

TERZO MEETING DI EMATOLOGIA NON ONCOLOGICA

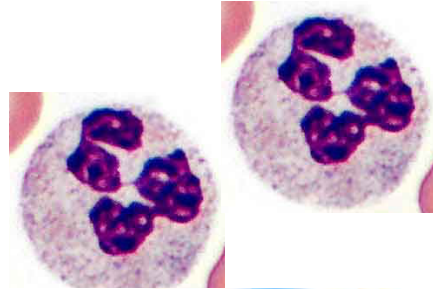
Boscolo Hotel Astoria
Firenze 26-27 gennaio 2017

Anticorpi anti-TPO: rilevanza epidemiologica e clinica

Monica Carpenedo

U.O Ematologia, ASST Ospedale San Gerardo di Monza

20 years age gap



Filgrastim
1991



Epoietin
1988



Romiplostim 2010
Eltrombopag 2011
(Italy)

Ab against EPO

VOLUME 346

FEBRUARY 14, 2002

NUMBER 7



PURE RED-CELL APLASIA AND ANTIERYTHROPOIETIN ANTIBODIES IN PATIENTS TREATED WITH RECOMBINANT ERYTHROPOIETIN

NICOLE CASADEVALL, M.D., JOELLE NATAF, M.D., BÉATRICE VIRON, M.D., AMIR KOLTA, M.D.,
JEAN-JACQUES KILADJIAN, M.D., PHILIPPE MARTIN-DUPONT, M.D., PATRICK MICHAUD, M.D., THOMAS PAPO, M.D.,
VALÉRIE UGO, M.D., IRÈNE TEYSSANDIER, B.S., BRUNO VARET, M.D., AND PATRICK MAYEUX, PH.D.

“ Serum samples from the 13 patients with **pure red-cell aplasia** were tested for neutralizing antibodies that could inhibit erythroid-colony formation by normal bone marrow cells in vitro. The presence of **antierythropoietin antibodies** was identified..”

TPO and TPO-receptor agonists (TPO-RA): a long journey



Prof. Endre Kelemen
(1921–2000)

He suggested that a '**thrombopoietin**' (1958) must exist, which regulated platelet production and was the missing link between the circulating platelet mass and the bone marrow megakaryocyte

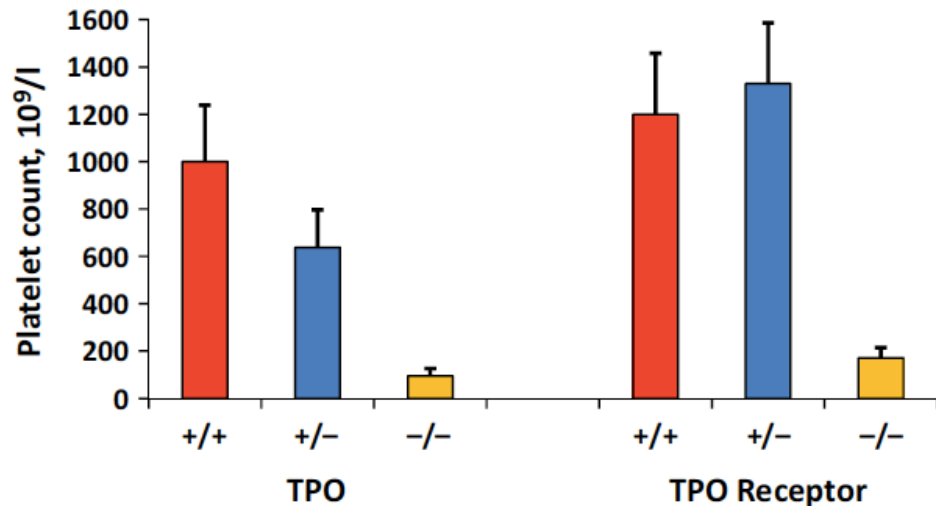
In 1959 he concluded that it was the circulating factor in thrombocytopenic plasma that stimulated an increase in platelet production and hastened the recovery from thrombocytopenia.

The discovery of c-mpl or MPL

- 1990: discovery and characterization of the murine myeloproliferative leukemia virus (MPLV)
- The virus causes an acute myeloproliferative syndrome in infected mice
- The responsible oncogene was cloned, and the protooncogene obtained

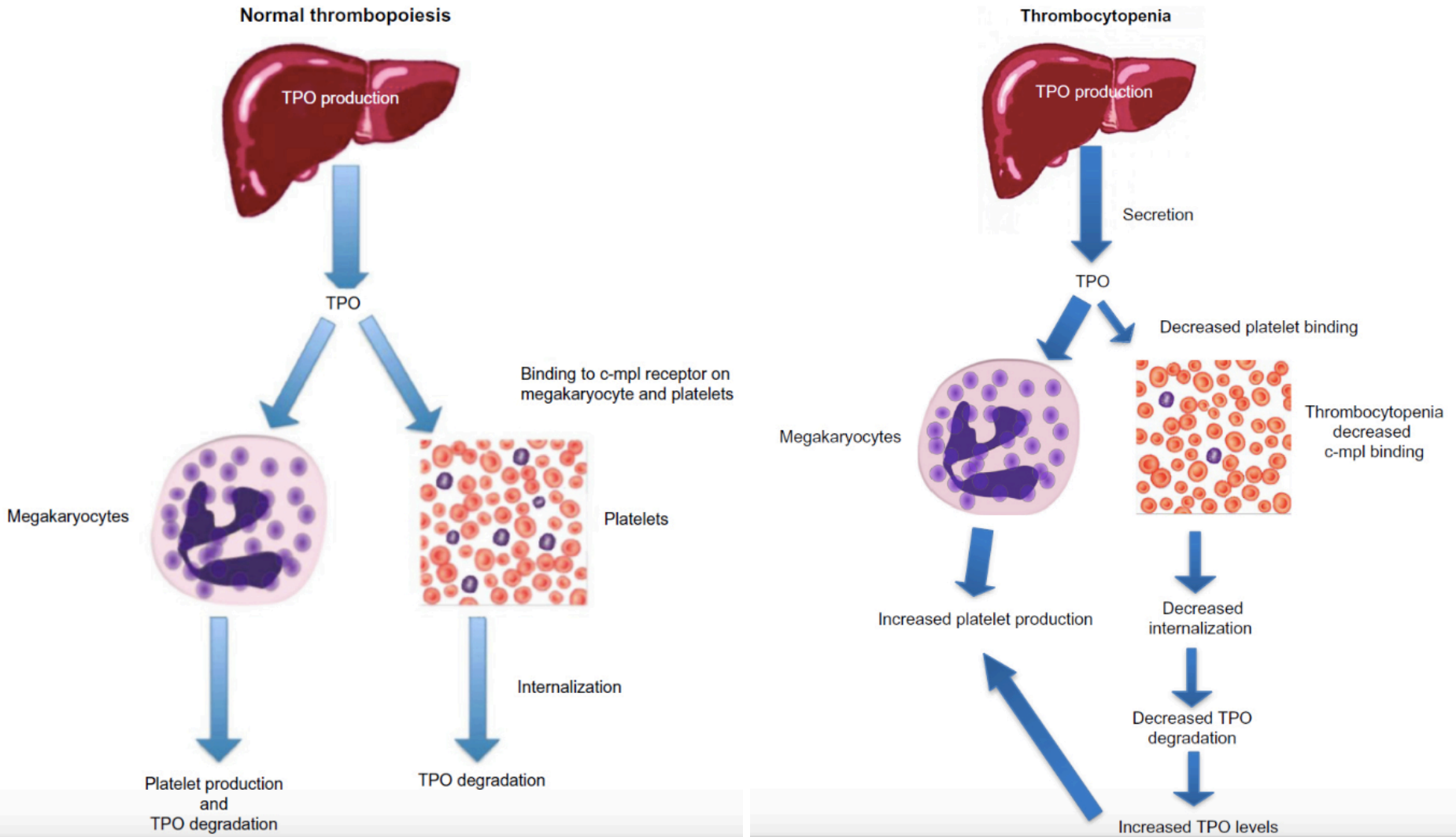
After 35 years of research...

- In 1994, five laboratories almost simultaneously reported the purification of TPO
- There is no specific 'sensor' of the platelet count
- TPO is produced constantly in the liver, enters the circulation, and is cleared by high affinity TPO receptors on platelets and maybe also megakaryocytes

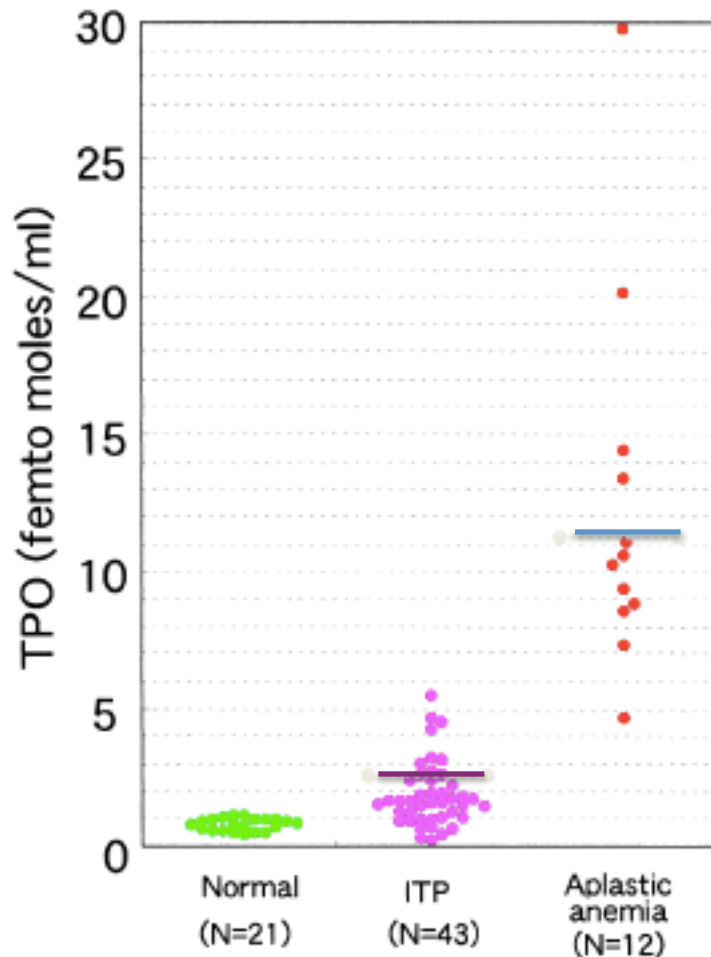


Kuter D, BJH 2014

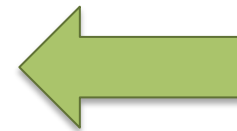
Thrombopoietin (TPO) in normal and thrombocytopenic people



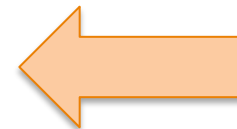
TPO level in healthy people and diseases



TPO is not increased in thrombocytopenic disorders such as immune thrombocytopenic purpura (ITP)



Where TPO level should be

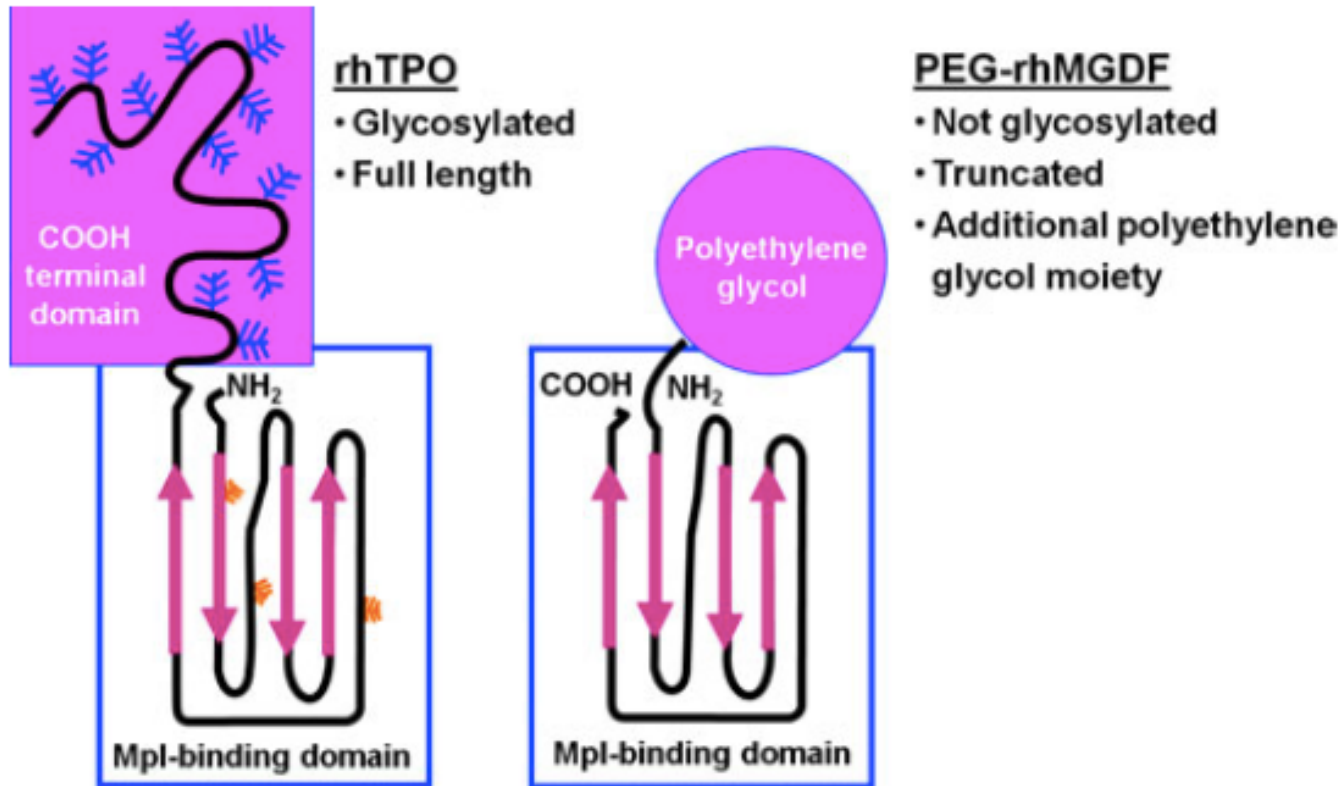


Where TPO actually is

Kosugi Br J Haematol 1996;93:704-706

Molecular structures of rhTPO and PEG-rHuMGDF

From 1994 to 2000: preliminary studies



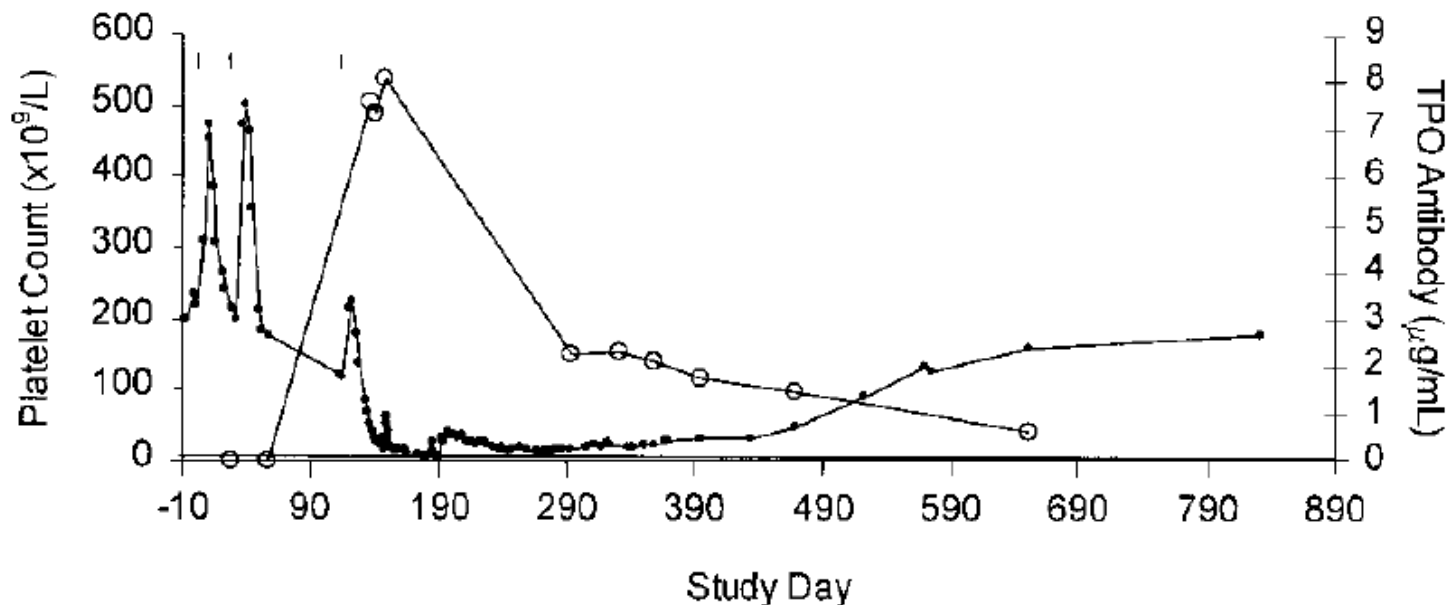
Kuter D, B J Haematol 2014

Thrombocytopenia caused by the development of antibodies to thrombopoietin

Junzhi Li, Chun Yang, Yuping Xia, Amy Bertino, John Glaspy, Michael Roberts, and David J. Kuter

(Blood. 2001;98:3241-3248)

- During development of recombinant thrombopoietins: 13 of 535 developed paradoxical thrombocytopenia due to the production of an autoantibody that neutralized PEG-rhMGDF and also cross-reacted with and neutralized the endogenous TPO



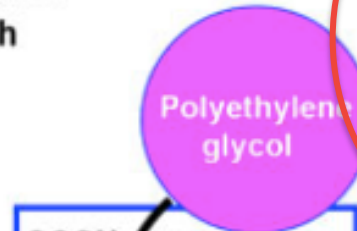
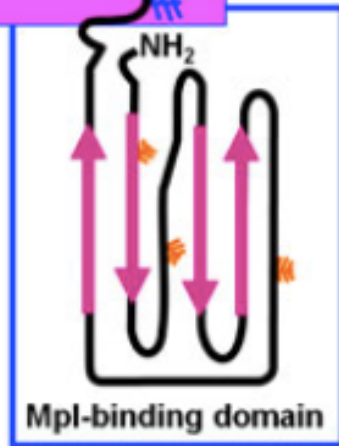
More immunogenicity of PEG-rhMGDF

Intravenous

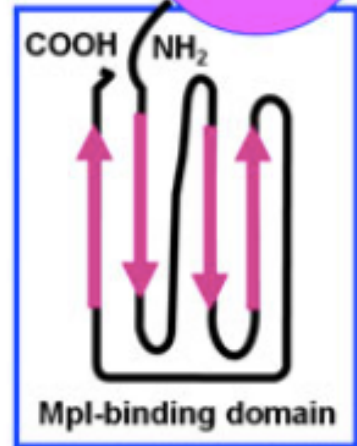
(but possible s.c induced Ab)



rhTPO
• Glycosylated
• Full length



PEG-rhMGDF
• Not glycosylated
• Truncated
• Additional polyethylene glycol moiety

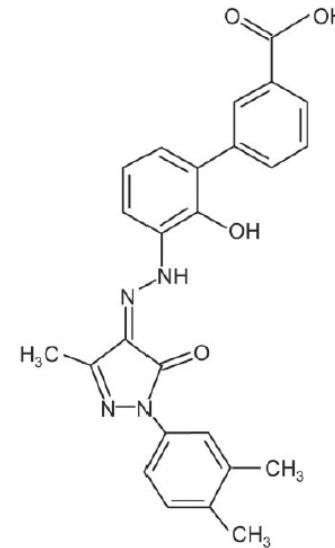
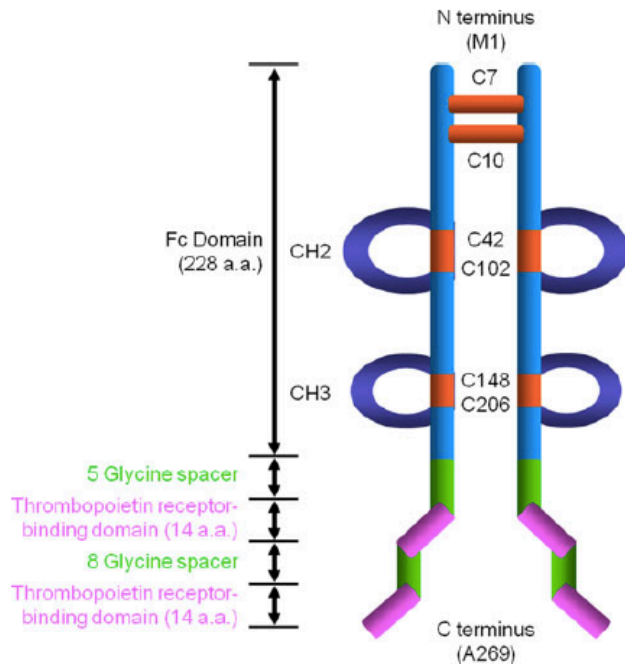


Subcutaneous

(mobilization of dendritic cells)

Kuter D, B J Haematol 2014

TPO-RA second generation



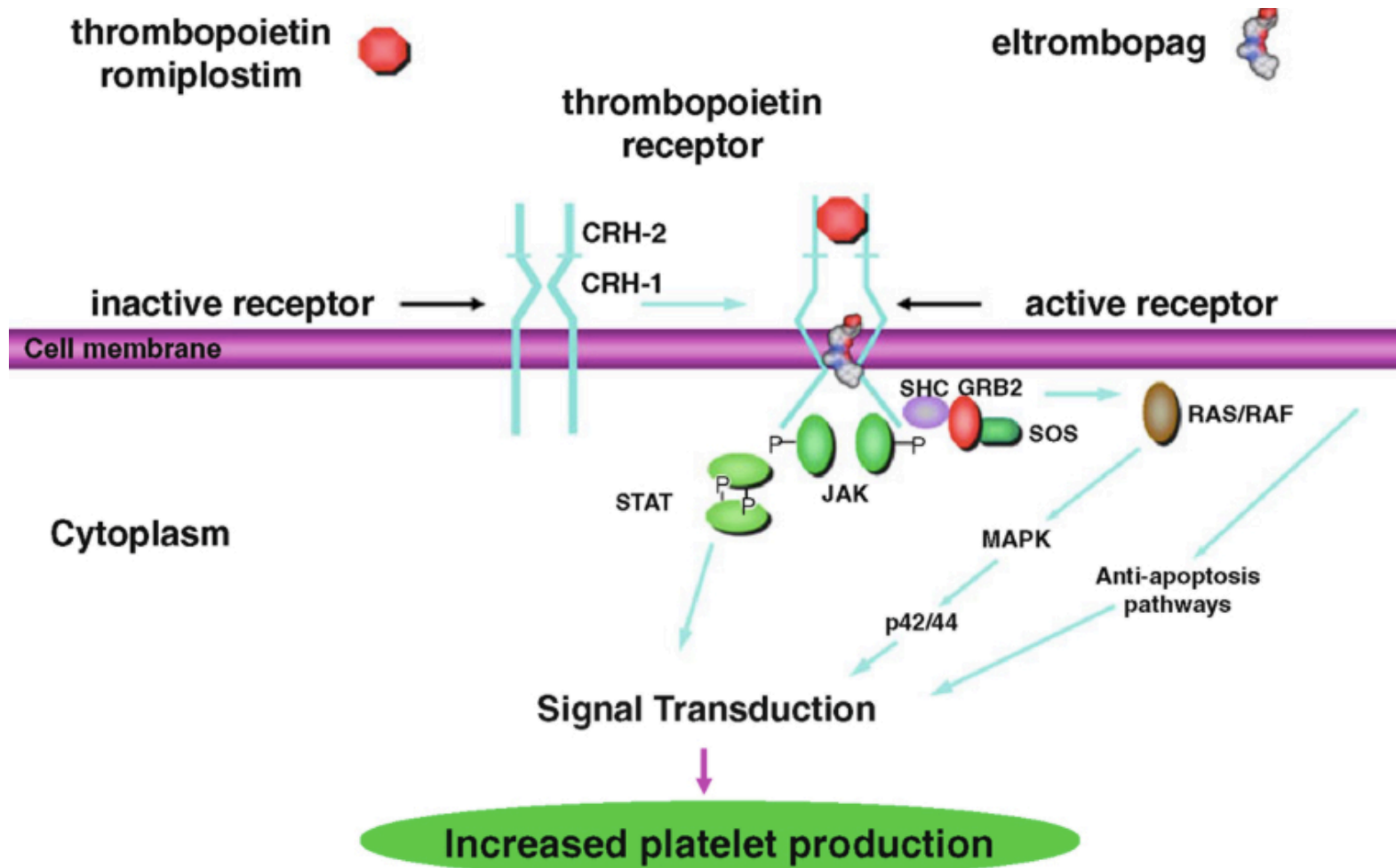
Romiplostim:

- “peptibody”
- no sequence homology with human TPO

Eltrombopag:

- small nonpeptide
- activate the TPO receptor = rhTPO

TPO-RA second generation

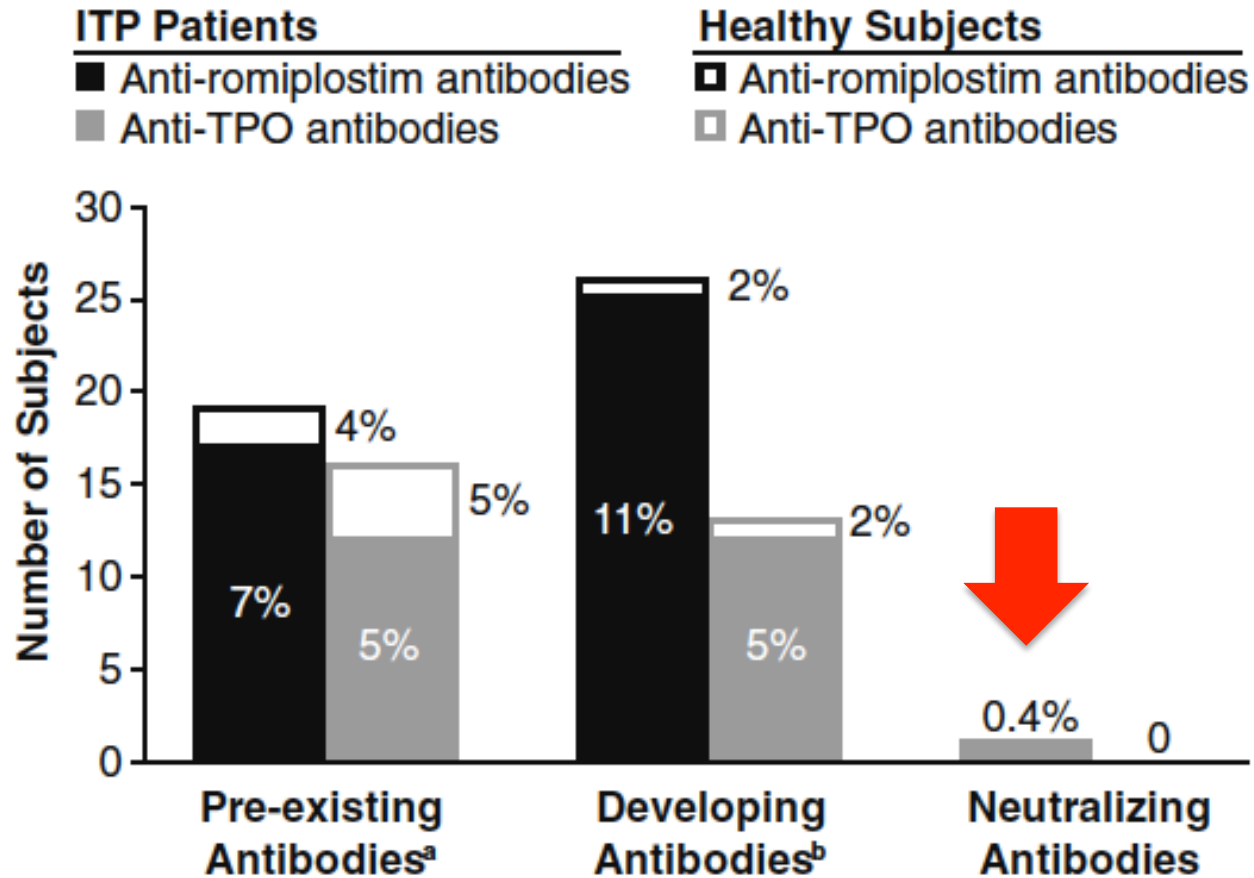


Neutralizing antibodies against second generation TPO-RA

- After development of 2nd gen TPO-RA:
- Description of 2 patients (out of 292 in 5 years of treatment) who developed neutralizing antibodies against romiplostim (Kuter, Br J Haematol. 2013 May;161:411-23), not cross-reacting with endogenous TPO
- Never reported cases of neutralizing antibodies against Eltrombopag until now

Immunogenicity of romiplostim

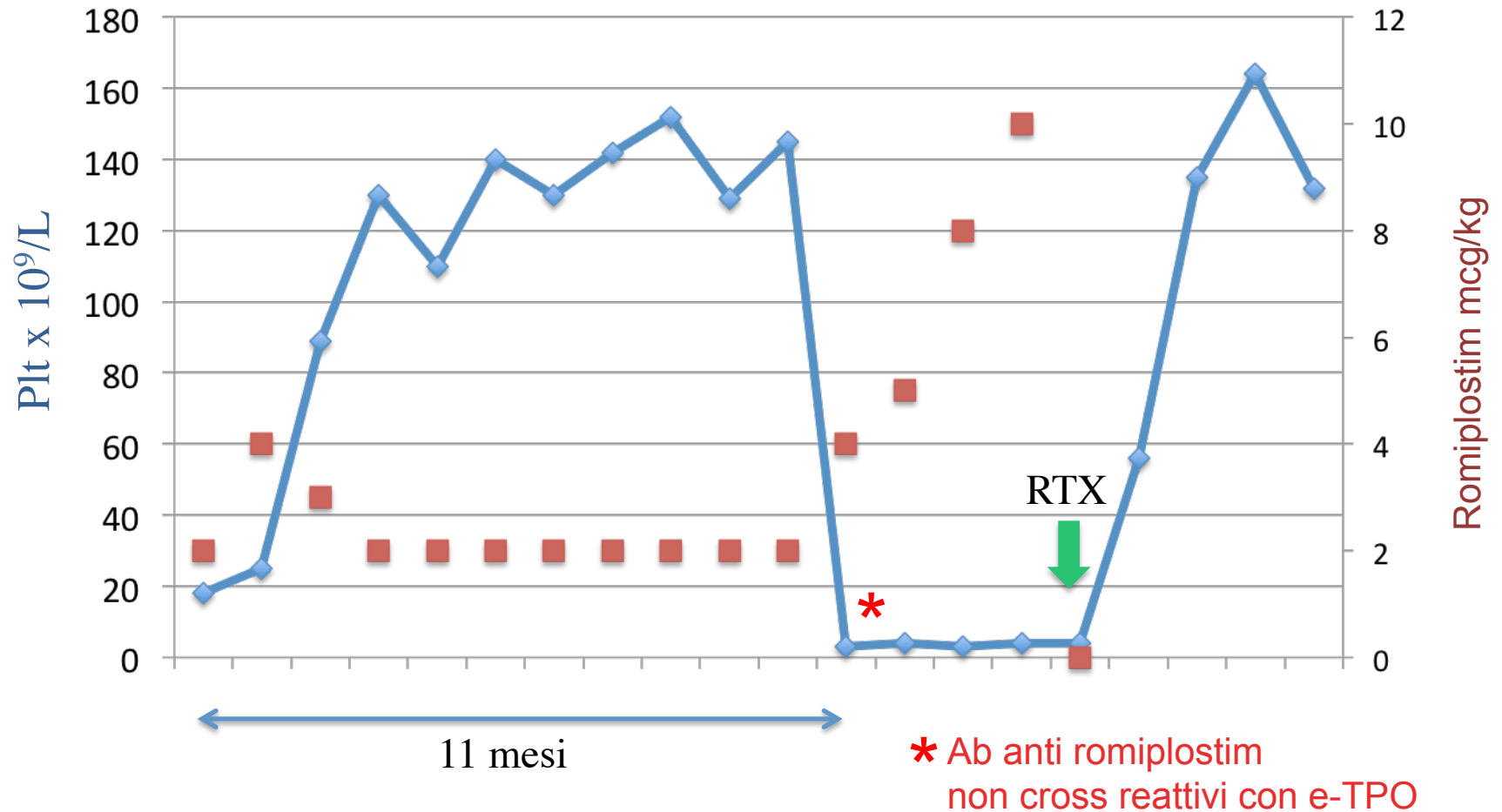
225 ITP patients, 45 healthy control



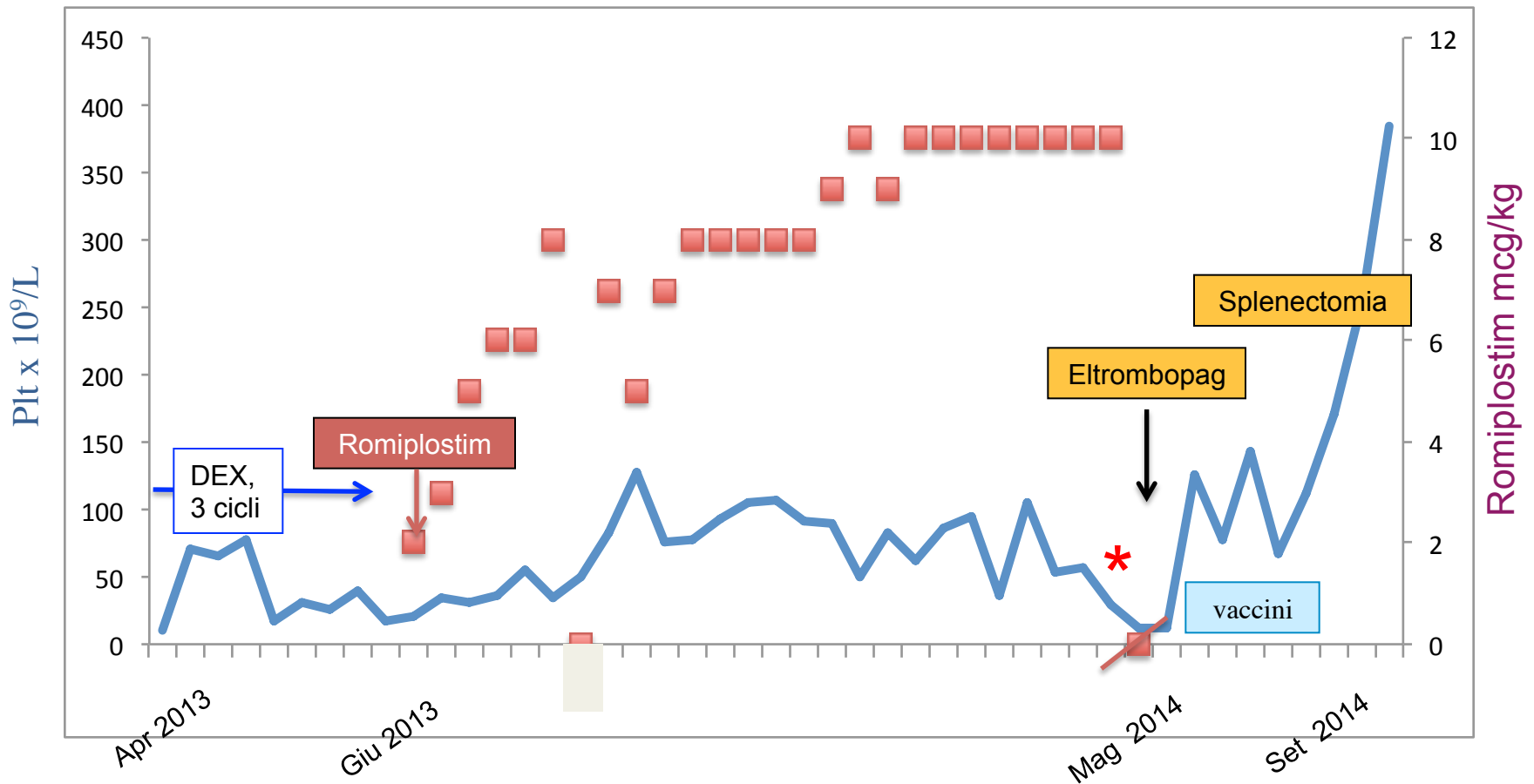
Jawa V et al. Ann Hematol 2010

P.B: femmina 37 anni

Precedenti terapie: prednisone, IGIV

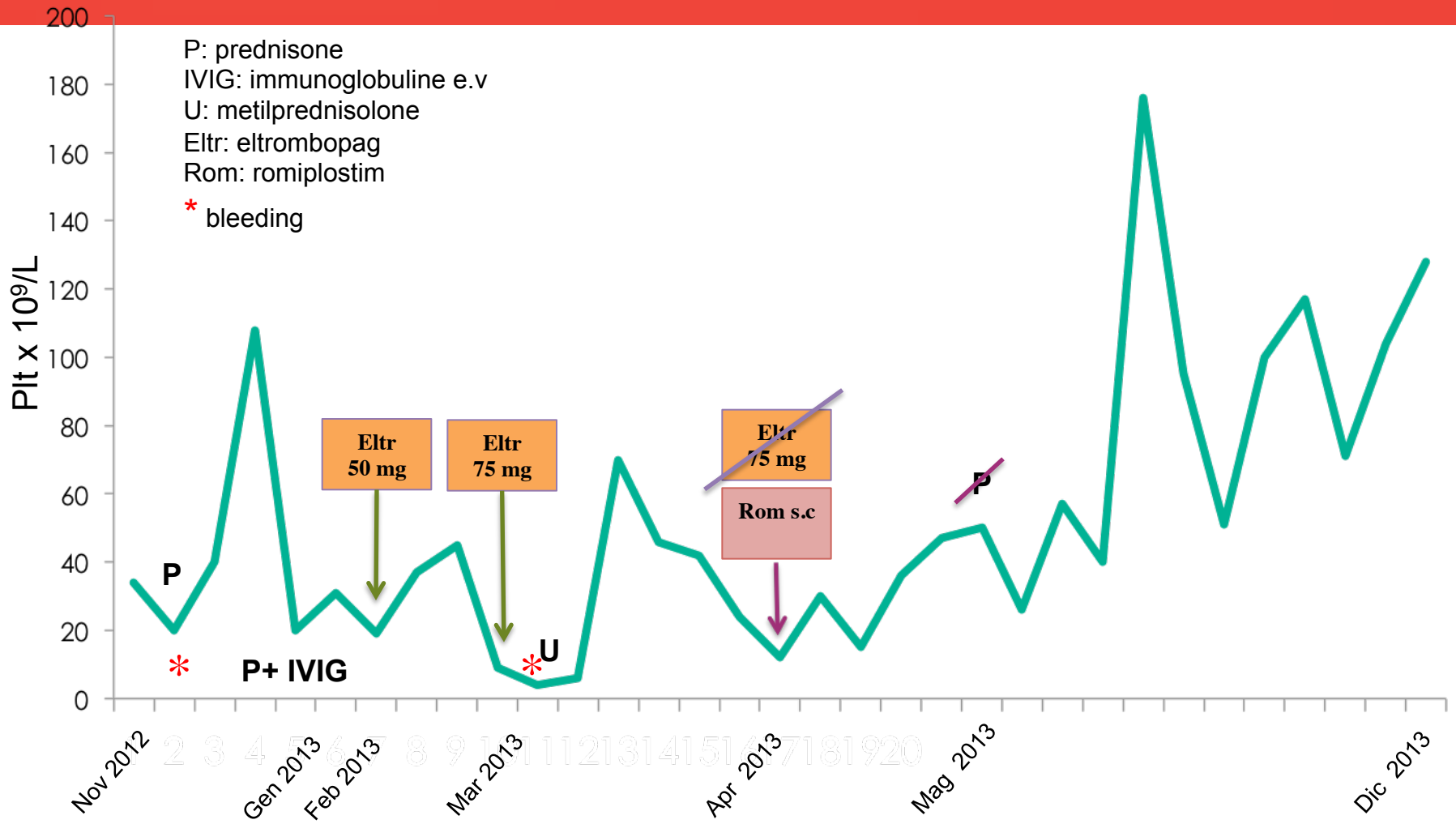


L.M; maschio, 19 anni

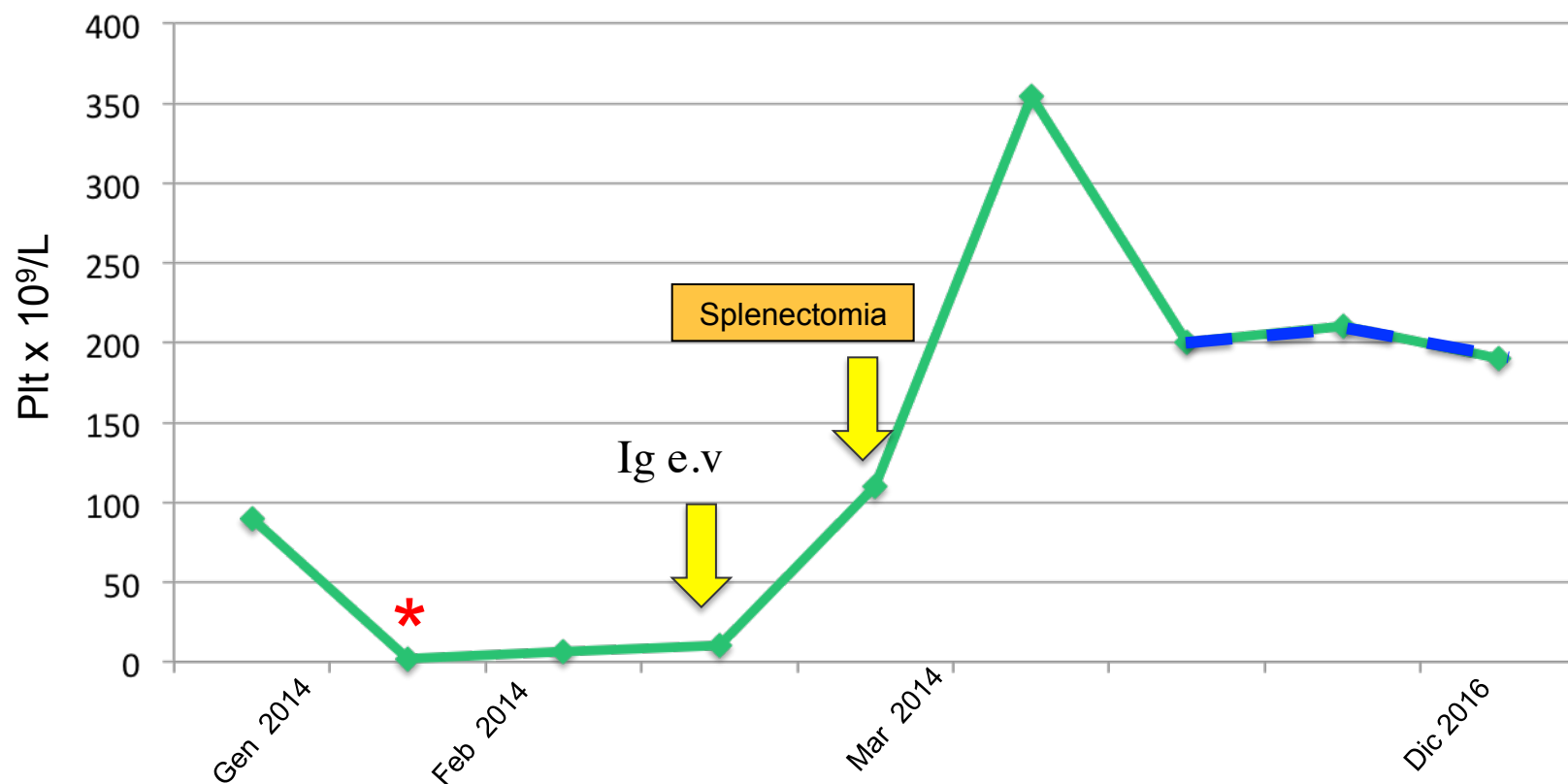


* Ab anti romiplostim
non cross reattivi con e-TPO

M.S; femmina, 38 anni



M.S; femmina, 38 anni



* Ab anti romiplostim
non cross reattivi con e-TPO

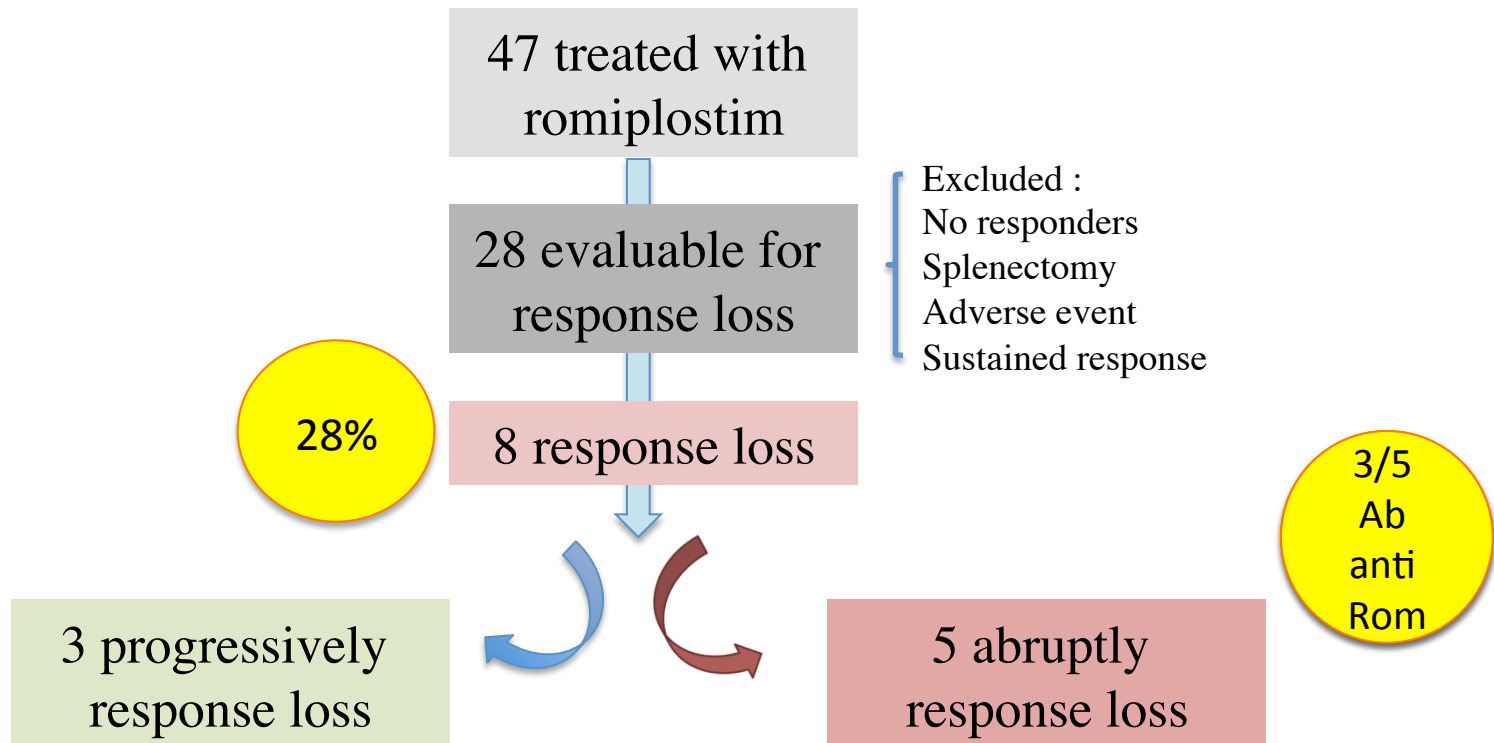
Neutralizing antibodies against TPO-RA in real life practice

- In a case series of 30 patients treated with romiplostim 5 patients lost response after initial recovery of platelet count (4 CR, 1 PR)
- In 3/5 patients who suddenly lost response neutralizing antibodies against romiplostim were detected
- A immunoassey using the principle of surface plasmon resonance –SPR, was performed by Amgen, in Thousands Oaks factory's lab.
- No cross reaction with endogenous TPO was documented in all patient samples

Carpenedo M & Cantoni S, Hem. Rep 2015

Response loss and development of neutralizing antibodies during long-term treatment with romiplostim in patients with immune thrombocytopenia: a case series

Monica Carpenedo¹, Silvia Cantoni², Veronica Coccini¹, Enrico Maria Pogliani³, Roberto Cairoli²



A immunoassay using the principle of surface plasmon resonance –SPR, was performed.
No cross reaction with endogenous TPO was documented

Eur J Haematol. 2016 Jul;97(1):101-103

Characteristics of patients who developed antibodies against romiplostim

n	Sex, age (yrs)	Previous ITP treatment	Duration of Rom before RL (months)	Type of response before RL	Ongoing dose of Rom before RL ($\mu\text{g}/\text{kg}$)	Type of RL	Anti-Rom Ab	Ab retest
1	F, 38	MIG, DEX, P	11	CR	2	Sudden drop	Positive	n.a
2	F, 38	MIG, DEX, P, EIt	12	CR	8	Sudden drop	Positive	Negative (at 9 months)
3	M, 19	MIG, DEX, P	11	CR	9	Sudden drop ¹	Positive	Negative (at 7 months)
4	M, 42	Spl, P, DEX,	4	R	10	Sudden drop	Negative	n.a
5	F, 56	MIG, DEX	5	R	6	Sudden drop	n.a	n.a
6	M, 61	MIG, P, VCR, RTX, spl	12	R	10	Slow drop	n.a	n.a
7	F, 65	MIG, P	3	R	5	Slow drop	n.a	n.a
8	M, 82	P; DEX + IVIG, danazol;	4	R	6	Slow drop	n.a	n.a

Carpenedo M et al, Eur J Haematol. 2016; 97:101-103

Action taken in patients who developed antibodies against romiplostim

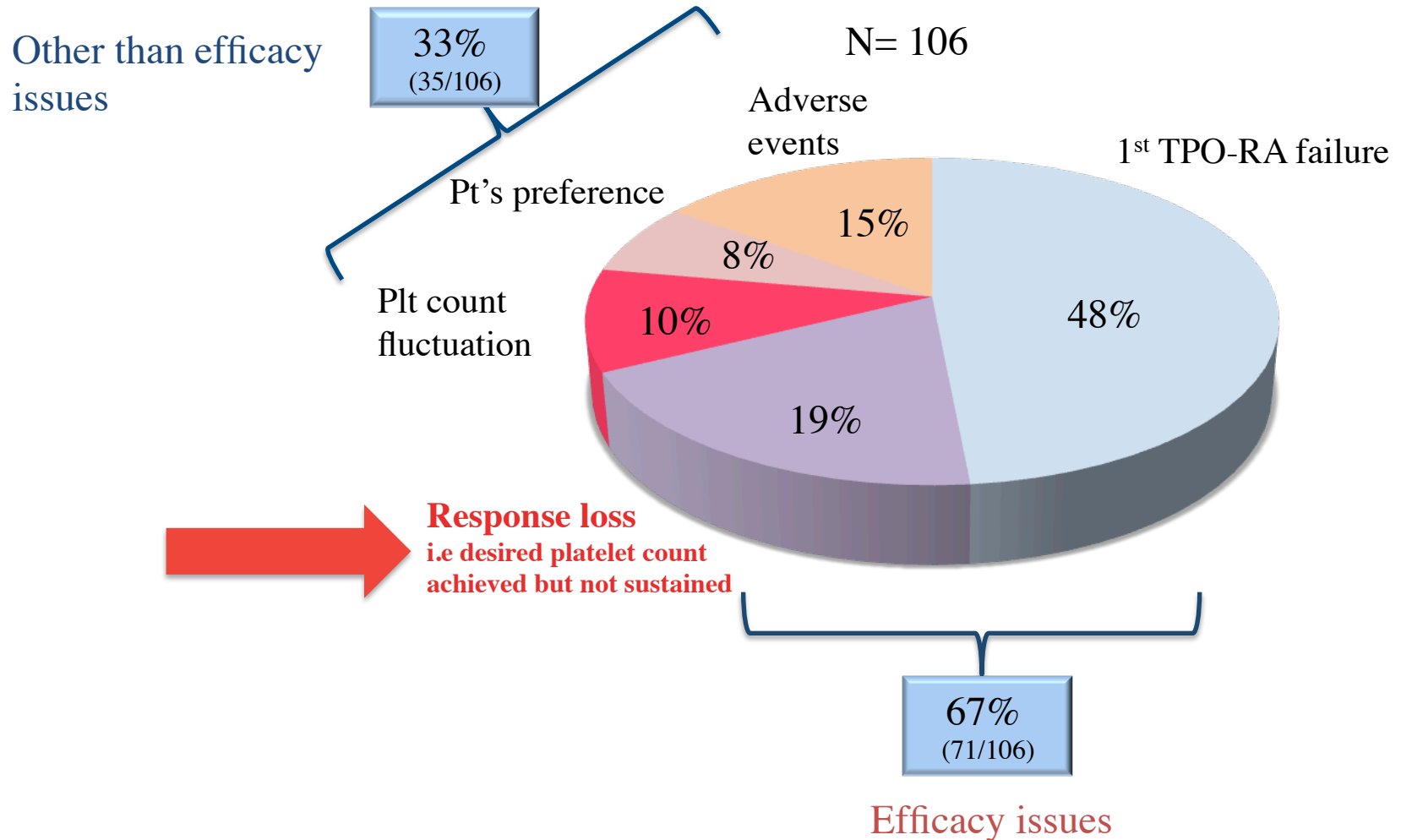
n	Sex, age (yrs)	Previous ITP treatment	Type of RL	Anti-Rom Ab	Ab retest	Action taken at RL	Outcome
1	F, 38	MIG, DEX, P	Sudden drop	Positive	n.a	RTX	CR, off therapy
2	F, 38	MIG, DEX, P, Eit	Sudden drop	Positive	Negative (at 9 months)	IVIg, spl	CR, off therapy
3	M, 19	MIG, DEX, P	Sudden drop ¹	Positive	Negative (at 7 months)	Eit as "bridge" to spl	CR, off therapy
4	M, 42	Spl, P, DEX,	Sudden drop	Negative	n.a	Eit	NR
5	F, 56	MIG, DEX	Sudden drop	n.a	n.a	RTX, Eit	CR in Eit
6	M, 61	MIG, P, VCR, RTX, spl	Slow drop	n.a	n.a	Eit	NR
7	F, 65	MIG, P	Slow drop	n.a	n.a	Eit	R
8	M, 82	P; DEX + IVIG, danazol;	Slow drop	n.a	n.a	Eit, RTX	NR

Carpenedo M et al, Eur J Haematol. 2016; 97:101-103

We need a definition...

- Response loss..?
- Definition: desired platelet count achieved but not sustained (even if treatment is ongoing)

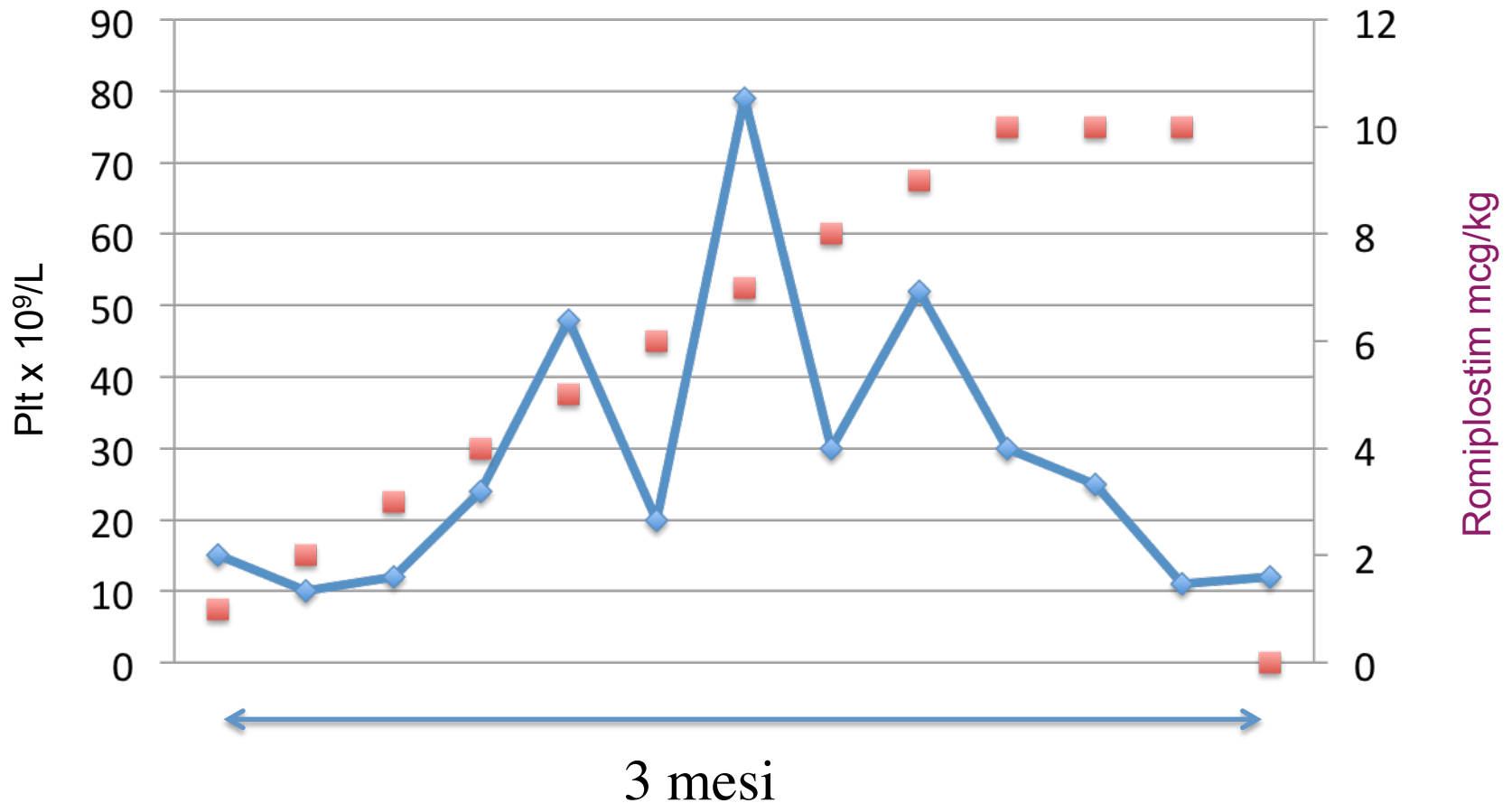
How frequent is a response loss during TPO-RA treatment?



Cantoni et al. in progress

Slow, progressive response loss

F 49 anni, prednisone, desametasone, eltrombopag



Different type of response loss

Slow response loss

- Previous R (not CR)
- No “allergic” symptoms
- Heavily pretreated pt
- TPO-RA switch may be not effective
- AAM: low number MK



Abrupt response loss

- Previous CR
- “allergic” symptoms may occur
- TPO-RA switch is effective
- AAM: high number MK

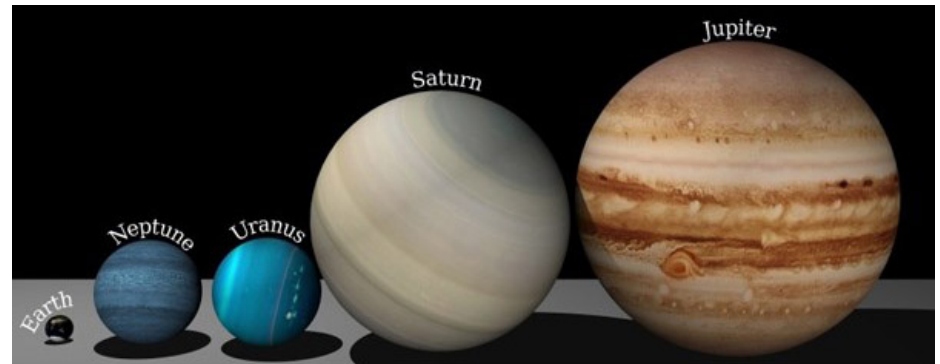
Cosa fare in caso di perdita di risposta al TPO-RA

- Anamnesi accurata per valutare la compliance
- Esame obiettivo per escludere manifestazioni allergiche cutanee, e valutazione diatesi emorragica
- Ematochimici (emocromo fx epatorenale), AAM
- Raccolta campione siero da stoccare per invio e ricerca Ab anti-romiplostim se perdita di risposta brusca
- Sospensione del trattamento

Dopo la sospensione del TPO-RA

- Monitorare la conta piastrinica a breve (dopo 3-4 giorni, poi settimanale) per cogliere eventuale rebound di piastrinopenia anche severa
- Se era presente manifestazione allergica cutanea impostare terapia con antistaminici e/o steroide fino a risoluzione dei sintomi
- Rivalutazione del paziente per definire eventuale nuova linea di terapia
- E' possibile eseguire switch tra TPO-RA per assenza di cross reattività degli Ab tra le due molecole

La rilevanza...



è sempre un fenomeno relativo...