Chronic Immune Thrombocytopenia: *Incorporating the New, Optimizing the Old, and Looking to the Future*

DONALD MOORE, PHARMD, BCPS, BCOP, DPLA, FCCP
LEVINE CANCER INSTITUTE, ATRIUM HEALTH, CHARLOTTE, NC

Disclosures

I have nothing to disclose. I will be discussing off-label indications.

Objectives

- Review the clinical burden, pathophysiology, and prevalence of immune thrombocytopenia (ITP)
- Summarize guideline recommendations for the management of chronic ITP
- Analyze the role of newer therapies in the treatment of chronic ITP
- Explore therapeutic agents currently in the drug development pipeline for the treatment of chronic ITP

Common Questions I Receive on ITP

How do I use IVIg in ITP?
How do I choose between or sequence rituximab and TPO agonists?
Do I ever retreat with rituximab?
How do I dose romiplostim in acute refractory ITP?
Do I ever discontinue TPO agonists in responders?
How do I choose between TPO agonists?
Can we sequence and/or switch between TPO agonists?
How do I use fostamatinib to treat ITP?
How do I manage fostamatinib-related adverse events?

Background

- Immune thrombocytopenia (ITP) is an acquired autoimmune bleeding disorder characterized by the destruction of platelets and megakaryocytes
- Incidence of 2-5 cases per 100,000 per year in general population
- Multimodal incidence with 3 unique age peaks
  - Childhood (<18 years)
  - Young adults (18-39)
  - Elderly (>60 years)
- Chronic ITP prevalence ranges from 5.6-20 cases per 100,000 persons
  - Prevalence of chronic ITP increases with advancing age

Cooper N, et al. *N Engl J Med.* 2019; 381(10):945-955.; Neunert C, et al. *Blood Adv.* 2019; 3(23):3829-3866.

Primary vs. Secondary ITP

- ITP can occur either as a primary or secondary disorder
  - Primary ITP: no clear underlying cause
  - Secondary ITP: induced by other disease or treatment
- Causes of secondary ITP
  - Autoimmune disorders
  - Lymphoproliferative disorders (ex. Chronic lymphocytic leukemia)
  - Medications (ex. Immune checkpoint inhibitors)
  - Infectious complications (ex. *Helicobacter pylori* infections)
  - Transfusion

Swinkels M, et al. *Front Immunol.* 2018; 9:880.

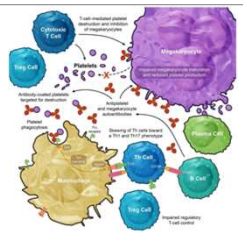
Pathophysiology

Production of antiplatelet autoantibodies

Immune-mediated platelet destruction via CD8+ T cell-induced autoimmune response

Macrophages phagocytose platelets

Impaired platelet production



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ITP Diagnosis

Diagnosis of ITP
- Platelet count <100x10^9/L
- Other causes of thrombocytopenia have been ruled out

ITP is a diagnosis of exclusion, ruling out other causes of isolated thrombocytopenia
- Differential diagnosis: alcohol abuse, drugs, infection, liver disease, primary hematologic disorder
- Other causes of thrombocytopenia have been ruled out

Patient history, physical examination, blood count, peripheral blood smear
- Bone marrow biopsy examination: may be needed if patients have systemic symptoms, abnormal signs, or suspicion of different diagnosis

Provan D, et al. *Blood Adv.* 2019; 3(22):3780-3817.

Primary ITP Classifications

Newly Diagnosed
- Duration of **less than 3 months**

Persistent
- Duration of **3-12 months**

Chronic
- Duration **>12 months**

Corticosteroid-dependent
- Ongoing need/frequent courses of steroids to maintain platelet count of at least 30x10^9/L and/or to avoid bleeding

Neunert C, et al. *Blood Adv.* 2019; 3(23):3829-3866.

Impact of Chronic ITP

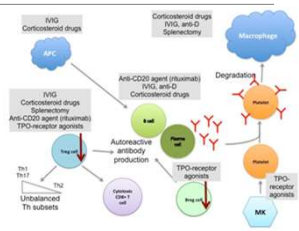
ITP can have significant impact on health-related quality of life (HRQoL)
- Restrictions in activities due to increased bleeding risk
- Anxiety due to bleeding risk
- Burden of treatment and monitoring

ITP-induced fatigue
- One of the most difficult to treat symptoms in ITP
- Reported in 39%-59% of adults with ITP
- Often goes underrecognized

Provan D, et al. *Blood Adv.* 2019; 3(22):3780-3817.

ITP Therapies

- First line therapies
  - Corticosteroids
  - Immune globulin
- Subsequent therapies
  - Rituximab
  - Thrombopoietin receptor agonists (TPO-RA)
  - Fostamatinib
  - Splenectomy
- Miscellaneous therapies
  - Azathioprine, cyclophosphamide, cyclosporine, danazol, dapsone, mycophenolate mofetil, vincristine



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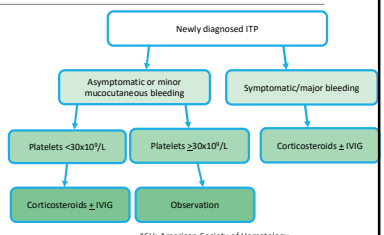
Newly Diagnosed ITP Algorithm (ASH)

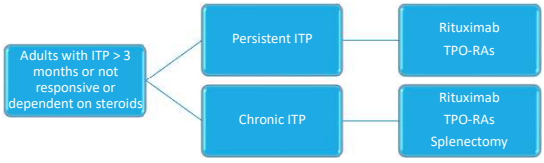
- Corticosteroids
  - Dexamethasone 40 mg daily x4 days
  - Prednisone 0.5-2 mg/kg daily until response, then taper
- IV Immune globulin (IVIG)
  - 1 gram/kg IV x2 days
  - Rapid response, but often not durable
  - Mostly utilized for patients with contraindications to steroids or as adjunct to steroids for when rapid response needed



Neunert C, et al. *Blood Adv.* 2019; 3(23):3829-3866.

ASH: American Society of Hematology

Persistent and Chronic ITP



Neunert C, et al. *Blood Adv.* 2019; 3(23):3829-3866.

How to Choose?

- Assess patient values and goals of treatment
  - Durable response → TPO agonist or splenectomy
  - Avoid long-term medication → rituximab or splenectomy
  - Avoid surgery → rituximab or TPO agonist
- Comorbidities
- Adverse event profiles of ITP therapies
- Goal-directed therapy
- Drug-drug interactions
- Adherence

Neunert C, et al. *Blood Adv.* 2019; 3(23):3829-3866.

Persistent and Chronic ITP

	Rituximab	Splenectomy	TPO Agonists
Time to response	7-56 days	1-24 days	7-14 days
Early response rate	50-60%	85%	70-80%
Durable response rate	20% off treatment	60-70%	70-80% on treatment
Remission	20%	60-70%	30-40%

Neunert C, et al. *Blood Adv.* 2019; 3(23):3829-3866.

Rituximab in ITP

Mechanism of Action	Anti-CD20 monoclonal antibody, depletes B-cells thereby decreasing antiplatelet autoantibodies
Dosing	375 mg/m$_2$ IV weekly x4 weeks Alternative dosing: ○ 1000 mg IV every other week x2 doses ○ 100 mg IV weekly x4 weeks
Place in Therapy	Subsequent therapy for persistent/chronic ITP May be preferred if cannot afford TPO-RA, want to avoid long-term treatment/surgery
Adverse Events	Infusion-related reactions, HBV reactivation
Pearls	○ Screen for HBV prior to therapy initiation ○ Retreatment with rituximab may produce response rates in ~80% of patients ○ Delayed onset of action compared to other ITP therapies (~1-8 weeks)

Lucchini E, et al. *Haematologica.* 2019; 104(6):1124-1135.

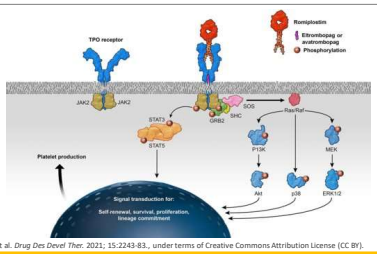
Thrombopoietin Receptor Agonists

Three thrombopoietin receptor agonists (TPO-RAs) approved by FDA for ITP

- Romiplostim – approved 2008
  - ITP with an insufficient response to corticosteroids, immune globulins, or splenectomy
- Eltrombopag – approved 2008
  - Chronic ITP with an insufficient response to corticosteroids, immune globulins, or splenectomy
- Avatrombopag – approved 2018
  - Chronic ITP with an insufficient response to a previous treatment

Nplate. Prescribing Information. Amgen Inc, 2021.; Promacta. Prescribing Information. Novartis, 2021.; Doptelet. Prescribing Information. AkaRx, 2021.

TPO- RAs Mechanism of Action



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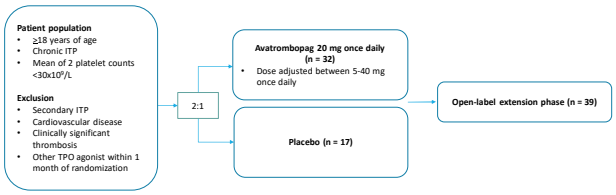
Avatrombopag Phase III trial

6-month, multicenter, randomized, double-blind, placebo-controlled phase III trial



Jurczak W, et al. *Br J Haematol.* 2018;183:479-490.

Avatrombopag Efficacy

End point	Avatrombopag (n = 32)	Placebo (n = 17)	P
Cumulative number of weeks of platelet response (≥50x10⁹/L)	12.4 weeks	0.0 weeks	<0.0001
Platelet response at day 8	21 (65.6%)	0 (0%)	<0.0001
Reduced use of concomitant ITP medication from baseline	5/15 (33.3%)	0/7 (0%)	-
Durable platelet response	11 (34.4%)	0 (0%)	0.009

Jurczak W, et al. *Br J Haematol.* 2018;183:479-490.

Differences Between TPO-RAs

	Avatrombopag	Eltrombopag	Romiplostim
Route of administration	Oral	Oral	Subcutaneous
Dosing	20-40 mg po daily or weekly	12.5-75 mg po daily	1-10 mcg/kg weekly
TPO receptor site of action	Transmembrane domain	Transmembrane domain	Extracellular domain
Time to response	~ 65% response at day 8	Median 12 days	1-2 weeks
Response rates	65%	~ 60-90%	~ 70-90%
Food Considerations	Administer with food	Taken on empty stomach Calcium-rich foods decrease absorption	None

Nplate. Prescribing Information. Amgen Inc, 2021.; Promacta. Prescribing Information. Novartis, 2021.; Doptelet. Prescribing Information. AkaRx, 2021.

Safety Differences Between TPO-RAs

	Avatrombopag	Eltrombopag	Romiplostim
Common adverse events	Headache, fatigue, contusion, epistaxis, upper respiratory tract infection, arthralgia, gingival bleeding, petechiae, nasopharyngitis	Anemia, nausea, pyrexia, alanine aminotransferase increased, cough, fatigue, headache, diarrhea	Arthralgia, dizziness, insomnia, myalgia, pain in extremity, abdominal pain, shoulder pain, dyspepsia, paresthesia
Warnings and precautions	• Thromboembolism	• Thromboembolism • Progression of MDS to AML • Hepatotoxicity	• Thromboembolism • Progression of MDS to AML • Loss of response due to development of neutralizing antibodies
Black box warnings	N/A	• Hepatotoxicity • Hepatic decompensation in patients with hepatitis C	N/A

Nplate. Prescribing Information. Amgen Inc, 2021.; Promacta. Prescribing Information. Novartis, 2021.; Doptelet. Prescribing Information. AkaRx, 2021.

Avatrombopag: Me-Too TPO-RA or Not?

Easier administration?
- Oral therapy – no injections like romiplostim
- Doses taken with meals – no food restrictions/need for low calcium meal like eltrombopag
- Dosing titrations use one oral formulation size – eltrombopag dose titrations may require additional prescriptions

Mechanism of action differences
- Transmembrane domain of TPO receptor – different than romiplostim; may be able to sequence agents?
  - Sequencing data with romiplostim/eltrombopag, but lacking with avatrombopag

Differences in safety
- May be preferred oral TPO-RA in patients with liver disease
  - Also has FDA approval for periprocedural thrombocytopenia in chronic liver disease

Tran TB, et al. *J Pharm Pract.* 2022; Sep 15;8971900221125827.

TPO Agonist Dosing

	Avatrombopag	Eltrombopag	Romiplostim
Initial Dose	20 mg once daily	50 mg once daily	1 mcg/kg/week
<50x10⁹/L	Increase one dose level; recheck platelets in 2 weeks*	Increase daily dose by 25 mg (if taking 12.5 mg once daily, increase to 25 mg once daily prior to increasing by 25 mg daily)	Increase weekly dose by 1 mcg/kg
50-200x10⁹/L	Maintain same dose	Maintain same dose	Maintain same dose
200x10⁹/L to 400x10⁹/L	Decrease one dose level; recheck platelets in 2 weeks	Reduce daily dose by 25 mg (if taking 25 mg once daily, decrease dose to 12.5 mg once daily); reassess in 2 weeks	Reduce weekly dose by 1 mcg/kg
>400x10⁹/L	Hold avatrombopag, check platelets twice per week; restart at one dose level lower once platelets <150x109/L	Hold therapy, check platelets twice weekly; restart when platelets <150x109/L; reduce daily dose by 25 mg (if taking 25 mg daily, reduce to 12.5 mg daily)	Hold therapy, check platelets once weekly; when platelet count <200x109/L, resume with weekly dose reduced by 1 mcg/kg

Nplate. Prescribing Information. Amgen Inc, 2021.; Promacta. Prescribing Information. Novartis, 2021.; Doptelet. Prescribing Information. AkaRx, 2021.

Romiplostim in Acute Refractory ITP

Is there an optimal starting dose of romiplostim? Especially in acute settings?

- Initial dose in labeling is 1 mcg/kg/week, but in phase III trial started at **3 mcg/kg/week**

DasGupta et al (2018)	Roumier et al (2021)
Single-center retrospective study, hospitalized patients with refractory ITP (n=18)	Multicenter, retrospective study in France, primary refractory acute ITP and severe bleeding (n=30)
Cohort 1: initial dosing 1 mcg/kg (n=4) Cohort 2: ≥2 mcg/kg (median 4.5 mcg/kg) (n=14)	Initial dose of 10 mcg/kg (n=26) First dose 5-8 mcg/kg, then 10 mcg/kg second dose (n=4)
Cohort 2 compared to cohort 1: • Time to platelets ≥10x10^9/L (2 vs. 4.5 days) • Platelets ≥30x10^9/L (42.9% vs. 25%) • Platelets ≥50x10^9/L (28.6% vs. 25%) • Clinically relevant nonmajor bleeding (28.6% vs. 75%) • Major bleeding (14.3% vs. 0%) • Length of stay (13.5 vs. 20 days)	Peak platelet response in first month: 531x10^9/L Platelets ≥500x10^9/L (n=16, 53%) Platelets ≥1000x10^9/L (n=9, 30%) → empiric aspirin given Major thrombotic events occurred in 2 patients (6.7%)

Kuter DJ, et al. *N Engl J Med.* 2010; 363:1889-99.; DasGupta RK, et al. *J Oncol Pharm Pract.* 2019; 25(3):567-576.; Roumier et al. *Am J Hematol.* 2021; 96:E44-E47.

TPO Agonist Pearls

- Those who achieve an initial response, >90% maintain that response at 5 years
- Rebound thrombocytopenia on TPO agonist cessation
  - Up to 30% of patients may achieve and maintain a durable response when TPO agonist tapered and withdrawn
  - Patients to be considered for tapering: normalized platelets (≥150x10^9/L), no history of major bleeding, no antiplatelet/anticoagulation, no therapy intensification for past 3-6 months
- Switching from one TPO agonist to another as sequential therapy
  - Effective in up to 50% of patients, reducing platelet fluctuation and adverse events ⍰ Limited to retrospective observational studies

Connell NT, Berliner N. *Blood.* 2019; 2027-2030.; Cooper N, Ghanima W. *N Engl J Med.* 2019; 381:945-955.; Cuker A, et al. *Res Pract Thromb Haemost.* 2020; 5(1):69-80.

Audience Question 1

Which of the following is a common clinical manifestation that can occur in chronic immune thrombocytopenia (ITP) that is often underrecognized, difficult to control, and impacts health-related quality of life?

A. Fatigue

B. Night sweats

C. Neuropathy

D. Early satiety

Audience Question 2

According to the American Society of Hematology 2019 ITP guidelines, thrombopoietin receptor agonists should be considered as a therapeutic option when patients have which of the following preferences?

A. Durable response

B. Avoid long-term therapy

C. Prefer surgery over medication

D. Brief/time limited therapy

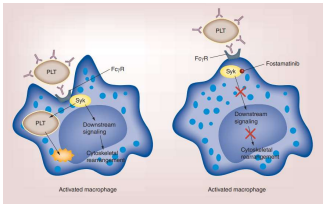
Fostamatinib Mechanism of Action

Spleen tyrosine kinase (Syk)

- Mediates downstream signal transduction and activation of immune receptor signaling in macrophages
  - Accelerated destruction of platelets in ITP through FcR activation

Fostamatinib – prodrug

- R406: active metabolite
- R406-mediated Syk inhibition reduces accelerated platelet destruction



FIT1 and FIT2: Fostamatinib vs. Placebo

FIT1 and FIT2: identically designed, parallel, multicenter, randomized, double-blind, placebo-controlled Phase III trials

Patient Population
- Primary ITP for at least 3 months
- Mean platelet count <30x10^9/L on at least 3 measurements within 3 months of study enrollment
- At least 1 prior therapy

Exclusion
- Secondary ITP
- Cardiovascular event
- Coagulopathy

2:1

Fostamatinib (n=101)
- 100 mg twice daily for 24 weeks
- Could be increased to 150 mg twice daily after at least 4 weeks

Placebo (n=49)

Primary Endpoint

Stable response: platelets ≥ 50x10^9/L on 4/6 visits during weeks 14-24

Secondary Endpoints

If baseline <15x10^9/L : achievement of platelets ≥ 30x10^9/L at least 20x10^9/L above baseline at weeks 12 and 24

Overall response: platelets ≥ 50x10^9/L within 12 weeks without rescue medication

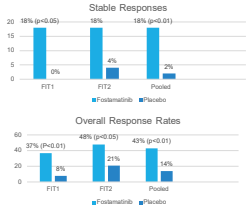
Bussel J, et al. *Am J Hematol.* 2018;93:921-30.

FIT 1/2 Baseline Characteristics

	Fostamatinib (n = 101)	Placebo (n = 49)
Age, median (range)	54 (20-88)	53 (20-78)
ITP classification		
• Persistent	6 (6%)	4 (8%)
• Chronic	95 (95%)	45 (92%)
Median ITP duration (range), years	8.7 (0.3-53)	7.8 (0.4-45)
Median number of prior ITP treatments (range)	3 (1-13)	3 (1-10)
Prior treatments		
• Corticosteroids	94 (93%)	47 (96%)
• IVIG or IV anti-D	52 (51%)	27 (55%)
• TPO agonist	47 (47%)	25 (51%)
• Rituximab	34 (34%)	14 (29%)
Baseline platelet count <15 x 10^9/L	54 (54%)	28 (57%)

Bussel J, et al. *Am J Hematol.* 2018;93:921-30.

FIT1/2 Results



- Median time to response: 15 days
- Stable response: 18% vs. 2%
- Overall response: 43% vs. 14%
- < 15x10^9/L at baseline
  - Platelets ≥ 30x10^9/L at least 20 x10^9/L above baseline
    - Week 12: 21% vs. 5%
    - Week 24: 15% vs. 0%
- Prior TPO: 17% stable response
  - No observed response differences based on prior treatments

Graphs recreated from Bussel J, et al. *Am J Hematol.* 2018;93:921-30.

Fostamatinib Safety

Adverse Event	Fostamatinib				Placebo			
	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
Any Adverse Event	32	35	16	83	42	19	15	75
Diarrhea	21	10	1	31	13	2	0	15
Nausea	16	3	0	19	8	0	0	8
Hypertension	17	9	2	28	10	0	2	13
ALT increase	5	6	0	11	0	0	0	0
AST increase	5	4	0	9	0	0	0	0
Neutropenia	3	2	1	6	2	0	0	2

*All numbers expressed as percentages.

Bussel JB, et al. *Am J Hematol.* 2019;94:546-553.

Fostamatinib Long-Term Data

FIT3: long-term, multicenter, open-label extension study
- Follow-on study for patients who had been enrolled in FIT1/2 (n=146)

Efficacy endpoints
- 18% of patients achieved a stable response
- 44% of patients achieved an overall response
- Median treatment duration 6.7 months

Safety
- No new safety outcomes
- No increase in incidence of adverse events observed at up to 31 months of treatment

Bussel JB, et al. *Am J Hematol.* 2019;94:546-553.

Second-Line Fostamatinib?

Post-hoc analysis of FIT trials compared patients receiving fostamatinib as second-line versus third-or-later line of therapy
- Platelet response ≥ 50x10^9/L: 25/32 (78%) second-line vs. 54/113 (48%) ≥ third line
- Less frequent bleeding events second-line (28%) vs. ≥ third line (45%)

Responses were durable between both groups

Safety profile similar between both groups

Boccia R, et al. *Br J Haematol.* 2020; 190:933-938.

Fostamatinib Place in Therapy

Precise place in therapy remains unclear
- Has demonstrated efficacy in patients who have been heavily pretreated
- However, low stable response rate (18%) → unlikely to replace rituximab and TPO agonists as subsequent/second-line therapies until there is comparative data
- Second-line fostamatinib appears to have better response rate than use in later lines
  - However, this may be natural history of disease and indicative of those patients who may be more difficult to treat
- Low stable response rate could be indicative of refractory ITP that is inherently more difficult to treat
  - Difficult to compare response rates of rituximab and TPO agonists as they were evaluated when there were less treatment options

Connell NT, et al. *Blood.* 2019;2027-2030.

Fostamatinib Safety Pearls

Hepatotoxicity
- Monitor liver function tests monthly
- May require interruption, dose reduction

Hypertension
- Mechanism: off-target inhibition of vascular endothelial growth factor
- Monitor blood pressure every 2 weeks until stable, then monthly
- Manage with standard antihypertensives

Diarrhea
- Give supportive care including hydration, dietary changes, antidiarrheals
- Hold for grade ≥3 diarrhea

Neutropenia
- Interrupt and/or dose reduce for absolute neutrophil count <1000

Embryo-fetal toxicity
- Counsel patients of potential risk to a fetus and to use effective contraception

Moore DC, et al. *Am J Health Syst Pharm.* 2019;76(11):789-794

Fostamatinib and Drug Interactions

Fostamatinib's active metabolite R406 is a CYP3A4 substrate

Strong CYP3A4 inhibitors
- Can increase exposure to R406
- Patients should be monitored closely for AEs and reduce fostamatinib dose in response to toxicity

Strong CYP3A4 inducers
- Can reduce exposure to R406 → avoid concomitant use with fostamatinib

Moore DC, et al. *Am J Health Syst Pharm.* 2019;76(11):789-794

Pros and Cons Between cITP Therapies

	Pros	Cons
Rituximab	• Shortest course of treatment	• Lower remission rates than splenectomy
Splenectomy	• Highest remission rates • No long-term treatment if successful	• Surgery is permanent • Operative complications
TPO-RA	• High response rates	• Chronic, indefinite therapy • Expensive • Monitoring of response
Fostamatinib	• Efficacy in heavily pretreated patients	• Chronic, indefinite therapy • Expensive

Cuker A, George JN. *Mayo Clinic Proc.* 2019; 94(11):2161-2163.; Connell NT, Berliner N. *Blood.* 2019; 2027-2030.

Audience Question 3

Which of the following best describes the differences in outcomes when using fostamatinib as second-line therapy compared to third-line-or-later therapy in the treatment of chronic ITP?

A. Lower adverse event rate

B. Lower platelet response rate

C. Higher platelet response rate

D. More bleeding events

Future Directions in ITP

RILZABRUTINIB AND SUTIMLIMAB

Bruton Tyrosine Kinase Inhibition in ITP

Bruton Tyrosine Kinase (BTK)
- Widely expressed in many cells and plays critical role in B-cell maturation, antibody production, and Fc-gamma receptor-mediated signaling pathways
- BTK inhibition has potential to inhibit Fc-gamma receptor-mediated macrophage function and reduce antibody production

Rilzabrutinib
- Oral, reversible, potent inhibitor of BTK; highly specific to BTK
- Covalently binds to BTK → contributes to long BTK-target engagement and durable inhibition with limited drug exposure
  - Clinical advantage and also can lead to rapid systemic clearance of drug → limit off-target toxic effects
  - High specificity to BTK may also limit off-target adverse events (i.e. atrial fibrillation)

Kuter DJ, et al. *N Engl J Med.* 2022; 386:1421-31.; Parish PC, et al. *Ann Hematol.* 2023; 102(1):237-238.

Rilzabrutinib

International, adaptive, open-label, dose-finding phase I-II clinical trial
- Intrapatient dose escalation with use of 3+3 design.
- Dose escalations allowed every 28 days based on investigator's judgement

200 mg once daily → 400 mg once daily → 300 mg twice daily → 400 mg twice daily

Primary efficacy endpoint: platelet response
- Defined as at least 2 consecutive platelet counts (separated by ≥5 days) of ≥50x10^9/L and an increase from baseline of at least 20x10^9/L without use of rescue medication

Primary safety endpoint: adverse events graded by Common Terminology Criteria for Adverse Events version 4.0

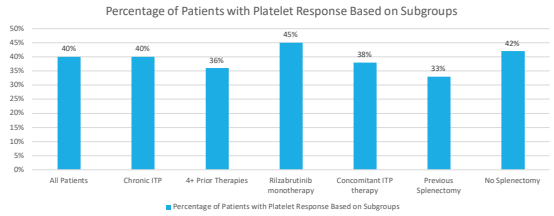
Kuter DJ, et al. *N Engl J Med.* 2022; 386:1421-31.

Rilzabrutinib

End Point	All patients (n=60)	Patients starting rilzabrutinib dose of 400 mg twice daily (n=45)
Primary endpoint: platelet response	40%	40%
Percent of weeks with platelet count ≥50x10^9/L • All patients • Patients with primary platelet response	 29% 65%	 28% 67%
Median number of weeks with platelet count ≥50x10^9/L • All patients • Patients with primary platelet response	 1 (0-26) 16 (2-26)	 0 (0-24) 21 (7-24)
Median number of days to first platelet count ≥50x10^9/L • All patients • Patients with primary platelet response	 11.5 (7-142) 10.5 (7-71)	 12.5 (8-142) 11.5 (8-71)

Kuter DJ, et al. *N Engl J Med.* 2022; 386:1421-31.

Platelet Response by Subgroup Analysis



Graph recreated from Kuter DJ, et al. *N Engl J Med.* 2022; 386:1421-31.

Rilzabrutinib Safety

Event	Adverse Events Due to Any Cause (n=60)				Treatment-Related Adverse Events (n=60)			
	Any Grade	Grade 1	Grade 2	Grade 3/4	Any Grade	Grade 1	Grade 2	Grade 3/4
Any adverse event	48 (80%)	43 (70%)	30 (50%)	8 (13%)	31 (52%)	27 (45%)	15 (25%)	0
Diarrhea	22 (37%)	19 (32%)	3 (5%)	0	19 (32%)	16 (27%)	3 (5%)	0
Nausea	21 (35%)	18 (30%)	3 (5%)	0	18 (30%)	16 (27%)	2 (3%)	0
Fatigue	12 (20%)	10 (17%)	2 (3%)	0	6 (10%)	5 (8%)	1 (2%)	0
Abdominal distension	6 (10%)	6 (10%)	0	0	4 (7%)	4 (7%)	0	0
Vomiting	4 (7%)	3 (5%)	1 (2%)	0	3 (5%)	2 (3%)	1 (2%)	0

Kuter DJ, et al. *N Engl J Med.* 2022; 386:1421-31.

Future Directions for Rilzabrutinib

Rilzabrutinib 400 mg twice daily dose chosen as dose for continued evaluation
- 40% platelet response rate
- Responses appear to be durable
- Most adverse events were mild-moderate (grade 1-2) in severity

LUNA3: randomized, double-blind phase III trial comparing rilzabrutinib to placebo in adults and adolescents (age ≥12 years) with persistent or chronic ITP

Kuter DJ, et al. *N Engl J Med.* 2022; 386:1421-31.

Complement Activation in ITP

Complement system – cascade of proteins mediating both innate and adaptive immunity
- Mechanism that may contribute to disease refractoriness in ITP is antigen antibody complex mediated activation of the complement system
- Approximately 50% of patients with ITP have autoantibodies that activate complement or have complement proteins detectable on the platelet surface
- Platelet destruction can be mediated by complement system

Sutimlimab: an anti-C1s antibody approved for the treatment of cold agglutinin disease
- Prevents activation of the classical complement pathway by inhibiting C1s in the C1 complex at the beginning of the complement cascade
- Hypothesized that C1 inhibition may increase platelet counts in patients with ITP

Broome C, et al. *Blood Adv.* 2023; 7(6):987-996.; Moore DC, Arnall JR. *Ann Pharmacother.* 2023; 57(8):970-977.

Sutimlimab

Open-label, single-arm, multicenter, 2-part phase I trial of sutimlimab in adult patients with ITP
- Part A: initial 11-dose treatment period (up to 21 weeks), followed by safety eval/washout (up to 9 weeks)
- Part B: extension period of 52 additional weeks of sutimlimab treatment

Inclusion
- Age ≥ 18 years with chronic ITP and lack of adequate platelet response to at least 2 prior therapies
- Platelet count ≤ $30x10^9$/L

Primary objective: evaluate safety and tolerability of sutimlimab in ITP
- Primary endpoint: incidence of treatment-related adverse events (TRAE), premature study terminations, clinical laboratory abnormalities of special interest (i.e. lupus panel)
- Efficacy objective: evaluate platelet response to sutimlimab by measuring change in platelet counts from baseline, during, and at the end of treatment in Parts A and B

Broome C, et al. *Blood Adv.* 2023; 7(6):987-996.

Sutimlimab

All patients received fixed biweekly fixed doses of sutimlimab via IV infusion
- 6500 mg if weight <75 kg
- 7500 mg if weight ≥75 kg

Patients requiring rescue therapy discontinued trial
- Platelet transfusion, IVIG, high-dose corticosteroids, anti-D immunoglobulin

Part A – n=12; Part B – n=7
- Median of 5.5 (range 2-10) prior treatments
- Median baseline platelet count $19x10^9$/L

Broome C, et al. *Blood Adv.* 2023; 7(6):987-996.

Safety & Efficacy

Safety
- Most frequently reported TRAE was fatigue
- Part A: 10/12 patients (83%) reported TRAEs
- Part B: 6/7 patients (86%) reported TRAEs
- No serious treatment-related infections were reported
- No patients discontinued due to a TRAE

Efficacy
- Mean platelet count increased to $54x10^9$/L by 24 hours after first dose of sutimlimab
- 5/12 patients (42%) achieved a platelet count response
  - All cases were durable (maintained ≥50% of visits)
- After washout period, platelet count returned to pretreatment levels

Broome C, et al. *Blood Adv.* 2023; 7(6):987-996.

Audience Question 4

Rilzabrutinib is a new therapeutic entity currently in development for chronic ITP. Which best describes the mechanism of action of rilzabrutinib?

A. Complement C1s inhibitor

B. Anti-CD20 small molecule inhibitor

C. Thrombopoietin receptor agonist

D. Bruton tyrosine kinase inhibitor

Conclusion

The treatment of chronic ITP should be based on a variety of factors including platelet counts, patient values and preferences, prior therapies, comorbidities, potential for drug–drug interactions, medication dosage forms, and patient's ability to adhere to medications and monitoring

Newer therapies in the treatment of ITP such as fostamatinib and avatrombopag add to the available therapeutic options and furthering of personalization of ITP-directed therapy for patients

Emerging therapies in the pipeline may provide new lines of therapy and different mechanism, adding to the armamentarium of ITP-directed pharmacotherapies