INTRODUCTION

Polycythemia vera (PV) is a myeloproliferative neoplasm characterized by clonal proliferation of the erythroid, myeloid, and megakaryocyte lineages. Increased erythrocyte production results in increased red blood cell mass, which contributes to mortality and significant morbidity.1,2 White blood cell (WBC) and platelet counts may also be elevated. Patients often suffer from burdensome symptoms, such as fatigue, pruritus, and night sweats, and may have enlarged spleens.2-4 PV is also associated with an increased risk of thrombosis and progression to myelofibrosis or acute myeloid leukemia (AML).2
Therapeutic goals include the prevention and management of thrombotic and bleeding complications, symptom control, and risk minimization for progression to post-PV myelofibrosis or AML. Recent guidelines have recommended all patients be managed with phlebotomy to maintain hematocrit < 45%, and with low-dose aspirin. Hydroxyurea and interferon-α (IFN-α) are recommended as initial therapies for high-risk patients. These agents can be interchanged for second-line therapy in the event of intolerance or refractoriness to first-line therapy. In particular, IFN-α is limited by tolerability issues. Pipobroman and busulfan are second-line therapies reserved for patients with a shorter life expectancy because of their leukemogenic effect.

Overactive Janus kinase (JAK)-signal transducers and activators of transcription (STAT) signaling resulting from gain-of-function mutations of JAK2, such as JAK2V617F and JAK2 exon 12, are causally linked to PV pathogenesis. Ruxolitinib is a JAK1/JAK2 inhibitor that has demonstrated clinical benefit in patients with myelofibrosis. Ruxolitinib is also active in preclinical models of PV. We investigated the clinical activity of ruxolitinib in patients with advanced PV or essential thrombocythemia in an open-label, phase 2 study (study INCB18424-256), and herein present data from patients with PV enrolled in this study.

The current study is registered at www.ClinicalTrials.gov (NCT00726232).

MATERIALS AND METHODS

Patients

Adult patients with a confirmed diagnosis of PV according to the World Health Organization criteria were enrolled. As determined by the investigator, patients with disease who were refractory to treatment with hydroxyurea or for whom hydroxyurea was contraindicated were eligible. Patients who refused further hydroxyurea treatment because of adverse events (AEs) were also eligible; these patients must have had a trial with hydroxyurea, and the investigator must have concurred that discontinuation of hydroxyurea was in the best interest of the patient. Further breakdown of intolerance versus resistance was not possible because the European LeukemiaNet (ELN) criteria for hydroxyurea resistance or intolerance were published >2 years after the current study was initiated. Patients were required to have hematocrit > 45% or 2 phlebotomies within the 24 weeks before enrollment, with at least 1 phlebotomy performed within 12 weeks before enrollment. Complete enrollment criteria are provided in the online supplemental material.

Study Design

Six to 8 patients were randomized to 1 of 3 ruxolitinib dose-finding cohorts: 10 mg twice daily, 25 mg twice daily, or 50 mg once daily. The dose-expansion cohort was determined not on the basis of predefined statistical analyses, but on a general review by both the sponsor and the investigators of the efficacy and safety data of patients enrolled in the dose-finding cohorts who completed at least 56 days of treatment. Details regarding dosing adjustments for hematologic or nonhematologic AEs as well as study visit evaluations, including timing of blood count measurements, are provided in the online supplemental material. At each study visit, patients used a numeric rating scale to rate pruritus, bone pain, night sweats, and fever on a scale of 0 (absent) to 10 (worst possible), reporting the worst level of symptoms experienced during the 7 days preceding the study visit.

The study was approved by the Institutional Review Boards of the participating institutions and was conducted in accordance with the Declaration of Helsinki, as described in the International Conference on Harmonisation’s Guideline for Good Clinical Practice and applicable regulatory requirements. All patients provided written informed consent.

Study Assessments

At the time this study was enrolling patients, the 2009 clinicohematologic criteria of the ELN represented the most current standardized definition for monitoring and assessing treatment response in patients with PV. Although published after this study was initiated, a modified version of these criteria was used to assess response in the current study. Complete response (CR) was defined as hematocrit < 45% without phlebotomy, a platelet count ≤ 400 × 10^9/L, a WBC count ≤ 10 × 10^9/L, a normal spleen as assessed by palpation, and no pruritus within the previous week. A partial response (PR) was defined as hematocrit <45% without phlebotomy after week 4. These criteria differed from the published 2009 ELN criteria in that splenomegaly was assessed using palpation instead of imaging, and symptom evaluation was limited to pruritus, because headache and microvascular symptoms were not assessed in the symptom questionnaire (see online supplemental material). These modified ELN criteria were generally similar to the original protocol-defined criteria for CR and PR (see online supplemental material) and were used to allow for a better comparison of response rates observed.
in this study versus future clinical trials in patients with PV. Although updated ELN criteria were released in April 2013,17 these could not be used in the current analysis because data that would be required to assess response according to the 2013 criteria were not collected during the current study (see online supplemental material).

Patients could be evaluated for response no sooner than week 12. Response required the following: 1) continuous absence of phlebotomy from week 4 through the time of response (minimum through week 12) and 2) hematocrit < 45%. To avoid assigning clinical significance to minor fluctuations in laboratory values, patients were considered to have maintained hematocrit < 45% until their hematocrit was ≥ 45% and also proportionally increased by ≥ 10% from the nadir.

The cumulative probability over time of achieving either a CR or PR as the observed first response, the cumulative probability over time of achieving a best response of CR or PR, and the durability of response were assessed using the Kaplan-Meier method. The percentages of patients with WBC counts > 10 × 10⁹/L or > 15 × 10⁹/L at baseline who achieved a sustained (ie, ≥ 12 weeks) reduction in their post-baseline WBC count to ≤ 10 × 10⁹/L were evaluated. The sustained reductions in the post-baseline platelet count to ≤ 400 × 10⁹/L in patients with platelet counts > 400 × 10⁹/L or > 600 × 10⁹/L at baseline were also evaluated. Hemoglobin, WBC, and platelet counts over time were summarized descriptively.

Analyses of changes in palpable spleen length included both the percentage of patients with a ≥ 50% reduction in spleen size among those patients with a spleen length measurement at baseline and the percentage of patients who achieved a nonpalpable spleen measurement among those patients with palpable spleen at baseline. Symptom analyses included both the percentage of patients with a ≥ 50% reduction and those with complete resolution of pruritus, night sweats, and bone pain in patients with symptoms at baseline. For the WBC count, platelet count, spleen, and symptom analyses, patients who discontinued treatment were counted as not having a response for all study visits that they would have completed up to the date of analysis based on their date of enrollment. AEs were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).18 AEs are reported regardless of causality because investigator-assessed attribution of AEs has been shown to be difficult to determine and of limited value.19 Methods for the pharmacodynamic and molecular analyses performed during the study are provided in the online supplemental material.

### RESULTS

#### Patients

Starting in July 2008, a total of 34 patients with PV from 6 centers in the United States and Italy were enrolled in the current ongoing study. Baseline characteristics of the patients reflected an advanced disease status (Table 1). The median hematocrit was 46.7%, and all patients had received at least 1 prior therapy, with the most common being hydroxyurea. The majority of patients (70.5%) required at least 2 phlebotomies within the 24 weeks before the first dose. At the time of data cutoff, the median follow-up duration was 154 weeks (range, 35 weeks-179 weeks) or 35.4 months (range, 8.1 months-41.2 months). Twenty-six of 34 patients (76%) remained on the study for at least 144 weeks (online supplemental material Fig. S1). Reasons for discontinuation included progression to myelofibrosis (3 patients), withdrawal of consent (2 patients), AEs (2 patients), and other causes (1 patient) (online supplemental material Fig. S2).

#### Efficacy

Response, as defined by modified 2009 ELN criteria, was achieved in 97% of patients by week 24 (Fig. 1a).

### TABLE 1. Baseline Demographic and Clinical Characteristics

| Characteristic | No. (N = 34) |
|---------------|-------------|
| Median age (range), y | 57.5 (21-81) |
| Female, % | 50.0 |
| Median mo since diagnosis (range) | 115 (9-266) |
| Median hematocrit (range), % | 46.7 (34.5-51.7) |
| Patients with ≥2 phlebotomies in 24 wks prior to first dose, % | 70.5 |
| Median platelet count (range), ×10⁹/L | 526.5 (170-927) |
| Median WBC count (range), ×10⁹/L | 13.2 (7.7-54.7) |
| Median palpable spleen length (range), cm | 9.0 (1-21) |
| JAK2V617F-positive, % | 100 |
| Median JAK2V617F allele burden (range), % | 72.0 (20-93) |
| No. of prior therapies, (%) | |
| 1 | 27 (79.4) |
| 2 | 5 (14.7) |
| 3 | 2 (5.9) |
| No. of prior medications used, (%) | |
| Hydroxyurea* | 31 (91.2) |
| Anagrelide | 3 (8.8) |
| IFN | 2 (5.9) |
| Busulfan | 2 (5.9) |
| Pipobroman | 2 (5.9) |
| Cytarabine | 1 (2.9) |
| Cyclophosphamide | 1 (2.9) |
| Omacetaxine mepesuccinate | 1 (2.9) |
| Pegylated IFN | 1 (2.9) |

Abbreviations: JAK, Janus kinase; IFN, interferon; WBC, white blood cell.

*The median palpable spleen length is for the 23 patients with a palpable spleen and for whom measurement was recorded at baseline.

* Three patients received previous chemotherapy and were deemed by the clinical investigator to not be candidates for hydroxyurea therapy. These patients met the eligibility criteria for study entry of hematocrit > 45%.
Twenty patients (59%) achieved a CR as their best response and 13 patients (38%) achieved a PR as their best response. The majority of CRs occurred within the first year (Fig. 1b). Response was durable; among responding patients, the probability of maintaining a hematocrit $<45\%$ without phlebotomy for 48 weeks and 144 weeks, respectively, was 85% and 61% (Fig. 1c). Of the 11 patients who lost their response by experiencing a hematocrit $\geq 45\%$ at any time after their initial response, 8 patients had a subsequent hematocrit $<45\%$ without an intervening phlebotomy, 2 patients discontinued therapy (AE of renal neoplasm, consent withdrawn), and 1 patient remains on therapy, but without an available follow-up hematocrit measurement before data cutoff.

Four patients required phlebotomy during the study; of these, 3 required phlebotomy within the first 15 days and did not require any further phlebotomy through the time of last follow-up. One patient did not respond to therapy and required 3 phlebotomies during the study, the last of which occurred on day 381. This patient was subsequently phlebotomy free for 88 weeks and was continuing on study at the time of the data cutoff. The reduction in phlebotomy requirements was reflected in the pattern of hemoglobin over time. The median hemoglobin at baseline was 146.0 g/L, reached a nadir of 115.5 g/L at week 12, and recovered to 128.0 g/L at week 144 (Fig. 2a).

Of 25 patients with a WBC count $>10 \times 10^9$/L at baseline, a sustained reduction in the WBC count to $\leq 10 \times 10^9$/L was achieved in 76% of patients. Of 15 patients with a WBC count $>15 \times 10^9$/L at baseline, a sustained reduction in the WBC count to $\leq 10 \times 10^9$/L was achieved in 73% of patients. The median WBC count at baseline in all 34 patients was $13.2 \times 10^9$/L; this decreased after treatment with ruxolitinib to $6.9 \times 10^9$/L at week 144 (Fig. 2b). Of 23 patients with a platelet count $>400 \times 10^9$/L at baseline, a sustained reduction to a platelet count of $\leq 400 \times 10^9$/L was achieved in 74% of patients. Of the 13 patients with a platelet count $>600 \times 10^9$/L at baseline, a sustained reduction to a platelet count $\leq 400 \times 10^9$/L was achieved in 69% of patients. The median platelet count at baseline in all 34 patients was $526.5 \times 10^9$/L; this was reduced with treatment to $281.0 \times 10^9$/L at week 144 (Fig. 2c).

Reduction in palpable spleen length was rapid. Among patients with palpable splenomegaly with a recorded spleen measurement at baseline, 70% achieved a $\geq 50\%$ reduction in palpable spleen at week 24. In addition, 44% of patients with palpable splenomegaly at baseline reduced their spleen size to become nonpalpable at week 24. By week 144, 64% of patients had achieved a $\geq 50\%$ reduction in palpable spleen length and 63% had reduced their spleen size to become nonpalpable (Fig. 2d). Clinically meaningful improvements in
pruritus, night sweats, and bone pain were observed within 4 weeks of the initiation of therapy and were maintained through week 144 (Fig. 3).

**Pharmacodynamic and Molecular Parameters**

All patients were found to be JAK2V167F-positive and had a JAK2V617F allele burden of ≥20% at baseline. Ruxolitinib treatment decreased the JAK2V617F allele burden by a mean of 8%, 14%, and 22%, respectively, after 48 weeks, 96 weeks, and 144 weeks (online supplemental material Fig. S3). The percentage of patients who achieved a partial (≥50%) reduction in the JAK2V617F allele burden at any time during the first year, any time during the first 2 years, and any time during the first 3 years of therapy were 5.9%, 14.7%, and 23.5%, respectively. No patients achieved a complete reduction (<1% JAK2V617F allele burden). Suppression of JAK-STAT

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**Figure 2.** Laboratory and clinical responses to treatment with ruxolitinib are shown. (a) The median hemoglobin levels with their interquartile ranges (IQRs) are shown. (b) The median white blood cell count with the IQR is shown. (c) The median platelet count with the IQR is shown. (d) The percentage of patients with a palpable spleen at baseline who achieved a ≥50% reduction in palpable spleen length and those who reduced their spleen size to nonpalpable at each visit are shown. Twenty-five patients had a palpable spleen at baseline; therefore, for the analysis of palpable to nonpalpable spleen length, the number was 25 at all visits except for week 144, when there were 24 evaluable patients (1 patient was missing data). Two patients had a palpable spleen at baseline but no specific measurement was recorded. Thus, for analysis of the ≥50% reduction in palpable spleen length, the number was 23 at all visits except for week 144, when there were 22 evaluable patients (1 patient had missing data).

**Figure 3.** Reduction in polycythemia vera-associated symptoms with ruxolitinib therapy is shown. The percentages of patients who were treated with ruxolitinib and who achieved a ≥50% reduction and a 100% reduction in pruritus, night sweats, and bone pain over the previous week among patients with symptom scores > 2 at baseline are shown. A 100% reduction corresponds to a score of 0 for individual symptoms.
signaling by ruxolitinib was demonstrated by decreased phosphorylated STAT3 (pSTAT3) levels in peripheral blood leukocytes (online supplemental material Fig. S4a). Changes in plasma levels of inflammatory markers and mediators, granulocyte leukocyte alkaline phosphatase, and microRNA expression after ruxolitinib treatment are described in the online supplemental material.

**Exposure and Safety**
At the time of data cutoff, there were 87.2 patient-years of exposure and the median duration of exposure was 152 weeks (range, 31 weeks-177 weeks) or 35.0 months (range, 7.1 months-40.7 months). At day 56, efficacy and safety were found to be similar among the 3 cohorts. Because the study envisaged a strategy of individual dose titration based on safety and efficacy, the sponsor and investigators agreed to expand the lowest starting dose that demonstrated efficacy (10 mg twice daily), with allowances for dose modification on an individual patient basis (online supplemental material Fig. S2). The mean and median total daily doses for the entire study were 25.3 mg and 21.7 mg, respectively, corresponding to a dose of approximately 10 mg twice daily.

Thrombocytopenia and anemia were the most common hematologic AEs and were primarily grade 1 (Table 2). Anemia of ≥ grade 3 occurred in 3 patients (9%) and thrombocytopenia of ≥ grade 3 occurred in 3 patients (9%) (1 patient had both). Of these 5 patients, 3 patients with anemia of ≥ grade 3 or thrombocytopenia of ≥ grade 3 and 1 additional patient with grade 2 anemia had worsening of their underlying disease (worsening splenomegaly, leukocytosis, or anemia). Of these 4 patients, 3 subsequently developed myelofibrosis and were discontinued from the study. Treatment-related anemia and thrombocytopenia were generally manageable with dose interruptions and/or reductions; there were no treatment discontinuations reported for these events.

The most common (≥10%) nonhematologic AEs, regardless of causality, were diarrhea (all grade 1 or 2) and pyrexia (mostly grade 1 or 2) (Table 2). Seventeen nonhematologic AEs of ≥ grade 3 were reported in 12 patients. Two patients experienced pneumonia; 1 continued treatment and the other patient’s dosing (15 mg twice daily) was briefly interrupted before continuing on study. Two patients experienced increased gamma-glutamyl transferase; no other liver function abnormalities or other concomitant AEs were reported at the time of this increase, and both patients continued treatment. One patient experienced pulmonary embolism that occurred immediately upon disembarking from an airplane after a long-distance flight; no other thromboembolic events were reported. No cases of transformation to AML were reported. Two patients discontinued treatment because of nonhematologic AEs of ≥ grade 3 (renal neoplasm, atrial flutter). Evaluation of AEs at the time of treatment discontinuation demonstrated no pattern of events to indicate a withdrawal syndrome.

**DISCUSSION**
The 2009 ELN clinicohematologic response criteria were developed to facilitate the assessment of investigational

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**TABLE 2.** Adverse Events Reported in ≥10% of All Patients, by MedRA Preferred Term

| Adverse Event                                      | Grade 1, No. (%) | Grade 2, No. (%) | Grade 3, No. (%) | Grade 4, No. (%) |
|----------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Hematologic (based on laboratory values)           |                 |                 |                 |                 |
| Anemia                                             | 18 (52.9)       | 5 (14.7)        | 2 (5.9)         | 1 (2.9)         |
| Thrombocytopenia                                   | 9 (26.5)        | 3 (8.8)         | 1 (2.9)         | 2 (5.9)         |
| Neutropenia                                        | 2 (5.9)         | 3 (8.8)         | 1 (2.9)         | 0               |
| Nonhematologic                                     |                 |                 |                 |                 |
| Diarrhea                                           | 5 (14.7)        | 3 (8.8)         | 0               | 0               |
| Pyrexia                                            | 5 (14.7)        | 1 (2.9)         | 1 (2.9)         | 0               |
| Back pain                                          | 5 (14.7)        | 1 (2.9)         | 0               | 0               |
| Cough                                              | 6 (17.6)        | 0               | 0               | 0               |
| Weight increase                                    | 2 (5.9)         | 4 (11.8)        | 0               | 0               |
| Herpes zoster                                      | 1 (2.9)         | 4 (11.8)        | 0               | 0               |
| Vomiting                                           | 3 (8.8)         | 1 (2.9)         | 1 (2.9)         | 0               |
| Abdominal pain                                     | 2 (5.9)         | 2 (5.9)         | 0               | 0               |
| Blood creatine phosphokinase increased             | 2 (5.9)         | 2 (5.9)         | 0               | 0               |
| Dizziness                                          | 4 (11.8)        | 0               | 0               | 0               |
| Hyperuricemia                                      | 4 (11.8)        | 0               | 0               | 0               |
| Influenza                                          | 3 (8.8)         | 1 (2.9)         | 0               | 0               |
| Upper respiratory tract infection                  | 1 (2.9)         | 3 (8.8)         | 0               | 0               |
| Asthenia                                           | 2 (5.9)         | 1 (2.9)         | 1 (2.9)         | 0               |

Abbreviation: MedRA, Medical Dictionary for Regulatory Activities.

Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).
therapies for the management of patients with PV, and include assessment of 5 clinically relevant factors (hematocrit, WBC count, platelet count, splenomegaly, and symptoms).16 Based on the modified 2009 ELN criteria used in this study, a response to ruxolitinib was achieved in 97% of patients by week 24; 59% of patients achieved a CR, with all 5 factors having normalized. Responses were durable and 26 patients (76%) remained on therapy after a median follow-up of approximately 3 years. Only 1 patient did not meet the modified 2009 ELN response criteria used in this analysis but was continuing on study at the time of last follow-up. Other therapies are being investigated in patients with PV, most notably pegylated IFN-α-2a. In two phase 2 studies, treatment with pegylated IFN-α-2a yielded high hematologic response rates (70%-82%) in both treatment-naïve and previously treated patients with PV.20-22 However, these studies did not assess an improvement in PV-related symptoms, which can significantly affect a patient’s quality of life.23 In addition, IFN-related AEs led to therapy discontinuation in 10%20 and 23%22 of patients, respectively, after a median follow-up of 21 months and 77 months. In the current study, ruxolitinib provided rapid and sustained relief of pruritus, night sweats, and bone pain, and no patients discontinued therapy as a result of AEs generally related to ruxolitinib after a median of approximately 3 years of therapy. The most common hematologic AEs were anemia and thrombocytopenia, which were predominantly grade 1, and were manageable with dose reductions or interruptions. The most common nonhematologic AE was low-grade diarrhea, which was observed at a similar rate (23.5%) as was noted in patients with myelofibrosis in the COMFORT-I (Controlled Myelofibrosis Study with Oral JAK inhibitor Treatment) study who received either ruxolitinib (23.2%) or placebo (21.2%).10

Progression to myelofibrosis was reported in 3 patients from this cohort with advanced PV, with a median time since PV diagnosis at the time of study entry of approximately 10 years and a median JAK2V617F allele burden of 72%. These results should be viewed within the context of published data that have demonstrated associations between longer disease duration (>10 years)24 and high JAK2V617F allele burden (>50%)25 with the risk of progression to myelofibrosis.

The marked reductions in pSTAT3, plasma levels of inflammatory markers and mediators, and granulocyte leukocyte alkaline phosphatase expression observed within 4 weeks of the initiation of ruxolitinib suggest that suppression of JAK signaling by ruxolitinib, with the resulting suppression of disease-related inflammation and granulocyte activation, may be the primary basis for the efficacy of ruxolitinib in patients with PV. However, evaluation of other possible effects of ruxolitinib, such as the change in microRNA expression presented herein, may help us to better understand the biologic effects of JAK1/JAK2 inhibition in patients with PV.

Current treatment options for patients with PV who are refractory to or intolerant of hydroxyurea are limited, and an effective, well-tolerated therapy remains an unmet need. Maintenance of hematocrit <45% is a rational goal to reduce thrombotic risk.26 Other disease-associated risk factors, such as leukocytosis27,28 and enlarged spleen,29 may also play an important role in defining patient outcomes. Therefore, it is notable that in our population of patients with advanced PV who were refractory to or intolerant of hydroxyurea, ruxolitinib reduced hematocrit to <45% without phlebotomy; normalized WBC and platelet counts; reduced palpable splenomegaly; and provided relief of pruritus, night sweats, and bone pain without overt toxicity. In addition, ruxolitinib was able to rapidly and durably manage these primary manifestations of PV in the majority of patients enrolled in the current study. This was similar to clinical study experience in patients with intermediate-2 or high-risk myelofibrosis, in whom ruxolitinib was able to reduce spleen volume and improve myelofibrosis-related symptoms and quality-of-life measures.10,12 In addition to providing clinical benefit with respect to primary disease manifestations, ruxolitinib therapy was associated with prolonged survival compared with placebo10,30 or best available therapy31 in patients with myelofibrosis. Additional controlled, larger, and longer-term studies are needed to fully address whether and how ruxolitinib may affect the natural history of patients with advanced PV.

In conclusion, the results of the current study demonstrated that patients with advanced PV who are refractory or intolerant to hydroxyurea achieve a clinically meaningful and durable benefit from treatment with ruxolitinib, therefore addressing an important unmet medical need. The ongoing phase 3 RESPONSE (Study of Efficacy and Safety in Polycythemia Vera Subjects Who Are Resistant to or Intolerant of Hydroxyurea: JAK Inhibitor INC424 (INCB018424) Tablets Versus Best Available Care; ClinicalTrials.gov identifier NCT01243944) and RELIEF (Switch Study From Hydroxyurea to Ruxolitinib for RELIEF of Polycythemia Vera Symptoms; ClinicalTrials.gov identifier NCT01632904) studies will further characterize the safety and efficacy of ruxolitinib in patients with PV.

FUNDING SUPPORT
This study was funded by Incyte Corporation. Additional pharmacodynamic and molecular analyses were funded by Associazione
Italiana per la Ricerca sul Cancro (AIRC). Studies in Pavia and Florence, Italy were supported by a grant from Ministero dell’Istruzione, dell’Università e della Ricerca (PRIN 2008) to Drs. Cazzola and Vannucchi and a grant from AIRC (Milan, Italy), “Special Program Molecular Clinical Oncology 5\times1000” to AIRC-Gruppo Italiano Malattie Mieloproliferative (project 1005). A detailed description of the AIRC-Gruppo Italiano Malattie Mieloproliferative project is available at www.progettoagmm.it. Editorial assistance provided by Evidence Scientific Solutions (Philadelphia, PA) was funded by Incyte Corporation.

CONFLICT OF INTEREST DISCLOSURES

Dr. Verstovsek received research funding from Incyte Corporation. Dr. Barbui received honoraria for participation on Novartis advisory boards. Dr. Kantarjian received grant support for The University of Texas MD Anderson Cancer Center from Incyte Corporation. Dr. Vannucchi participated in a Novartis advisory board meeting. Drs. He and Sandor are employees of and own stock in Incyte Corporation. Dr. Contel was a past salaried employee of Incyte Corporation. Dr. Mookerjee has stock options and was a past salaried employee of Incyte Corporation and is currently a salaried employee of GlaxoSmithKline and owns stock in AstraZeneca. Dr. Rambaldi was invited by and paid by Novartis to be a paid speaker at corporate symposia.

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