Regulatory Considerations for the Development of ITP Therapies in Japan

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The views expressed in this presentation are those of the author and do not necessarily reflect the official views of the PMDA.

Treatment Landscape for Adult ITP in Japan

Current treatment approach

- H.pylori assessment/eradication is considered early when applicable.
- Corticosteroids remain the standard 1st line therapy.
- For corticosteroid-resistant or dependent disease, TPO-RAs, rituximab, and splenectomy are established options.
- Recently approved agents further broaden choices.

Approved drugs (approval year)

- Eltrombopag (2010)
- Romiplostim (2011)
- Rituximab (2017)
- Fostamatinib (2017)
- efgartigimod alfa (2022)
- Avatrombopag (2025)
- Rilzabrutinib (2026)

Target Population Selection

- The target patient population should be appropriately selected, taking into account the intended clinical positioning of the drug and its potential impact on efficacy assessment.

- The following factors may affect the interpretation of efficacy and should be carefully considered.
  - **Disease stage**
    - Newly diagnosed ITP should generally not be included, because it may include spontaneous remission, making interpretation more difficult.
    - If persistent and chronic ITP are both enrolled, the pooled evaluation should be justified.
  - **Prior / Concomitant therapies**
    - To exclude delayed effects of prior therapies, a sufficient period during which discontinuation or prohibited dose modification of prior treatments should be specified before trial enrollment.
    - If the intended population is “inadequate responders,” the protocol should define this concept unambiguously.

Primary Endpoint

- An increase in platelet count is considered the most appropriate primary endpoint for the following reasons.
  - The principal objective of ITP treatment is to secure a platelet count sufficient to prevent clinically significant bleeding.
  - Platelet count can be objectively measured and is associated with bleeding risk and prognosis.

- Sustained platelet response has recently been used frequently that can mitigate the impact of intra-patient fluctuations in platelet count.
  - To capture the treatment effect adequately, the timing, duration, and monitoring frequency of assessments should be appropriately defined.

- Other potential treatment goals may include reducing corticosteroid use and avoiding more toxic treatments.
  - However, their appropriateness should be carefully evaluated, because there is limited precedent for using such outcomes as primary efficacy endpoints.

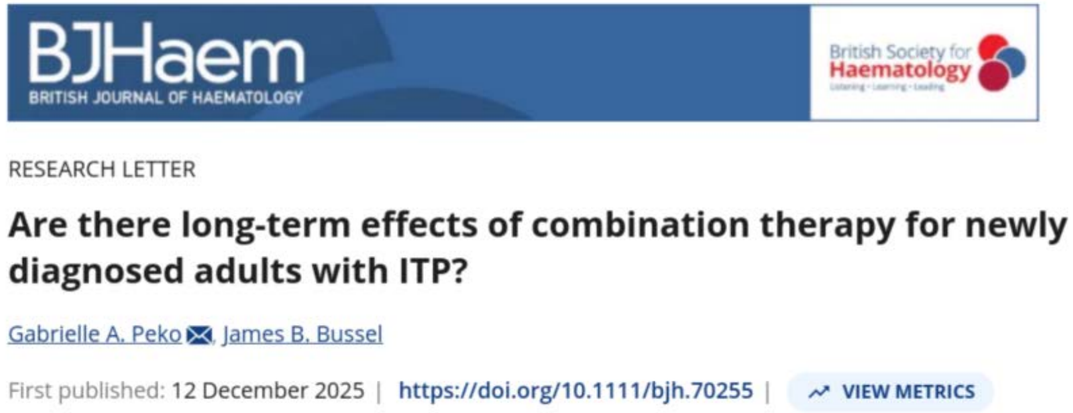
Key Secondary Endpoints

- Given that the primary goal of ITP treatment is to prevent bleeding, the clinical relevance of platelet count increases should be supported by evidence of prevention or reduction of bleeding events. Important secondary endpoints may include:
  - Incidence of bleeding events
  - Avoidance of rescue therapy

- It is also important to evaluate excessive elevations in platelet count and the occurrence of thromboembolic events.

Future perspective: Treatment aimed at treatment-free status

- Although treatment options for 2L ITP therapy have expanded, the burden on patients associated with long-term continuous treatment has become an important issue.
- Recently, sustained remission off-treatment (SROT) after discontinuation of TPO-RAs and remission induction through early combination therapy have been investigated.



Consideration for development of drugs aimed at treatment-free status

- In the development of drugs intended to achieve treatment discontinuation or remission in ITP, the following points should be considered.
  - ➢ It should be demonstrated that ITP can be safely managed even after treatment discontinuation.
    - Clinically meaningful efficacy endpoints should be clearly defined.
    - Long-term efficacy and safety should be evaluated.
  - ➢ The clinical trial design should allow the observed efficacy to be attributed to the investigational drug.
    - The target population should be selected by considering the potential impact of spontaneous remission and prior therapies on efficacy assessment.
    - An appropriate control group should be established to enable comparison with the natural history of the target population and with existing treatment options.

Summary

- In Japan, ITP treatment is selected based on H. pylori status, bleeding symptoms, platelet count, and prior treatment response, with corticosteroids as first-line therapy and multiple second-line options available.
- Target population selection is critical for interpretable efficacy assessment. Trial design should minimize confounding from: Spontaneous remission, delayed effects of prior therapies and concomitant treatments.
- Platelet response remains the most established and objective primary endpoint. Bleeding-related outcomes should support the clinical relevance of platelet response.
- For therapies aiming at remission or treatment discontinuation, safe disease management after treatment discontinuation and attribution of observed efficacy to the investigational drug should be evaluated.