

General Heme



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DISCLOSURE

Relevant Financial Relationship(s)

Speaker Bureau - None

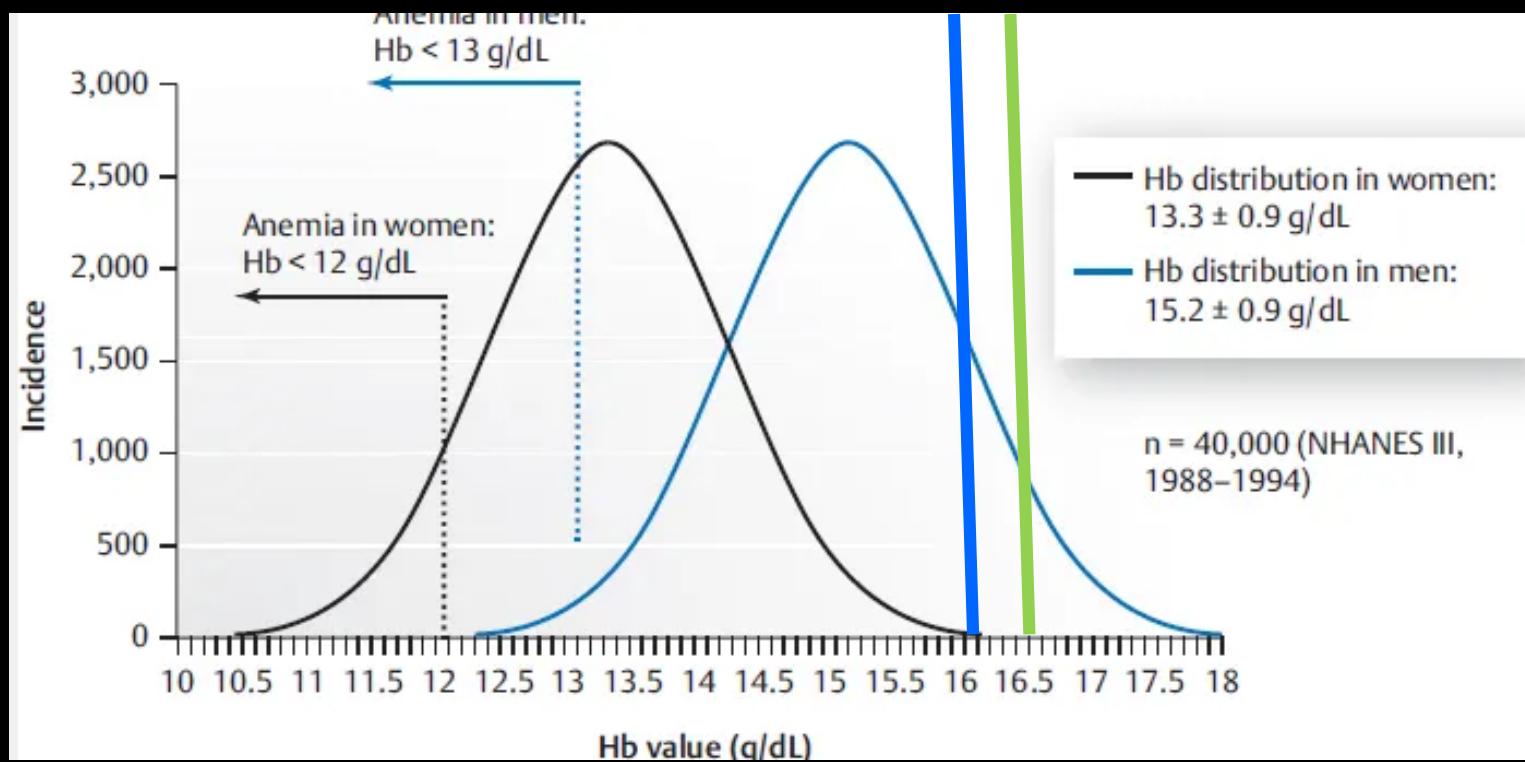
Consultant – None

Today

- New causes of erythrocytosis
- ITP

Erythrocytosis

- Hemoglobin > Men: 18.5 g/dl or Women 16.5 g/dl
 - WHO cut-off too sensitive
 - M:16.5/49% F:16/48%
- High hematocrit and other blood counts up
- Big question – Polycythemia vera vs other causes



Differential Diagnosis

- **Polycythemia vera**
- **Hypoxia**
 - Lung disease
 - High altitude
 - Sleep apnea (nocturnal desaturation)
- **Impaired oxygen delivery**
 - Smoking

Polycythemia

- Clonal bone marrow disease
- Increases risk of thrombosis
- Findings
 - High hematocrit
 - Other counts raised
 - Suppressed EPO
 - Thrombosis

Hypoxia

- Elevation
 - Adds ~1% to Hct for every 1000 meters
- Lung disease
- Cardiac disease
- Smoking
 - Adds ~ 1.5% to Hct

Testosterone

- Increased sensitivity to EPO
- Onset months
 - Can take several months to resolved

Erythrocytosis

- Testosterone increases red cell count
 - Direct stem cell effect
 - Increase sensitivity to EPO
 - Increase iron absorption
 - Lowers hepcidin
- Average hematocrit rise 4%
 - > 54%: 0.5%

Figure 1. Time relation between hematocrit and duration of testosterone therapy

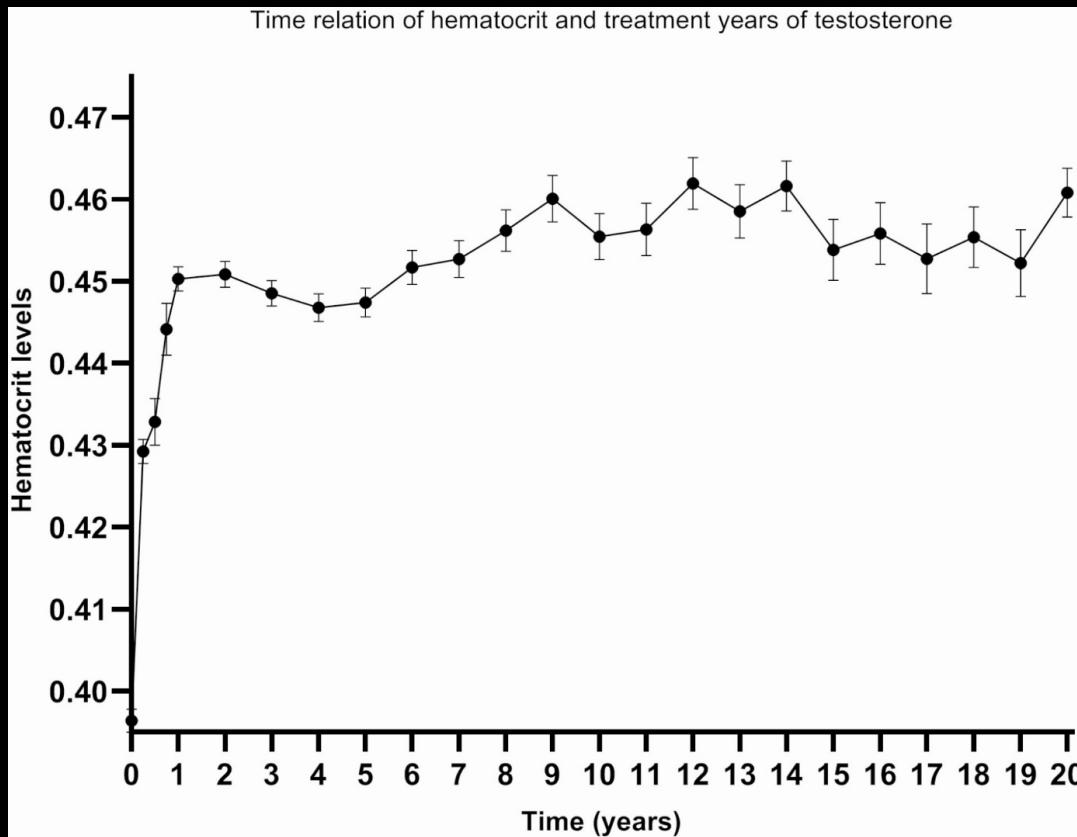
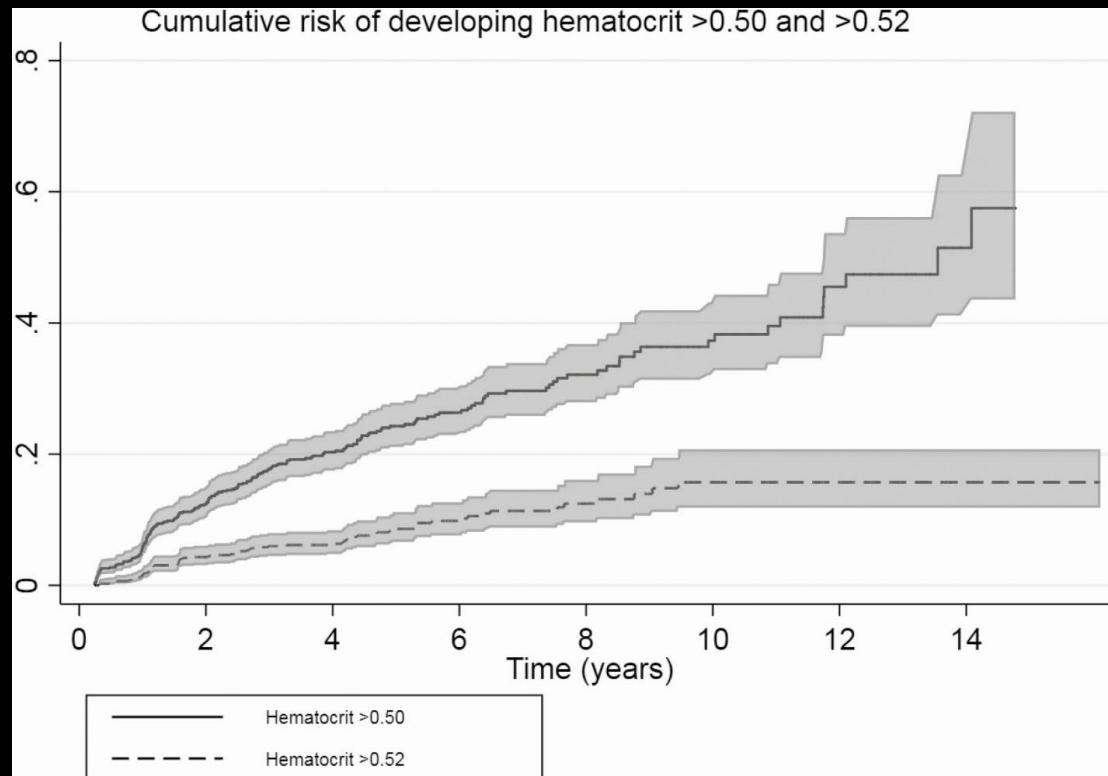


Figure 2. Nelson-Aalen curve for the cumulative risk of developing hematocrit levels >0.50 and >0.52 .



Erythrocytosis

- Hct > 54%
 - Phlebotomy
 - Transdermal testosterone
- “Pseudo-erythrocytosis”
 - Use of wrong cbc range

Other Important Causes

- Renal
 - Cancer
 - Big renal cysts
 - Renal artery stenosis
- Hepatic
 - Hepatomas
 - Hepatitis
 - Hemangiomas
- Endocrine Tumors

SGLT2 Inhibitors

- Raises Hct by 2-4%
- Increasing reports of erythrocytosis
- Decrease hepcidin
- Increase EPO

Congenital

- High affinity hemoglobin
- HIF pathway defects
- EPO receptor defects
- Clues
 - Family history
 - Only red cells elevated
 - Young age

Work-up

- Hemoglobin electrophoresis
- “Erythrocytosis Panel”
 - HIF pathway
 - EPO-R

Hemochromatosis

- Carries of HFE mutations can have erythrocytosis
 - Not due to higher iron levels
- Both homozygous and heterozygous

Work-up I

- Suspicion for PRV increases if
 - Other counts elevated
 - Splenomegaly
 - Aquagenic pruritus
- JAK2 mutation assay
 - Abnormal in 99% of PRV
 - Diagnostic test

Work-Up II

- Erythropoietin levels
 - PRV if below normal
- Oxygen saturation
- Sleep Studies
- Carboxyhemoglobin
- Renal/Liver imaging
- Hemoglobin electrophoresis
- Congenital work-up

Idiopathic Erythrocytosis

- Negative work-up
- Acquired erythrocytosis
- ? Novel mutations
- Management unknown
- Phlebotomize for symptoms

Therapy

- PRV
 - Phlebotomy
 - Hydroxyurea
 - Ruxolitinib
- Secondary
 - Congenital cardiac – NO!
 - Lung disease hct > 57%
 - Oxygen, CPAP, ...



Immune Thrombocytopenia: Consensus and Controversy

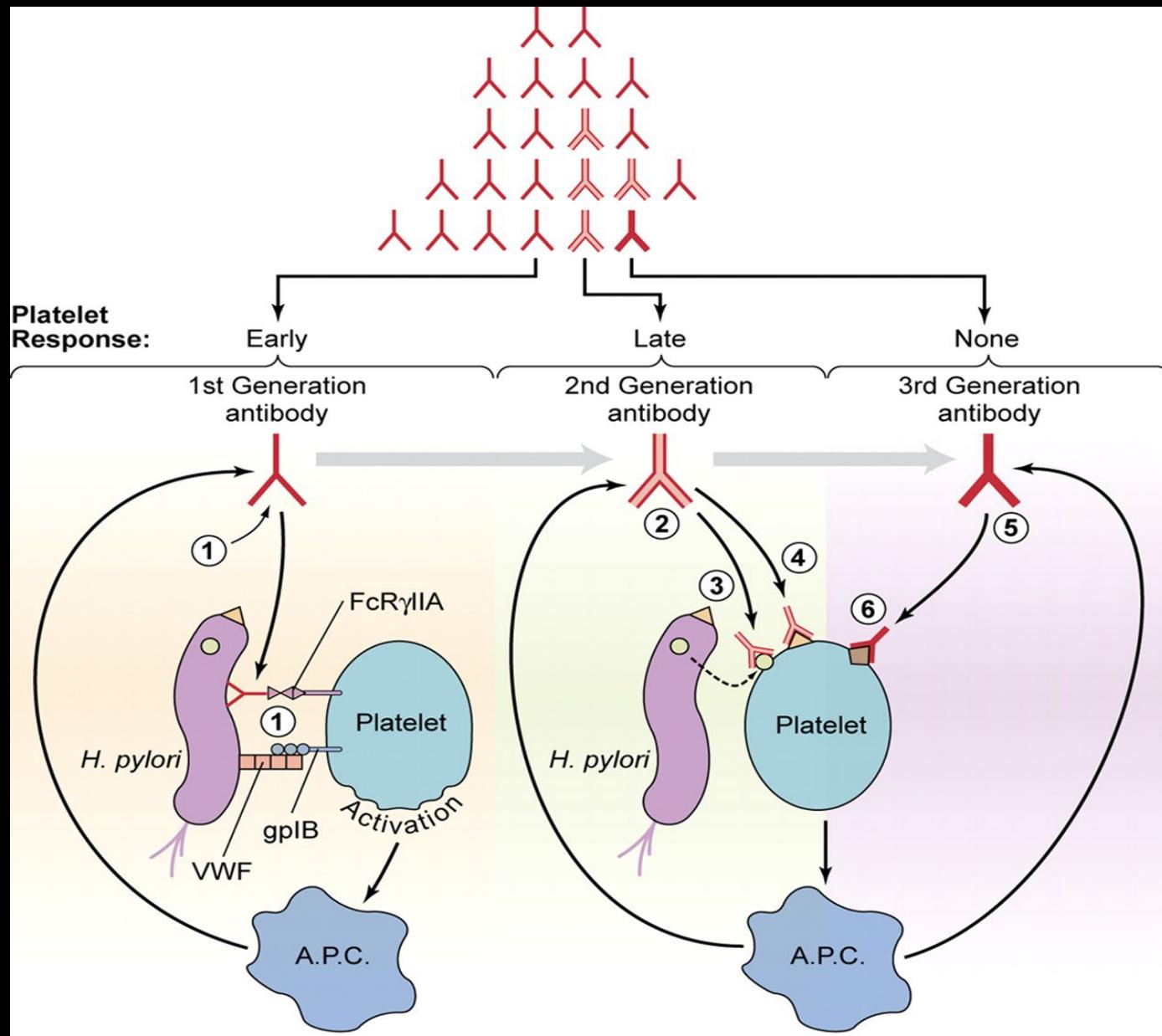
- **Consensus:** ITP is associated with low platelets
- **Controversy:** every other aspect of ITP

Immune Thrombocytopenia

- **Most common heme autoimmune disease (1:20-50,000)**
- **Natural history**
 - Children: 90% resolve after initial therapy
 - Adults: 30% resolve after initial therapy

Etiology

- Most patients have antibodies directed against GP IIb/IIIa
- Some evidence for initiation by viral infection and then epitope spreading to platelet proteins



The Diagnosis ITP

Thrombocytopenia in an otherwise healthy person without an obvious other cause



Bone Marrow Testing

- Not indicated if everything else “fits”
- Indications
 - Platelets don’t respond
 - Blood smear looks odd
 - Patients over 65?

Other Testing

- HIV
- CMV, EBV if indicated
- TSH (?)
- **Antiplatelet antibodies**
 - Specific not sensitive (Versiti)
- ANA? (I don't)

Ultimate Test

- If patient responds well to ITP therapy then they have ITP!



Overview of Therapy

- **Prednisone**
- **Dexamethasone**
- **Methylprednisolone**
- **Immune Globulin**
- **Anti-D**
- **Splenectomy**
- **Rituximab**
- **Campath**
- **Cyclophosphamide**
- **Azathioprine**
- **Mycophenolate**
- **Danazol**
- **Vincristine**
- **Dapsone**
- **Interferon**
- **Combined chemotherapy**
- **Stem cell transplant**
- **Neumega**
- **Romiplostim**
- **Eltrombopag**
- **Vitamin C**
- **Staph A column**

Key Principle

- Global mortality of ITP is < 1%
- In many studies deaths from complications of therapy equal those from bleeding.
- Treat the patient not the number

When to Treat

- Guided by counts and bleeding
 - > 50,000 - no therapy
 - < 20,000 - some therapy
 - 20-50,000
 - Treat if bleeding or evidence of platelet dysfunction

Initial Therapy

- Steroids for all
- IVIG for very low counts or severe bleeding

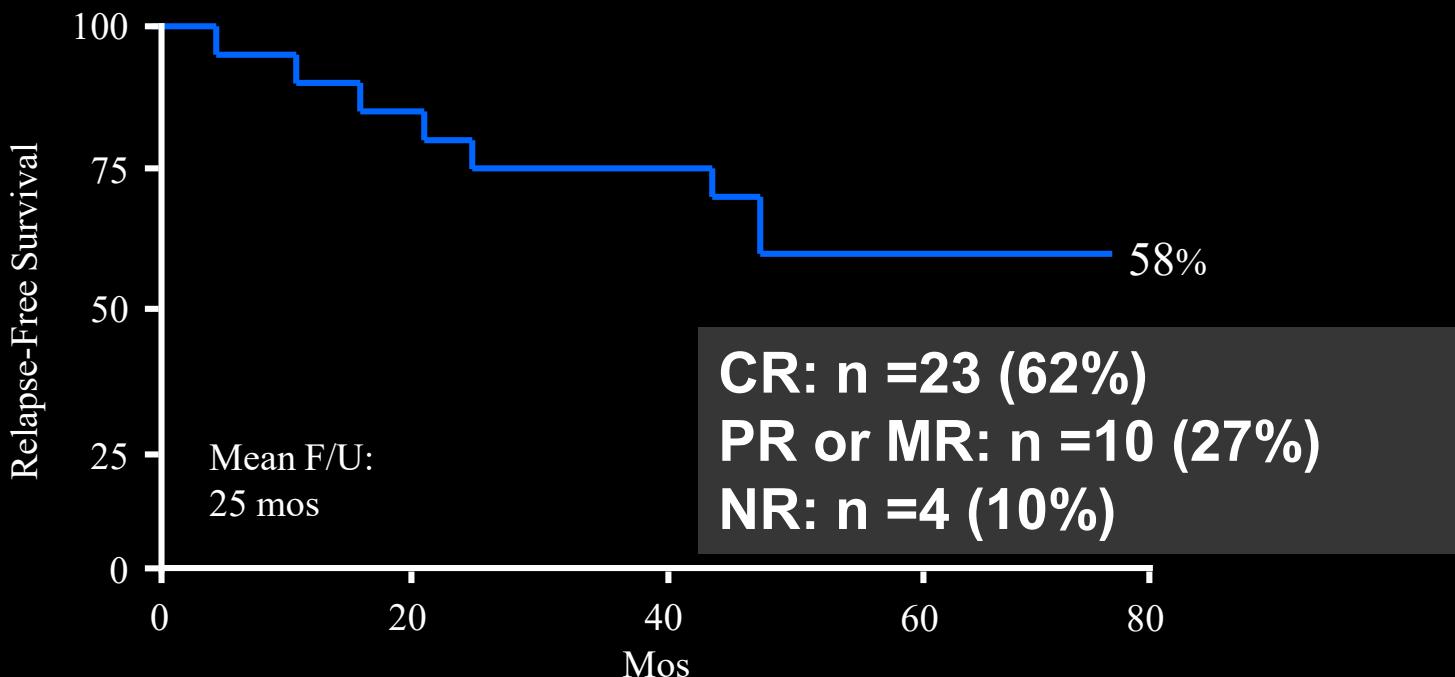
Steroids

- Decrease antibody production
- Decrease splenic uptake of platelets
- Increases platelet production
- First line therapy
 - Prednisone 60 mg/day
 - **Dexamethasone 40 mg/day for 4 days**
- May take up to a week to work
- Rarely "cures" people

Dexamethasone as Initial Treatment for ITP: Study Design

	Single-Center Study	Multi-Center Study
N	37	95
Age, yrs	18-65	2-70
Regimen	Once per mo x 6 cycles	Biweekly x 4 cycles
Response	Assessed at Day 28 after completion of latest cycle	Assessed at Day 60 after treatment
Rescue	Prednisone 0.25 mg/kg/day	Dexamethasone 0.035 mg/kg/day

Single-Center Study: Response to High-Dose Dexamethasone

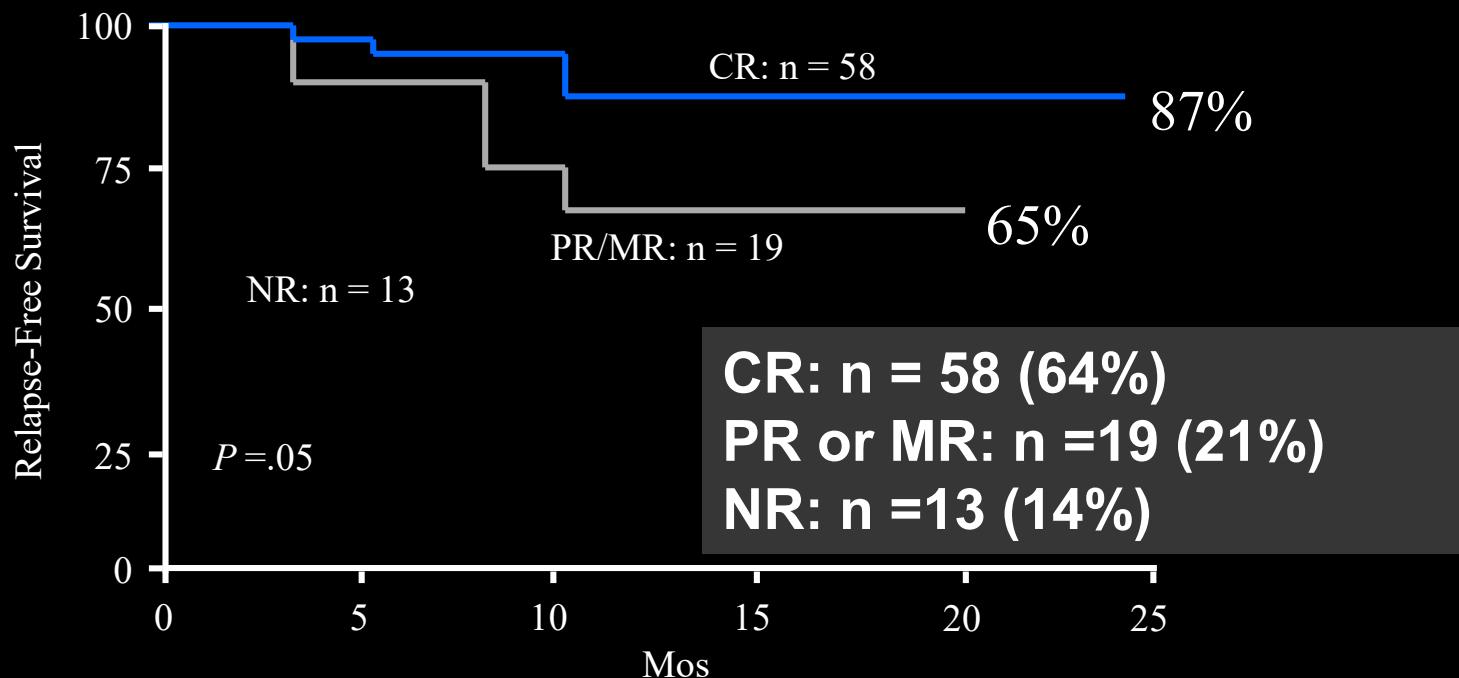


- **Relapse-free survival: 97% at 6 mos, 58% at 50 mos**
- **<6 cycles: no impact on ORR**

This research was originally published in Blood. Mazzucconi M, et al. Blood. 2007;109:1401-1407.

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Multicenter Study: Response to High-Dose Dexamethasone



- At 15 mos of follow-up, 5 relapses each among subjects who achieved CR or PR/MR

This research was originally published in Blood. Mazzucconi M, et al. Blood. 2007;109:1401-1407.

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Expected Response

- Initial response: 80-90%
 - Response seen in 85% of patients by 3rd day with Dex
- "Curative" response: 30-50%

Fast Therapy

- Immune Globulin
- Anti-D

Immune Globulin

- Lots of theories on how IVIG works
- 1 gram/kg x 1
- Very effective in inducing rapid rise in platelets counts (<24 hours)
- Side effects:
 - Large amounts of volume and time
 - Headaches
 - Thrombosis esp. in older patients
 - \$\$\$\$\$\$\$



What if bleeding and not responding?

Refractory Patients

- Rare patients fail all measures to get platelet count up
- “Platelet Boilermaker”
 - IVIG 1 gm/kg continuous over 24 hours
 - 1 platelet pheresis pack over 6 hours x 4
 - Response > 80%
 - Does not work if patient is alloimmunized
- Eltrombopag

Other Desperate Measures

- Vincristine 1.4mg/m² days 1, 4, 7, 10



When to Declare Steroid Failures

- Some patients may need several repeated acute therapies before going into remission
- Patients with ITP over 3-6 month unlikely to spontaneously remit

Splenectomy

- Oldest therapy for ITP
- Rates of splenectomy falling in USA
 - Many patients opt for medical therapy
 - Acceptance of lower platelet counts as safe
 - $> 20\text{-}30,000/\mu\text{L}$ ok
 - Patient convinced it is not curative

Response Rates

- Initial response 85% of patients
- "Cures" ITP ~66% of time
 - Most long term studies show “plateau”
- Mortality much less than 1%
- Risk of overwhelming sepsis

OHSU Data

- 1994-2017
- N = 84
- Median 3 medications (1-6)
- 11% with major steroid complications
- 44% performed urgently

OHSU Data

- CR = 83.5% PR = 7.5% NR = 9%
- CR = 19% relapsed
 - PR = 33%
- Overall 69% with sustained response
 - Consistent with systemic review of 2623 patients

When and If to do Splenectomy

- Sooner
 - Counts < 5-10,000/uL
 - Patients desires
 - Patient otherwise healthy
- Later
 - Counts 10-30,000/uL
 - Patient desires
 - Poor health

Splenectomy

- Good
 - Curative in most patients
 - The oldest and best therapy
- Bad
 - Not 100%
 - Surgical complications
 - Prone to odd but severe infections



Rituximab for ITP: Effectiveness

- Rule of Three's
 - Response Rate
 - 1/3 - Complete response
 - 1/3 - Partial response
 - 1/3 -No response

Table 2. Comparison of the data on the effect of four doses and one dose of rituximab treatment in chronic ITP. Different authors used different response criteria; in order to allow comparison, the previously published results were fitted as best possible to the response criteria.

Author	Age	Rituximab dose	n	CR	PR	Relapse*	Patients in continuous remission
Zaja et al. ⁵	Adult	4×375 mg/m ²	15	6/15 (40%)	2/15 (13%)	3/8 (38%)	5/15 (33%)
Shanafelt et al. ³	Adult	4×375 mg/m ²	12	5/12 (42%)	1/12 (8%)	2/6 (33%)	4/12 (33%)
Giagounidis et al. ⁴	Adult	4×375 mg/m ²	12	5/12 (42%)	4/12 (33%)	2/9 (22%)	7/12 (58%)
Cooper et al. ²	Adult	4×375 mg/m ²	57	18/57 (32%)	13/57 (23%)	13/31 (42%)	18/57 (32%)
Braendstrup et al. ⁶	Adult	4×375 mg/m ²	39	7/39 (18%)	10/39 (26%)	—	—
Wiley et al. ⁸	Children	4×375 mg/m ²	19	11/19 (58%)	4/19 (21%)	9/15 (60%)	6/19 (32%)
Summary of published data			154	52/154 (34%)	34/154 (22%)	29/69 (42%)	40/115 (35%)

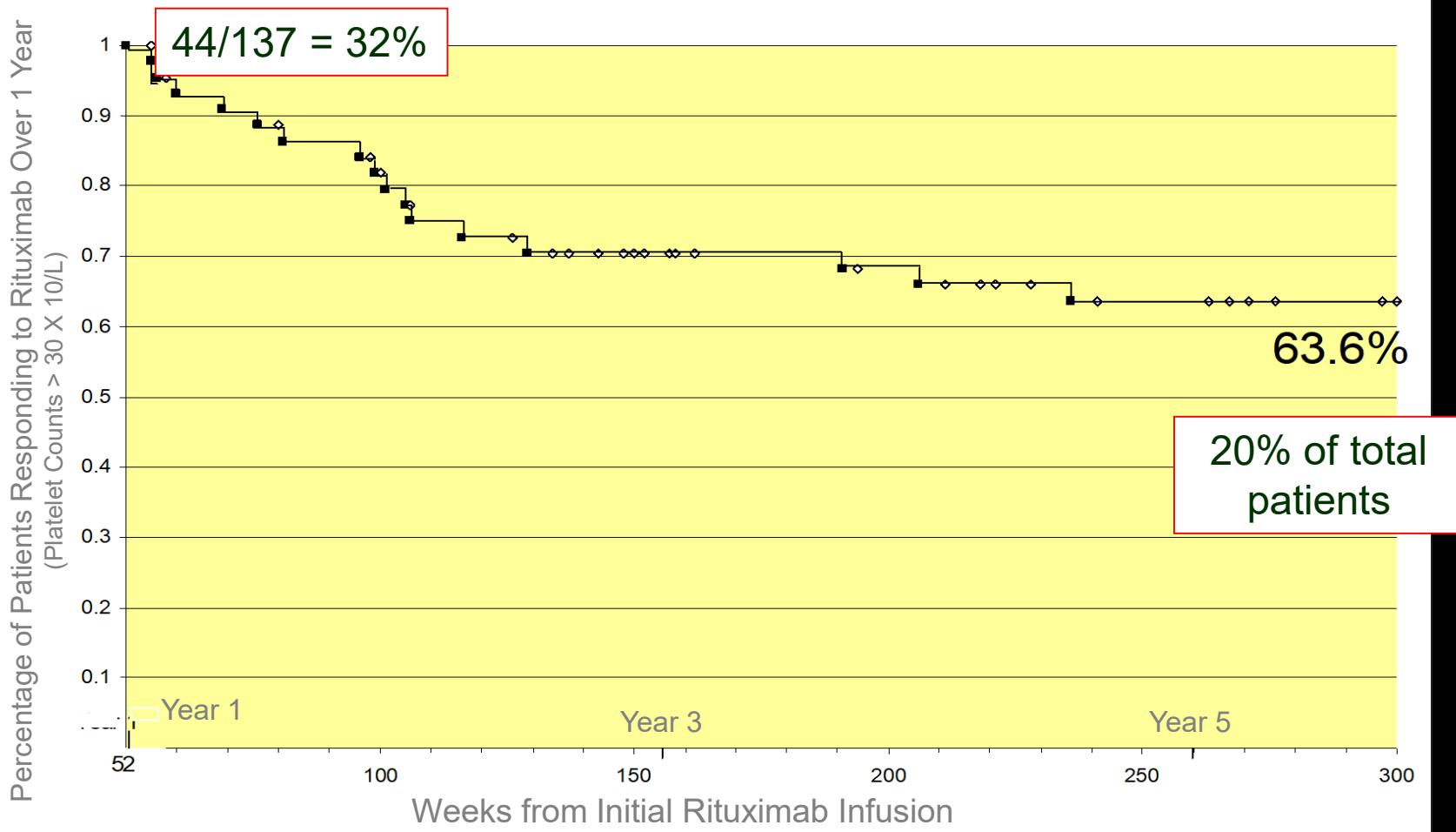
Rituximab: Timing of Response

- VARIABLE!!
 - 1/3 - one week
 - 1/3 - one month
 - 1/3 - several months
 - Median time to response is 6 weeks
- Most patients will not get a rapid response!

Duration of Response

- About 60-70% stay in remission (short term)
- Many patient will go back into remission with retreatment (some even longer!)
- Duration does not appear to be associated with B cell depletion

Duration of Response to Rituximab in 44 Patients with Chronic ITP with Response > 1 Year from Initial Infusion



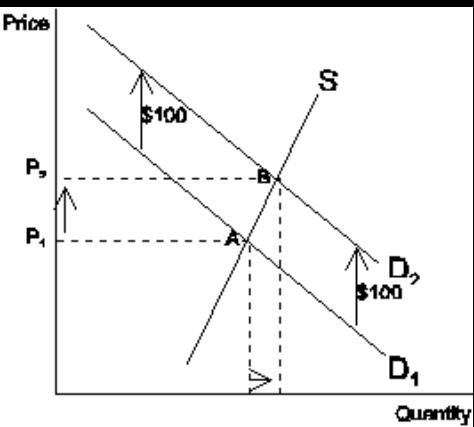
Role of Rituximab

- Second line therapy
- Take time for response
- Responses may not be permanent
- Patient treatment free for long durations



Econ 101: Supply and Demand

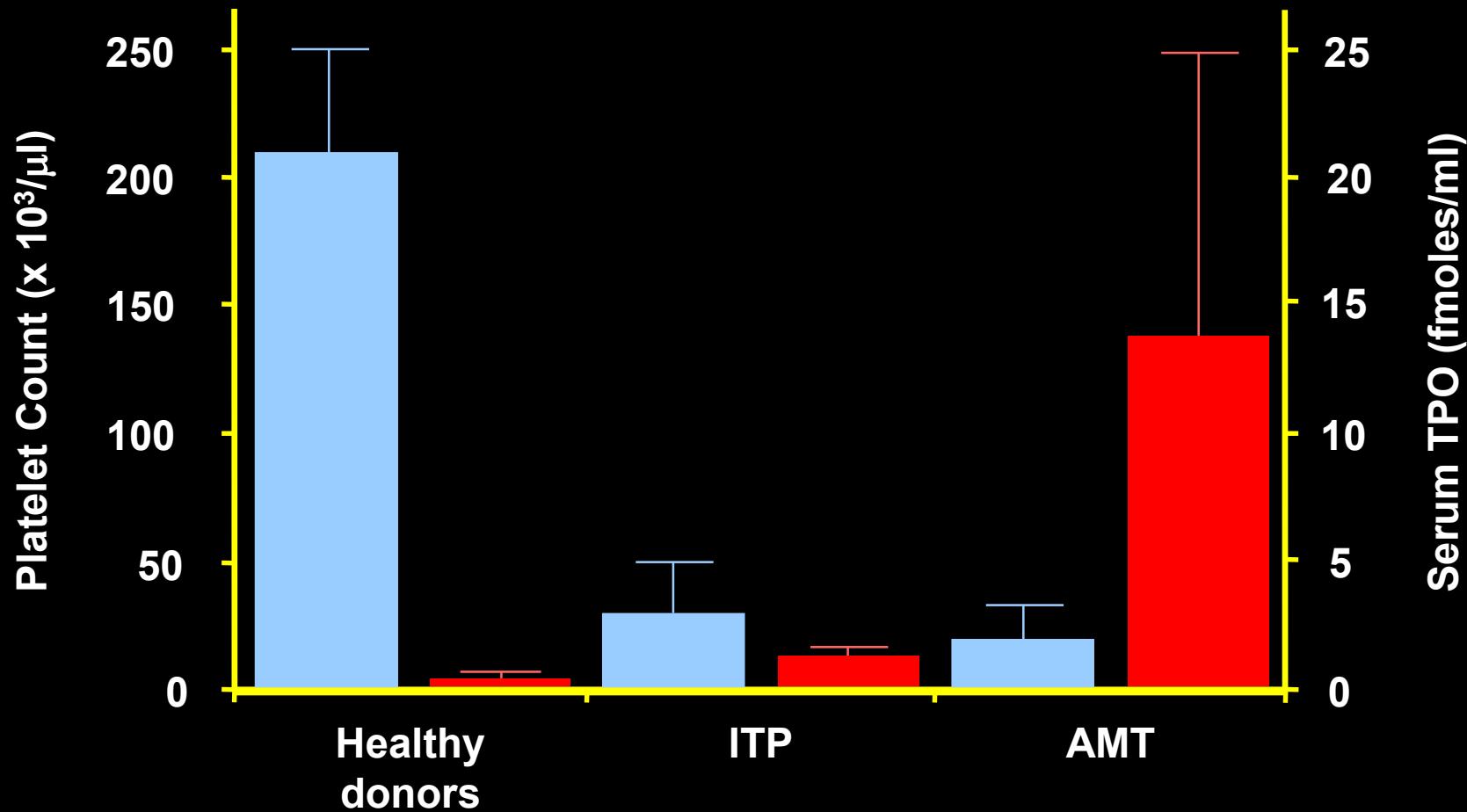
- All therapy for ITP works on Demand side (reduce platelet destruction)
- Is there a role for Supply-side economics in ITP?



ITP: A Failure of Production

- Platelet production increased only slightly in ITP
- Megakaryocyte number not increased or only slightly
- TPO levels not elevated
 - Regulated by meg mass?

Thrombopoietin Levels in ITP



THE MEGAKARYOCYTES IN IDIOPATHIC THROMBOCYTOPENIC
PURPURA, A FORM OF HYPERSPLENISM

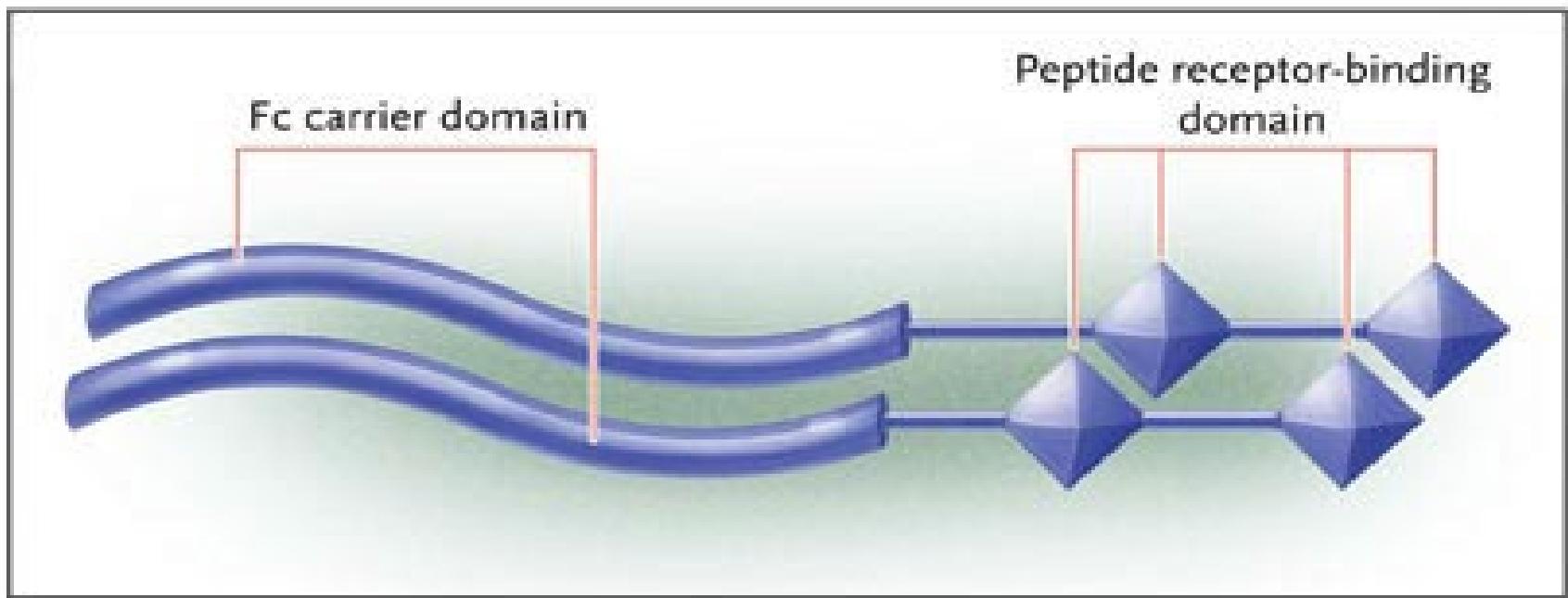
By WILLIAM DAMESHEK, M.D., AND CAPTAIN EDWARD B. MILLER, A.U.S.

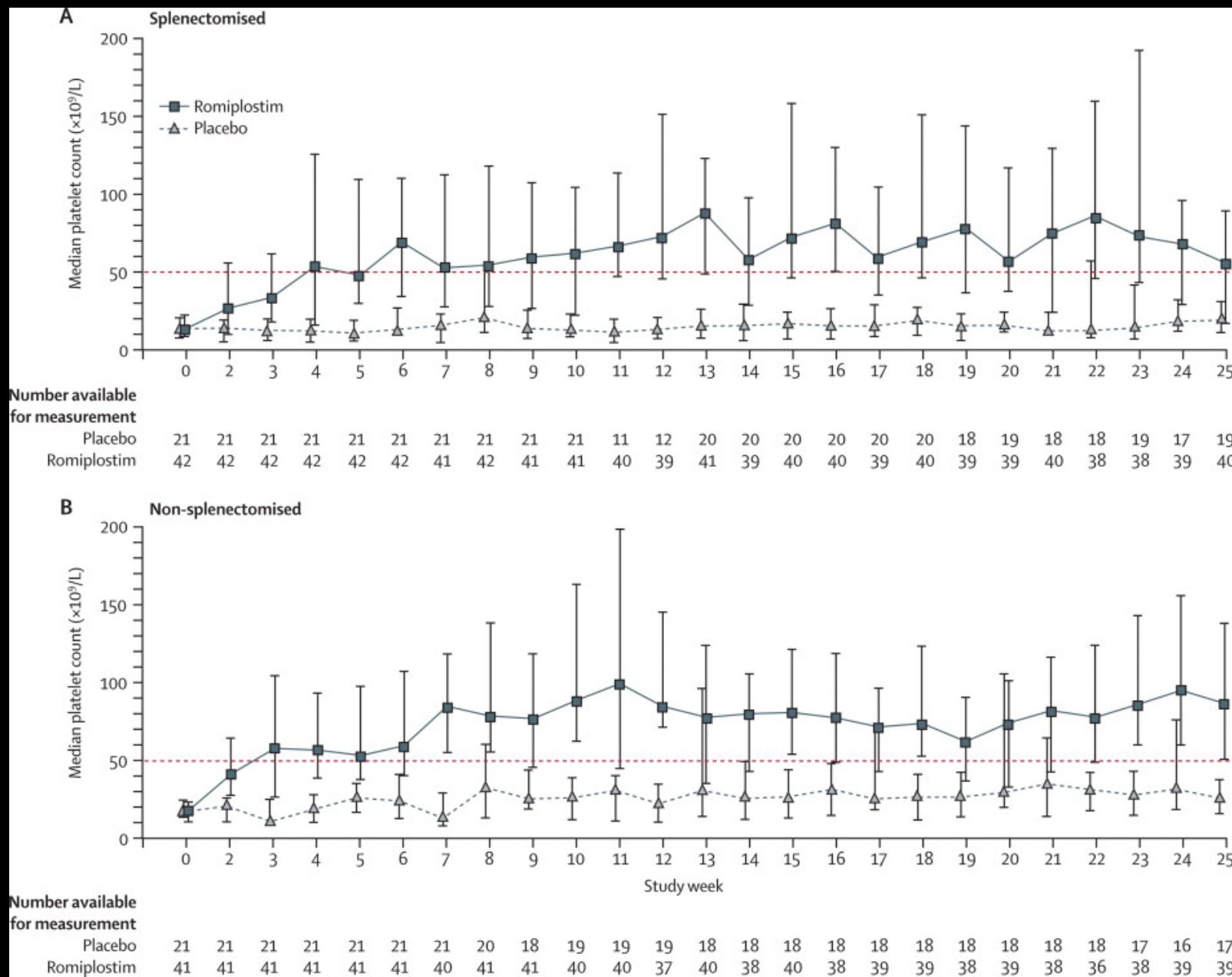
1. The blood platelets are considerably reduced.
2. The bone marrow shows normal or increased numbers of megakaryocytes.
3. The megakaryocytes show a greatly diminished productivity of platelets.

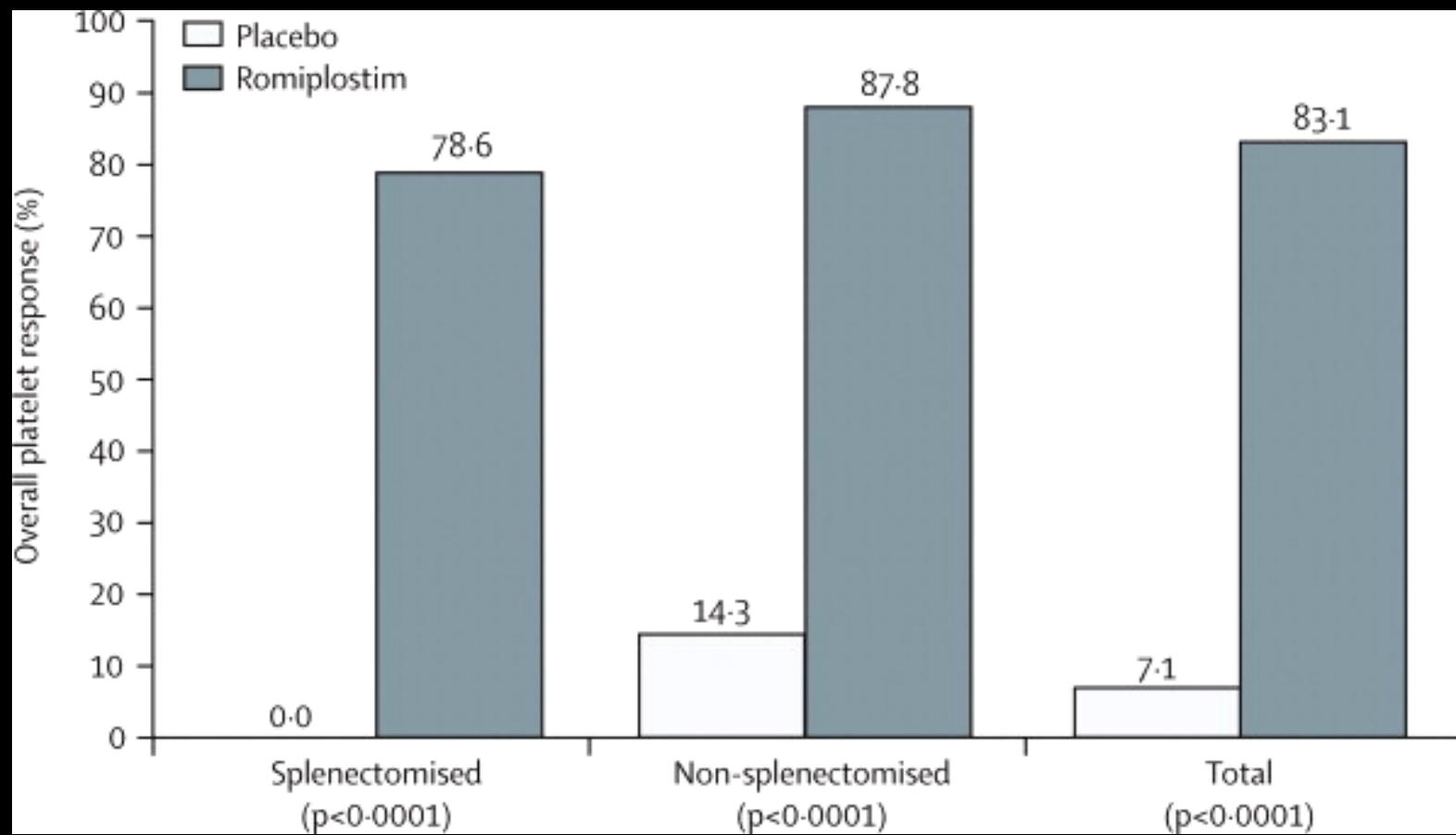
Blood 1:27-51, 1946

TPO – The New Age

- **Romiplostim**
 - Peptide binds to TPO receptor but has no homology to TPO
 - Fc fragment extends circulation
- **Eltrombopag/Avatrombopag**
 - Chemical that binds TPO receptor

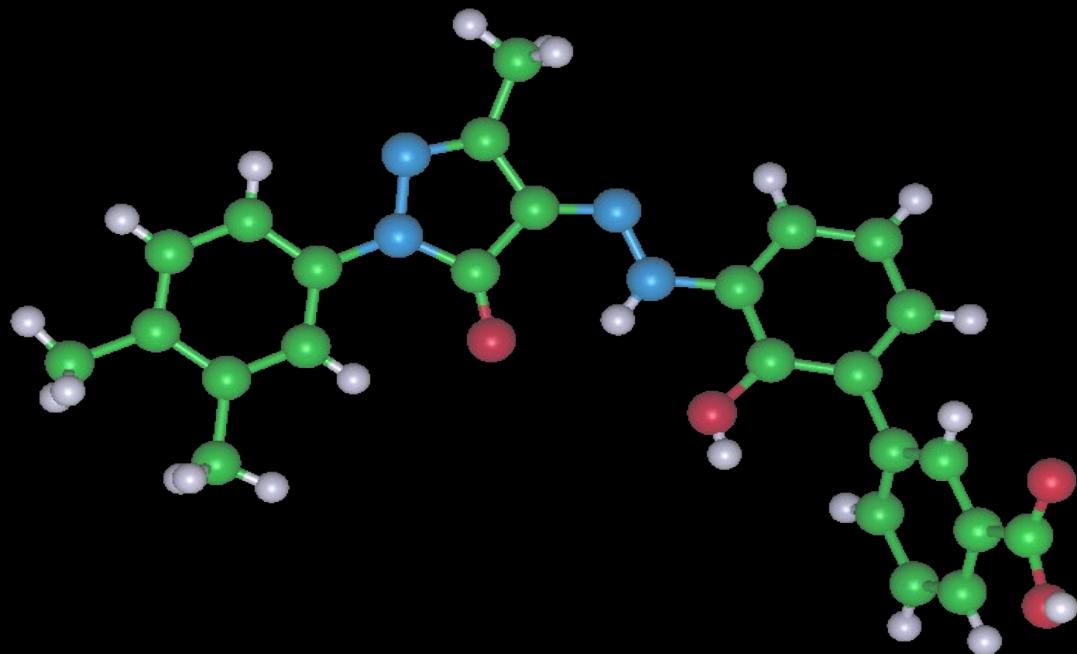




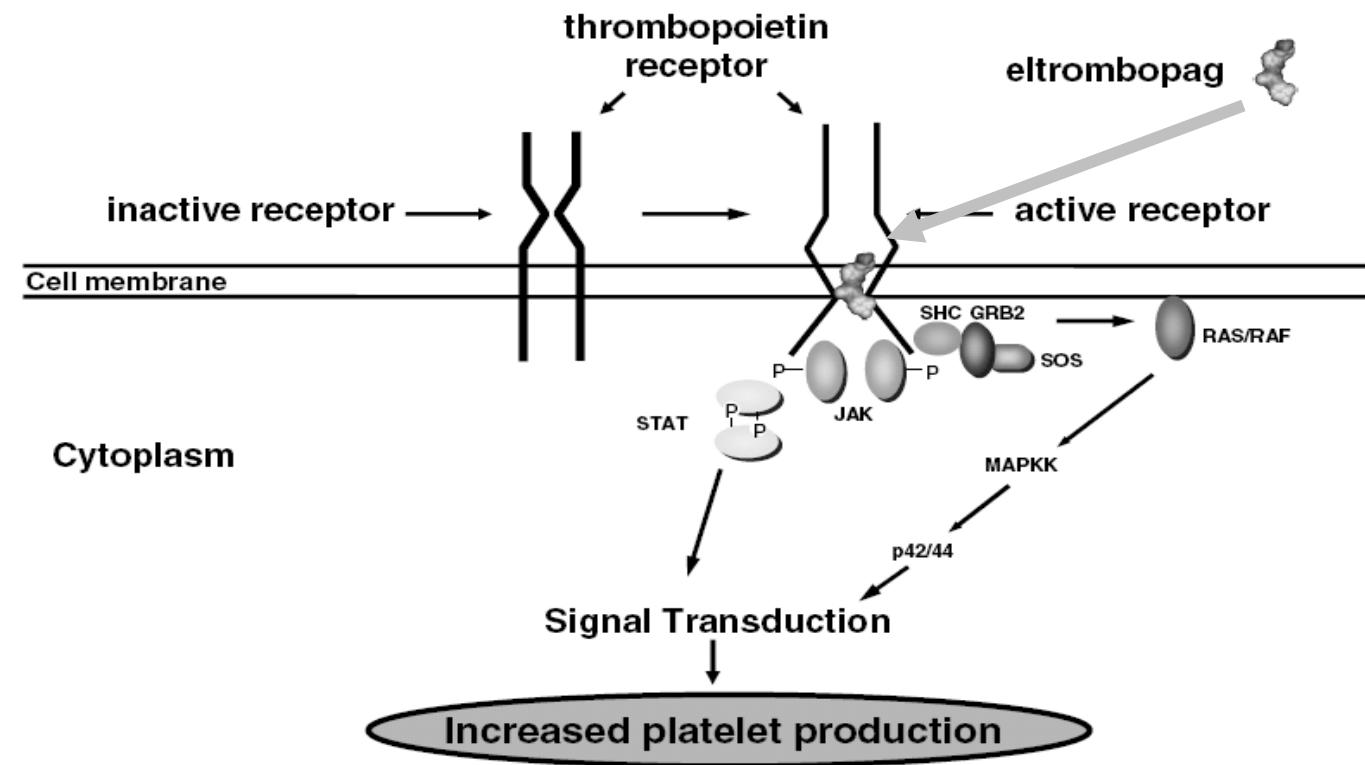


Eltrombopag/Avatrombopag

- Small molecule that interacts with TPO receptors

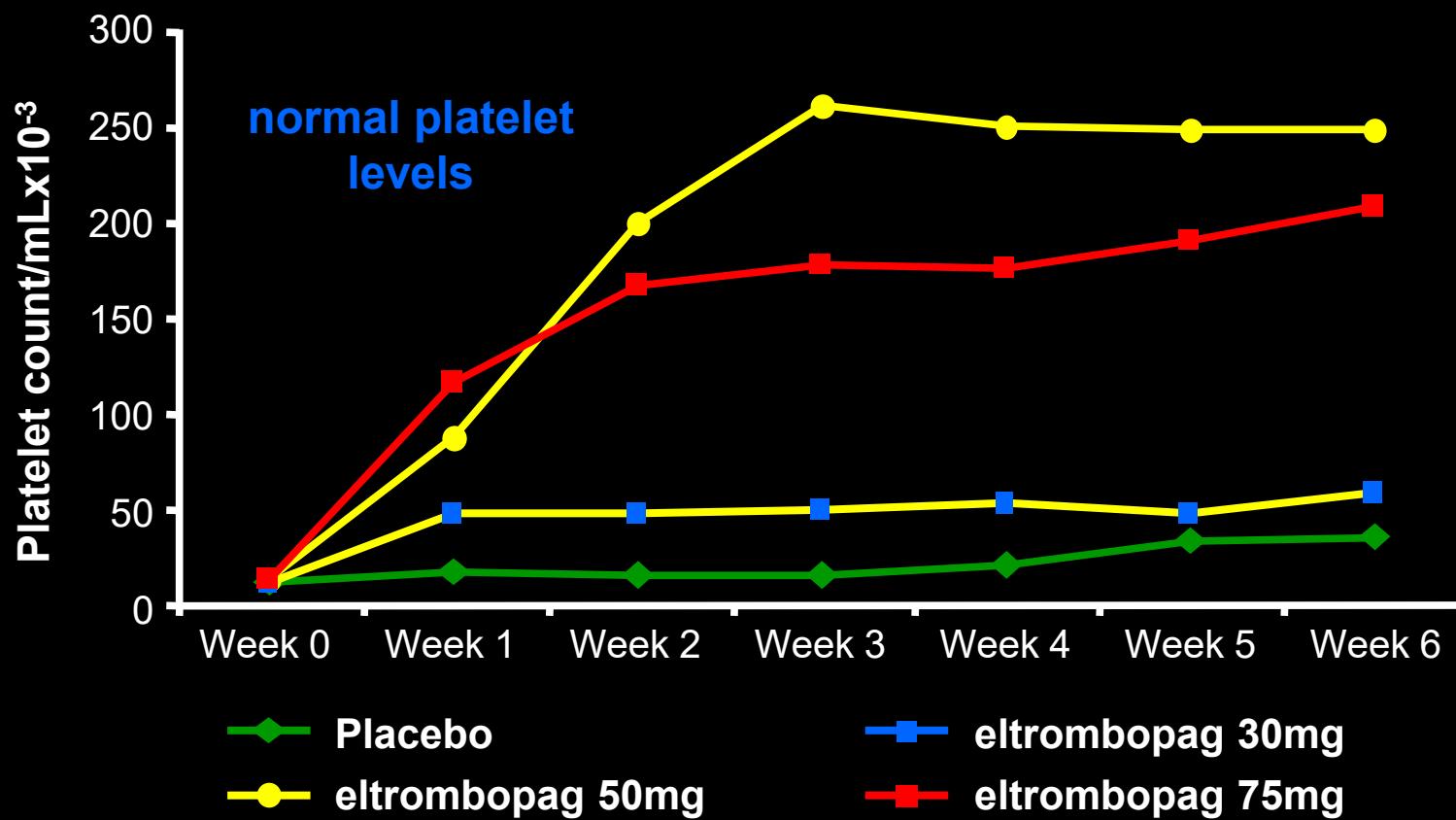


eltrombopag - Mechanism of Action



Eltrombopag - Phase II

Mean platelet counts after each week of therapy

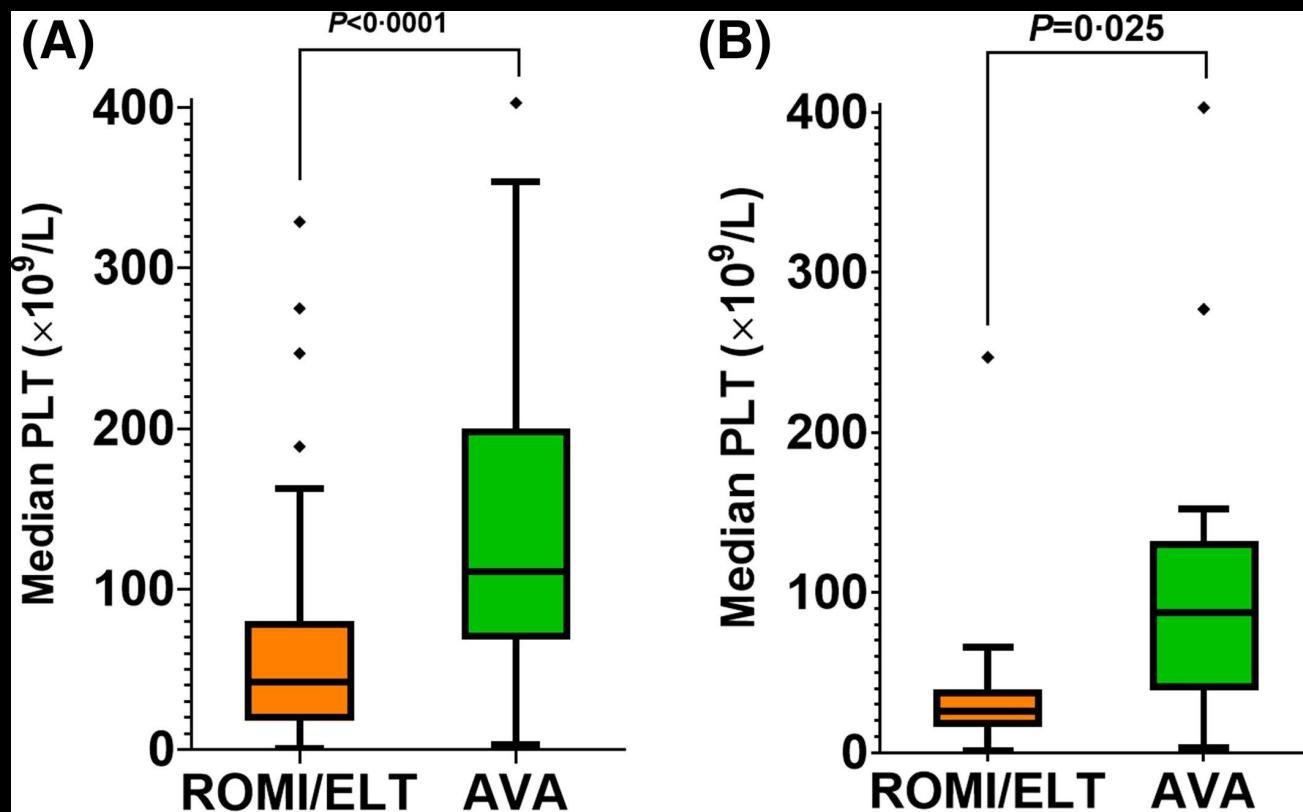


Current Use

- Moving to earlier in therapy
- Second line after steroids
- First line in severe cases
- Steroid sparing therapy
- Pre-procedure

Avatrombopag

- Study of 14 patients not respond to TPO-agonist
- 12 had platelet response





Other Things

- Campath
- Cyclophosphamide
- Azathioprine
- Mycophenolate
- Danazol
- Vincristine
- Dapsone
- Interferon
- Combined chemotherapy
- Stem cell transplant
- Neumega
- Vitamin C
- Staph A column
- Fostamatinib

Fostamatinib

- Novel agent for ITP
- SYK inhibitor
 - Blocks macrophage uptake of platelets
- Early data
 - 50% some response
 - 20% sustain response
 - Very durable
 - Diarrhea side effect ~ 20%

Mycophenolate

- Only RCT early ITP
- Maybe 50% response rate in refractory ITP

Research

- Sutimlimab
- BTK inhibitors
- Fc receptor blockers

An Approach

- Dexamethasone 40mg x 4 repeat q14 x 4
 - Only dexamethasone exposure
 - Saves other agents

2nd Line

- **Splenectomy**
 - Oldest and most effective therapy
- **Rituximab**
 - Only 20% “cure” rate
- **TPO agonist**
 - Increasing use

