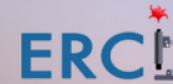




1ST
**European Research
Consortium on ITP Meeting**



INNOVATIONS IN IMMUNE THROMBOCYTOPENIA

Venice Monaco & Grand Canal Hotel

November 18-19, 2024

Francesco Rodeghiero

Hematology Project Foundation - Vicenza, Italy

**Updating definitions and outcome criteria in ITP:
an ERCI IWG initiative**

Disclosures of Francesco Rodeghiero

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda			X				
Argenx						X	



Chronology of Terminology and Guidelines in ITP

Consensus on Terminology
Definitions and Outcome criteria

Evolution of Guidelines and
new drugs availability

- 1996 George et al: 1st tentative to rank evidence
- 2001 **Rituximab** - Stasi et al, 2001
- 2008 **Romiplostim** - FDA August 2008
EMA November 2008
- Eltrombopag** - FDA November 2008
EMA December 2008
- 2009
- 2010 1st International Consensus Report - Provan et al, 2010
- 2011 ASH guidelines based on GRADE - Neunert et al, 2011

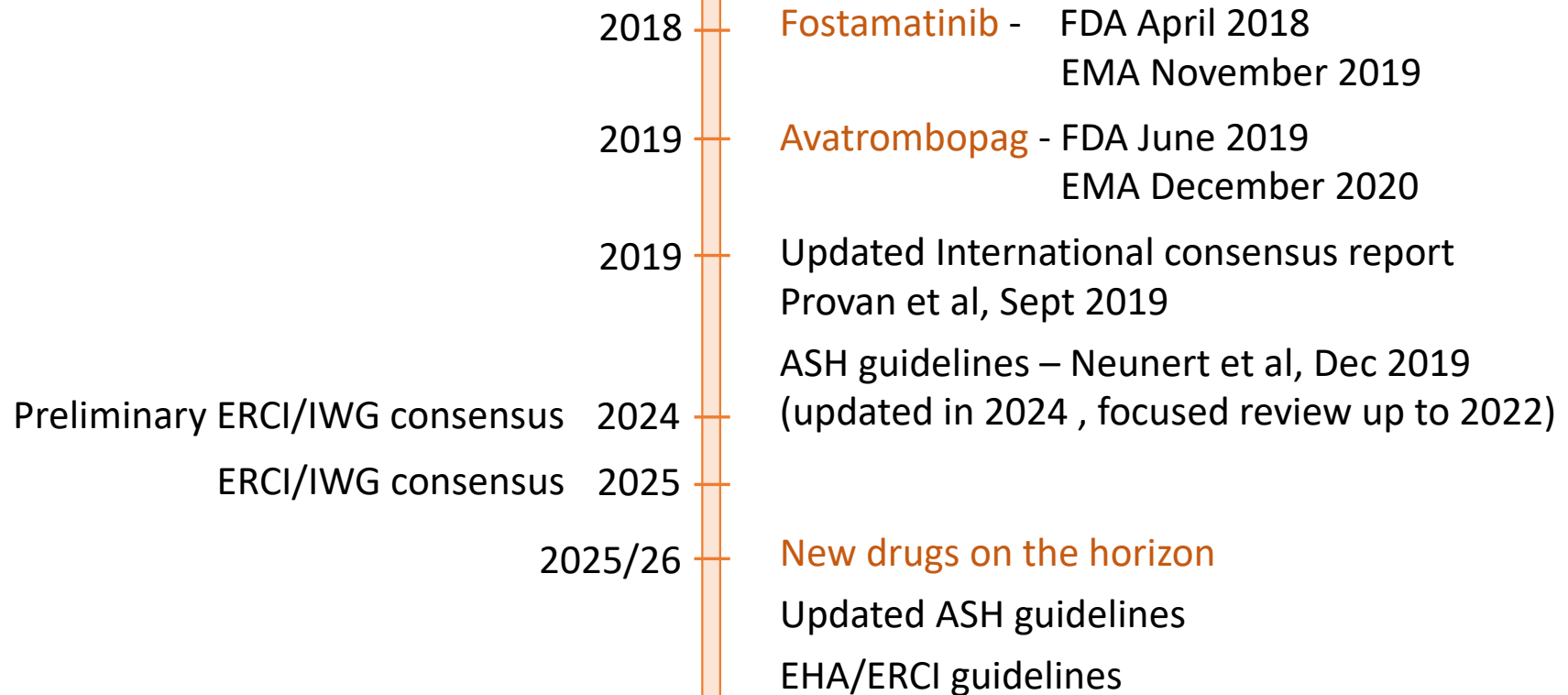
IWG consensus on terminology,
definitions and outcome criteria
Rodeghiero et al, 2009



Chronology of Terminology and Guidelines in ITP

Consensus on Terminology Definitions and Outcome criteria

Evolution of Guidelines and new drugs availability



Lack of impact of 2009 IWG consensus

■ Unfavorable timing:

- ✓ Efficacy of **romiplostim** in patients with *chronic* immune thrombocytopenic purpura: a double-blind randomised controlled trial. Kuter DJ, et al. *Lancet*. 2008

■ Emulation effect:

- ✓ **Eltrombopag** for management of *chronic* immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. Cheng G, et al. *Lancet*. 2011
- ✓ **Fostamatinib** for the treatment of adult persistent and *chronic* immune thrombocytopenia: results of two phase 3, randomized, placebo-controlled trials. Bussel J, et al. *Am J Hematol*. 2018.
- ✓ Phase 3 randomised study of **avatrombopag**, a novel thrombopoietin receptor agonist for the treatment of *chronic* immune thrombocytopenia. Jurczak W, et al. *Br J Haematol*. 2018



Old and New agents

*Investigational for ITP at the time of publication.

†Approved for other indications, but off-label for ITP.

‡Can be used as an emergency treatment, but is considered a class for the purpose of defining multi-drug refractory ITP, not primary refractoriness.

Drug Class	
Initial/Emergency Therapies	
Glucocorticoids	Prednisone and its derivatives, Dexamethasone
Intravenous immunoglobulins	
Anti-RhD immune globulin	
Maintenance Therapies	
Thrombopoietic agents	Includes thrombopoietin receptor agonists (TPO-RAs) and recombinant human thrombopoietin (rhTPO)
SYK inhibitors	Fostamatinib, Sovleplenib* , Sevidoplenib*
Anti-CD20 monoclonal antibodies	Rituximab†
B-cell activating factor pathway antagonists	Ianalumab* , Belimumab*
BTK inhibitors	Rilzabrutinib*
Neonatal Fc receptor antagonists	Efgartigimod*
Complement inhibitors	Sutimlimab†
Anti-CD38 monoclonal antibodies	Daratumumab†, mezagitamab* , CM313*
Salvage Therapies	
Other immunosuppressants/immunomodulators†	Mycophenolate mofetil, azathioprine, cyclosporine, vincristine‡, vinblastine‡, danazol, progestins, dapson, sirolimus
Splenectomy‡	



A common language for ITP: task not yet accomplished!

- Heterogeneity of terminology and clinical definitions in adult idiopathic thrombocytopenic purpura: a critical appraisal from a systematic review of the literature. Ruggeri M, ... Rodeghiero F. *Haematologica*. 2008
- Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Rodeghiero F, et al. *Blood*. 2009
- Extensive variability in platelet, bleeding, and QOL outcome measures in adult and pediatric ITP: Communication from the ISTH SSC subcommittee on platelet immunology. Al-Samkari H, et al. *J Thromb Haemost*. 2021

Definition of Critical Bleed endorsed by ISTH. Sirotich E, et al. *J Thromb Haemost*. 2021



Two sides of a coin?

Guidelines



Provide **Evidence** grading and **Recommendation** Strength (statistical approach may be required)

- PICO model
(**P**opulation/**P**atient - **I**ntervention
Comparator – **O**utcome)
- In a specific **P**opulation does **I**ntervention or
Comparator result in better **O**utcome?

Statistical approach may be required

Terminology



Provide **general definitions** on:

- Patient characteristics
- Distinct goals of treatment
- Distinct outcomes
- Type of interventions
- Class of drugs
- Aspects of the disease

Consensus reached through progressive agreements among experts

Terminology wide relevance

- Real life studies and comparative trials based on PICO model are relevant for good clinical practice.
- Systematic reviews, meta-analysis, general reviews ...
- A common terminology is desirable for all approaches

PICO MODEL

Patient/Population	Intervention	Comparison	Outcomes
Who is your patient? <ul style="list-style-type: none">• Age, sex, race or patient• Primary problem• Health status	What do you plan on doing for the patient? <ul style="list-style-type: none">• Diagnostic test• Medication• Procedure	What alternative are you considering? <ul style="list-style-type: none">• Another test, medication or procedure• Watchful waiting	What do wish to accomplish? <ul style="list-style-type: none">• Accurate diagnosis• Relieve or improve symptoms• Maintain function

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Flow of ERCI/IWG consensus project

Increased awareness for revising terminology and definitions

Steering committee: F. Rodeghiero, C. Neunert (co-chairs), H. Al-Samkari, D. Arnold, J. Bussel, N. Cooper, W. Ghanima, T.J González-López, R. Grace, M.L. Lozano, T. Kühne, M. Michel, G. Moulis, D. Provan, F. Zaja

Selection of new terms requiring definition and reevaluation of 2009 definitions

2024: Production of many progressive draft documents

Latest draft to be proposed to the Expanded Expert Group (18 members) and 5 Patients' Representatives
Interaction with Regulatory Agencies

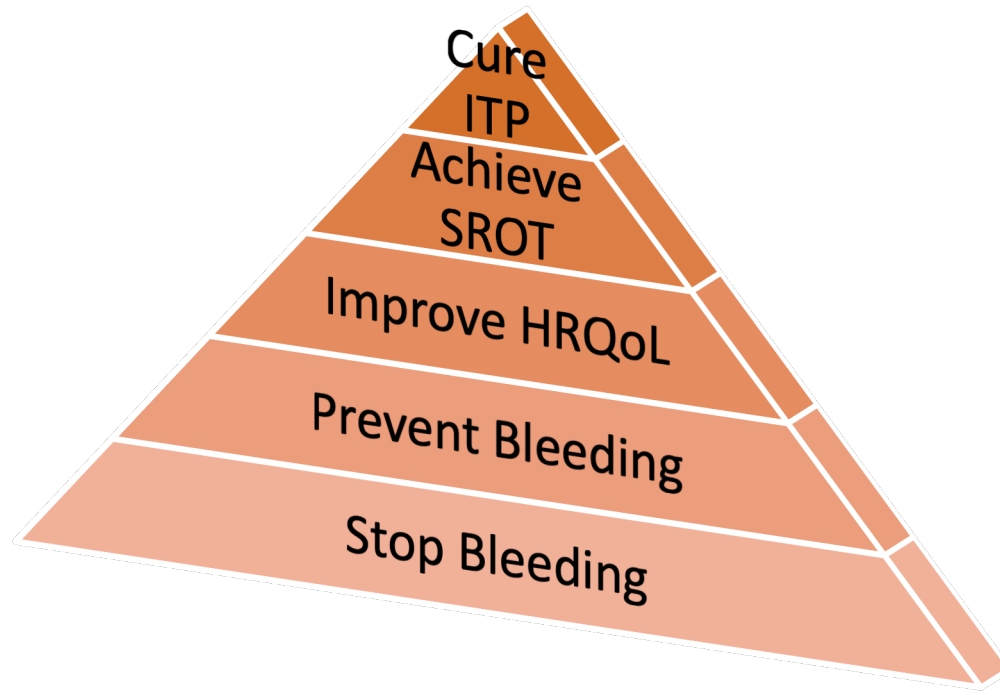
A view on topics in ERCI/IWG consensus

Summary

I. Treatment Goals	V. Response Criteria	X. Outcomes for clinical trials in ITP
Primary Treatment Goal	Response and Complete Response	XI. Reporting of bleeding outcome in clinical trials
Secondary Treatment Goals	Non-response to a specific agent	Bleeding in Adult ITP
Future Directions	Transient Response	Bleeding in Pediatric ITP
II. Phases of disease	Loss of Response	XII. Recommendations for HRQoL measures
Duration	Spontaneous Response	HRQoL Measures for Adult Patients
Recurrence	Sustained Response Off-Treatment (SROT)	HRQoL Measures for Pediatric Patients
Remission	Time to response and response duration	
Exacerbation	VI. Refractory ITP	
III. Severity of disease	ITP refractory to initial/emergency therapies	
Severe ITP	Multi-drug refractory	
Mild ITP	VII. Classification of Bleedings	
Persistent Isolated Mild Thrombocytopenia (PIMT)	Critical bleeding	
IV. Treatment types	Major Bleeding	
Initial/Emergency Treatments	Relevant Bleeding	
Maintenance Treatment	Minor Bleeding	
Splenectomy	VIII. Primary and Secondary ITP	
Treatments requiring episodic administration	IX. Criteria for inclusion in clinical trials	
Treatments requiring ongoing drug administration		



Main Goals in ITP management



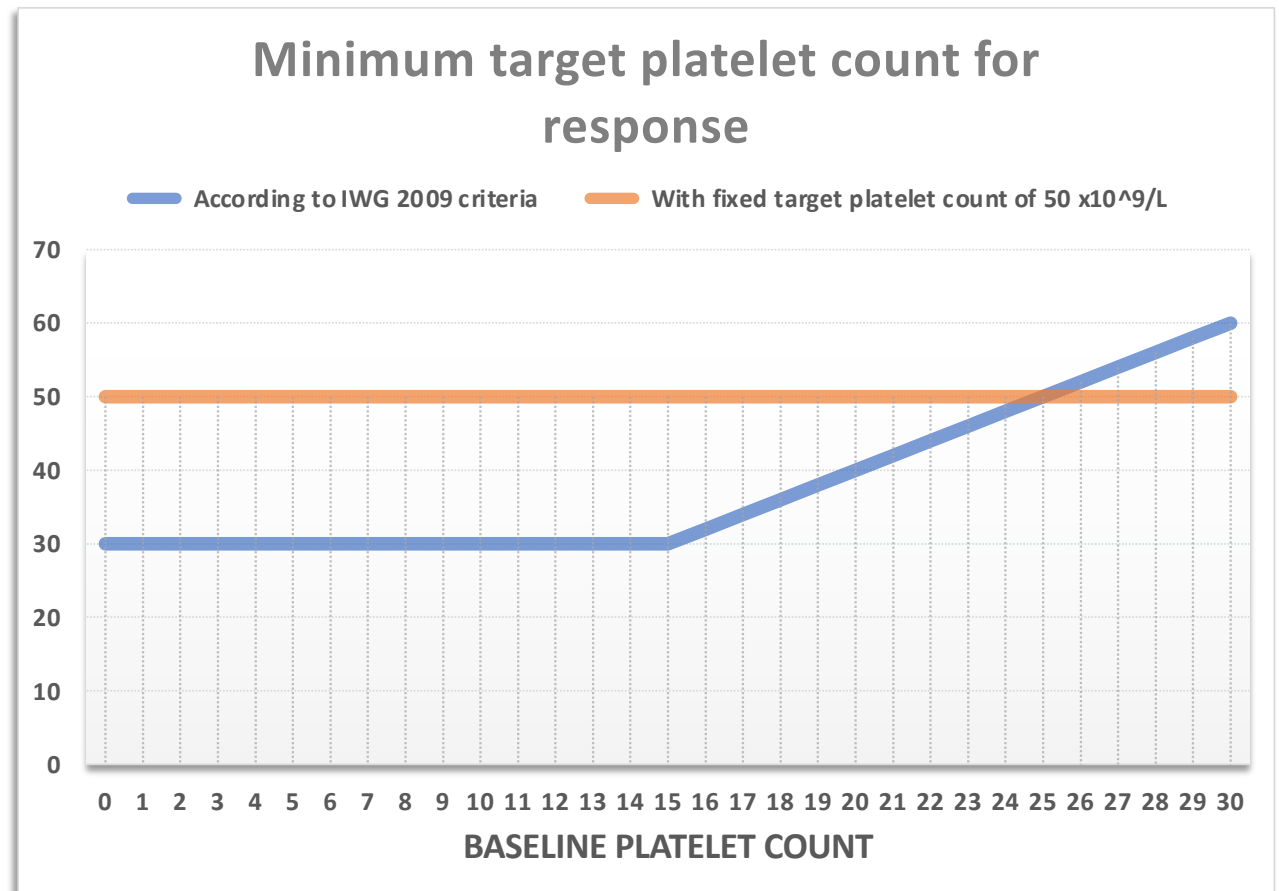
Pyramid of goals: This structure highlights the progression from essential treatment goals, like stopping bleeding, to more comprehensive and long-term objectives, culminating in the aspirational goal of curing ITP. Each level builds upon the previous one, showing how immediate treatment priorities support more sustained and comprehensive health outcomes.



Response achievement according to baseline platelet count

- IWG: plt $>30 \times 10^9/L$ and doubling of the baseline count
- Pharma companies/ clinical trials: $>50 \times 10^9/L$

More severe patients are favored with IWG criteria



Looking ahead

Excerpt from IWG 2009 standardization paper

- Consensus criteria and definitions could be used by investigational clinical trials or cohort studies or real life studies.
- Adoption of these recommendations would serve
 - to improve communication among investigators and between physicians and patients
 - to enhance comparability among clinical trials,
 - to facilitate meta-analyses and development of therapeutic guidelines
 - to provide a standardized framework for regulatory agencies

To reach our goal

- It is of primary importance to avoid any ambiguity.
- Revision of previous definitions and terminology should be justified by the correction of existing ambiguity and/or by new evidence
- Revision of definition should result in a clear benefit for the patients.