**Treatment of immune thrombocytopenia with eltrombopag in patients who had and who had not received prior rituximab: post-hoc analysis of the EXTEND study**

Therapeutic options for immune thrombocytopenia (ITP) in second line include splenectomy, rituximab, thrombopoietin receptor agonists (TPO-RAs), a spleen tyrosine kinase inhibitor, and immunosuppressants.1,2

Eltrombopag is a TPO-RA approved in Europe for treatment of patients aged ≥1 year, with ITP lasting ≥6 months from diagnosis refractory to other treatments (e.g. corticosteroids).3–6

This subanalysis of EXTEND (NCT00351468)7,8 assessed whether eltrombopag efficacy and/or safety were different among patients with and without prior rituximab treatment.

EXTEND was a phase 3, open-label extension study evaluating eltrombopag safety and efficacy for up to 8–8 years in adults with ITP. It included patients with an ITP diagnosis ≥6 months from previous eltrombopag trials (see methods in the supporting information).3–5,7,9 Eltrombopag was dose-adjusted to maintain target platelet counts of ≥50 to <200 × 10^9/l; full methods and results are reported elsewhere.7,8

Baseline characteristics, efficacy (platelet count increase), and safety were analysed using the full analysis set (FAS). In this subanalysis, evaluating response to eltrombopag, patients were grouped according to whether they had received rituximab previously (ritux+[]) or not (ritux[−]). Ritux[+] patients were assessed separately based on when they last received rituximab (last rituximab dose either ≥1 year from diagnosis or <1 year from last trial). Overall response rate (ORR) was defined as proportion of patients with post-baseline platelet counts (no rescue therapy) of ≥50 × 10^9/l at least once. Descriptive statistics and time-to-event analyses for efficacy endpoints are provided.

Of 302 patients in EXTEND, 70 (23%) were ritux+[] and 232 (77%) were ritux[−] [Fig S1 (including patient disposition)]. Higher proportions of ritux[+] than ritux[−] patients had undergone splenectomy, received ≥5 prior ITP therapies, and were more likely to have had a baseline platelet count of ≤15 × 10^9/l in their prior eltrombopag trial, confirming that ritux[+] patients had more advanced ITP at baseline (Table I).

In the FAS, 53/70 (76%) ritux[+] and 208/232 (90%) ritux[−] patients responded (platelet counts ≥50 × 10^9/l) at least once with a comparable mean average dose for both groups (Fig S1; Table I). Among patients with <50 × 10^9/l at baseline, median [95% confidence interval (CI)] times to platelet counts ≥50 × 10^9/l were 3–1 (2–1–6–1) for ritux[+] patients (n = 46/60) vs 2–1 (2–0–2–3) weeks for ritux[−] patients (n = 175/197). Likewise, among patients with <100 × 10^9/l at baseline, median (95% CI) times to platelet counts ≥100 × 10^9/l were 8–1 [3–3–22–4; n = 45/67] vs 4–4 (3–1–6–1; n = 178/222) weeks respectively (Fig S2). In all, n = 11/70 (16%) ritux[+] and 63/232 (27%) ritux[−] patients responded at 24 weeks’ treatment (Fig S3); proportions increased to 44% (11/25) and 59% (63/106), respectively, in those patients with evaluable platelet counts [Fig 1A (data to Week 44)]. Proportions of withdrawals from EXTEND [35 (50%) ritux[+] and 132 (57%) ritux[−]] appeared similar.

Splenectomised ritux[+] patients appeared to have lower ORRs to eltrombopag versus non-splenectomised ritux[+] patients (32/47, 68% vs 21/23, 91%). In contrast, splenectomised and non-splenectomised ritux[−] patients appeared to have similar ORRs (62/68, 91% and 146/164, 89% respectively; Fig S1), suggesting that non-response to both splenectomy and rituximab indicated a generally refractory patient group. Nevertheless, the ORR to eltrombopag remained >60% in splenectomised ritux[+] patients, and long-term eltrombopag treatment appeared effective in a substantial proportion of these difficult-to-treat patients. Similarly, the ORR decreased in both groups with increasing number of prior ITP therapies (1–3 vs 4–5 vs ≥6); this appeared especially pronounced in the ritux[+] group [ritux[+]: 12/13, 92%; 20/25, 80%; and 21/32, 66% vs ritux[−]: 159/176, 90%; 32/35, 91%; and 17/21, 81%, respectively (Figs 1A and S4A)]. Notably, 66% of those not responding after ≥6 ITP therapies (an extremely difficult subgroup to treat)

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Fig 1. (A) Proportion of ritux[+] and ritux[−] patients with platelet counts of $\geq 50 \times 10^9/l$ over time (up to 44 weeks presented) in patients with evaluable platelet counts. (B) Proportion of ritux[+] patients with platelet counts of $\geq 50 \times 10^9/l$ over time (up to 44 weeks presented), stratified by time since prior rituximab treatment (ITT population). Data are presented only up to Week 44 because patient numbers decreased for multiple reasons (including AEs, patient decision, lack of efficacy, other) and there were only 70 patients in the ritux[+] group; platelet data were available up to Week 457 for a very limited number of patients. Platelet counts that were not classed as responses were: all platelet counts after an on-study splenectomy, platelet counts within seven days after a platelet transfusion, and platelet counts while taking an increased ITP medication or within six weeks after the end of an increased ITP medication. AE, adverse event; ITP, immune thrombocytopenia; ITT, intention to treat; ritux[+], patients with prior rituximab treatment; ritux[−], patients without prior rituximab treatment.
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Table I. Patient demographics, disease and baseline characteristics.

| Characteristics                                      | Ritux[+] | Ritux[−] | Total   |
|------------------------------------------------------|----------|----------|---------|
|                                                      | n = 70   | n = 232  | n = 302 |
| Mean (SD) age, years                                 | 53.0 (13.6) | 47.7 (16.0) | 48.9 (15.6) |
| Female, n (%)                                        | 43 (61)  | 158 (68) | 201 (67) |
| Race, n (%)*                                         |          |          |         |
| African American/African heritage                    | 1 (1)    | 3 (1)    | 4 (1)   |
| American Indian or Alaskan native                    | 2 (3)    | 11 (5)   | 13 (4)  |
| Asian                                                 | 1 (1)*   | 44 (19)* | 45 (15)* |
| White                                                 | 66 (94)  | 174 (75) | 240 (79) |
| Time since diagnosis, n (%)                          |          |          |         |
| <1 year                                              | 1 (1)    | 6 (3)    | 7 (2)   |
| 1–<2 years                                           | 8 (11)   | 39 (17)  | 47 (16) |
| 2–<5 years                                           | 15 (21)  | 64 (28)  | 79 (26) |
| 5–<10 years                                          | 16 (23)  | 44 (19)  | 60 (20) |
| ≥10 years                                            | 20 (29)  | 52 (22)  | 72 (24) |
| Splenectomised, n (%)                                | 47 (67)  | 68 (29)  | 115 (38) |
| Concomitant ITP medication at baseline, n (%)         | 23 (33)  | 78 (34)  | 101 (33) |
| Prior ITP medication, n (%)*                          |          |          |         |
| 1                                                    | 0        | 67 (29)  | 67 (22) |
| 2                                                    | 5 (7)    | 70 (30)  | 75 (25) |
| 3                                                    | 8 (11)   | 39 (17)  | 47 (16) |
| 4                                                    | 11 (16)  | 27 (12)  | 38 (13) |
| 5                                                    | 14 (20)  | 8 (3)    | 22 (7)  |
| ≥6                                                   | 32 (46)  | 21 (9)   | 53 (18) |
| Baseline platelet count in prior eltrombopag study, n (%) |         |          |         |
| ≤15 × 10^9/l                                         | 36 (51)  | 90 (39)  | 126 (42) |
| >15–<30 × 10^9/l                                     | 28 (40)  | 121 (52) | 149 (49) |
| 30–50 × 10^9/l                                       | 6 (9)    | 18 (8)   | 24 (8)  |
| >50 × 10^9/l                                         | 0        | 1 (<1)   | 1 (<1)  |
| Mean (SD) exposure to eltrombopag, years             | 1.9 (1.5) | 2.8 (2.0) | 2.6 (1.9) |
| Median exposure to eltrombopag, years (range)        | 2.1 (2 days–6.3 years) | 2.4 (14 days–8.8 years) | 2.4 (2 days–8.8 years) |
| Mean (SD) dose, mg/day                               | 53.4 (20.0) | 49.2 (21.9) | 50.2 (21.6) |
| Median (range) dose, mg/day                          | 59.9 (11–75) | 50.0 (1–75) | 50.8 (1–75) |
| Patients with at least 1 dose of ≥75 mg/day, n (%)   | 42 (60)  | 122 (53) | 164 (54) |
| Patients with modal dose ≥75 mg/day, n (%)           | 36 (51)  | 97 (42)  | 133 (44) |

ITP, immune thrombocytopenia; ritux[+], patients with prior rituximab treatment; ritux[−], patients without prior rituximab treatment; SD, standard deviation.

*Percentages do not add up to 100 because of rounding.
†East Asian.
‡Asian included: Central/South Asian, n = 4; East Asian, n = 33; Southeast Asian, n = 7. Asian patients comprised 1% of the ritux[+] group versus 19% of the ritux[−] group; however, excluding these patients from eltrombopag analyses because of potential plasma exposure differences did not affect observed response rates.
§Missing data for 10 ritux[+] patients and 27 ritux[−] patients.
¶Unknown baseline platelet data for two ritux[−] patients.
‡Modal dose refers to the most common dose of eltrombopag. The higher dose was considered to be the modal dose if a patient took eltrombopag at two dose levels for an equal number of days.

Responded to eltrombopag at least once. Romiplostim and fostamatinib are also associated with lower response rates in splenectomised patients and those unresponsive to multiple treatments.3,4,10,11

Response rates within two weeks of starting eltrombopag were higher in ritux[+] patients with >1 year since last rituximab dose (29/54, 54%) compared with ≤1 year (5/16, 31%; Fig 1B, Figs S1B and S1B); ORRs, however, appeared similar [41/54, 76% (>1 year) vs 12/16, 75% (≤1 year); Fig S1]. Patients with ≤1 year since last rituximab dose appeared more likely to be on eltrombopag 75 mg/day (63%) than those with >1 year (48%); this higher eltrombopag dose probably contributed to the similar ORRs observed in both groups.

Overall, adverse event (AE) incidence appeared similar between ritux[+] (97%) and ritux[−] (90%) patients (Table S1). Fatigue, nasopharyngitis, influenza, and oropharyngeal pain occurred >10% more frequently in ritux[+] patients. Immunoglobulin levels may have contributed to
higher nasopharyngitis and influenza rates in ritux+ patients, but levels were not measured systematically. Bleeding AEs were observed in 24 (34%) ritux+ and 60 (26%) ritux− patients. Grade 3 and 4 AEs are shown in Table SII, and the most frequently occurring AEs, stratified by splenectomy status, are shown in Table SIII.

The incidence of serious AEs appeared similar between ritux+ [n = 22 (31%)] and ritux− [n = 74 (32%)] patients; cataracts [n = 3 (4%) and n = 13 (6%) respectively] and pneumonia [n = 1 (1%) and n = 7 (3%) respectively] were most common. Most patients (78%) with cataracts had ≥1 confounding risk factor, e.g., previous chronic steroid use.7

Thromboembolic AEs were uncommon, with similar incidences of serious thromboembolic AEs apparent between groups, although myocardial infarction occurred in three ritux+ patients and one ritux− patients.

Higher proportions of patients with ≤1 year since last rituximab dose had headaches, upper respiratory tract infections, abdominal pain, and pyrexia than those with >1 year (Table SIV); this did not seem to be explained by increased eltrombopag dose in those with ≤1 year since last rituximab dose.

One limitation of this EXTEND study post-hoc analysis was the absence of statistical testing; the analysis itself was not powered to address specific hypotheses.

In summary, there were apparent numerical differences in response rates and certain AEs with long-term eltrombopag use between patients who previously received rituximab and those who had not. Some differences were dependent on the time of starting eltrombopag relative to when rituximab was administered. Efficacy differences appeared to be largely a function of severity of the underlying ITP, including splenectomy and more prior treatments. Importantly, however, eltrombopag was effective and generally well tolerated, regardless of previous rituximab, splenectomy, or both.

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Author contributions
OM was involved in the design of the study, the acquisition, analysis, and interpretation of the data, and in critically revising the manuscript. RSMW was involved in the acquisition, analysis, and interpretation of data, and in critically revising the manuscript. AK was involved in the design of the study, the acquisition, analysis, and interpretation of the data, and in critically revising the manuscript.

Conflicts of interest
OM reports honoraria from Amgen and Novartis for advisory boards and lectures, and honoraria from Grifols and Swedish Orphan Biovitrum AB for advisory boards. RSMW reports grants and personal fees from Novartis, GlaxoSmithKline, Bayer, Bristol Myers Squibb, Pfizer, and Roche. MS and JM are employees of Novartis Pharma AG; JM has shares in Novartis Pharma AG. JBB reports consultancy fees from Rigel, Principia, Regeneron, Dova, Momenta, RallyBio, Amgen, Novartis, Argenx, UCB, Regeneron, UCB, 3S (Shenyang) Bio and data safety monitoring board fees from CSL Behring. AK and MNS have no conflicts of interest to disclose.

Data sharing
Novartis is committed to sharing with qualified external researchers access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymised to respect the privacy of patients who have participated in the trial, in line with applicable laws and regulations. This trial data availability is in accordance with the criteria and process described on www.clinicalstudydatarequest.com.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Most frequently occurring AEs (≥10% in either group) regardless of relationship to study drug.

Table SII. Most frequently occurring Grade 3/4 AEs (≥2% of patients in total population) regardless of relationship to study drug.

Table SIII. Most frequently occurring AEs (≥10% in either rituximab group or rituximab group and ≥5% in splenectomised or non-splenectomised patients) stratified by splenectomy status.

Table SIV. Most frequently occurring AEs (≥10% in rituximab (+) group) stratified by time since last rituximab treatment.

Fig S1. Summary of patient disposition and response rates (platelet count ≥50 × 10^9/l at least once without rescue therapy) in rituximab (+) and rituximab (−) patients during EXTEND. The relative percentages of those with prior exposure to rituximab in the prior trials are TRA100773A: 28% (placebo group) versus 7–23% (eltrombopag group; mean percentage across three doses: 13.6%); TRA100773B: 21% (placebo group) versus 22% (eltrombopag group); RAISE: 19% (placebo group) versus 21% (eltrombopag group); REPEAT: 21% (eltrombopag group). ITP, immune thrombocytopenia; rituximab (+), patients with prior rituximab treatment; rituximab (−), patients without prior rituximab treatment.

Fig S2. Kaplan–Meier plot of time to platelet count ≥50 × 10^9/l (A), and ≥100 × 10^9/l (B) in rituximab (+) and rituximab (−) patients. Patients with baseline platelet count more than or equal to the threshold value or with no valid postbaseline platelet assessments (due to rescue therapy) are excluded. CI, confidence interval; rituximab (+), patients with prior rituximab treatment; rituximab (−), patients without prior rituximab treatment.

Fig S3. Proportion of rituximab (+) and rituximab (−) patients with platelet count ≥50 × 10^9/l over time (up to 44 weeks presented) in all patients, regardless of treatment discontinuation, with denominator fixed at n=70 for rituximab (+) and n=232 for rituximab (−) patients (A). Data are presented up to Week 44 because patient numbers decreased for multiple reasons (including AEs, patient decision, lack of efficacy, other) after this time point; however, platelet data were available up to Week 457 for a limited number of patients (see Figure S3B). Platelet counts that were not classed as responses were: all platelet counts after an on-study splenectomy, platelet counts within 7 days after a platelet transfusion, and platelet counts while taking an increased ITP medication or within 6 weeks after the end of an increased ITP medication. Proportion of rituximab (+) and rituximab (−) patients with platelet count ≥50 × 10^9/l over time (up to 456 weeks presented) in all patients, regardless of treatment discontinuation, with denominator fixed at n=70 for rituximab (+) and n=232 for rituximab (−) patients (B). Full data are presented up to Week 456. In addition to the number of responders at each time point, the numbers of evaluable patients are also presented in the table below the figure as variable denominators. The final Week 457 time point is not presented (n=0 for rituximab (+) patients and n=1 for rituximab (−) patients; evaluable patients: n=0 for rituximab (+) and n=1 for rituximab (−)). AE, adverse event; ITP, immune thrombocytopenia; rituximab (+), patients with prior rituximab treatment; rituximab (−), patients without prior rituximab treatment.

Fig S4. Scatterplots of platelet count over time for individual rituximab (+) patients by the number of prior ITP therapies (A), and time since last rituximab treatment (B). ITP, immune thrombocytopenia; rituximab (+), patients with prior rituximab treatment.

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