AZIENDA ULSS N. 6 - VICENZA
DIVISIONE DI EMATOLOGIA

VII edizione

FONDAZIONE
PROGETTO
EMATOLOGIA

GIORNATE EMATOLOGICHE VICENTINE

VII edizione

La moderna terapia della piastrinopenia immune nell'adulto

Vicenza , 11 ottobre 2016

Francesco Zaja

Udine

Outlines

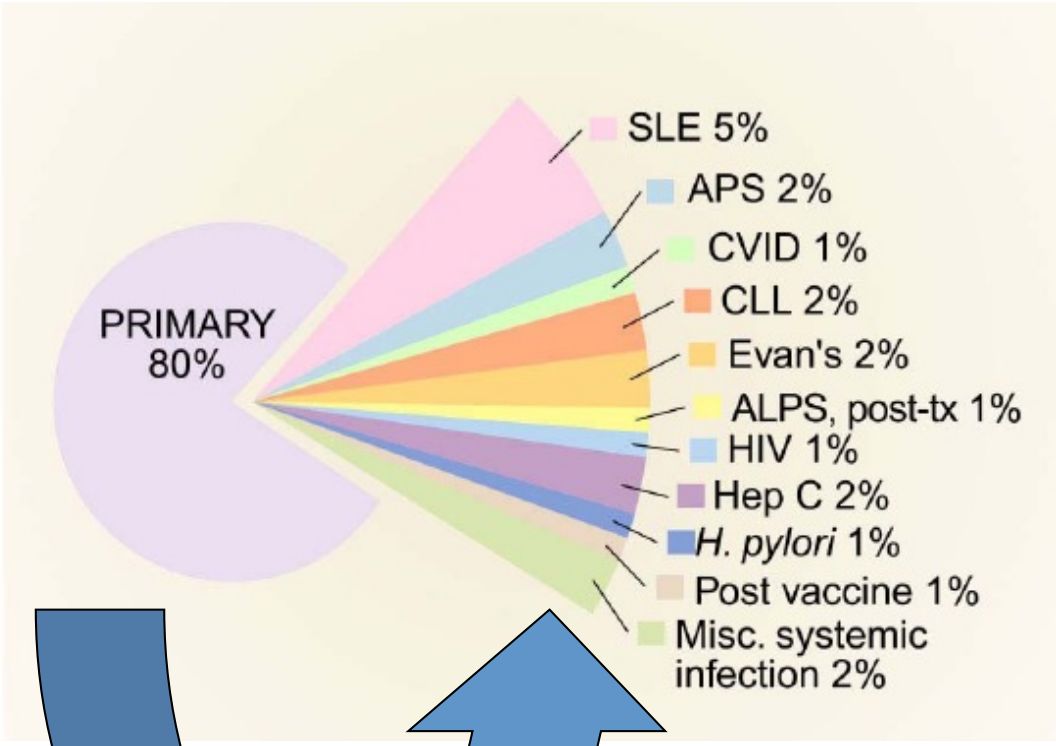
1. Considerazioni di carattere generale
2. Steroidi
3. Splenectomia
4. Rituximab
5. TPO-RAs

blood

Prepublished online Apr 24, 2009;
doi:10.1182/blood-2009-01-129155

The ITP syndrome: pathogenic and clinical diversity

Douglas B. Cines, James B. Bussel, Howard A. Liebman and Eline T. Luning Prak



Increase identification of inciting events and immune defects

Pathophysiology of primary ITP

1. Increased platelet destruction
2. Impaired platelet production
3. Inadequate TPO serum level

Primary ITP in adults: therapy

When ? Which patients ? Which therapy ?

Symptomatic

- bleeding
- PLT < 20-30.000 x 10^9/L

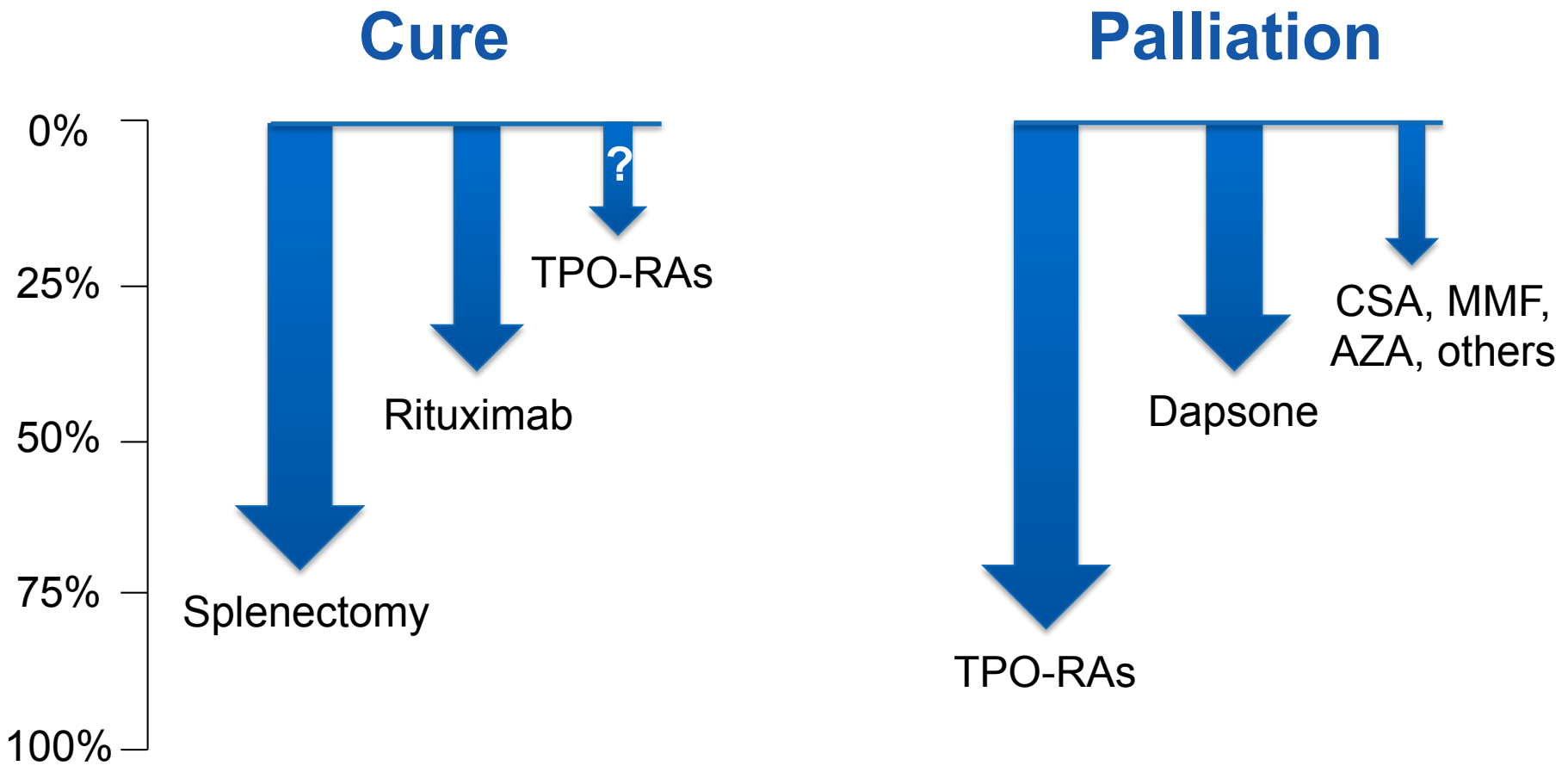
Variables

- age/sex
- occupation/activities
- comorbidities/treatments
- pregnancy
- expectations, other

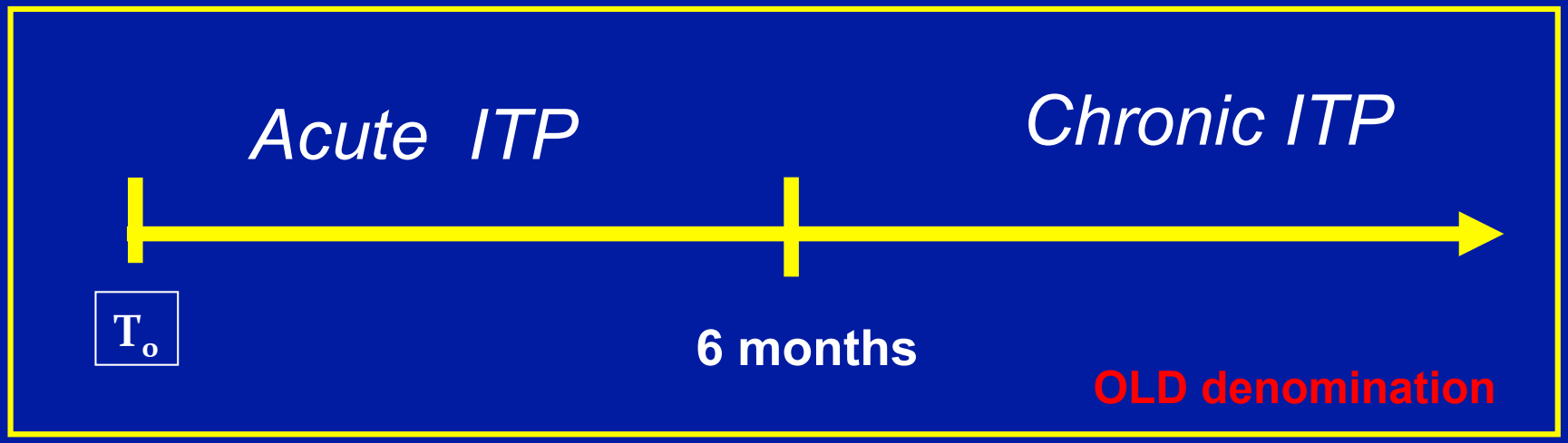
Goals:

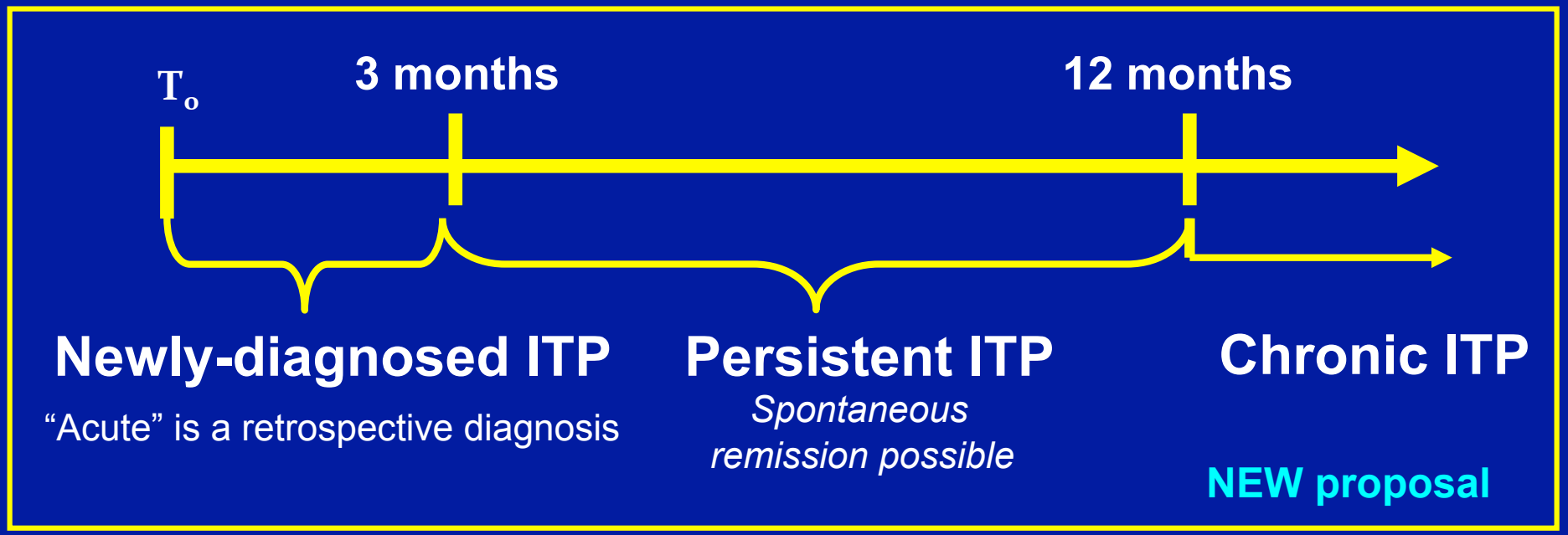
- prevention of bleeding
- cure
- QoL

Goals of treatment in ITP



ITP: phases of the disease



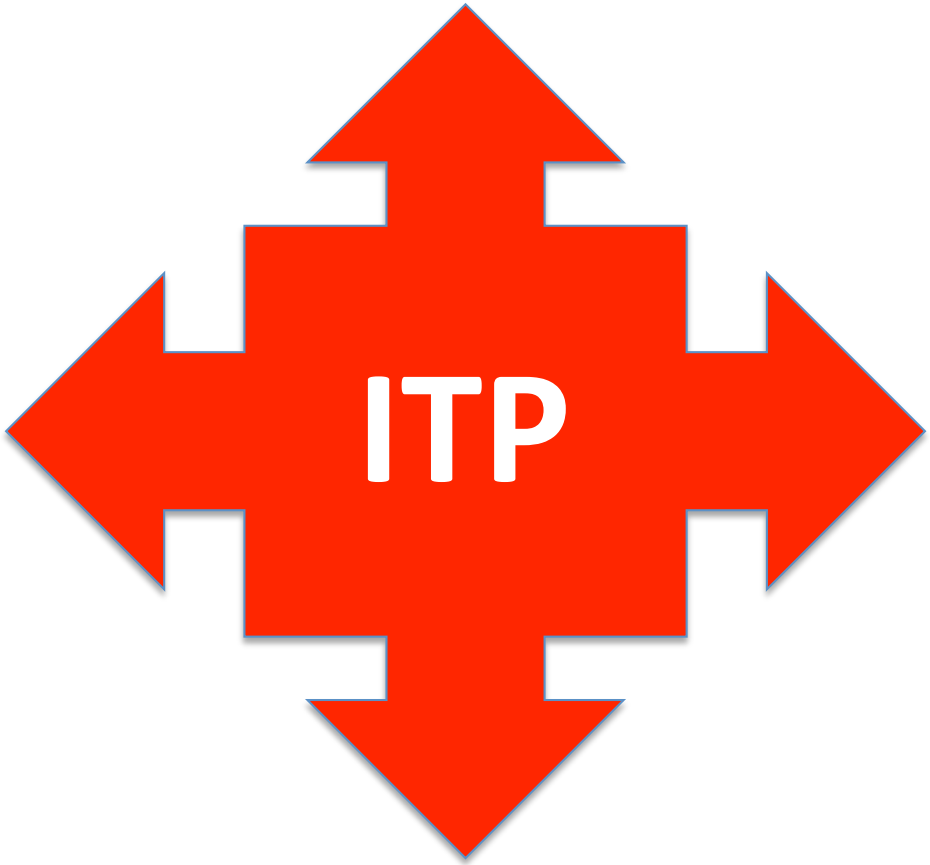


Steroid

- PDN vs DEXA
- Timing

TPO-RAs

- Rom vs Eltr
- Timing



Splenectomy

- LPS vs LPT
- Timing

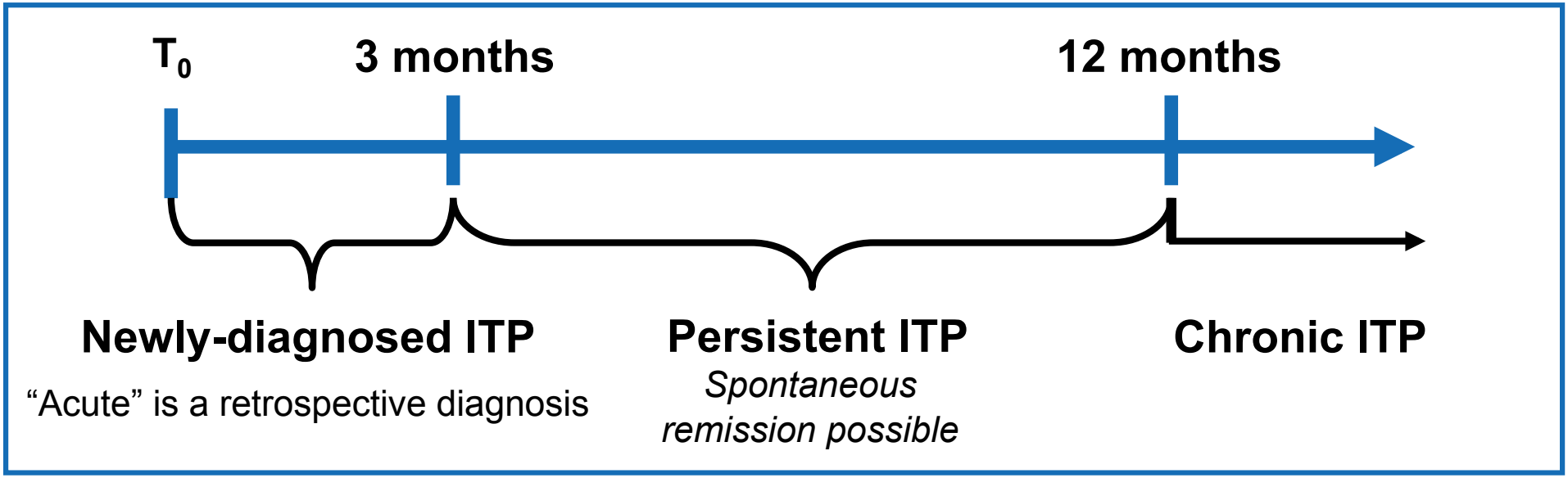
Rituximab

- Low vs standard
- Timing

- Azathioprine
- Cyclosporin A
- MMF
- Danazol
- Dapson
- Vincristine
- Cyclophosphamide
- …

Steroid

ITP: phases of the disease



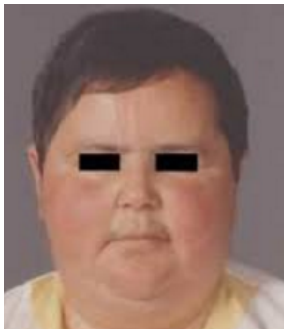
- **Steroid**
- IVIG
- Platelet transfusion

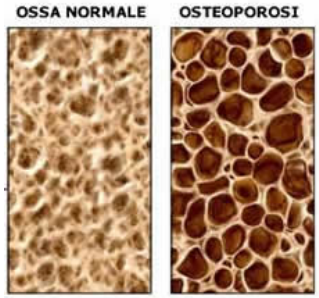
- **Steroid**

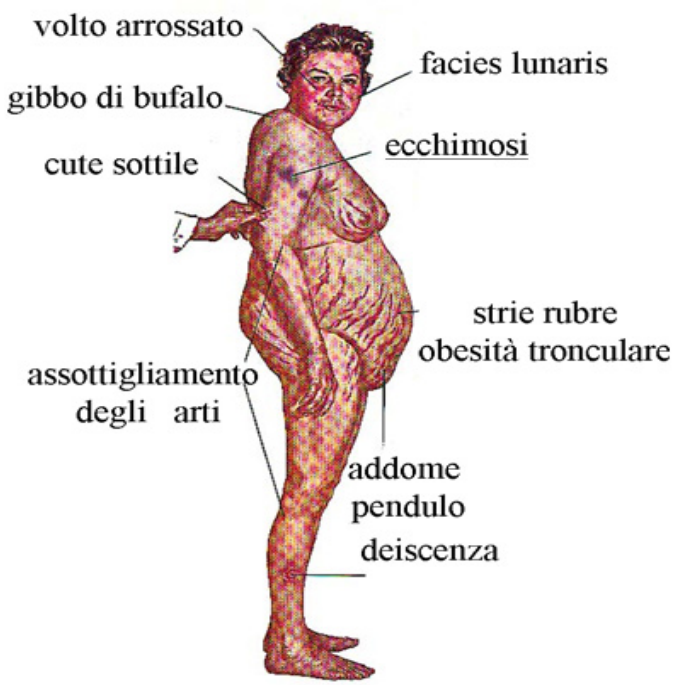
Adapted from Rodeghiero F, et al. Blood 2009;113:2386–93.

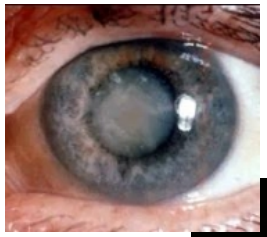
AZA, azathioprine; CSA, cyclosporin; MMF, mycophenolate mofetil; TPO-RA, thrombopoietin receptor agonist.

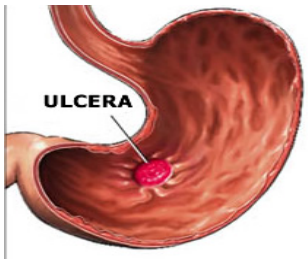
Steroid side effects

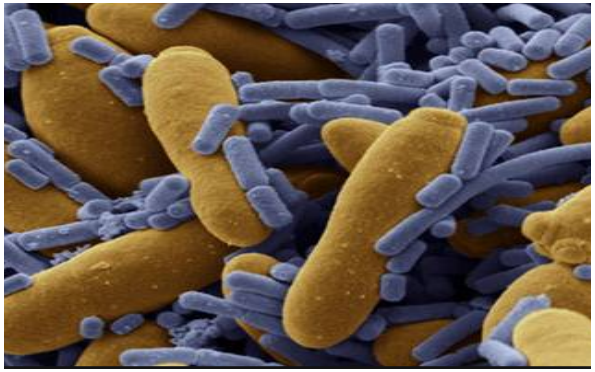


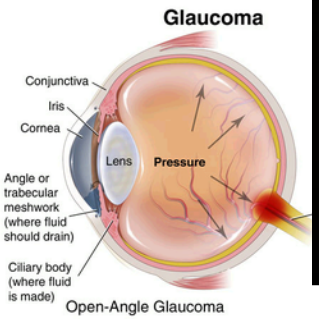






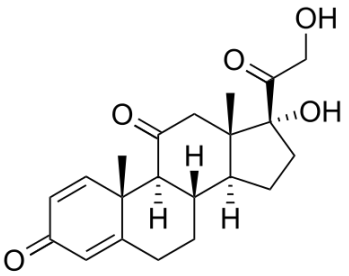






Steroid therapy in primary ITP in adults

Prednisone:

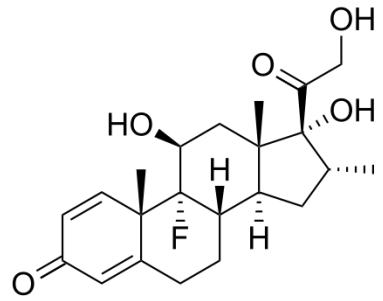


- 0.5–2 mg/kg/d, 2–6 weeks
- Early response: 60–80%
- Most responses occur within 7–10 days
- Lack of substantial increase in the platelet count by 3 weeks is generally considered to indicate treatment failure
- Sustained responses after the discontinuation of steroid therapy occur in 5–30% of patients

Prednisone vs Dexamethasone as first-line therapy in adults with ITP

Why Dexamethasone?

- Longer half-life than prednisone
- No mineralocorticoid effect
- Potent anti-plasma cell agent



References	Therapy	Sustained response (%)
Cheng et al. NEJM 2003[1]	40 mg x 4 days x 1 cycle	42
Borst et al. Ann Hematol 2004[2]	40 m x 4 daysx 1–6 cycles	59
Mazzucconi et al. Blood 2007[3]	40 mg x 4 days x 4 cycles	67
Zaja et al. EHA 2010[4]	40 mg x 4 days x 3 cycles	30
Zaja et al.Blood 2010[5]	40 mg x 4 days x 1 cycle	36
Gudbrandsdottir et al. Blood 2013[6]	40 mg x 4 days x 1–6 cycles	37
Sakamoto et al. JTT 2014[7]	4 days x 1–5 cycles	65

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

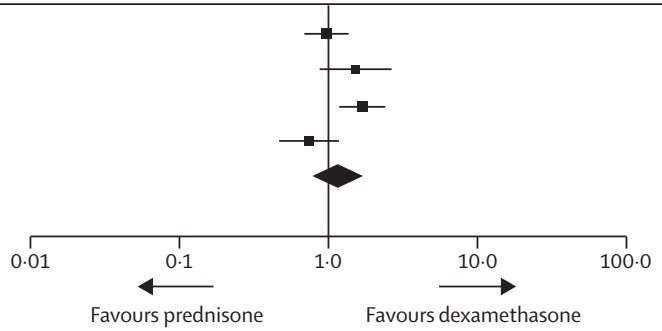
A

Overall response at 6 months or longer after treatment.

	High-dose dexamethasome		Standard-dose prednisone		Weight	Risk ratio, M-H, random (95% CI)
	Events	Total	Events	Total		
Wei (2015)	38	95	40	97	28·1%	0·97 (0·69–1·37)
Din (2014)	32	61	10	29	20·6%	1·52 (0·87–2·65)
Mashhadi (2012)	27	30	16	30	27·6%	1·69 (1·18–2·41)
Bae (2010)	19	57	27	60	23·7%	0·74 (0·47–1·18)
Total patients	**116**	**243**	**93**	**216**	**100·0%**	**1·16 (0·79–1·71)**

Heterogeneity τ^2=0·11, χ^2=10·16, df=3 (p=0·02); I^2=70%

Test for overall effect: Z=0·77 (p=0·44)



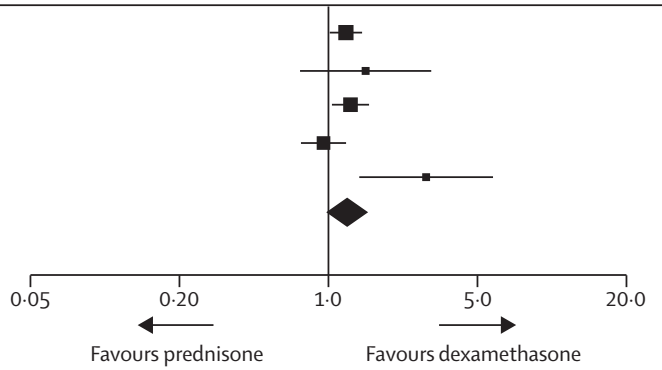
B

Overall response within 14 days of treatment.

	High-dose dexamethasome		Standard-dose prednisone		Weight	Risk ratio, M-H, random (95% CI)
	Events	Total	Events	Total		
Wei (2015)	78	95	67	97	30·8%	1·19 (1·01–1·40)
Din (2014)	26	65	8	29	7·3%	1·45 (0·75–2·81)
Mashhadi (2012)	30	30	24	30	28·9%	1·24 (1·03–1·50)
Bae (2010)	37	51	39	51	25·8%	0·95 (0· 76–1·19)
Praituan (2009)	16	18	6	18	7·1%	2·67 (1·36–5·23)
Total patients	**187**	**259**	**144**	**225**	**100·0%**	**1·22 (1·00–1·49)**

Heterogeneity τ^2=0·03, χ^2=10·18, df=4 (p=0·04); I^2=61%

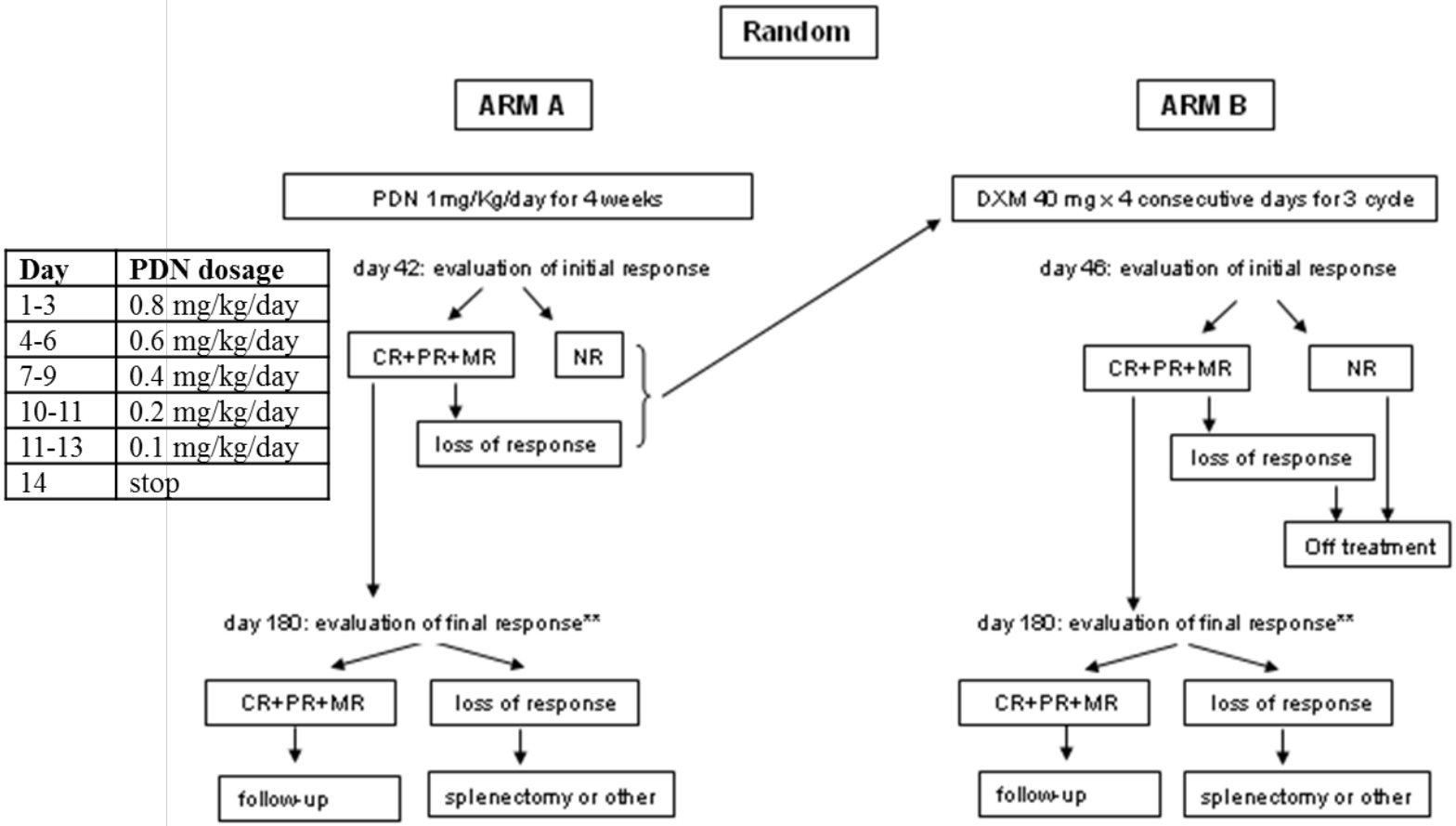
Test for overall effect: Z=1·98 (p=0·05)



Mithoowani S. et al, Lancet Haematol 2016

Standard dose Prednisone vs high-dose Dexamethasone for the treatment of untreated adult ITP: GIMEMA ITP 0207

Day	PDN dosage
1-3	0.8 mg/kg/day
4-6	0.6 mg/kg/day
7-9	0.4 mg/kg/day
10-11	0.2 mg/kg/day
11-13	0.1 mg/kg/day
14	stop



** day 180: from the evaluation of initial response

GIMEMA ITP 0207. Available at: https://clinicaltrials.gov/ct2/show/NCT00657410. Accessed September 2016.

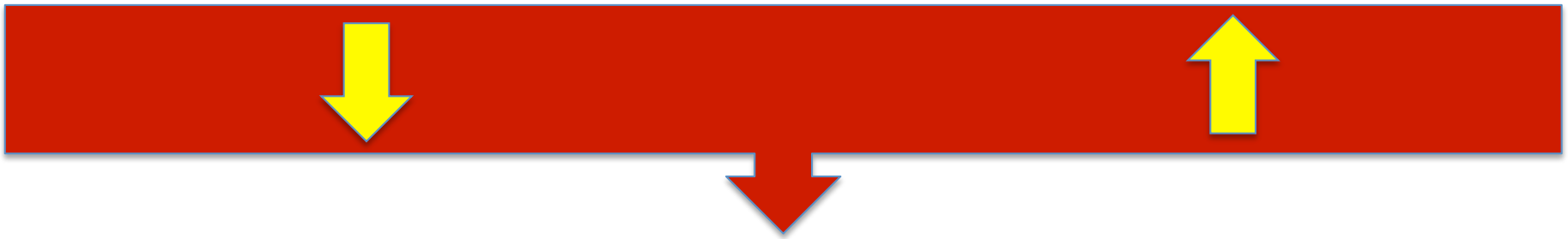
Pathogenesis of ITP

Natural immunosuppressive cells

- $CD4^{+}CD25^{+}Foxp3^{high}$ Tregs)
- MD suppressor cells (MDSCs)

Autoreactive lymphocytes

- CD4+ T cells
- B cells

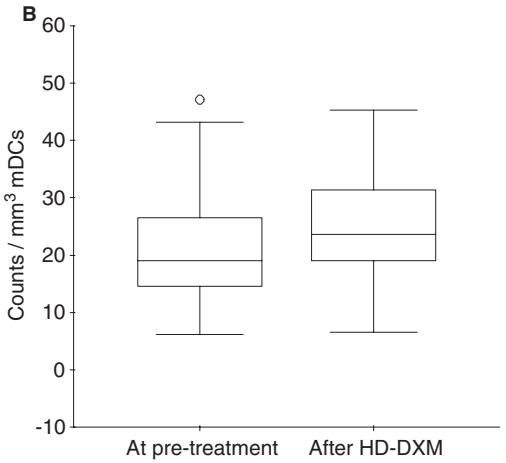


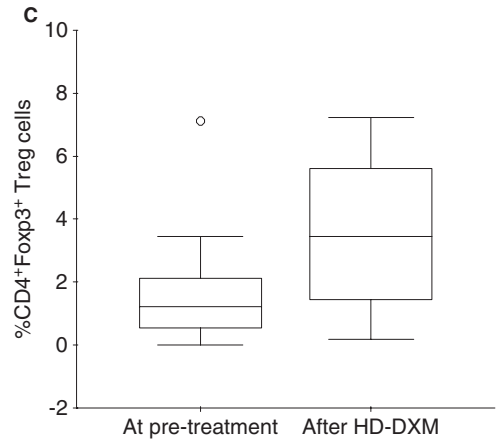
ITP development/activity

Slide courtesy of F. Zaja.

MD, myeloid-derived; Tregs, T regulatory cells.

Circulating dendritic cells subsets and CD4$^+$Foxp3$^+$ regulatory T cells before and after high-dose dexamethasone in chronic ITP





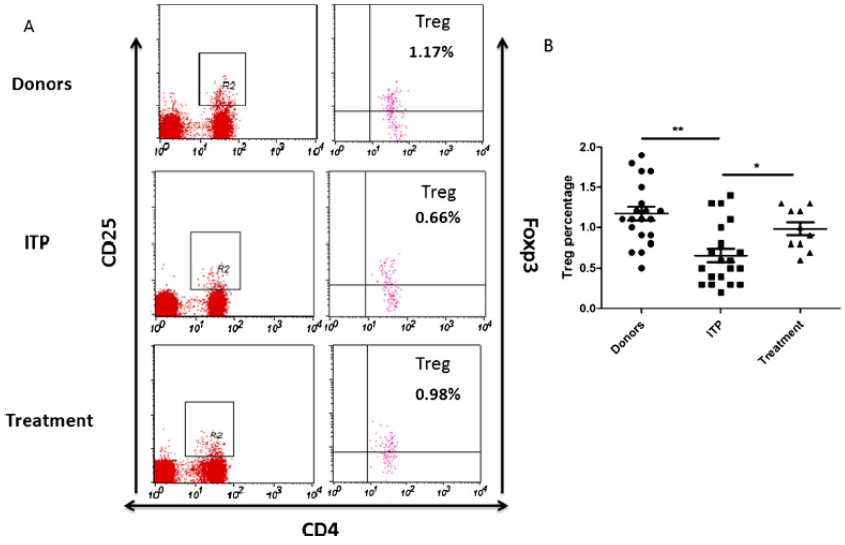
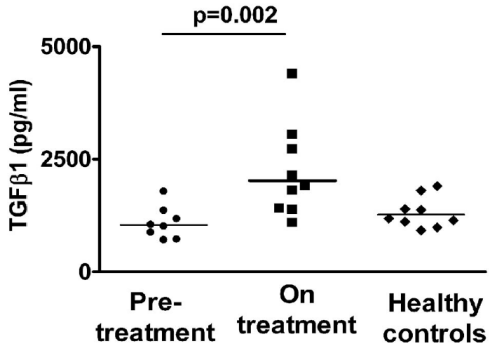
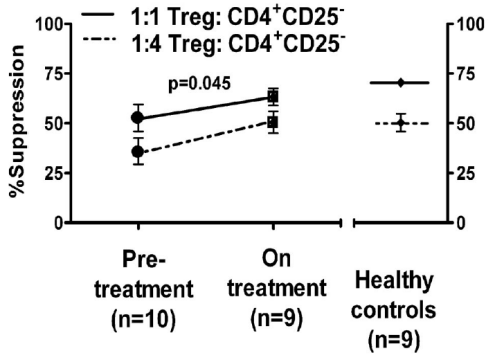


Fig. 3. Dexamethasone up-regulates the Treg cell levels in ITP. A, Representative dot plots of Treg cells (CD4$^+$CD25hiFoxp^{3+} cells) in Donors, ITP and Treatment groups; B, The mean ± SD of the percentage of Treg cells in different groups. $^*p<0.05$,$^{**}p<0.01$.

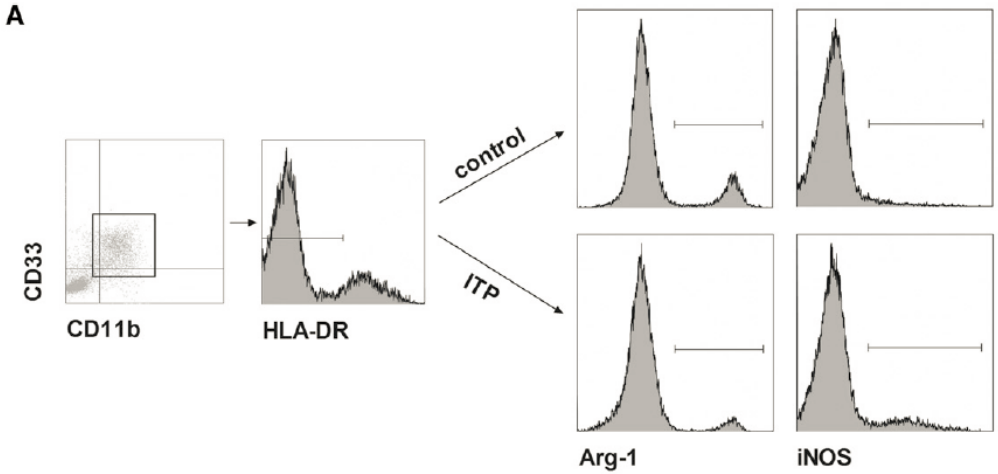


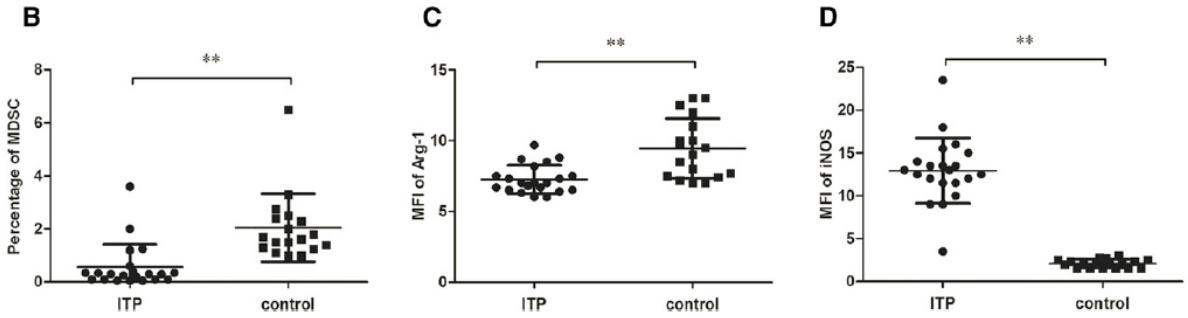


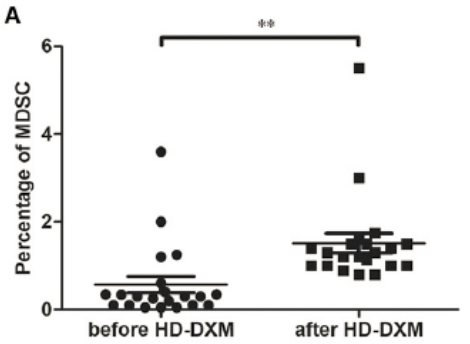
HD-DXM, high-dose dexamethasone; mDC, myeloid dendritic cells.

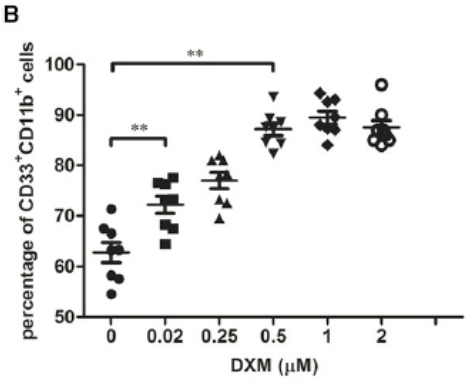
Ling Y, et al. EJ H 2007;79:310–6, Li J, et al. Immunol Lett 2013;154:42–8, 1. Stasi R, et al. Blood 2008;110:2924–30; 2. Bao W, et al. Blood 2010;116:4639–45.

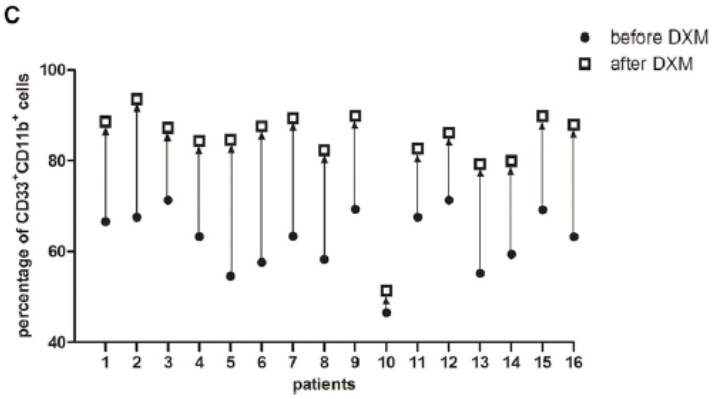
High-dose dexamethasone corrects impaired MDSC function via Ets1 in ITP







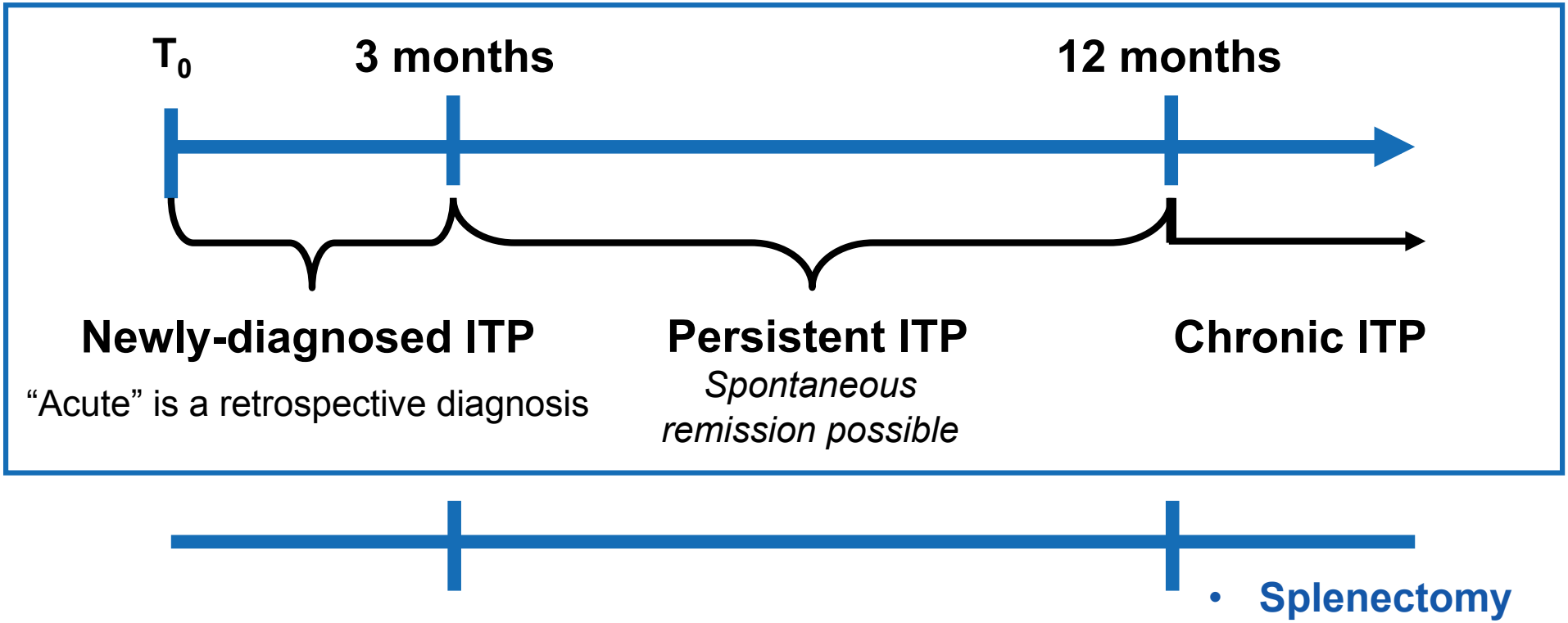




Hou Y, et al. Blood 2016;127:1587–97.

Splenectomy

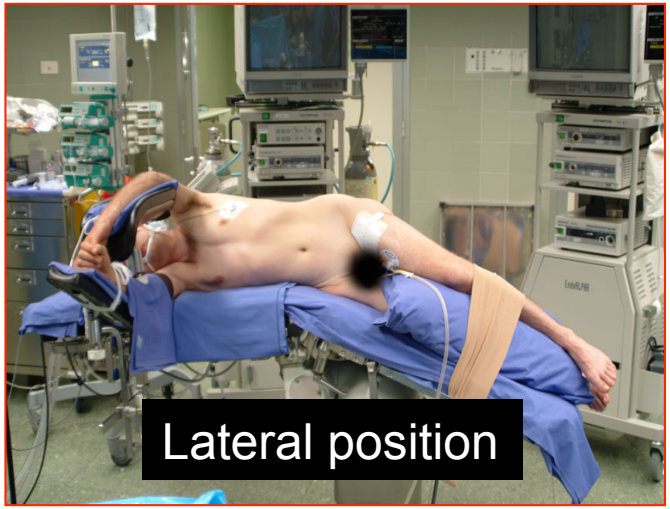
ITP: phases of the disease

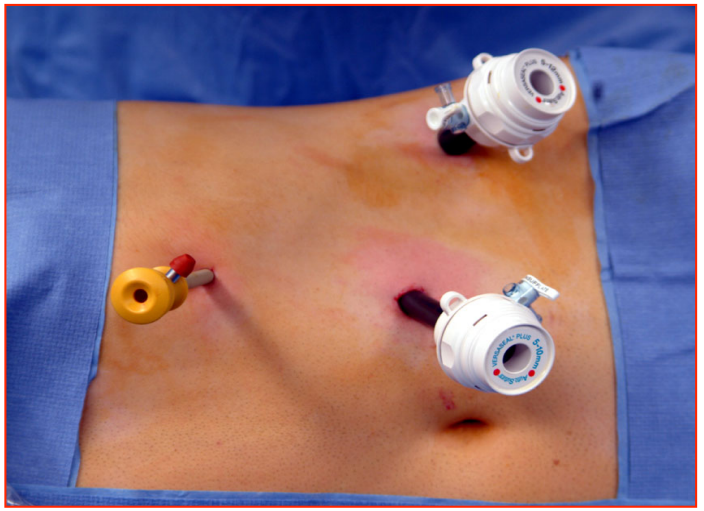


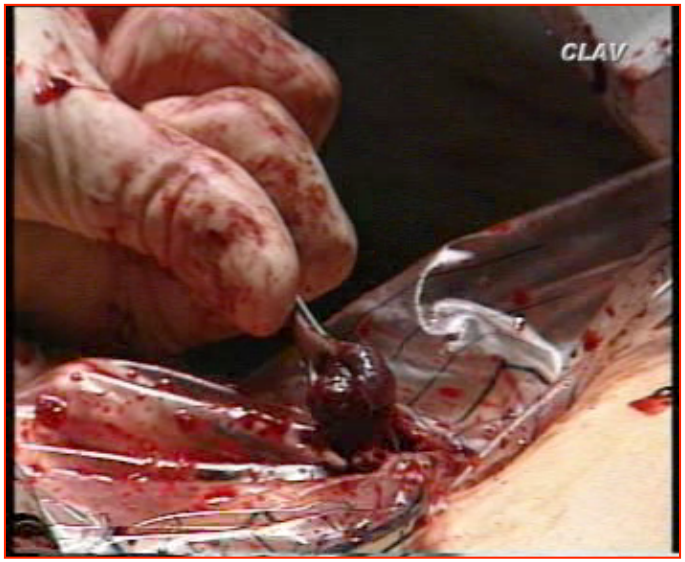
Adapted from Rodeghiero F, et al. Blood 2009;113:2386–93.

AZA, azathioprine; CSA, cyclosporin; MMF, mycophenolate mofetil; TPO-RA, thrombopoietin receptor agonist.

Laparoscopic splenectomy for ITP







Courtesy of Prof. Terrosu, University of Udine.

Splenectomy as a curative treatment for ITP: a retrospective analysis

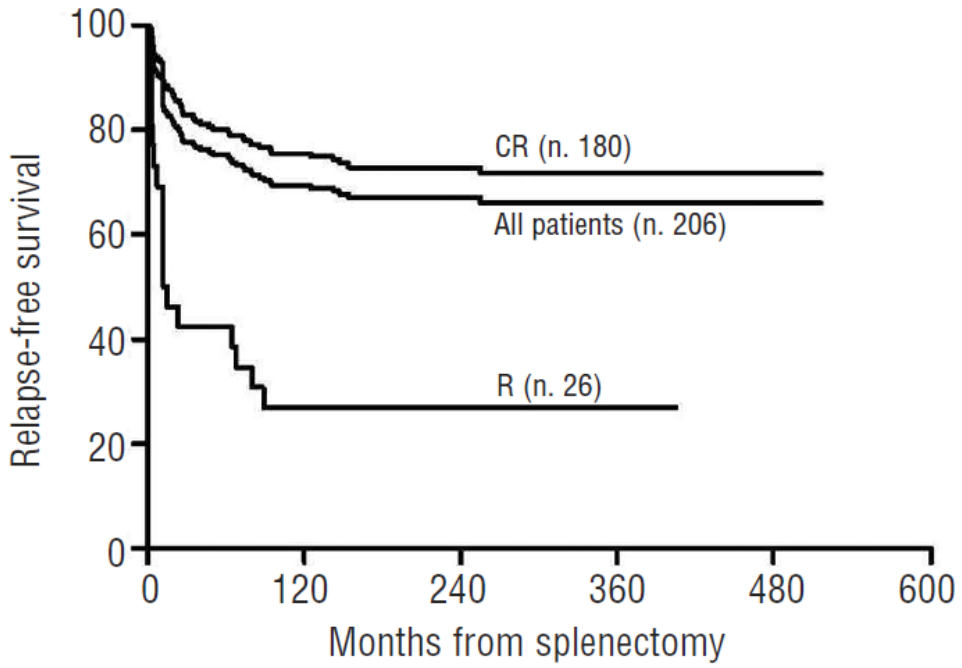


Figure 1. Relapse-free survival (RFS). RFS was 67% (95%CI: 61.3-74.1%) for all responding patients, 73% (95% CI: 66.2-79.5%) for CR patients and 27% (95% CI: 10-43%) for R patients (P<0.001). CR: complete response (PLT>100 x 10^9/L), R: Response (PLT 30-100 x 10^9/L).

Table 4. Long-term complications.

	N. of events (%)	All patients (233)	Refractory patients (95)	Stable responders (138)	P
Infections					
Lung	63 (40%)	41 (18%)	23 (24%)	18 (13%)	0.03
Gastrointestinal/ urogenital/skin	41 (26%)	21 (9%)	13 (14%)	8 (6%)	0.06
Other (minor recurrent infections)	53 (33%)	28 (12%)	14 (14.5%)	14 (10%)	0.31
Fatal (sepsis)	2 (1%)	2 (1%)	1 (1%)	1 (0.7%)	1.00
Overall	159 (100%)	73 (31%)	40 (42%)	33 (24%)	0.004
Thrombosis					
Stroke/TIA	4 (15.5%)	4 (2%)	2 (2%)	2 (1.4%)	1.00
DVT/PE	12 (46%)	8 (3.5%)	4 (4%)	4 (2.8%)	0.71
AMI	6 (23%)	6 (2.5%)	4 (4%)	2 (1.4%)	0.22
Fatal (2 strokes + 2 AMI)	4 (15.5%)	4 (2%)	3 (3%)	1 (0.7%)	0.30
Overall	26 (100%)	18 (8%)	10 (10.5%)	8 (6%)	0.21
Hemorrhage					
Grade 1-2	221 (92%)	47 (20%)	41 (43%)	6 (4%)	<0.0001
Grade 3-4	17 (7%)	16 (7%)	13 (14%)	3 (2%)	<0.0001
Fatal (intracranial)	3 (1%)	3 (1.2%)	3 (3%)	0 (0%)	<0.0001
Overall	241(100%)	58 (25%)	49 (51.5%)	9 (6.5%)	<0.0001

AMI, acute myocardial infarction; CR, complete response (PLT > 100 x 10^9/L); DVT, deep vein thrombosis; PE, pulmonary embolism; PLT, platelet count; R, response (PLT 30–100 x 10^9/L); TIA, transient ischaemic attack.

Vianelli N, et al. Haematologica 2013;98:875–80.

Decline in the rate of splenectomy over time

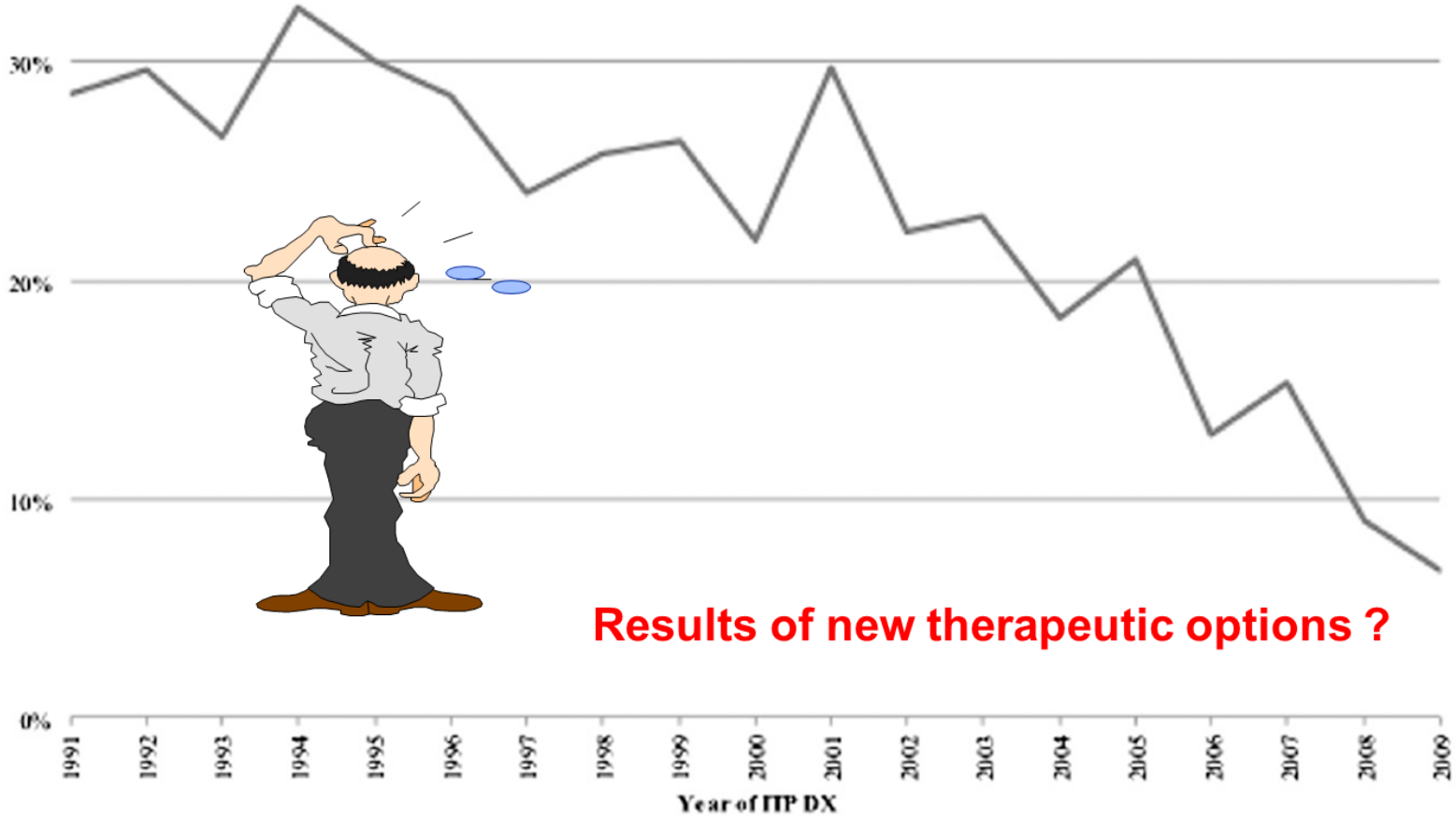


Figure 2. Decline in the rate of splenectomy over time.

Adapted from Boyle S, et al. Blood 2013;121:4782–90.

Preparation for splenectomy

To better select patients who will benefit from splenectomy

- Clinical predictors of response
- Sites of PLT sequestration
- Accessory spleens

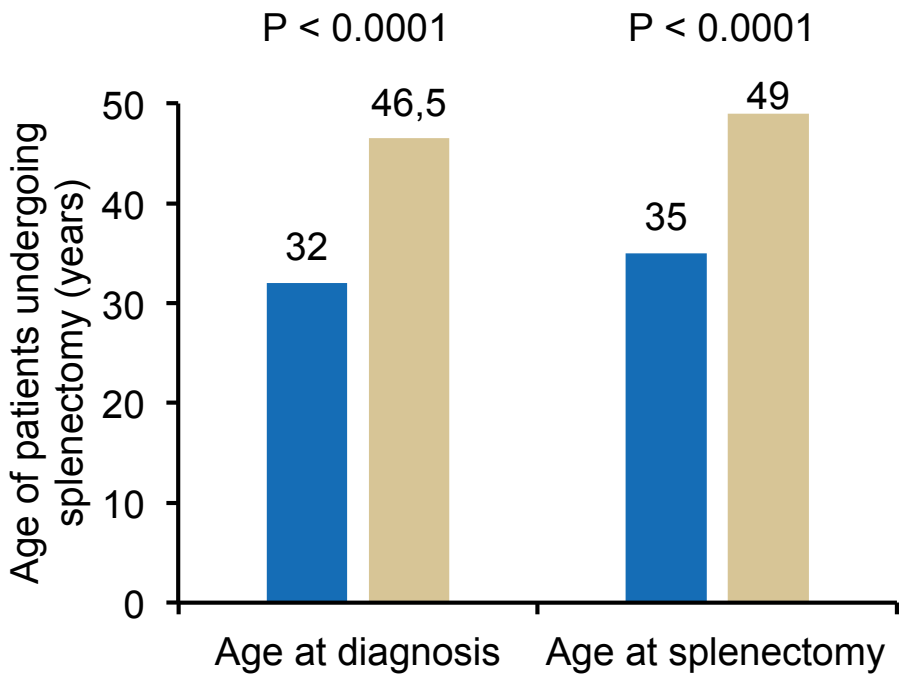
To reduce the risk of short and long-term complications

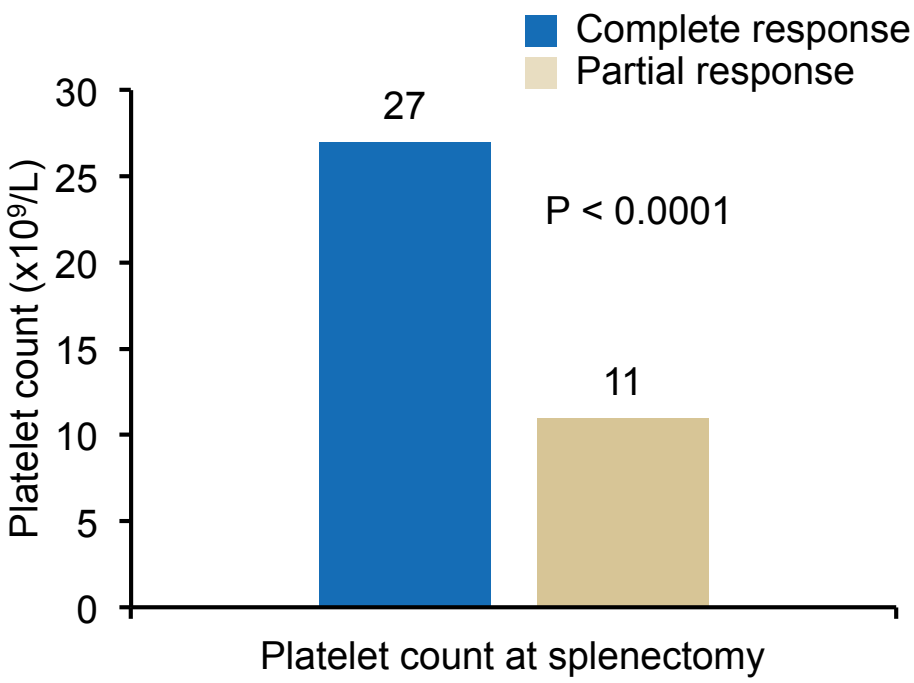
- Vaccines
- Safe PLT count pre-splenectomy*
- Antithrombotic prophylaxis

*There is a general consensus to consider a PLT count ≥ 50 x 10^9/L.

Slide courtesy of F. Zaja.

Clinical predictors of response to splenectomy in ITP patients





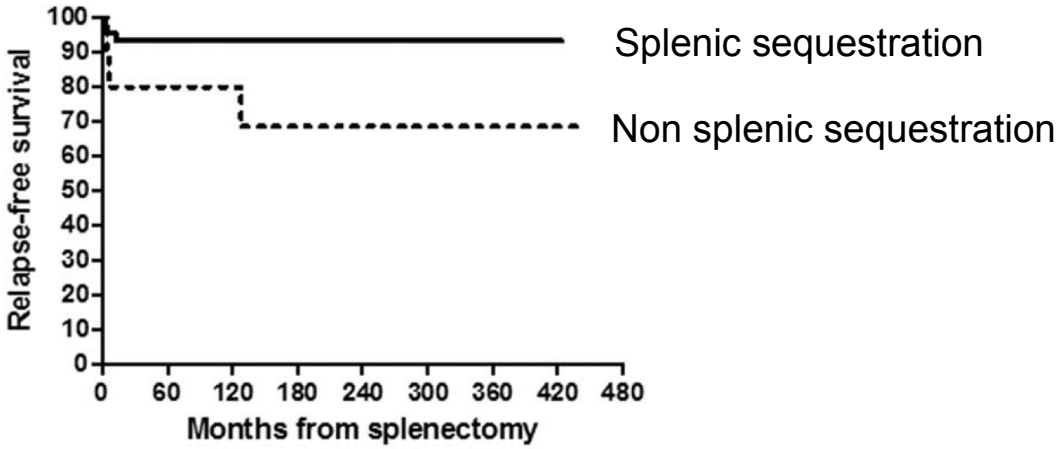
- Predictive of favourable response to splenectomy:
  - Younger age (P < 0.0001)
  - Higher platelet count at splenectomy (P < 0.0001)
  - Number of former therapies (P < 0.01)

Vianelli N, et al. Haematologica 2005;90:72–7.

The choice of second-line therapy in steroid-resistant ITP: role of platelet kinetics

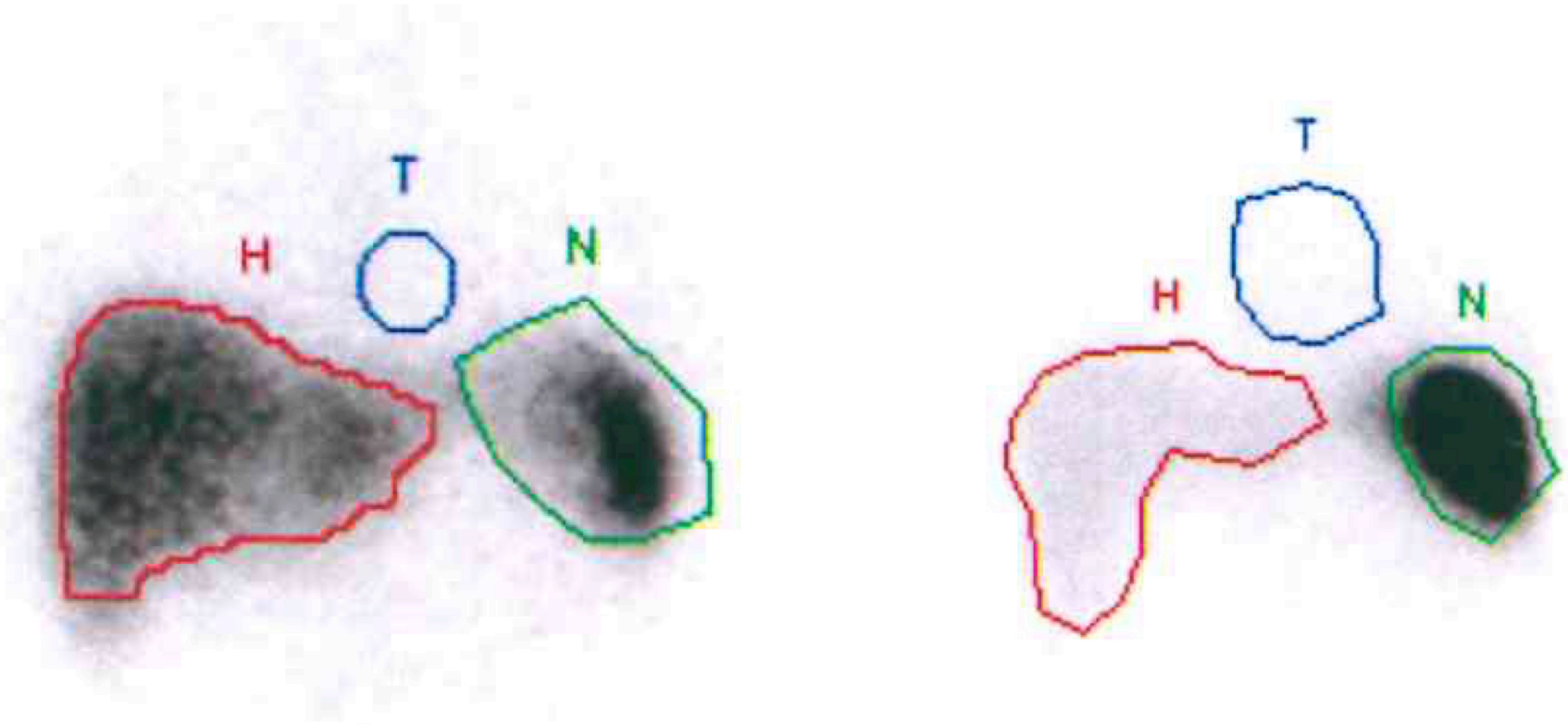
TABLE II. Results of Platelet Kinetic Study and Response to Splenectomy

Characteristic	No. of patients (%)	Response (CR + R) no, (%)	*P*	CR, no (%)	*P*	Stable response (CR+R) no, (%)	*P*
Type of platelet sequestration							
Splenic	52/70 (74%)	50 (96%)	0.0028	46 (88%)	0.005	44/52 (85%)	0.0083
Nonsplenic	18/70 (26%)	12 (67%)		10 (56%)		9/18 (50%)	
Hepatic	10 (14%)	5 (50%)		4 (40%)			
Mixed	8 (12%)	7 (88%)		6 (75%)			
Platelet turnover							
Normal/reduced	14/34 (41%)	12 (86%)	1	11 (79%)	0.46	11/14 (79%)	0.46
Increased	20/34 (59%)	16 (80%)		13 (65%)		13/20 (65%)	
Platelet half-life							
Below median value	37/70 (53%)	34 (92%)	0.69	31 (91%)	1	30/37 (81%)	0.77
Above median value	33/70 (47%)	29 (85%)		26 (79%)		25/33 (76%)	



Palandri F, et al. Am J Hematol 2014;89:1047–50.

^{111}In-labelled platelet scintigraphy



Mixed sequestration

Splenic sequestration

Slide courtesy of Dr. Milella, Niguarda Hospital, Milan .

Rituximab

Exposure to non-corticosteroid treatments in adult primary immune thrombocytopenia before the chronic phase in the era of thrombopoietin receptor agonists in France. A nationwide population-based study

Guillaume Moulis [a,b,c,*], Maryse Lapeyre-Mestre [b,c,d], Jean-Louis Montastruc [b,c,d,e], Laurent Sailler [a,b,c]

Treatments	**%**
Rituximab	58
Splenectomy	22
TPO-RA	17
IVIg	15
Danazol	14
Dapsone	11

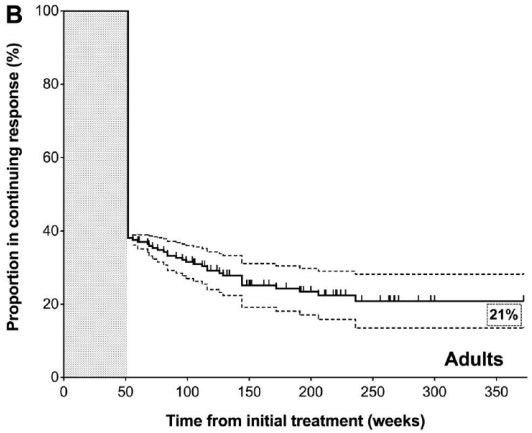
Autoimmunity Reviews 2015

Long-term effect of rituximab salvage therapy in adults with ITP

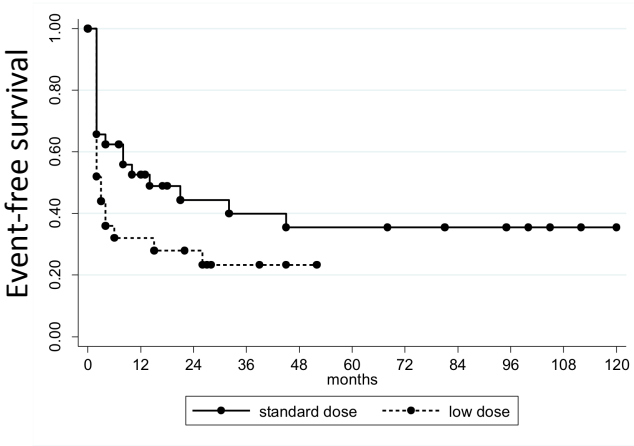
Patients	72
LTR	**21%**

Patients	32
LTR	**40%**

Patients	248
LTR	**39%**



Patel et al. Blood 2012



Zaja et al. Am J Hematol 2012

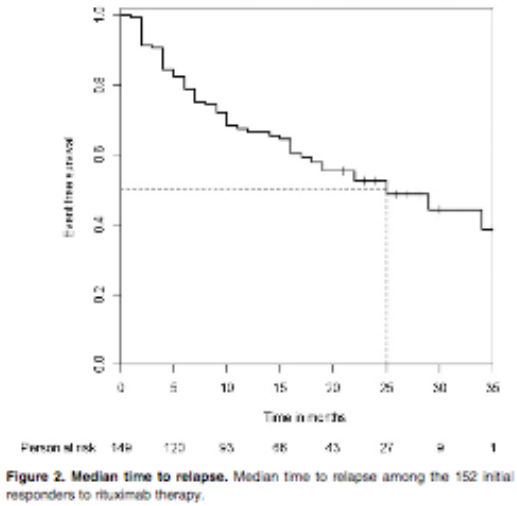
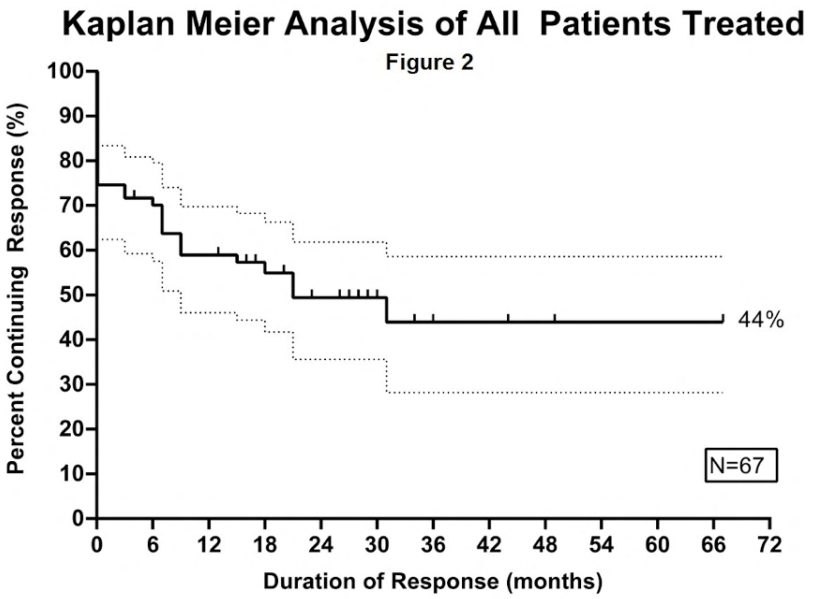


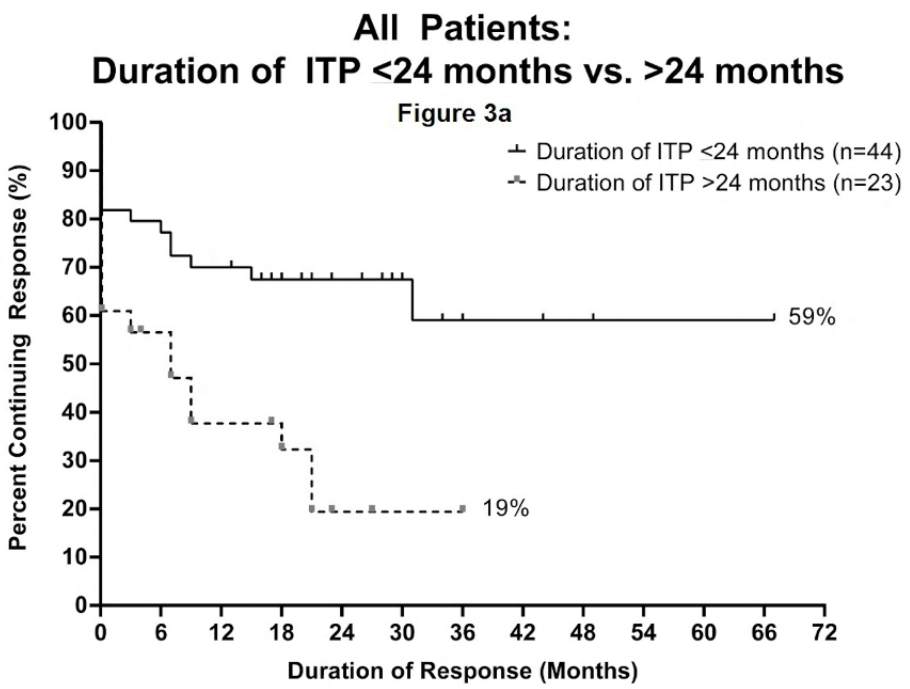
Figure 2. Median time to relapse. Median time to relapse among the 152 initial responders to rituximab therapy.

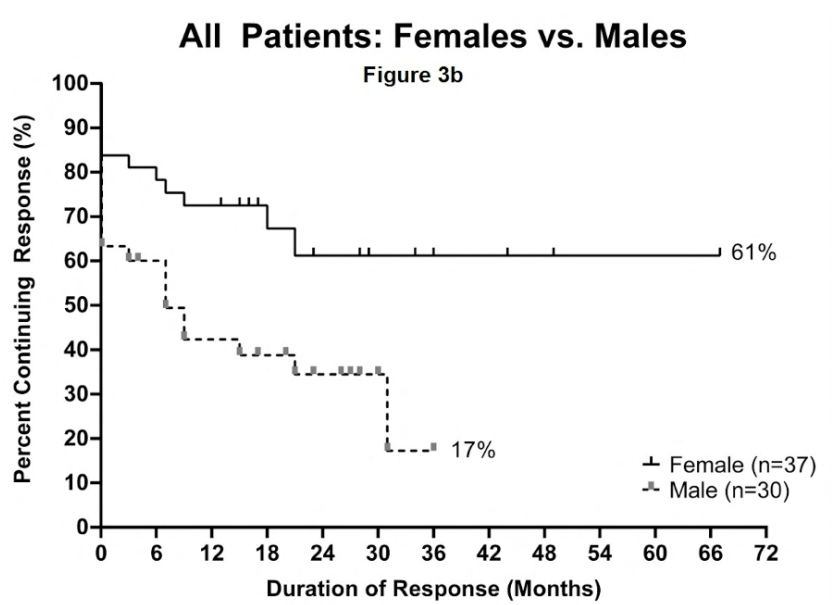
Khellaf et al Blood 2014

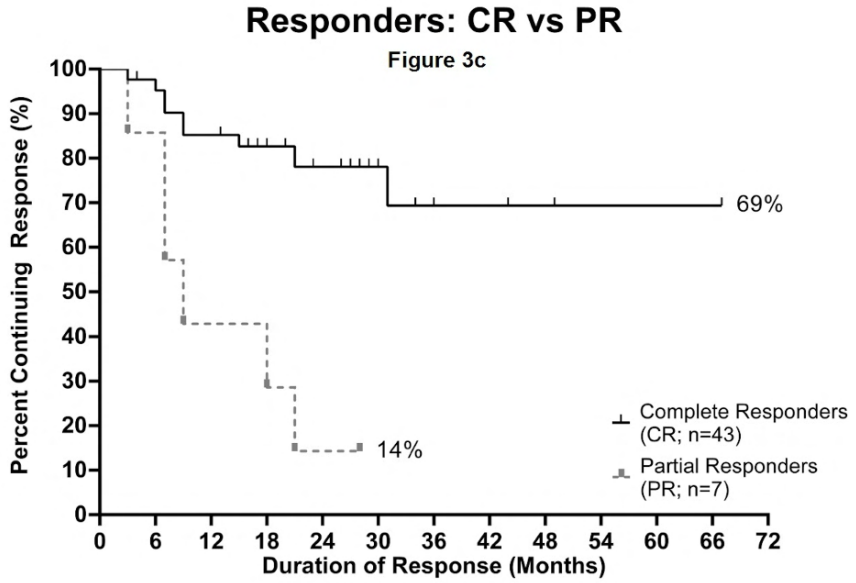
Can we predict the response to Rituximab in adult patients with ITP ?

3 x Dexamethasone + Rituximab in ITP









Bussel et al. Haematologica 2014

Rituximab in primary ITP in adults: multicenter Italian experience

Number of patients	103
Median age, years (range) Patients < 40 years	46 (16-82) 38 (37%)
Women	61 (59%)
Median ITP duration, months (range)	20 (1-403)
1 line of previous therapy 2 lines of previous therapy ≥ 3 lines of previous therapy	49 (48%) 37 (36%) 17 (16%)
Previous splenectomy	11 (11%)
Median platelet count before Rituximab	15 x 10^9/L
Rituximab dose	375 mg/m^2 x 4
Median time of observation (months)	**59 (range 2-164)**

EJH submitted

Clinica Ematologica, Udine

Outcome

Overall response rate: 55% (57/103)

Complete response rate: 36% (37/103)

Relapse rate:

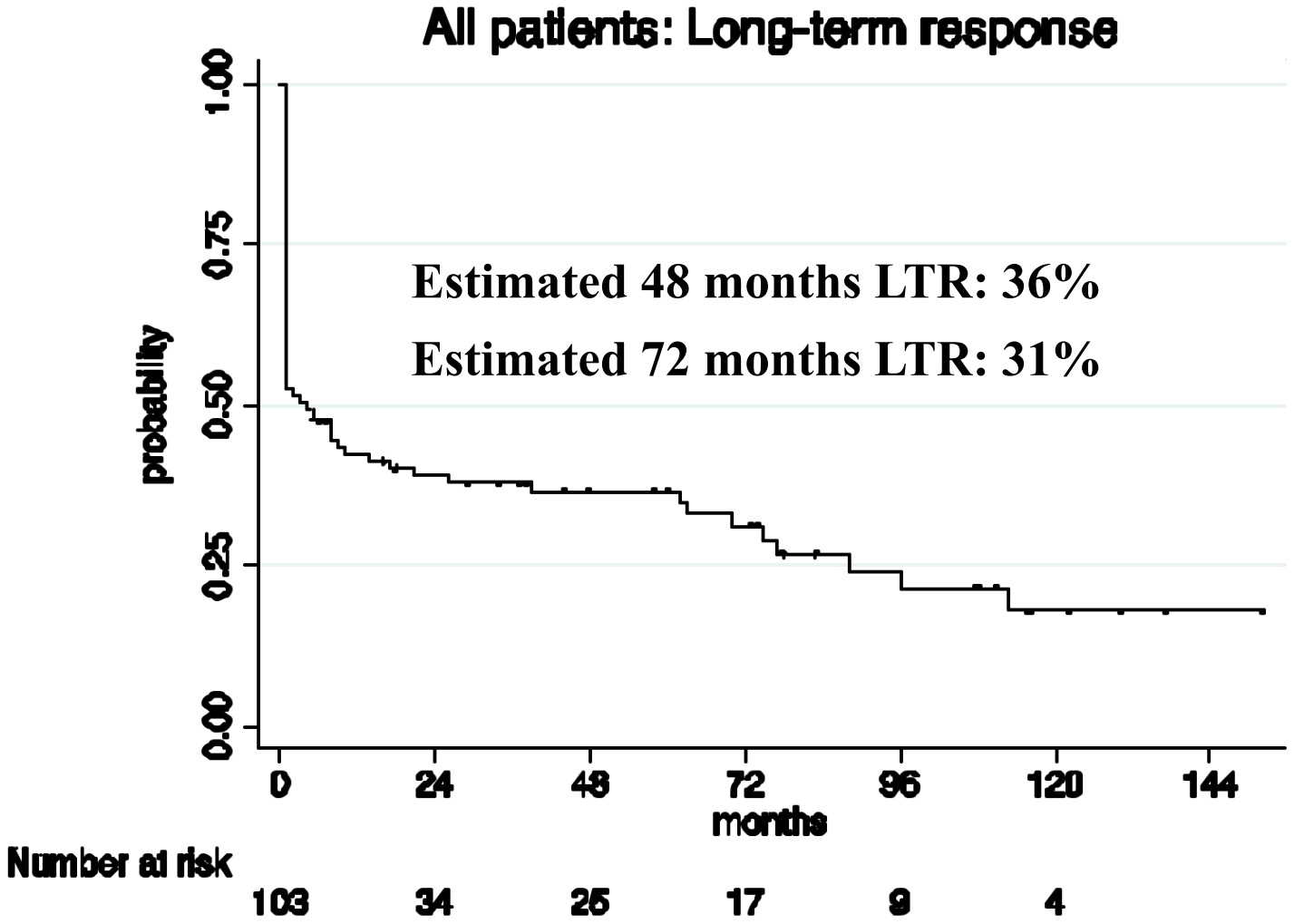
- Patients achieving ORR: 46% (26/57)
- Patients achieving CR: 38% (14/37) P= 0.109
- Patients achieving PR: 60% (12/20)

Median response duration: 38 months (range 1-152)

Long-term response: 54% (31/57) of responders

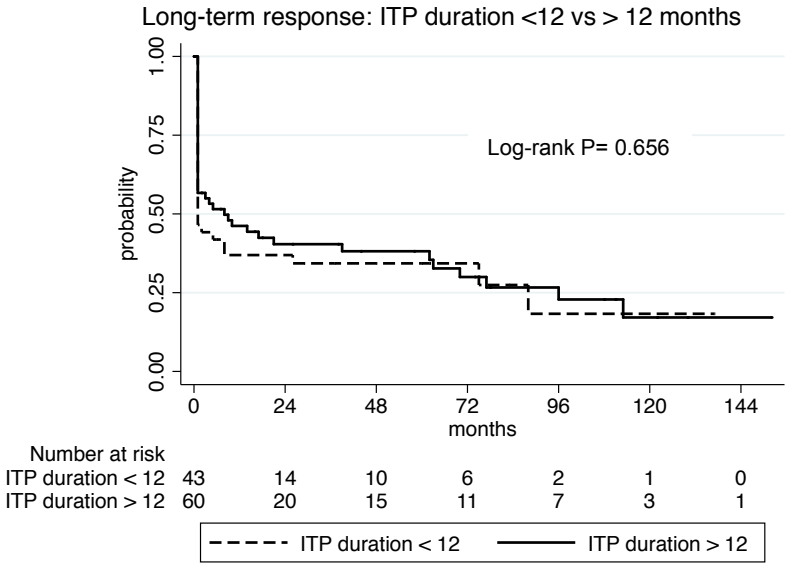
30% (31/103) of the entire study population

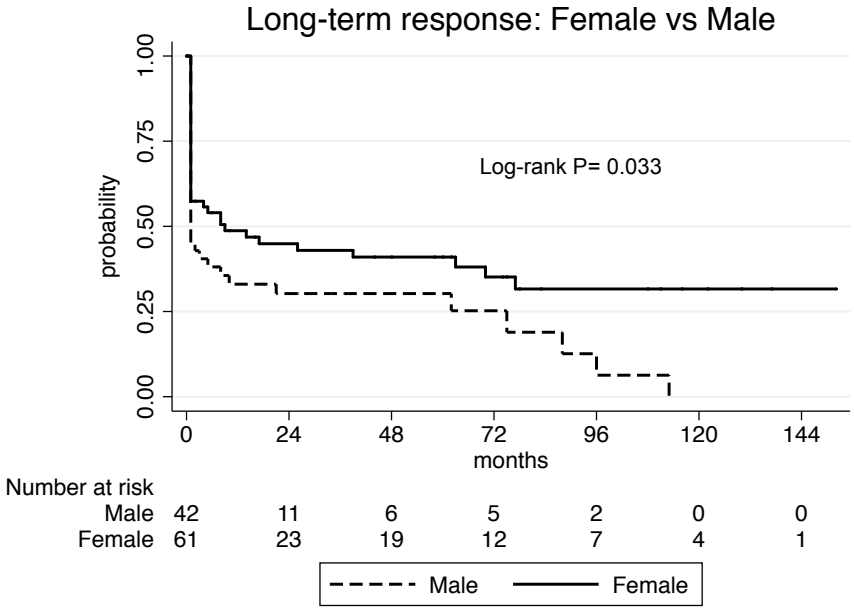
EJH submitted

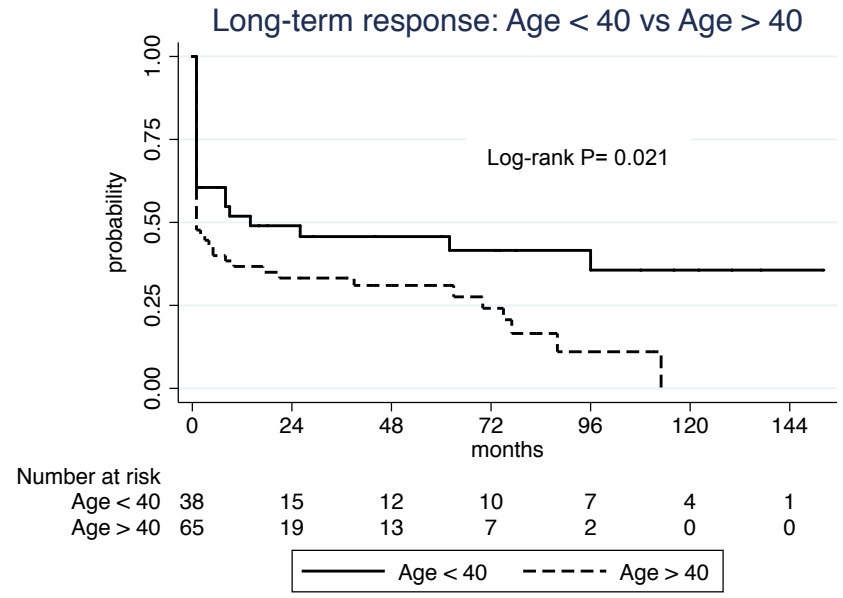


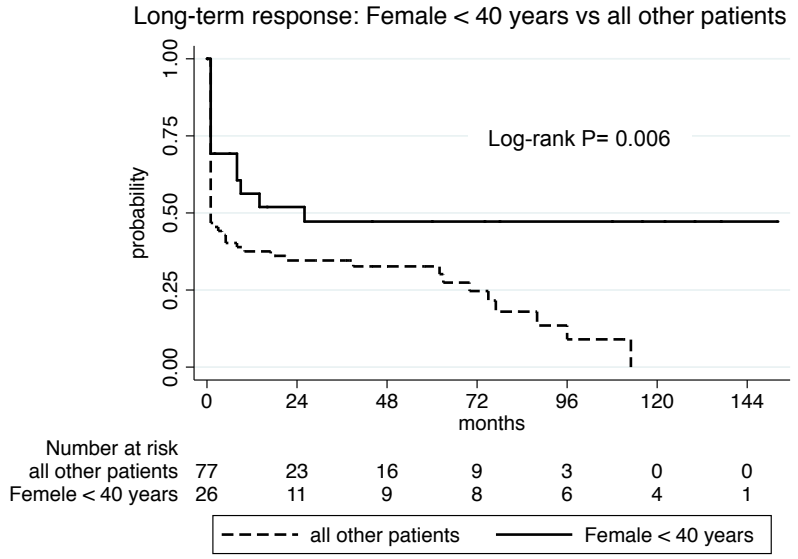
EJH submitted

Clinica Ematologica, Udine







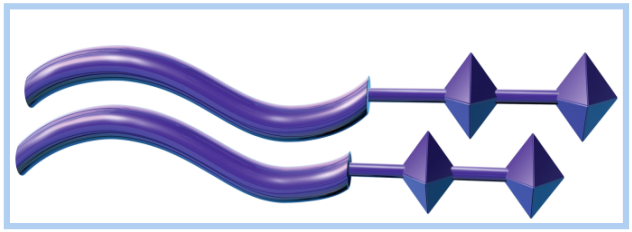


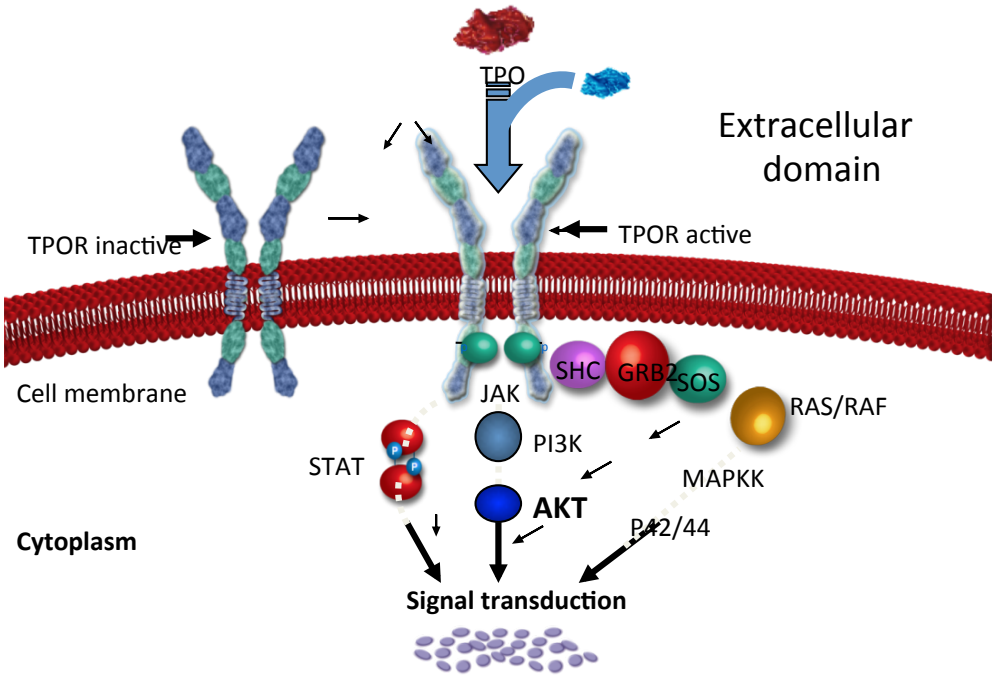
EJH submitted

Clinica Ematologica, Udine

TPO-RAs

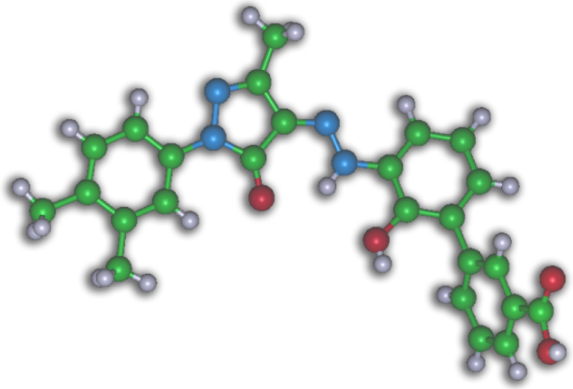
Romiplostim

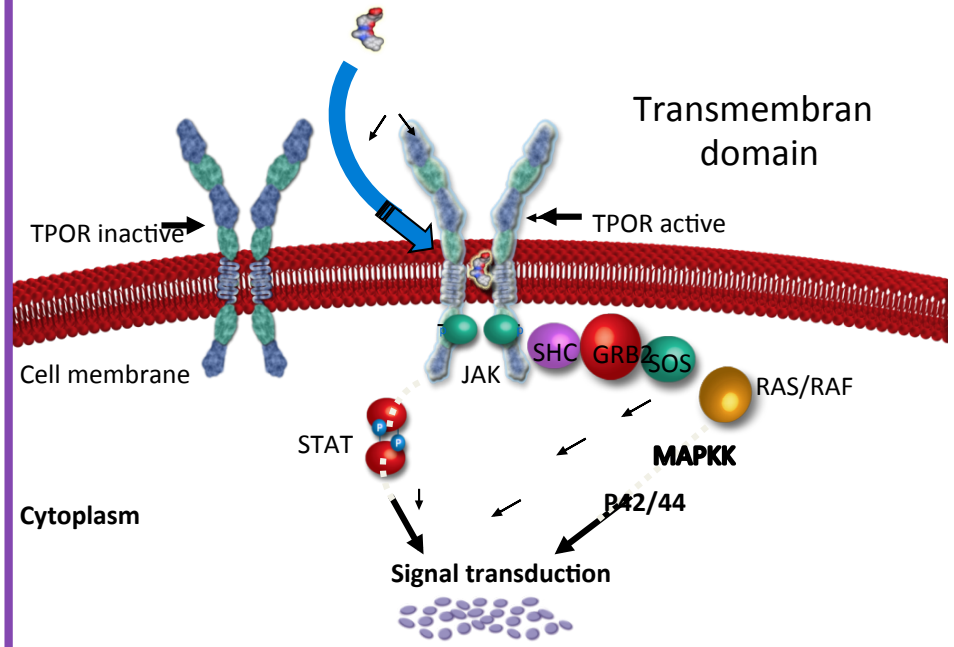




Increased platelet production and MKC prolipheration

Eltrombopag

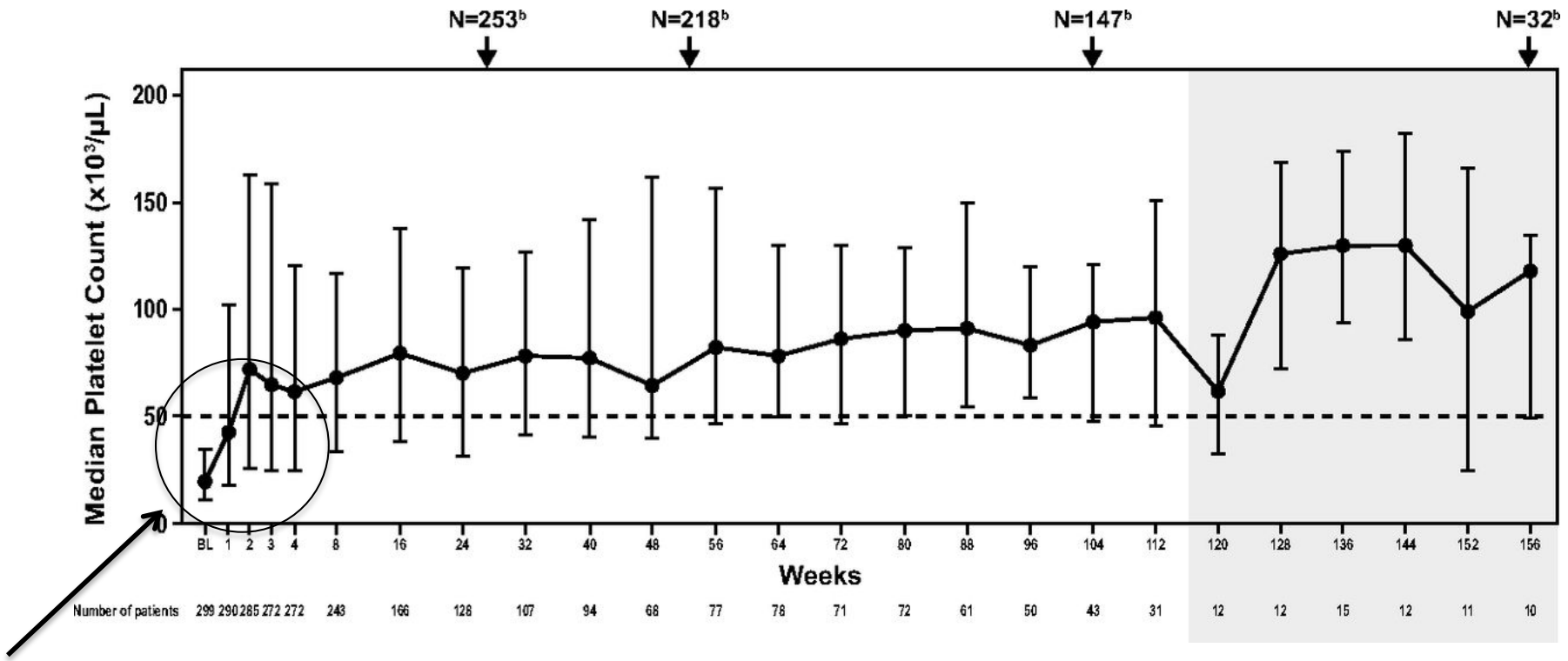




Increased platelet production

TPO mimetics in ITP

Short term activity	70-80%
Long term activity	70%



EXTEND study, Saleh et al 2013

Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: results of the long-term, open-label EXTEND study

Mansoor N. Saleh,[1] James B. Bussel,[2] Gregory Cheng,[3] Oliver Meyer,[4] Christine K. Bailey,[5] Michael Aming,[5] and Andres Brainsky,[5] on behalf of the EXTEND Study Group Blood 2013

Patient group	Responders*, n (%)
All patients†	257/302 (85)
Baseline platelet count	
<30,000/μL	170/211 (81)
30,000–50,000/μL	51/52 (98)
>50,000/μL	36/39 (92)
ITP medication use at baseline	
Yes	87/101 (86)
No	170/201 (85)
Splenectomy status	
Splenectomised	92/115 (80)
Non-splenectomised	165/187 (88)
Response in previous study	
Yes	144/154 (94)
No	104/138 (75)

TPO-m: implications of route of administration

Eltrombopag

- Oral administration
- Every day
- Biodisponibility altered by food

Romiplostim

- sc administration
- Every week
- H or self administration

RESEARCH ARTICLE

AJH

Thrombopoietin receptor agonists for preparing adult patients with immune thrombocytopenia to splenectomy: results of a retrospective, observational GIMEMA study

Francesco Zaja,[1]* Wilma Barcellini,[2] Silvia Cantoni,[3] Monica Carpenedo,[4] Giuseppe Caparrotti,[5] Valentina Carrai,[6] Nicola Di Renzo,[7] Cristina Santoro,[8] Massimo Di Nicola,[9] Dino Veneri,[10] Federico Simonetti,[11] Anna M. Liberati,[12] Valeria Ferla,[2] Francesca Paoloni,[13] Enrico Crea,[13] Stefano Volpetti,[1] Enrica Tuniz,[1] and Renato Fanin[1]

In patients with immune thrombocytopenia (ITP) refractory to corticosteroids and intravenous immunoglobulins (IVIG), splenectomy may result at higher risk of peri-operative complications and, for this reason, potentially contraindicated. The thrombopoietin receptor agonists (TPO-RAs) romiplostim and eltrombopag have shown high therapeutic activity in primary ITP, but data of efficacy and safety regarding their use in preparation for splenectomy are missing. Thirty-one adult patients, median age 50 years, with corticosteroids and/or IVIG refractory persistent and chronic ITP who were treated with TPO-RAs (romiplostim= 24; eltrombopag= 7) with the aim to increase platelet count and allow a safer execution of splenectomy were retrospectively evaluated. Twenty-four patients (77%) responded to the use of TPO-RAs with a median platelet count that increased from 11 × 10^9/L before starting TPO-RAs to 114 × 10^9/L pre-splenectomy, but a concomitant treatment with corticosteroids and/or IVIG was required in 19 patients. Twenty-nine patients underwent splenectomy while two patients who responded to TPO-RAs subsequently refused surgery. Post-splenectomy complications were characterized by two Grade 3 thrombotic events (1 portal vein thrombosis in the patient with previous history of HCV hepatitis and 1 pulmonary embolism), with a platelet count at the time of thrombosis of 260 and 167 × 10^9/L, respectively and one Grade 3 infectious event. TPO-RAs may represent a therapeutic option to improve platelet count and reduce the risk of peri-operative complications in ITP candidates to splenectomy. An increased risk of post-splenectomy thromboembolic events cannot be ruled out and thromboprophylaxis with low-molecular weight heparin is generally recommended.

TABLE II. Response to Thrombopoietin Receptor Agonists Treatment

	All	Romiplostim	Eltrombopag	*P*-value
Patients	31	24	7	
Median duration of treatment (days)	86.5	87.0	84	0.6768
Response (%)	24 (77.4)	19 (79.2)	5 (71.4)	0.6417
Concomitant therapy (corticosteroid/IVIG)	19 (61.3)	17 (70.8)	2 (28.6)	0.0434
Median platelet count before splenectomy (× 10^9/L)	114	114	133.5	0.1484

Number of splenectomy	29
Laparoscopic splenectomy **Laparotomic splenectomy**	26 (90%) 3 (10%)
Response after splenectomy Response Complete Response	 22 (76%) 21 (72%)
Post splenectomy complications: Thrombosis grade 3* Bleeding grade 4 Infectious grade 3	4 in 3 patients 2* 1 (PLT 30 x 10^9/L) 1

*	Age	Days end of TPO-RAs	Days from splenectomy	PLT count x 10^9/L	Predisponing factors	Prophylactic heparin
# 1	33	Eltromb. 44	14	260	HCV hepatitis	yes
# 2	32	Romipl. 6	5	178	no	no

Zaja et al AJH 2016

Switching of TPO-R agonist in ITP

Romiplostim

Eltrombopag

- Lack of efficacy
- Platelets count fluctuations
- Side effects
- Patients' preference

A retrospective pilot evaluation of switching thrombopoietic receptor-agonists in immune thrombocytopenia

Mehdi Khellaf,[1] Jean-François Viallard,[2] Mohamed Hamidou,[3] Stéphane Cheze,[4] Françoise Roudot-Thoraval,[5] François Lefrere,[6] Olivier Fain,[7] Sylvain Audia,[8] Jean-François Abgrall,[9] Jean-Marie Michot,[10] Charles Dauriac,[11] Sophie Lefort,[12] Emmanuel Gyan,[13] Mathilde Niault,[14] Jean-Marc Durand,[15] Laetitia Languille,[1] David Boutboul,[16] Philippe Bierling,[17] Marc Michel,[1] and Bertrand Godeau[1]

46 ITP patients switching from romiplostim or eltrombopag or *vice versa*

1st TPO-RA	Reasons for switch, n	2nd TPO-RA	
Romiplostim	→	**Eltrombopag**	
n=35	Treatment failure, 13	Response rate	6/13 (46%)
	Platelet-count fluctuation, 11	Platelet-count stabilized	6/11 (55%)
	Side effect, 3	Good tolerance	3/3 (100%)
Eltrombopag	→	**Romiplostim**	
n=11	Treatment failure, 10	Response rare	8/10 (80%)
	Side effect, 1	Good tolerance	1/1 (100%)

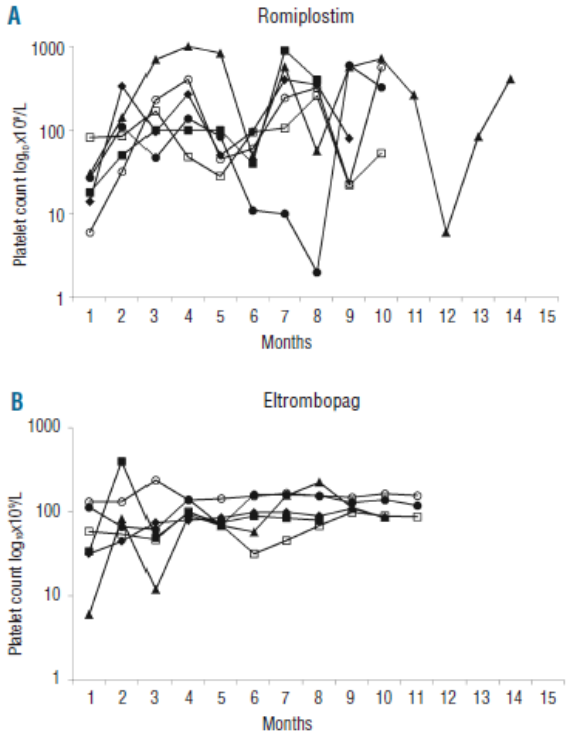


Figure 1. Platelet-count fluctuations of 6 patients under romiplostim (A) and their attenuation after switching to eltrombopag (B).

Remission and platelet responses with romiplostim in primary immune thrombocytopenia: final results from a phase 2 study

- ITP duration ≤ 6 months
- Treatment with romiplostim for ≤12 months.
- Patients with platelet counts ≥ 50 x 10^9/L at the end of 12 months entered a dose taper in which the romiplostim dose was decreased as long as PLT counts were maintained.
- Remission (PLT count ≥ 50 x 10^9/L for 24 consecutive weeks with no ITP treatments) was evaluated in patients once romiplostim was discontinued

Remission was observed in 24 patients (32%).

No significantly predictors of remission.

Newland et al. BJH 2016

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche.

Eltrombopag as Second line Therapy in adult patients with primary Immune Thrombocytopenia (ESTIT study) in an attempt to achieve long-term remission: a single arm multicenter phase II clinical and biological study

GIMEMA Study ITP0815

EudraCT number 2015-001327-23

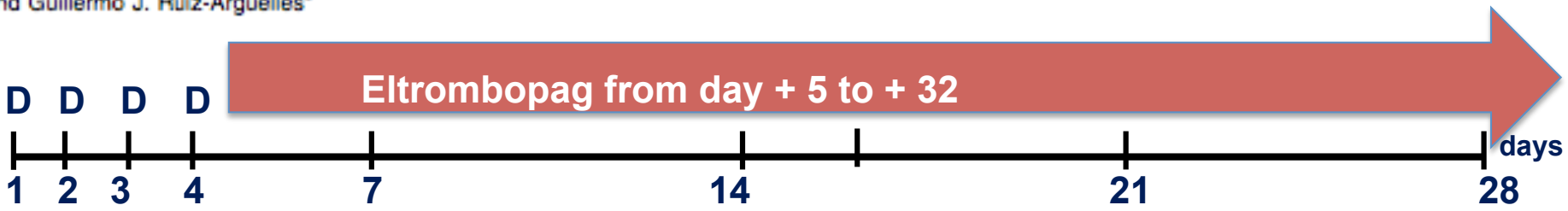
Clinical Trial Number 2402998

CLINICAL TRIALS AND OBSERVATIONS

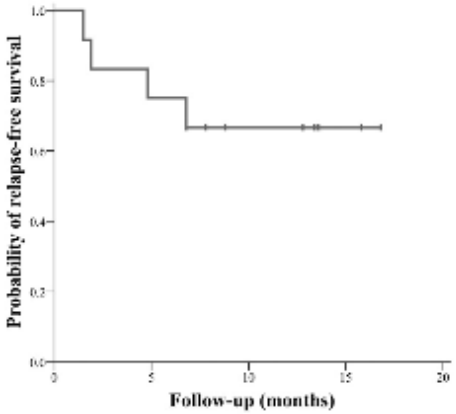
Eltrombopag and high-dose dexamethasone as frontline treatment of newly diagnosed immune thrombocytopenia in adults

BLOOD, 19 JUNE 2014 • VOLUME 123, NUMBER 25

David Gómez-Almaguer,[1] Miguel A. Herrera-Rojas,[1] José C. Jaime-Pérez,[1] Andrés Gómez-De León,[1] Olga G. Cantú-Rodríguez,[1] César H. Gutiérrez-Aguirre,[1] Luz Tarín-Arzaga,[1] Jesús Hernández-Reyes,[2,3] and Guillermo J. Ruiz-Arguelles[3]

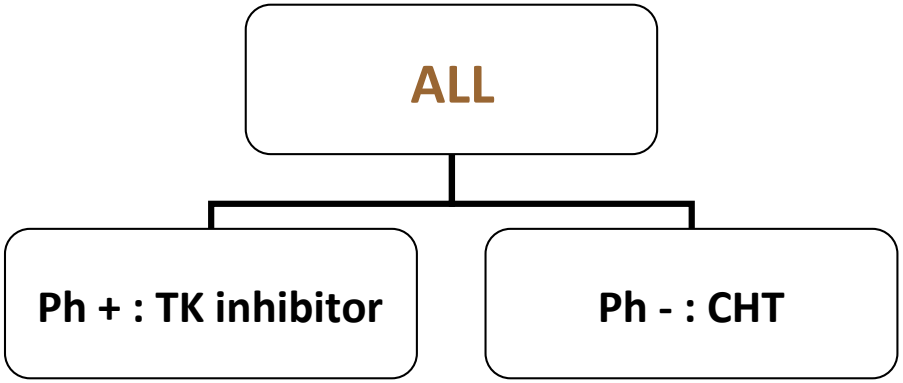


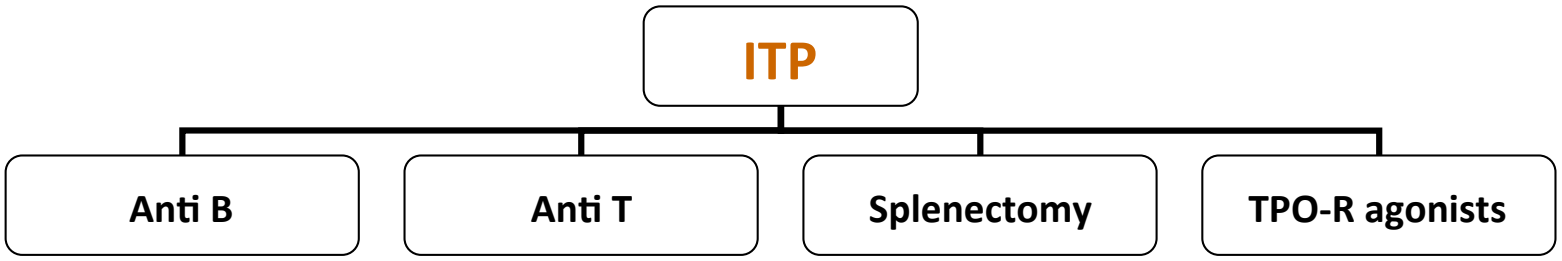
Patients	12
Median age, years	50 (20-80)
M/F	6/6
Median PLT count	7 x 10^9/L
Median follow up	12.5 months



	After Dexamethasone	Eltrombopag Month 1	Eltrombopag Month 3	Eltrombopag Month 6	Relapse rate
ORR	10 (83%)	12 (100%)	12 (100%)	9 (75%)	4 (33%)
CR	5 (42%)	10 (83%)	7 (58%)	6 (50%)	2 (40%)

La moderna terapia della piastrinopenia immune





Alcune considerazioni finali

Steroidi:

- Trattamento a breve termine
- ? PDN = Dexa

Splenectomia laparoscopica:

- Giovani
- Sequestro splenico
- Corretta preparazione alla splenectomia

Rituximab:

- Uso non tardivo
- Giovani, ? donne
- Possibile impiego pre splenectomia

TPO-RAs:

- Pazienti R/R
- Anziani: impiego a lungo termine
- Giovani: terapia ponte di medio termine
- Studi in corso per valutare un possibile uso anticipato di qs agenti

Ringraziamenti

Prof. Renato Fanin

Gruppo "linfomi e piastrinopenie"

- Stefano Volpetti
- Giulia Perali
- Maddalena Mazzucco
- Elisa Lucchini
- Sara Frisoli

GIMEMA

AIL Udine