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**Abstract title** RESULTS OF COMFORT-I, A RANDOMIZED, DOUBLE-BLIND PHASE III TRIAL OF THE JAK1 AND JAK2 INHIBITOR RUXOLITINIB (INCB018424) VERSUS PLACEBO FOR PATIENTS WITH MYELOFIBROSIS

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**Background:** Dysregulated JAK-STAT signaling is a key feature in myelofibrosis, which is characterized by splenomegaly, debilitating symptoms, cytopenias and shortened survival. There are currently no effective drug therapies for myelofibrosis. Ruxolitinib is a selective JAK1 and JAK2 inhibitor with demonstrated clinical activity in myelofibrosis.

**Aims:** COMFORT-I was designed to determine the safety and efficacy of ruxolitinib relative to placebo in patients with myelofibrosis.

**Methods:** All study participants signed informed consent. Patients with intermediate-2 or high-risk myelofibrosis were randomized to start placebo or ruxolitinib at a dose of 15 or 20 mg PO BID depending on baseline platelet count ( $100-200 \times 10^9/L$  or  $>200 \times 10^9/L$ , respectively). The dose was optimized for efficacy and safety during treatment. The primary endpoint was the proportion of patients with  $\geq 35\%$  reduction in spleen volume at week 24 of therapy, assessed by blinded central review of spleen MRI or CT. Secondary endpoints were durability of spleen response, changes in symptom burden as assessed daily by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0, and survival. Additional exploratory endpoints included change in quality of life (QoL) measured by the EORTC-QLQ-C30, fatigue measured with the PROMIS Fatigue Scale, molecular and serum biomarkers, and transfusion dependence.

**Results:** 309 patients were randomized: 155 to ruxolitinib and 154 to placebo. Median follow-up was 32.2 weeks. The proportion of patients with  $\geq 35\%$  reduction in spleen volume at 24 weeks was 41.9% vs 0.7% (ruxolitinib vs placebo,  $p < 0.0001$ ). Median duration of response has not been reached. At week 24, the proportion of patients with  $\geq 50\%$  improvement in symptom score was 45.9% vs 5.3% (ruxolitinib vs placebo,  $p < 0.0001$ ) and the mean percent change in total symptom score was an improvement of 46.1% vs a worsening of 41.8% (ruxolitinib vs placebo,  $p < 0.0001$ ). There were 10 vs 14 deaths (ruxolitinib vs placebo, HR 0.67,  $p = 0.33$ ). Improvement in symptoms was rapid, with the majority of patients showing significant benefit within the first 4 weeks. Changes in both QoL and fatigue mirrored changes in the modified MFSAF v2.0 symptom score over time, and all showed improvement relative to placebo regardless of changes in hemoglobin. The most common AEs of any grade seen in  $> 20\%$  of patients on either arm of the study were (ruxolitinib vs placebo) abdominal pain (10.3% vs 41.1%), thrombocytopenia (34.2% vs 9.3%), fatigue (25.2% vs 33.8%), anemia (31% vs 13.9%), diarrhea (23.2% vs 21.2%), and peripheral edema (18.7% vs 22.5%). Anemia and thrombocytopenia were manageable and rarely (0.6% ruxolitinib vs 0.7% placebo, each) led to withdrawal from the study.

**Summary/Conclusion:** In this study, ruxolitinib demonstrated marked clinical benefits in spleen size, debilitating symptoms, and QoL that were rapid in onset and sustained. Anemia and thrombocytopenia were among the most common AEs but they were manageable, as demonstrated by the low withdrawal rate due to these events. The overall safety profile relative to placebo in myelofibrosis was acceptable.

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