Combination therapies for refractory disease.

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Tomás José González-López. Conflicts of Interest.

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis	X		X		X	X	
Amgen	X		X		X	X	
Grifols	X		X		X	X	
Sobi	X		X		X	X	
Argenx			X		X		
UCB			X		X		
Alpine			X		X		
Momenta			X		X	X	
Nuvig			X				
Lilly			X				

Refractory ITP (Refractory disease)

Definitions

NR: platelet count **< 30 × 10^9/L** or **a < 2-fold increase in baseline** platelet count or **bleeding**

Loss of CR or R: platelet count **< 100 × 10^9/L** or **bleeding (for CR)** or **< 30 × 10^9/L** or **a < 2-fold increase in baseline** platelet count or **bleeding (for R)**

Timing of assessment of response to ITP treatment: **variable**, **dependent on the type of treatment**

Rodeghiero F, et al. Blood. 2009;113:2386-93.

Individual agents for ITP treatment; time to the first peak response

Agent/treatment	Time to initial R, days	Time to peak R, days
Prednisone	4–14	7–28
Dexamethasone	2–14	4–28
IVIg	1–3	2–7
Anti-D	1–3	3–7
Rituximab	7–56	14–180
Splenectomy	1–56	7–56
Vincristine	7–14	7–42
Vinblastine	7–14	7–42
Danazol	14–90	28–180
Azathioprine	30–90	30–180
Romiplostim	5–14	14–60
Eltrombopag	7–28	14–90

IVIg, intravenous immunoglobulin.

Rodeghiero F, et al. Blood. 2009;113:2386-93.

Definition of refractory ITP: (all criteria must be met)

Failure to **achieve** at least **R** or a **loss of R after splenectomy**

Need for treatment(s) (including, but not limited to, low-dose corticosteroids) to **minimize** the **risk** of clinically significant **bleeding**

- Patients who require on-demand or adjunctive therapy alone are not classed as refractory

Primary ITP confirmed by **excluding** any **additional, unrelated causes** of **thrombocytopenia**

IVIg, intravenous immunoglobulin.

Rodeghiero F, et al. Blood. 2009;113:2386-93.

Multirefractory ITP

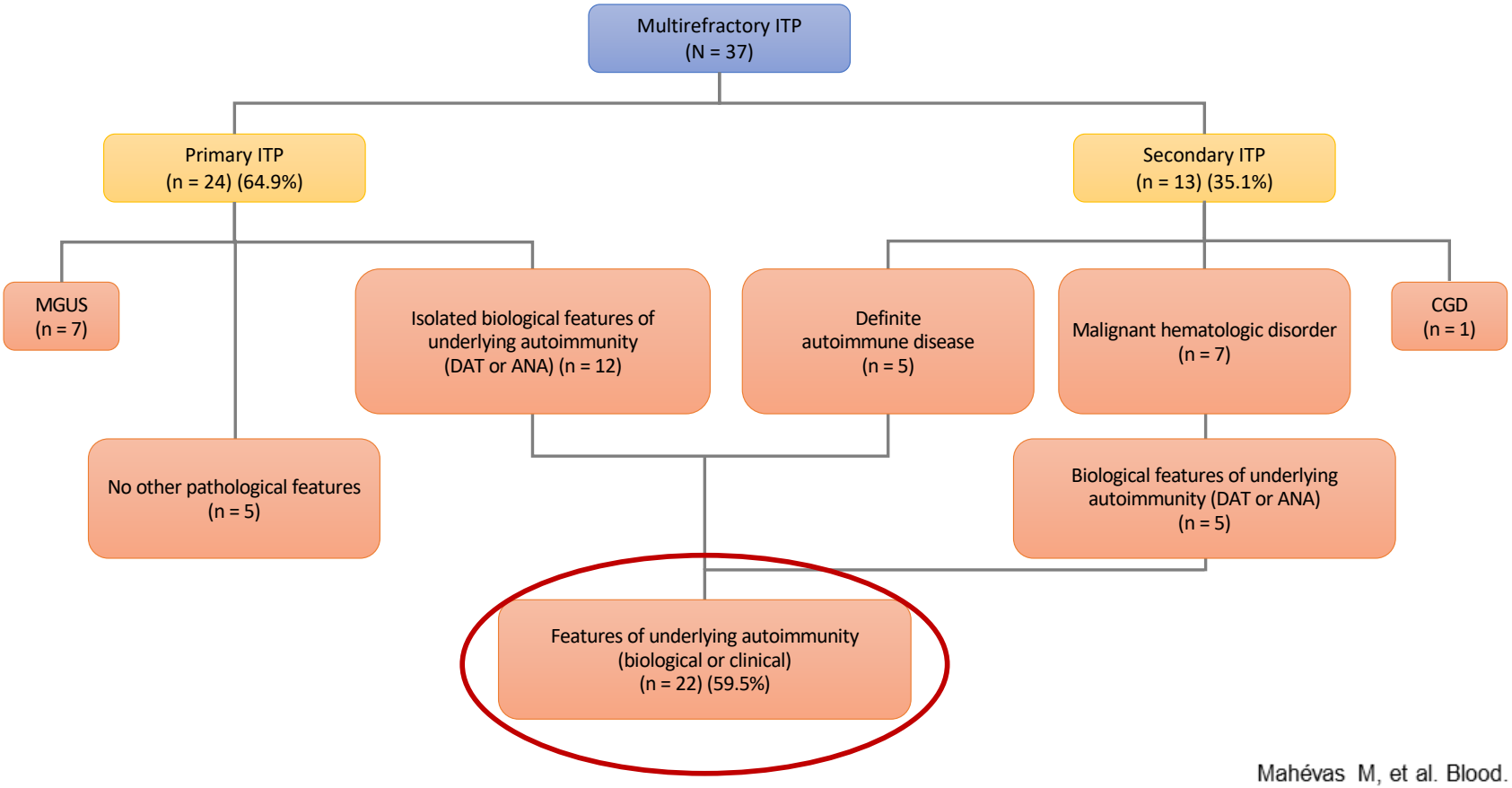
Definition of multirefractory ITP.

Patients with **severe** (i.e. symptomatic) **chronic ITP** who are **not responding** to **rituximab, splenectomy** (or if splenectomy was contraindicated), and **TPO-RAs** licensed in France **(romiplostim and eltrombopag)** **used at the maximum approved dose** (10 mg/kg body weight per week for romiplostim, 75 mg/day for eltrombopag), excluding patients in whom TPO-RAs had to be stopped because of severe side effects

- Multirefractory ITP patients could have achieved a **transient response** to **corticosteroids and/or IVIg** because these treatments are considered first line and/or rescue therapies

Mahévas M, et al. Blood. 2016;128:1625-30.

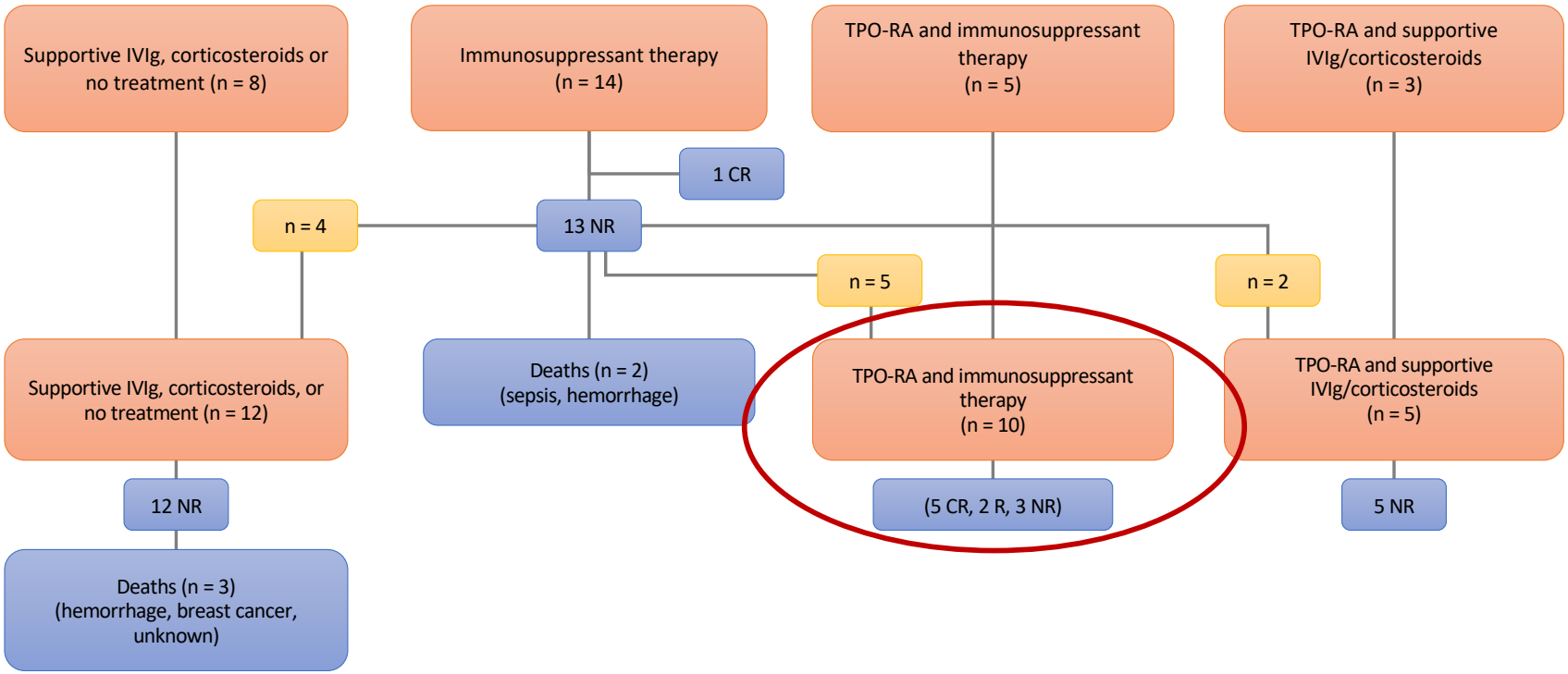
Overview of initial characteristics of multirefractory ITP patients



Mahévas M, et al. Blood. 2016;128:1625-30.

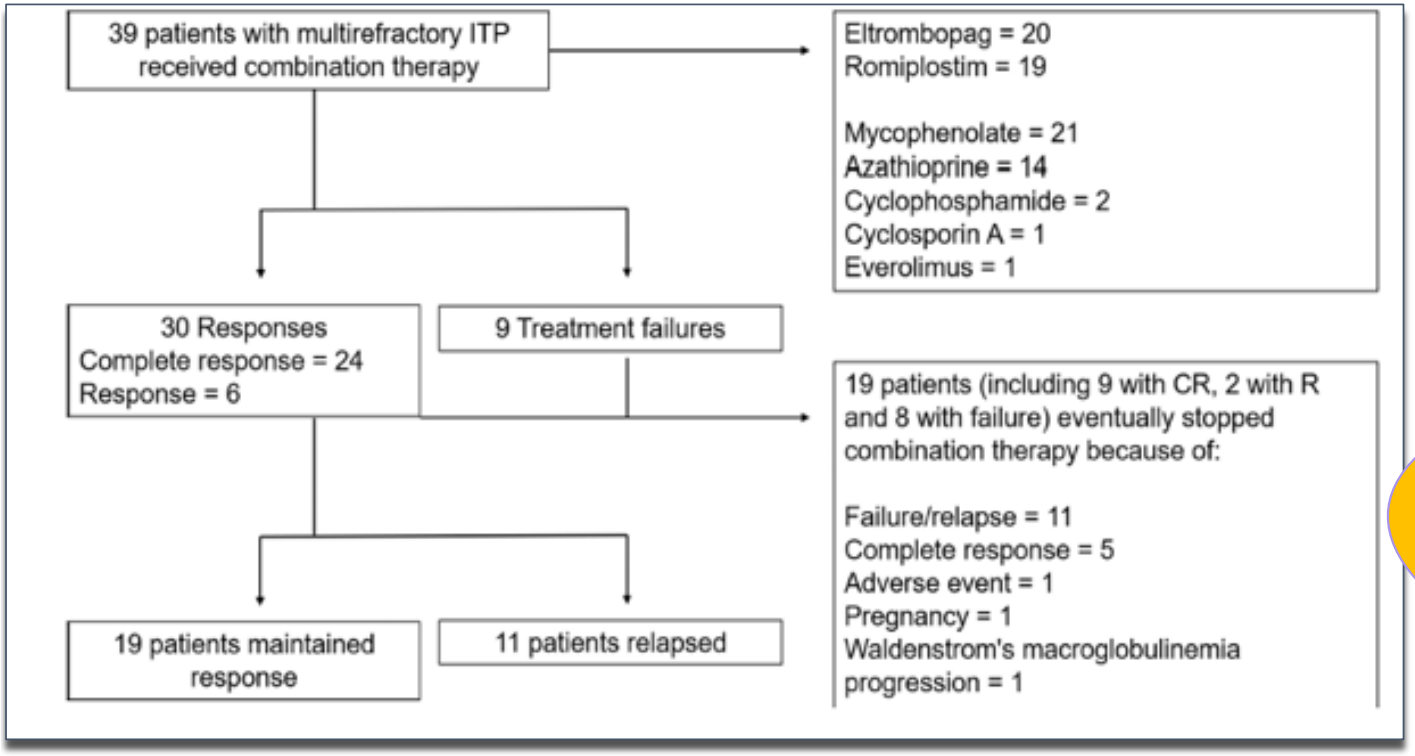
Response to therapy of multirefractory ITP patients

30 multirefractory ITP patients without malignant hematological disorder



Mahévas M, et al. Blood. 2016;128:1625-30.

Multi-refractory ITP: Update on the French Experience



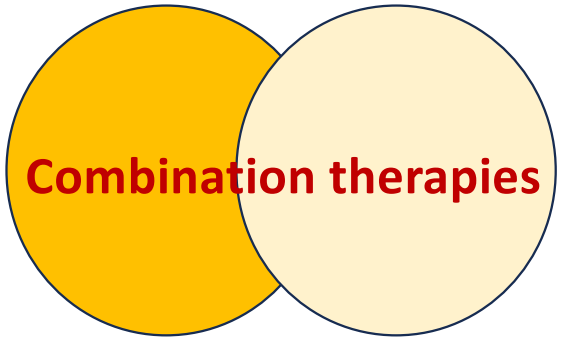
- **77% achieved at least a response**
- **After a median follow--up of 21 months**
  - **63% in response**
  - **37% relapsed**

Multi-refractory defines as **failure to response to rituximab, romiplostim and eltrombopag and splenectomy** (except if splenectomy was contra-indicated or refused by the patient)

Crickx et al. Br J Haematol. 2023;00:1–7.

Combination therapies in refractory ITP

Combination therapies; advantages and disadvantages



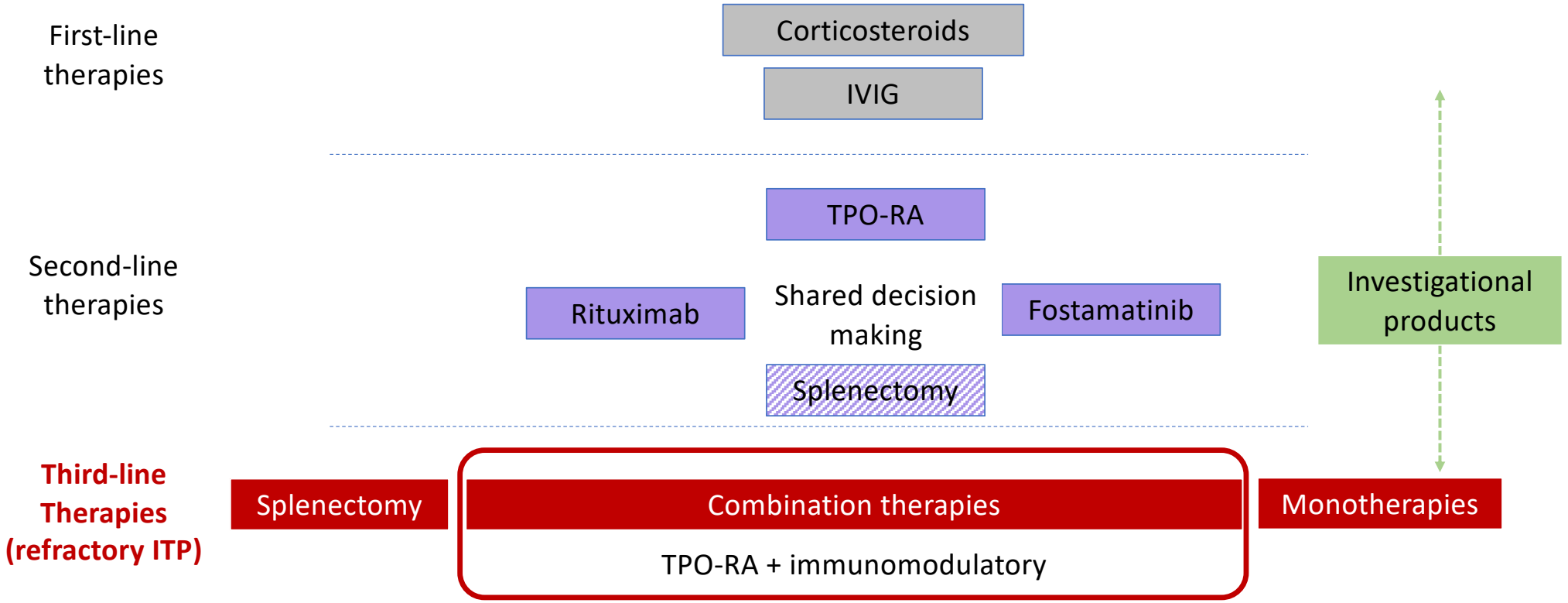
Advantages

- Higher response/remission rates
- Quicker time to response

Disadvantages

- Potential for increased toxicity
- Higher cost

Current Therapeutic Approach to Treatment of ITP



Modified from 1-Matzdorff A et al. Qual Res Treat. 2023;46:5-44; 2-Neunert C et al. Blood Adv. 2019;3:3829-3866; 3- Provan D et al. Blood avd 2019; 26:3:3780-3817; Ghanima et al. Blood 2021; 24; 137(20):2704-2714

TPO-RA, thrombopietin receptor agonists; IVIG, IV immunoglobulin

Combination therapies in refractory ITP: pre-TPO-RA era

Boruchov DM, et al. Blood. 2007

- Acute treatment (**IVIg, anti-D, vincristine, and vinblastine**); **17 patients; R 66%; SAEs: 6% thrombosis**
- Maintenance treatment (danazol and azathioprine); **18 patients; R** at **4 months 71%; SAEs: 6% ileus**

Gómez-Almaguer D, et al. Blood. 2010

- **Rituximab and alemtuzumab**; **11 patients**
- **CR 45%; PR 55%**
- **SAEs:** 0% kidney or liver SAEs; **18% HSV; 36% UTI; 9% death** from unclear cause

Arnold DM, et al. Blood. 2010

- **Azathioprine, CSA, MMF**; **19 patients**
- **CR 11%; PR 63%**
- **SAEs:** 0% kidney or liver SAEs; **32% infections**; 16% gum hypertrophy and tremors

Combination therapies in refractory ITP: post-TPO-RA era (I)

Wang S, et al. Int J Hematol. 2012
- 2 treatment arms
  - **rhTPO + danazol**; 73 patients; **R 60%**
  - **Danazol**; 19 patients; **R 37%**
- **SAEs: 9% visual field defects**

Cui ZG, et al. Chin Med J. 2013
- 2 treatment arms
  - **rhTPO + CSA**; 19 patients; **R** at **3 months 71%**
  - **rhTPO**; 19 patients; **R** at **3 months 13%**
- **SAEs:** 0% kidney or liver SAEs, or thrombosis or infections

Choi PY, et al. Blood. 2015
- **Dexamethasone + CSA, then rituximab afterwards**; **20 patients**
- **R** at **6 months 60%**
- **SAEs: 5% infections; 15% hypertension**

Combination therapies in refractory ITP: post-TPO-RA era (II)

Zhou H, et al. Blood. 2015
- 2 treatment arms
  - **rhTPO + rituximab**; 77 patients; **CR 45%; SAEs: 26% infections**
  - **Rituximab**; 38 patients; **CR 23%; SAEs: 21% infections**
- **SAEs in both arms:** 0% kidney or liver SAEs, or thrombosis

Gudbrandsdottir S, et al. Br J Haematol. 2020
- **CSA/MMF, TPO-RA, and IVIg**; **18 patients**
- **CR + PR 72%**
- **SAEs:** 6 cases of hypertension

Feng FE, et al. Lancet Haematol. 2017
- 2 treatment arms
  - **Danazol + ATRA**; 45 patients; **R 47%**
  - **Danazol**; 48 patients; **R 15%**
- **SAEs in danazol only arm: 6% liver SAEs**

Combination therapies in refractory ITP: post-TPO-RA era (III)

Mahévas M, et al. Blood. 2016

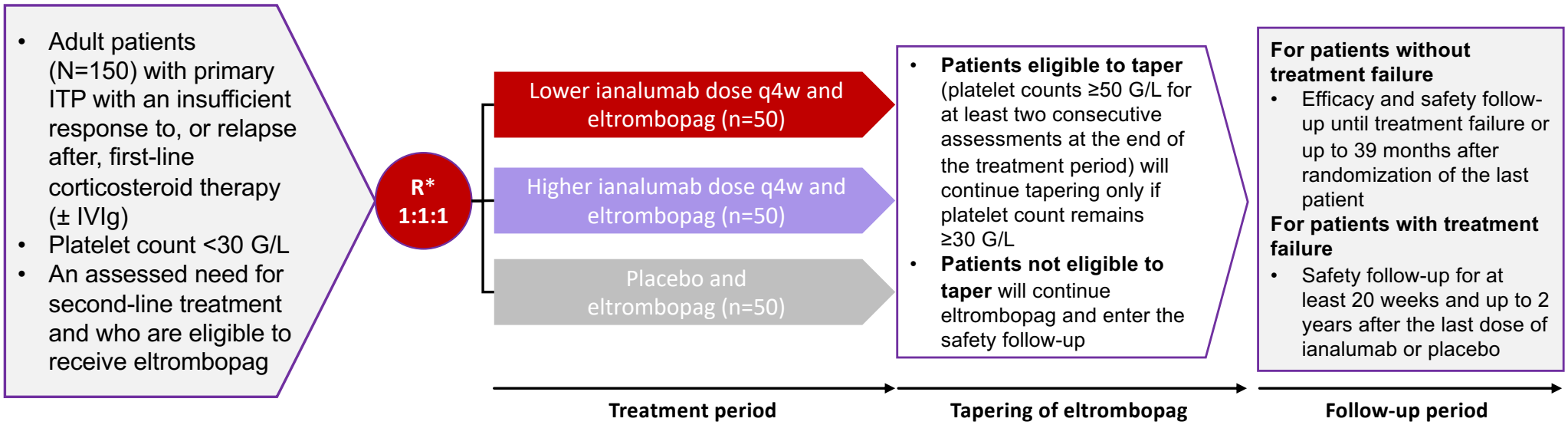
- **4 treatment arms**
  - **Supportive IVIg, GCs, or no treatment**; 12 patients; **12 NR**
  - **Immunosuppressants**; 14 patients; **R 7%**
  - **TPO-RA + immunosuppressants**; 10 patients; **R 70%** (15 months of follow-up)
  - **TPO-RA and supportive IVIg/GCs**; 5 patients; **R 30%**
- **SAEs: 24% thrombosis, 40% infections, 3% sepsis**

Mahévas M, et al. Haematologica. 2020

- BAFF may be involved in the failure of B cell depleting therapy with rituximab
- Phase 2b trial of synergy of **rituximab + belimumab (anti-BAFF antibody)**
- 13/15 patients (86.7%) achieved an initial overall response at Week 12, with 9 patients (60%) in CR
- **SAEs: 0%**

VAYHIT2: Ianalumab in addition to second-line eltrombopag

VAYHIT2 study design (NCT05653219) is a randomized, double-blind, placebo-controlled, Phase III study



VAYHIT3: Ianalumab in ITP with at least two prior lines of therapy

A Phase 2 Study of Ianalumab in Patients with Primary Immune Thrombocytopenia Previously Treated with at Least Two Lines of Therapy: Interim Results from VAYHIT3

David J. Kuter[1], Tomas Jose Gonzalez-Lopez[2], Karolin Trautmann Grill[3], Mathias Rummel[4], Philip Choi[5], Alessandra Borchiellini[6], Muhlis Cem Ar[7], Huyen Anh Michael Tran[8], Tie Nan Zhu[9], Jae-Ho Yoon[10], Nichola Cooper[11], Thomas Stauch[12], Pinar Tarkun[13], Fabienne Le Gac[14], Alex Allepuz[14], Patrick Urban[14], Renxin Lin[15], Charlotte Bradbury[16]

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Avatrombopag plus fostamatinib combination as treatment in patients with multirefractory immune thrombocytopenia

Retrospective, multicenter, two countries, observational study

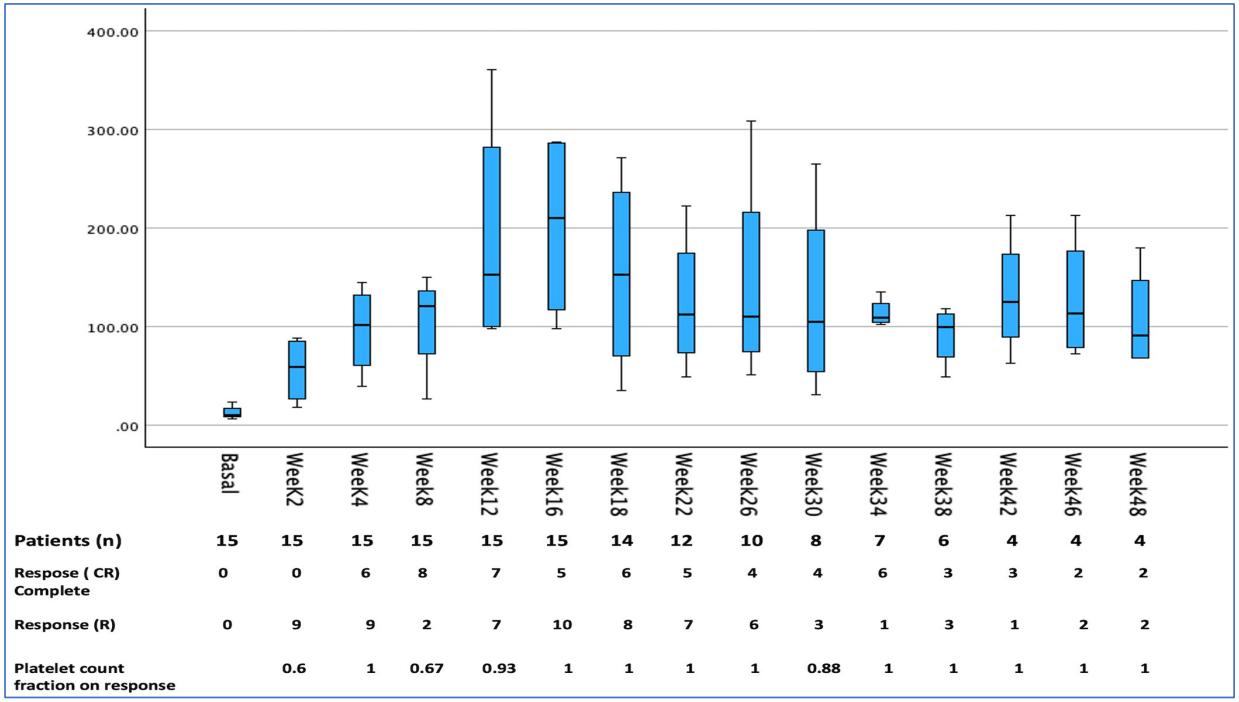
N 18
Median 5 treatments prior to combination

OR 83%
15/18 Overall response; 8/15 CR

15 days
(range: 8–35 days)
Median time to response

Relapse 27%
Relapsed during dose tapering

Platelet count response and evolution in responding patients



	Basal	WeeK2	WeeK4	Week8	Week12	Week16	Week18	Week22	Week26	Week30	Week34	Week38	Week42	Week46	Week48
Patients (n)	15	15	15	15	15	15	14	12	10	8	7	6	4	4	4
Respose (CR) Complete	0	0	6	8	7	5	6	5	4	4	6	3	3	2	2
Response (R)	0	9	9	2	7	10	8	7	6	3	1	3	1	2	2
Platelet count fraction on response		0.6	1	0.67	0.93	1	1	1	1	0.88	1	1	1	1	1

[a] Response PC 30-100 x 10^9/L and complete response PC >100 x 10^9/L. AVA,

Mingot Castellano BJH 2024; DOI: 10.1111/bjh.19602

New drugs for ITP

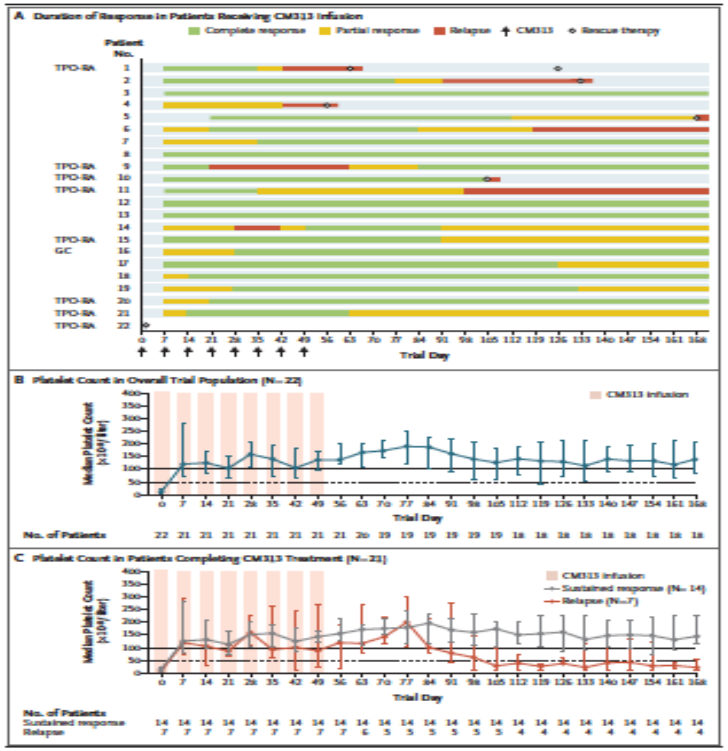
Will they be combined with other drugs in the future?

Anti-CD38 (CM313) provides high response rates in ITP

Single arm phase 1–2, study to evaluate the safety and efficacy of CM313 in adults with ITP

- **CM313 was administered IV** at a dose of 16 mg /kg weekly for 8 weeks, followed by a 16-week follow-up period.
- **Median number of previous therapies: 4**

- **Response: 21/22 (95%) patients had 2 consecutive platelet counts of >50X 10^9 during the treatment period.**
- **Median time to response** (1st platelet count of ≥50 x 10^9) : **1 week (range, 1 to 3)**
- **Safety:** most common AE: **infusion-related reaction** (32% of the patients) and **upper respiratory tract infections** (32%)

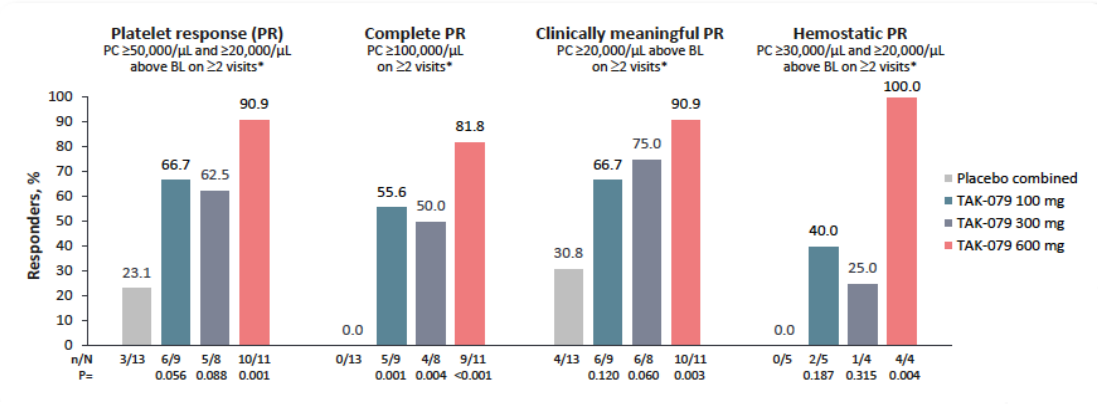


Chen et al. N Engl J Med 2024;390:2178-90

Chen et al. N Engl J Med 2024;390:2178-90

Mezagitamab (TAK-079) in chronic or persistent ITP.

Interim results from a phase 2, randomized, double-blind, placebo-controlled study.



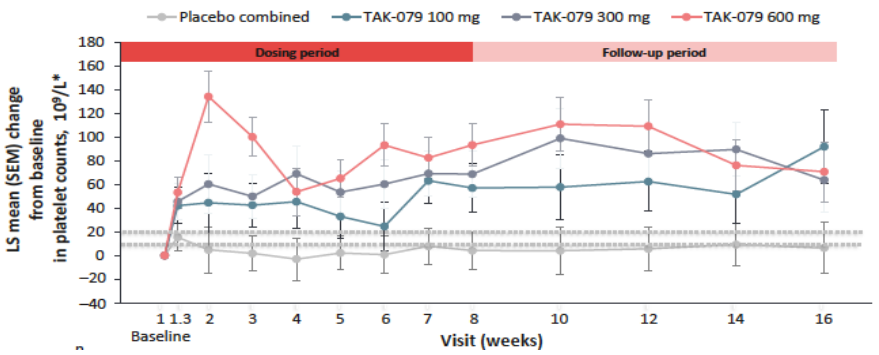
Participants received once weekly subcutaneous mezagitamab or placebo for 8 doses, followed by ≥8 weeks of safety follow-up

In <u>Mezagitamab</u> *versus* <u>Placebo</u> groups:

14.3% versus 0% => AEs leading to discontinuation.

17.9% versus 23.1% => Grade ≥3 TEAEs

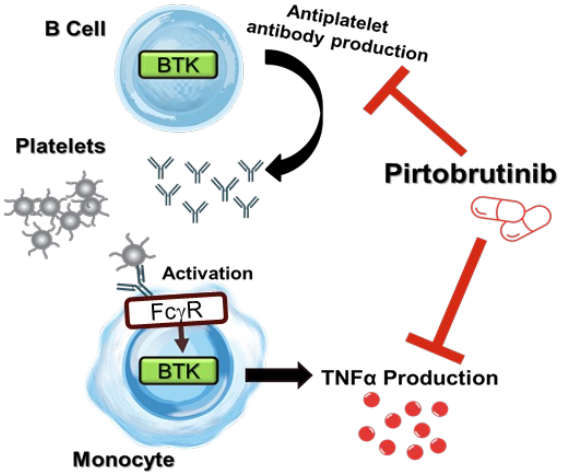
14.3% versus 7.7% => serious adverse events



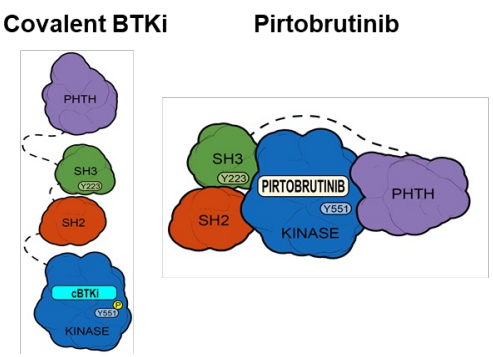
Kuter et al. ISTH 2024

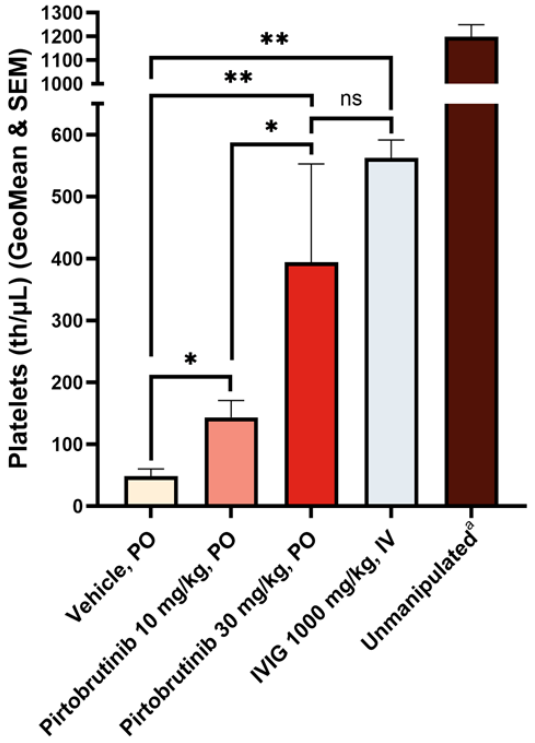
Kuter et al. ISTH 2024

Preclinical ITP Characterization of Pirtobrutinib: A Non-Covalent, Reversible, Bruton Tyrosine Kinase Inhibitor



Pirtobrutinib may stabilize BTK in a closed inactive conformation[4]





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Immunomodulation and TPO-RAs?
Other combinations?

Could ITP be cured with monotherapies/combination therapies in the near future?

Probably YES!

Conclusions

- **ITP pathogenesis is very heterogeneous**. **For refractory patients, combination therapy may be more effective than single-agent therapy.**

- **Successful combination therapies** may include a **TPO-RA** and **medication(s) with different mechanisms of action to inhibit platelet destruction**

- Since chronic ITP can involve more than just accelerated platelet destruction, **≥ 2 agents may be required in combination therapy to provide optimal effective management**

A prayer for Valencia, please!