Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study

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See Comment page 9

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Summary

Background In the pivotal RESPONSE study, ruxolitinib, a Janus kinase (JAK)1 and JAK2 inhibitor, was superior to best available therapy at controlling haematocrit and improving splenomegaly and symptoms in patients with polycythaemia vera with splenomegaly who were inadequately controlled with hydroxyurea. In this study, we assessed the efficacy and safety of ruxolitinib in controlling disease in patients with polycythaemia vera without splenomegaly who need second-line therapy.

Methods RESPONSE-2 is a randomised, open-label, phase 3b study assessing ruxolitinib versus best available therapy in patients with polycythaemia vera done in 48 hospitals or clinics across 12 countries in Asia, Australia, Europe, and North America. Eligible patients (aged ≥18 years) with polycythaemia vera, no palpable splenomegaly, and hydroxyurea resistance or intolerance were stratified by their hydroxyurea therapy status (resistance *vs* intolerance) and randomly assigned (1:1) by an interactive response technology provider using a validated system to receive either oral ruxolitinib 10 mg twice daily or investigator-selected best available therapy (hydroxyurea [at the maximum tolerated dose], interferon or pegylated interferon, pipobroman, anagrelide, approved immunomodulators, or no cytoreductive treatment). Investigators and patients were not masked to treatment assignment; however, the study sponsor was masked to treatment assignment until database lock. The primary endpoint was the proportion of patients achieving haematocrit control at week 28. Analyses were done according to an intention-to-treat principle, including data from all patients randomly assigned to treatment. This study is registered with ClinicalTrials.gov (NCT02038036) and is ongoing but not recruiting patients.

Findings Between March 25, 2014, and Feb 11, 2015, of 173 patients assessed for eligibility, 74 patients were randomly assigned to receive ruxolitinib and 75 to receive best available therapy. At randomisation, best available therapy included hydroxyurea (37 [49%] of 75 in the best available therapy group), interferon or pegylated interferon (ten [13%] of 75), pipobroman (five [7%] of 75), lenalidomide (one [1%] of 75), no treatment (21 [28%] of 75), and other (one [1%] of 75). Haematocrit control was achieved in 46 (62%) of 74 ruxolitinib-treated patients versus 14 (19%) of 75 patients who received best available therapy (odds ratio 7·28 [95% CI 3·43–15·45]; p<0·0001). The most frequent haematological adverse events of any grade were anaemia (ten [14%] of 74 in the ruxolitinib group *vs* two [3%] of 75 in the best available therapy group) and thrombocytopenia (two [3%] *vs* six [8%]). No cases of grade 3–4 anaemia or thrombocytopenia occurred with ruxolitinib; one patient (1%) reported grade 3–4 anaemia and three patients (4%) reported grade 3–4 thrombocytopenia in the group receiving best available therapy. Frequent grade 3–4 non-haematological adverse events were hypertension (five [7%] of 74 *vs* three [4%] of 75) and pruritus (0 of 74 *vs* two [3%] of 75). Serious adverse events occurring in more than 2% of patients in either group, irrespective of cause, included thrombocytopenia (none in the ruxolitinib group *vs* two [3%] of 75 in the best available therapy group) and angina pectoris (two [3%] of 74 in the ruxolitinib group *vs* none in the best available therapy group). Two deaths occurred, both in the best available therapy group.

Interpretation RESPONSE-2 met its primary endpoint. The findings of this study indicate that ruxolitinib could be considered a standard of care for second-line therapy in this post-hydroxyurea patient population.

Funding Novartis.

Introduction

Polycythaemia vera is a myeloproliferative neoplasm characterised by clonal stem-cell proliferation of erythroid, myeloid, and megakaryocytic cell lines.[1,2] Most patients have an activating Janus kinase 2 (*JAK2*) mutation (*JAK2* Val617Phe or exon 12 mutation), leading to an overactive JAK–STAT signalling pathway, unregulated myeloid cell proliferation, and imbalances in cytokine production.[1,3] Polycythaemia vera is characterised by erythrocytosis, with an associated increase in white blood cell and platelet counts in about 40% of patients.[4] Patients with polycythaemia vera are at high risk of vascular complications, which are associated with advanced age, history of thrombosis, and leukocytosis,[5]

Research in context

Evidence before this study

We searched PubMed for articles published in the past 10 years (July 1, 2006–July 1, 2016) that reported findings from phase 3 studies assessing commercially available therapies in patients with polycythaemia vera who were resistant to or intolerant of hydroxyurea. The search terms used were "polycythemia vera AND hydroxyurea AND resistance", "polycythemia vera AND second-line", and "polycythemia vera AND phase 3". Before our study, the only phase 3 study assessing treatment in this setting was the RESPONSE study, which investigated the Janus kinase (JAK)1 and JAK2 inhibitor ruxolitinib in patients with polycythaemia vera who had an inadequate response to or unacceptable side-effects from hydroxyurea and presented with splenomegaly. Other studies assessed the use of anagrelide or busulfan in patients with polycythaemia vera who were resistant to or intolerant of hydroxyurea. Both agents showed efficacy, but the studies were small (≤15 patients with polycythaemia vera). Busulfan, in particular, was associated with a high rate of transformation. Interferon was considered a second-line therapy for patients with polycythaemia vera and was assessed in two phase 2 studies, with positive results. However, patients in these two studies were not resistant to or intolerant of hydroxyurea. Of interest, the use of interferon was reported in the prospective RESPONSE study; however, response rates were inferior to those of ruxolitinib in patients with polycythaemia vera who had an inadequate response to or intolerable side-effects from hydroxyurea. Our search also identified reviews of the current treatment landscape for patients with polycythaemia vera. In general, these reviews highlighted the few treatment options for those who are resistant to or intolerant of hydroxyurea, with JAK inhibitors representing a new therapeutic option for patients with polycythaemia vera in need of second-line therapy.

Added value of this study

Findings from our randomised phase 3b study showed that ruxolitinib is superior to best available therapy at providing control of haematocrit, inducing complete haematological remission, and improving disease-associated symptoms in patients with polycythaemia vera who have an inadequate response to or have unacceptable side-effects from hydroxyurea therapy, regardless of spleen size.

Implications of all the available evidence

Our findings, taken together with other studies in patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea, show that ruxolitinib is safe and effective in these patients and could be considered a standard of care for second-line therapy in this patient population.

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and these patients also have a shortened life expectancy.[6] Genetic instability predisposes to clonal evolution, and patients might progress to postpolycythaemia vera myelofibrosis or acute myeloid leukaemia.[7,8] Patients with polycythaemia vera also have a substantial symptom burden, including pruritus, fatigue, and night sweats.[9] Additionally, splenomegaly can be observed in about 30% of patients during the course of the disease.[9]

Therapeutic options aim to reduce thrombotic risk and include phlebotomy and low-dose aspirin; cytoreductive drugs, usually hydroxyurea, are given to patients with high-risk disease.[10] A prospective randomised trial unequivocally showed that maintenance of haematocrit level at less than 45% resulted in a four-times lower incidence of death from cardiovascular causes or major thrombosis than did maintaining haematocrit at 45–50%.[11] A subsequent multivariable analysis found that a white blood cell count of greater than 11×10^9 cells per L was an independent risk factor for thrombosis.[12] Improvement of polycythaemia vera-related symptoms during follow-up has already been shown to improve quality of life.[13]

In some patients, conventional therapies can lose effectiveness over time.[14,15] Although hydroxyurea is well tolerated in most patients, about 15–20% of patients become resistant or intolerant,[14,15] with hydroxyurea resistance affecting survival and increasing the risk of progression to myelofibrosis.[4,14] Additionally, patients who are intolerant of hydroxyurea can have adverse side-effects, such as drug-induced fever, mouth ulcers, leg ulcers, and skin malignancies, which necessitate discontinuation of first-line therapy.[16]

Patients who are resistant to or intolerant of hydroxyurea have few therapeutic options.[5] Ruxolitinib, a JAK1 and JAK2 inhibitor, was approved in the European Union[17] on Jan 22, 2015, for patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea and in the USA[18] on Dec 4, 2014, for patients who have had an inadequate response to or are intolerant of the treatment. These approvals were based on findings from the phase 3 RESPONSE study, which showed ruxolitinib to be superior to the best available therapy at controlling haematocrit, improving splenomegaly, and improving symptoms in patients with polycythaemia vera and disease-associated splenomegaly who had an inadequate response to or unacceptable side-effects from hydroxyurea.[13] This benefit occurred regardless of the degree of splenomegaly at baseline.[19]

Although splenomegaly is an important indicator of advanced disease[20] and has been associated with decreased survival,[21] only 18% of patients who are resistant to or intolerant of hydroxyurea by European LeukemiaNet (ELN) criteria have splenomegaly.[15] We present findings from the primary analysis of the RESPONSE-2 study, a phase 3b study in patients without palpable splenomegaly who had an inadequate response to or unacceptable side-effects from hydroxyurea.

Methods

Study design and participants

RESPONSE-2 is a prospective, randomised, open-label, multicentre, phase 3b study assessing the efficacy and safety of ruxolitinib versus best available therapy in patients with polycythaemia vera without splenomegaly who need second-line therapy. The study was done in 48 hospitals or clinics across 12 countries (Australia, Belgium, Canada, France, Germany, Hungary, India, Israel, Italy, Korea, Spain, and Turkey; appendix pp 6–7). The study was approved by the institutional review board or central ethics committee at each participating institution and was done in accordance with the Declaration of Helsinki.

See Online for appendix

Eligible patients were aged 18 years or older with a diagnosis of polycythaemia vera according to WHO criteria,[2] an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or lower, no palpable splenomegaly, no previous treatment with JAK inhibitors, and were phlebotomy dependent. Patients were judged to be phlebotomy dependent if their haematocrit was 40–45% with two phlebotomies or more spaced at least 4 weeks apart within 24 weeks before screening, or if their haematocrit level was higher than 45% with at least one phlebotomy within 16 weeks before screening. Before randomisation, eligible patients with haematocrit greater than 45% entered a haematocrit control period to ensure that their haematocrit was similar and controlled at study initiation, preventing any potential bias; a haematocrit between 40–45% achieved with phlebotomy within 14 days before randomisation was required. Eligible patients also had to meet the definition of hydroxyurea resistance (an inadequate response to hydroxyurea treatment) or intolerance (unacceptable side-effects from hydroxyurea treatment) according to modified ELN criteria (appendix p 1).[22] Patients with inadequate liver or renal function (defined by grade ≥2 hepatic encephalopathy, hepatocellular disease, direct bilirubin concentration ≥2 times the upper limit of normal [ULN], alanine aminotransferase ≥2·5 times the ULN, or an estimated glomerular filtration rate <30 mL/min/1·73 m² or on dialysis), a platelet count lower than 100×10^9 platelets per L or an absolute neutrophil count of lower than 1×10^9 cells per L, active infections, or patients who were pregnant or lactating or unable to comply with the protocol were ineligible. Additionally, patients were excluded if they had impaired gastrointestinal function that could substantially change the absorption of ruxolitinib, had an active malignancy during the previous 5 years (except for treated cervical intraepithelial neoplasia, basal cell, or squamous-cell carcinoma of the skin, with no recurrence for 3 years), clinically significant cardiac disease, a history of progressive multifocal leukoencephalopathy, or other conditions that, in the opinion of the treating investigator, would jeopardise patient safety. Prohibited past medications included pegylated interferon-alfa-2a within 5 weeks of screening, previous ^{32}P therapy or JAK inhibitor therapy, ongoing treatment with a potent systemic CYP3A4 inhibitor at screening, or ongoing or previous participation in an investigational study within 30 days of baseline or within five half-lives of the investigational drug. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to receive either ruxolitinib or best available therapy. Patients were stratified by whether they had an inadequate response to hydroxyurea or unacceptable side-effects from hydroxyurea. Each patient was enrolled by the treating investigator and was assigned a sequential patient number; the investigator then contacted the provider of interactive response technology, which included a telephone-based interactive voice response system and a web-based interactive response system. Each patient was randomly assigned by using a validated system that automated the random assignment of patient numbers to randomisation numbers linked to the treatment groups. Investigators and patients were not masked to treatment assignment in this open-label study; the study sponsor remained masked to treatment allocation until database lock for the primary analysis except for patient emergencies or regulatory reporting requirements.

Procedures

The starting dose of oral ruxolitinib tablets (Novartis Pharmaceuticals, Basel, Switzerland) was 10 mg twice daily and could be titrated, in 5 mg increments, throughout treatment if there was inadequate efficacy or if safety concerns arose (maximum 25 mg twice daily, minimum 5 mg once daily; appendix pp 1–2). Single-agent best available therapy was chosen by the investigator based on standard clinical practice and clinical experience and could include hydroxyurea (at the maximum tolerated dose), interferon or pegylated interferon, pipobroman, anagrelide, approved immunomodulators such as lenalidomide and thalidomide, or no cytoreductive treatment (observation alone). Cytoreductive agents in the best available therapy control group were used only as monotherapy because many of the available therapies when combined with hydroxyurea possess an increased potential for leukaemic transformation.[10,23] The best available therapy regimen could be changed if the patient had an insufficient response to the treatment or if therapy-related toxic effects occurred that necessitated drug discontinuation. All patients were to receive low-dose aspirin (75–150 mg/day), unless medically contraindicated.

Patient hospital and clinic visits were planned every 4 weeks from randomisation up to week 28 or end of treatment, whichever occurred first. Assessments done at each study visit included patient questionnaires, vital signs, electrocardiogram measurements, physical

examination, adverse events, concomitant medications, medical resource use, and blood sampling or laboratory assessments.

Analysis of the primary outcome took place when all patients completed week 28 or discontinued study treatment before week 28. Patients randomly assigned to best available therapy could cross over to ruxolitinib from week 28 if they did not meet the primary endpoint or later if treatment was shown to be ineffective (ie, haematocrit level >45% or if they received phlebotomy) or safety-related reasons. Data after crossover were excluded from the primary analysis. A long-term follow-up is planned for up to 5 years after the last patient is randomised; this follow-up will explore the long-term safety and efficacy of ruxolitinib in this patient population.

Ruxolitinib dose could be increased by 5 mg twice a day in increments (up to 25 mg twice a day) for inadequate efficacy (ie, haematocrit increase of 3 or greater percentage points from baseline, white blood cell count greater than the ULN, palpable spleen). Dose reductions of 5 or 10 mg twice a day (down to a minimum dose of 5 mg once a day) were required for patients with haemoglobin lower than 100 g/L or platelets less than 75×10^9 platelets per L. Dose interruptions were required for patients with a haemoglobin lower than 80 g per L, a platelet count of less than 50×10^9 platelets per L, or an absolute neutrophil count of less than $1\cdot0\times10^9$ cells per L (appendix pp 1–2).

The safety population included all patients who received at least one dose of study medication, including those who received no cytoreductive treatment; safety assessments were done at each study visit by the treating physician by use of physical examination, electrocardiography, serum chemistry, haematology, and urinalysis. The safety analyses included data up to 30 days after discontinuation from randomised treatment. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.03. Adverse events, regardless of cause, occurring in at least 5% of patients in either treatment group up to week 28 are summarised; additionally, rates were adjusted for patient-year exposure and reported for those occurring at a rate of at least ten per 100 patient-years in either treatment group.

Patients could withdraw from the study or be discontinued by the treating investigator at any time; patients were discontinued because of withdrawal of consent, patient or physician decision, pregnancy, study drug discontinuation for safety reasons, protocol deviation, loss to follow-up, or death. The data were centrally reviewed, and statistical analysis of the data was done by Novartis personnel.

Outcomes

The primary endpoint was the proportion of patients who achieved haematocrit control at week 28. Haematocrit control was defined as the absence of phlebotomy eligibility between weeks 8 and 28, with phlebotomy eligibility occurring only once after randomisation and before week 8. Phlebotomy eligibility was defined as confirmed haematocrit level higher than 45% and at least 3 percentage points higher than baseline, or confirmed haematocrit level higher than 48%,[24] and was validated based on findings from the CYTO-PV study (appendix p 1).[11] The primary endpoint was assessed in all patients randomised to treatment. Patients with missing assessments that prevented the study of the primary endpoint were considered non-responders. Samples for haematology assessments were sent to a local laboratory, which was used for all haematology parameters for a given patient throughout the study. Samples were collected 7 days before or following the scheduled patient visit. Phlebotomy details for patients who met phlebotomy eligibility criteria were entered into the electronic case report form by the treating physician.

The key secondary endpoint was the proportion of patients achieving complete haematological remission (haematocrit control, white blood cell count $<10\times10^9$ cells per L, and platelet count $\leq400\times10^9$ platelets per L) at week 28. Other secondary endpoints were the durability of haematocrit control and complete haematological remission (proportion of patients achieving haematocrit control and complete haematological remission at weeks 52 and 80), the change in phlebotomy eligibility over time, change in haematocrit level over time, change in spleen length, change in ECOG status, transformation-free survival, overall survival, safety, and changes in patient-reported outcomes. Patient-reported outcomes were assessed from baseline to week 28 by several questionnaires, which were the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS), the Pruritus Symptom Impact Scale (PSIS), the EuroQol-5D-5L (EQ-5D-5L), the Work Productivity and Activity Impairment (WPAI), and the Patient Global Impression of Change (PGIC; appendix p 3). The MPN-SAF TSS assesses ten disease-related symptoms on a scale of 0 (absent) to 10 (worst imaginable). In patients with a baseline MPN-SAF TSS of 20 or higher, we assessed the proportion of those achieving complete resolution of disease-related symptoms, defined as a reduction in MPN-SAF TSS of 10 points or more from baseline that was maintained from week 16 to week 28. Details of other patient-reported outcomes have been listed in the appendix (p 3).

Statistical analysis

The sample size was calculated based on the results for the haematocrit control portion of the compound primary endpoint of the RESPONSE trial.[13] Under the assumption of a haematocrit control rate of 20% in the best available therapy group and 50% in the ruxolitinib group (corresponding to an odds ratio of 4·0), a total of 116 patients were needed to detect a significant difference

between treatment groups with two-sided t-test at the significance level of 0·05 and 90% power. We planned to enrol 130 patients (65 in each group) to allow for an estimated 10% attrition rate. The efficacy analysis for the primary and key secondary endpoints was done according to an intention-to-treat principle, including data from all patients randomly assigned to treatment. Patients with missing assessments that prevented investigation of the primary and secondary endpoints were regarded as non-responders. Assessments of change and percentage change from baseline included all patients with measurements at baseline and after baseline. We used logistic regression to identify whether treatment effects were the same across subgroups of hydroxyurea therapy status (intolerant *vs* resistant), sex (men *vs* women), age group (≤60 *vs* >60 years), and risk category (low [no risk factors] *vs* high [one or two risk factors in patients aged >60 years or with thromboembolic history, or both]).

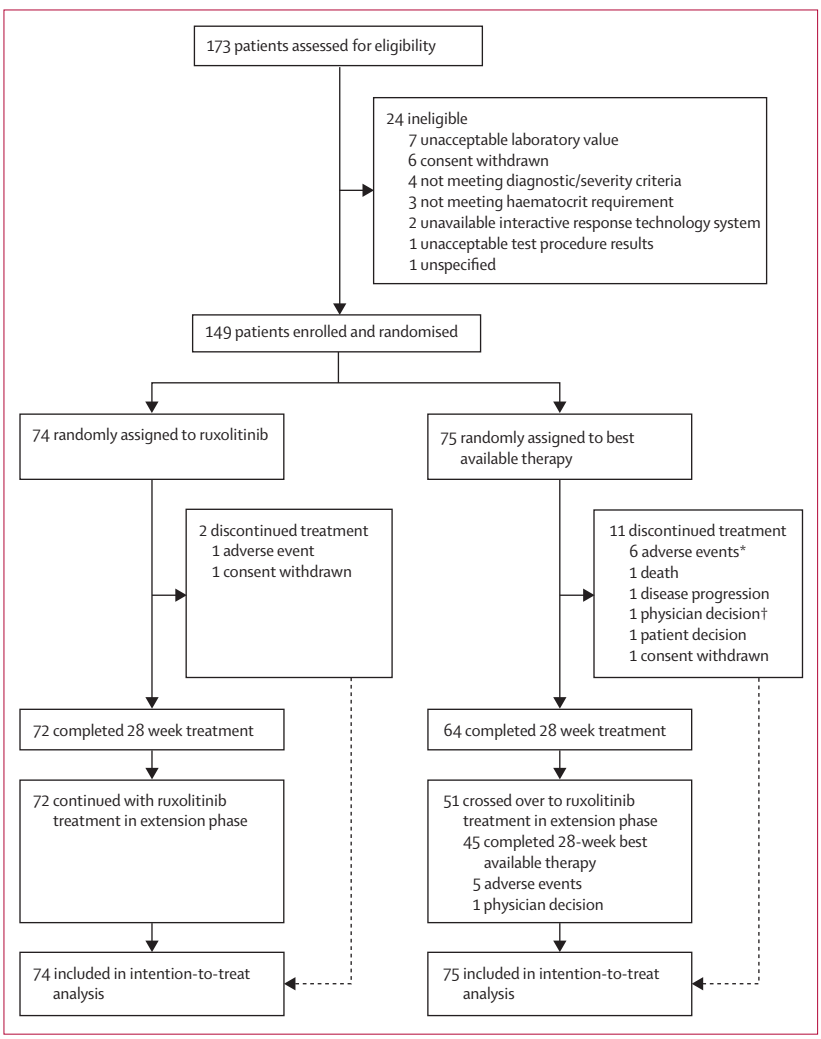

Figure 1: **Trial profile**
*Five of these patients who were removed because of adverse events were crossed over to ruxolitinib. †1 patient was crossed over to ruxolitinib treatment because of physician decision.

Other secondary efficacy endpoints were not alpha controlled, and statistical tests were done for descriptive purposes only and were not adjusted for multiple comparisons. Symptom assessments included all patients with available baseline symptom measures. SAS version 9.4 was used for all statistical analyses. The data cutoff date was Sept 29, 2015. This study is registered with ClinicalTrials.gov, number NCT02038036.

Role of the funding source

The study was sponsored and designed by Novartis. Data were analysed and interpreted by the sponsor in collaboration with all the authors; the sponsor was unaware of the treatment group assignments until database lock. The corresponding author had full access to all of the data, prepared the first draft of the report with assistance from a medical writer funded by Novartis, and made the final decision to submit the report for publication. CB, MK, and NM had access to the raw data. All authors reviewed and amended the report, take responsibility for the accuracy and completeness of the data, and verify that the study as reported conforms to the protocol and statistical analysis plan.

Results

Between March 25, 2014, and Feb 11, 2015, a total of 173 patients were screened for eligibility; 149 eligible patients were enrolled and randomly assigned to receive either ruxolitinib (n=74) or best available therapy (n=75; figure 1). In general, baseline characteristics were similar between treatment groups; however, there were slight differences in median age and sex between the groups (table 1). Overall, 105 (70%) of 149 patients across both treatment groups had received only one previous antineoplastic therapy (ie, hydroxyurea). At randomisation, best available therapy included hydroxyurea for 37 (49%) of 75 patients, interferon or pegylated interferon for ten (13%), pipobroman for five (7%), lenalidomide for one (1%), no treatment in 21 (28%), and other treatment for one (1%). When analysed by country, the choice of best available therapy was similar to that observed for the overall study population (appendix p 4). Hydroxyurea was the most commonly used treatment in all countries; interferon was used in four of 12 countries and no cytoreductive treatment in nine countries (appendix p 4).

The median duration of exposure to study treatment was 42·2 weeks (IQR 33·1–55·1) in the ruxolitinib group and 28·4 weeks (27·9–31·4) in the best available therapy group. In the ruxolitinib group, the median dose intensity was 20·0 mg per day (IQR 20·0–25·3). Overall, 21 (28%) of 74 patients given ruxolitinib had a dose reduction, six (8%) of 74 had an interruption, and two (3%) of 74 patients discontinued treatment. The primary reasons for dose changes or interruptions were adverse events in 21 (28%) of 74 patients, insufficient efficacy in 20 (27%), and modifications as per protocol in 16 (22%) patients.

By week 28, two patients (3%) in the ruxolitinib group and 11 (15%) in the best available therapy group had discontinued their randomised treatment (figure 1). The primary reasons for discontinuation in the best available treatment group were adverse events (n=6), and consent withdrawal, death, disease progression, physician decision, and patient decision (n=1 for each reason). 51 (68%) of 75 patients crossed over to ruxolitinib at or after week 28; 45 of these patients completed best available therapy treatment before crossing over, and the other six had discontinued best available therapy because of an adverse event (n=5) or physician decision (n=1). Adverse events that led to discontinuation of treatment in these five patients were mood disorder (in a patient treated with interferon), cough, pain, mouth and vaginal ulcers, upper respiratory tract infection, and urticaria (n=1 for each event; one patient had both upper respiratory tract infection and urticaria). Of the two patients who discontinued treatment in the ruxolitinib group, one patient discontinued treatment because of adverse events (hypoesthaesia and fatigue); the second patient withdrew consent.

46 (62%) of 74 patients in the ruxolitinib group had achieved haematocrit control at week 28 compared with 14 (19%) of 75 patients assigned to best available therapy (odds ratio [OR] 7·28 [95% CI 3·43–15·45], p<0·0001; figure 2). In both treatment groups, haematocrit control was achieved by a greater proportion of patients who had unacceptable side-effects from previous hydroxyurea therapy than by patients who had an inadequate response to previous hydroxyurea treatment (figure 2). Overall, the primary efficacy results were consistent across all subgroups assessed, including sex, age (≤60 *vs* >60 years of age), and risk (data not shown).

In the ruxolitinib group, haematocrit level decreased from baseline (mean 42·8% [SD 1·5]; median 43·0% [IQR 41·7–44·0]) to week 28 (40·2% [4·1]; 40·5% [38·0–42·6]), whereas haematocrit in the best available therapy group increased from baseline (42·7% [1·4]; 42·7% [41·7–44·0]) to week 28 (44·9% [3·8]; 45·1% [42·8–46·7]; appendix p 8). In general, mean haematocrit was lower throughout the study in the ruxolitinib group than in the best available therapy group (appendix p 8). The proportion of patients undergoing phlebotomy procedures between baseline and week 28 was lower in the ruxolitinib group (14 [19%] of 74 patients) than in the best available therapy group (45 [60%] of 75 patients; appendix p 10). 13 (18%) of 74 patients in the ruxolitinib group and 28 (37%) of 75 patients in the best available therapy group had one or two phlebotomies, with substantially fewer patients in the ruxolitinib group receiving more than two phlebotomies (1/74 [1%]) than in the best available therapy group (17/75 [23%]). Overall, the total number of phlebotomies was higher in the best available therapy group (98) than in the ruxolitinib group (19).

For the key secondary endpoint of complete haematological remission, in all patients randomly assigned to treatment, 17 (23%) of 74 patients in the ruxolitinib group achieved complete haematological remission compared with four (5%) of 75 patients in the best available therapy group (OR 5·58 [95% CI 1·73–17·99]; p=0·0019; figure 3). Similar to the primary endpoint,

	Ruxolitinib group (n=74)	Best available therapy group (n=75)
Age (years)		
Median (IQR)	63 (54–71)	67 (61–74)
Age >60 years	46 (62%)	57 (76%)
Sex		
Men	39 (53%)	47 (63%)
Women	35 (47%)	28 (37%)
Median time since diagnosis (years)	6·5 (2·9–10·7)	6·7 (3·2–10·6)
Previous lines of antineoplastic therapies		
One	53 (72%)	52 (69%)
More than one	21 (28%)	23 (31%)
Median duration of previous hydroxyurea therapy (months)	33·95 (6·80–79·31)	42·61 (6·86–84·30)
Previous hydroxyurea treatment status		
Inadequate response	30 (41%)	30 (40%)
Unacceptable side-effects	44 (59%)	45 (60%)
Positive for *JAK2* Val617Phe mutation*	72 (97%)	69 (92%)
History of previous thromboembolic event	21 (28%)	18 (24%)
Percentage haematocrit level		
Mean (SD)†	42·8% (1·46)	42·7% (1·44)
Median (IQR)†	43·0% (41·7–44·0)	42·7% (41·7–44·0)
White blood cell count, $\times 10^9$ cells per L	12·0 (8·19)	13·0 (8·06)
Mean platelet count, $\times 10^9$ platelets per L	469·5 (295·96)	471·5 (350·38)
Two or more phlebotomies within 24 weeks before screening	58 (78%)	57 (76%)

Data are n (%), median (IQR), or mean (SD). *For five patients (ruxolitinib, n=2; best available therapy, n=3), the *JAK2* V617F mutation was not confirmed by central laboratory assessment; these patients were not included as *JAK2* V617F mutation positive. †Following haematocrit control period before randomisation.

Table 1: **Baseline characteristics**

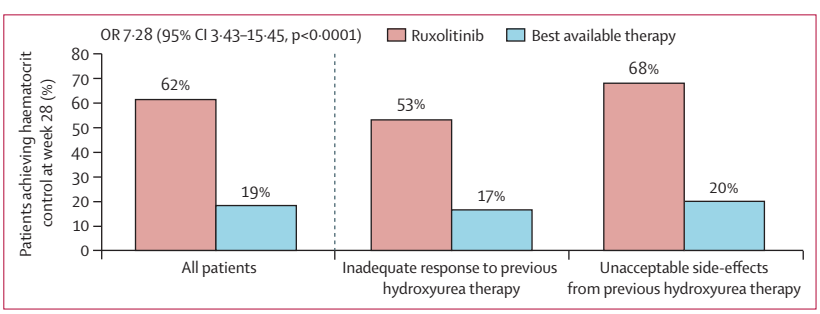

Figure 2: **Haematocrit control at week 28**
OR=odds ratio.

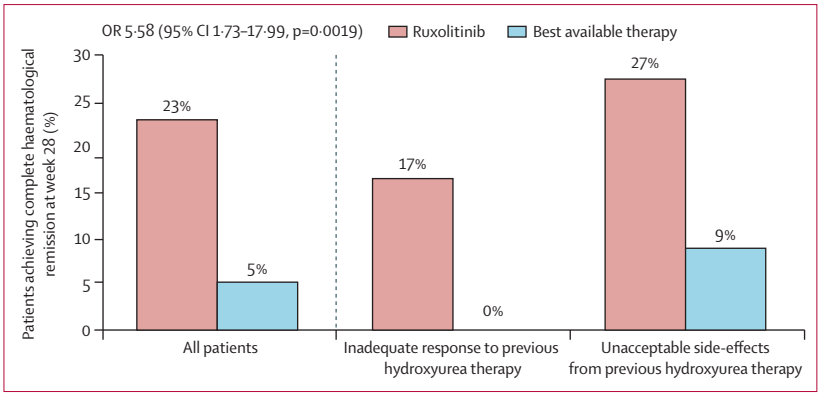

Figure 3: **Complete haematological remission at week 28**
OR=odds ratio.

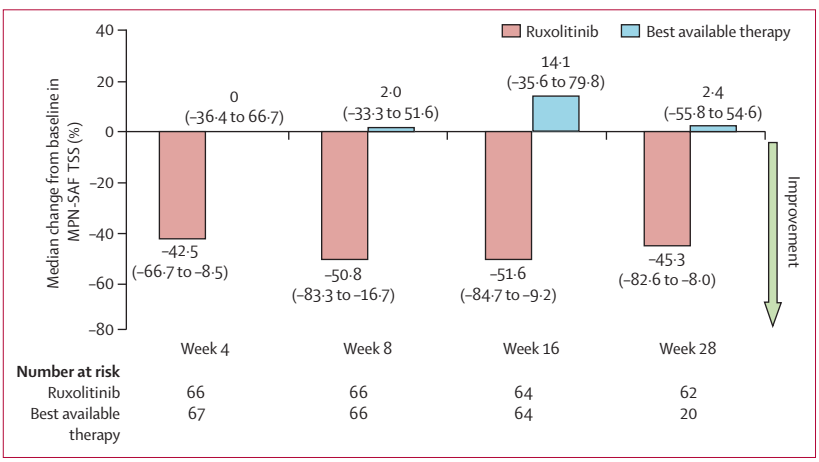

Figure 4: **Median change from baseline in MPN-SAF TSS**
Symptom assessments included all patients with available baseline and post-baseline symptom measures. MPN-SAF TSS=Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score.

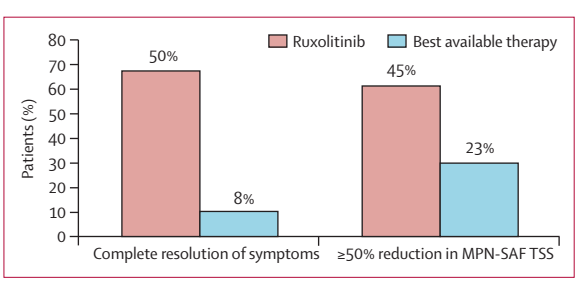

Figure 5: **Patients achieving complete resolution of polycythaemia vera-related symptoms and ≥50% reduction in MPN-SAF TSS at week 28**
MPN-SAF TSS=Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score. OR=odds ratio. *MPN-SAF TSS reduction of ≥10 points from baseline at week 16 and maintained until week 28 (for patients with a baseline score of ≥20; ruxolitinib, n=34; best available therapy, n=26).

complete haematological remission was achieved in a slightly higher proportion of patients with unacceptable side-effects from previous hydroxyurea therapy than in patients with an inadequate response to previous hydroxyurea in both treatment groups (figure 3). Patients in the ruxolitinib group had lower mean white blood cell counts on treatment than did patients in the best available therapy group (appendix p 8). Mean white blood cell counts in the ruxolitinib group were 10×10^9 cells per L or less from week 8 onwards, whereas they remained greater than 10×10^9 cells per L throughout the study in the best available therapy group. Mean platelet counts also decreased over time but were similar in both treatment groups throughout most of the study (appendix p 9).

Patients in the ruxolitinib group had an overall improvement in polycythaemia vera-related symptoms and quality of life compared with patients in the best available therapy group. The median percentage change from baseline in MPN-SAF TSS (on which negative scores indicate improvement) was –45·3% (IQR –82·6 to –8·0) for patients in the ruxolitinib group and 2·4% (–55·8 to 54·6) for patients in the best available therapy group at week 28 (figure 4). Improvements in symptoms were seen at each visit after baseline in patients in the ruxolitinib group, but a slight worsening in symptoms was noted in patients in the best available therapy group (figure 4). Reductions in MPN-SAF TSS with ruxolitinib were rapid and were observed as early as week 4—the first assessment after the baseline assessment (figure 4). By contrast, MPN-SAF TSS in the best available therapy group increased at week 4 and continued to increase through week 28 (figure 4). At week 28, 29 (45%) of 64 patients in the ruxolitinib group had a 50% or greater reduction (ie, improvement) in MPN-SAF TSS compared with five (23%) of 22 patients receiving best available therapy (figure 5); a larger proportion of patients in the ruxolitinib group than in the best available therapy group achieved a 50% or greater reduction in MPN-SAF TSS at each study visit (appendix p 11). Additionally, of patients with an MPN-SAF TSS of at least 20 at baseline, 17 (50%) of 34 patients treated with ruxolitinib achieved complete resolution of disease-related symptoms compared with two (8%) of 26 patients treated with best available therapy (figure 5). Furthermore, improvements were noted in all individual symptoms with ruxolitinib, whereas most symptoms worsened with best available therapy (data not shown).

Rapid improvements in the severity of pruritus as measured on the PSIS were recorded in patients treated with ruxolitinib; by contrast, patients receiving best available therapy had a worsening in pruritus symptom severity at most assessments (appendix p 12). Additionally, 28 (68%) of 41 patients in the ruxolitinib group rated the change in their itching as much improved or very much improved at week 28; but only three (15%) of 20 patients in the best available therapy group had a corresponding response (appendix p 13). This trend was observed throughout the study, with more than half of all assessed patients treated with ruxolitinib reporting much improved or very much improved pruritus at each timepoint.

Improvements were also recorded in scores from the PGIC, EQ-5D-5L, and WPAI questionnaires in patients in the ruxolitinib group at week 28; but little to no improvement was observed in those in the best available therapy group (appendix pp 14–16). In the ruxolitinib group, 44 (60%) of 74 patients rated the change in their overall condition as much improved or very much improved on the PGIC at week 28 compared with only four (5%) of 75 patients in the best available therapy group (appendix p 14). Additionally, a higher proportion of patients in the ruxolitinib group reported having no problems in all five dimensions of the EQ-5D-5L and greater improvements in work productivity and greater reductions in activity impairment than did those in the best available therapy group (appendix pp 15–16).

Given that this primary analysis included data only up to week 28, we were unable to present analyses for some of the secondary endpoints (eg, the durability of haematocrit control and complete haematological remission, survival). These endpoints will be analysed at week 80, and findings from these analyses will be presented in future publications. Changes in spleen length and ECOG status will also be presented in these analyses with a longer follow-up.

Overall, 59 (80%) of 74 patients in the ruxolitinib group had one or more adverse events up to week 28 compared with 60 (80%) of 75 in the best available therapy group (table 2). Headache, constipation, hypertension, and weight increase were the most reported any-grade adverse events in the ruxolitinib group, with each event affecting seven (9%) of 74 patients. In the best available therapy group, pruritus (15 [20%] of 75 patients), headache (8 [11%]), and upper respiratory tract infection (7 [9%]) were the most reported any-grade adverse events (table 2). Both ruxolitinib and best available therapy were associated with few grade 3–4 non-haematological adverse events (table 2); the only grade 3–4 non-haematological adverse events occurring in more than one patient were hypertension (reported in five [7%] of 74 patients in the ruxolitinib group and three [4%] of 75 patients of the best available therapy group) and pruritus (two [3%] of 75 patients in the best available therapy group). Two (3%) of 74 patients treated with ruxolitinib had hypercholesterolaemia compared with none in the best available therapy group. Grade 3–4 infections (influenza and bronchitis) occurred in two (3%) of 74 patients in the ruxolitinib group and one (1%) of 75 in the best available therapy group (cellulitis; table 2). Herpes zoster infection (grade 1–2) occurred in one (1%) of 74 patients in the ruxolitinib group but was not reported in the best available therapy group. No pneumonia or tuberculosis reactivation was diagnosed in the ruxolitinib group, and bacterial pneumonia (grade 3) was reported in one (1%) of 75 patients in the best available therapy group.

Haematological adverse events were mostly grades 1–2. The most frequent haematological adverse events (occurring in ≥5% of patients) were anaemia, which occurred in ten (14%) of 74 patients in the ruxolitinib group and two (3%) of 75 patients in the best available therapy group, and thrombocytopenia, which occurred in two (3%) of 74 in the ruxolitinib group and six (8%) of 75 patients in the best available therapy group (table 2). No cases of grade 3–4 anaemia or thrombocytopenia occurred in the ruxolitinib group; in the best available therapy group, one patient (1%) reported grade 3–4 anaemia and three patients (4%) reported thrombocytopenia.

When adjusted for exposure, the rate of all adverse events per 100 patient-years was lower with ruxolitinib than with best available therapy (99·3 ruxolitinib *vs* 140·7 best available therapy; appendix p 5). The rate of

	Ruxolitinib group (n=74)			Best available therapy group* (n=75)		
	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4
Any adverse event	46 (62%)	12 (16%)	1 (1%)	40 (53%)	18 (24%)	2 (3%)
Non-haematological adverse events						
Headache	7 (9%)	0	0	8 (11%)	0	0
Constipation	7 (9%)	0	0	4 (5%)	0	0
Weight increase	7 (9%)	0	0	1 (1%)	0	0
Peripheral oedema	6 (8%)	0	0	2 (3%)	0	0
Pain in extremity	6 (8%)	0	0	2 (3%)	1 (1%)	0
Pyrexia	6 (8%)	0	0	1 (1%)	0	0
Asthenia	5 (7%)	0	0	5 (7%)	1 (1%)	0
Arthralgia	5 (7%)	0	0	2 (3%)	1 (1%)	0
Abdominal pain	5 (7%)	0	0	1 (1%)	0	0
Cystitis	5 (7%)	0	0	0	0	0
Pruritus	4 (5%)	0	0	13 (17%)	2 (3%)	0
Fatigue	4 (5%)	1 (1%)	0	6 (8%)	0	0
Influenza	4 (5%)	1 (1%)	0	4 (5%)	1 (1%)	0
Dizziness	4 (5%)	0	0	4 (5%)	0	0
Nasopharyngitis	4 (5%)	0	0	2 (3%)	0	0
Haematoma	4 (5%)	0	0	1 (1%)	0	0
Back pain	4 (5%)	0	0	0	0	0
Diarrhoea	3 (4%)	0	0	5 (7%)	1 (1%)	0
Night sweats	2 (3%)	0	0	5 (7%)	0	0
Upper respiratory tract infection	2 (3%)	0	0	7 (9%)	0	0
Hypertension	2 (3%)	4 (5%)	1 (1%)	0	3 (4%)	0
Cough	2 (3%)	0	0	1 (1%)	1 (1%)	0
Erythema	1 (1%)	0	0	2 (3%)	1 (1%)	0
Bronchitis	1 (1%)	1 (1%)	0	1 (1%)	0	0
Angina pectoris	1 (1%)	1 (1%)	0	0	0	0
Tinnitus	1 (1%)	0	0	0	1 (1%)	0
Erythromelalgia	1 (1%)	0	0	0	1 (1%)	0
Lipase increase	0	1 (1%)	0	0	1 (1%)	0
Increased blood lactate dehydrogenase	0	1 (1%)	0	1 (1%)	0	0
Increased gamma-glutamyltransferase	0	1 (1%)	0	1 (1%)	0	0
Increased blood uric acid	0	1 (1%)	0	0	0	0

(Table 2 continues on next page)

	Ruxolitinib group (n=74)			Best available therapy group* (n=75)		
	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4
(Continued from previous page)						
Hypoesthaesia	0	1 (1%)	0	0	0	0
Aphthous stomatitis	0	0	0	2 (3%)	1 (1%)	0
Mouth ulceration	0	0	0	2 (3%)	1 (1%)	0
Aquagenic pruritus	0	0	0	1 (1%)	1 (1%)	0
Septic shock	0	0	0	0	0	1 (1%)
Gastrointestinal haemorrhage	0	0	0	0	1 (1%)	0
Cellulitis	0	0	0	0	1 (1%)	0
Atrial fibrillation	0	0	0	0	1 (1%)	0
Cardiac failure	0	0	0	0	1 (1%)	0
Vomiting	0	0	0	0	1 (1%)	0
Bronchial aspiration	0	0	0	0	1 (1%)	0
Hyponatraemia	0	0	0	0	1 (1%)	0
Syncope	0	0	0	0	1 (1%)	0
Suicidal ideation	0	0	0	0	1 (1%)	0
Renal failure	0	0	0	0	1 (1%)	0
Respiratory failure	0	0	0	0	1 (1%)	0
Actinic keratosis	0	0	0	0	1 (1%)	0
Bacterial pneumonia	0	0	0	0	1 (1%)	0
Squamous cell carcinoma	0	0	0	0	1 (1%)	0
Bladder cancer	0	0	0	0	1 (1%)	0
Breast cancer	0	0	0	0	1 (1%)	0
Haematological adverse events						
Anaemia	10 (14%)	0	0	1 (1%)	1 (1%)	0
Thrombocytopenia	2 (3%)	0	0	3 (4%)	2 (3%)	1 (1%)
Thrombocytosis	2 (3%)	0	0	1 (1%)	2 (3%)	1 (1%)
Haematocrit increase	0	0	0	3 (4%)	1 (1%)	0
Leukocytosis	0	1 (1%)	0	0	1 (1%)	0
Neutropenia	0	1 (1%)	0	0	1 (1%)	0

Data are number of events (%). *Data after crossover for patients randomly assigned to best available therapy are not included. Grade 1–2 events reported in 5% or more patients in either treatment group and all grade 3 or grade 4 events in either treatment group are reported. Only events occurring within 30 days of treatment discontinuation are included. No deaths occurred in the ruxolitinib group; two (3%) of 75 patients in the best available therapy group died (one from septic shock and one from disease progression).

Table 2: **Adverse events occurring up to week 28, regardless of causality**

exposure-adjusted grade 3–4 adverse events was also lower in the ruxolitinib group (25·6 *vs* 45·4 per 100 patient-years; appendix p 5).

In-situ malignant melanoma was diagnosed in one patient in the ruxolitinib group but was not suspected to be related to ruxolitinib treatment, and non-melanoma skin cancer (grade 3 squamous-cell carcinoma) was diagnosed in one patient in the best available therapy group. The patient in the best available therapy group had a strong history of non-melanoma skin cancer (two malignant lesions and one premalignant lesion) and during the study had two procedures for surgical removal of malignant melanoma (on the right shoulder and back); no other treatments were provided for non-melanoma skin cancer. Up until data cutoff, four patients had thrombotic events: one in the ruxolitinib group (grade 1 phlebitis) and three in the best available therapy group (grade 1 superficial thrombophlebitis, grade 3 recurrent syncope due to cerebral microangiopathy, and grade 2 necrosis of the toe on the right foot).

Serious adverse events occurring in more than 2% of patients in either group, regardless of causality, included thrombocytopenia in two (3%) of 75 patients in the best available therapy group and angina pectoris in two (3%) of 74 patients in the ruxolitinib group. Of the two patients who reported angina pectoris, one had a history of chronic ischaemic heart disease and atrial fibrillation, and the other had a history of coronary artery disease. Other serious adverse events in the ruxolitinib group were gastrointestinal inflammation, general physical health deterioration (concurrent with cardiovascular insufficiency and loss of appetite), bronchitis, urosepsis, postprocedural haemorrhage, increased blood creatinine, increased blood lactate dehydrogenase and blood uric acid (based on laboratory values), dehydration, dizziness, exertional dyspnoea, and venous haemorrhage (n=1 for each event). Other serious adverse events in the best available therapy group included anaemia, neutropenia, thrombocytosis, atrial fibrillation, cardiac failure, gastrointestinal haemorrhage, rectal haemorrhage, cellulitis, influenza, pneumonia, septic shock, bronchial aspiration, hyponatraemia, bladder cancer, breast cancer, syncope, renal failure, respiratory failure, and extremity necrosis (n=1 for each event).

No patients randomly assigned to ruxolitinib died during the study; however, two (3%) of 75 patients in the best available therapy group died. One death was due to septic shock and occurred on day 152; this patient received no medication as their initial study treatment until day 30, when they started mercaptopurine as a concomitant medication. The second death was due to disease progression and occurred on day 224, which was 30 days after treatment discontinuation; this patient received pegylated interferon and received their last dose on day 48.

Discussion

The results of this study showed that ruxolitinib was superior to best available therapy at controlling haematocrit level in patients with polycythaemia vera who had an inadequate response to or unacceptable side-effects from previous hydroxyurea therapy. Additionally, more than 80% of patients treated with ruxolitinib were phlebotomy-free compared with 40% of patients treated with best available therapy, further highlighting the benefit provided by ruxolitinib treatment. Ruxolitinib also led to an improved symptom burden and quality of life. Patients treated with ruxolitinib experienced improvements in all polycythaemia vera-associated symptoms, including pruritus, whereas patients treated with best available therapy experienced worsening of most symptoms.

Most patients in RESPONSE-2 had received only one previous line of treatment at enrolment. All patients had received hydroxyurea therapy previously, which is regarded as the standard first-line treatment for patients with high-risk polycythaemia vera. Therefore, this finding suggests that, for various reasons (eg, progressive leukocytosis or a high symptom burden irrespective of age or previous thrombosis), all patients were judged to be high risk by their physicians, allowing for the assessment of ruxolitinib as a true second-line therapy in polycythaemia vera. Patients enrolled in RESPONSE-2 had polycythaemia vera and an inadequate response to or unacceptable side-effects from hydroxyurea according to modified ELN criteria; however, patients had a shorter disease history compared with those in previous studies[11] and had no palpable splenomegaly (as per entry criteria), suggesting that RESPONSE-2 represents a patient population with earlier-stage polycythaemia vera.

Although bias can be a concern in an open-label study, patient-reported data were similar in a double-blind (COMFORT-I)[25] and an open-label study (COMFORT-II)[26] in myelofibrosis, suggesting that the design did not bias patient-reported data. The proportion of patients achieving haematocrit control with ruxolitinib versus best available therapy was similar in both RESPONSE (60·0% with ruxolitinib *vs* 19% with best available therapy) and RESPONSE-2 (62% with ruxolitinib *vs* 19% with best available therapy).[13,27] Furthermore, patients treated with ruxolitinib in both studies had greater reductions in MPN-SAF TSS and pruritus severity than did patients treated with best available therapy. Additionally, ruxolitinib led to reductions in *JAK2* Val617Phe allele burden in the patients in RESPONSE.[13] Given the short follow-up in RESPONSE-2, these data were not reported here but will be included in future reports with longer follow-up. Taken together, findings from RESPONSE and RESPONSE-2 show that ruxolitinib is an effective second-line therapy in patients with polycythaemia vera (post-hydroxyurea therapy), irrespective of spleen size.

Both phase 3 studies reflect the few treatment options for patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea. Despite these patients deriving suboptimal responses from previous hydroxyurea therapy, many patients were still treated with hydroxyurea in the RESPONSE studies (59% in RESPONSE and 49% in RESPONSE-2). Although this approach could be viewed as unacceptable treatment in this patient population, or as biasing results in favour of ruxolitinib, to allow physicians to treat patients as they would in routine clinical practice was considered the most ethical way of treating patients receiving standard therapy. Therefore, both studies allowed investigators to use hydroxyurea as best available therapy, provided that it was administered at a tolerated dose and, in the opinion of the investigator, the patient was likely to derive some benefit from the treatment. Overall, the most frequently used treatments were hydroxyurea or no cytoreductive therapy, which is representative of clinical practice[28] and in line with international recommendations.[10]

Interferon is recommended as first-line or second-line therapy in polycythaemia vera,[10] but its use has been limited by treatment-related toxicities, not receiving approval in many countries, and the absence of data from randomised, controlled, phase 3 trials.[5] In two small non-randomised studies (n=37 and n=43)[29,30] and a phase 1–2 dose-escalation study (n=51),[31] interferon led to high haematological responses in patients with polycythaemia vera; however, most patients were not hydroxyurea resistant or intolerant.[32] Although the number of patients receiving interferon (n=12) in RESPONSE-2 is too small for a direct comparison, the rate of haematocrit control was almost three-times higher with ruxolitinib (62%) than with interferon (25%). Similar proportions of patients achieving haematocrit control were observed in RESPONSE (60·0% with ruxolitinib *vs* 23·1% with interferon); none of the 13 patients treated with interferon in RESPONSE achieved a spleen response.[13,27,32] This small subset is, to our knowledge, the only subset of patients that are specifically intolerant or resistant to hydroxyurea who have been treated with interferon, and further studies are needed for interferon to become a widely accepted standard of care in such patients. However, following crossover to ruxolitinib, patients showed improvement in haematological and spleen response, with an overall reduction in phlebotomies and most patients achieving a spleen response.[33]

Some small studies (≤15 patients) have investigated other treatments as second-line therapy in patients with polycythaemia vera. In one retrospective review,[34] anagrelide led to clinical responses but only in combination with hydroxyurea. Busulfan was effective in elderly patients (aged 61–93 years) but was associated with a high rate of transformation.[35] Alternatively, patients might stop hydroxyurea and receive only phlebotomy, since they might not be candidates for other cytotoxic treatments. However, although phlebotomy can control haematocrit, it does not affect leukocyte count, spleen size, or symptomatology, and can even worsen symptoms such as pruritus in some patients. Moreover, whether durable and stable control of haematocrit can interfere with disease complications compared with the temporary control obtained with phlebotomy alone will be important to understand. In this study, more than two-thirds of patients in the best available therapy group crossed over to receive ruxolitinib, including ten (77%) of 13 patients receiving interferon. This finding further indicates, in a prospective assessment, the need for more active drugs in this patient setting.

Although the short follow-up of this study precludes any conclusions about vascular complications, an important finding is that patients treated with ruxolitinib in both RESPONSE and RESPONSE-2 had fewer thromboembolic events compared with those given best

available therapy; there were two thromboembolic events with ruxolitinib (one in each study) versus nine with best available therapy across both studies (six in RESPONSE and three in RESPONSE-2). This finding could have been attributable to better control of haematocrit[11] or white blood cell count[12] with ruxolitinib, given that baseline risk factors were similar in both treatment groups. Although leukocytosis has been associated with an increased risk of thrombosis,[12] only haematocrit control (<45%) has been definitively shown to lower rates of cardiovascular death and major thrombosis, compared with a target of 45–50%.[11] Patients receiving ruxolitinib had a mean haematocrit that remained below 42% throughout most of the study, whereas the mean haematocrit of patients treated with best available therapy remained higher than baseline (45%). Additionally, a greater proportion of patients who received ruxolitinib achieved control of white blood cell and platelet counts (ie, achieved complete haematological remission)—haematological parameters that are often higher in patients with polycythaemia vera and could be associated with an increased risk of thromboembolic events.[12,14] However, neither the rates of thromboembolic events nor the reduction in thrombotic risk were predefined efficacy endpoints in either study.

In this study, ruxolitinib was generally well tolerated, with nearly all patients in the ruxolitinib group continuing to receive ruxolitinib at data cutoff. The safety profile of ruxolitinib in RESPONSE-2 was similar to that observed in previous studies.[13,36] Anaemia and thrombocytopenia were the most frequent haematological adverse events in patients receiving ruxolitinib, consistent with its mechanism of action as a JAK1 and JAK2 inhibitor. Cytopenias were mostly low grade, with exposure-adjusted rates of grade 3–4 cytopenias being higher in the best available therapy group. Furthermore, adverse events observed with ruxolitinib were similar to those seen in the COMFORT studies of patients with myelofibrosis.[25,26] Grade 1–2 Herpes zoster infection occurred in one patient in the ruxolitinib group; no cases of pneumonia or reactivation of tuberculosis were reported. Notably, the proportion of patients who had weight gain, hypertension, or hypercholesterolaemia was higher in the ruxolitinib group than in the best available therapy group. Control of cardiovascular risk factors is crucial in polycythaemia vera, and patients should be monitored and treated according to clinical guidelines.

Treatment with hydroxyurea has been associated with the development of skin lesions, including non-melanoma skin cancer[37] In RESPONSE-2, no patients treated with ruxolitinib developed non-melanoma skin cancer at the time of data cutoff; one patient treated with best available therapy developed squamous cell carcinoma, which led to early discontinuation from the study. In-situ malignant melanoma was diagnosed in one patient in the ruxolitinib group, but this patient did not discontinue treatment because of this adverse event. Previous hydroxyurea therapy in the ruxolitinib and best available therapy groups could be an underlying cause of the observed cases of non-melanoma skin cancer in the RESPONSE studies.

RESPONSE-2 showed that ruxolitinib was superior to best available therapy at providing safe and comprehensive control of haematocrit and improving symptoms and quality of life in patients with polycythaemia vera who have an inadequate response to or have unacceptable side-effects from hydroxyurea and who have a non-palpable spleen. Overall, ruxolitinib showed a safety profile consistent with that in previous studies. Taken together, findings from RESPONSE and RESPONSE-2 indicate that ruxolitinib could be considered a standard of care for second-line therapy in this post-hydroxyurea patient population.

Contributors

FPas, CB, MK, NM, and GS contributed to study conception and design. FPas, MG, FPal, ME, GB, TD, JC, AMV, and GS contributed to provision of study materials and patients. FPas, MG, FPal, ME, GB, TD, JC, AMV, SS, CB, MK, and NM obtained the data. MK did the statistical analysis. FPas, MG, ME, AMV, SS, CB, MK, NM, and GS analysed and interpreted the data. All authors drafted and approved the report for submission.

Declaration of interests

FPal, ME, and GB have nothing to disclose. FPas has participated in speakers bureaus and advisory boards for Novartis. MG has participated in speakers bureaus and advisory boards for Novartis, Shire, and AOP Orphan. TD has received consultancy fees from Shire and Alexion and has participated in advisory boards for Novartis. JC has received research funding from CSL Behring and TEM International and has participated in advisory boards for the AABB. AMV has received research funding and participated in advisory boards for Novartis and has participated in speakers bureaus for Novartis and Shire. SS has received consultancy fees from Novartis. CB and MK are employees of Novartis. NM was an employee of Novartis at the time this study was done and during drafting and submission of the report. GS has participated in speakers bureaus for Novartis, has received research funding and honoraria from Novartis, and has received honoraria from Celgene, Bristol-Myers Squibb, and Gilead.

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References

1 Vannucchi AM. Insights into the pathogenesis and management of thrombosis in polycythemia vera and essential thrombocythemia. *Intern Emerg Med* 2010; **5:** 177–84.

2 Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood* 2009; **114:** 937–51.

3 Levine RL, Pardanani A, Tefferi A, Gilliland DG. Role of JAK2 in the pathogenesis and therapy of myeloproliferative disorders. *Nat Rev Cancer* 2007; **7:** 673–83.

4 Tefferi A, Rumi E, Finazzi G, et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. *Leukemia* 2013; **27:** 1874–81.

5 Reiter A, Harrison C. How we identify and manage patients with inadequately controlled polycythemia vera. *Curr Hematol Malig Rep* 2016; **11:** 356–67.

6 Passamonti F, Rumi E, Pungolino E, et al. Life expectancy and prognostic factors for survival in patients with polycythemia vera and essential thrombocythemia. *Am J Med* 2004; **117:** 755–61.

7 Passamonti F, Rumi E, Caramella M, et al. A dynamic prognostic model to predict survival in post-polycythemia vera myelofibrosis. *Blood* 2008; **111:** 3383–87.

8 Marchioli R, Finazzi G, Landolfi R, et al. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. *J Clin Oncol* 2005; **23:** 2224–32.

9 Geyer H, Scherber R, Kosiorek H, et al. Symptomatic profiles of patients with polycythemia vera: implications of inadequately controlled disease. *J Clin Oncol* 2016; **34:** 151–59.

10 Barbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol* 2011; **29:** 761–70.

11 Marchioli R, Finazzi G, Specchia G, et al. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med* 2013; **368:** 22–33.

12 Barbui T, Masciulli A, Marfisi MR, et al. White blood cell counts and thrombosis in polycythemia vera: a subanalysis of the CYTO-PV study. *Blood* 2015; **126:** 560–61.

13 Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med* 2015; **372:** 426–35.

14 Alvarez-Larrán A, Pereira A, Cervantes F, et al. Assessment and prognostic value of the European LeukemiaNet criteria for clinicohematologic response, resistance, and intolerance to hydroxyurea in polycythemia vera. *Blood* 2012; **119:** 1363–69.

15 Alvarez-Larrán A, Kerguelen A, Hernández-Boluda JC, et al. Frequency and prognostic value of resistance/intolerance to hydroxycarbamide in 890 patients with polycythaemia vera. *Br J Haematol* 2016; **172:** 786–93.

16 Randi ML, Ruzzon E, Luzzatto G, Tezza F, Girolami A, Fabris F. Safety profile of hydroxyurea in the treatment of patients with Philadelphia-negative chronic myeloproliferative disorders. *Haematologica* 2005; **90:** 261–62.

17 European Medicines Agency. Summary of opinion (post authorisation) for Jakavi (ruxolitinib). http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/002464/WC500180876.pdf (accessed Nov 16, 2016).

18 FDA. FDA approved ruxolitinib. http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm425732.htm (accessed Nov 16, 2016).

19 Vannucchi AM, Verstovsek S, Jones MM, et al. Efficacy of ruxolitinib by baseline spleen volume in patients with polycythemia vera resistant to or intolerant of hydroxyurea. *Blood* 2014; **124:** 1840 (abstract).

20 Vannucchi AM, Antonioli E, Guglielmelli P, et al. Prospective identification of high-risk polycythemia vera patients based on JAK2(V617F) allele burden. *Leukemia* 2007; **21:** 1952–59.

21 Abdulkarim K, Ridell B, Johansson P, Kutti J, Safai-Kutti S, Andreasson B. The impact of peripheral blood values and bone marrow findings on prognosis for patients with essential thrombocythemia and polycythemia vera. *Eur J Haematol* 2011; **86:** 148–55.

22 Barosi G, Birgegard G, Finazzi G, et al. A unified definition of clinical resistance and intolerance to hydroxycarbamide in polycythaemia vera and primary myelofibrosis: results of a European LeukemiaNet (ELN) consensus process. *Br J Haematol* 2010; **148:** 961–63.

23 Finazzi G, Caruso V, Marchioli R, et al. Acute leukemia in polycythemia vera: an analysis of 1638 patients enrolled in a prospective observational study. *Blood* 2005; **105:** 2664–70.

24 Crisa E, Venturino E, Passera R, et al. A retrospective study on 226 polycythemia vera patients: impact of median hematocrit value on clinical outcomes and survival improvement with anti-thrombotic prophylaxis and non-alkylating drugs. *Ann Hematol* 2010; **89:** 691–99.

25 Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med* 2012; **366:** 799–807.

26 Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med* 2012; **366:** 787–98.

27 Verstovsek S, Vannucchi AM, Griesshammer M, et al. Ruxolitinib versus best available therapy in patients with polycythemia vera: 80-week follow-up from the RESPONSE trial. *Haematologica* 2016; **101:** 821–29.

28 Kaifie A, Kirschner M, Wolf D, et al. Bleeding, thrombosis, and anticoagulation in myeloproliferative neoplasms (MPN): analysis from the German SAL-MPN-registry. *J Hematol Oncol* 2016; **9:** 18.

29 Kiladjian JJ, Cassinat B, Chevret S, et al. Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. *Blood* 2008; **112:** 3065–72.

30 Quintás-Cardama A, Abdel-Wahab O, Manshouri T, et al. Molecular analysis of patients with polycythemia vera or essential thrombocythemia receiving pegylated interferon alpha-2a. *Blood* 2013; **122:** 893–901.

31 Gisslinger H, Zagrijtschuk O, Buxhofer-Ausch V, et al. Ropeginterferon alfa-2b, a novel IFNα-2b, induces high response rates with low toxicity in patients with polycythemia vera. *Blood* 2015; **126:** 1762–69.

32 Hasselbalch HC, Bjørn ME. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med* 2015; **372:** 1670.

33 Kiladjian J, Guglielmelli P, Griesshammer M, et al. Ruxolitinib treatment following interferon in patients with polycythemia vera: An analysis from the RESPONSE trial. *Haematologica* 2016; **101** (suppl 2)**:** E1360 (abstract).

34 Ahn IE, Natelson E, Rice L. Successful long-term treatment of Philadelphia chromosome-negative myeloproliferative neoplasms with combination of hydroxyurea and anagrelide. *Clin Lymphoma Myeloma Leuk* 2013; **13** (suppl 2)**:** S300–04.

35 Alvarez-Larrán A, Martínez-Avilés L, Hernández-Boluda JC, et al. Busulfan in patients with polycythemia vera or essential thrombocythemia refractory or intolerant to hydroxyurea. *Ann Hematol* 2014; **93:** 2037–43.

36 Verstovsek S, Passamonti F, Rambaldi A, et al. A phase 2 study of ruxolitinib, an oral JAK1 and JAK2 inhibitor, in patients with advanced polycythemia vera who are refractory or intolerant to hydroxyurea. *Cancer* 2014; **120:** 513–20.

37 Antonioli E, Guglielmelli P, Pieri L, et al. Hydroxyurea-related toxicity in 3411 patients with Ph'-negative MPN. *Am J Hematol* 2012; **87:** 552–54.