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To the editor:

Ruxolitinib for essential thrombocythemia refractory to or intolerant of hydroxyurea: long-term phase 2 study results

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Essential thrombocythemia (ET) is a Philadelphia chromosome–negative myeloproliferative neoplasm (MPN) characterized by persistent thrombocytosis, excessive bone marrow megakaryocyte proliferation, and normal erythrocyte mass.[1] Symptoms may include bone pain, pruritus, night sweats, numbness, fatigue, early satiety, headache, and dizziness.[2] Treatment includes low-dose aspirin for microvascular disturbances and cytoreduction with hydroxyurea in patients with high-risk disease.[3-5] For many patients, ET is controlled well with hydroxyurea; however, resistance/intolerance occurs in 20% of patients.[6]

ET is associated with dysregulated Janus kinase (JAK) signaling.[7-9] Ruxolitinib is an oral JAK1/JAK2 inhibitor with clinical benefit in patients with other MPNs, myelofibrosis (MF),[10,11] and polycythemia vera (PV).[12,13] We report the long-term efficacy and safety of ruxolitinib treatment in the ET cohort of an open-label, phase 2 study of patients with PV or ET refractory to or intolerant of hydroxyurea (conducted July 2008 to April 2009; NCT00726232). Long-term results from the PV cohort were previously published.[14]

Thirty-nine patients with ET were enrolled, including 26 in the dose-finding phase and 13 in the expansion phase (supplemental Methods, available on the *Blood* Web site). Baseline patient characteristics are shown in supplemental Table 1. Seventeen prior thromboembolic or hemorrhagic events occurred in 10 patients; those occurring in >1 patient were portal vein thrombosis (n = 3), mesenteric thrombosis (n = 2), and transient ischemic attack (n = 2); gastrointestinal bleeding (n = 3) was the only hemorrhagic event. Prior antithrombotic treatment was recorded in 33 (84.6%) patients, including 25 (64.1%) who received aspirin. At data cutoff (22 February 2016), 20 (51.3%) patients were ongoing (Figure 1A).

Median platelet count decreased rapidly through the first 4 weeks of therapy, with 25-mg twice-daily (baseline, 857 $\times$ 10^9/L; week 4, 482 $\times$ 10^9/L) and 50-mg once-daily starting doses (baseline, 920 $\times$ 10^9/L; week 4, 486 $\times$ 10^9/L), stabilizing through week 8 (25 mg twice daily, 564 $\times$ 10^9/L; 50 mg once daily, 454 $\times$ 10^9/L). A rapid decrease in median white blood cell (WBC) count was noted by 4 weeks of treatment in the full patient population (baseline, 8.15 $\times$ 10^9/L; week 4, 5.20 $\times$ 10^9/L), after which median WBC count remained within normal ranges (approximately 5-8 $\times$ 10^9/L). Median hemoglobin level decreased over the first 8 weeks of treatment in the full patient population (baseline, 138 g/L; week 8, 118 g/L), stabilizing thereafter (range, 112-124 g/L).

After 8 weeks of treatment, platelet, WBC, and hemoglobin levels remained stable in patients who received a starting dose of 25 mg twice daily (Figure 2A-C). Blood counts over time were similar among patient subgroups defined by the total average daily ruxolitinib dose. All patients who received a starting dose of 25 mg twice daily had baseline platelet counts >400 $\times$ 10^9/L (n = 22); 4.6%, 9.1%, and 13.6% of these patients achieved a platelet count ≤400 $\times$ 10^9/L at weeks 12, 48, and 312, respectively (Figure 2D). Of the patients with baseline platelet count >600 $\times$ 10^9/L (n = 20), 55.0%, 40.0%, and 45.0% achieved a platelet count ≤600 $\times$ 10^9/L at weeks 12, 48, and 312, respectively (Figure 2E). The goal of platelet reduction is to reduce the risk of thrombotic complications; however, there is no clear evidence that a target level of 400 $\times$ 10^9/L reduces this risk better than does 600 $\times$ 10^9/L.[15]

Treatment with a starting dose of 25 mg twice daily was associated with improvements in ET-related symptoms (patient-rated from 0 [not present] to 10 [worst imaginable] in the preceding 7 days at each study visit). Among evaluable patients with baseline symptom scores >0 and a symptom score recorded at week 12, a ≥50% improvement from baseline at week 12 in bone pain was achieved by 46.7% (7/15), pruritus by 50.0% (6/12), night sweats by 75.0% (6/8), numbness/tingling in the fingers/toes by 64.7% (11/17), and weakness by 35.3% (6/17). An observational study showed that the substantial symptom burden associated with ET can affect quality of life,[16] and European LeukemiaNet (ELN) response criteria for ET include symptom improvement on the Myeloproliferative Neoplasm Symptom Assessment Form.[17] Therefore, improvement in these symptoms may be an important clinical outcome.

At baseline, 24 (61.5%) patients were positive for the *JAK2*V617F mutation. Minimal decrease from baseline in *JAK2*V617F allele burden was observed after 24 weeks of ruxolitinib treatment (median percentage change, −2.8%; n = 22 evaluable patients). However, allele burden was reduced with longer ruxolitinib exposure (median [range] percentage change, −19.8% [−92.6% to 100%] at week 144 [n = 16]; −33.3% [−96.0% to 46.3%] at week 192 [n = 15]; and −60.0% [−100% to 21.1%] at week 312 [n = 12]; Figure 2F). Reduction in allele burden is not included in the current ELN response

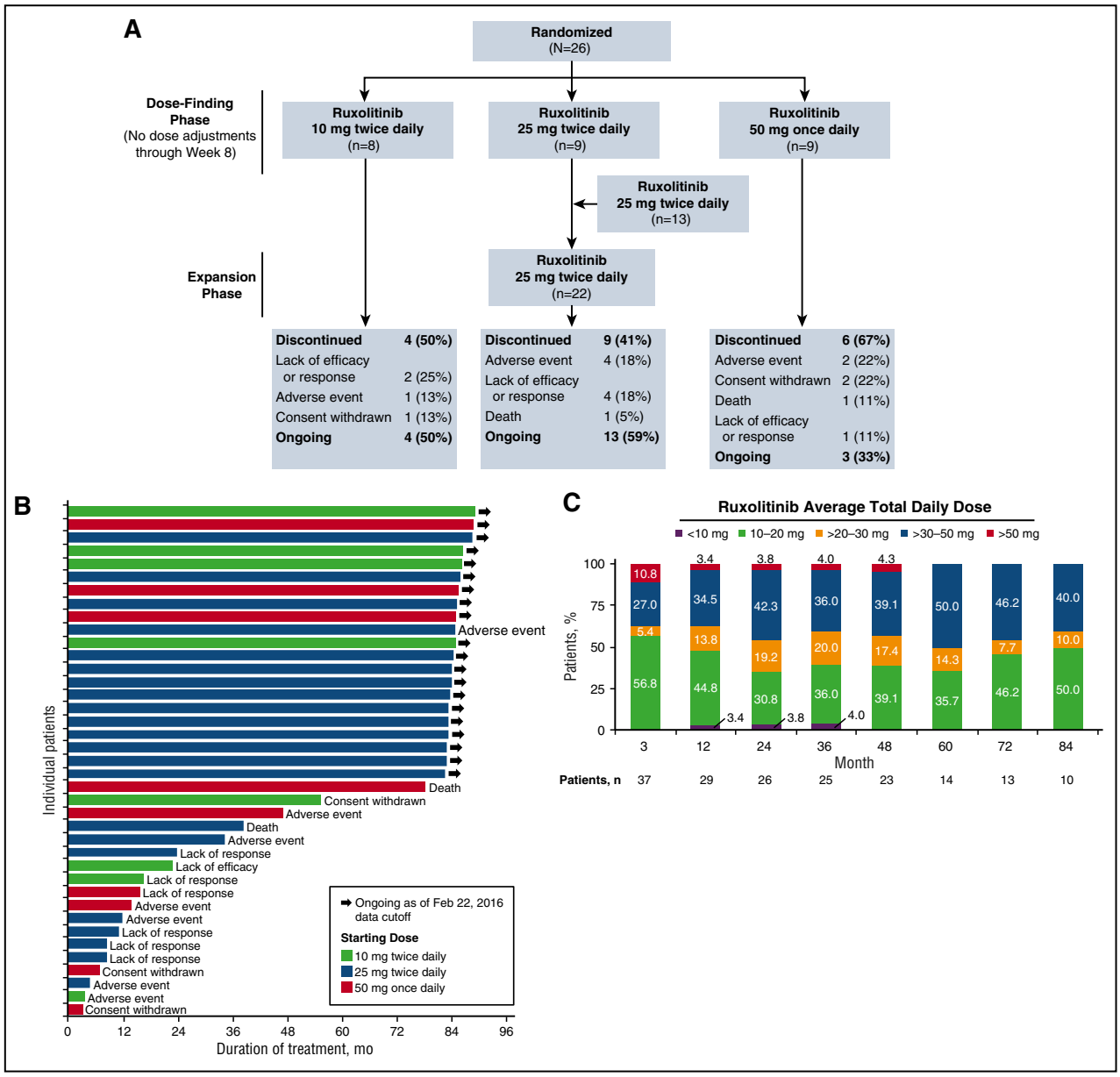

Figure 1. Patient disposition, duration of treatment, and ruxolitinib exposure. (A) Study flowchart. The 7 adverse events, regardless of treatment, that led to discontinuation were severe blood creatine phosphokinase increase, severe gastrointestinal disorder, Kaposi sarcoma, moderate left-foot pain, severe multiorgan failure, moderate renal failure, and mild right-foot pain (n = 1 each). Consent was withdrawn because of concern over weight gain, concern over fatigue, and planning a pregnancy (n = 1 each). Death was due to progressive heart failure in 1 patient and multiple vertebral osteolytic lesions due to Paget's disease in the other patient. (B) Duration of treatment in individual patients. (C) Ruxolitinib daily dosage distribution over time: patients from all ruxolitinib starting dose groups were included and analyzed by ruxolitinib average total daily dose.

criteria,[17] consistent with the lack of a single reliable marker of disease in ET, despite general activation of the Janus kinase/signal transducer and activator of transcription pathway.[18-21]

At the time of data cutoff, median (range) exposure to ruxolitinib was 358.6 weeks (82.8 months; 13-384 weeks). Most patients (56.4%) received ruxolitinib for ≥312 weeks (72 months; Figure 1B). The median (range) total daily dose for all patients was 30 mg (10-70 mg), which corresponds to approximately 15 mg twice daily. However, many patients had total daily doses >30 mg (Figure 1C).

During the first 8 weeks of treatment, the most common nonhematologic adverse events (AEs) were weight increase, cough, diarrhea, and pyrexia; the most common new or worsening hematologic laboratory abnormalities were anemia and leukopenia (supplemental Table 2).

The majority of AEs that occurred with long-term ruxolitinib treatment were grade 1/2 (Common Terminology Criteria for Adverse Events, version 3.0; supplemental Table 3). Among patients who started ruxolitinib at 25 mg twice daily, the most common all-grade nonhematologic AEs regardless of causality were cough, weight increase, blood creatine phosphokinase increase, bronchitis, and headache. The most common new or worsening grade 3/4 hematologic AE was neutropenia (n = 3, 13.6%).

Two patients who started ruxolitinib at 25 mg twice daily had on-study thrombotic events (63-year-old woman, pulmonary embolism [day 1091], resolved with antithrombotic agents; 62-year-old woman, mild myocardial ischemic event, treated and considered resolved the same day). Both patients received aspirin at the time of the event and remained on study.

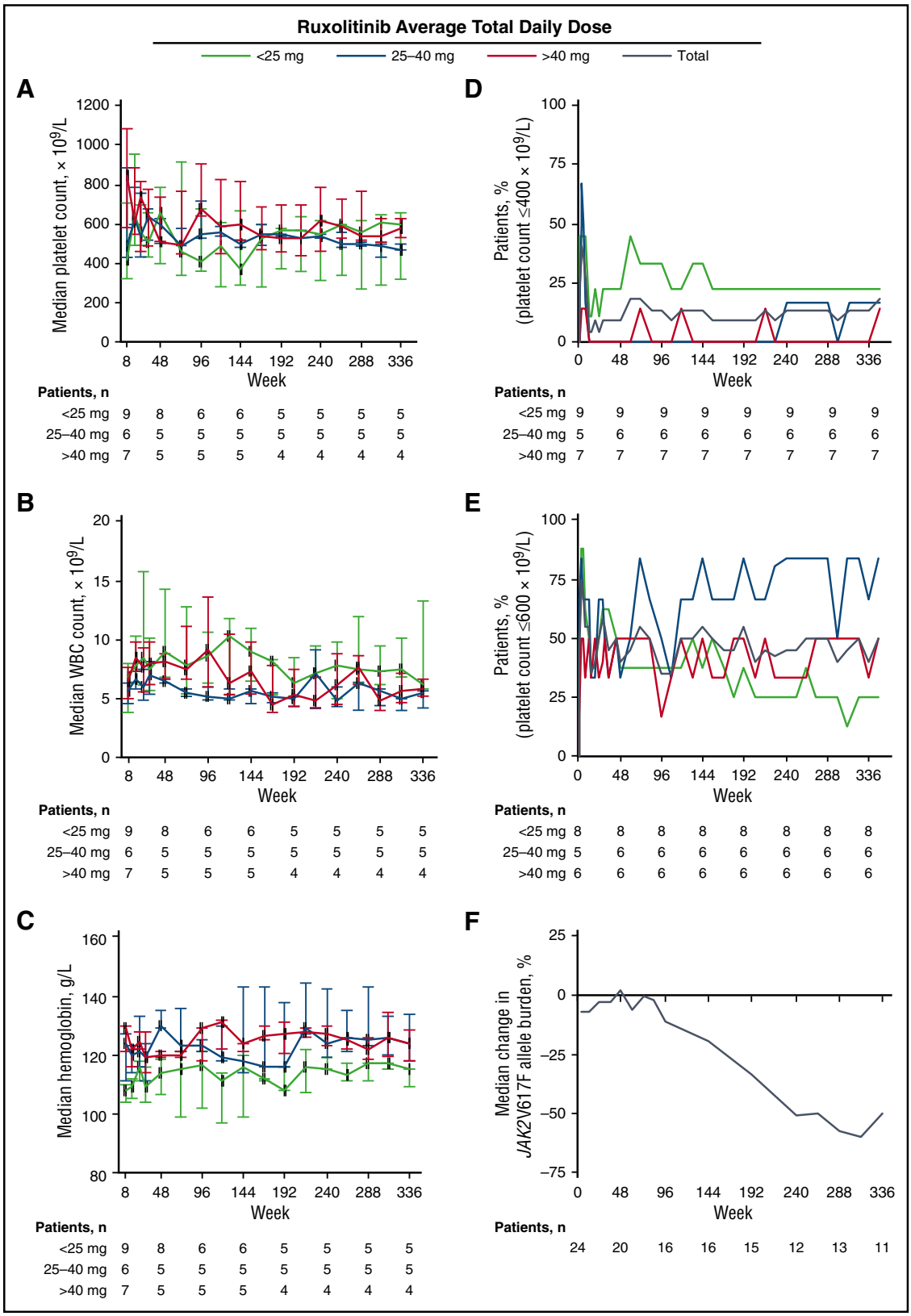

Figure 2. Hematologic findings. Median platelet counts (A), WBC counts (B), and hemoglobin levels (C) over time beginning at week 8 are displayed by ruxolitinib average total daily dose among patients treated with a starting dose of 25 mg twice daily. Error bars are interquartile ranges. The proportion of patients with platelet counts $>400 \times 10^9$/L at baseline and $\leq 400 \times 10^9$/L after baseline (D) and platelet counts $>600 \times 10^9$/L at baseline and $\leq 600 \times 10^9$/L after baseline (E) are displayed by ruxolitinib average total daily dose among patients treated with a starting dose of 25 mg twice daily. (F) Median percentage change from baseline in *JAK2*V617F allele burden includes all patients regardless of ruxolitinib starting dose to ensure a sufficiently large patient population. Time points that included data from <5 patients were excluded. Allele burden was assessed with a quantitative real-time polymerase chain reaction assay; *JAK2*V617F-negative samples were confirmed by a quantitative single-nucleotide extension assay.

Four hemorrhagic events occurred in 3 patients who started ruxolitinib at 25 mg twice daily (epistaxis [n = 2], gingival bleeding [n = 1], vaginal hemorrhage [n = 1]). All were grade 1 and were considered unrelated to study treatment.

Among patients who started ruxolitinib at 25 mg twice daily, infections of any grade were reported in 16 (72.7%) patients. Grade ≥3 infections were reported in 2 patients (67-year-old woman, pneumococcal bacteremia [day 2482], resolved with antibiotics; 90-year-old woman, pneumonia [day 1115], resolved with sequelae following inpatient treatment). Three patients had grade 1/2 herpes zoster. Transformations to acute myeloid leukemia or post-ET MF were not reported; however, reasons for hydroxyurea resistance/intolerance were not recorded, and it is possible that the risk of transformation was low in this population. Among patients who started ruxolitinib at 10 mg twice daily or 50 mg once daily, infections occurred in 5 patients (62.5%) and 6 patients (66.7%), respectively.

In conclusion, the results of the current study, which focused on a number of individual components of clinical response, demonstrated that patients with ET who are refractory to or intolerant of hydroxyurea can achieve clinically meaningful and durable reductions in platelet and WBC counts and improvements in ET-related symptoms with ruxolitinib treatment.

The online version of this article contains a data supplement.

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Conflict-of-interest disclosure: S.V. has participated in advisory boards for Incyte Corporation. F.P. has participated in advisory boards for and received honoraria from Novartis. H.Z., M.G., and A.A. are employees of Incyte Corporation. A.M.V. has participated in advisory boards for and received honoraria and research funding from Novartis. The remaining authors declare no competing financial interests.

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