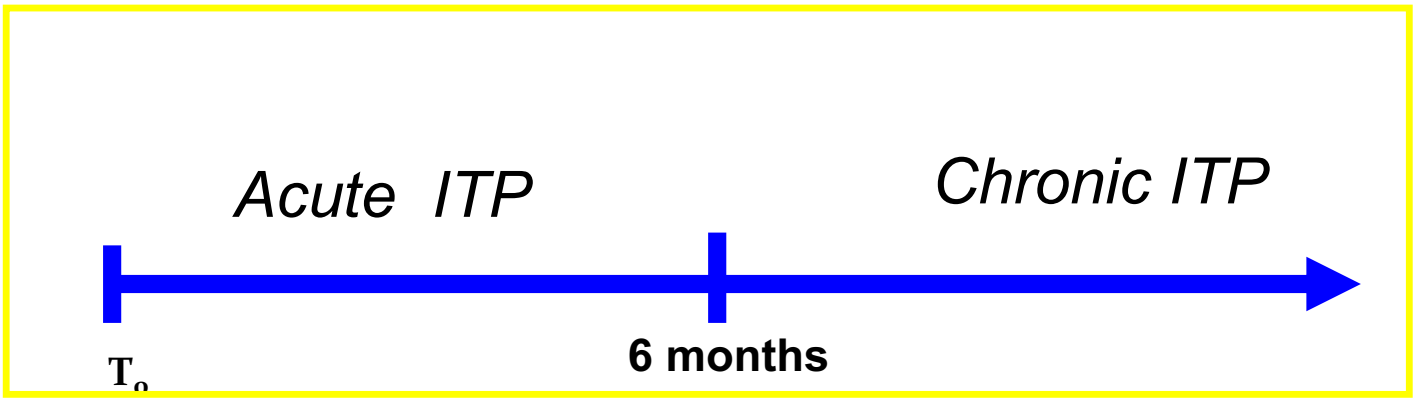
- Secondary ITP refers to autoimmune thrombocytopenia occuring in other diseases (infections, autoimmune diseases, hematological malignancies)

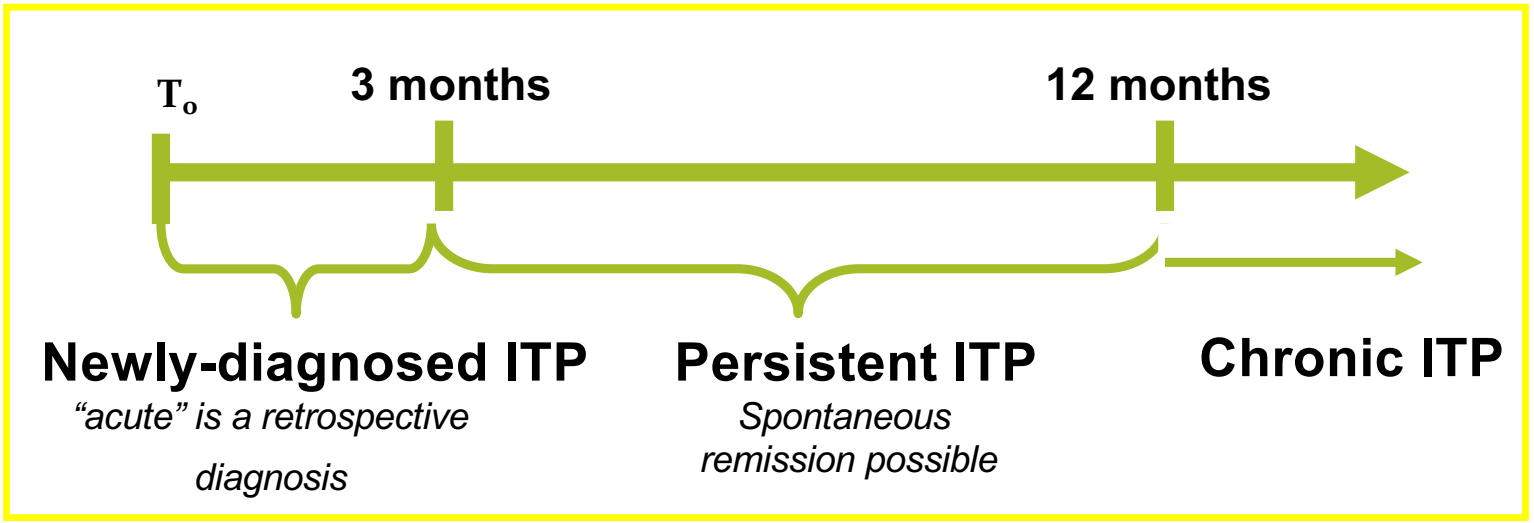
- ITP nomenclature:

✓ **newly – diagnosed** from 0 to 3 months
✓ **persistent** from 4 to 12 months
✓ **chronic** > 12 months
✓ **refractory ITP**: risk of bleeding or hemorrhage despite splenectomy
✓ **severe ITP**: presence of bleeding requiring treatment or therapy modification

Rodeghiero F et al; Blood. 2009

ITP: phases of the disease



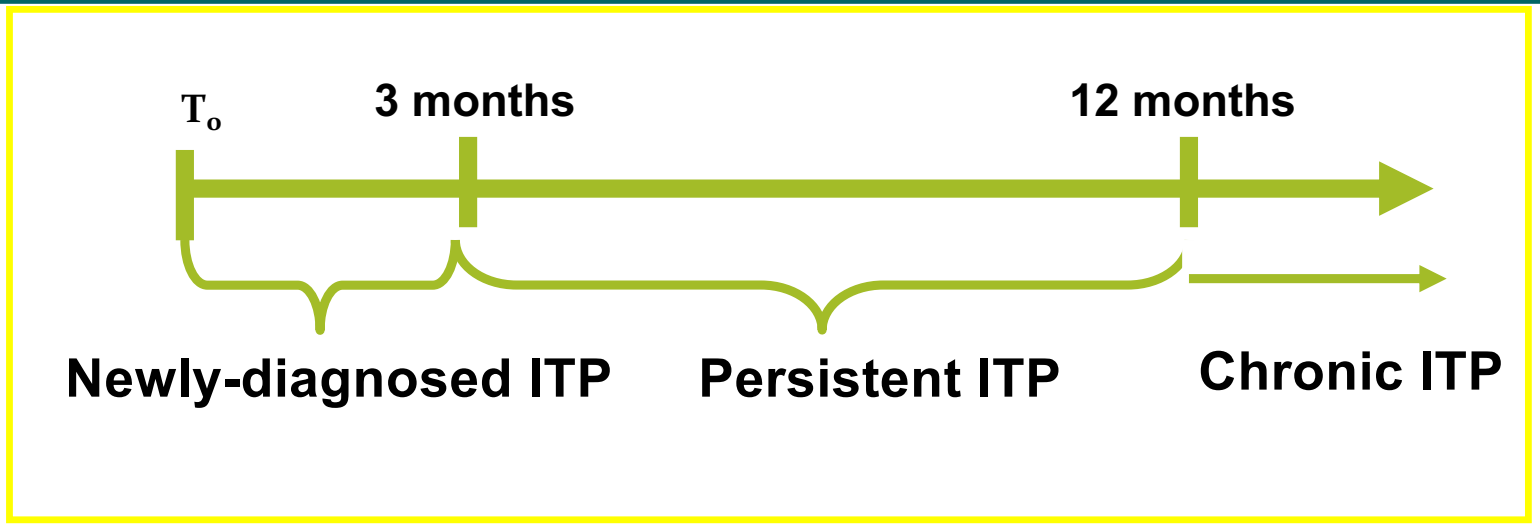


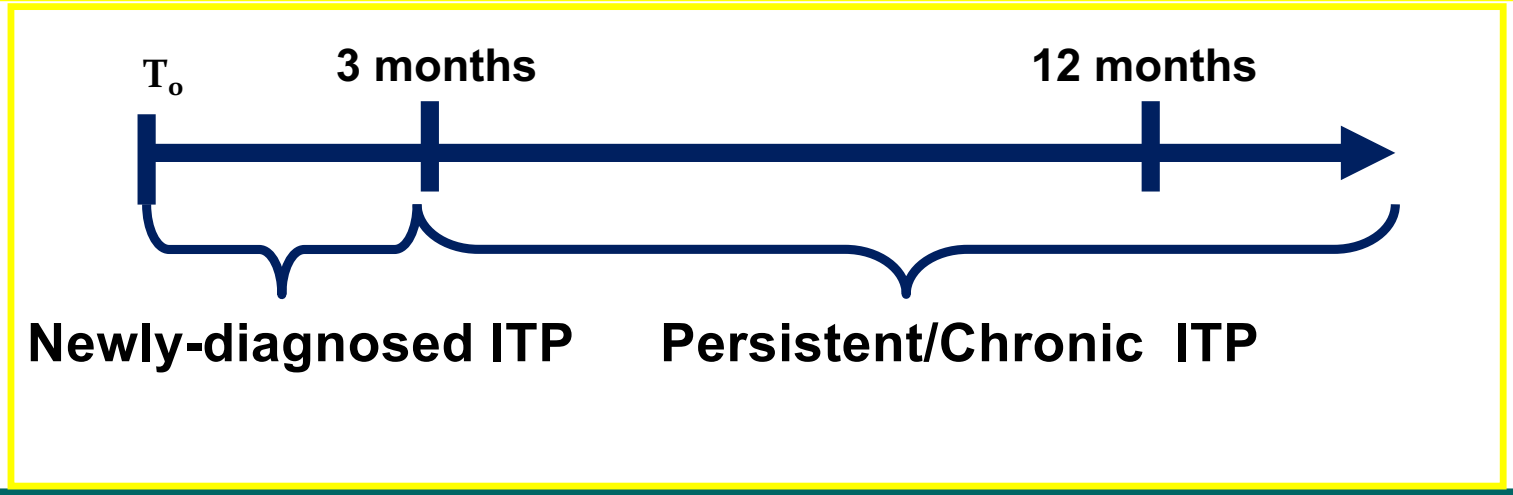
Rodeghiero F et al, Blood. 2009

Therapeutic goals

Phase of disease	Aim of treatment
Initial treatment	Obtain a safe platelet count (rapidly) to reduce bleeding or bleeding risk
Persistent disease	Defer/avoid toxic Immunosuppression or splenectomy
Chronic disease	Curative aim
Refractory patients (after splenectomy)	Minimize the risk of bleeding; to increase the PLT count is not the main goal

ITP: phases of the disease





Therapeutic goals

Phase of disease	Aim of treatment
Initial treatment	Obtain a safe platelet count (rapidly) to reduce bleeding or bleeding risk
Persistent/Chronic disease	"Personalized" treatment
Refractory patients (after ????)	Minimize the risk of bleeding; to increase the PLT count is not the main goal

2020

CLINICAL GUIDELINES

blood advances

10 DECEMBER 2019 • VOLUME 3, NUMBER 23

American Society of Hematology 2019 guidelines for immune thrombocytopenia

Cindy Neunert,[1] Deirdra R. Terrell,[2] Donald M. Arnold,[3,4] George Buchanan,[5] Douglas B. Cines,[6] Nichola Cooper,[7] Adam Cuker,[8] Jenny M. Despotovic,[9] James N. George,[2] Rachael F. Grace,[10] Thomas Kühne,[11] David J. Kuter,[12] Wendy Lim,[13] Keith R. McCrae,[14] Barbara Pruitt,[15] Hayley Shimanek,[16] and Sara K. Vesely[2]

REVIEW ARTICLE

blood advances

26 NOVEMBER 2019 • VOLUME 3, NUMBER 22

Updated international consensus report on the investigation and management of primary immune thrombocytopenia

Drew Provan,[1] Donald M. Arnold,[2] James B. Bussel,[3] Beng H. Chong,[4] Nichola Cooper,[5] Terry Gernsheimer,[6] Waleed Ghanima,[7,8] Bertrand Godeau,[9] Tomás José González-López,[10] John Grainger,[11] Ming Hou,[12] Caroline Kruse,[13] Vickie McDonald,[14] Marc Michel,[9] Adrian C. Newland,[1] Sue Pavord,[15] Francesco Rodeghiero,[16] Marie Scully,[17] Yoshiaki Tomiyama,[18] Raymond S. Wong,[19] Francesco Zaja,[20] and David J. Kuter[21]

ASH 2019 Guidelines

From «Clinical Questions» (PICO format) to recommedations, through evidence synthesis (systematic review) and evidence to decision (resources, feasibility, patient value and preferences)

Work wholly funded by ASH

Do not cover emergent treatment and ITP therapies introduced after 2017

No assessment of «third-line» agents
- lack of data
- variable outcome
- no manner to compare

Definition of:
- Steroide dependance
- Response
- Bleeding severity

IWG 2019 Guidelines

Literature search of PUBMED in July 2018

Grading of evidence

Consensus among experts

Work supported by unrestricted educational grants from 3 pharmaceutical companies

ASH guidelines

1. Should steroids or observation be used for adult newly diagnosed ITP and platelet count **<** 30 x 10^9/L who are asymptomatic or have minor bleeding ?

STEROIDS SUGGESTED

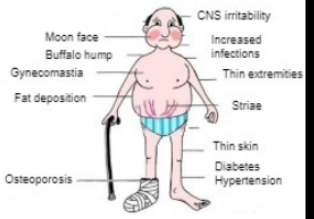
- ✓ observation may be appropriate for a subset of patients
- ✓ consideration to the severity of thrombocytopenia, use of antiplatelet/anticoagulation, need of procedures, age
- ✓ admission to the hospital if platelet count < 20 x 10^9/L (outpatient-management if an established ITP diagnosis)

2. Should steroids or observation be used for adult newly diagnosed ITP and platelet count **≥** 30 x 10^9/L who are asymptomatic or have minor bleeding ?

STEROIDS NOT RECOMMENDED

- ✓ steroid may be appropriate for elderly patients (> 60 year old)
- ✓ consideration to the severity of thrombocytopenia, use of antiplatelet/anticoagulation, need of procedures, age

Good Practice



- The panel agreed that best practice is to ensure adequate follow-up for potential corticosteroid side effects.
- This includes close monitoring for hypertension, hyperglycemia, sleep and mood disturbances, gastric irritation or ulcer formation, glaucoma, and osteoporosis.
- Given the neurotoxicity and impact of corticosteroids on mental health, the panel also encouraged assessment of HRQoL (depression, fatigue, mental status etc.) while patients are receiving corticosteroids.

Inpatient Versus Outpatient Management

- The need for admission is variable across the range of platelet counts in these recommendations (0-20 x 10^9/l and 20-150 x 10^9/l)
- Hospitalization should be considered for patients:
  - Who are refractory to treatment
  - There is uncertainty about the diagnosis
  - Those with significant comorbidities for bleeding risk
  - With more serious mucosal bleeding
  - With social concerns
- Patients not admitted to the hospital should receive education

Good Practice Statement: Ensure follow up with a hematologist within 24-72 hours of diagnosis

Duration and type of corticosteroids in newly diagnosed ITP

High-dose dexamethasone compared with prednisone for previously untreated primary immune thrombocytopenia: a systematic review and meta-analysis

Siraj Mithoowani, Kathleen Gregory-Miller*, Jennifer Goy, Matthew C Miller, Grace Wang, Nastaran Noroozi, John G Kelton, Donald M Arnold*

Summary

Background Whether high-dose dexamethasone has long-term efficacy and safety in previously untreated patients with immune thrombocytopenia is unclear. We did a systematic review and a meta-analysis of randomised trials to establish the effect of high-dose dexamethasone compared with prednisone for long-term platelet count response.

Lancet Haematol 2016; 3: e489–96

Published Online

	n	Mean age (years)	Female sex (%)	Disease stage	Median duration of follow-up	Dexamethasone (40 mg/day for 4 days)	Prednisone (1 mg/kg per day)	Long-term response	Initial response
Wei (2015)[7]	192	44 (18–75)	136/192 (71%)	Newly-diagnosed	5 months	1 or 2 cycles*	28 days	6 months	10 days or 28 days†
Bae (2010)[19]	151	44 (··)	105/151 (70%)	Newly-diagnosed	··	1 or 2 cycles‡	28 days	6 months	7 days
Din (2014)[20]	94	30 (16–64)	50/90 (56%)	Newly-diagnosed	16 months	3 cycles§	28 days	6 months	14 days
Mashhadi (2012)[21]	60	26 (18–48)	47/60 (78%)	Newly-diagnosed	·· (range 12–48 months)	1 cycle	28 days	6 months	7 days
Praituan (2009)[22]	36	42 (··)	28/36 (78%)	Newly-diagnosed‖	6 months	1 cycle, followed by prednisolone 30 mg per day for 10 days	14 days¶	··	5 days

Data are mean (range) or n/N (%). Prednisone dosing does not include dose tapering. *Second cycle of dexamethasone was given if there was no response by day 10. †Initial response was assessed within 10 days in the dexamethasone group and within 28 days in the prednisone group. ‡Second cycle of dexamethasone was given if there was no response by 6 months. §With or without maintenance dexamethasone 0·035 mg/kg per day between 14 day cycles and for 3 months after the last cycle. ‖Five of 36 patients had relapsed.

Table 1: **Randomised trials of high-dose dexamethasone versus prednisone in adults**

	n	Control group	Experimental group
Bellucci (1988)[23]	207 adults; 143 children	Standard-dose prednisone 1·0 mg/kg per day for 3 weeks	Low-dose prednisone 0·25 mg/kg per day for 3 weeks
Mazzucconi (1985)[24]	69 adults; 61 children	Standard-dose prednisone 1·5 mg/kg per day until positive response	Low-dose prednisone 0·5 mg/kg per day until positive response
Fujisawa (2000)[26]	0 adults, 87 children	High-dose prednisone 2·0 mg/kg per day for 14 days	High-dose intravenous methylprednisolone 5·0 mg/kg per day for 5 days or 30·0 mg/kg per day for 3 days
Albayrak (1994)[25]	0 adults, 38 children	High-dose oral methylprednisolone 30·0 mg/kg per day for 7 days	High-dose oral methylprednisolone 50·0 mg/kg per day for 7 days

High dose was classified as greater than or equal to 2·0 prednisone equivalent units per day (ie, ≥2 mg/kg of prednisone per day). Standard dose was classified as >0·5 to <2·0 prednisone-equivalent units (eg, 1 mg/kg of prednisone per day); low dose was classified as less than or equal to 0·5 prednisone-equivalent units per day.

Table 2: **Randomised trials of different corticosteroid regimens in adults and children**

ASH-ITP newly diagnosed

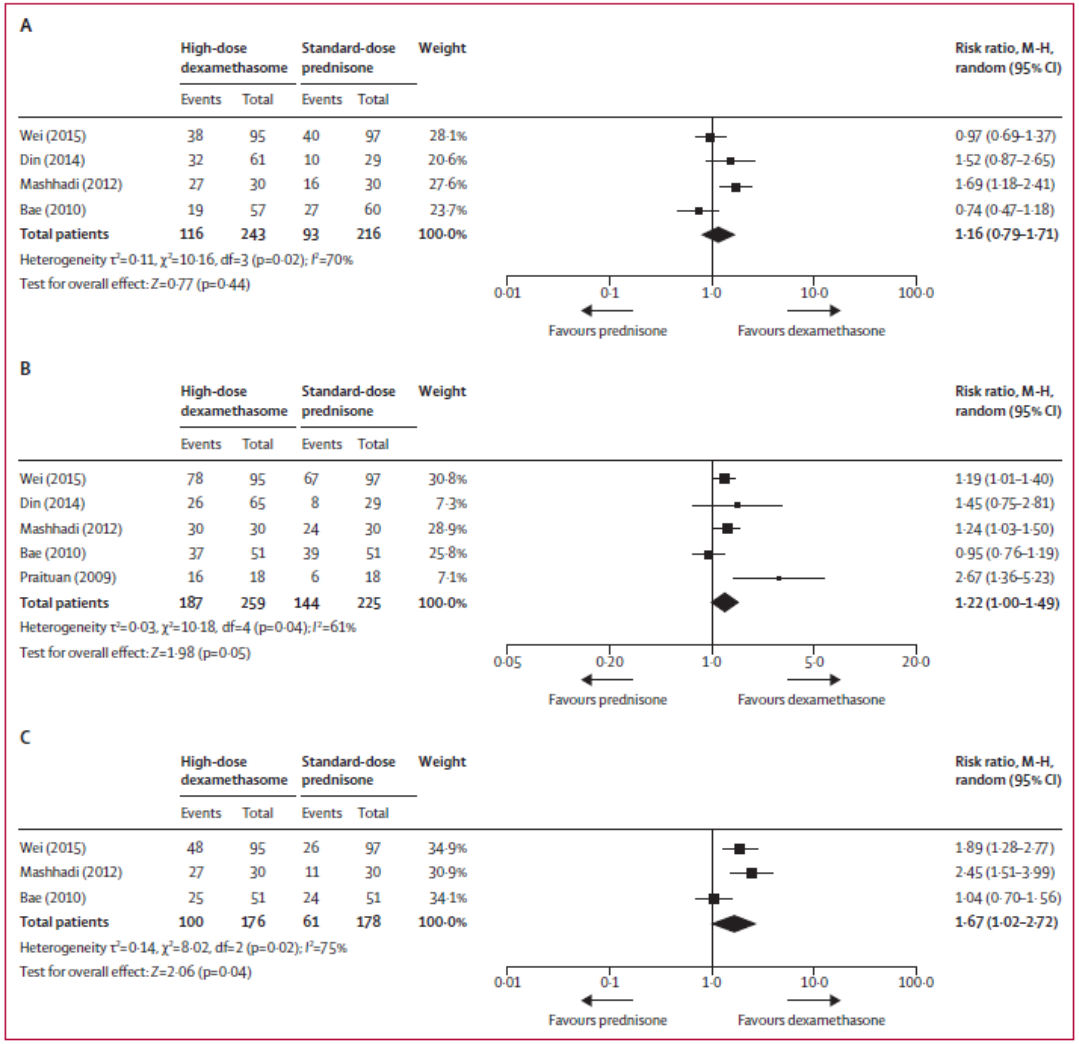
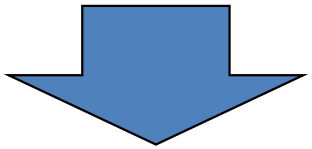


Figure 2: **Platelet count responses in adults after treatment with high-dose dexamethasone versus standard-dose prednisone**
(A) Overall response at 6 months or longer after treatment. (B) Overall response within 14 days of treatment. One trial assessed initial response at 10 days in the dexamethasone group and at 28 days in the prednisone group.[7] (C) Complete response within 14 days of treatment. One trial assessed initial response at 10 days in the dexamethasone group and at 28 days in the prednisone group.[7] M-H=Mantel-Haenszel.

Question	Outcome 1	Outcome 2
Should adult ITP newly diagnosed be treated with prednisone or dexamethasone ?	• Durable response • QoL • Response within 7 day	• Major bleeding • Remission • Response within 1 month

- Remission rate increase with dexa
- Number of cycles, lenght of treatment and plt count were not consistent
- QoL data were missing
- Response within 7 day better with dexa
- No difference between response at 1 month, durable response and major bleeding



BOTH TREATMENTS ARE ACCEPTABLE INITIAL THERAPY

Up- front rituximab ?

Rituximab plus standard of care for treatment of primary immune thrombocytopenia: a systematic review and meta-analysis

Shaan Chugh, Saeed Darvish-Kazem, Wendy Lim, Mark A Crowther, Waleed Ghanima, Grace Wang, Nancy M Heddle, John G Kelton, Donald M Arnold

	N	ITP stage*	Intervention	Standard of care	Placebo	Definition of CR (×10⁹ platelets per L)	Definition of PR (×10⁹ platelets per L)	Follow-up (months)
Ghanima and colleagues[20]	109	Corticosteroid-resistant or relapsed after corticosteroid treatment	Rituximab 375 mg/m² intravenous weekly for 4 weeks	Low-dose prednisone (<7·5 mg/day) was permitted throughout the study	Yes	≥100	>30 and doubling from baseline	19·5
Gudbrandsdottir and colleagues[16]	133	Treatment-naive	Rituximab 375 mg/m² intravenous weekly for 4 weeks	Dexamethasone 40 mg orally per day for 4 days every 1–4 weeks for up to six cycles	No	≥100	≥50	6†
Arnold and colleagues[18]	60	Newly diagnosed or relapsed	Rituximab 375 mg/m² intravenous weekly for 4 weeks	Corticosteroids, IVIG, RhIg for up to 8 weeks	Yes	≥100	>30 and doubling from baseline	6
Li and colleagues[19]	62	Newly diagnosed or resistant to drug treatment	Rituximab 100 mg intravenous weekly for 4 weeks	Dexamethasone 40 mg orally per day for 4 days; and prednisone taper for 28 days	No	≥100	≥50	12
Zaja and colleagues[17]	103	Treatment-naive patients with newly diagnosed, persistent, or chronic disease	Rituximab 375 mg/m² intravenous weekly for 4 weeks	Dexamethasone 40 mg orally per day for 4 days for one cycle; corticosteroids and IVIG permitted up to 28 days	No	≥100	≥50	6

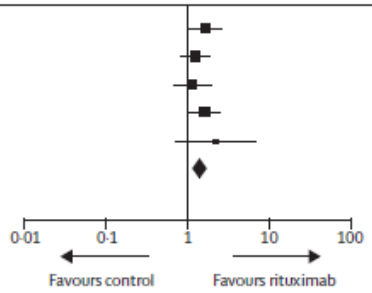
ITP=immune thrombocytopenia. IVIG=intravenous immunoglobulin. RhIg=rhesus immunoglobulin. CR=complete platelet count response. PR=partial platelet count response. *All patients had primary ITP and had not had splenectomy at enrolment. †3 years of follow-up were attained by 26 (42%) patients assigned to rituximab and dexamethasone and 25 (35%) patients assigned to dexamethasone.

A Complete response

	Rituximab		Control		Weight	Relative risk (95%CI)
	Events	Patients	Events	Patients		
Zaja and colleagues[17]	26	49	17	52	22·4%	1·62 (1·01–2·60)
Li and colleagues[19]	21	31	17	31	30·8%	1·24 (0·83–1·85)
Arnold and colleagues[18]	17	32	12	26	17·8%	1·15 (0·68–1·95)
Gudbrandsdottir and colleagues[16]	34	70	19	63	24·9%	1·61 (1·03–2·52)
Ghanima and colleagues[20]	9	55	4	54	4·0%	2·21 (0·72–6·75)
Total	**107**	**237**	**69**	**226**	**100·0%**	**1·42 (1·13–1·77)**

τ^2=0·00; χ^2=2·40, df=4 (p=0·66); I^2=0%

Z=3·07 (p=0·002)

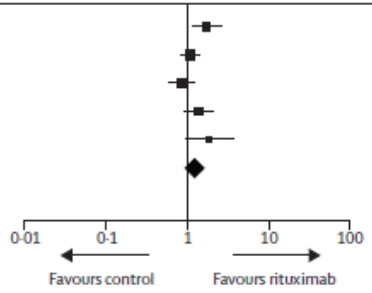


B Partial response

	Rituximab		Control		Weight	Relative risk (95%CI)
	Events	Patients	Events	Patients		
Zaja and colleagues[17]	31	49	19	52	19·6%	1·73 (1·14–2·63)
Li and colleagues[19]	25	31	23	31	26·1%	1·09 (0·83–1·42)
Arnold and colleagues[18]	20	32	19	26	22·2%	0·86 (0·60–1·22)
Gudbrandsdottir and colleagues[16]	35	70	23	63	20·3%	1·37 (0·92–2·05)
Ghanima and colleagues[20]	19	55	10	54	11·8%	1·87 (0·96–3·64)
Total	**130**	**237**	**94**	**226**	**100·0%**	**1·26 (0·95–1·67)**

τ^2=0·06; χ^2=10·23, df=4 (p=0·04); I^2=61%

Z=1·61 (p=0·11)



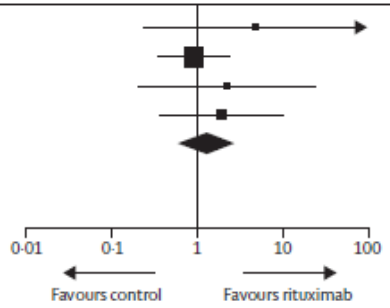
At 6th month

A Bleeding events

	Rituximab		Control		Weight	Relative risk (95%CI)
	Events	Patients	Events	Patients		
Zaja and colleagues[17]	2	31	0	31	6·4%	5·00 (0·25–100·08)
Arnold and colleagues[18]	7	32	6	26	62·4%	0·95 (0·36–2·48)
Gudbrandsdottir and colleagues[16]	2	62	1	71	10·2%	2·29 (0·21–24·65)
Ghanima and colleagues[20]	4	55	2	54	21·0%	1·96 (0·38–10·28)
Total	**15**	**180**	**9**	**182**	**100·0%**	**1·34 (0·63–2·87)**

τ^2=0·00; χ^2=1·70, df=4 (p=0·64); I^2=0%

Z=0·76 (p=0·44)

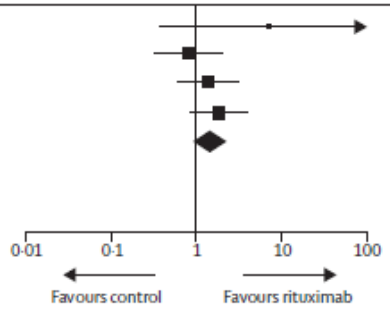


B Infection

	Rituximab		Control		Weight	Relative risk (95%CI)
	Events	Patients	Events	Patients		
Zaja and colleagues[17]	3	31	0	31	2·7%	7·00 (0·38–130·10)
Arnold and colleagues[18]	7	32	7	26	26·8%	0·81 (0·33–2·02)
Gudbrandsdottir and colleagues[16]	11	62	9	71	33·5%	1·40 (0·62–3·15)
Ghanima and colleagues[20]	15	55	8	54	37·0%	1·84 (0·85–3·98)
Total	**36**	**180**	**24**	**182**	**100·0%**	**1·40 (0·87–2·26)**

χ^2=3·07, df=3 (p=0·38); I^2=2%

Z=1·37 (p=0·17)



Question	Outcome 1	Outcome 2
Should adult ITP newly diagnosed be treated with CTS and rituximab or CTS alone ?	• Durable response • QoL • Response within 1 month • Major bleeding	• Infection • Remission • Mortality

- ✓ Sustained response increase with R-CST
- ✓ A fair number of patients in each group required additional treatment
- ✓ QoL and major bleeding data were missing
- ✓ Wide CI on prioritized outcomes
- ✓ Increase cost of R

CTS ALONE CONTINUE TO BE FAVORED AS INITIAL THERAPY

IWG guidelines

Recommendations for initial treatment of newly diagnosed patients

Corticosteroids are the standard initial treatment for adults with ITP who need treatment and do not have a relative contradiction: predniso(lo)ne at 1 mg/kg (maximum dose 80mg, even in patients weighing > 80 kg) for 2 weeks, to a maximum of 3 weeks, or dexamethasone 40 mg/d for 4 days, repeated up to 3 times.

If a response is seen the predniso(lo)ne should be tapered, aiming to stop predniso(lo)ne by 6 weeks (maximum 8 weeks), even if the platelet count drops during the taper.
If there is no response to the initial dose within 2 weeks, the predniso(lo)ne should be tapered rapidly over 1 week and stopped.
Longer courses of steroids should be avoided, although occasional patients may benefit from continuous low-dose corticosteroids (eg, #5 mg/d).

Use of IVIg (1 g/kg on 1 or 2 consecutive days or 0.4 g/kg per day for 5 days), or IV anti-D (50-75 mg/kg once) where available, may be appropriate in patients with bleeding, at high risk for bleeding, who require a surgical procedure, or who are unresponsive to predniso(lo)ne

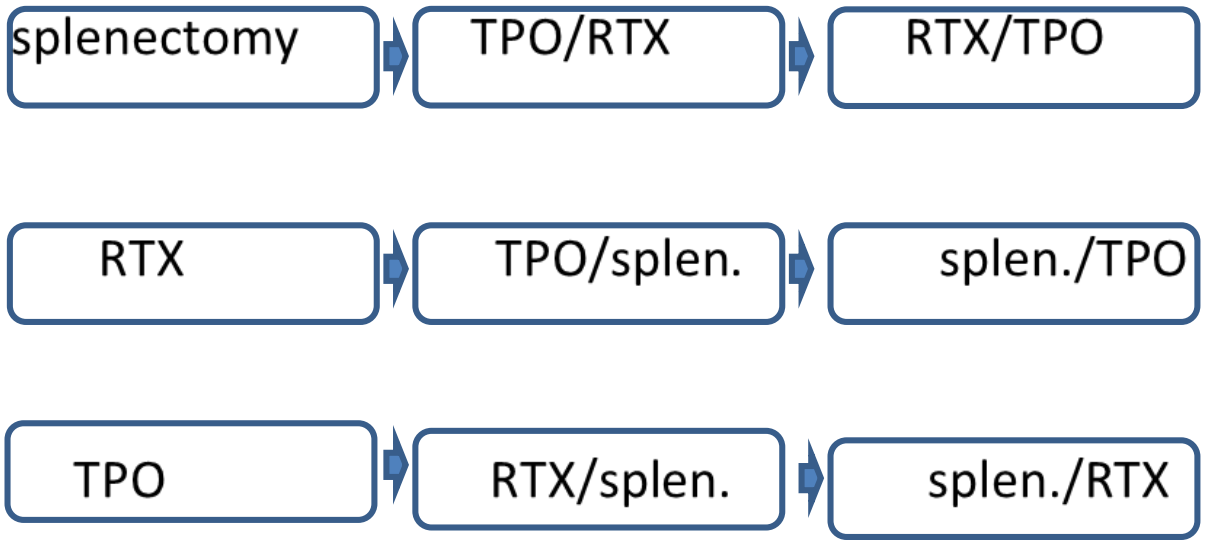
Certain patients may have relevant contraindications to high-dose corticosteroid therapy (eg, insulin-dependent diabetes, uncontrolled diabetes, psychiatric disorders, active infection) and may be managed with only IVIg or IV anti-D as initial therapy.

TPO receptor agonists (TPO-RAs) and rituximab are not considered initial therapies.

Second – line therapy in adult with ITP

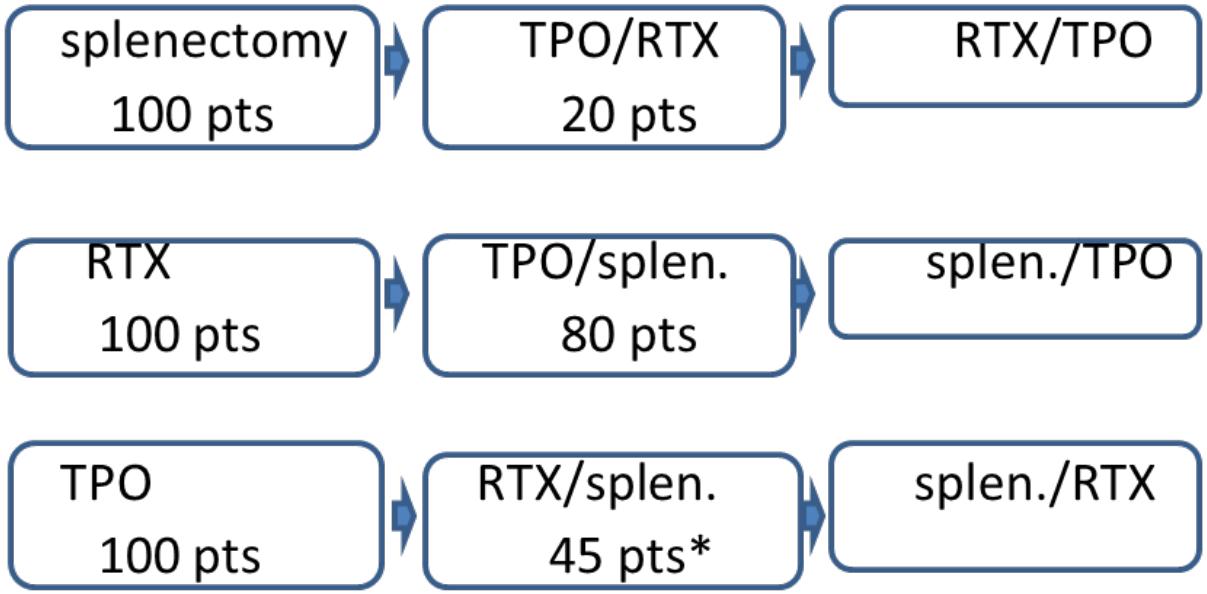
Should adult ITP lasting > 3 months who are CTS dependent or have no response to CTS undergo to splenectomy of be treated with TPO-RA or with Rituximab ?

Uncertainty about the optimal sequence of ITP treatment



Uncertainty about the optimal sequence of ITP treatment

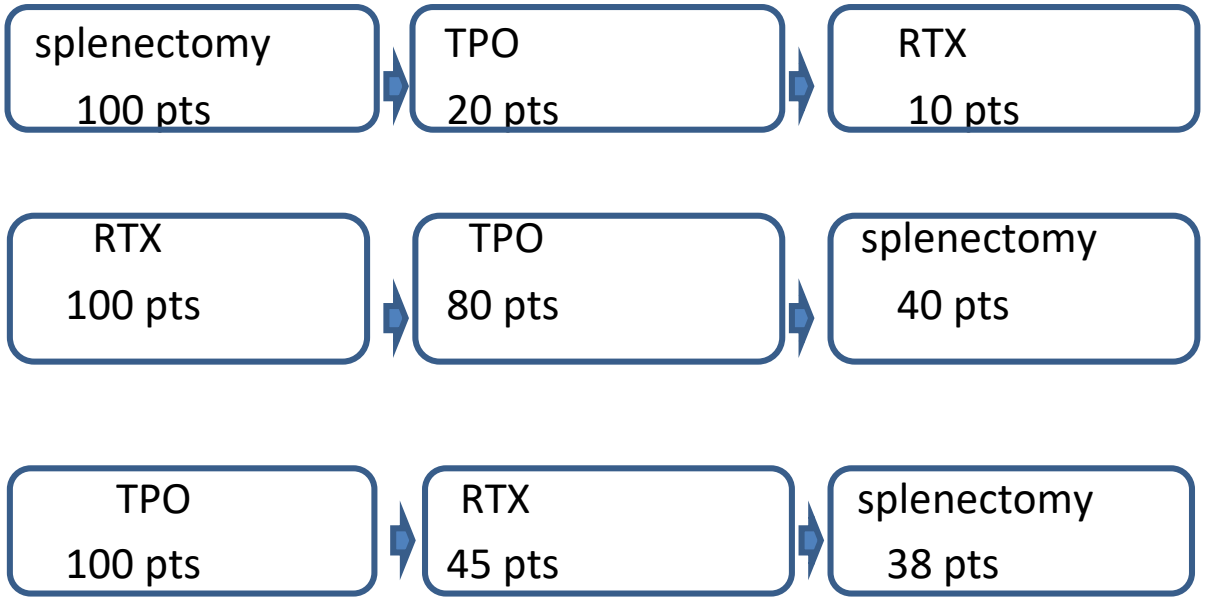
After 5 years follow-up



*: EXTEND study, Wong RSM et al, Blood 2017

Uncertainty about the optimal sequence of ITP treatment

After 10 years follow-up



	Splenectomy	Rituximab	TPO-RA
Advantages	• High response rate • Durable CR • Single treatment • Cost efficent	• Short course	• High response rate • Durable CR
Limitations	• Surgical procedure • Morbidity • VTE risk • Sepsis	• Lower durable • Risk of infusion reactions • HBV reactivaton • Cost	• Need for continuos treatment • Cost • VTE risk

Neunert C, ASH 2019

Response and remission rates (indirect comparison from literature data)

	Rituximab	Splenectomy	TPO-RA
Response within 1 month	314/506 (62.1%)	3342/3855 (86.7%)	448/682 (65.7%)
Durable response (at 6 months)	80/203 (39.4%)	79/149 (53%)	225/356 (63.2%)
Remission (at the end of follow-up)	134/571 (23.5%)	1017/1479 (68.8%)	-

Neunert C, ASH 2019

Major bleeding and adverse outcomes (indirect comparison from literature data)

	Rituximab	Splenectomy	TPO-RA
Major bleeding	2.2%	4.6%	3.5%
Infection	3.7%	10%	6.9%
Thrombosis	2.2%	2.4%	2.5%
Operative complications	-	12.8%	-

Neunert C, ASH 2019

Splenectomy vs TPO-RA

Recommendation

In adult with ITP lasting > 3 months, ASH suggests either splenectomy or TPO-RA

Avoid surgery/non – surgical candidate: TPO-RA

Avoid long-term medication: splenectomy

Neunert C, ASH 2019

Splenectomy vs Rituximab

Recommendation

In adult with ITP lasting > 3 months, ASH suggests Rituxmab rather than splenectomy

Neunert C, ASH 2019

TPO vs Rituximab

Recommendation

In adult with ITP lasting > 3 months, ASH suggests TPO-RA rather than Rituximab

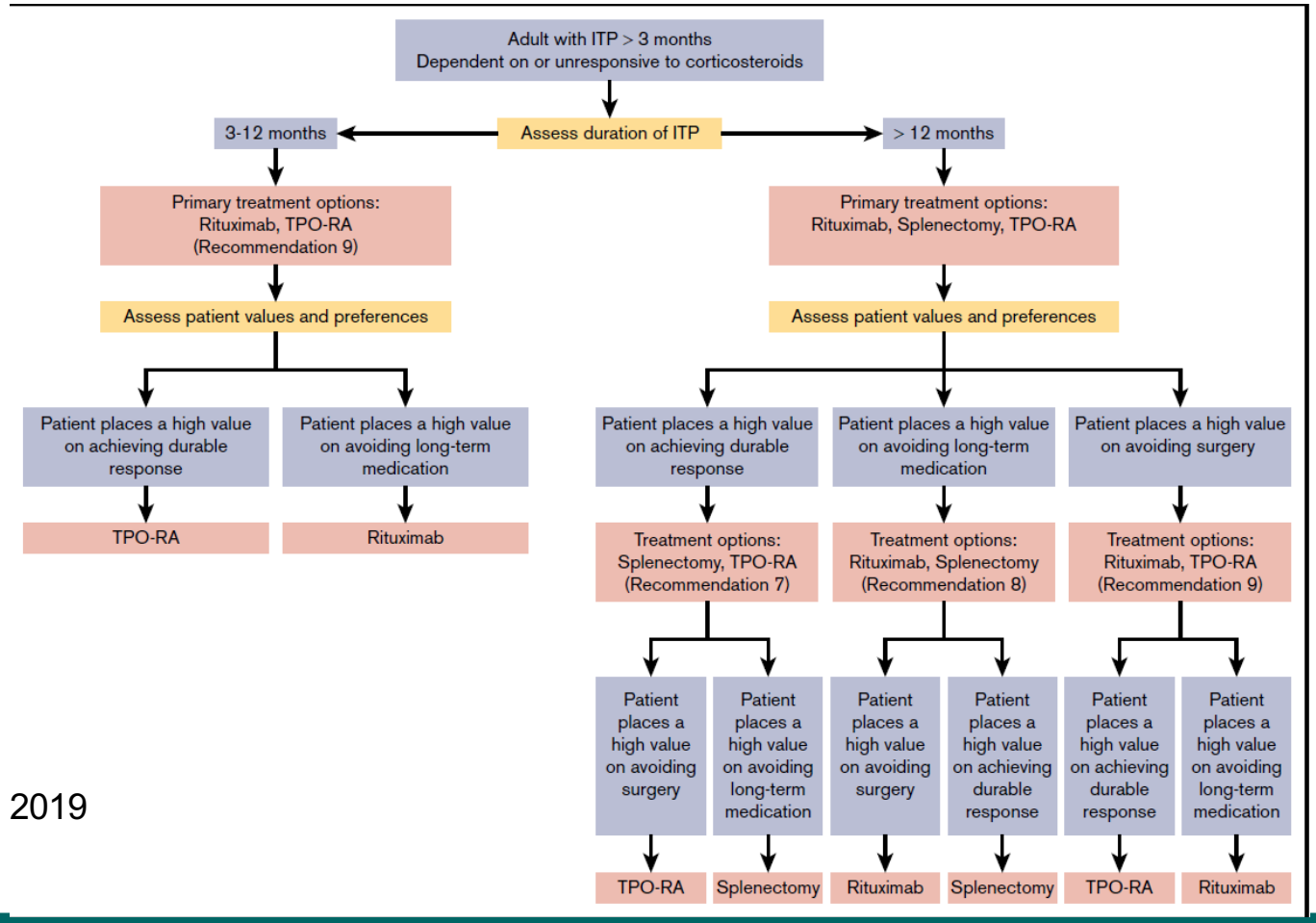
Neunert C, ASH 2019

- There is no single second-line treatment that is optimal for all patients with ITP

- The choice of treatment should be individualized, based on:
  - duration of ITP
  - frequency of bleeding
  - comorbidities
  - age of patient
  - medication adherence
  - cost
  - availability

- Patient education and shared decision-making are encouraged

ASH-ITP persistent/chronic



Neunert C, ASH 2019

IWG: Treatment for persistent/chronic ITP

Medical therapies with robust evidence:

- Romiplostin, Eltrombopag, Avatrombopag
- Rituximab
- Fostamatinib

Medical therapies with less robust evidence:

- Immunosuppressive agents
- Danazol
- Dapsone

Surgical therapy:

- Splenectomy

IWG; Blood Advances, 2019

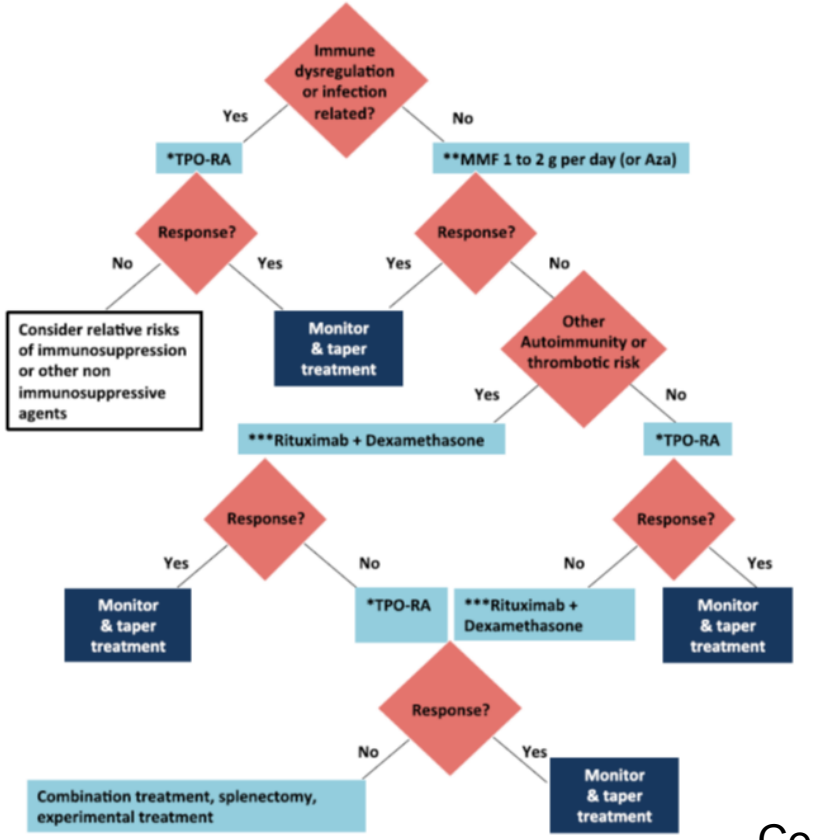
IWG: Treatment for ITP patients failing multiple therapies

Recommendations:

- Reconsider the diagnosis
- Reassess the need for treatment
- Splenectomy?
- Other therapies if not already attempted
- In TPO-RA: switiching strategy
- Multitherapy
- Clinical trial

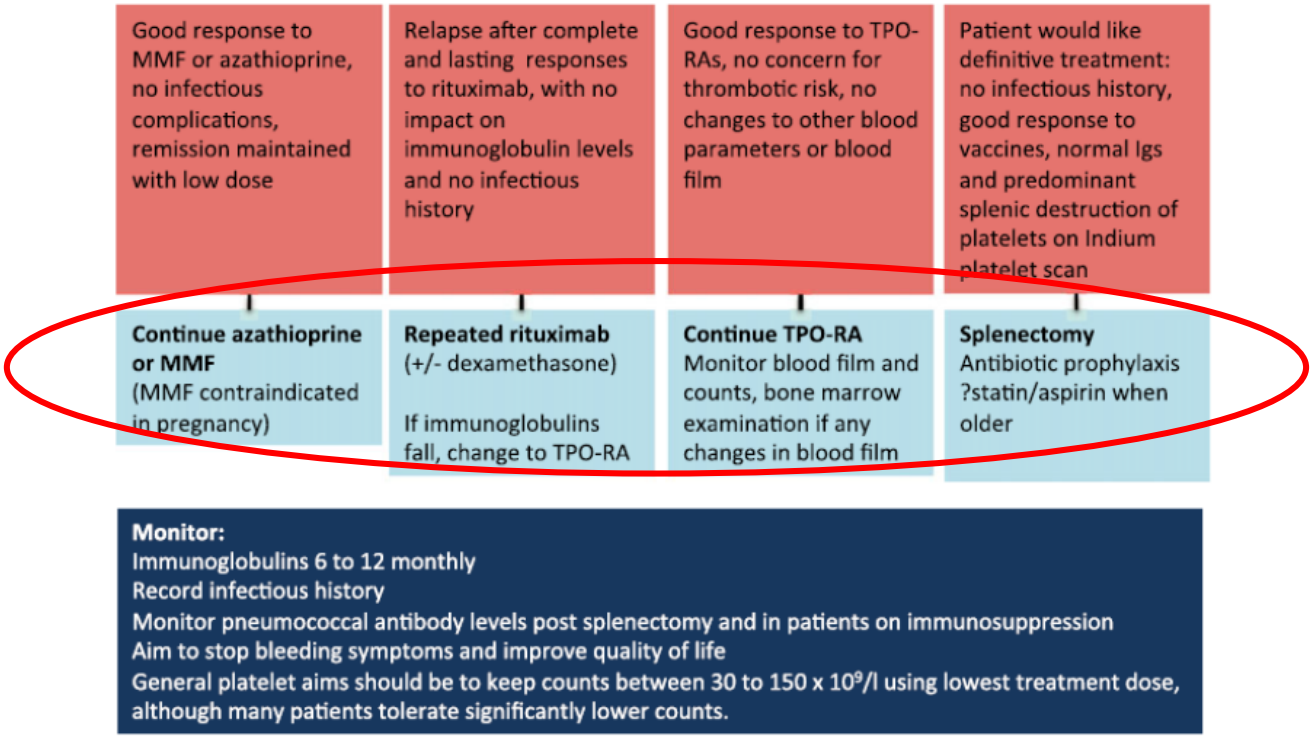
IWG; Blood Advances, 2019

Treatment guidelines for persistent ITP



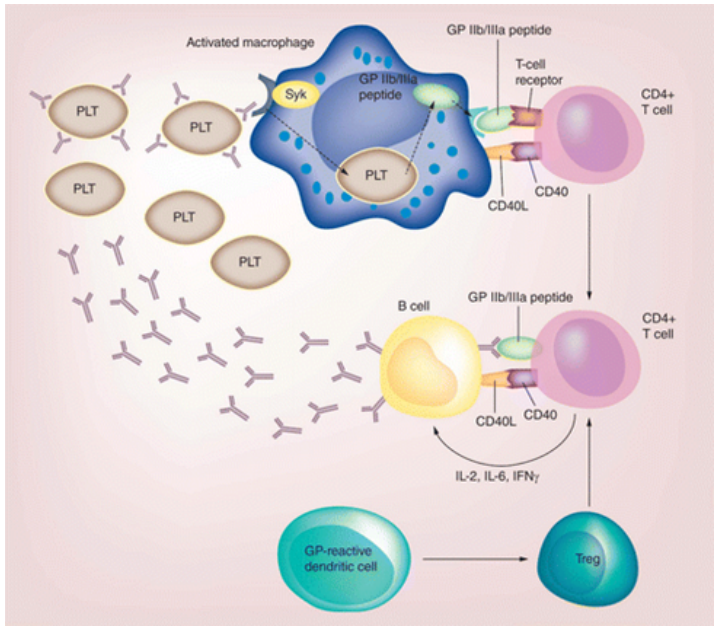
Cooper N, Br J Haematol, 2017

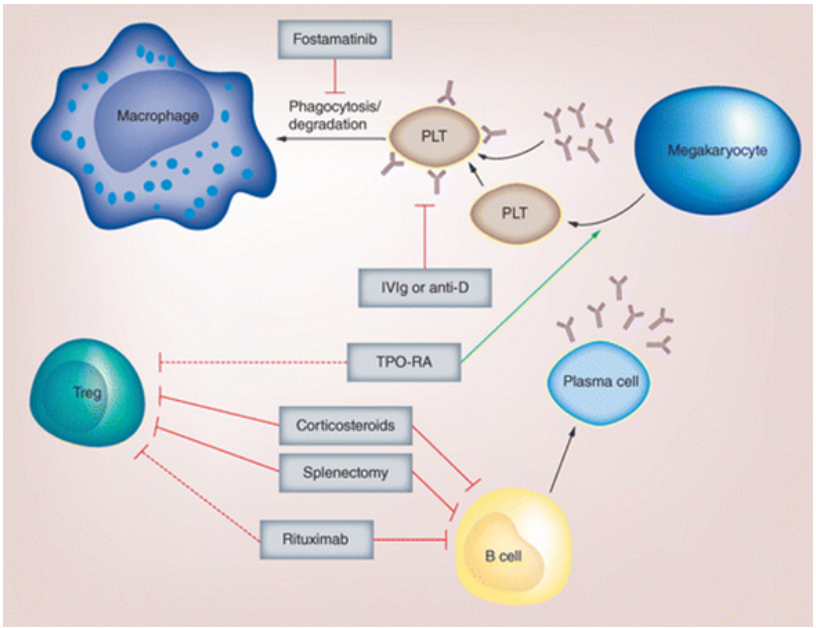
Treatment guidelines for chronic ITP



Cooper N, Br J Haematol, 2017

NEW DRUGS in ITP treatment





Received: 10 April 2018 | Revised: 17 April 2018 | Accepted: 22 April 2018

DOI: 10.1002/ajh.25125

RESEARCH ARTICLE

WILEY AJH

Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials

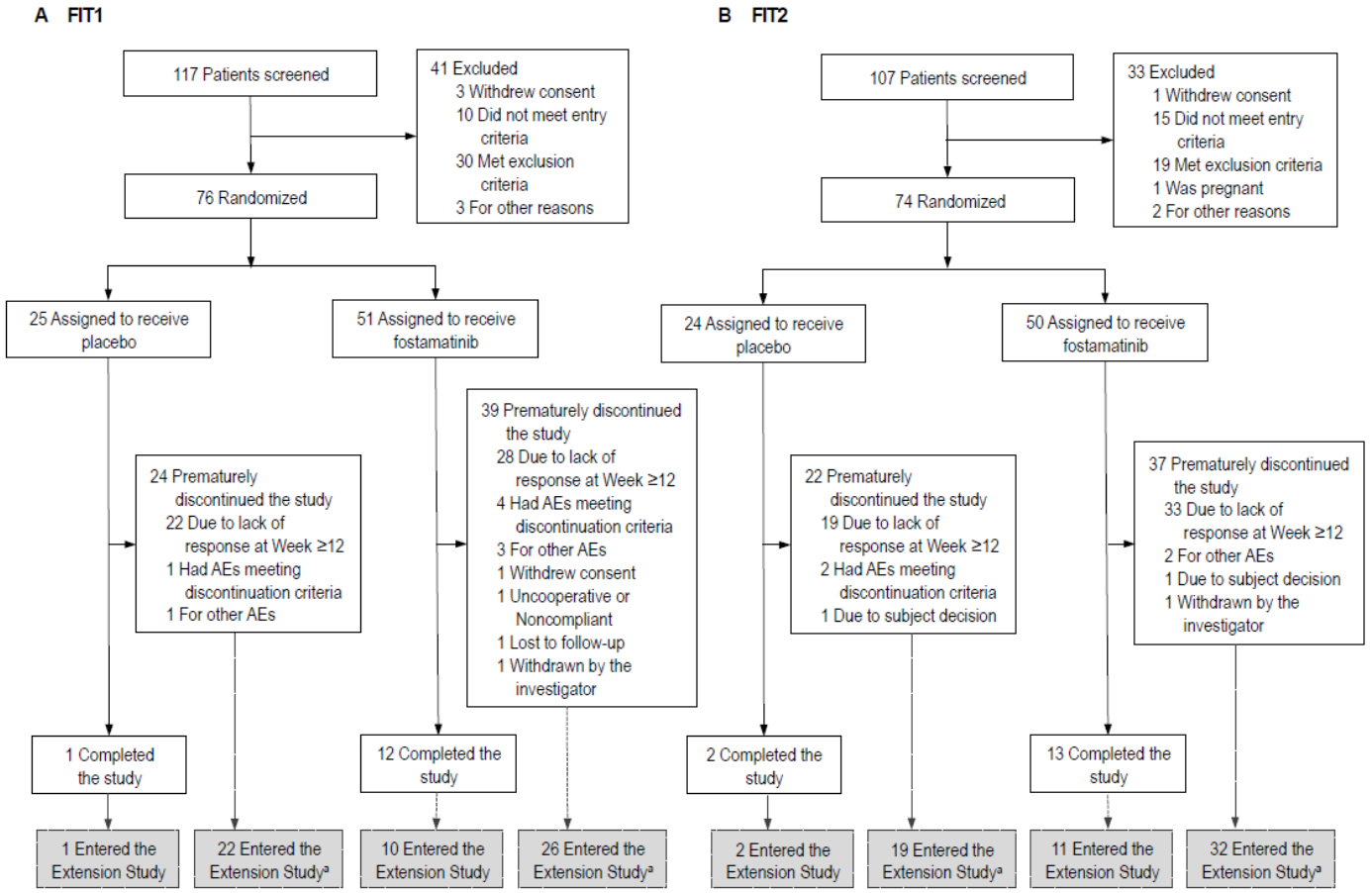
James Bussel[1] | Donald M. Arnold[2] | Elliot Grossbard[3] | Jiří Mayer[4] | Jacek Treliński[5] | Wojciech Homenda[6] | Andrzej Hellmann[7] | Jerzy Windyga[8] | Liliya Sivcheva[9] | Alhossain A. Khalafallah[10] | Francesco Zaja[11] | Nichola Cooper[12] | Vadim Markovtsov[3] | Hany Zayed[3] | Anne-Marie Duliege[3]

Adult persistent/chronic ITP in two parallel, multi-center, randomized, placebo-controlled (2 active:1 placebo), double-blind phase 3 studies, each 24 weeks in duration; one performed in North America, Australia and Europe (047) and one in Europe (048).

The median duration of ITP at study entry was 8.5 years

Patients were heavily pretreated with ITP therapies: 94% had received corticosteroids, 47% thrombopoietin-receptor agonists, 32% rituximab and 35% splenectomy

Bussel J et al, AJH. 2018



[a]Patients who entered the Extension Study due to lack of response at Week ≥12

Bussel J et al, AJH. 2018

TREATMENT

- Fostamatinib 100 mg BID (increase to 150 mg BID after 4 weeks on platelet count)
- Concomitant ITP treatment allowed without any change
- Rescue therapies allowed (IGIV, platelet transfusion)

EFFICACY ASSESSMENT

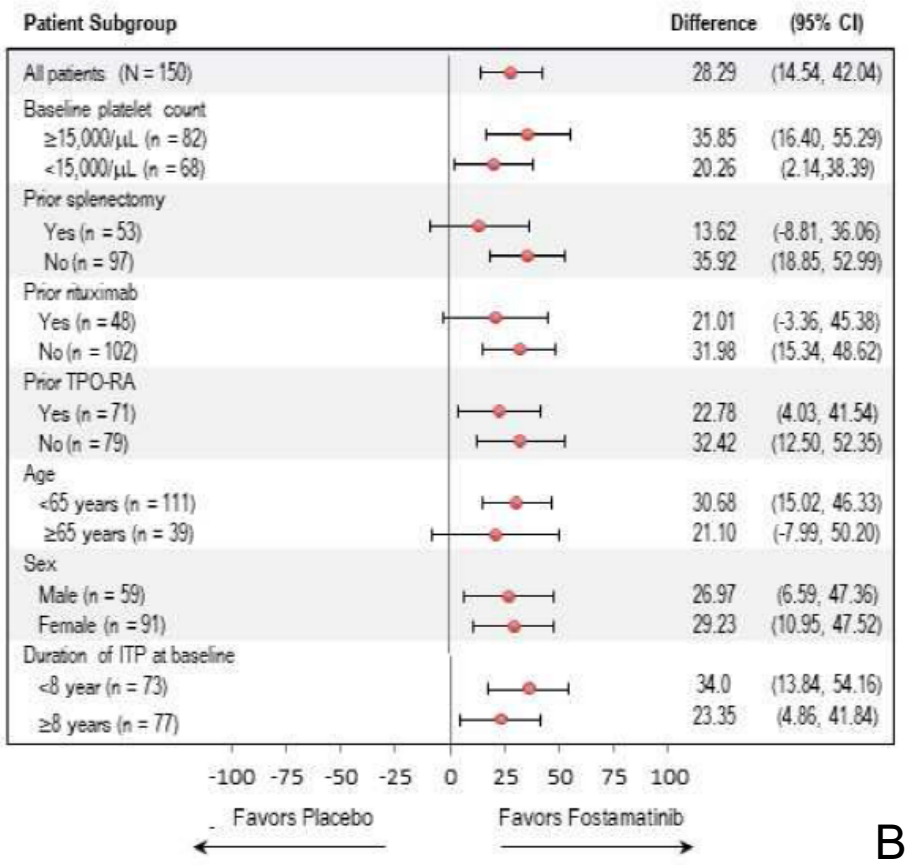
- Primary endpoint: *stable response* at week 24 (platelet count > 50 x 10^9/L at least 4 of 6 clinic visits)
- Secondary endpoint (post hoc assessment): *overall response (*platelet count > 50 x 10^9/L within the first 12 weeks)

Bussel J et al, AJH. 2018

EFFICACY

	FIT 1			FIT 2			Pooled		
	Placebo N= 25	**Fostamatinib N= 51**	**p**	**Placebo N= 24**	**Fostamatinib N= 50**	**p**	**Placebo N= 49**	**Fostamatinib N= 101**	**p**
Stable response	0 (0%)	9 (18%)	0.026	1 (4%)	9 (18%)	0.152	1 (2%)	18 (18%)	0.0003
Overall response	8%	37%	0.007	21%	48%	0.025	7 (14%)	43 (43%)	0.0006

Bussel J et al, AJH. 2018



Bussel J et al, AJH. 2018

SAFETY

75% patients experienced ≥1 AE with the majority (72%) being mild or moderate in severity.

52% patients experienced ≥1 treatment-related AE.

The most common AEs were:

- diarrhea (28%)
- hypertension (15%)
- petechiae (15%)
- epistaxis (14%).

Serious AEs were reported in 27 of 123 pts (22%)

Bleeding-related SAEs were experienced by 11 patients, 10 of whom were non-responders.

AEs leading to study drug withdrawal occurred in 15 of 101 pts (15%) including diarrhea (n=5), liver enzyme elevations (n=3), and neutropenia (n=2)

Bussel J et al, AJH. 2018

blood®
Prepublished online February 25, 2019;
doi:10.1182/blood-2018-11-852491

Fostamatinib for the treatment of chronic immune thrombocytopenia

Nathan T. Connell and Nancy Berliner

In April 2018 FDA approved fostamatinib for the treatment of chronic ITP with an insufficent response to at least one prior line therapy

Monthly monitoring of liver function test and neutrophil count

Blood pressure must be checked every 2 weeks

Vaccinations are suggested

Cost considerations: one month of Fostamatinib $ 11.340
Eltrombopag $ 9.900
Romiplostim $ 8.660

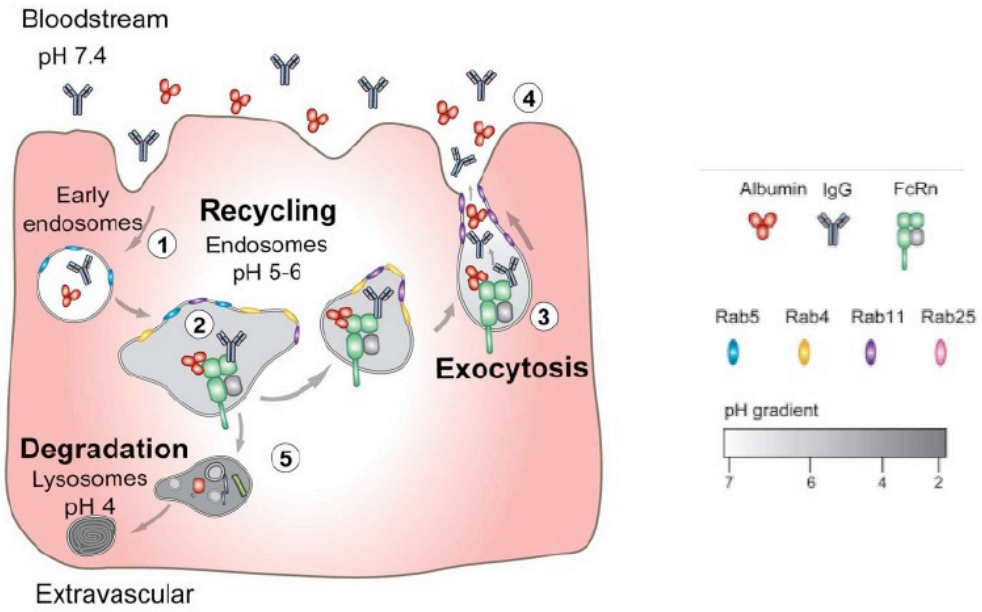
blood®
Prepublished online February 25, 2019;
doi:10.1182/blood-2018-11-852491

Fostamatinib for the treatment of chronic immune thrombocytopenia

Nathan T. Connell and Nancy Berliner

TABLE: Therapies for relapsed or resistant ITP [4-6,15,26-29]

Therapy	Response Rate	Time to Response	Toxicity	Duration of Response
Splenectomy	Overall: 80% Stable: 66%	1 - 24 days	• Surgical complications • Infection (2-3 times baseline risk) • Thrombosis (~ 2 times baseline risk)	Approximately 2/3 of patients will require no further therapy
Rituximab	Overall: 60% Stable: 40%	1 - 8 weeks	• Hypersensitivity reactions • Immune suppression • Hepatitis B reactivation	20-25% sustained at 5 years, although patients may be retreated
Thrombopoietin mimetics (e.g. romiplostim, eltrombopag)	Overall: >80% Stable: 40-50%	2 - 3 weeks	• Rebound thrombocytopenia • Thrombosis • Hepatotoxicity (eltrombopag) • Increased marrow reticulin deposition (1.8 - 7%)	Continuous as long as drug is administered In patients who have an initial response, >90% of patients maintain that response at 5 years
Syk inhibitor (fostamatinib)	Overall: 43% Stable: 18%	2 - 8 weeks	• Diarrhea, nausea • Hypertension • Neutropenia	Unknown, but assumed to be continuous as long as drug is administered



- Neonatal Fc Receptor (FcRn) is responsible for IgG recycling
- Rozanolixizumab, a subcutaneous infused, humanized monoclonal antibodiey, targets the IgG-binding region of FcRn, reducing IgG recycling and accelerating its lysosomial degradation
- Rozanolixuzumab lowers IgG levels (also pathogenetic IgG antibody); does not affect IgA, IgM, IgE, albumin level.

2020

REGULAR ARTICLE

blood advances

Phase 2 multiple-dose study of an FcRn inhibitor, rozanolixizumab, in patients with primary immune thrombocytopenia

Tadeusz Robak,[1] Maciej Kaźmierczak,[2] Isidro Jarque,[3,4] Vasile Musteata,[5] Jacek Treliński,[1] Nichola Cooper,[6] Peter Kiessling,[7] Ute Massow,[7] Franz Woltering,[7] Rose Snipes,[8] Juan Ke,[9] Grant Langdon,[10] James B. Bussel,[11] and Stephen Jolles[12]

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8 SEPTEMBER 2020 • VOLUME 4, NUMBER 17

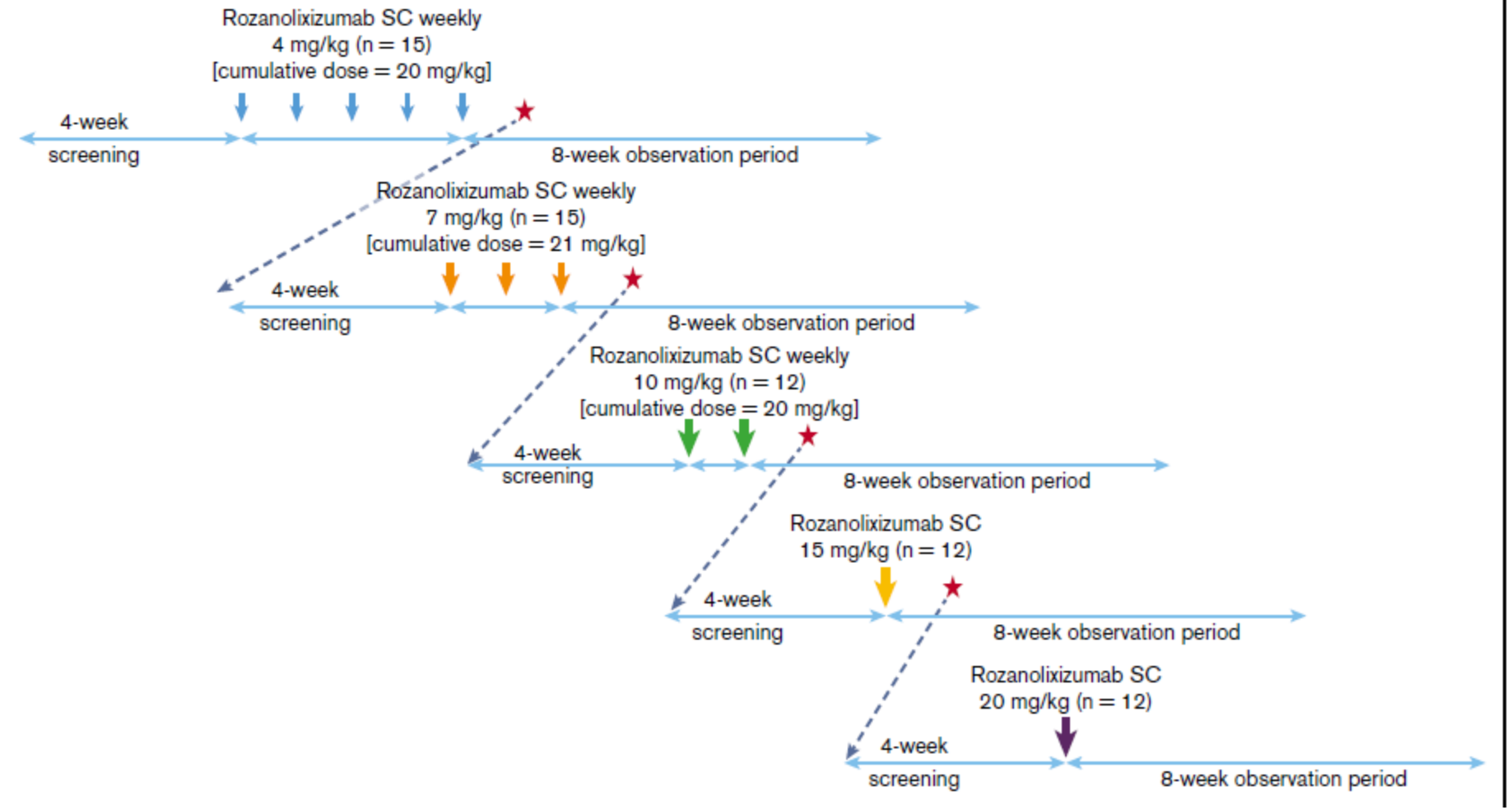

Rozanolixizumab SC weekly
4 mg/kg (n = 15)
[cumulative dose = 20 mg/kg]
4-week
screening
8-week observation period
Rozanolixizumab SC weekly
7 mg/kg (n = 15)
[cumulative dose = 21 mg/kg]
4-week
screening
8-week observation period
Rozanolixizumab SC weekly
10 mg/kg (n = 12)
[cumulative dose = 20 mg/kg]
4-week
screening
8-week observation period
Rozanolixizumab SC
15 mg/kg (n = 12)
4-week
screening
8-week observation period
Rozanolixizumab SC
20 mg/kg (n = 12)
4-week
screening
8-week observation period

Table 1. Baseline patient demographics and disease characteristics (safety set)

	Rozanolixizumab					
	Single-dose cohorts		Multiple-dose cohorts			All patients
Characteristic	20 mg/kg (n = 12)	15 mg/kg (n = 12)	2 × 10 mg/kg (n = 12)	3 × 7 mg/kg (n = 15)	5 × 4 mg/kg (n = 15)	(N = 66)
Median age (range), y	60.5 (25-78)	49.5 (23-69)	46.0 (23-69)	54.0 (20-73)	66.0 (21-86)	54.0 (23-86)
Sex, n (%)						
Female	9 (75.0)	7 (58.3)	7 (58.3)	11 (73.3)	8 (53.3)	42 (63.6)
Male	3 (25.0)	5 (41.7)	5 (41.7)	4 (26.7)	7 (46.7)	24 (36.4)
Ethnicity, n (%)*						
Asian	0	0	0	0	2 (13.3)	2 (3.0)
White	12 (100)	12 (100)	12 (100)	15 (100)	13 (86.7)	64 (97.0)
Platelet count, × 10^9/L†						
Median (range)	19.0 (4-37)	22.5 (6-38)	14.0 (6-53)	11.0 (5-24)	15.0 (5-36)	15.5 (4-53)
Mean (SD)	18.0 (10.8)	21.2 (9.3)	18.4 (13.8)	13.4 (5.4)	18.4 (10.7)	17.7 (10.2)
Median duration of disease (range), y	4.9 (0.4-10.7)	5.8 (0.5-24.1)	8.1 (0.4-30.8)	5.2 (0.3-36.2)	7.1 (1.7-28.6)	5.8 (0.3-36.2)
No. of previous lines of ITP therapy (%)	10 (83.3)	8 (66.7)	11 (91.7)	12 (80.0)	13 (86.7)	54 (81.8)
Median (range)	2.0 (1-8)	3.0 (1-8)	2.0 (1-6)	6.5 (1-15)	6.0 (1-16)	4.0 (1-16)
Treatment or drug, n (%)‡						
Immunoglobulins	2 (16.7)	5 (41.7)	3 (25.0)	7 (46.7)	8 (53.3)	25 (37.9)
Azathioprine	3 (25.0)	4 (33.3)	3 (25.0)	6 (40.0)	8 (53.3)	24 (36.4)
Eltrombopag	1 (8.3)	1 (8.3)	5 (41.7)	7 (46.7)	6 (40.0)	20 (30.3)
Splenectomy	3 (25.0)	2 (16.7)	2 (16.7)	7 (46.7)	5 (33.3)	19 (28.8)
Romiplostim	2 (16.7)	1 (8.3)	2 (16.7)	6 (40.0)	7 (46.7)	18 (27.3)
Cyclosporin	1 (8.3)	3 (25.0)	1 (8.3)	4 (26.7)	5 (33.3)	14 (21.2)
Dexamethasone	2 (16.7)	1 (8.3)	2 (16.7)	4 (26.7)	3 (20.0)	12 (18.2)
Danazol	1 (8.3)	2 (16.7)	1 (8.3)	2 (13.3)	5 (33.3)	11 (16.7)
Rituximab	1 (8.3)	1 (8.3)	0	6 (40.0)	2 (13.3)	10 (15.2)
Fostamatinib	0	0	1 (8.3)	1 (6.7)	6 (40.0)	8 (12.1)
Prednisolone	3 (25.0)	1 (8.3)	1 (8.3)	0	3 (20.0)	8 (12.1)

STUDY OBJECTIVES

- Safety and tolerability
- Clinical efficacy
- Change in IgG level

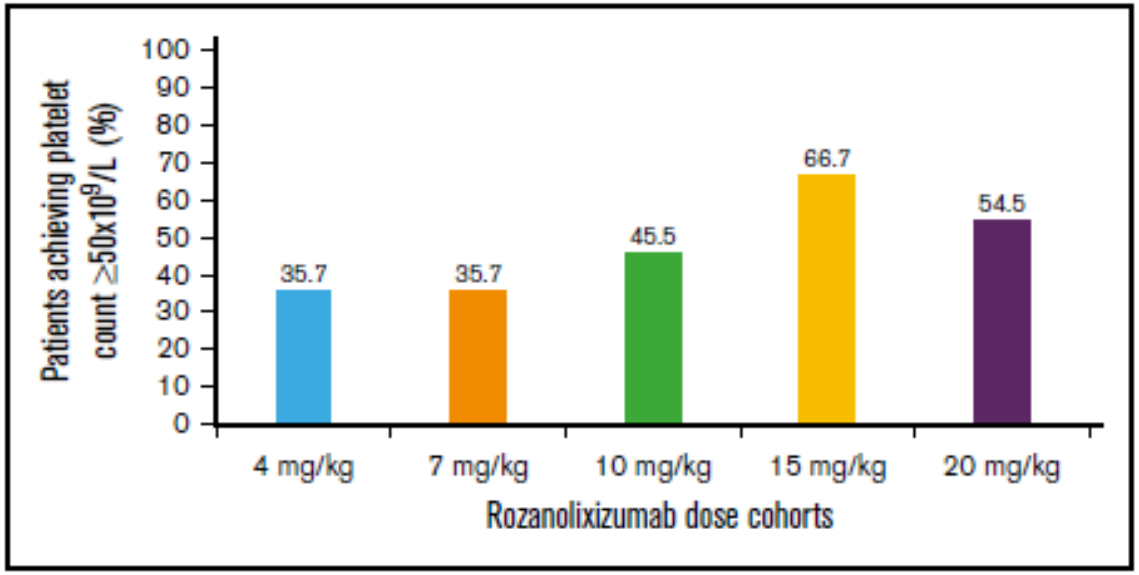
(exclusion criteria for eligibility: IgG level ≤ 6 g/L)

SAFETY AND TOLERABILITY

Table 2. AE profile for the safety set

	Rozanolixizumab					
	Single-dose cohorts		Multiple-dose cohorts			All patients
AEs	20 mg/kg (n = 12)	15 mg/kg (n = 12)	2 × 10 mg/kg (n = 12)	3 × 7 mg/kg (n = 15)	5 × 4 mg/kg (n = 15)	(N = 66)
Any AE	12 (100)	11 (91.7)	7 (58.3)	9 (60.0)	12 (80.0)	51 (77.3)
Serious AEs	0	2 (16.7)	1 (8.3)	0	1 (6.7)	4 (6.1)
AEs related to rozanolixizumab	9 (75.0)	7 (58.3)	1 (8.3)	1 (6.7)	1 (6.7)	19 (28.8)
Severe AEs	0	1 (8.3)	1 (8.3)	0	1 (6.7)	3 (4.5)
Discontinuations as a result of AEs	0	0	0	0	0	0
Deaths	0	0	0	0	0	0
Most common AEs*						
Headache	9 (75.0)	5 (41.7)	3 (25.0)	6 (40.0)	3 (20.0)	26 (39.4)
Diarrhea	2 (16.7)	2 (16.7)	1 (8.3)	2 (13.3)	1 (6.7)	8 (12.1)
Vomiting	4 (33.3)	2 (16.7)	0	0	0	6 (9.1)
Pyrexia	3 (25.0)	1 (8.3)	1 (8.3)	0	0	5 (7.6)
Upper respiratory tract infection	0	1 (8.3)	1 (8.3)	1 (6.7)	1 (6.7)	4 (6.1)
Most common AEs related to rozanolixizumab*†						
Headache	8 (66.7)	5 (41.7)	1 (8.3)	1 (6.7)	0	15 (22.7)
Vomiting	3 (25.0)	2 (16.7)	0	0	0	5 (7.6)
Diarrhea	2 (16.7)	2 (16.7)	0	0	0	4 (6.1)

CLINICAL EFFICACY



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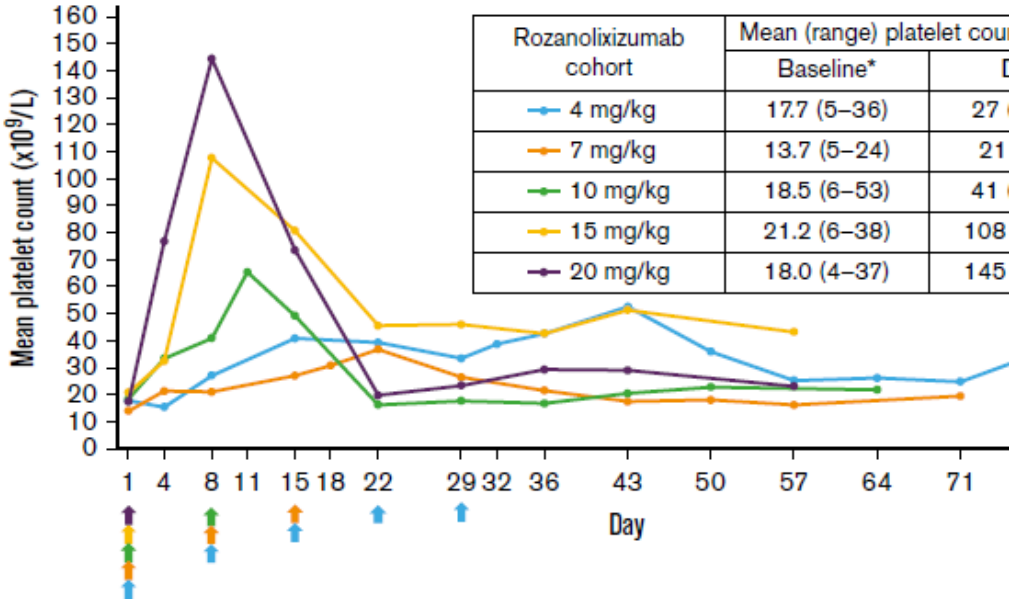
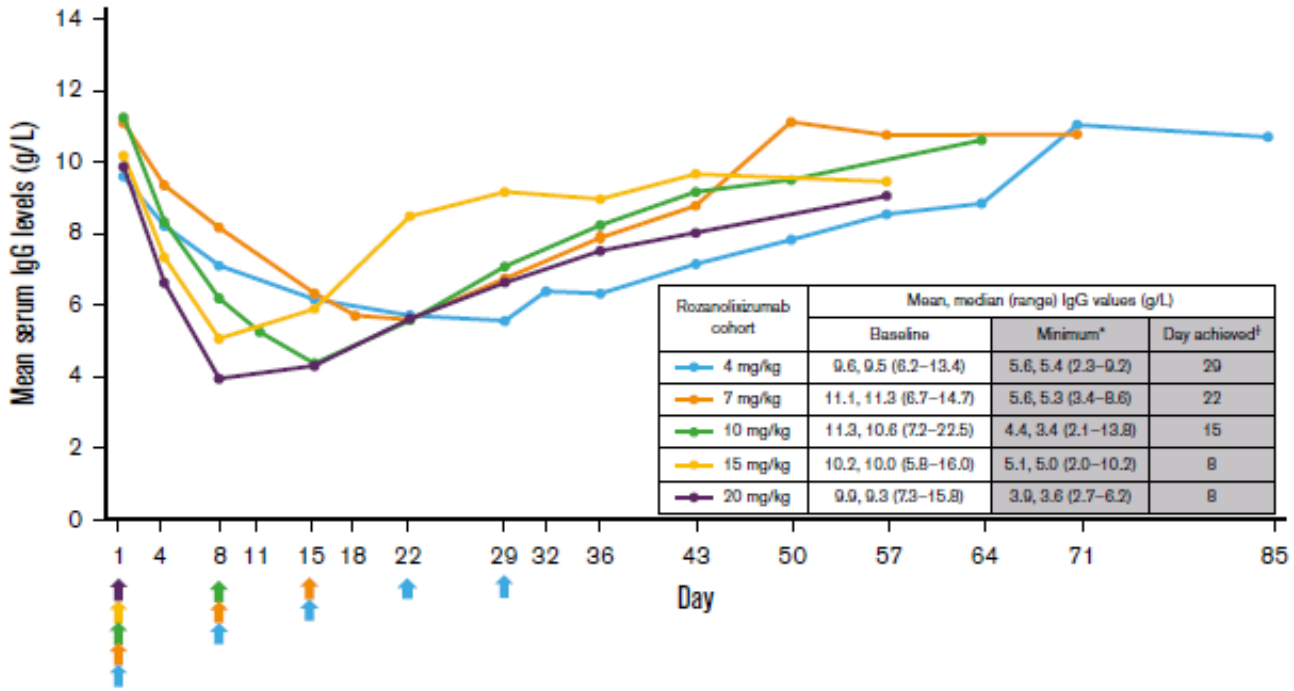


Rozanolixizumab cohort	Mean (range) platelet cou	
	Baseline*	D
4 mg/kg	17.7 (5–36)	27
7 mg/kg	13.7 (5–24)	21
10 mg/kg	18.5 (6–53)	41
15 mg/kg	21.2 (6–38)	108
20 mg/kg	18.0 (4–37)	145

CHANGE IN IgG LEVELS

A



Rozanolixizumab cohort	Mean, median (range) IgG values (g/L)		
	Baseline	Minimum*	Day achieved†
4 mg/kg	9.6, 9.5 (6.2–13.4)	5.6, 5.4 (2.3–9.2)	29
7 mg/kg	11.1, 11.3 (6.7–14.7)	5.6, 5.3 (3.4–8.6)	22
10 mg/kg	11.3, 10.6 (7.2–22.5)	4.4, 3.4 (2.1–13.9)	15
15 mg/kg	10.2, 10.0 (5.8–16.0)	5.1, 5.0 (2.0–10.2)	8
20 mg/kg	9.9, 9.3 (7.3–15.9)	3.9, 3.6 (2.7–6.2)	8

CONCLUSIONS

- Rozanolixizumab treatment at doses up to 20 mg/kg was generally well tolerated with an acceptable safety profile and demonstrable efficacy.
- Single doses of rozanolixizumab (15 and 20 mg/kg) demonstrated the fastest onset of action (1 week) both for platelet count increase and IgG decrease.
- Rozanolixizumab treatment provided substantial, transient reduction of serum IgG levels with no association with infections.
- These safety, tolerability, efficacy, and pharmacodynamic data support the ongoing phase 3 development of rozanolixizumab as a maintenance treatment in patients with primary ITP (NCT04200456).

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DOI: 10.1002/ajh.25680

RESEARCH ARTICLE

AJH WILEY

Phase 2 study of efgartigimod, a novel FcRn antagonist, in adult patients with primary immune thrombocytopenia

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TABLE 1 Summary of demographics and baseline characteristics

	Placebo (N = 12)	Efgartigimod 5 mg/kg (N = 13)	Efgartigimod 10 mg/kg (N = 13)	Total (N = 38)
Age (years), median (range)	38.5 (19-69)	41.0 (22-77)	46.0 (29-62)	41.0 (19-77)
Gender, n (%)				
Male	5 (41.7)	4 (30.8)	9 (69.2)	18 (47.4)
Female	7 (58.3)	9 (69.2)	4 (30.8)	20 (52.6)
ITP Classification, n (%)				
Newly diagnosed (≤3 months)	-	2 (15.4)	-	2 (5.3)
Persistent (>3 and ≤ 12 months)	3 (25.0)	1 (7.7)	4 (30.8)	8 (21.1)
Chronic (>12 months)	9 (75.0)	10 (76.9)	9 (69.2)	28 (73.7)
Duration of ITP (years), median (range)	3.51 (0.3-47.8)	4.46 (0.1-34.2)	5.42 (0.7-28.7)	4.82 (0.1-47.8)
Baseline platelet count ($\times 10^9$/L), mean (range)	18.3 (4-40)	17.3 (6-49)	15.3 (5-35)	16.9 (4-49)
Baseline platelet count $< 15 \times 10^9$/L, n (%)	6 (50.0)	7 (53.8)	7 (53.8)	20 (52.6)
Number of prior treatments for ITP, median (range)	2.0 (1–7)	2.0 (1–8)	1.0 (0–10)	2.0 (0-10)
Number of patients with prior ITP therapy, n (%)	12 (100.0)	13 (100.0)	12 (92.3)	37 (97.4)
Prior ITP therapy				
Corticosteroids n (%)	9 (75.0)	11 (84.6)	12 (92.3)	32 (84.2)
IVIg or anti-D Ig, n (%)	5 (41.7)	4 (30.8)	2 (15.4)	11 (28.9)
TPO-RA, n (%)	4 (33.3)	6 (46.2)	4 (30.8)	14 (36.8)
Rituximab, n (%)	3 (25.0)	4 (30.8)	2 (15.4)	9 (23.7)
Immunosuppressants, n (%)	5 (41.7)	3 (23.1)	1 (7.7)	9 (23.7)
Danazol, n (%)	1 (8.3)	1 (7.7)	-	2 (5.3)
Splenectomy, n (%)	1 (8.3)	2 (15.4)	3 (23.1)	6 (15.8)
Other, n (%)	3 (25.0)	2 (15.4)	-	5 (13.2)
Number of patients with concurrent ITP therapy at baseline, n (%)	8 (66.7)	11 (84.6)	8 (61.5)	27 (71.1)
Concurrent ITP therapy at baseline				
Corticosteroids, n (%)	3 (25.0)	10 (76.9)	6 (46.2)	19 (50.0)
TPO-RA, n (%)	3 (25.0)	4 (30.8)	3 (23.1)	10 (26.3)
Immunosuppressants, n (%)	1 (8.3)	-	1 (7.7)	2 (5.3)
Other, n (%)	1 (8.3)	1 (7.7)	-	2 (5.3)

Note: percentages are based on N.
Abbreviations: Ig, immunoglobulin; ITP, immune thrombocytopenia, IVIg, intravenous immunoglobulin; N, number of patients in the analysis set; n, observed number of patients within each treatment group; TPO-RA, thrombopoietin receptor agonist.

Four weekly doses

RESULTS

	Placebo N= 12	Efgartigimod 5 mg/Kg (N= 13)	Efgartigimod 10 mg/Kg (N= 13)
Safety			
At least 1 AE*	7 (58.3%)	9 (69.2%)	11 (84.6%)
At least 1 SAE	-	-	1 (7.7%)
Efficacy			
Platelet count ≥ 50 x 10^9/L at any time	6 (50%)	7 (58.3%)	7 (58.3%
Platelet count ≥ 100 x 10^9/L at any time	1 (8.3%	6 (46.2%)	5 (38.5%)
Platelet count ≥ 50 x 10^9/L for 10 days	0 (%)	6 (46.2%)	4 (30.7%)

* Most common AE were cutaneous bleeding symptoms, hypertension, headache. No deaths reported

bjh research paper

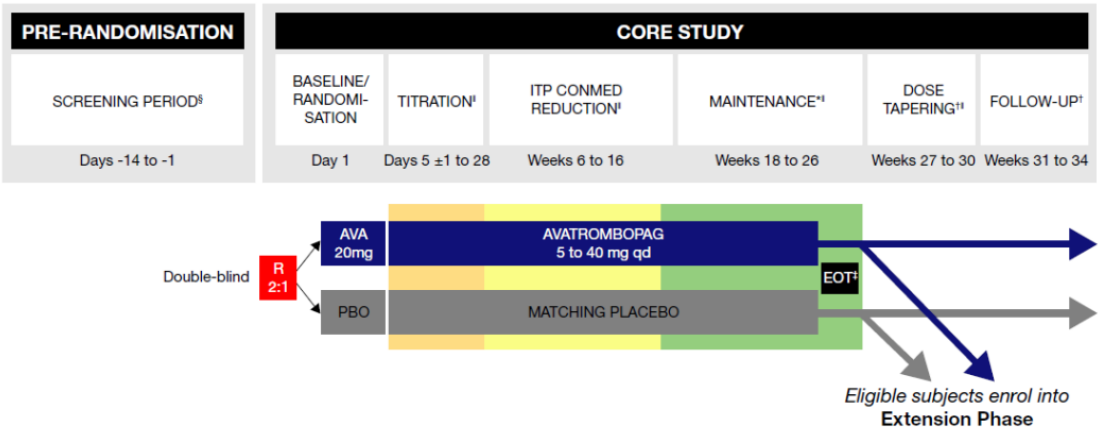
Phase 3 randomised study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia

Wojciech Jurczak,[1] Krzysztof Chojnowski,[2] Jiří Mayer,[3] Katarzyna Krawczyk,[1] Brian D. Jamieson,[4] Wei Tian[4] and Lee F. Allen[4]

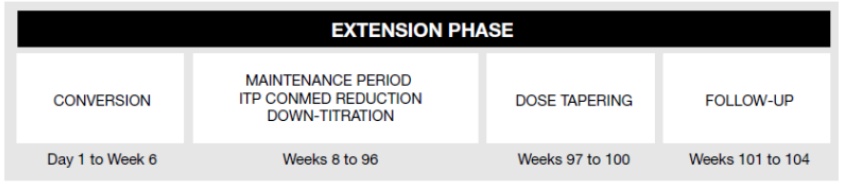
 British Journal of Haematology, 2018, **183,** 479–490

First published online 7 September 2018
doi: 10.1111/bjh.15573

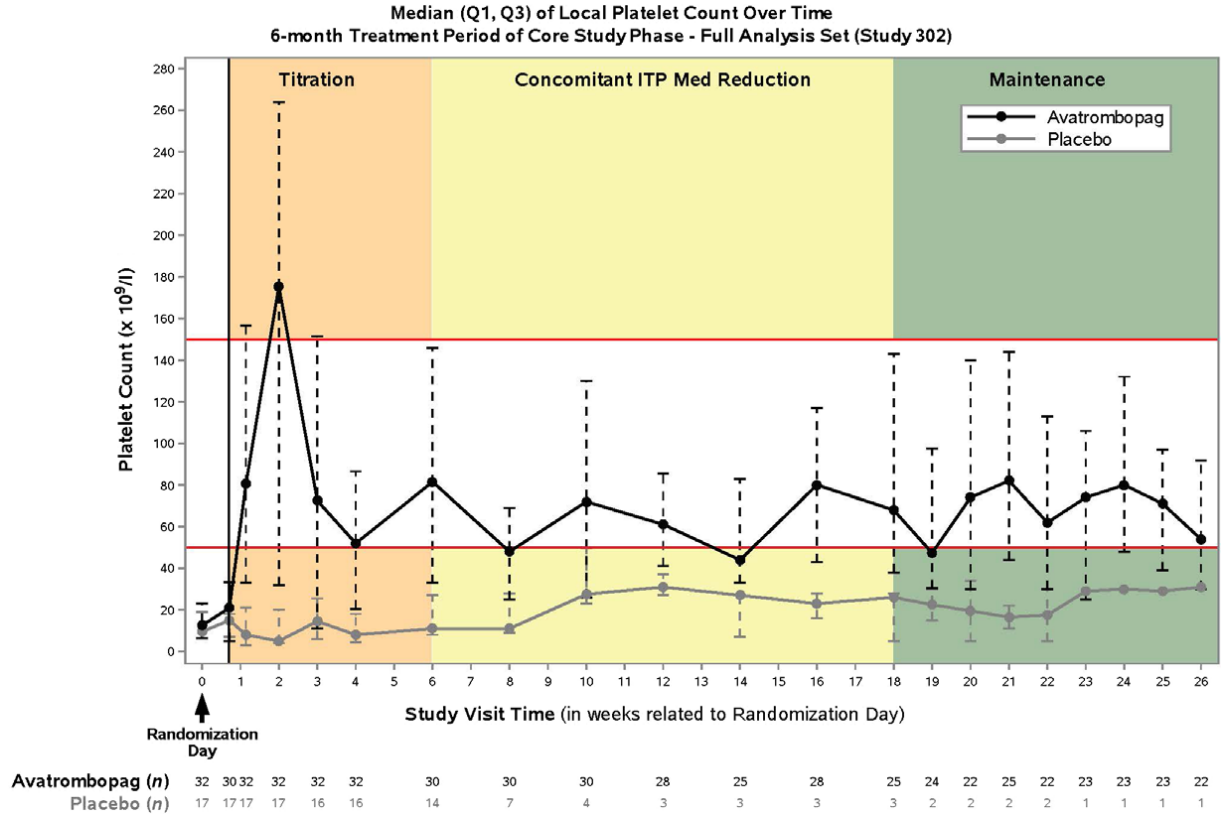
(A) Core study design



(B) Extension phase design



Avatrombopag can be administered orally with food, has no significant hepatotoxicity



Three patients (94%) reported a thromboembolic event in the core study:

- ✓ 1 deep vein thrombosis (day 8),
- ✓ 1 asymptomatic pulmonary embolism (day 154)
- ✓ 1 cerebrovascular event (day 89).

One additional thromboembolic event of jugular vein thrombosis (day 335) was reported in the open-label extension phase.

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Article type : Guidelines

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Practical guidance for the management of adults with Immune Thrombocytopenia during the COVID-19 pandemic

Pavord S, Thachil J, Hunt B, Murphy M, Lowe G, Laffan M, Makris M, Newland A, Provan D, Grainger J, Hill Q.

- Significant thrombocytopenia is uncommon in COVID-19 positive patients until end stage disease.

- Very low platelet counts of <20 x 10^{9}/l, or a sudden fall in the platelet count >50% over 24-48 hours may indicate an immune aetiology.

- Other causes of immune thrombocytopenia, such as Heparin-Induced-Thrombocytopenia, MicroAngiophatic Haemolytic Anemia and drugs, should be considered before a diagnosis of ITP is made.

First-line therapy for ITP during COVID-19 pandemic

- There is little evidence to inform the optimal management of a patient presenting with new or relapsed acute ITP.

- In patients who are **negative** for COVID-19, TPO-RAs may be preferred as first line treatment, to avoid corticosteroids which may increase risk of COVID-19 infection during the pandemic.

- In patients who are **positive** for COVID-19, TPO-RAs may potentially increase the thrombotic complications and identifying eltrombopag hepatotoxicity may be difficult.

- If steroids are used as first line therapy, the dose and duration should be kept to the minimum necessary.
- A starting dose of 20mg daily may be considered in non-bleeding patients, with increase to 1mg/kg after 3-5 days if there has been no response.
- Steroid doses should be tapered after 2 weeks – slowly if there has been good response, rapidly if there is no response.
- Intravenous immunoglobulin (1g/kg) may be necessary if immediate elevation of the platelet count is required to control bleeding. It may also be used as second line treatment if there is failure to respond to steroids.
- Tranexamic acid in COVID-19 infected patients should be used as required for the management of bleeding in ITP patients, but avoided in those with frank DIC.
- Platelet transfusions should only be given if bleeding is thought to be life threatening, or at a critical site

- *Patients with chronic ITP should remain on their usual treatment.*
- They should be vigilant with self-isolation and shielding measures as appropriate.
- Splenectomised patients should be stringent with their antibiotic prophylaxis and up to date with vaccinations.
- Regular patient contact should be maintained and appointments conducted by telephone or online platforms.

Thrombotic risk associated with ITP

- One should be mindful of a potential further increase in thrombotic risk in patients with COVID-19 from ITP or its treatment.
- ITP patients hospitalised with COVID-19 should receive weight-based LMWH thromboprophylaxis provided platelets are ≥ 30 x 10^9/L and there are no hemorrhagic features.
- ITP patients hospitalised with COVID-19 whose platelets are <30 x 10^9/L in whom LMWH is considered unsafe, should have intermittent pneumatic compression until LMWH can be restarted.
- Regular assessment of both bleeding and thrombotic risk should be made throughout the course of the hospital stay and on discharge.

Vicenza experience during COVID pandemic

ID patients	Age at ITP diagnosis (years)	Sex	Platelet at diagnosis (x 10^9/L)	Symptoms	CODIV 19	therapy	Follow-up duration (weeks)	PLT last follow-up (x 10^9/L)	Complications during follow-up
VS	27	F	3	Cutaneous bleeding + epistaxis	N	P + Ig	4	487	None
AL	21	M	4	Cutaneous bleeding + gingival bleeding and oral cavity bullae	N	P + Ig	4	129	None
MP	43	M	6	Cutaneous bleeding + oral cavity bullae	N	P + Ig	4	133	None
GD	62	F	2	Melena + intracranic bleeding	N	D + Ig	4	162	Pneumonitis*
VM	75	F	18	None	N	P	4	112	None

Table 1

F: female

M: male

P: prednisone, 1 mg/Kg/b.w./day for 21 days, then tapering

Ig: intravenous immune globulins, 1 g/Kg/b.w./day for 2 days

D: dexamethasone, 40 mg/day for 4 days

*: previous diagnosis of high grade non-hodgkin lymphoma, treated with rituximab and polichemotherapy

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Article type : Letters

Clinical characteristics, management and outcome of Covid-19-associated immune thrombocytopenia. A French multicenter series.

Matthieu Mahévas[1], Guillaume Moulis[2], Emmanuel Andres[3], Etienne Riviere[4], Margaux Garzaro[5], Etienne Crickx[1], Vivien Guillotin[3], Marion Malphettes[5], Lionel Galicier[5], Nicolas Noel[6], Luc Darnige[7], Louis Terriou[8], Claire Guerveno[9], Mateo Sanchis-Borja[10], Thomas Moulinet[11], Benoit Meunier[12] , Mikael Ebbo[12], Marc Michel[1] and Bertrand Godeau[1].

-14 ITP patients with RT-PCR confirmed SARS-CoV-2 infection
(14 days median time from COVID manifestation to ITP diagnosis)

-11/14 patients had initial platetet count ≤ 10 x 10^9/L

-4/14 patients had severe bleeding symptoms

-4/14 patients were treated with *corticosteroids* alone: initial response after 10 days (median)
-1/14 patient was treated with *dexamethasone* (40 mg/day for 4 days): CR after 5 days

None of these 5 patients experienced a worsensing of COVID-19 pneumonia

-9/14 patients were treated with *IVIG* (alone in 4, with corticosteroid in 1, with TPO-RA in 4) with a rapid initial response

After a median follow-up of 60 days, 3/14 patients had a relapse

No thrombosis was observed

The outcome of COVID-19 was favorable in all cases

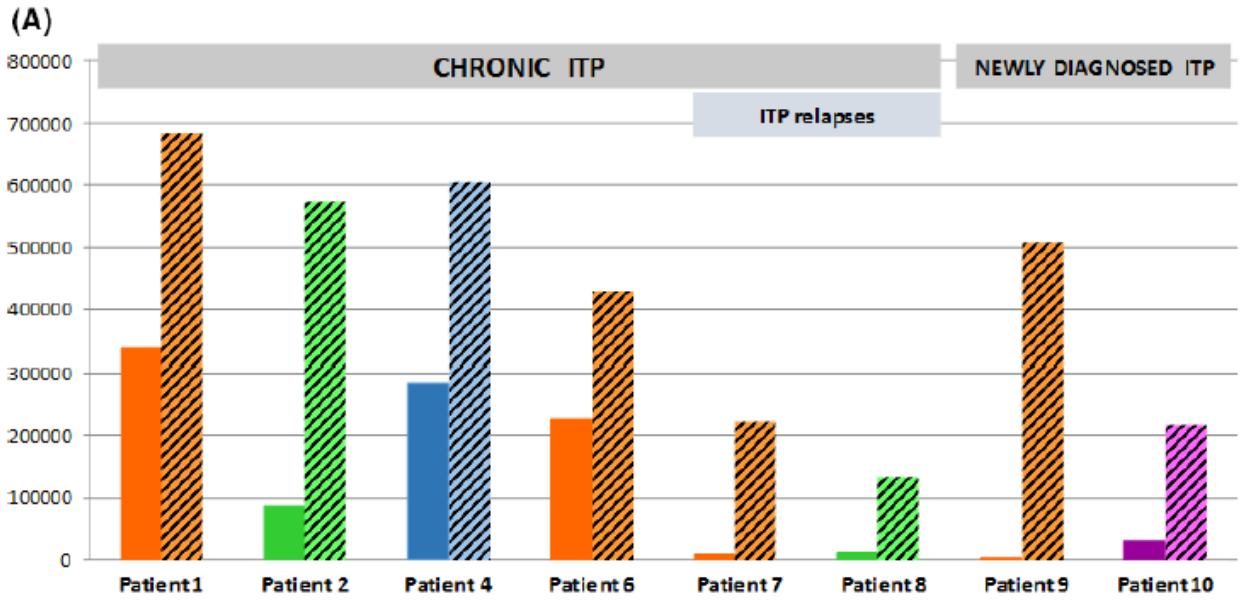
bjh short report

doi: 10.1111/bjh.17077

bjh BRITISH JOURNAL OF HAEMATOLOGY

Paradoxical effect of SARS-CoV-2 infection in patients with immune thrombocytopenia

de la CRUZ-BENITO *et al.*



Platelet at day 1 (plain column) and at day 8 (striped column)

GRAZIE per l'ATTENZIONE