JERRY SCOTT DAY 2024

Management of Relapsed and Refractory Immune Cytopenias

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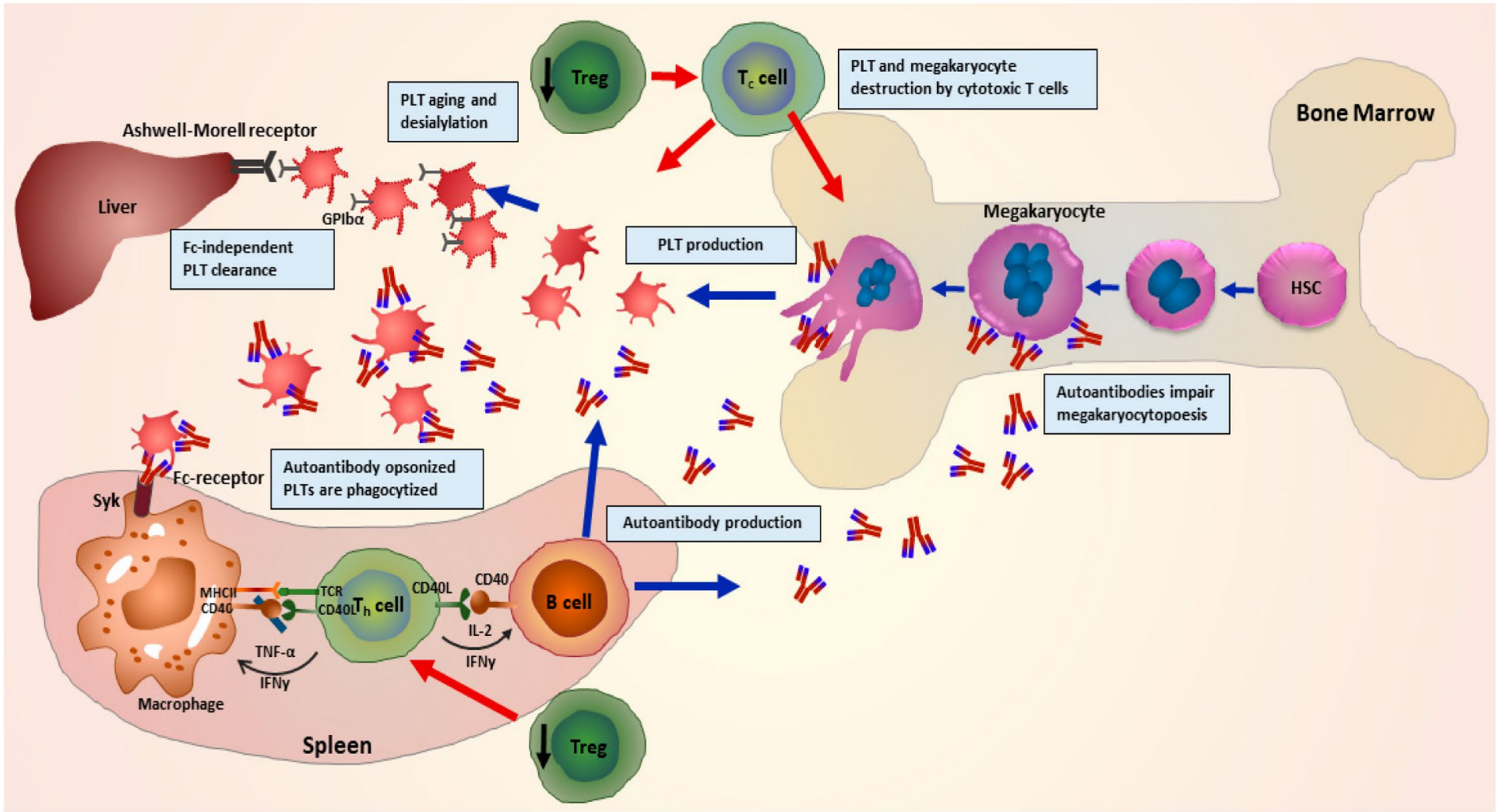
Disclosures

- None

Objectives

- Review pathophysiology and presentation of autoimmune cytopenias (AIHA and ITP)
- Discuss approach and evidence for treatment of refractory and relapsed disease
- Outline future therapeutic considerations under development

Immune thrombocytopenia (ITP)



- Autoimmune disease causing isolated plts < 100
  - 2 to 5 per 100 000 individuals annually
- Pathophysiology a mix of increased plt destruction and impaired plt production
- clinical presentation can vary from asymptomatic to major bleeding (5%)
  - Common petechiae, mucocutaneous bleeding

Singh et al. (2021) J Clin Med

ITP: Therapy

- How do we define ITP?
  - newly diagnosed (< 3 months)
  - persistent (3-12 months)
  - chronic (>12 months)
- Who do we treat?
  - Platelet count <20-30
  - *<50 with increased risk of bleeding (I.e falls risk, angiodysplasia, on anticoagulation, surgery)
- **What are the goals of treatment?**
  - Raise plt count >20-30(50) (**not** normalize counts as 75% of ITP become chronic)
  - Minimize treatment toxicity

ITP: first line therapy

- 2019 ASH consensus guidelines
  - Prednisone 0.5-2mg/kg/day (maximum 80mg) po for 2-3 weeks then taper or Dexamethasone 40mg po daily x 4 days maximum 3 times q2-4 weeks
    - If plts >50 taper and stop by 6-8 weeks (even if plts drop)
    - If no response within 2 weeks, taper steroids over 1 week then stop and consider next line tx
- Steroid refractory if over 6-8 weeks steroids or >3 months with plts < 30
  - risk of hospitalization in first year 15%

- The problem: 80% of patients are steroid responsive but only 20% persist

Neunert et al. (2019) Blood advances

R/R ITP: rule out differential diagnosis

Differential diagnosis of ITP		
Pseudothrombocytopenia	No symptoms, in vitro phenomena	Platelet aggregation on peripheral-blood smear, repeat platelet count in citrated blood
Renal or liver disease	Symptoms, signs, and clinical history	Renal function and liver-function tests and imaging of abdomen, including liver and spleen
Myelodysplastic syndrome, acute leukemia	Other cytopenias and abnormal peripheral-blood smear	Peripheral-blood smear, bone marrow aspirate and biopsy, with flow cytometry and cytogenetic testing
Aplastic anemia	Pancytopenia	Bone marrow aspirate and biopsy with cytogenetic testing
Genetic diseases that cause thrombocytopenia (e.g., Bernard–Soulier syndrome and *MYH9*-related disorders)	Young age at presentation, family history of thrombocytopenia, abnormal size and morphologic features of platelets or abnormalities seen in neutrophils on peripheral-blood smear, other clinical abnormalities (e.g., renal disease and deafness in patients with *MYH9*-related disorders)	Peripheral-blood smear, mean platelet volume, genomic testing
Thrombotic thrombocytopenic purpura	Neurologic or cardiac symptoms	Schistocytes on peripheral-blood smear, elevated LDH level, low haptoglobin and ADAMTS13 levels, direct antiglobulin test–negative hemolytic anemia
Heparin-induced thrombocytopenia	Venous thrombosis, previous exposure to heparin	Platelet factor 4–heparin antibody tests, platelet-activation assays

Consider BMBx, especially in older pts not responding to IVIG/steroids*

R/R ITP: consider secondary causes & directed therapy

Secondary causes of ITP		
Use of certain drugs	Sudden onset after initiation of new medication (common drugs include quinine or quinidine, acetaminophen, abciximab, carbamazepine, rifampicin, and vancomycin)	Tests to detect drug-dependent antibodies, if available
Lymphoproliferative disorder (e.g., chronic lymphocytic leukemia and Hodgkin's lymphoma)	Weight loss, night sweats, lymphadenopathy or splenomegaly	Complete blood count; peripheral-blood flow cytometry, bone marrow flow cytometry, or both; bone marrow aspirate and biopsy; protein electrophoresis imaging of abdomen, chest, and neck to assess lymphadenopathy and spleen size (as appropriate)
Immunodeficiency syndrome (e.g., common variable immunodeficiency and autoimmune lymphoproliferative syndrome)	Hypogammaglobulinemia, cytopenias, frequent infections (especially chest or sinus infections), colitis, lymphadenopathy, splenomegaly	Immunoglobulin quantification, lymphocyte subset count, genetic testing
Infection (e.g., HIV and AIDS, HBV, HCV, cytomegalovirus, EBV, and *Helicobacter pylori*)	Other suggestive symptoms and signs; at-risk populations	Serologic and PCR tests for HIV, HBV, HCV, cytomegalovirus, and EBV; breath or stool antigen tests for *H. pylori*
Other autoimmune disease (e.g., systemic lupus erythematosus, rheumatoid arthritis and antiphospholipid syndrome)	Arthralgias or arthritis, hair loss, sun sensitivity, mouth ulcers, rash, thromboembolism	Tests for antinuclear antibodies, rheumatoid factor, anti–cyclic citrullinated peptide antibodies, antiphospholipid antibodies
Evans syndrome	Thrombocytopenia and direct antiglobulin test–positive hemolytic anemia	Peripheral-blood smear; measurements of haptoglobin and LDH levels; direct antiglobulin test

Cooper & Ghanima (2019) N Eng J Med

2019 ASH clinical ITP guidelines

- "Based on these considerations, the panel acknowledged that there is no single second-line treatment that is optimal for all adult patients with ITP."

Recommendation 7

In adults with ITP lasting ≥3 months who are corticosteroid-dependent or have no response to corticosteroids, the ASH guideline panel *suggests* either splenectomy or a TPO-RA (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Recommendation 8

In adults with ITP lasting ≥3 months who are corticosteroid-dependent or have no response to corticosteroids, the ASH guideline panel *suggests* rituximab rather than splenectomy (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

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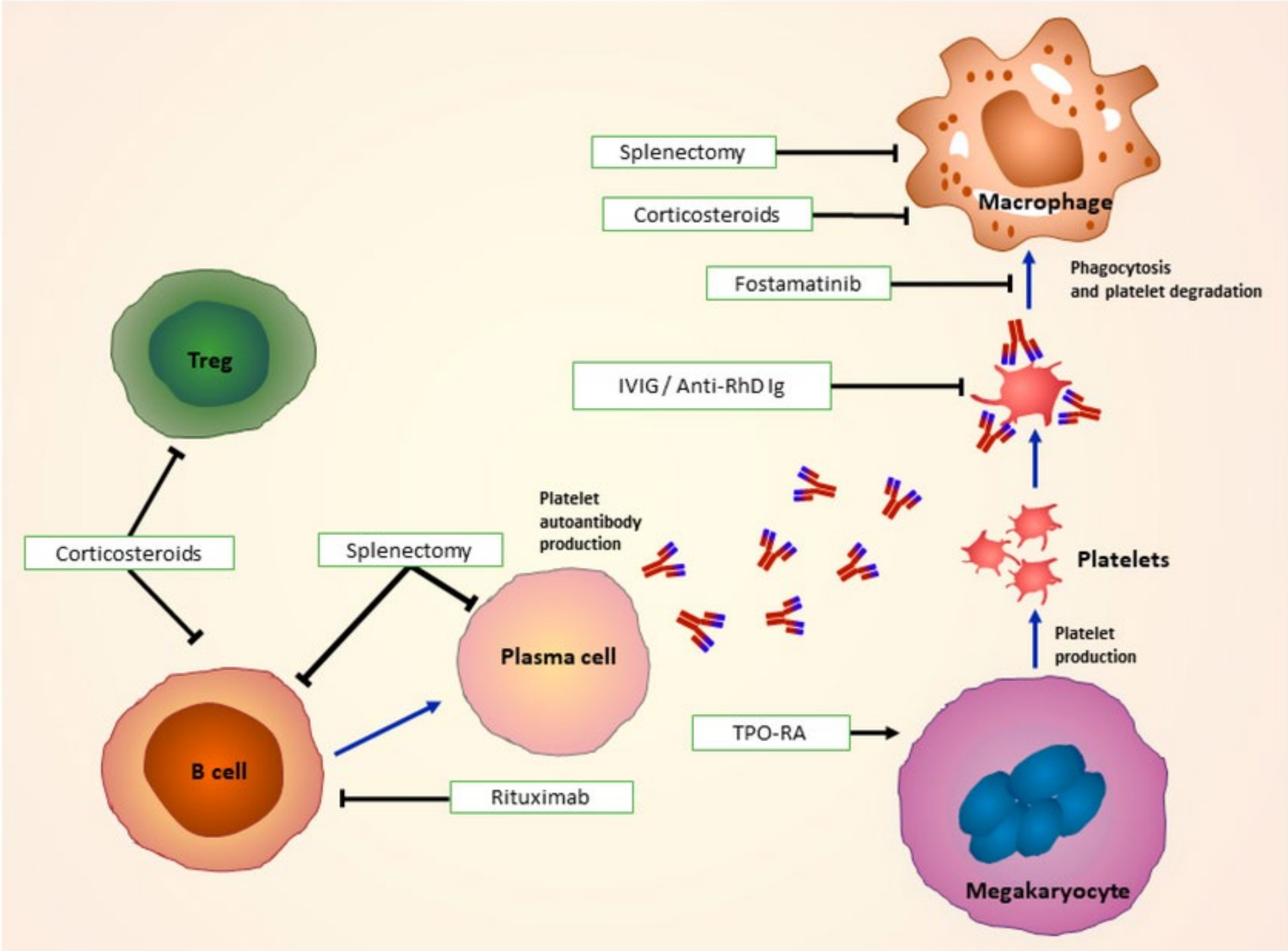
Recommendation 9

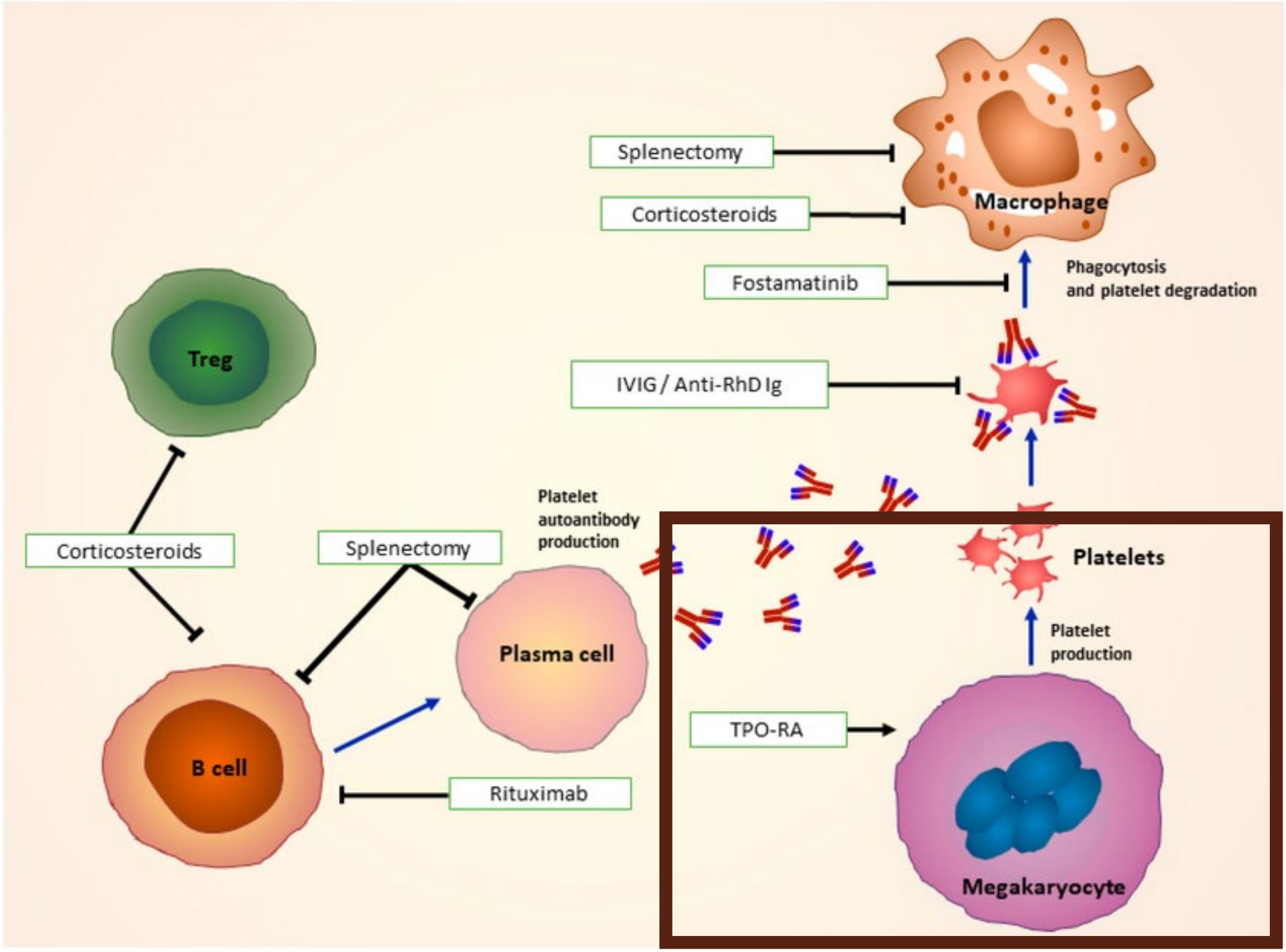
In adults with ITP lasting ≥3 months who are corticosteroid-dependent or have no response to corticosteroids, the ASH guideline panel *suggests* a TPO-RA rather than rituximab (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remark:** These recommendations are the result of dichotomous evaluation of treatments that are often being considered simultaneously. Each of these second-line treatments may be effective therapy and therefore the choice of treatment should be individualized based on duration of ITP, frequency of bleeding episodes requiring hospitalization or rescue medication, comorbidities, age of the patient, medication adherence, medical and social support networks, patient values and preferences, cost, and availability. Patient education and shared decision-making are encouraged. If possible, splenectomy should be delayed for at least 1 year after diagnosis because of the potential for spontaneous remission in the first year. Patients who value avoidance of long-term medication may prefer splenectomy or rituximab. Patients who wish to avoid surgery may prefer a TPO-RA or rituximab. Patients who place a high value on achieving a durable response may prefer splenectomy or TPO-RAs.

ITP “directed” therapies



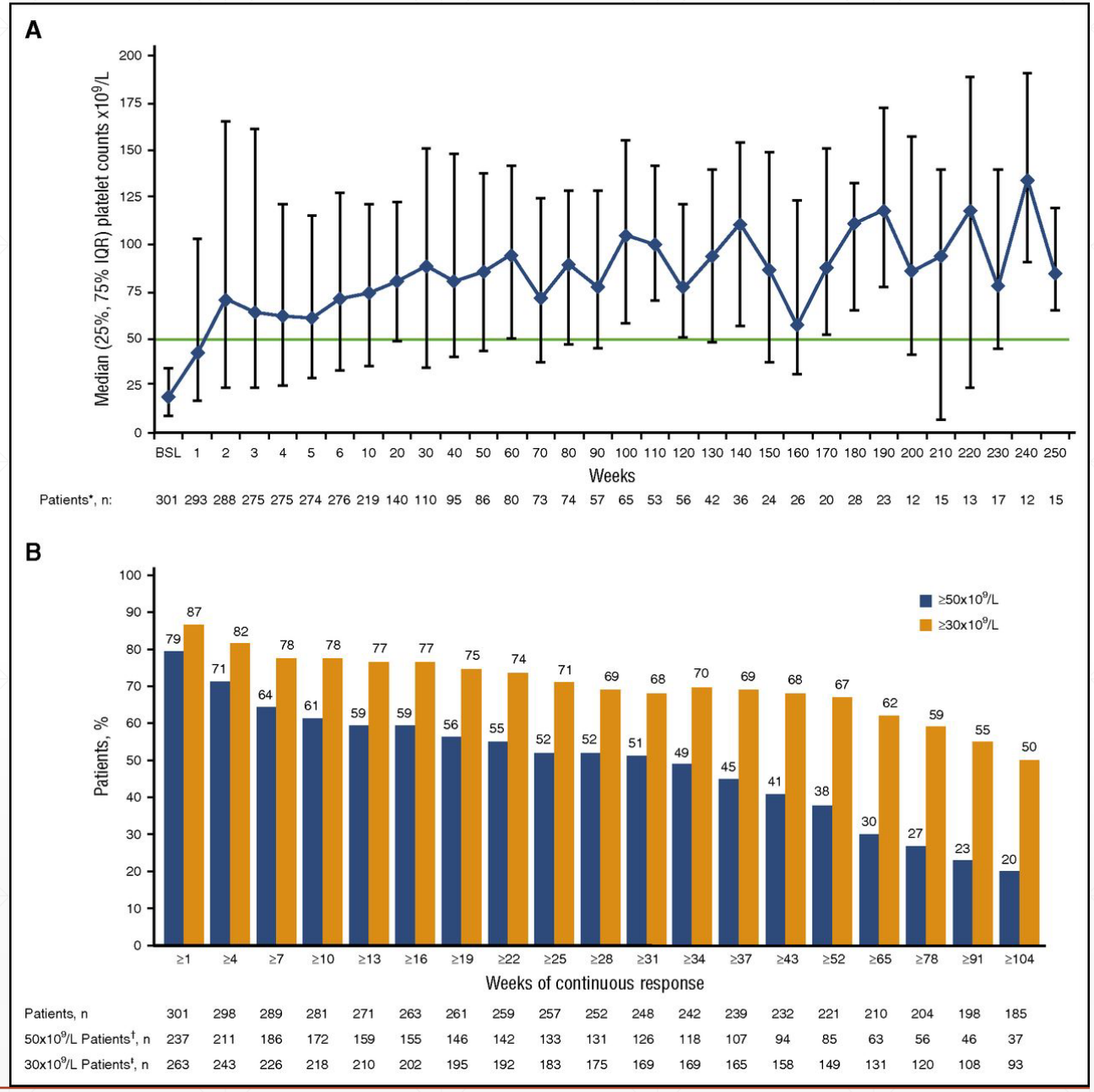
TPO-RA

- TPO receptor agonists
- megakaryocyte stimulation



EXTEND trial

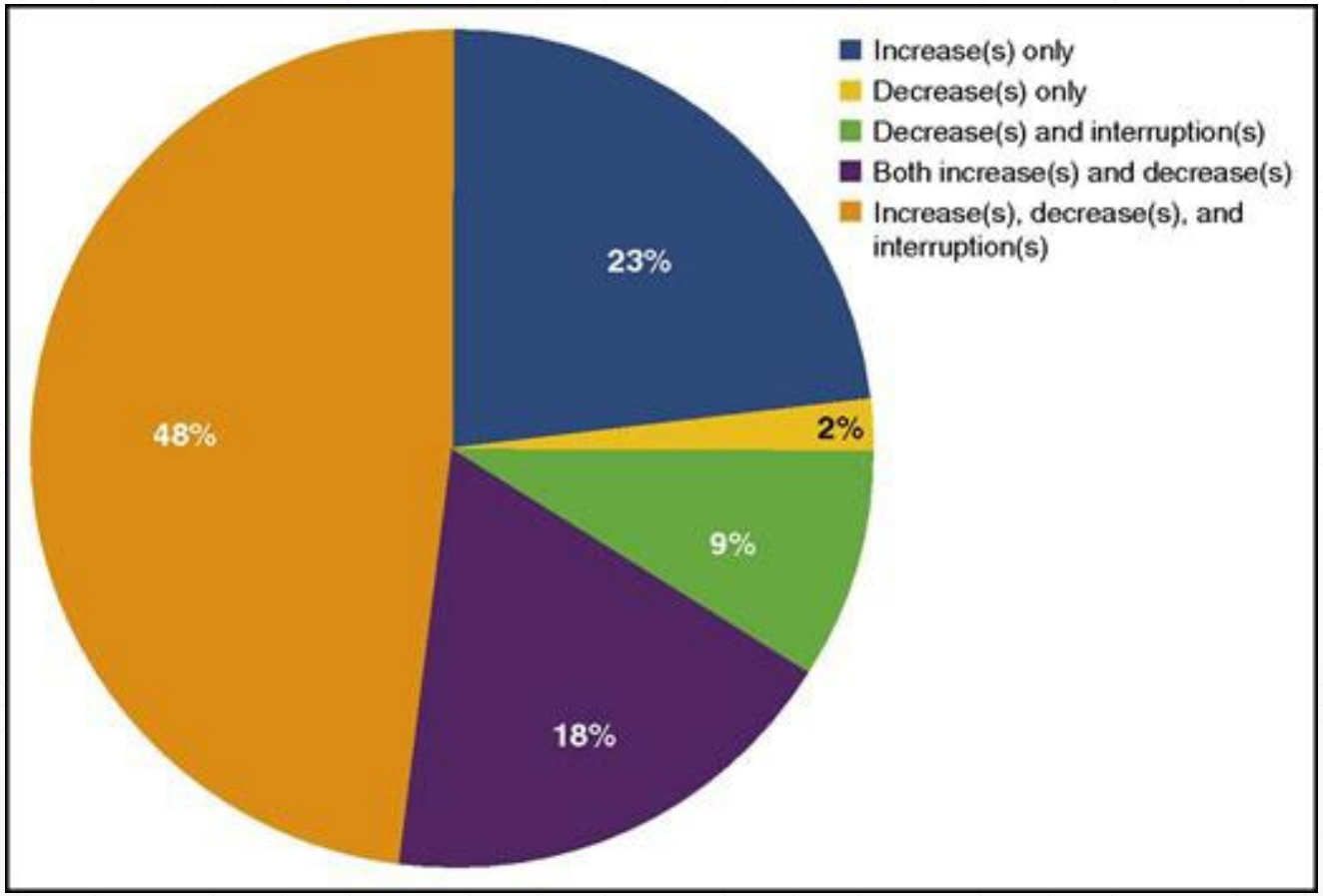
- phase 2/3 open label trial of n= 302 pts with chronic/persistent ITP for median of 2.37 years receiving eltrombopeg 50mg po daily
- Previous therapies included steroids (81%), IVIG (46%), rituximab (23%), splenectomy (38%)
- 85% achieved response plts >50 with 52% of responders persisting to 25 weeks or longer
- Less likely to respond: # previous therapies, prior splenectomy
- bleeding decreased from 57% to 16% at 1 year
- majority responded within 2 weeks of treatment



Wong et al. (2017) Blood

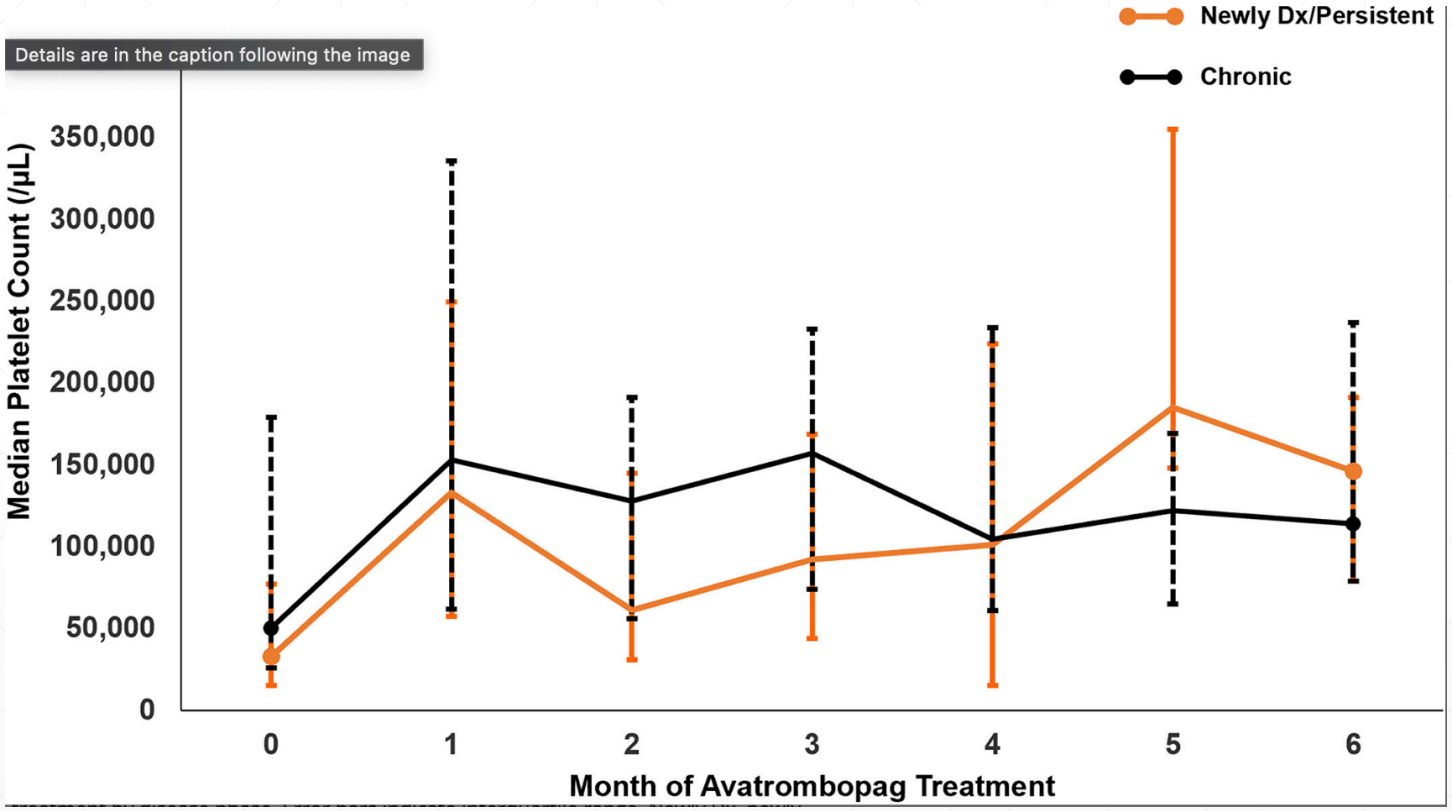
EXTEND trial: side effects & cons

- 55% patients discontinued therapy
  - 14% side effects
  - 11% lack of response
  - 13% patient preference
- many food/ drug interactions as a strong chelator
- SE varied
  - hepatobiliary (15%)
  - thromboembolic (6%)
  - bone marrow fibrosis (2/302)
  - headache
  - cataracts
  - cerebral infarct
- majority relapse with discontinuation of therapy



Avatrombopeg for ITP

- FDA approved for cITP and periprocedural chronic liver disease
- Recent multicenter observational cohort study n=75 show efficacy in early ITP (91% response, 86% plts >50) and chronic (96% response, 81% plts >50)
- less liver toxicity & no food interactions
- variable funding based on prior therapies based on province



Virk et al. (2024) Am J Hem

Practical issues with TPO-RA

- For patients not responding to a TPO-RA, 50-80% will respond with switching to a different one with durable platelet responses and eradication of undesirable side effects
  - Romiplostim to eltrombopeg 100% RR vs eltrombopeg to romiplostim 66% RR
- 10-30% will retain remission status once weaned/discontinuation of therapy

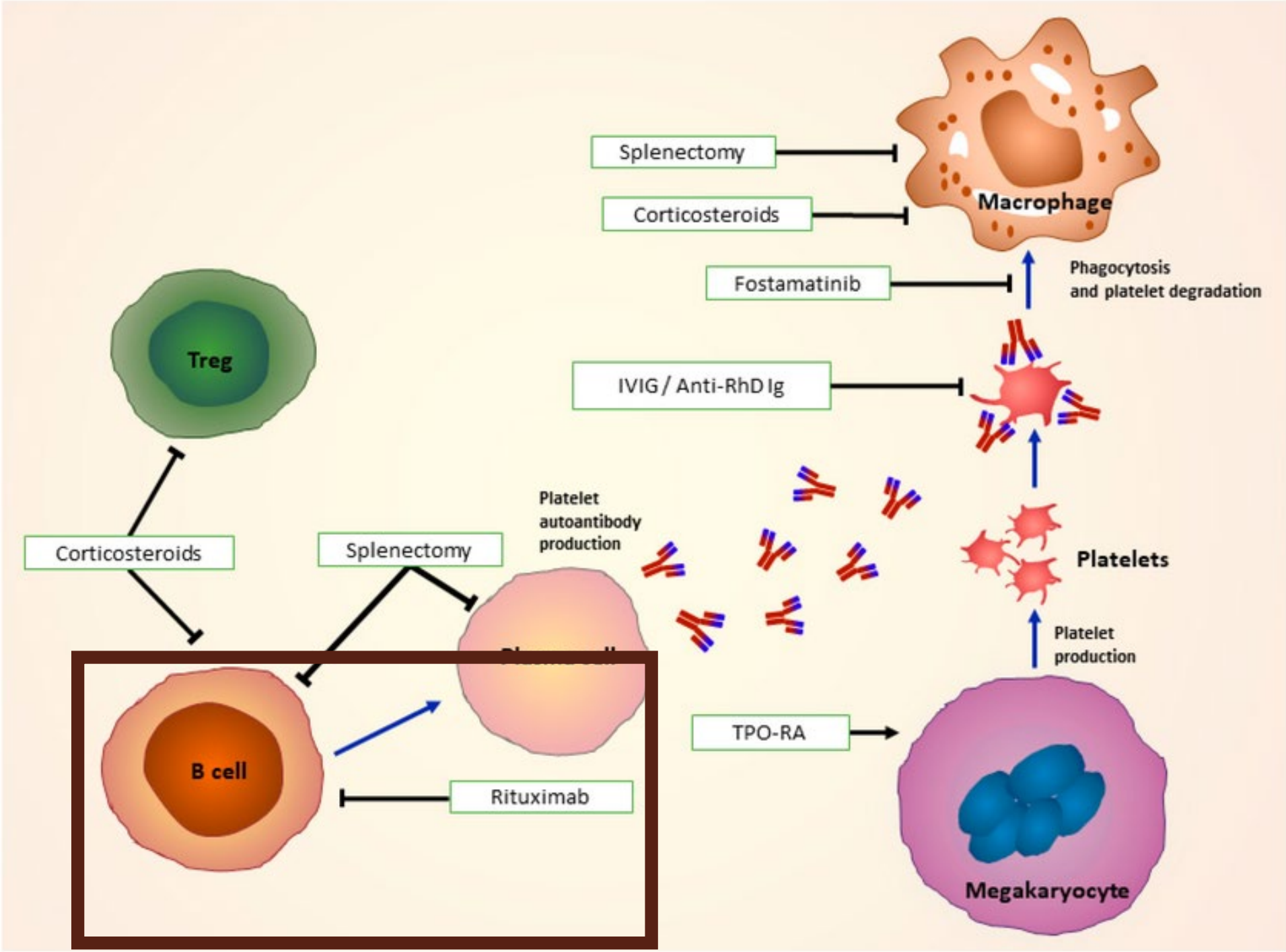
R/R ITP: TPO-RA

Agent	Dosage	Onset of Action	Durability of Effect	Side Effects and Cautions
Thrombopoietin-receptor agonists†				
Romiplostim*	1–10 µg per kilogram, subcutaneously once weekly	1–2 wk	Response achieved and maintained in 40–60% of patients receiving continuing therapy; response maintained after discontinuation in 10–30% of patients	Headache, muscle aches, possible increased risks of thrombosis and myelofibrosis
Eltrombopag*	25–75 mg orally daily	1–2 wk	Response achieved and maintained in 40–60% of patients receiving continuing therapy; response maintained after discontinuation in 10–30% of patients	Gastrointestinal symptoms, transaminitis, cataract, possible increased risks of thrombosis and myelofibrosis; should be taken 4 hr after and 2 hr before food containing cations (e.g., iron, and calcium from milk or other dairy products)
Avatrombopag*	5–40 mg orally daily	1–2 wk	Response achieved in 65% of patients within 8 days after treatment	Headache, arthralgia, possible increased risk of thrombosis

stop at 4 wks if no response

Rituximab

- CD20 monoclonal antibody



R/R ITP: Rituximab

- First study in 2001 Stasi et al showed 25 cITP patients had ORR 52% with 28% sustained responses
  - Many studies have shown ORR ~60% with long term remissions ~20-30%
- More likely to achieve remission if <40, female or disease duration <12 months
  - Consider earlier for autoimmune associated ITP
    - i.e ORR 85%, 74% CR and 60% sustained in CVID
- SE: infusion reactions (15-60%), hypogammaglobulinemia (10-20%) cleared at 1 year (worsened if previous autoimmune disease i.e CVID), infections (2.3 per 100 pt years at 24 months), HBV reactivation, PML (rare), late onset neutropenia
- Responses may be by 4 weeks, 8 weeks or as late as 3 months

Lucchini et al. (2019) Haematologica

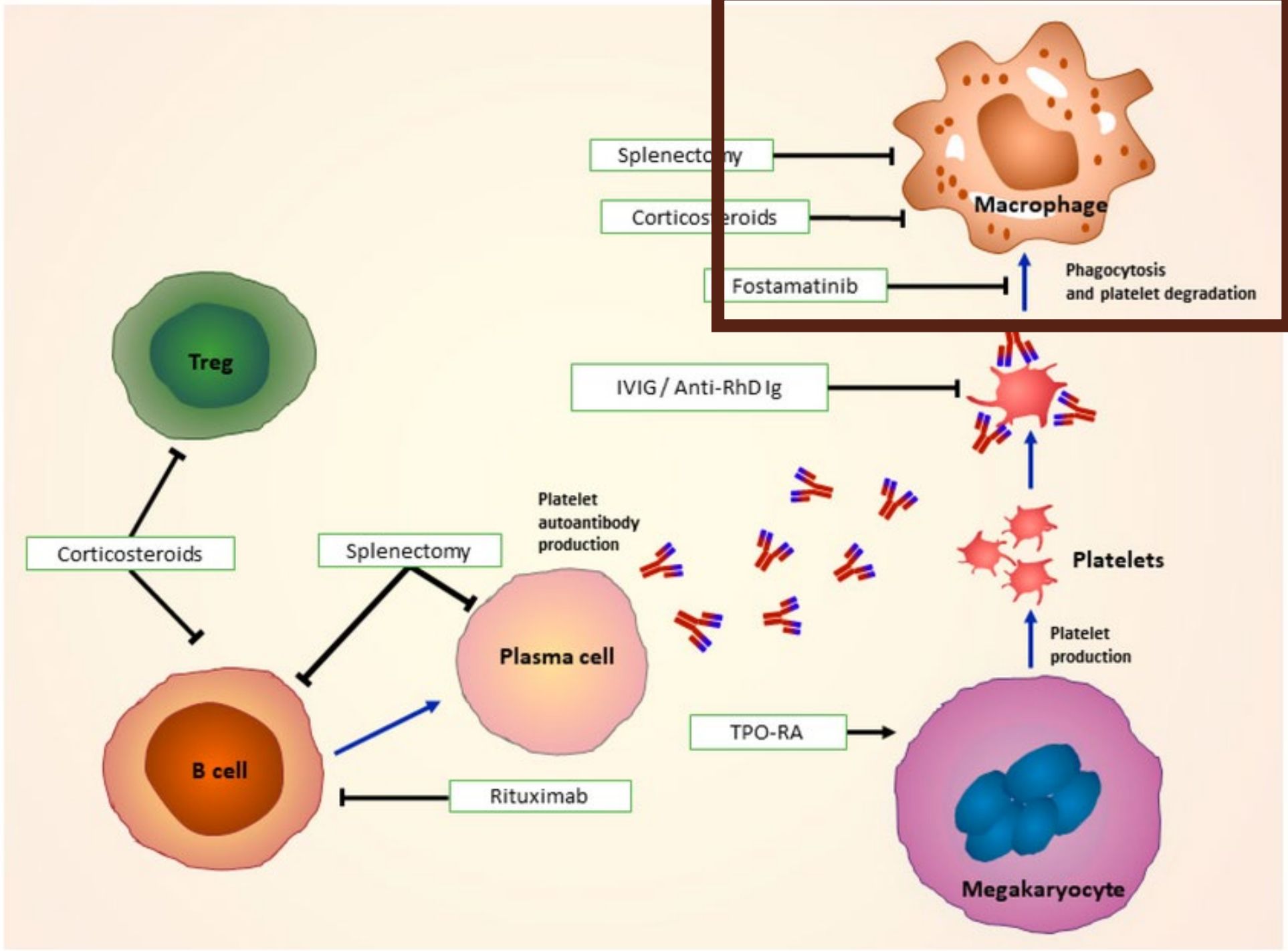
R/R ITP: Rituximab

- Dosing: 375mg/m2 weekly x 4 IV is better than 100mg/m2 IV twice weekly q2wks
  - Zaja et al. n=48 indirect, non-randomized trial both ORR 60.5% and 12 and 24 month cumulative relapse free survival rates 61% were improved from the standard dose (39%, 45%)
  - some repeat studies have shown no difference ?
- Retreatment
  - likely will response 50-80%, better if >12 month previous response

Agent	Dosage	Onset of Action	Durability of Effect	Side Effects and Cautions
Rituximab	375 mg per square meter of body-surface area intravenously weekly for 4 wk or 1 g administered twice with 2 wk between doses; lower doses (100–200 mg) weekly for 4 wk have also been shown to be effective	1–8 wk	Sustained response in 60% of patients at 6 mo and 30% at 2 yr; treatment can be repeated	Infusion-related side effects (chills, upper respiratory discomfort, bronchospasm), neutropenia, hypogammaglobulinemia, serum sickness; increased risks of infections and progressive multifocal leukoencephalopathy (very rare); should not be used in patients with evidence of active HBV infection (HBV surface antigen) or previous HBV infection (antibodies against hepatitis B core antigen)

Fostamatinib

- spleen tyrosine kinase (Syk) inhibitor



FIT1/FIT2: fostamatinib in chronic ITP

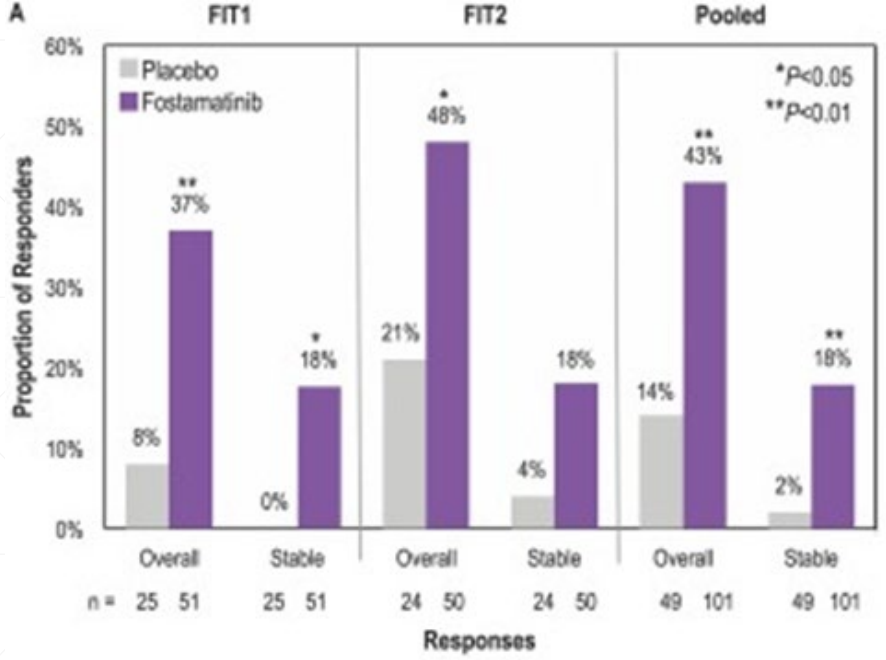
- two parallel phase 3 multicenter randomized placebo controlled trials in patients with c/pITP randomized 2:1 fostamatinib 50mg po BID (n=101) to placebo (n=49) for 24 weeks with dose increase in non-responders to 150mg BID after 4 weeks
- Primary endpoint plts >50 at >4 of 6 biweekly visits without rescue
- included pts failed splenectomy, TPO-RA and/or rituximab with a median duration of ITP for 8.5 years

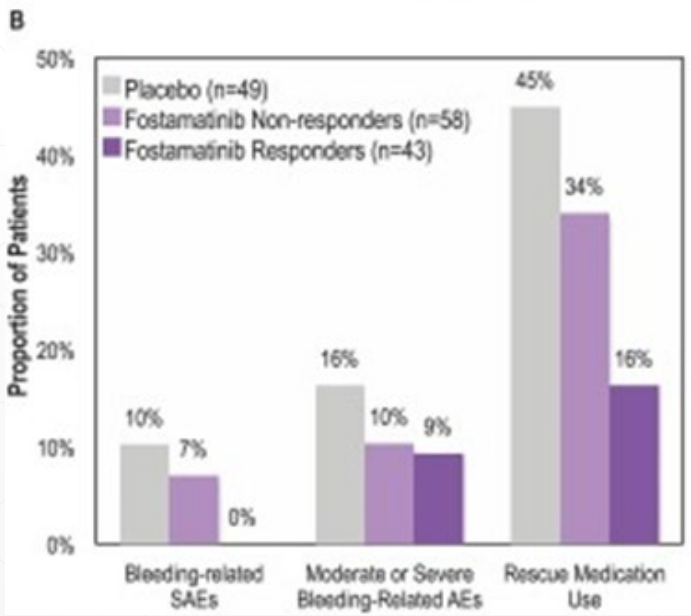
Agent	Dosage	Onset of Action	Durability of Effect	Side Effects and Cautions
Fostamatinib*	50–150 mg orally twice daily	1–2 wk	Response achieved and maintained in 18–43% of patients receiving continuing therapy	Hypertension, nausea, diarrhea, transaminitis

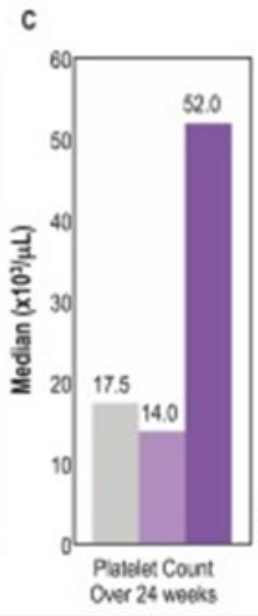
Bussel et al. (2018) Am J Hematol

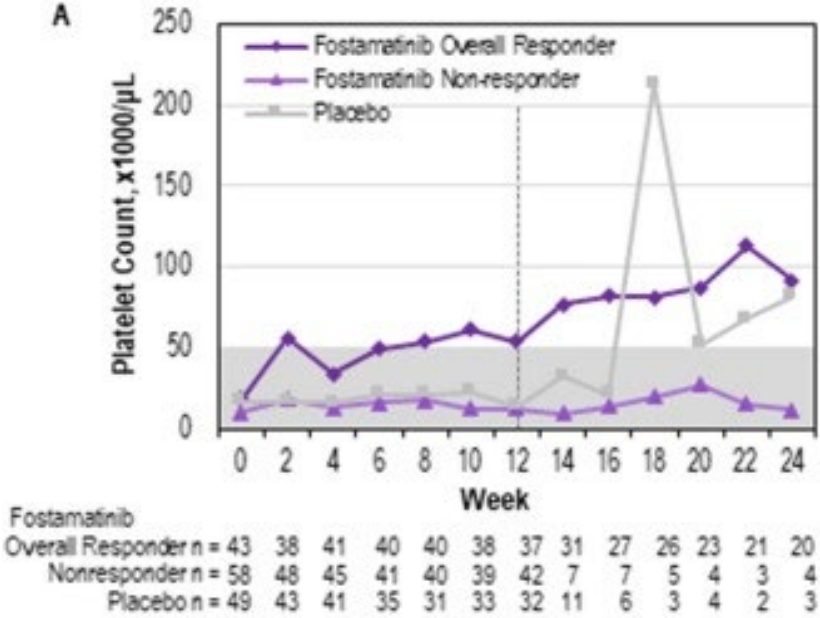
FIT1/FIT2

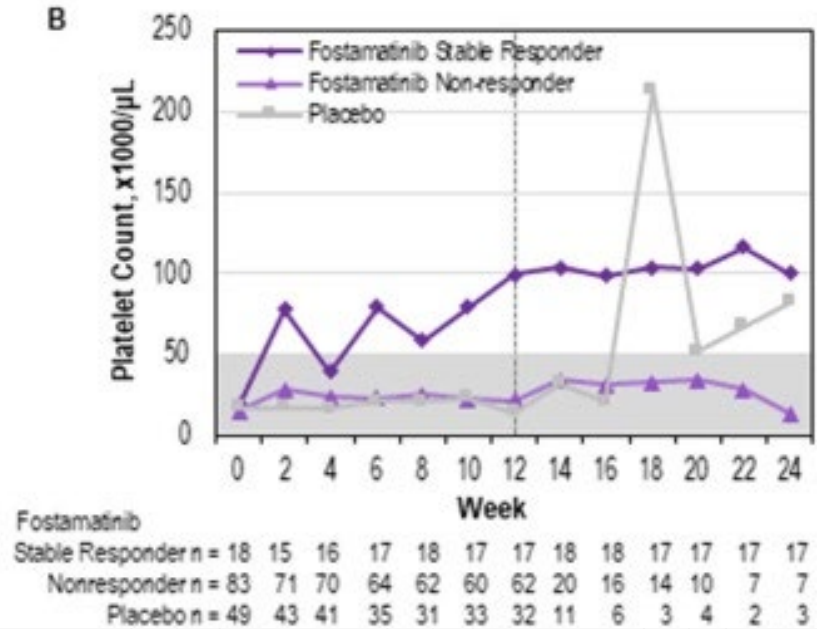
- ORR 43%, Plts > 50 at 4 weeks in 18% vs 2% placebo
  - 34% of failed TPO-RA responded
- SE: headaches, n/v/d, hepatobiliary, bleeding
- Recommendation to discontinue at 12 wks if no response





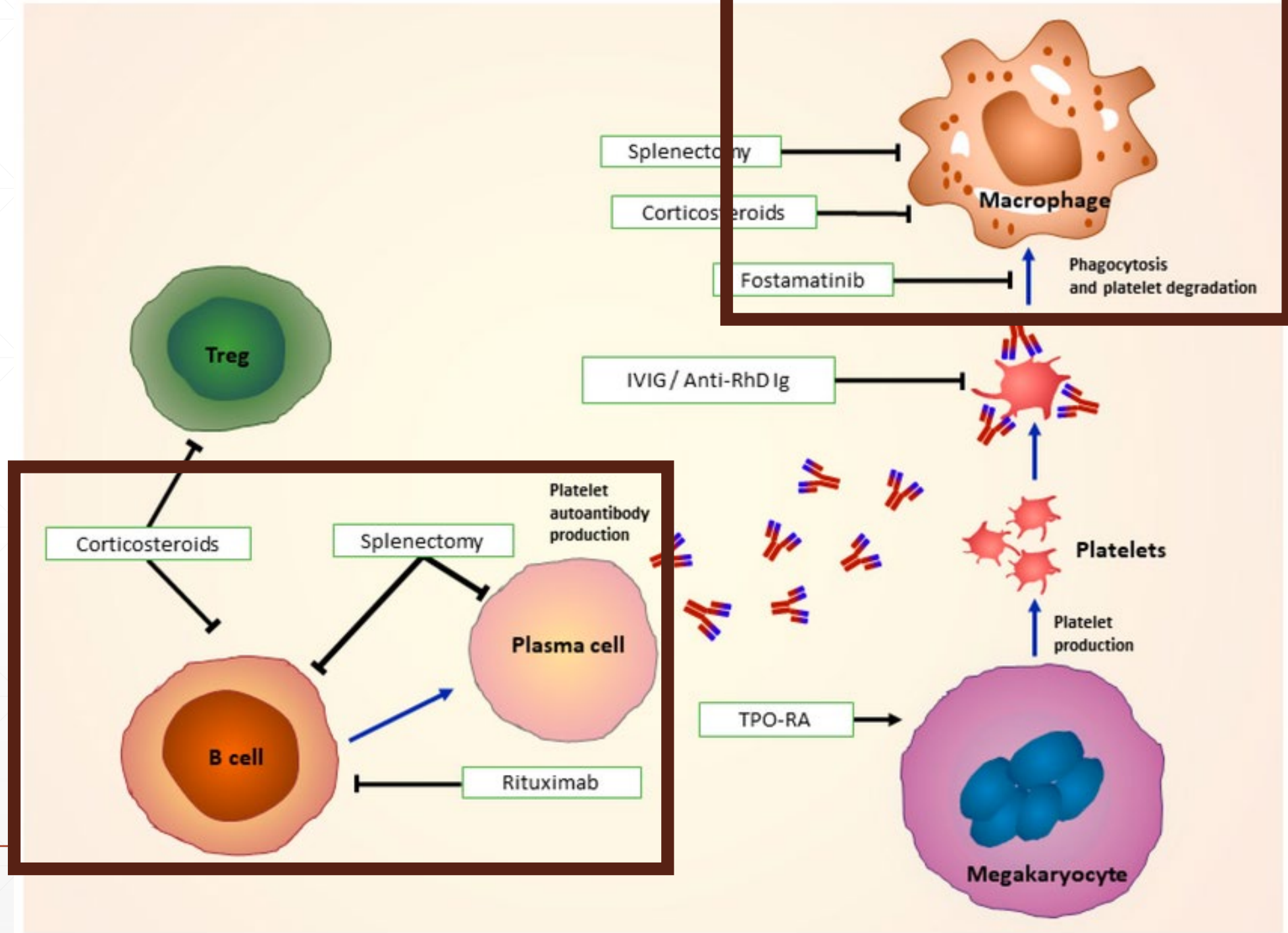






Bussel et al. (2019) Am J Hematol

Splenectomy



R/R ITP: Splenectomy

- 2019 Guidelines & Consensus
  - Delay 1-2 year post diagnosis*
  - Recommendation for trial of Rituximab prior to splenectomy
    - vaccination schedule
- Goal plts 50 prior to splenectomy surgery
  - Steroids, IVIG, TPO-RA, plt transfusion if <10
- 80-90% response rates, 20 yr RFS 67%
- If still refractory post, image for accessory spleen
- Cons
  - Surgical risk and complications, encapsulated organism infections lifelong, need for vaccine boosters, VTE risk
  - AVOID in older patients, cardiovascular disease

Recommendations for surgical therapy for persistent and chronic ITP in adults

1. Splenectomy is associated with long-term treatment-free remissions. It is recommended to wait ≥12 to 24 months from diagnosis before performing splenectomy because of the chance of remission or stabilization of a platelet count at a hemostatic level (Grade C recommendation).
2. When available, indium-labeled autologous platelet scanning may be useful prior to splenectomy to confirm that the spleen is the main site of platelet sequestration (Grade B recommendation).
3. Laparoscopic splenectomy is as effective as open splenectomy in terms of response and is more comfortable for the patient (Grade B recommendation).
4. Postoperative thromboprophylaxis should be considered in patients undergoing splenectomy as long as the platelet count is >30 to 50 × 10^9/L (Grade C recommendation).
5. Splenectomy should be performed by a surgeon experienced in identifying accessory splenic tissue, which is common and should be removed (Grade C recommendation).
6. Appropriate vaccination against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* must be provided ≥2 weeks before splenectomy and maintained according to national guidelines; recent treatment (within 6 months) with rituximab may impair vaccination efficacy.
7. Patients should be informed of the long-term risks of splenectomy (increased rates of thrombosis, infection, and cancer) and educated to follow advice aimed at mitigating these complications (Grade C recommendation).
8. Antibiotic prophylaxis should be given as per national guidelines (Grade C recommendation).

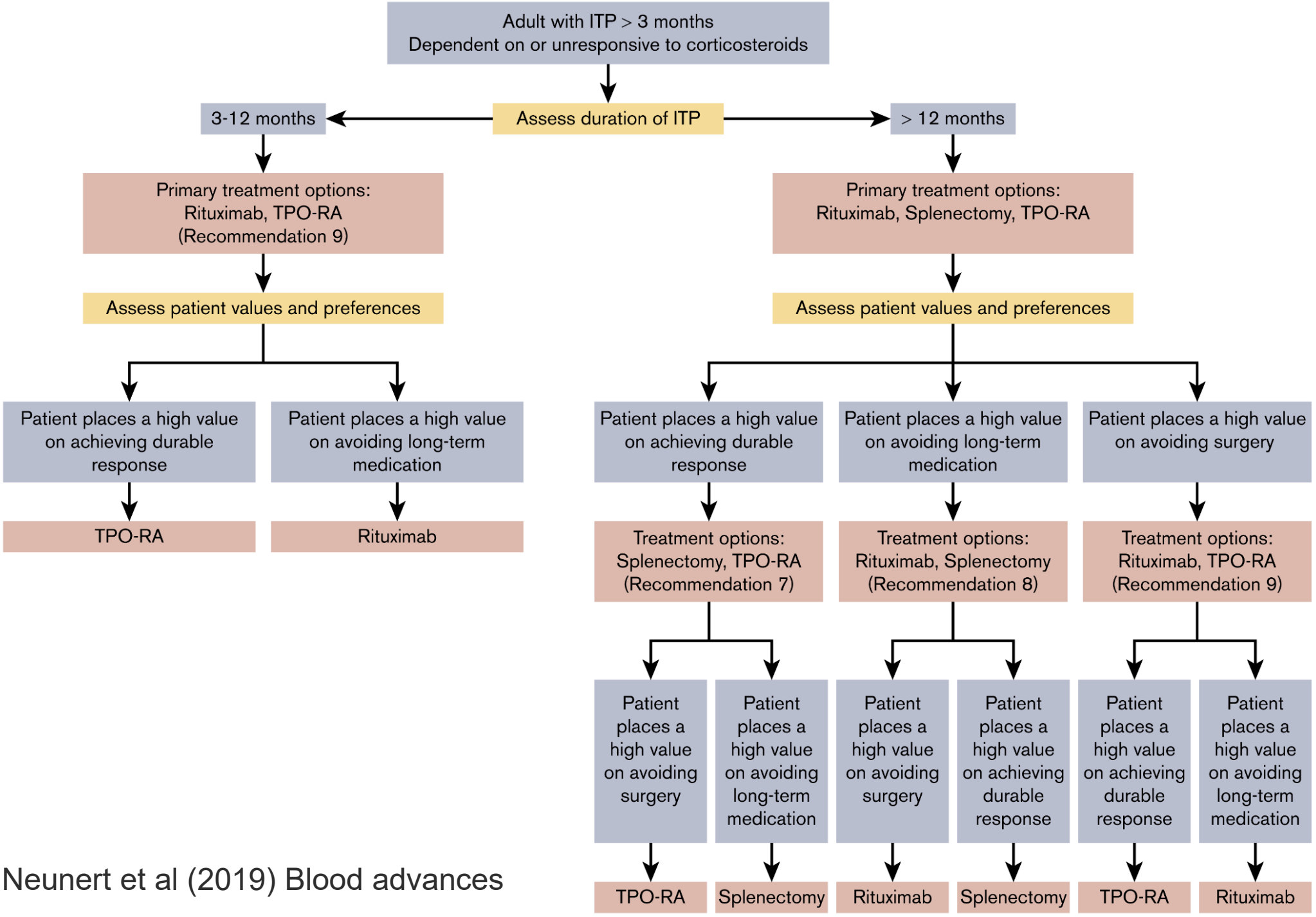
R/R ITP: immunosuppression grab bag

Azathioprine	1–2 mg per kilogram orally (maximum, 150 mg daily)	6–12 wk	Response in 30–60% of patients	Weakness, sweating, neutropenia, transaminitis, increased risk of cancer
Mycophenolate mofetil	500 mg orally twice daily for 2 wk, with gradual increase to 1 g twice daily	4–8 wk	Response in 30–60% of patients	Headache, gastrointestinal symptoms, fungal skin infections, teratogenic in pregnancy, increased risk of cancer
Danazol	400–800 mg orally daily	3–6 mo	Response in 30–60% of patients	Hirsutism, acne, amenorrhea, transaminitis; this androgenic agent should not be used in patients with prostate cancer
Dapsone	75–100 mg orally daily	3 wk	Response in 30–60% of patients	Gastrointestinal symptoms, methemoglobinuria, rash, hemolytic anemia (in patients with glucose-6-phosphate dehydrogenase deficiency)
cyclosporine A	3-6mg/kg/d max 200mg	4wk	Response 30-50%	gingival hyperplasia, HTN, renal
cyclophosphamide	50-200mg/d	4wk	Response 10-70%,	bone marrow suppression infertility, secondary malignancy infection, CI in pregnancy

?older

?? mix and match based on patient preference & clinical scenario

- Comorbidities
- Age of patient
- Medication adherence
- Patient preferences
  - anxiety about low platelets
  - Pills vs injections vs IV medications vs surgery
  - Chronic vs limited administration
- Medical/social supports
- Cost
- Availability
- Pregnancy consideration



Neunert et al (2019) Blood advances

2nd line decisions for ITP

- When to choose Rituximab first?
  - patient preference
  - before splenectomy
  - Female, young <40, secondary autoimmune disease

- When to choose TPO-RA first?
  - patient preference
  - need for rapid response
    - Cons: $$$, continuous therapy
  - ?preferred as more durable response

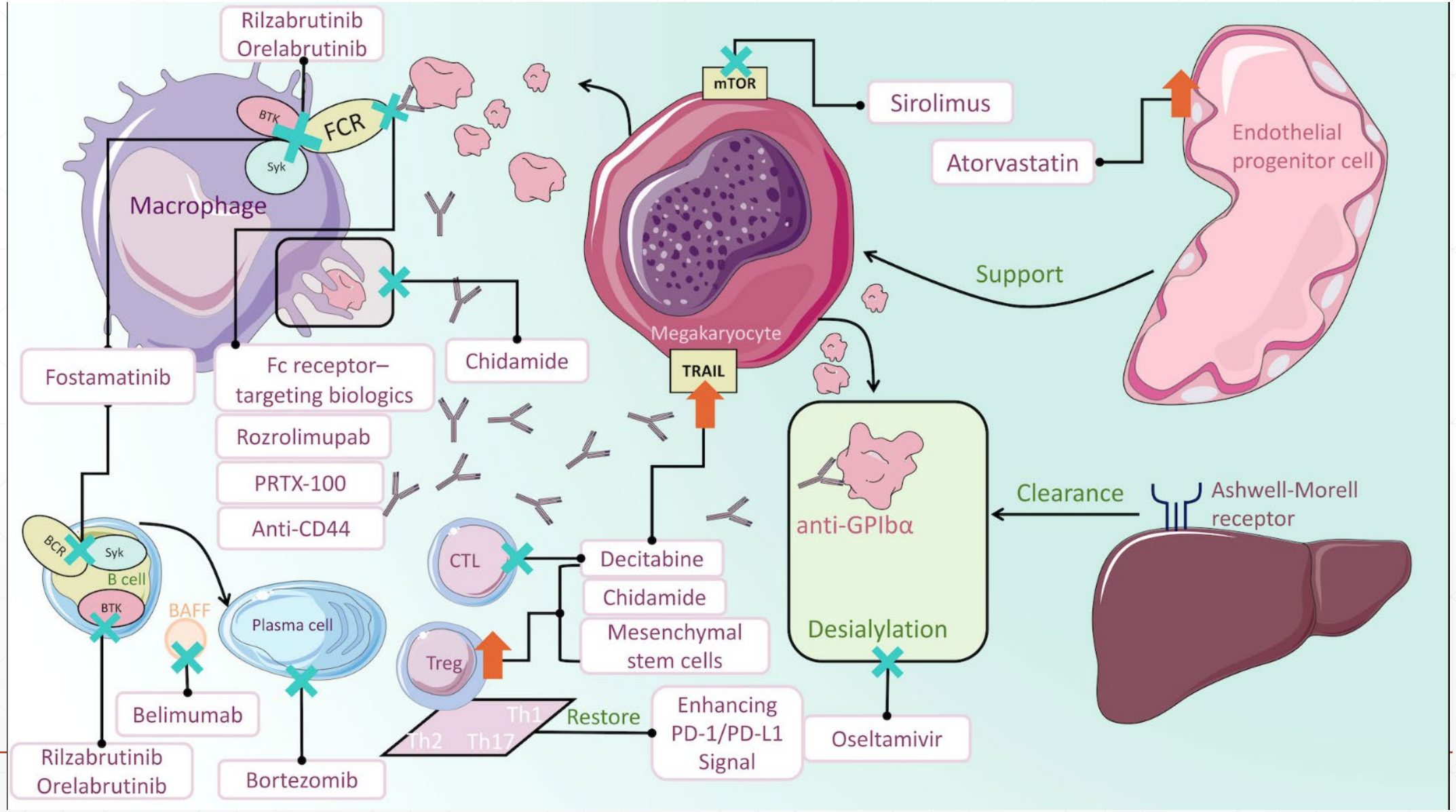
What do we do in emergency bleeding in ITP

- Plts < 20 with major bleeding
  - Methylprednisolone IV > prednis(ol)one po (?)
  - IVIG 1g/kg x 2 days

    plts <10 first presentation
  - +/- plt transfusion
  - Vincristine 1-2 mg IV for 2-4 weeks or vinblastine 10mg IV 1-3 weeks
    - 71% increase plt count at 7 days, 68% at 1 month however not durable and significant toxicity
  - No clear role for PLEX
- Supportive care
- Antifibrinolytics
  - tranexamic acid po/IV

Therapy	Route of administration	Mechanism of action	Dosage	Response rate	Adverse effects
Romiplostim	Subcutaneous injections	TPO-RA	1-10 μg/kg once weekly	Overall response of 75%; durable response at 6 mo is 65%; 10% to 30% may achieve treatment remission	Headache, muscle aches, venous and arterial thromboembolism, possible increase in bone marrow reticulin, and collagen fibrosis
Eltrombopag	Oral (restricted diet)	TPO-RA	25-75 mg once daily		Headache, venous and arterial thromboembolism, elevated liver enzymes, possible increase in bone marrow reticulin, and collagen fibrosis
Avatrombopag	Oral	TPO-RA	20-40 mg once daily	65% at day 8*	Headaches, arthralgia, and venous and arterial thromboembolism
Rituximab	Intravenous administration	Immunosuppressive; anti-CD20	Infusions of 375 mg/m^2 each week for 4 weeks or 1000 mg every other week, for 2 weeks†	Initial response rate 60%; durable response rate at 6-12 mo is ~40% and at 5 y is ~20% to 30%	Infusion-related side effects (chills, upper respiratory discomfort, and bronchospasm), neutropenia, hypogammaglobulinemia, serum sickness, increased risks of infection and progressive multifocal leukoencephalopathy (very rare).
Fostamatinib	Oral	Immunosuppressive; splenic tyrosine kinase inhibitor	100-150 mg twice daily	Overall response 43%‡; stable response 18%§	Hypertension, diarrhea, nausea, and transaminitis

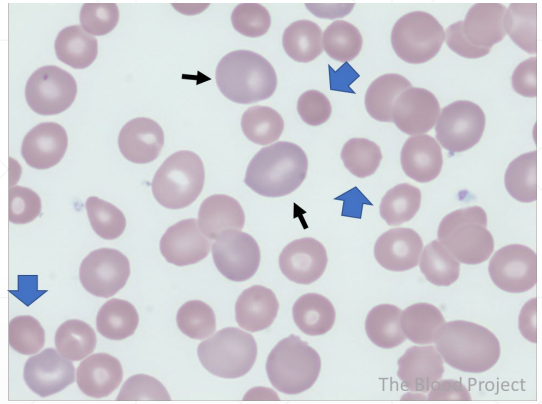
ITP: Novel Therapies and Beyond



Lv et al. (2022) Frontiers in Immunol

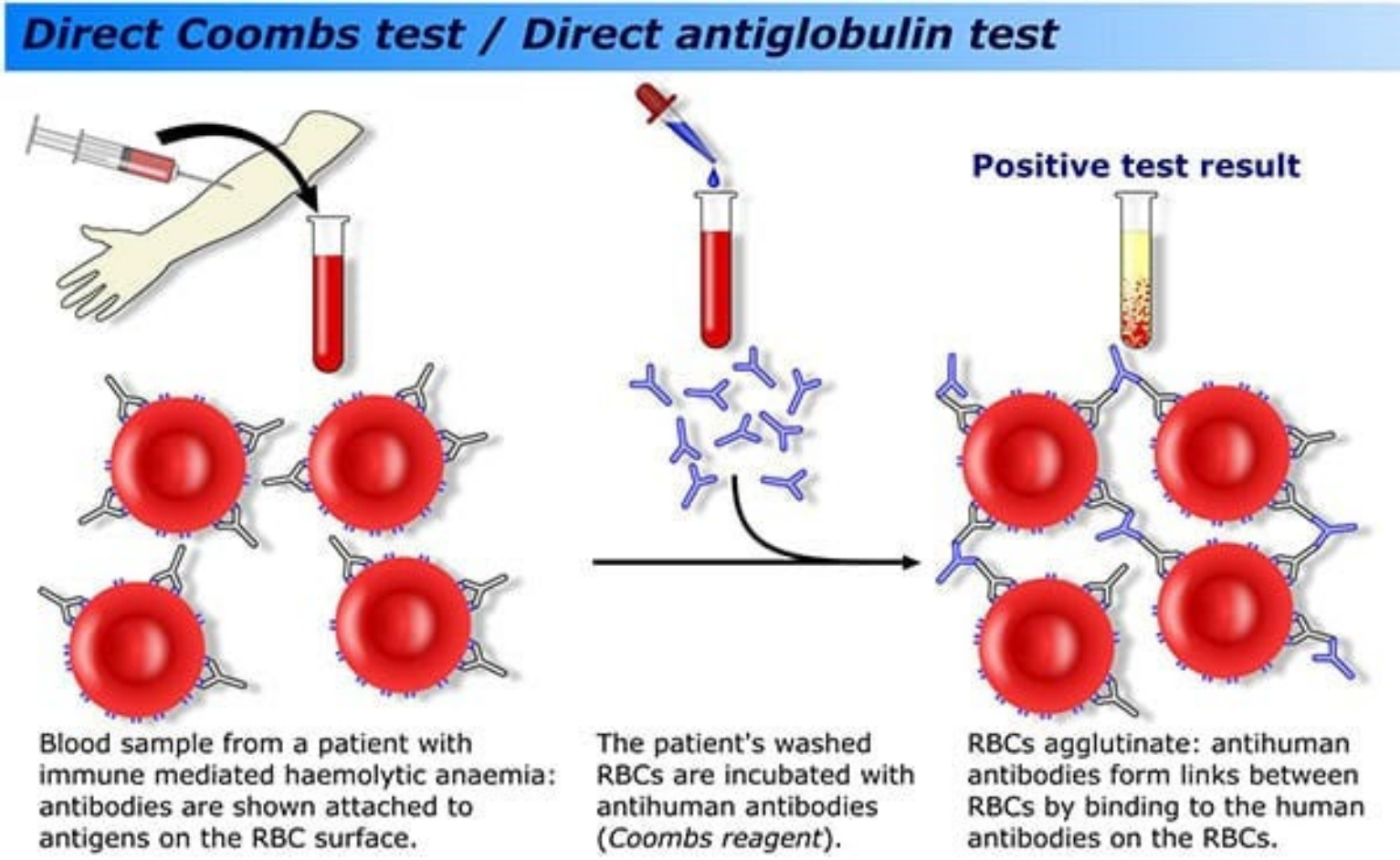
Autoimmune hemolytic anemia(s)

- Acquired erythrocyte destruction from autoantibodies +/- complement activation leading to extravascular hemolysis
- Incidence 1 per 100,000/yr
- 50% idiopathic



Warm-antibody autoimmune hemolytic anemia (wAIHA)	Cold-antibody autoimmune hemolytic anemia (cAIHA)	Atypical autoimmune hemolytic anemia
Primary wAIHA Secondary wAIHA Drug-induced AIHA	Cold agglutinin disease (CAD) Secondary cold agglutinin syndrome (CAS) Paroxysmal cold hemoglobinuria (PCH)	Mixed warm and cold AIHA DAT-negative AIHA

Diagnosis of AIHA

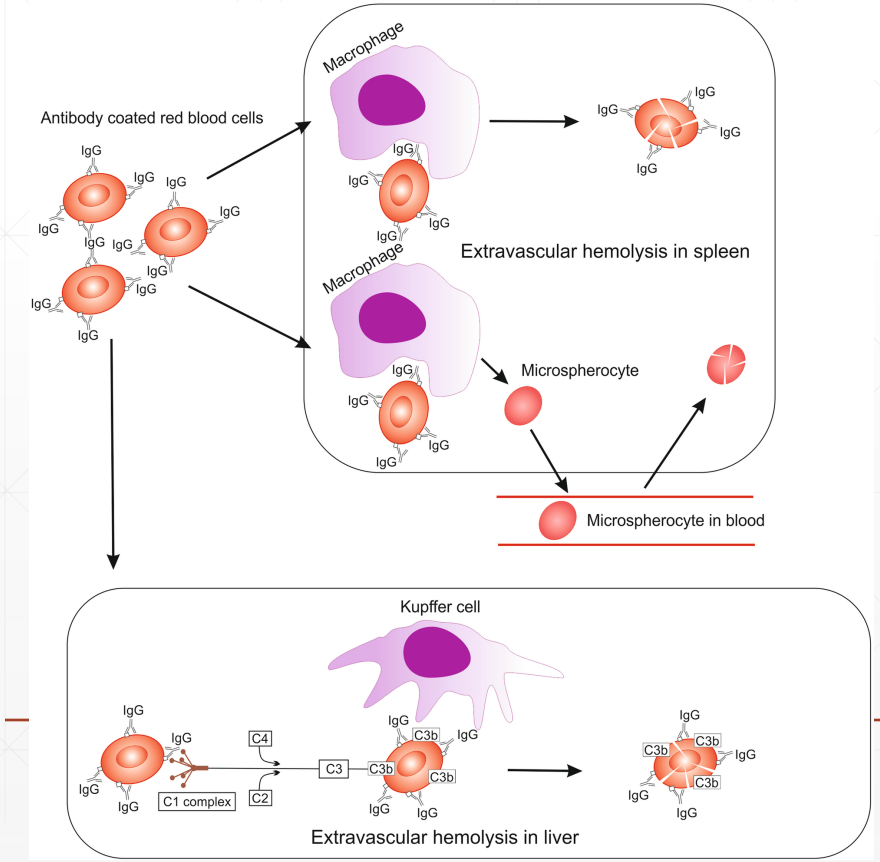


- Hemolysis
  - LDH ↑, haptoglobin ↓, d bili ↑, reticulocytes ↑, Hgb ↓
  - Spherocytes on smear
- DAT (coombs test)
  - IgG (wAIHA 70%)→wAIHA
  - C3d (CAD 20%)→ CAD/CAS
  - mixed (10%)

*- IgA mediated AIHA

wAIHA

- polyclonal autoantibodies mostly to Rh system
  - IgG autoantibodies (IgG1 IgG3) 35%
  - IgG + C3d (56%)
  - C3d (9%) with no cold agglutination



Associated Conditions (50%)

- Lymphoproliferative disease
  - CLL, HL, NHL
- Solid malignancy
  - Thymoma, ovarian, prostate
- Autoimmune
  - SLE, Sjogren, systemic sclerosis, RA, colitis, PBC, Evans syndrome
- Viral infections
  - HCV, HIV, VZV, CMV, COVID
- Bacterial infections
  - TB, pneumococcal
- Leishmania parasites
- Bone marrow or solid organ transplantation
- Primary immune deficiency syndromes (CVID, ALPS)
- Sarcoidosis

mortality 30-57% in ICU

Acute and very severe onset

- Hb<6 g/dL and/or hemodinamic instability

- methylprednisolone 100-200 mg/day for 7-10 days or 250 to 1000 mg/day for 1-3 days, then follow the oral schedule of predniso(lo)ne (right panel)
- Transfusion 1 blood unit/day, monitor post transfusion Hb and hemolysis
- Ivlg 0.4 g/kg/d x 5 d, particularly if infection is present
- early rituximab 375 mg/kg/wk for 4 wk in case of no response in 1 wk
- Consider PEX in case of no response in 7-10 days
- Test endogenous EPO if reticulocytopenia
- LMWH prophylaxis if no contraindications

Relapse or no response

- Perform BM evaluation
- Consider enrolment in a clinical trial
- mycophenolate mofetil, cyclosporine or cyclophosphamide as steroid sparing agents

Non acute/severe onset

- Hb 6-8 g/dL, anemia well tolerated, no comorbidity, and age <40 yrs
- Hb 8-10, anemia well tolerated

- predniso(lo)ne 1-1.5 mg/kg/d for 3-4 wks, then taper according to the following schedule: 10 mg/wk until 0.5 mg/kg/d, then 5 mg/wk until stop
- Monitor blood counts, reticulocytes, LDH, unconj bilirubin every 1-2 wk, and hold on taper if Hb <10 mg/dL and hemolysis active

If very severe ← **Relapse or no response**

- Rituximab 100 mg /wk for 4 wks. Hold on the last dose of steroids for the 4 rituximab wks

Relapse or no response

- Perform BM evaluation
- Rituximab 375 mg/kg/wk for 4 wks. Hold on the last dose of steroids for the 4 wks
- Test endogenous EPO if reticulocitopenia

tapered over 4-6 months
80% response

**cyclophosphamide in severe or LPD

If refractory, rule out secondary causes for directed therapy

- Lymphoproliferative disease
  - CLL, HL, NHL
- Solid malignancy
  - Thymoma, ovarian, prostate
- Autoimmune
  - SLE, Sjogren, systemic sclerosis, RA, colitis, PBC, Evans syndrome
- Viral infections
  - HCV, HIV, VZV, CMV, COVID
- Bacterial infections
  - TB, pneumococcal
- Leishmania parasites
- Bone marrow or solid organ transplantation
- Primary immune deficiency syndromes (CVID, ALPS)
- Sarcoidosis
- (Dx: PNH, congenital HA)

2nd line decisions in wAIHA

- When to add Rituximab?
  - severely anemia patients (hgb <80) should have considered prednisone + Rituximab as first line
    - 2 prospective randomized trials showed twice the rate of long-term responses versus steroids alone
  - Autoimmune disease, i.e Evans syndrome
- When to add erythropoiesis-stimulating agents?
  - if inadequate reticulocytosis or endogenous EPO levels or failing 2nd line rituximab
    - 55% patients responded by day 15, 70% within 3 months in recent studies of AIHA and CAD
- When to use IVIG?
  - sick patients, *sepsis, autoimmune disease
  - total dose of 2g/kg (0.4g/kg for 5 days or 1g/kg for 2 days) inhibits extravascular hemolysis by saturating reticuloendothelial system and FcR + clearance of autoantibodies

More 2nd line decisions in AIHA

- When do we suggest splenectomy?
  - 3rd line or beyond
    - response rates are high (70-80%) but disadvantages are many and infectious risks likely too high compared to other therapies

R/R wAIHA CLL-directed therapy

- B cell lymphocyte depleting therapy/CLL clone directed therapy preferred

RCD	Second or >	81-100	Small series of relapsed/refractory wAIHAs (17 patients)
R-CVP	Second or >	95	Small series of relapsed/refractory wAIHAs (17 patients)
Rituximab + bendamustine	Second or >	81	26 patients with progressive CLL, and active wAIHA
Alemtuzumab: 30 mg × 3/wk for 4-12 wk	Third or >	100	Small series of relapsed/refractory wAIHAs and progressive CLL (8 patients)
Cyclosporine: 3-5 mg/kg per day	Third or >	56	Small series of relapsed/refractory wAIHAs (16 patients)
Splenectomy	Third or >	69-78	Old reports and small series; splenectomy is currently discouraged
Ofatumumab: Cycle 1: day 1, 300 mg; and day 8, 1000 mg; further cycles 1000 mg on day 1, monthly	n/a	n/a	Case report
Obinutuzumab: Cycle 1: day 1 100 mg; and day 2, 900 mg; further cycles 1000 mg on day 1, monthly	n/a	n/a	Case report
Ibrutinib: 420 mg/d	n/a	n/a	Case reports: phase 2 trial ongoing
Venetoclax: 200-400 mg/d	n/a	n/a	Case reports

Treatment	Dose	ORR	Time to response	Approach	SE/cons
Prednisone *1st line	1-2 mg/kg per day 3-4 wks Methylpred 100-200mg/day to 7-10 days or 250-1000mg 1-3 days prior if sick	80-90% (CR 20-30%)	7-25d *steroid failure if no response by 3 weeks	Gradual taper after 3-4 weeks then 10mg/wk until 0.5mg/kg/day then 5mg/wek then stop Hold if Hgb dips <100 and hemolysis	DM, HTN, peptic ulcers, osteoporosis, adrenal suppression, myopathy, psychosis, delayed healing, insomnia, menstrual irregularity, weight gain
IVIG *if severe, pregnancy	0.4g/kg per day for 5 d	30-40%	1-5d	Lasts 3 weeks, **consider for infection related (ICU)	Infusion reactions (IgA def), VTE, renal failure, serum viscosity
Rituximab ***2nd line**	375mg/m2 per week x 4	~80% (RFS 60% at 3y) 100% primary	3-6wk	Can consider 1g days 1, 15 with other autoimmune Start Within 1 week if unresponsive	HBV reactivation, lamuvidine proph required up to 18 months if not vaccinated

3rd line and beyond cont'd

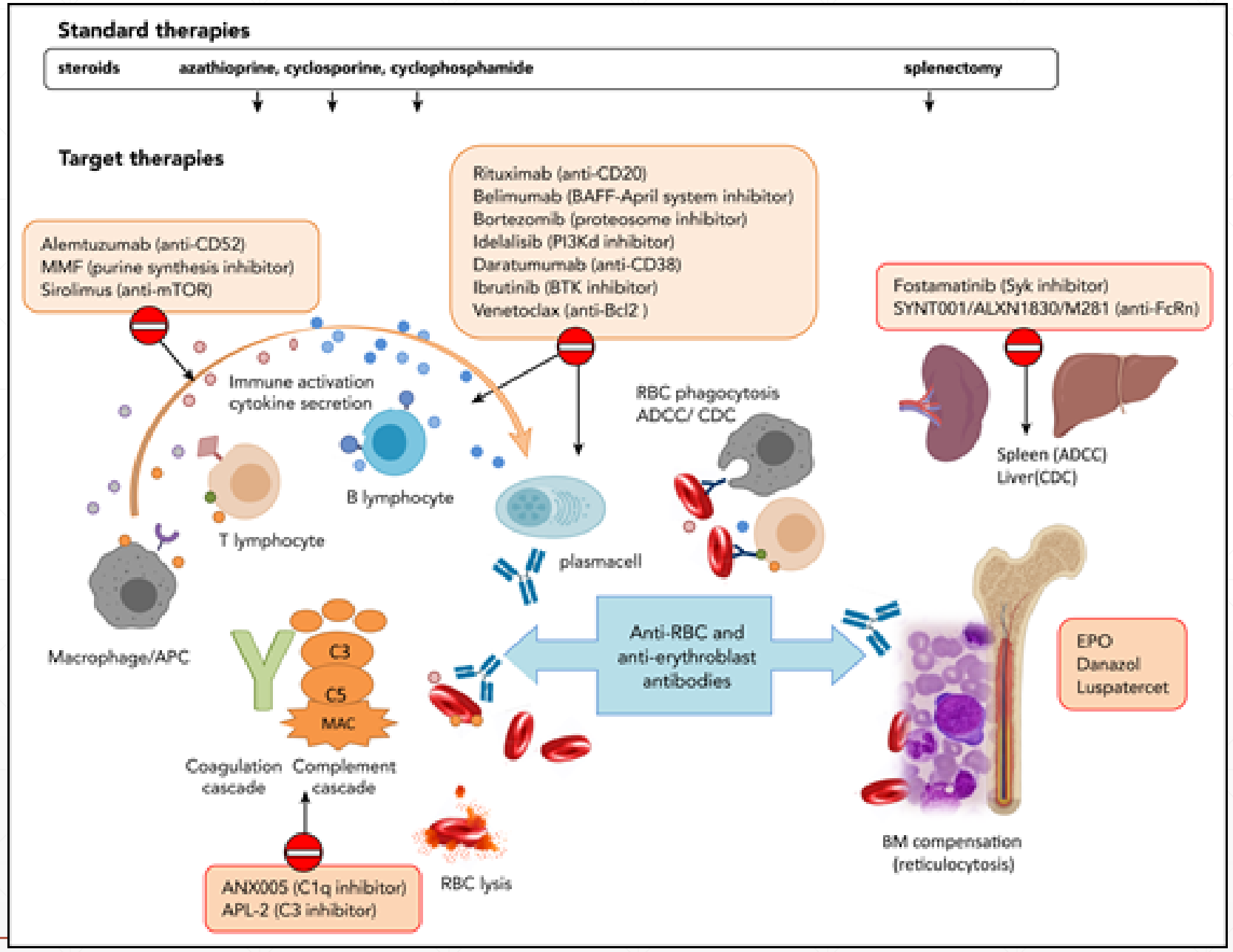
Treatment	Dose	ORR	Time to respond	Approach	SE/cons
Cyclophosphamide	50-100mg per day or 800mg/m2 IV monthly for 4-5 cycles	50-70%	2-6 wks	Highly hemolytic disease, secondary to CTD or LPD	Myelosuppression, infection, urotoxicity, secondary malignancy, teratogenicity, infertility
Mycophenolate mofetil	500mg po twice per day	25-100%	1-3 months	Mostly pediatric, transplant related	Nausea, headache, diarrhea
Danazol	200mg 2 times per day	20-50%	1-3 months	Steroid sparing	Androgenic (avoid in men with prostatic adenoma or carcinoma), liver toxicity

3rd line and beyond

Treatment	Dose	ORR	Time to response	Approach	SE/Cons
Splenectomy		~80% (cure 20-50%)	7-10d 3rd line and beyond	Avoid >65-70, VTE risk, immunodiffiency, systemic autoimmune, LPD, cardiopulmonary disease No clear timing suggested, likely still wait 1yr	Infections (encapsulated organisms), VTE
Azathioprine	2-4mg/kg per day	~60%	1-3 mo	Steroid sparing agent secondary autoimmune system, IVD, autoimmune hepatitis **pregnancy**	Myelotoxicity (thiopurine methyltransferase deficiency deficiency), liver toxicity
Cyclosporine	2.5mg/kg twice per day	~60%	1-3 mo	Steroid sparing agent, autoimmune, **Evans syndrome**, BMF	Kidney damage, HTN, infections, nausea, hair growth

The future of R/R wAIHA

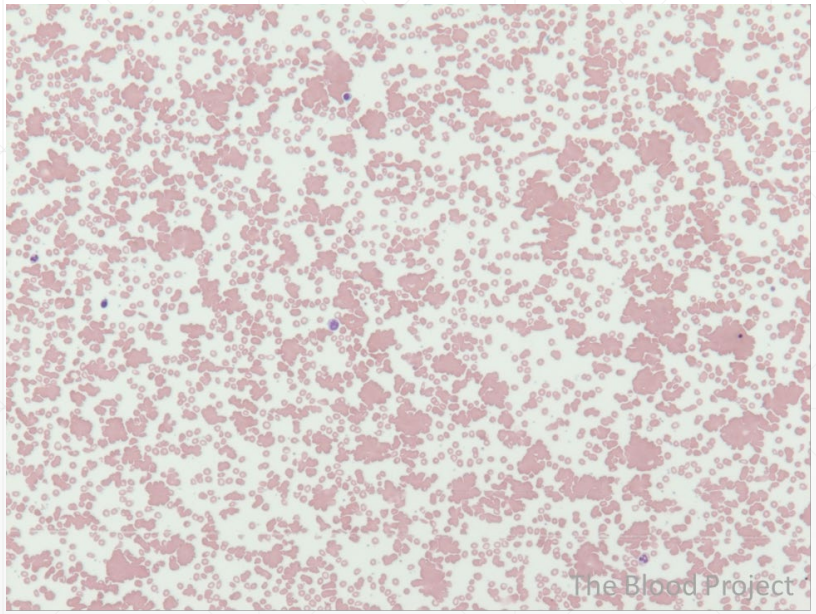
- Fostamatinib
  - Syk (46% response rate)
- Rilzabrutinib
  - Bruton kinase inhibitor (64% response rates)
- bortezomib
  - selective proteasome inhibitor
- sirolimus
  - Evans Sx



Barcellini & Fattizzo (2021) Blood

Cold agglutinin disease/syndrome

- autoimmune hemolytic anemia from cold agglutinins (usually monoclonal IgMk recognizing RBC antigens below core body temperature) leading to complement mediated hemolysis
  - incidence 0.5 in 1.9 cases per million per yr



- Cold induced acrocyanosis/Raynaud in 40-90%
- Associated conditions
  - Lymphoproliferative disorder
    - LPL/MZL (often MYD88 negative)
    - Waldenstrom's macroglobulinemia
  - Solid tumors
  - Infections
    - mycoplasma, viral infections
  - Autoimmune disease
  - Post allo-SCT

Diagnosis & Workup

Hemolysis
LDH ↑, haptoglobin ↓, d bili ↑, reticulocytes ↑, Hgb ↓, Spherocytes +/- agglutination

DAT (coombs) + monospecific C3d+ (+/- weak IgG (20%) bound at 4 degrees

Cold agglutinin titre ≥64 degrees C

+ "Primary" although often clonal B cell peripheral lymphoproliferative d/o +/- IgM

→ Cold Agglutinin Disease (CAD)

→ Cold Agglutinin Syndrome (CAS)

+ "secondary"
(B cell lymphoma, malignancy, CTD, M. pneum)

- Workup cont'd
  - urine hemosiderin
  - ?thermal amplitude
  - C3/C4
- Secondary causes
  - SPEP, SFLC, IgG (IgMk)
  - BMBx (LPL or MZL, MYD88 common)
  - flow cytometry
  - Infectious workup

Paroxysmal cold hemoglobinuria *Donath Landsteiner test

Management of CAD

- Clinical phenotype variable
  - Hgb <80 (27%)
  - Hgb 80-100 (37%)
  - Hgb > 100 (24%)
  - compensated Hgb (12%)
- Symptoms
  - acrocyanosis/Raynaud's
  - anemia symptoms
- Triggers
  - cold, infections, vaccinations, surgery, trauma
- Treatment goals
  - maintain hgb to minimize symptoms

Treatment

All pts

- **cold avoidance***
- **folic acid support**
- **DVTp high risk**

Hgb <70-80?

- Blood transfusions via warmer
- Removal of cold agglutinins
  - PLEX in acute hemolysis daily 1-1.5 volume
- EPO*

Refractory

- eradication of B cell clone
  - Rituximab +/- Bendamustine

Refractory

- Complement inhibition
  - sutimlimab (only FDA approved)

CAD treatment: what to avoid

- Steroids
  - 14-69% responses but <20% remission and high doses required
- International Consensus meeting→ “not recommended to use steroids, azathioprine or cyclophosphamide”
- British Society of Haematology → “consider prednisone 1mg/kg/day if anemia severe or life-threatening”
- Consensus opinion=NO role for steroids
- Splenectomy
  - futile as extravascular hemolysis occurs in liver
- Nonspecific immunosuppression (i.e cyclophosphamide, azathioprine)

1st line therapy in CAD: B cell clone directed

Target	Treatment	Study (Reference)	Study design	ORR[1] (%)	CR[2] rate (%)	Median response duration (months)	Toxicity
B-cell directed theapies	Rituximab monotherapy	Berentsen et al., 2004 (78) Schöllkopf et al., 2006 (79)	Prospective, non-randomized	45-55	<5	6.5-11	Low
	Rituximab plus fludarabine	Berentsen et al., 2010 (80)	Prospective, non-randomized	76	21	>66	Significant
	Rituximab plus bendamustine	Berentsen et al., 2017 (81) Berentsen at al. 2020 (61)	Prospective, non-randomized	78	53	>88	Moderate, manageable
	Bortezomib monotherapy	Rossi et al., 2018 (82)	Prospective, non-randomized	32	16	>16	Low
	Ibrutinib monotherapy	Jalink et al., 2021 (83)	Retrospective	100	NR[1]	ND[1]	Low

Berentsen et al. (2023) Frontiers

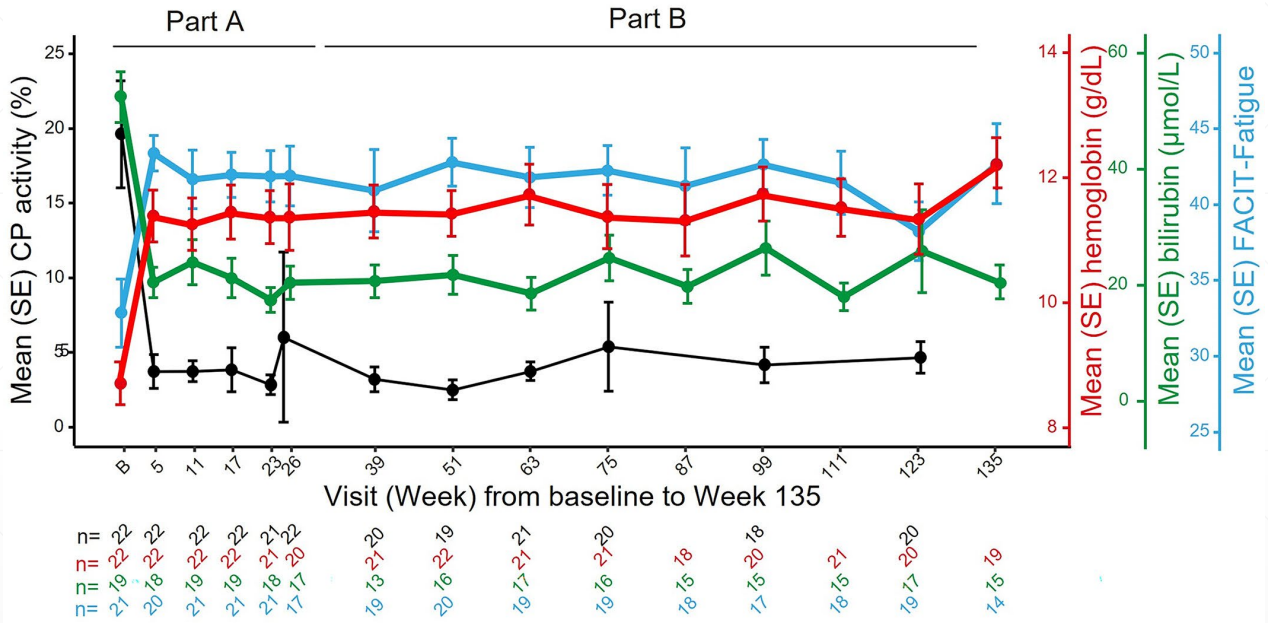
2nd line: complement mediated for CAD

Target	Treatment	Study (Reference)	Study design	ORR[1] (%)	CR[2] rate (%)	Median response duration (months)	Toxicity
Complement-directed therapies	Sutimlimab	Röth et al. (CARDINAL study) 2021 (70)	Prospective, non-randomized	>73[3]	NR[1]	>24	Low
		Röth et al. (CADENZA study) 2021 (77)	Prospective, randomized				
	Pegcetacoplan	Grossi et al., 2018	Part of prospective phase 2 study	ND/ high[3]	NR[1]	ND[1]	Low

[1]ORR, overall response rate; ND, not determined; NR, not relevant.
[2]CR, complete response. Criteria for CR included eradication of detectable bone marrow lymphoproliferative disorder.
[3]ORR was not an endpoint of this study. Estimated ORR is based on data from the original publication.

2nd line: complement inhibition FDA approved 2017

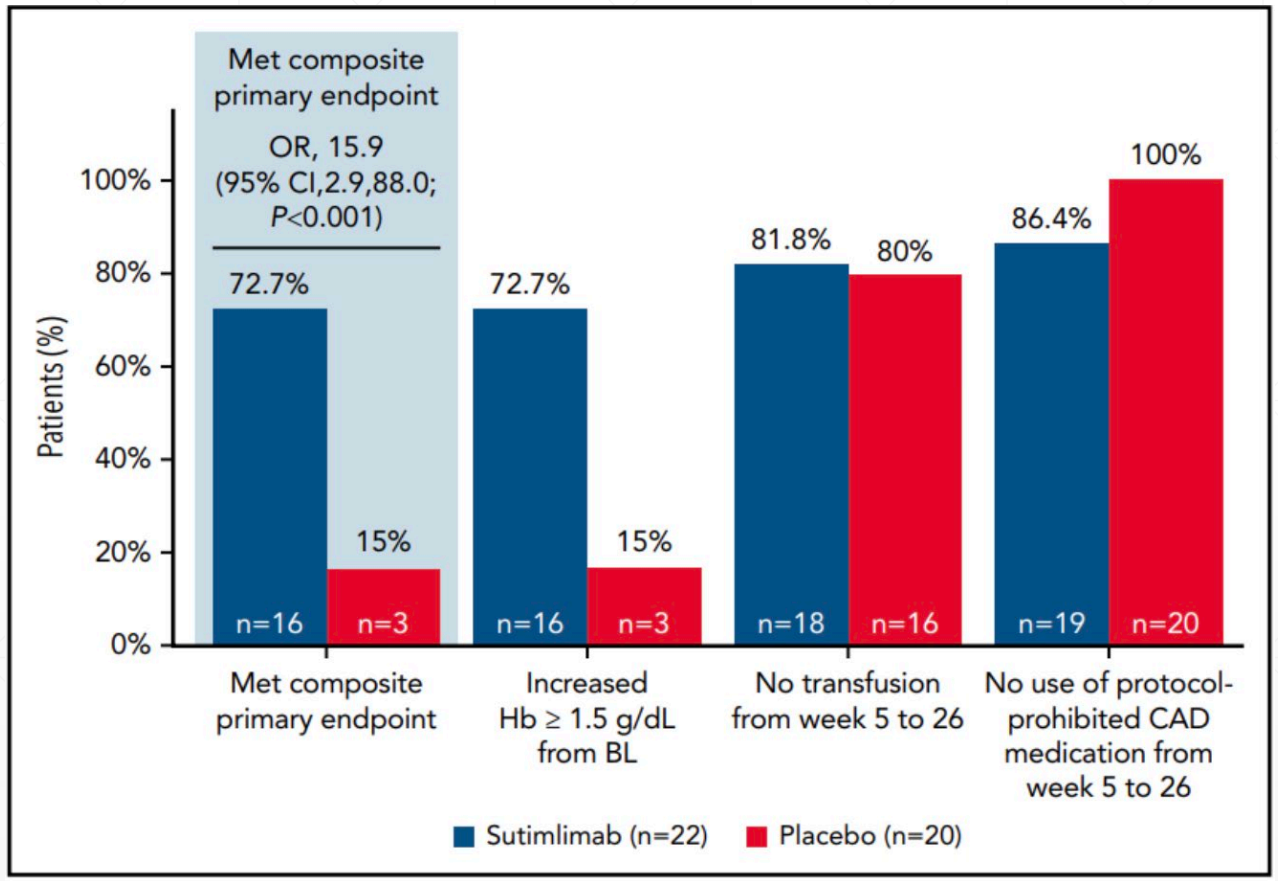
- CARDINAL study
  - sutimlimab, humanized monoclonal antibody to C1s, inhibits C1 complex and classical complement pathway
  - 26 wk multicenter open label phase 3 study n=24 therapy given IV day 0, 7 then q2wks
  - Inclusion:
    - CAS with recent transfusion within 6 months
    - Composite endpoint normalization of hgb to 120 or increase by 20 pts
  - 54% met composite endpoint, 3 non-responders



- =2 year extension study showed sustained QOL, normalized hemolysis markers to 144 weeks
  - all relapsed within 9 weeks of treatment cessation

2nd line: complement inhibition FDA approved 2017

- CADENZA trial
- 26 week phase 3 RCT double blinded sutlimlimab n=19 vs placebo n=20
  - excluded CAS from infection, rheumatologic disease, active hematologic malignancy, transfusion within 12 months
- primary endpoint composite hgb >15 from baseline, absence of blood transfusions or rescue therapy from wk 5-26
- sutimlimab pts reported more headache, HTN, rhinitis, Raynaud, acrocyanosis than placebo



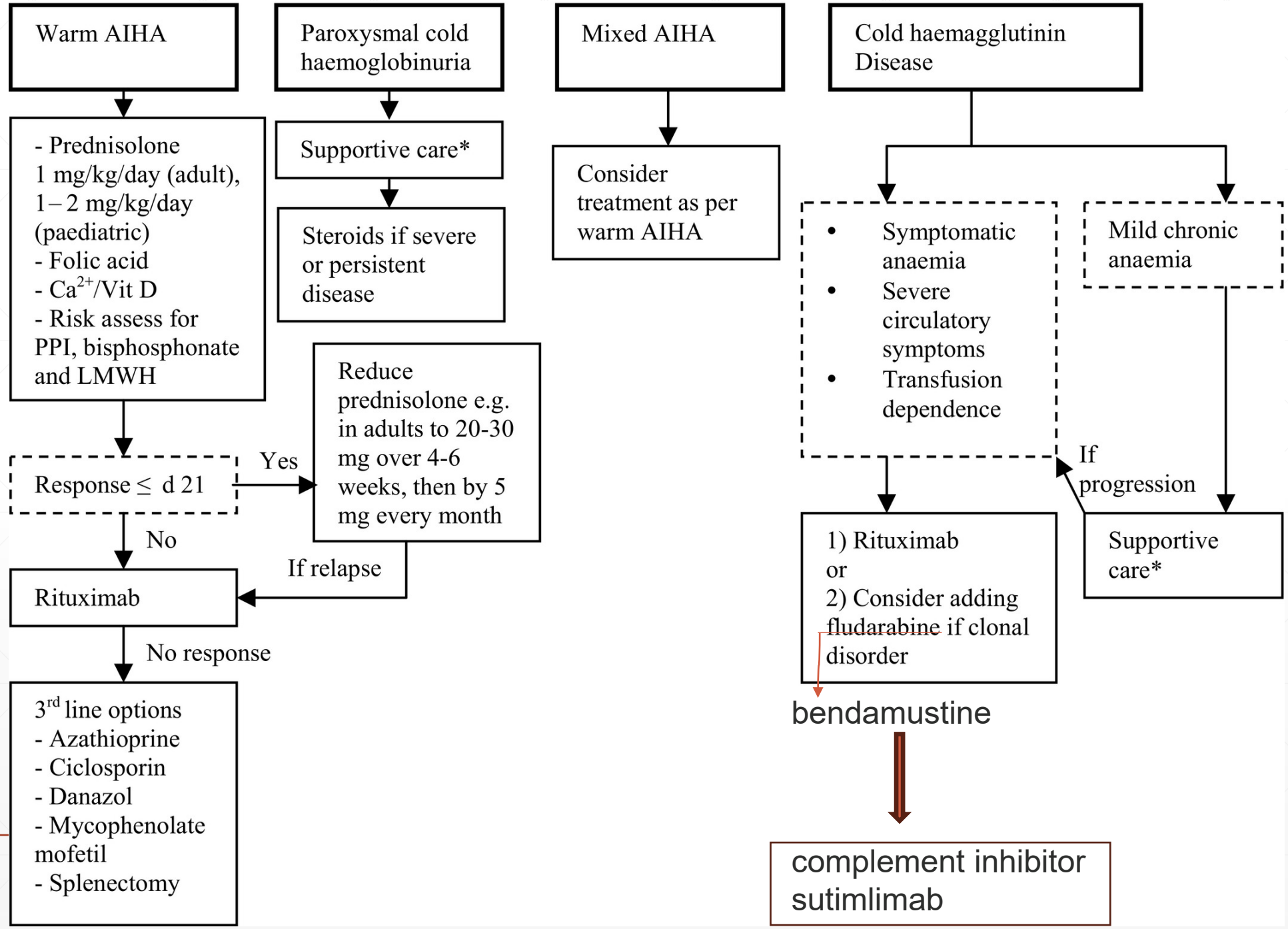
Roth et al. (2022) Blood

How to choose therapies in CAD

- When to choose B cell or complement directed therapy?
  - B cell directed: prominent circulatory symptoms
    - most first line: rituximab monotherapy
    - moderate to severe: rituximab + bendamustine
  - complement directed: need for urgent increase/critically anemic
    - *chronic therapies, $$, biweek IV
- What to do in an emergency?
  - PLEX (80% IgM is in bloodstream) +/- sutimlimab

AIHA summary

vitamin D 800IU daily, 700-1200 mg calcium daily for all
if prednisone dose >7.5mg/day >3 months in postmenoausal women and men >50 consider bisphosphonate



CAS treatment

- most often in association with infection (M.pneumoniae, EBV, CMV, COVID) or malignancy
  - antibiotics + transfusion support
- Treatment is to target secondary cause, supportive management and may consider CAD directed therapies if dire

Conclusion

- Immune mediated cytopenias are driven by complicated immune dysregulation
- Steroids are the mainstay of most first line therapy but many patients require further therapies
- Second line and beyond therapies should be considered based on patient specific characteristics which target mechanisms of disease
- Careful evaluation of possible differential diagnosis or secondary processes should be considered in refractory patients
- Novel directed therapies are in the works for many types of immune cytopenias

Questions?

- thanks!

Extra slides

Drug Induced AIHA

- Antibiotics
  - Cephalosporins, beta lactamase inhibitors, cotrimoxazole
- Antiviral drugs HAART
- Anti-PD1 monoclonal antibodies
  - Nivolumab, pembrolizumab
- Chemotherapy
  - Carboplatin, oxaliplatin
- NSAIDS
  - Diclofenac
- methyldopa

Tx= stop the drug +/- rescue tx in meantime
Timing?

ITP platelet thresholds

Table 6. Consensus-based recommendation for target platelet counts for surgery or medical therapy in adults

Type of surgery	Target platelet count, × 10^9/L
Dental prophylaxis (descaling, deep cleaning)	≥20 to 30
Simple extractions	≥30
Complex extractions	≥50
Regional dental block	≥30
Minor surgery*	≥50
Major surgery	≥80
Major neurosurgery	≥100
Splenectomy	See "Subsequent therapy: surgical"
Obstetrics	See "Thrombocytopenia presenting during pregnancy"
Single antiplatelet agent or anticoagulant (ie, 1 antiplatelet agent, warfarin, or TSOAC)	≥30 to 50
Dual antiplatelet or anticoagulant (ie, 2 antiplatelet agents or 1 antiplatelet agent plus warfarin or TSOAC)	≥50 to 70

Provan et al. (2019) Blood Advances

Future ITP therapies

Intervention /Treatment	Mechanism	Phase	Condition/ Disease	Route of administration	Identifier
SKI-O-703	Syk inh	2	Persistent and chronic ITP	Oral	NCT04056195
HMPL-523	Syk inh	1	ITP	Oral	NCT03951623
Orelabrutinib	BTK inh	2	Refractory ITP	Oral	NCT05020288
Rilzabrutinib (PRN1008)	BTK inh	3	Persistent or chronic ITP	Oral	NCT04562766
Bortezomib	Proteasome inh	2	ITP	IV	NCT03013114
Bortezomib+R vs. RTX	Proteasome inh Anti-CD20	3	Newly diagnosed ITP	SC vs. IV	NCT03443570
Decitabine	Demethylation	3	Newly diagnosed ITP	IVGTT	NCT03252457
Oseltamivir	Sialidase inh	3	ITP	Oral	NCT03520049
Efgartigimod	FcRn-targeting therapeutic	3	ITP	IV	NCT04188379 NCT04225156
Efgartigimod	FcRn-targeting therapeutic	3	ITP	SC	NCT04812925 NCT04687072
Rozanolixizumab	FcRn-targeting therapeutic	3	Persistent or chronic ITP	SC	NCT04596995 NCT04224688 NCT04200456
HBM9161	FcRn-targeting therapeutic	2/3	ITP	IV	NCT04428255
GL-2045	FcR–targeting biologics	1	ITP	SC IV	NCT03275740
Atorvastatin	Improve endothelial function	2/3	Newly diagnosed ITP	Oral	NCT03692754
Chidamide	Histone deacetylase inh	2	Refractory ITP	Oral	NCT03838354
UC-MSCs	Improving immune tolerance	N/A	Refractory ITP	–	NCT04014166

inh, inhibitor; IV, intravenous injection; RTX, rituximab; SC, subcutaneous injection; IVGTT, intravenously guttae; UC-MSCs, human umbilical cord-derived mesenchymal stem cells; N/A, not available.

Intervention /Treatment	Mechanism	Phase	Condition/ Disease	N	Major results	Adverse events	Identifier	Ref
Fostamatinib	Syk inh	2	Chronic refractory ITP	16	a. R: 75% b. SR: 50%	a. 3 patients ended the study for toxicity b. GI toxicity was most common	NCT00706342	Podolanczuk 2008 (30)
Fostamatinib	Syk inh	3	Persistent/ chronic ITP	150	a. Stable response: 18% b. OR: 43% c. Median time to response: 15 d d. Response within 8 w: 83%	Diarrhea 31% Hypertension 28% Nausea 19% Dizziness 11% ALT increase 11%	NCT02076399 NCT02076412	Bussel2018 (31)
Rilzabrutinib (PRN1008)	BTK inh	1/2	Relapsed ITP	60	a. R: 40%	Grade 1 or 2 and transient.	NCT03395210	Kuter2022 (32)
Decitabine	Demethylation	2	Refractory ITP	45	a. CR: 17.78% b. PR: 33.33% c. SR: 44.44%	AE: 28.89%	NCT01568333	Zhou2019 (33)
Oseltamivir	Sialidase inh	2	Newly diagnosed ITP	96	a. R dex+ose vs. dex 86% vs. 66% b. SR dex+ose vs. dex 53% vs. 30%	Fatigue 12% vs. 17% GI reactions 19% vs. 6% Insomnia 16% vs. 9% Anxiety 12% vs. 6%	NCT01965626	Sun2021 (34)
Rozanolixizumab	FcRn-targeting therapeutic	2	ITP	66	R: 50%	Headache 22.7% Vomiting 7.6% Diarrhea 6.1%	NCT02718716	Robak2020 (35)

Efgartigimod	FcRn-targeting therapeutic	2	ITP	38	a. Platelet count $\geq 50 \times 10^9$/L on at least two occasions: 46.2% b. Platelet count $\geq 50 \times 10^9$/L for a cumulative duration of more than 10 d: 38.5%	No dose-related safety observations	NCT03102593	Newland2019 (36)
Sirolimus	mTOR inh	1/2	Chronic and/or refractory autoimmune cytopenia	30	a. 6% patients with multilineage cytopenias secondary to CVID, ES, or SLE achieved CR b. All children with ALPS achieved CR	Mucositis 33.33%	NCT00392951	Bride2016 (37)
PRTX-100	SpA	1/2	Persistent/ chronic ITP	6	Platelet count elevation was observed on Day 3 and remained elevated for 2-3 w	Acceptable safety profile	NCT02566603 NCT02401061	Bussel2016 (38)
Rozrolimupab (Sym001)	Recombinant anti-D monoclonal antibodies	2	RhD^+ ITP	61	a. R after 72 hours: 62% b. R within 24 hours: 23% c. Median duration: 14d	Headache 20%	NCT00718692	Robak2012 (39)

N, patient number; inh, inhibitor; R, response; SR, sustained response; GI, gastrointestinal; OR, overall response; d, day; w, week; ALT, alanine transaminase; CR, complete response; PR, partial response; AE, adverse event; dex, dexamethasone; ose, oseltamivir; CVID, common variable immunodeficiency; ES, Evans syndrome; SLE, systemic lupus erythematosus; ALPS, autoimmune lymphoproliferative syndrome; SpA, staphylococcus protein A.

New & future therapies for R/R wAIHA

Treatment	Dose schedule	Response rate, %	Comments
Parsaclisib (PI3Ki)	1 to 2.5 mg/d	n/a	Open-label phase 2 study
Pegcetacoplan (C3i)	270 mg-360 mg/d	40-50	Open-label phase 2 study
Orilanolimab (FcRni)	n/a	n/a	Open-label phase 1b/2 study: phase 2 randomized, double-blind, placebo-controlled study
Nipocalimab (FcRni)	IV infusion every 2 or 4 wk	n/a	Phase 2 randomized, double-blind, placebo-controlled study
Fostamatinib (SyKi)	100 to 150 mg, twice daily	44 (time to response 2-30 wk)	Open-label phase 2 study; phase 3 randomized, double-blind, placebo-controlled study
Bortezomib (proteasome-i)	1.3 mg/m^2 subcutaneous ×2/wk for 2 wk	n/a	Open-label phase 2 study in association with anti-CD20 MoAb
Interleukin-2	Cycle 1: 1.5 million IU per day for 9 wk; further cycles: 3 million IU per day for 16 wk	n/a	Open-label phase 1/2 study
Daratumumab (anti-CD38 MoAb)	16 mg/kg week IV	n/a	Case reports in AIHA secondary to BM transplant
Sirolimus (mTORi)	2 mg/m^2 (adjusted to achieve a steady state of 5–10 ng/mL)	100	Cases reports of AIHA secondary to combined liver, small bowel, and pancreas transplant
Abatacept (CTLA-4 Ig)	10 mg/kg monthly	100	Case reports in AIHA secondary to BM transplant
Imlifidase (ADCCi)	n/a	n/a	Studied in IgG-mediated diseases and transplant rejection

Rituximab + another agent

Author	Treatment	Number of patients	Median age, years (range)	F:M	ITP phase	ORR	6 months	12 months	24 months
Zhou 2015[56,73]	Rituximab 100 mg weekly for 4 weeks + rhTPO 300 μg/kg/day for 14 days	77	42 (13-82)	65%:35%	Median ITP duration 12.5 months (3-72)	93% (50% CR) *	67.2%	24.6%	NA
	Rituximab 100 mg weekly for 4 weeks	38	42.5 (12-68)	66%:34%	Median ITP duration 11 months (3-65)	93% (50% CR) *	55.6%	18.5%	NA
Choi 2015[71]	Rituximab 100 mg weekly for 4 weeks + dexa 40 mg days 1-4 + cyclosporine 2.5-3 mg/kg/day (days 1-28)	20	NA	55%:45%	ND or Persistent ITP: 7; Chronic ITP: 13	NA	60%*	92%	76%
Li 2015[72]	Rituximab 100 mg weekly for 4 weeks + rhTPO 300 μg/kg/day for 14 days	14	52 (18-76)	93%:7%	Unknown	93% (50% CR) *	71% (40% CR)	NA	NA
Gomez-Almaguer 2017[74]	Eltrombopag 50 mg/day, days 1-28 + dexa 40 mg days 1-4 + rituximab 100 mg weekly for 4 weeks	13	40 (16-61)	62%:38%	ND	100% (92% CR) *	NA	80%	70%

F:M: female to male ratio; ITP: immune thrombocytopenia; ORR: overall response rate; rhTPO: recombinant human thrombopoietin; CR: complete response; NA: not available; dexa: dexamethasone; ND: newly diagnosed. *Response rates calculated considering as denominator only patients who responded to rituximab. °Response rates calculated considering as denominator all treated patients. ^response = platelet count ≥30x10⁹/L; °response = platelet count ≥50x10⁹/L.

= Combination Rituximab with other agents work, is it necessary?

CLL-associated wAIHA: 1st line

Prednisone: 1 mg/kg per day for 3-4 wk	First	84-90	Response rates comparable with those reported for primary wAIHA, but relapse risk is higher
Dexamethasone: 40 mg/d for 4 d, 2-6 cycles every 2-4 wk	First	100	Response rates comparable with those reported for primary wAIHA, but relapse risk is higher
Rituximab: 375 mg/m^2 weekly for 4 wk	Second or >	72-80	Single agent in patients with indolent CLL; if ineffective, CLL therapy should be pursued

- treat first line similar to non-CLL related wAIHA unless CLL directed therapy required

Rituximab + Dexamethasone studies

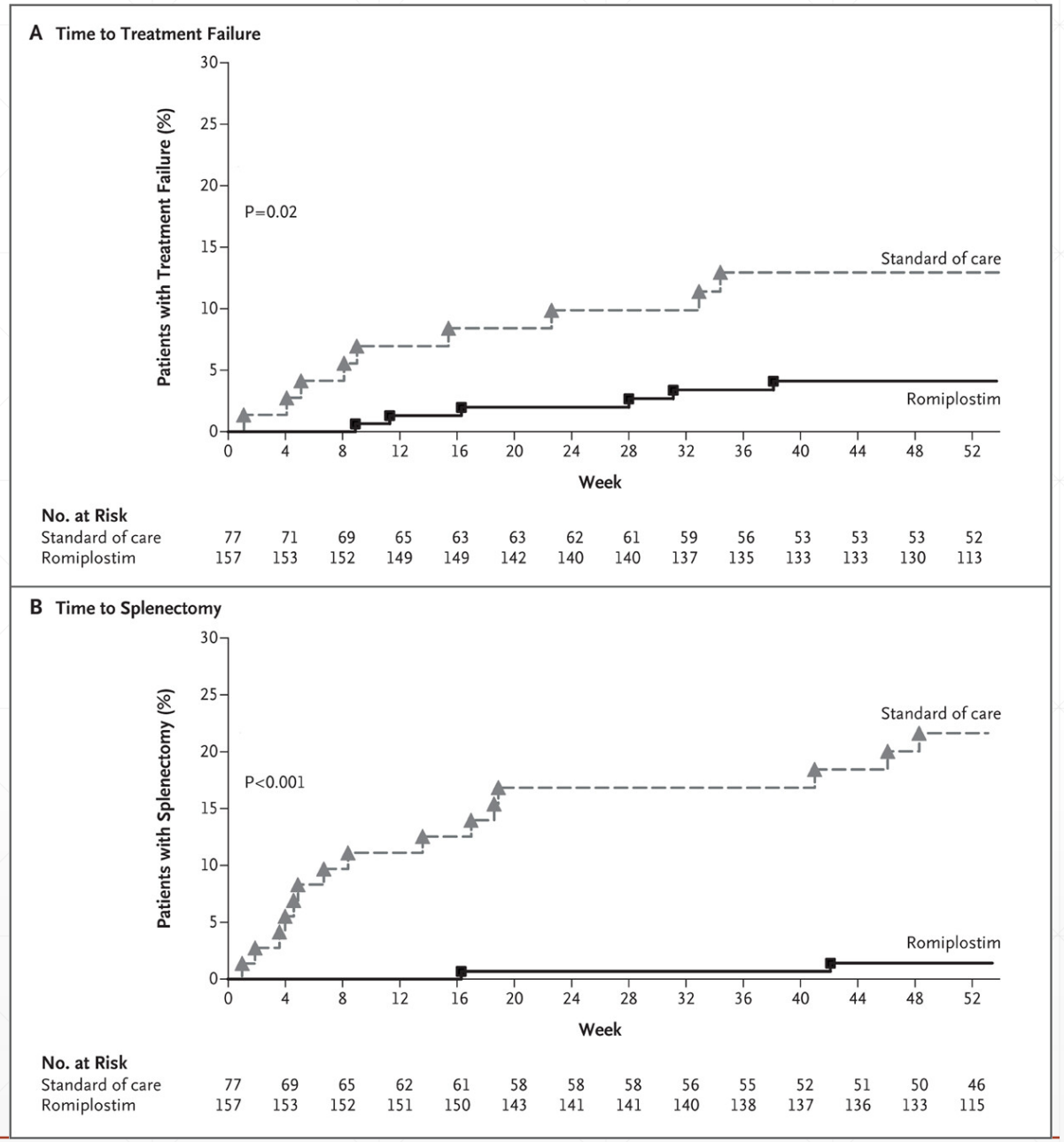
Author	Treatment	Number of patients	Median age, years (range)	F:M	ITP phase	Early response	6 months	12 months	24 months	36 months	Last follow-up
Zaja 2010[49]	375 mg/m² x 4 weekly + 1 cycle dexa (40 mg/day for 4 days)	49	49 (33-65)	55%:45%	Previously untreated	37%° at week 4	63%	50%	47%	43%	43% 30-months estimated probability of duration of response
Gudbrandsdottir 2013[50]	375 mg/m² x 4 weekly + up to 6 cycles dexa (40 mg/day for 4 days every 1 to 4 weeks)	62	51 (36-63)	58%:42%	ND	NA	57%°	53%	NA	NA	NA
Bussel 2014[54]	375 mg/m² x 4 weekly + 3 cycles dexa (28 mg/m²/day for 4 days)	41	36 (18-64)	53%:46%	Median ITP duration: 16 (1-286) months	88% at week 8°	82%	65%	58%	50%	47% estimated sustained response at 64 months FU
Chapin 2016[55]	375 mg/m² x 4 weekly + 3 cycles dexa (28 mg/m²/day for 4 days)	49	37	53%:45%	Duration of ITP: range 0 – 258 months	NA	NA	NA	NA	NA	33.3% sustained response at 72 months FU°

F:M: female to male ratio; ITP: immune thrombocytopenia; dexa: dexamethasone; ND: newly diagnosed; NA: not available; FU: follow-up; yrs: years. Response rates are calculated using as denominator all the patients treated with rituximab. °response = platelet count ≥50x10⁹/L

= Combination Rituximab with steroids (i.e Dexamethasone) better than alone

s/c TPO-RA: Romiplostim

- open label, randomized multicenter trial of ITP patients without splenectomy receiving standard of care (n=77) vs weekly sc romiplostim (n=157)
- primary endpoint treatment failure or splenectomy, secondary plt >50
- higher response seen with romiplostim (2.3x) than standard of care (p<0.001) with 9% vs 36% needing splenectomy rescue
- less bleeding but not severe bleeding
- most common SE similar to eltrombopeg, headache, fatigue, thrombotic events (4%), bleeding (52%)



Kuter et al. (2010) NEJM