Efficacy, safety, and survival with ruxolitinib in patients with myelofibrosis: results of a median 3-year follow-up of COMFORT-I

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Online Supplement

Detailed methods

Patients and study design

Patients enrolled in COMFORT-I had intermediate-2 or high-risk primary myelofibrosis (MF) according to the International Prognostic Scoring System[1] or post–polycythemia vera MF or post-essential thrombocythemia MF according to the 2008 World Health Organization criteria, had splenomegaly (palpable ≥5 cm below the left costal margin), and had a platelet count ≥100 × 10^9/L. Detailed inclusion and exclusion criteria have been previously described.[2] Eligible patients were randomized 1:1 to ruxolitinib or placebo given orally twice a day (BID). The starting dose of ruxolitinib was based on baseline platelet count: 15 mg BID for a baseline platelet count between 100 and 200 × 10^9/L or 20 mg BID for patients with a baseline platelet count >200 × 10^9/L. Doses could be decreased for safety or increased to enhance efficacy, as specified by the study protocol.[2]

The primary analysis occurred when all patients had either completed the week 24 evaluation or discontinued from the study and half of those remaining in the study completed the week 36 visit. Patients in the placebo group could crossover to ruxolitinib prior to the primary analysis based on defined criteria for worsening splenomegaly. After the primary analysis was completed, the study was unblinded and all remaining patients receiving placebo were allowed to crossover to ruxolitinib.[2] The protocol was designed by Incyte Corporation and approved by the institutional review board at each participating site. The study sponsor's clinical and statistical teams analyzed and interpreted the data in collaboration with the investigators. All authors had access to the aggregate study data and any additional analyses upon request. The study was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice. All patients provided written informed consent.[2]

Assessments

The primary endpoint was the proportion of patients achieving a ≥35% reduction from baseline in spleen volume at week 24, assessed by abdominal imaging (magnetic resonance imaging or computed tomography).[2] Spleen volume was measured at baseline, weeks 12, 24, 36, 48, 60, 72, and every 24 weeks thereafter. Palpable spleen length was assessed at baseline and at each study visit. Symptom burden, assessed by the modified MF Symptom Assessment Form version 2.0 electronic diary,[2,3] was measured up to week 24. Quality of life was evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 at baseline and each study visit. Adverse events were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Statistical analysis

The current analysis is a prospectively defined analysis of efficacy and safety, the timing of which was prespecified to occur when all patients either reached the 144-week assessment or discontinued from the study. Changes from baseline in spleen volume and palpable spleen length were based on observed cases and summarized descriptively. Durability of spleen volume reduction was evaluated using the Kaplan-Meier method in patients who achieved a ≥35% reduction from baseline in spleen volume. Loss of a ≥35% spleen volume reduction was defined as the first <35% spleen volume reduction from baseline that was also a ≥25% increase from nadir. Overall survival, a prespecified secondary endpoint, was assessed using the Kaplan-Meier method for the intent-to-treat (ITT) population with patients assessed per their original randomized treatment regardless of subsequent crossover. Survival time was measured from study start to last known status of the patient and was not censored at time of discontinuation from randomized treatment. The Cox proportional hazards model and log-rank test were used to calculate the hazard ratio with 95% confidence interval and *P*-value,

respectively. The Kaplan-Meier method was used to estimate discontinuation rates at years 1, 2, and 3 based on time to discontinuation in the ruxolitinib arm. The incidence (conditional probability of event) of new-onset or worsening grade ≥3 anemia and thrombocytopenia (based on laboratory data) and of new-onset or worsening all-grade and grade ≥3 nonhematologic adverse events were calculated using the life table method based on the time to first event censored at the date of last laboratory evaluation for anemia and thrombocytopenia and the earlier of discontinuation or date of data cutoff for nonhematologic adverse events. Because the majority of the anemia and thrombocytopenia events occurred early in the study, the incidence of new-onset or worsening grade 3 or 4 anemia or thrombocytopenia was assessed at 6-month intervals in patients originally randomized to ruxolitinib; the placebo group was included only in the first 6-month interval because all patients receiving placebo discontinued or crossed over to ruxolitinib within 3 months of the primary analysis. The incidence of nonhematologic events was assessed in yearly intervals for patients originally randomized to ruxolitinib. Per the life table method, the incidence of each adverse event was based on the effective sample size of the time interval, which was the number of patients at risk at the beginning of the interval minus half of the censored patients during the time interval.

To better understand the effect of patients from the placebo arm crossing over to ruxolitinib treatment on survival measurement, two exploratory analyses were performed. The first exploratory analysis used the rank-preserving structural failure time (RPSFT) method, a statistical method used in oncology trials to adjust for possible crossover effect.[4-6] This method adjusts for crossover in the placebo group by relating the portion of observed survival time after crossover to active treatment to a multiplicative coefficient that represents either the beneficial or the harmful effect of treatment on survival, and applies this coefficient to estimate survival times as if crossover in the placebo group had not occurred. The hazard ratio was estimated using Cox regression analysis of reconstructed survival times, and the 95% confidence interval was estimated using the bootstrap method. As the null hypothesis of the RPFST method was

the original ITT analysis, the method does not alter the *P*-value from the original ITT analysis. Additional model description and implementation details, including re-censoring of the reconstructed survival time, are described by Robins and Tsiatis[4] and Korhonen et al.[7] In the second analysis, a parametric statistical modeling of overall survival using the generalized Gamma distribution was conducted;[8,9] this involved fitting a three-parameter regression model to the observed survival data that resulted in a smooth curve representing an estimated survival function curve. The survival function curve was then visually compared with the Kaplan-Meier curve over the period used for the model to understand how well it reflected the actual data. The fitted model was subsequently used to calculate the corresponding hazard of death for patients originally randomized to ruxolitinib and those randomized to placebo.

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Supplemental Data Table 1. Causes of death by randomized treatment allocation.*

Cause of death, n	Ruxolitinib (N=155)	Placebo (N=154)
Acute leukemia		1
Acute myeloid leukemia	2	2
Acute myeloid leukemia progression		1
Anastomotic hemorrhage		1
Anemia, systemic		1
Cardiac arrest		1
Cardiac failure congestive		1
Cerebral hemorrhage		1
Completed suicide		1
Congestive heart failure resulting from pneumonia		1
Death	1	
Disease progression	6	9
Disease progression and cardiac failure		1
Gastrointestinal hemorrhage		1
Graft versus host disease	1	
Intestinal perforation		1
Intra-abdominal hemorrhage		1
Leukemia or underlying leukemia	1	1
Leukemic transformation	1	
Muscular weakness	1	
Metastatic colon cancer		1
Multi-organ failure		1
Myelodysplastic syndrome disease progression		1
Myelofibrosis	3	3
Myelofibrosis progression	1	

Myelofibrosis with possible transformation to acute myeloid leukemia and pneumonia		1
Myeloproliferative disease		1
Myocardial infarction	2	
Non-small cell lung cancer metastatic	1	
Pancreatic carcinoma	1	
Pneumonia	1	1
Pneumonia, multi-organ failure	1	
Pneumonia and septic shock	1	
Renal failure	1	
Respiratory failure	1	
Road traffic accident		1
Sepsis or septic shock	3	3
Shock hemorrhagic		1
Shock, respiratory and cardiac failure; hemorrhage following splenectomy	1	
Splenic infarction	1	
Splenic rupture		1
Staphylococcal infection		1
Subdural hematoma	1	1
Subdural hemorrhage	1	
Surgical complications		1
Unknown	9	11
Total	42	54

*Causes of death were collected verbatim as reported during long-term follow-up, thus cause of death was not available for all patients.

Supplemental Data Table 2. Incidence of new-onset grade 3 or 4 nonhematologic adverse events regardless of causality.

	Ruxolitinib			
Incidence, %	0-<12 months (n=155)	12-<24 months (n=130)	24-<36 months (n=103)	≥36 months (n=82)
Fatigue	6.2	0.9	3.3	0
Pneumonia	5.6	3.6	3.5	0
Abdominal pain	4.2	0	3.2	0
Arthralgia	2.1	0	0	0
Diarrhea	2.1	0	0	0
Dyspnea	2.1	0.9	2.2	2.5
Pain in extremity	2.1	0	1.1	0
Hyperuricemia	1.4	0.9	0	2.5
Fall	1.4	0.9	0	0
GI hemorrhage	1.4	0.9	0	0
Septic shock	1.4	0	0	0
Muscular weakness	1.4	0	1.1	0
Hypoxia	1.4	0	2.2	0
Sepsis	0.7	1.7	2.2	0
Epistaxis	0.7	1.7	0	0
Renal failure acute	0.7	0.9	2.2	2.4
Abdominal pain upper	0.7	0	2.2	0
Myocardial infarction	0	0.9	0	4.8

Percentage of patients for each event was based on the effective sample size of the time interval (number of patients at risk at the beginning of the interval minus half of the censored patients during the time interval). Adverse event is included if the incidence was ≥2 patients at any yearly interval. GI: gastrointestinal.

Supplemental Data Table 3. Summary of treatment-emergent (grade 3 or higher) and SAEs reported during study drug interruption.

	Ruxolitinib (N=59)	
Adverse event	**Grade ≥3**	**Any SAE**
Number (%) of patients with any adverse event	27 (45.8)	21 (35.6)
Anemia	9 (15.3)	3 (5.1)
Thrombocytopenia	5 (8.5)	0
Hemoglobin decreased	2 (3.4)	1 (1.7)
Pneumonia	2 (3.4)	2 (3.4)
Sepsis	2 (3.4)	1 (1.7)
Disseminated intravascular coagulation	1 (1.7)	0
Neutropenia	1 (1.7)	0
Platelet count decreased	1 (1.7)	1 (1.7)
Cardiac failure congestive	1 (1.7)	1 (1.7)
Abdominal pain	1 (1.7)	1 (1.7)
Gastrointestinal hemorrhage	1 (1.7)	1 (1.7)
Nausea	1 (1.7)	0
Obturator hernia	1 (1.7)	1 (1.7)
Esophageal varices hemorrhage	1 (1.7)	1 (1.7)
Rectal hemorrhage	1 (1.7)	1 (1.7)
Retroperitoneal hematoma	1 (1.7)	0
Vomiting	1 (1.7)	1 (1.7)
Asthenia	1 (1.7)	0
Fatigue	1 (1.7)	0
Systemic inflammatory response syndrome	1 (1.7)	0
Diverticulitis	1 (1.7)	0
Lung infection	1 (1.7)	1 (1.7)
Perirectal abscess	1 (1.7)	1 (1.7)
Pseudomonas sepsis	1 (1.7)	1 (1.7)

Urinary tract infection	1 (1.7)	1 (1.7)
Fall	1 (1.7)	0
Post-procedural hemorrhage	1 (1.7)	1 (1.7)
Tibia fracture	1 (1.7)	1 (1.7)
Troponin increased	1 (1.7)	0
Bone pain	1 (1.7)	0
Acute myeloid leukemia	1 (1.7)	1 (1.7)
Delirium	1 (1.7)	0
Renal failure acute	1 (1.7)	0
Dyspnea	1 (1.7)	1 (1.7)
Pneumonia aspiration	1 (1.7)	0
Pneumonitis	1 (1.7)	1 (1.7)
Pulmonary hypertension	1 (1.7)	0
Febrile neutropenia	0	1 (1.7)
Diastolic dysfunction	0	1 (1.7)
Pyrexia	0	1 (1.7)
Urosepsis	0	1 (1.7)

All patients receiving placebo at the primary analysis crossed over or discontinued within 3 months of the primary analysis; therefore, no additional data beyond what were previously reported (Verstovsek S, Mesa RA, Gotlib J, et al. Efficacy, safety and survival with ruxolitinib in patients with myelofibrosis: results of a median 2-year follow-up of COMFORT-I. Haematologica. 2013;98(12):1865-1871) are available for these patients. SAEs: serious adverse events.

Supplemental Data Table 4. Summary of treatment-emergent (grade 3 or higher) and SAEs reported after study drug discontinuation.

	Ruxolitinib (N=78)	
Adverse event	**Grade ≥3**	**Any SAE**
Number (%) of patients with any adverse event	31 (39.7)	32 (41.0)
Thrombocytopenia	6 (7.7)	2 (2.6)
Pneumonia	3 (3.8)	4 (5.1)
Renal failure acute	3 (3.8)	1 (1.3)
Sepsis	3 (3.8)	3 (3.8)
Abdominal pain	2 (2.6)	2 (2.6)
Acute myeloid leukemia	2 (2.6)	3 (3.8)
Disease progression	2 (2.6)	2 (2.6)
Dyspnea	2 (2.6)	1 (1.3)
Hypokalemia	2 (2.6)	0
Hypotension	2 (2.6)	1 (1.3)
Myocardial infarction	2 (2.6)	2 (2.6)
Splenic infarction	2 (2.6)	2 (2.6)
Acute respiratory failure	1 (1.3)	1 (1.3)
Anemia	1 (1.3)	1 (1.3)
Anuria	1 (1.3)	0
Asthenia	1 (1.3)	1 (1.3)
Atrial fibrillation	1 (1.3)	0
Cardiac arrest	1 (1.3)	0
Cardiac failure congestive	1 (1.3)	1 (1.3)
Cholecystitis infective	1 (1.3)	1 (1.3)
Clostridial infection	1 (1.3)	1 (1.3)
Confusional state	1 (1.3)	0
Death	1 (1.3)	1 (1.3)
Disseminated intravascular coagulation	1 (1.3)	0

Edema	1 (1.3)	0
Epistaxis	1 (1.3)	0
Fatigue	1 (1.3)	1 (1.3)
Febrile neutropenia	1 (1.3)	0
Hemoglobin decreased	1 (1.3)	0
Hepatosplenomegaly	1 (1.3)	1 (1.3)
Hyperbilirubinemia	1 (1.3)	0
Hyperglycemia	1 (1.3)	0
Hypoxia	1 (1.3)	0
Lactic acidosis	1 (1.3)	0
Leukocytosis	1 (1.3)	0
Malnutrition	1 (1.3)	0
Muscular weakness	1 (1.3)	1 (1.3)
Pancreatic carcinoma	1 (1.3)	1 (1.3)
Platelet count increased	1 (1.3)	0
Portal vein thrombosis	1 (1.3)	0
Pulmonary edema	1 (1.3)	0
Pulmonary tuberculosis	1 (1.3)	1 (1.3)
Pyrexia	1 (1.3)	3 (3.8)
Renal failure	1 (1.3)	1 (1.3)
Renal tubular necrosis	1 (1.3)	0
Respiratory failure	1 (1.3)	1 (1.3)
Septic shock	1 (1.3)	1 (1.3)
Splenic hemorrhage	1 (1.3)	1 (1.3)
Subdural hematoma	1 (1.3)	1 (1.3)
Subdural hemorrhage	1 (1.3)	1 (1.3)
Supraventricular tachycardia	1 (1.3)	0
Transaminases increased	1 (1.3)	0
Transient ischemic attack	1 (1.3)	1 (1.3)

Abdominal pain upper	0	1 (1.3)
Cellulitis	0	1 (1.3)
Dehydration	0	1 (1.3)
Diarrhea	0	1 (1.3)
Fall	0	1 (1.3)
Pneumonia aspiration	0	1 (1.3)
Postoperative wound infection	0	1 (1.3)

All patients receiving placebo at the primary analysis crossed over or discontinued within 3 months of the primary analysis; therefore, no additional data beyond what were previously reported (Verstovsek S, Mesa RA, Gotlib J, et al. Efficacy, safety and survival with ruxolitinib in patients with myelofibrosis: results of a median 2-year follow-up of COMFORT-I. Haematologica. 2013;98(12):1865-1871) are available for these patients. SAEs: serious adverse events.

Supplemental Data Figure 1. Generalized Gamma distribution–based model of overall survival and hazard of death.