P-06

Presented at the
Inaugural European Focus on Myeloproliferative Neoplasms and Myelodysplastic Syndromes
Lisbon, Portugal • May 4–5, 2012

Consistent Benefit of Ruxolitinib Over Placebo Across Myelofibrosis Patient Subgroups: Results From COMFORT-I

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Introduction

- Myelofibrosis (MF) is a rare and life-threatening myeloproliferative neoplasm characterized by constitutional symptoms (fever, night sweats, weight loss), cytopenias, and splenomegaly[1]
- A wide spectrum of disease characteristics exists across the MF patient population[2,3]
  - Certain patient characteristics (age, constitutional symptoms, hemoglobin, white blood cells, and blood blasts) have been shown to predict clinical course and survival[3,4]
  - Patients may also experience a variety of debilitating symptoms, in addition to constitutional symptoms,[5] which can have a profound impact on patient outcomes
- Dysregulated JAK-STAT signaling resulting from gain-of-function mutations and/or high circulating levels of inflammatory cytokines plays a key role in the pathogenesis of MF[6]
- In the COMFORT-I study, treatment with the JAK1/JAK2 inhibitor ruxolitinib significantly reduced spleen volume and improved MF-related symptoms in patients with MF compared with placebo[7]

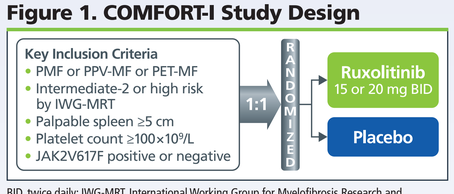
Objective

- To evaluate the consistency of ruxolitinib efficacy across patient subgroups in COMFORT-I

Methods

- COMFORT-I is a phase III, double-blind, randomized placebo-controlled study[7]
- Eligible patients were randomized 1:1 to placebo or ruxolitinib at a dose of 15 mg or 20 mg by mouth twice daily depending on baseline platelet count (100–200×10^9/L or >200×10^9/L, respectively) (Figure 1)

Figure 1. COMFORT-I Study Design



BID, twice daily; IWG-MRT, International Working Group for Myelofibrosis Research and Treatment; PET-MF, post–essential thrombocythemia-myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post–polycythemia vera-myelofibrosis.

- The primary endpoint of COMFORT-I was the proportion of patients achieving ≥35% reduction from baseline in spleen volume (assessed by MRI or CT) at Week 24
- Secondary endpoints included the duration of maintenance of spleen volume reduction, proportion of patients with ≥50% reduction in total symptom score (TSS) from baseline to Week 24 using the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary,[8,9] change in TSS from baseline to Week 24, and overall survival
- MF symptoms were assessed on a scale of 0 (absent) to 10 (worst imaginable) and included night sweats, itching (pruritus), abdominal discomfort, pain under ribs on the left side, feeling of fullness (early satiety), muscle/bone pain, and inactivity
- The TSS was the average of the sum of daily individual symptom scores with the exception of inactivity, which was analyzed separately
- Analyses
  - Mean percentage change from baseline in spleen volume and TSS were calculated for each patient subgroup
    - MF subtype (primary MF [PMF], post–polycythemia vera-MF [PPV-MF], post–essential thrombocythemia-MF [PET-MF])
    - Age (≤65 and >65 years)
    - International Prognostic Scoring System (IPSS) risk group (intermediate-2 and high risk)
    - Presence/absence of JAK2V617F mutation
    - Baseline hemoglobin (≥10 and <10 g/dL)
    - Baseline palpable spleen length (≤10 and >10 cm)
    - Baseline TSS quartile
  - Overall survival was estimated by the Kaplan-Meier method according to original randomization group, regardless of crossover to ruxolitinib, for each subgroup of the intent-to-treat population

Results

Patients

- A total of 309 patients were randomized: 155 to ruxolitinib (median age 66 years) and 154 to placebo (median age 70 years)
- Treatment groups were balanced in terms of demographics and baseline disease characteristics[7]

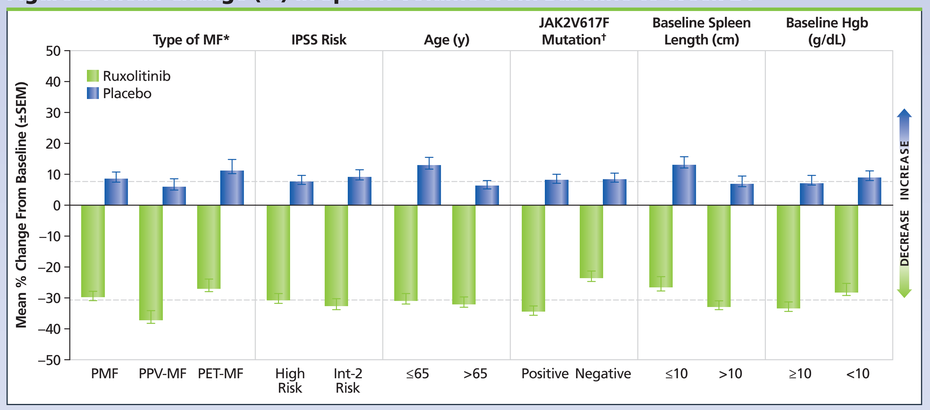
Spleen Volume and TSS

- Mean percent change from baseline to Week 24 in spleen volume consistently decreased in patients receiving ruxolitinib treatment and consistently increased in patients receiving placebo across all subgroups evaluated (Figure 2)
- Mean percent change from baseline to Week 24 in TSS consistently improved (ie, decreased) with ruxolitinib treatment and consistently worsened with placebo across all subgroups evaluated (Figure 3)
- Mean percent changes in spleen volume and TSS for ruxolitinib-treated patients across subgroups were similar to those of ruxolitinib-treated patients in the overall study population (31.6% and 46.1%, respectively)
- Spleen volume reduction and symptom improvement were seen with ruxolitinib treatment regardless of the presence or absence of the JAK2V617F mutation
- Patients treated with ruxolitinib experienced reductions in spleen volume and improvements in TSS regardless of baseline symptom severity as measured by baseline TSS quartile
  - In ruxolitinib-treated patients, the mean percent change in spleen volume ranged from –28.0% in quartile 1 (lowest baseline TSS) to –34.8% in quartile 4 (highest baseline TSS) versus +8.1% in all placebo patients
  - Mean percent change in TSS for ruxolitinib-treated patients ranged from –40.5% in quartile 1 to –48.2% in quartile 4; the mean percent change in all placebo patients was +41.8%

Overall Survival

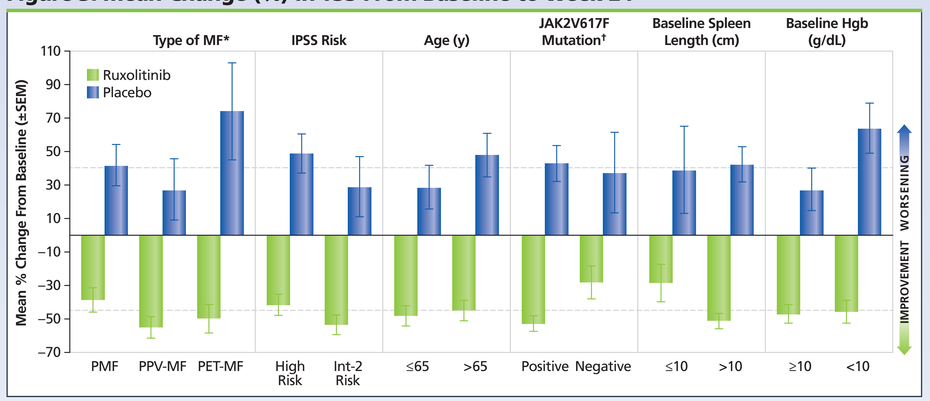
- Improved survival across all subgroups is suggested by hazard ratios consistently favoring ruxolitinib over placebo, although differences did not achieve statistical significance in this post hoc analysis (Figures 4A–4D)
- Patients with low hemoglobin who received placebo had a particularly poor prognosis, whereas patients with low hemoglobin who were treated with ruxolitinib appeared to achieve a relative benefit (HR=0.59) consistent with that observed in other subgroups (Figure 4C)

Figure 2. Mean Change (%) in Spleen Volume From Baseline to Week 24



*P-value for interaction of MF subtype by treatment=0.52. †P-value for interaction of mutation status by treatment=0.07. Dashed lines represent the mean percent change from baseline for overall treatment group. Hgb, hemoglobin; IPSS, International Prognostic Scoring System; MF, myelofibrosis; PET, post–essential thrombocythemia; PMF, primary myelofibrosis; PPV, post–polycythemia vera; SEM, standard error of mean.

Figure 3. Mean Change (%) in TSS From Baseline to Week 24

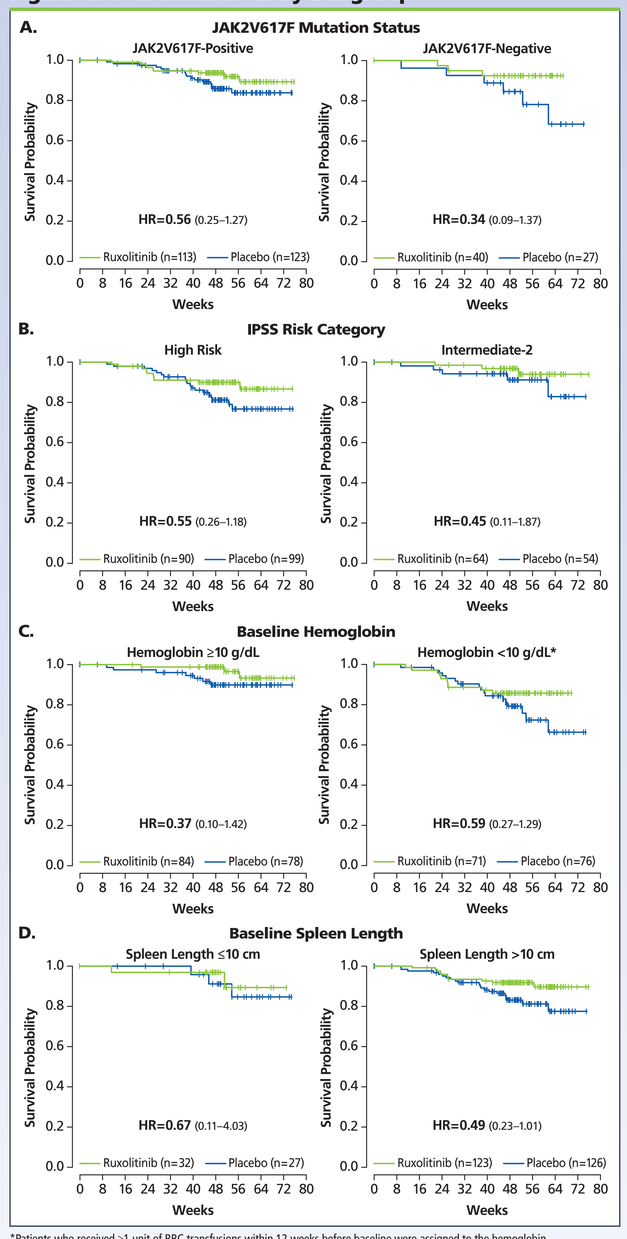


*P-value for interaction of MF subtype by treatment=0.46. †P-value for interaction of mutation status by treatment=0.11. Dashed lines represent the mean percent change from baseline for overall treatment group. Hgb, hemoglobin; IPSS, International Prognostic Scoring System; MF, myelofibrosis; PET, post–essential thrombocythemia; PMF, primary myelofibrosis; PPV, post–polycythemia vera; SEM, standard error of mean.

Conclusions

- **In the COMFORT-I study, ruxolitinib was effective in reducing spleen volume and improving MF-related symptoms regardless of the subgroup evaluated**
- **In patients receiving placebo, spleen size and MF-related symptoms worsened across subgroups**
- **The present subgroup analyses suggest a consistent survival benefit with ruxolitinib over placebo across the subgroups evaluated**
- **Despite limitations (size of individual subgroups, number of comparisons), the treatment effect was similar to that in the overall COMFORT-I population[7]**

Figure 4. Overall Survival by Subgroup



*Patients who received ≥1 unit of RBC transfusions within 12 weeks before baseline were assigned to the hemoglobin <10 g/dL subgroup. HR, hazard ratio; RBC, red blood cell.

The COMFORT-I clinical trial was sponsored by Incyte Corporation.

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