bjh short report

Fostamatinib is an effective second-line therapy in patients with immune thrombocytopenia

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Abstract

Fostamatinib demonstrated efficacy in phase 3 trials of adults with immune thrombocytopenia (ITP). *Post hoc* analysis compared patients who received fostamatinib as second-line therapy (after steroids ± immunoglobulins) versus third-or-later-line therapy (after ≥2 prior lines of therapy including a second-line agent). Platelet responses ≥50 000/μl were observed in 25/32 (78%) second-line and 54/113 (48%) third-or-later-line patients. Bleeding events were less frequent in second-line (28%) versus third-or-later-line (45%) patients. Responses once achieved tended to be durable in both groups. The safety profile was similar in both groups. In this *post hoc* analysis, fostamatinib was more effective as second-line than third-or-later-line therapy for ITP.

Keywords: autoimmune, platelet, spleen tyrosine kinase, SYK, idiopathic thrombocytopenic purpura.

Immune thrombocytopenia (ITP) is an autoantibody-mediated, heterogeneous disorder characterized by decreased platelet counts and increased risk of bleeding.[1,2] The goals of ITP treatment are to increase platelet counts to haemostatic levels to reduce and prevent bleeding. The American Society of Hematology 2019 Guidelines and Updated International Consensus Report for management of ITP recommend a minimum platelet count of 20 000–30 000/μl but to individualize treatment.[1–3] Initial treatment is generally with corticosteroids with intravenous immunoglobulin if needed.[1–4] Approved second-line treatments include the spleen tyrosine kinase (SYK) inhibitor fostamatinib and thrombopoietic receptor agonists (TPO-RA): eltrombopag, avatrombopag, and romiplostim.[2,5,6] Anti-CD20 antibody (rituximab) and splenectomy are also widely used options, as are immunosuppressants and alternative medicines.[2,7,8] There is very limited evidence to guide sequencing of treatments since only single-arm or placebo-controlled trials exist.[2,5,9–11]

Fostamatinib demonstrated efficacy in 8/16 patients in a phase 2 study.[12] In two phase 3, randomized, double-blind, placebo-controlled trials in heavily pretreated patients

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(median 3 and up to 14 prior treatments) with long-standing ITP (median 8·4 years), responses were observed within 12 weeks in 43% of 101 patients receiving fostamatinib and 14% of 49 patients receiving placebo ($P = 0.0006$).[13] Most had previously failed treatment with rituximab, TPO-RA, and/or splenectomy and some subsequently responded to fostamatinib. However, those who were earlier in their ITP appeared to have a higher response rate to fostamatinib.[13,14]

To evaluate fostamatinib earlier in the disease course, *post hoc* analysis of the phase 3 and open-label extension studies compared patient subgroups by line of therapy (second-line versus third-or-later-line) and stage of disease (persistent versus early or late chronic ITP).

Methods

Patients were included from two randomized studies[13] — FIT-1 (NCT02076399) and FIT-2 (NCT02076412) — and an open-label extension — FIT-3 (NCT02077192),[14] with a data cut-off date of December 2019. This *post hoc* analysis assessed the proportion of patients achieving platelet responses of ≥50 000/μl and of ≥30 000/μl at any visit (without rescue therapy within four weeks). Durability of response was calculated as percentage of treatment days patients maintained their response, measured from date of a qualifying platelet count (50 000/μl or 30 000/μl) to date of loss of response (two consecutive platelet counts <30 000/μl or ≤20 000/μl, respectively, or use of rescue therapy).

Results

Lines of therapy

In the phase 3 studies, 32 of 145 patients received fostamatinib as second-line therapy, following only steroids (corticosteroids or anabolic steroids [danazol in two]) with or without intravenous immunoglobulins (IVIG or IV anti-D). The other 113 patients received fostamatinib as third-or-later-line therapy following ≥1 previous second-line treatment (median 4, range 2–14); prior treatments included steroids ± immunoglobulins, rituximab, splenectomy, TPO-RA, cyclosporin, azathioprine, mycophenolate mofetil, vincristine, and/or dapsone. The two groups differed in duration of ITP, proportion with persistent ITP, baseline platelet count, and, by definition, number of prior therapies (Table 1).

A platelet response of ≥50 000/μl was achieved by 25/32 (78%) second-line patients and 54/113 (48%) third-or-later-line patients. Response to fostamatinib decreased with each additional prior line of therapy, with 64%, 52%, and 36% of patients achieving a response on third-, fourth- and fifth-line therapy, respectively (Fig 1A). Overall, 79/145 (54%) patients achieved ≥1 count ≥50 000/μl. Sixty-four (81%) of responders attained ≥50 000/μl within 12 weeks of starting fostamatinib including 19/25 (76%) second-line responders, 14 (56%) of whom responded within four weeks (Fig 2).

Table 1. Baseline demographics and disease characteristics in patients who received fostamatinib as second-line therapy and in patients who received ≥3 lines of therapy.

Baseline characteristics	Fostamatinib as second-line therapy ($n = 32$)	Fostamatinib as third-or-later-line therapy ($n = 113$)
Age, median (range) in years	50 (20–88)	54 (20–87)
Sex, *n* (%)		
Female	19 (59)	68 (60)
Male	13 (41)	45 (40)
Time since ITP diagnosis, median (range) in years	2·6 (0·3–50·2)	9·7 (0·6–53·0)
Type of ITP, *n* (%)		
Persistent (3–12 months' duration)	5 (16)	5 (4)
Chronic (>12 months' duration)	27 (84)	108 (96)
Baseline platelet count, median (range)[a]	21 500/μl (1000–34 000/μl)	15 000/μl (1000–156 000/μl)
Prior ITP medications, *n* (%)		
Corticosteroids	31 (97)	106 (94)
Immunoglobulins	9 (28)	68 (60)
TPO-RA agonists	0	68 (60)
Rituximab	0	47 (42)
Splenectomy	0	51 (45)

ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.

[a]In three second-line patients and 10 third-or-later-line patients, platelet counts were >30 000/μl at baseline (Day 1), but their average pretreatment (screening) platelet counts were <30 000/μl.

Durability of response was measured as percentage of treatment days that patients maintained a response (achieving ≥50 000/μl and not falling below 30 000/μl on two consecutive counts or using rescue therapy). Response was maintained for a median of 83% of treatment days in second-line patients (median 33 months, range <1–54 months) and 86% of treatment days in third-or-later-line patients (median 13 months; range <1–56 months; Fig 1B). Platelet responses consistently ≥50 000/μl were observed in 16/25 (64%) second-line and 34/54 (63%) third-or-later-line responders. One responder had previously responded to placebo.

Response of ≥30 000/μl was observed in 30/32 (94%) second-line patients and 71/113 (63%) third-or-later-line patients. Response rates decreased with increased lines of therapy (Fig 1A). Durability of response (achieving ≥30 000/μl and not falling below 20 000/μl on two consecutive counts or using rescue therapy) occurred a median of 92% of treatment days in second-line patients (median 21 months, range 1–54 months) and 88% in third-or-later-line patients (median 7·2 months; range <1–56 months; Fig 1B and Figure S1).

Fifteen of 32 (47%) second-line and 46/113 (41%) third-or-later-line patients received rescue therapy. At data cut-off, nine (28%) second-line patients continued therapy with fostamatinib (up to 55 months) as did 27 (24%) third-or-later-line patients.

Duration of ITP

In the phase 3 studies, 10 (7%) of 145 patients had persistent ITP, 19 (13%) patients had 1–2 years of ITP, and 116 (80%) had longer-term disease. Response to fostamatinib of ≥50 000/μl was achieved in 9/10 (90%) patients with persistent ITP, 11/19 (58%) patients with 1 to <2 years of ITP, and 59 (51%) of 116 patients with 2–53 years of ITP.

Safety results

The most common adverse events (AEs) were similar between second-line and third-or-later-line patients; AEs were reported in 72% of second-line and 94% of third-or-later-line patients (Table SI). AEs were mild in 16% vs. 24%, moderate in 22% vs. 45%, and severe in 34% and 25% of second-line vs. third-or-later-line patients, respectively. Bleeding events occurred in 28% and 45% of second-line and third-or-later-line patients and were mild (19% and 22%), moderate (3% and 19%), and severe (6% and 4%). Serious AEs were reported in 11 (34%) second-line and 34 (30%) third-or-later-line patients, with no major differences between groups.

Discussion

The dominant pathophysiology of ITP involves autoantibody-mediated phagocytosis of platelets by macrophages through the Fcγ receptor complex, which requires signalling through SYK. SYK-signalling in B cells and dendritic cells may also contribute to disease pathophysiology.[15] Presentation of platelet autoantigens by macrophages to $CD4^+$ T helper cells enables B cells to produce autoantibodies and develop into memory B cells and long-lived autoantibody-making plasma cells.[16] In the spleen, expanded T follicular helper cells, a subset of $CD4^+$ T cells, help drive B-cell differentiation and platelet autoantibody production.[17] This pathway likely contributes to chronicity in ITP and may be associated with epitope spreading, increased autoantibody levels, and T-cell involvement, rendering ITP harder to manage.[18,19] We hypothesize that early treatment of ITP with SYK inhibition may interrupt disease progression by blocking phagocytosis of antibody-coated platelets and thus subsequent events.[20,21]

In the current analysis, response rates to platelet counts ≥50 000/μl were observed more frequently when fostamatinib was used as second-line therapy for ITP (78% of patients responded) compared to later lines of therapy, with 64%, 52%, and 36% of patients achieving a response on third-, fourth-, and fifth-line therapy, respectively. The greater platelet response to second-line therapy was consistent with fewer bleeding events in these patients. Although rates of response varied, response, once achieved, was maintained (durable)

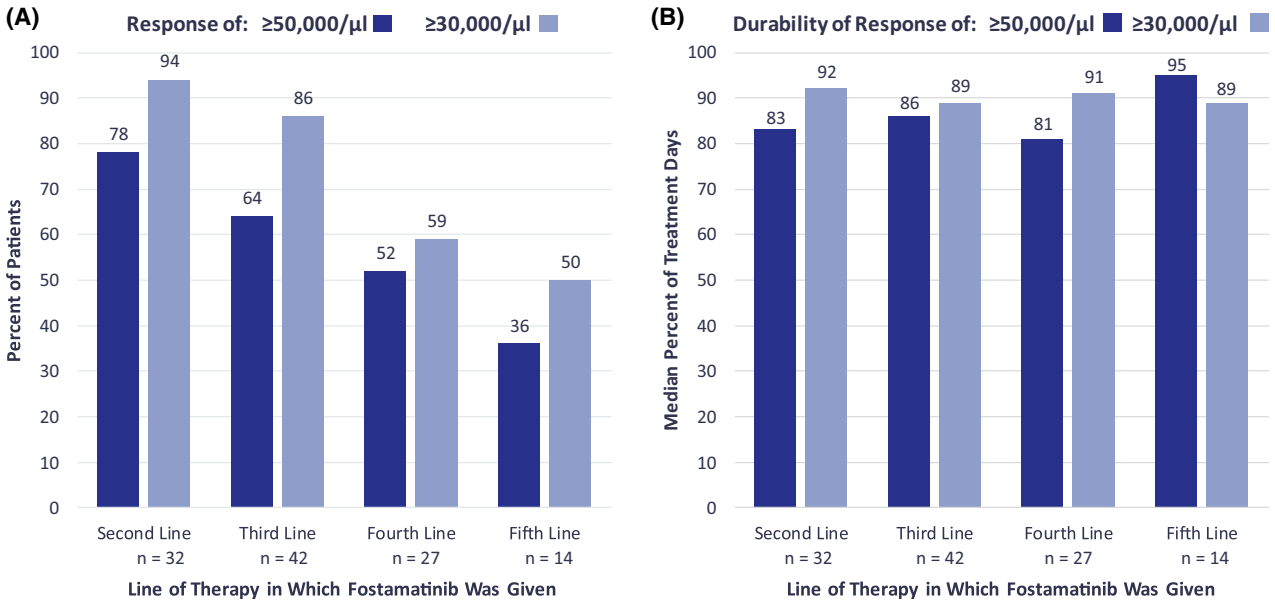

Fig 1. Response rate and durability of response in patients receiving fostamatinib as second-line, third-line, fourth-line, or fifth-line therapy. (A) Response, defined as ≥1 platelet count ≥50 000/μl (dark blue) or ≥30 000/μl (light blue) at any visit (not within 4 weeks of rescue therapy). (B) Durability of response: median percent of treatment days that patients maintained a response of ≥50 000/μl (dark blue) or ≥30 000/μl (light blue), with loss of response at the first of two platelet counts <30 000/μl or <20 000/μl, respectively, at least four weeks apart or use of rescue therapy. Thirty patients who received fostamatinib as sixth-line to tenth-line therapy are not shown. [Colour figure can be viewed at wileyonlinelibrary.com]

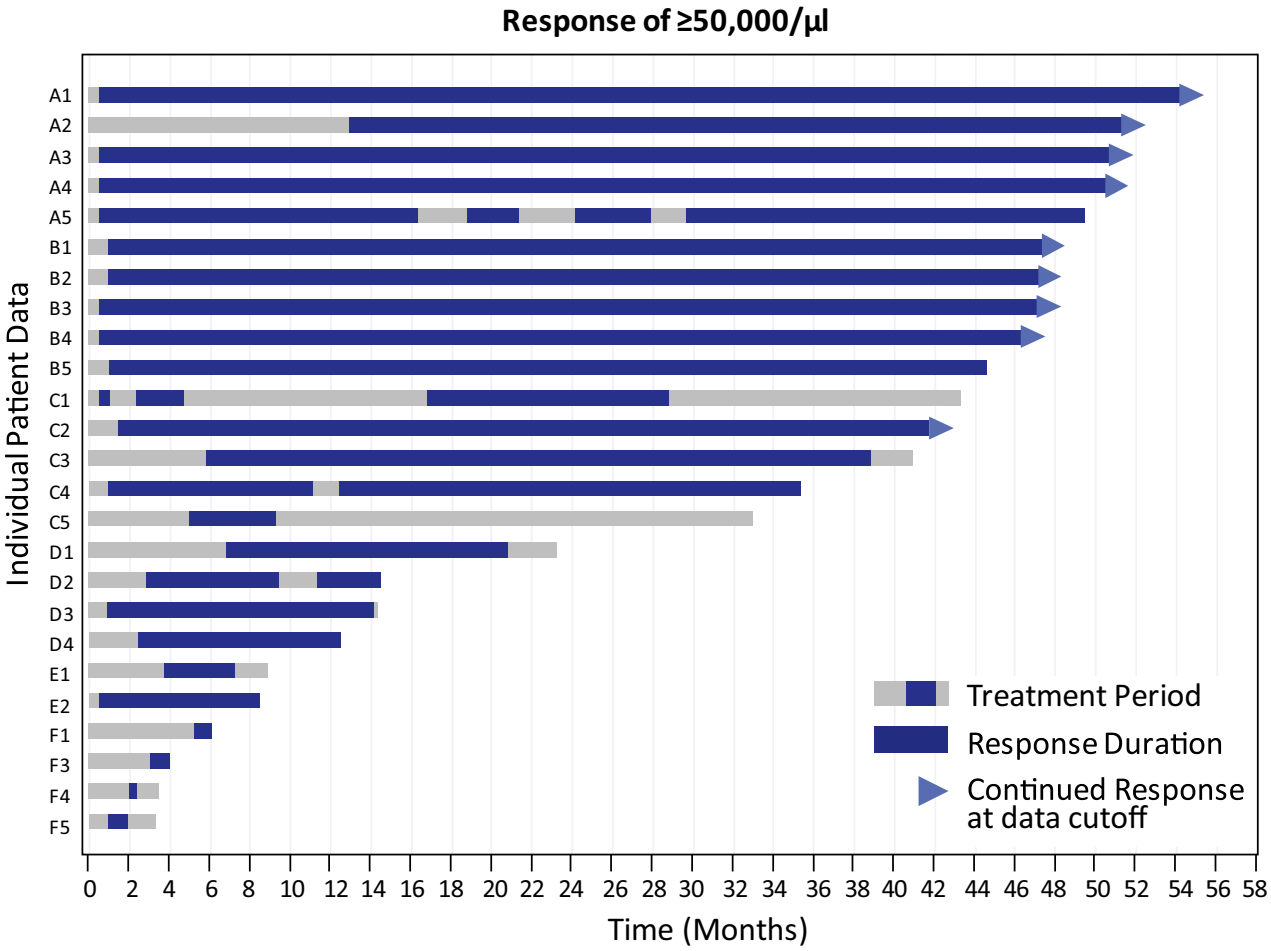

Fig 2. Duration of response and duration of treatment in patients receiving fostamatinib as second-line therapy. Each bar represents the period of treatment for one patient with a response of ≥50 000/μl (n = 25). Maintenance of response (dark blue line) is shown until loss of response, defined as two platelet counts of <30 000/μl at least four weeks apart or use of rescue therapy. Second-line therapy patients who did not have a response of ≥50 000/μl are not shown. [Colour figure can be viewed at wileyonlinelibrary.com]

irrespective of number of prior lines of therapy. Patients with persistent ITP tended to do better than those with chronic disease. Non-responders were more likely to have received more treatments and have a longer duration of ITP; this could possibly be related to T-cell-mediated ITP since autoreactive T cells may be more prevalent in patients with long-standing disease.[6,22]

Limitations to this *post hoc* analysis of fostamatinib clinical trial data include the absence of randomization of lines of treatment prior to receiving fostamatinib; and the relatively small number of patients in the second-line therapy and especially persistent subgroups. The analysis would also have benefitted from study of disease processes, e.g. anti-platelet autoantibodies, epitope spreading, and/or autoreactive T cells. Discussion of AEs was minimized in this report, other than comparison between second-line and third-or-later-line patients, since all had been previously reported.[13,14]

In summary, fostamatinib was more effectively, and as safely, used as second-line therapy for ITP compared to later lines. Additional studies are needed to confirm the current analyses and to explore whether fostamatinib may prevent disease progression.

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Ethics Approval and Informed Consent

All participants provided written informed consent. These studies were approved by independent ethics committees at participating centers and were carried out in compliance with the Declaration of Helsinki.

Author contributions

JBB, RB, NC, WG, ST, and LKT contributed to the design of the studies and/or these post hoc analyses in collaboration with clinical advisors, study investigators, and employees of Rigel Pharmaceuticals. All authors contributed to data acquisition, analysis, and/or interpretation in collaboration with study investigators and biometrics staff at Rigel Pharmaceuticals. LKT and JB wrote the manuscript with contributions from a medical writer (acknowledged), and all other authors provided critical revisions. All authors approved the final version of the manuscript.

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Conflict of interests

RB: Consultancy: AMAG, Amgen, Bristol Myers Squibb, Daiichi Sankyo, Inc, Secura Bio; Speakers Bureau: Amgen, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Inc, Rigel. NC: Consultancy: Amgen, Novartis, Principia, Rigel; Honoraria: Amgen, Novartis, Principia; Membership on an entity's Board of Directors or advisory committees: Amgen, Novartis, Principia, Rigel. WG: Research funding: Bayer, Bristol Myers Squibb, Novartis, Pfizer; Consultancy: Amgen, Novartis; Honoraria: Amgen, Bayer, Novartis. MAB: Consultancy: Best Doctors, Gerson Lehrman; Honoraria: AbbVie, Takeda; Speakers Bureau: AbbVie, Incyte, Rigel, Takeda; Employment: Arizona Oncology. QH: Research funding: Alexion; Honoraria: Apellis, Bioverativ, a Sanofi company; Speakers Bureau: Novartis. MS: Research funding: Amgen; Honoraria: Amgen, Novartis. MDT: Research funding: Novo Nordisk, Takeda; Consultancy: Grifols, Magellan Healthcare, Novo Nordisk, Octapharma, Roche, Takeda; Honoraria: Grifols, Novo Nordisk, Takeda; Speakers Bureau: Grifols, Novo Nordisk, Octapharma, Takeda; Membership on an entity's Board of Directors or advisory committees: Grifols, Takeda; Employment: Bleeding and Clotting Disorders Institute; Other, President and Owner: Michael Tarantino, MD, SC. LKT, ST: Employment: Rigel; Equity ownership: Rigel. JBB: Consultancy: Amgen, Argenx, Dova, Kezar Life Sciences, Momenta, Novartis, Rallybio, Regeneron, Rigel, UCB; Honoraria: Amgen, Argenx, GlaxoSmithKline, Momenta, Novartis, Rallybio, Regeneron, Rigel, Tranquil, UCB; Speakers Bureau: 3SBio, Novartis, Physician Education Resource; Membership on an entity's Board of Directors or advisory committees: Amgen, Argenx, Dova, GlaxoSmithKline, Kezar Life Sciences, Momenta, Novartis, Rallybio, Regeneron, Rigel, Tranquil, UCB.

Supporting Information

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

Fig S1. Duration of response and duration of treatment in patients receiving fostamatinib as second-line therapy.

Table SI. Most commonly reported AEs occurring in ≥10% of patients receiving fostamatinib as second-line therapy or third-or-later-line therapy.

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