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Abstract title  RESULTS OF COMFORT-I, A RANDOMIZED, DOUBLE-BLIND PHASE III TRIAL OF THE JAK1 AND JAK2 INHIBITOR RUXOLITINIB (INCBO18424) VERSUS PLACEBO FOR PATIENTS WITH MYELOFIBROSIS

Author  M.D., Ph.D. Verstovsek, Srdan, The University of Texas M.D. Anderson Cancer Center, Houston, United States of America (Presenting author)

Co-author(s)  Mesa, Ruben, Mayo Clinic, Scottsdale, United States of America
Gotlib, Jason, Stanford Cancer Center, Stanford, United States of America
Levy, Richard, Incyte Corporation, Wilmington, United States of America
Gupta, Vikas, Princess Margaret Hospital, Toronto, Canada
DiPersio, John, Washington University School of Medicine, St. Louis, United States of America
Catalano, John, Frankston Hospital, Frankston, Australia
Deininger, Michael, University of Utah Huntsman Cancer Institute, Salt Lake City, United States of America
Miller, Carole, Saint Agnes Cancer Institute, Baltimore, United States of America
Silver, Richard, Weill Cornell Medical College, New York, United States of America
Taipaz, Moshe, University of Michigan, Ann Arbor, United States of America
Winton, Elliott, Emory University School of Medicine, Atlanta, United States of America
Harvey, Jimmie, Birmingham Hematology & Oncology, Birmingham, United States of America
Arcasoy, Murat, Duke University Health System, Durham, United States of America
Hexner, Elizabeth, University Of Pennsylvania Health System, Philadelphia, United States of America
Lyons, Roger, Cancer Care Center of South Texas, San Antonio, United States of America
Pouquet, Ronald, UCLA Medical Hematology & Oncology, Los Angeles, United States of America
Raza, Azra, Columbia Presbyterian Medical Center, New York, United States of America
Vaddi, Kris, Incyte Corporation, Wilmington, United States of America
Erickson-Vilitanen, Sue, Incyte Corporation, Wilmington, United States of America
Koumenis, Iphigenia, Incyte Corporation, Wilmington, United States of America
Sun, William, Incyte Corporation, Wilmington, United States of America
Sandor, Victor, Incyte Corporation, Wilmington, United States of America
Kantarjian, Hagop, M.D. Anderson Cancer Center, Houston, United States of America

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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 x 10^9/L or >200 x 10^9/L, respectively). The dose was optimized for efficacy and safety during treatment. The primary endpoint was the proportion of patients with ≥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 ≥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 ≥50% improvement in symptom score was 46.9% 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.

Has the submitted material been published in a journal (printed or online)?
No

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No

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