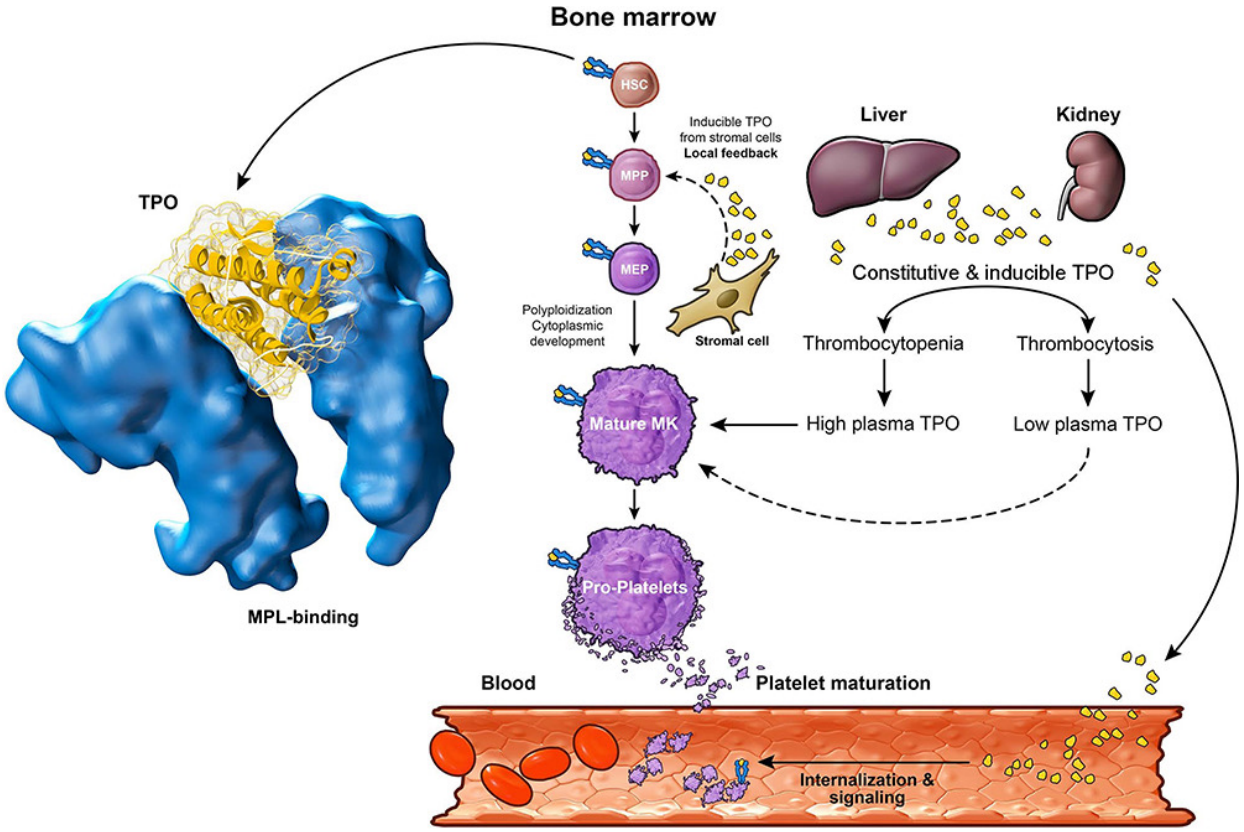
MARIA L LOZANO
HOSPITAL JM MORALES MESEGUER, UNIVERSITY OF MURCIA,
IMIB-PASCUAL PARRILLA, CIBERER

What's new with TPO-RA

Disclosures

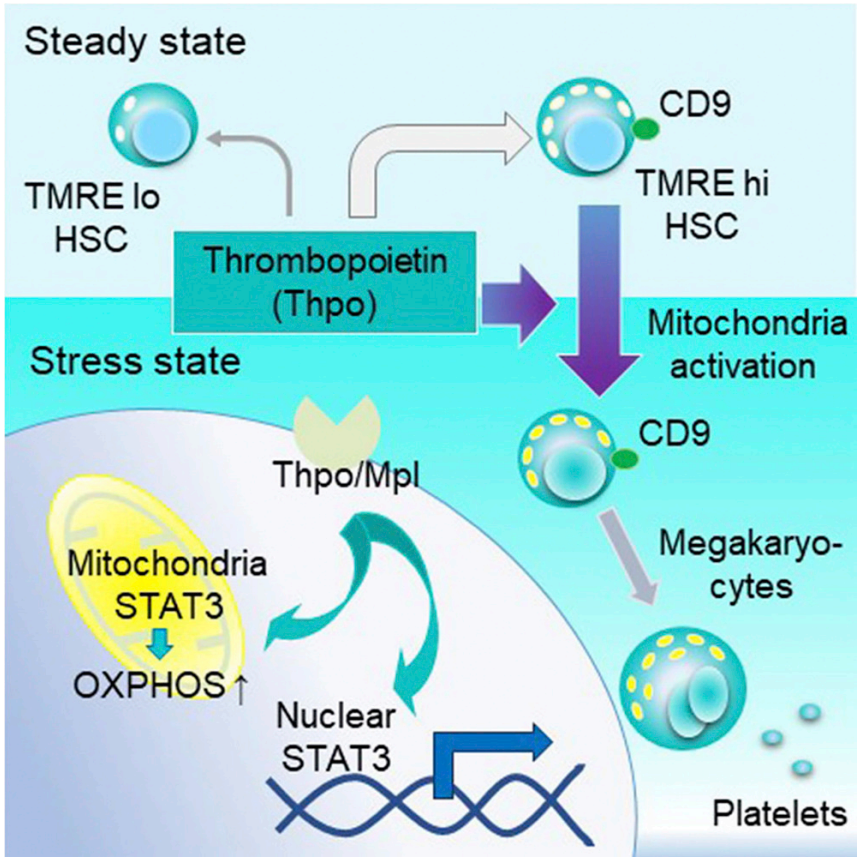
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen	x					x	
Novartis						x	
Argenx						x	
Sobi			x			x	
UCB						x	
Grifols			x			x	
Fujimori Kogyo Co	x						
Terumo	x						

Structure and MoA of thrombopoietin



Bussel JB, et al. Drug Des Devel Ther. 2021;15:2243-2268

Thrombopoietin Primes Hematopoietic Stem Cells to Megakaryocyte-Lineage Differentiation



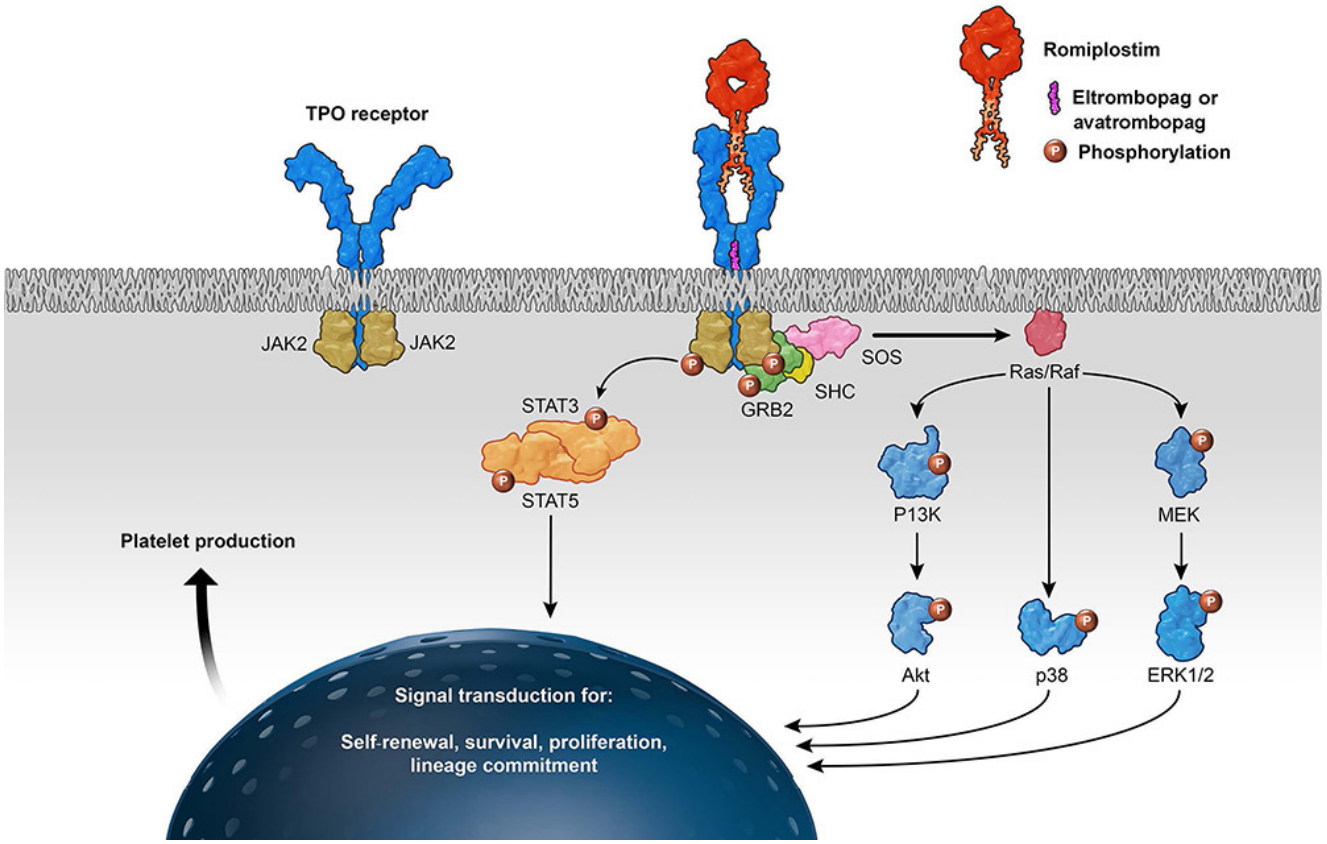
Nakamura-Ishizu A, et al. Cell Reports 2018; 25: 1772-1785.e6

Characteristics of thrombopoietin-receptor agonists (TPO-RA)

	Romiplostim	Eltrombopag	Avatrombopag	Lusutrombopag	Hetrombopag
Structure	Peptide TPO-RA	Small molecule/ non-peptide TPO-RA	Small molecule/ non-peptide TPO-RA	Small molecule/ non-peptide TPO-RA	Small molecule/ non-peptide TPO-RA
Binding site	Binds competitively to the extracytoplasmic domain of the TPO-R in same ways as TPO	Binds to the transmembrane and juxta-membrane domains of the TPO-R	Binds to the transmembrane domain of the TPO-R	Binds to the transmembrane domain of the TPO-R	Binds to the transmembrane domain of the TPO-R
Effect on endogenous thrombopoietin	Can displace TPO from its receptor	No displacement of TPO, may be additive	No displacement of TPO, may be additive	No displacement of TPO, may be additive	No displacement of TPO, may be additive
Confirmed signaling pathways	JAK2/STAT5 P13K/Akt ERK STAT3	JAK2/STAT5 P13K/Akt ERK	JAK2/STAT5 STAT3 ERK	JAK2/STAT5 STAT3	JAK2/STAT5 P13K/Akt ERK STAT3
Route of administration	Subcutaneous	Oral	Oral	Oral	Oral
Dosing frequency	Weekly	Daily	Daily	Daily	Daily
Approved indications by FDA and EMA	· Immune thrombocyto-penia (adults and children)	· Immune thrombocyto-penia (adults and children) · Hepatitis C–associated thrombocytopenia (adults) · Severe aplastic anemia (adults and children)	· Periprocedural thrombo-cytopenia in chronic liver disease patients (adults) · Immune thrombocyto-penia (adults)	· Periprocedural thrombo-cytopenia in chronic liver disease patients (adults)	· None so far

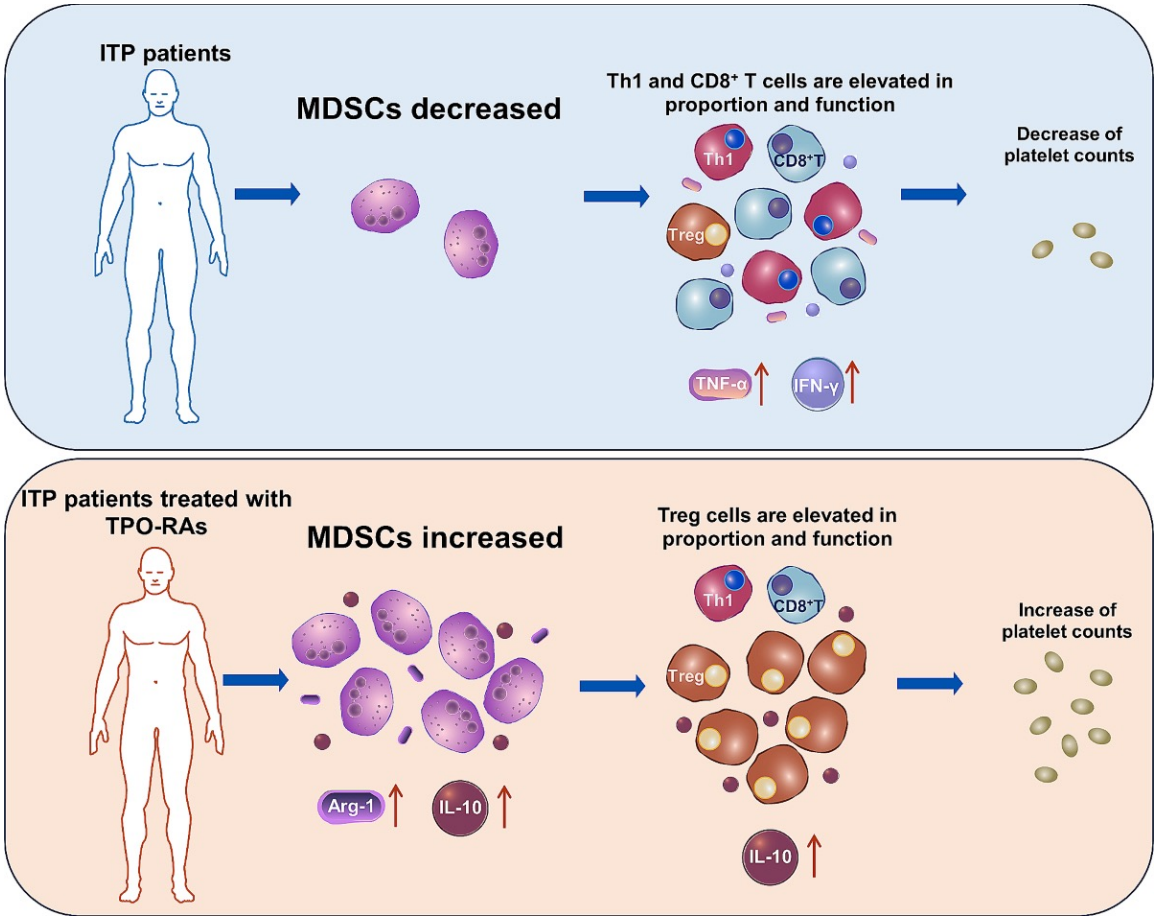
Gebetsberger J, et al. Hämostaseologie 2024; 4:316-325

Cellular mechanism of action of thrombopoietin receptor agonists



Bussel JB, et al. Drug Des Devel Ther. 2021;15:2243-2268

TPO-RA treatment regulates MDSCs-mediated immunomodulatory effects in ITP



Zhu Y, et al. Ann Hematol. 2024;103:2729-2741

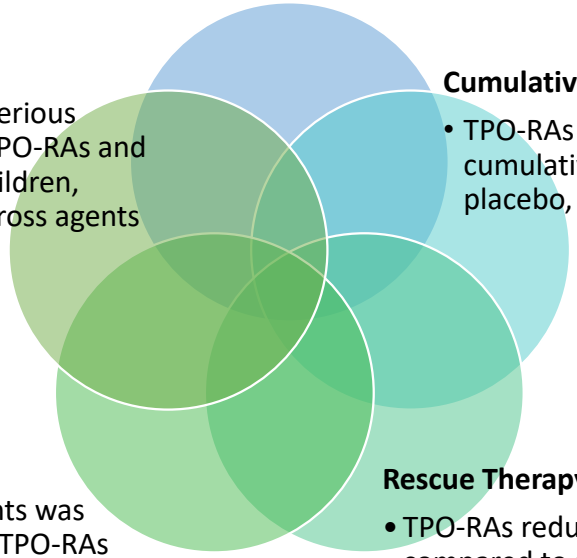
Efficacy and safety of thrombopoietin receptor agonists in children and adults with persistent and chronic immune thrombocytopenia

Overall Platelet Response in Adults:

- **Avatrombopag** demonstrated a higher overall response rate compared to **eltrombopag** and **hetrombopag**, and this difference was statistically significant. There was no significant difference in efficacy between avatrombopag and **romiplostim**

Safety Profile:

- The incidence of adverse events and serious adverse events was similar between TPO-RAs and placebo groups for both adults and children, indicating a favorable safety profile across agents



Cumulative Weeks of Platelet Response:

- TPO-RAs generally showed a significantly longer cumulative duration of platelet response than placebo, both in adults and children

Bleeding Events:

- The incidence of any bleeding events was significantly lower for adults using TPO-RAs compared to placebo. However, this reduction was not consistently observed in children

Rescue Therapy:

- TPO-RAs reduced the need for rescue therapy compared to placebo in both adults and children, with a consistent effect across studies

Li T, et al. Expert Opin Pharmacother. 2023;24:763-774

Adverse Effects of TPO-RAs

Rebound Thrombocytopenia

- A temporary drop in platelets in ~10% of cases, requiring dose adjustment.

Thrombocytosis:

- High platelet counts (>1000×10^9/L) can be seen with all TPO-RA; aspirin may be used if extreme.

Eltrombopag and romiplostim

- Both: Thromboembolic events, mild (usually reversible) bone marrow fibrosis
- Eltrombopag: Elevated liver enzymes (ALT/AST), cataracts, portal vein thrombosis in liver disease.
- Romiplostim: reduced platelet activation threshold.

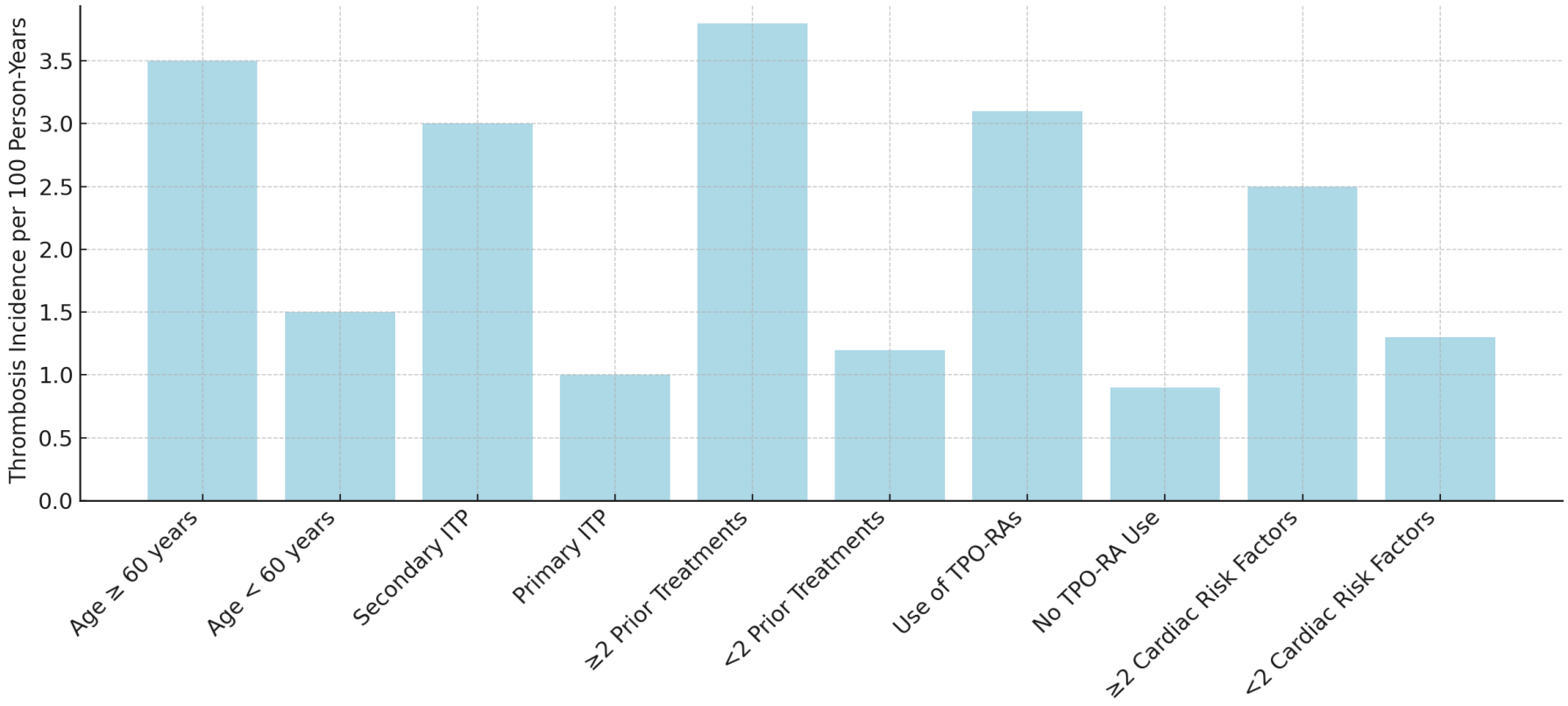
Avatrombopag

- Thromboembolic events; headache; no significant bone marrow or eye-related effects.

Antibody Formation

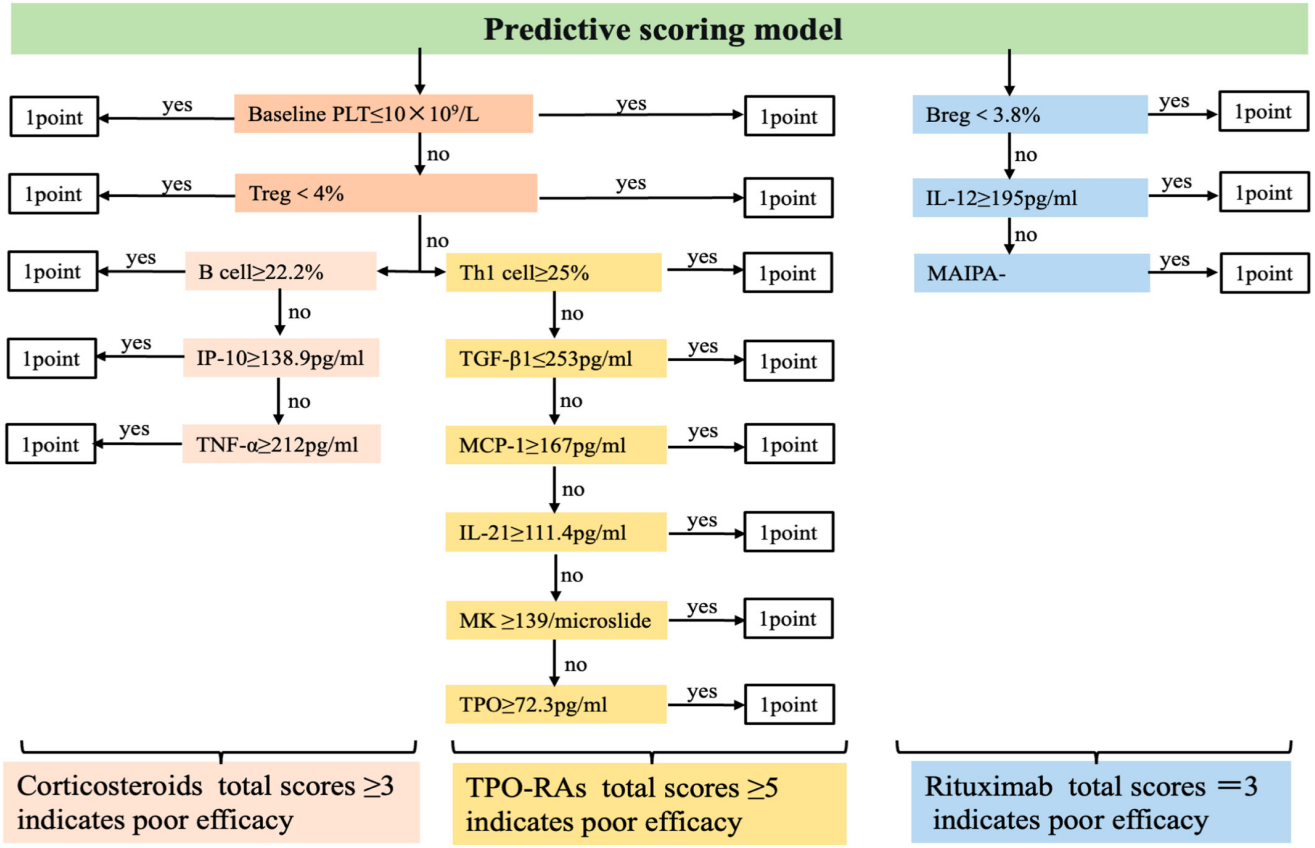
- Rare with romiplostim, no significant impact on platelet levels.

Incidence of thrombosis in ITP patients by risk factors



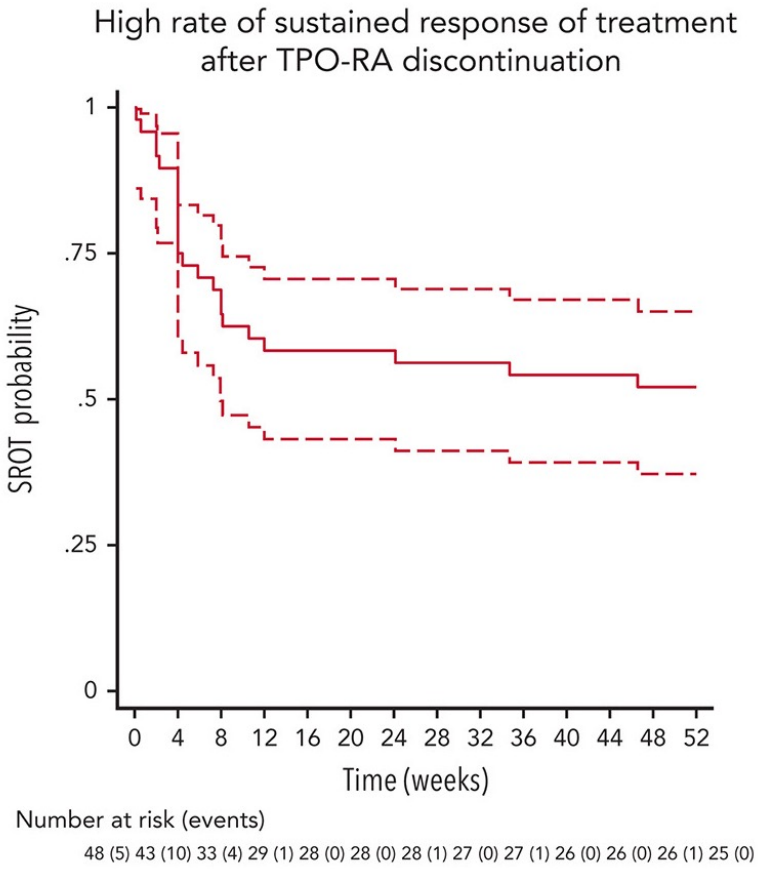
Goncalves I, et al. Res Pract Thromb Haemost. 2024; 8:102342

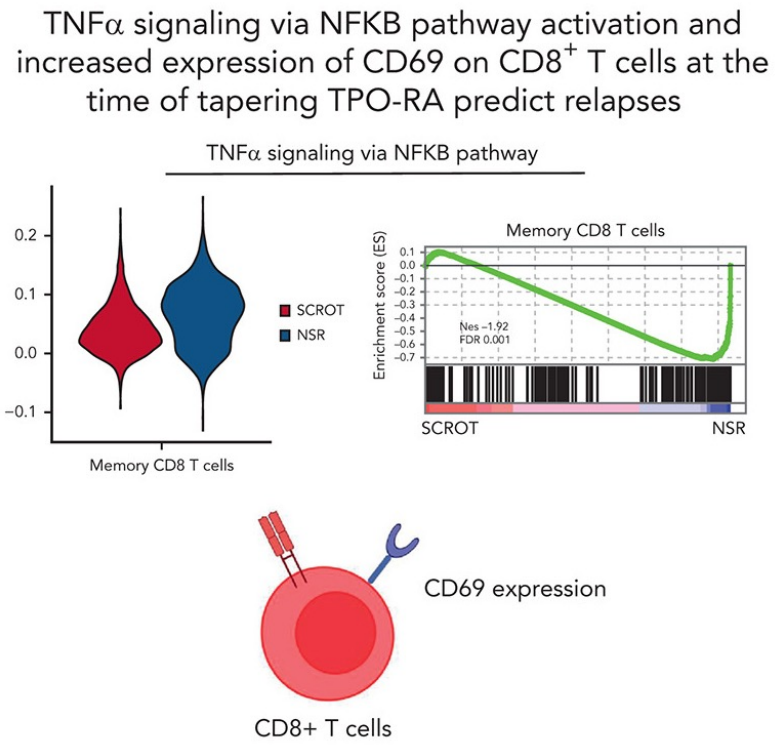
Development and validation of predictive models



Xu M, et al. Br J Haematol 2024; 205:1108-1120

Biological determinants of treatment-free response: STOPAGO

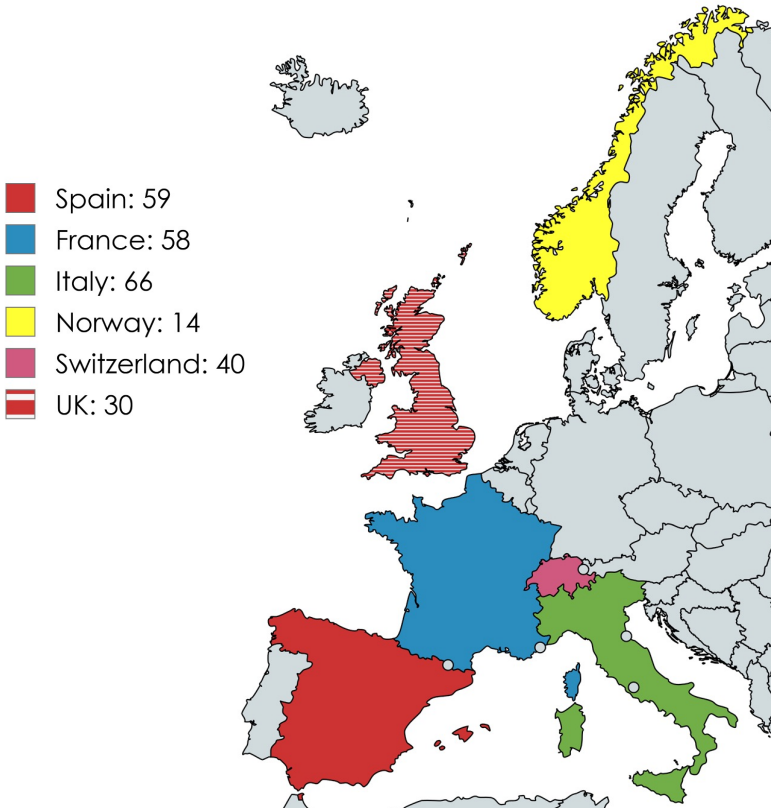




Guillet S., et al. Blood. 2023;141:2867-2877

Vertex 3 Study: TPO-RA Use in Primary Immune Thrombocytopenia Across Europe

A retrospective analysis of 267 patients in 16 European institutions



Data collected (CRF with 350 variables)

Demographics	Diagnosis	Previous therapies	TPO-RA
	• Comorbidities • Hemorrhage score		• Hemorrhage score • Disease stage • Response • Adverse events • Switching • Response off therapy

ERC
EUROPEAN RESEARCH CONSORTIUM ON ITP
Together to improve knowledge on ITP