278 Consistent Benefit of Ruxolitinib Over Placebo in Spleen Volume Reduction and Symptom Improvement Across Subgroups and Overall Survival Advantage: Results From COMFORT-I

Program: Oral and Poster Abstracts
Type: Oral
Session: 634. Myeloproliferative Syndromes: Clinical Advances I
Monday, December 12, 2011: 7:00 AM
Room 6B (San Diego Convention Center)

Srdan Verstovsek, MD, PhD[1], *Ruben A. Mesa, MD*[2], *Jason Gotlib, MD, MS*[3], *Richard S. Levy, MD*[4*], *Vikas Gupta, MD, FRCP, FRCPath*[5], *John F. DiPersio, MD, PhD*[6], *John Catalano, MD*[7], *Michael W. Deininger*[8], *Carole B. Miller, MD*[9*], *Richard T. Silver, MD*[10], *Moshe Talpaz, MD*[11], *Elliott F. Winton, MD*[12], *Jimmie H. Harvey Jr., MD*[13*], *Murat O. Arcasoy, MD*[14], *Elizabeth Hexner, MD*[15], *Roger M. Lyons, MD*[16], *Ronald Paquette, MD, PhD*[17*], *Azra Raza, MD*[18], *Kris Vaddi, PhD*[4*], *Sue Erickson-Viitanen, PhD*[4*], *William Sun, PhD*[4*], *Victor A. Sandor, MD, CM*[4*] *and Hagop M. Kantarjian*[1]

[1]*University of Texas MD Anderson Cancer Center, Houston, TX*
[2]*Mayo Clinic, Scottsdale, AZ*
[3]*Medicine/Hematology, Stanford University Cancer Institute, Stanford, CA*
[4]*Incyte Corporation, Wilmington, DE*
[5]*Medical Oncology & Hematology, Princess Margaret Hospital, Toronto, ON, Canada*
[6]*Washington University School of Medicine, St. Louis, MO*
[7]*Frankston Hospital, Frankston, Victoria, Australia*
[8]*University of Utah Huntsman Cancer Institute, Salt Lake City, UT*
[9]*Saint Agnes Cancer Institute, Baltimore, MD*
[10]*Weill Medical College of Cornell University, New York, NY*
[11]*University of Michigan, Ann Arbor, MI*
[12]*Emory University School of Medicine, Atlanta, GA*
[13]*Birmingham Hematology & Oncology Associates, Birmingham, AL*
[14]*Duke University Health System, Durham, NC*
[15]*Abramson Cancer Center at The University of Pennsylvania, Philadelphia, PA*
[16]*Cancer Care Centers of South Texas/US Oncology, San Antonio, TX*
[17]*UCLA Medical Hematology & Oncology, Los Angeles, CA*
[18]*Columbia Presbyterian Medical Center, New York, NY*

Background: Overactive JAK-STAT signaling as a result of gain-of-function mutations (eg, JAK2V617F) and/or high circulating levels of inflammatory cytokines is considered to play a key role in the pathogenesis of myeloproliferative neoplasms. Ruxolitinib, a selective oral inhibitor of JAK1 and JAK2, demonstrated a significant reduction in spleen volume (SV) and improvements in myelofibrosis (MF)-related symptoms in a double-blind placebo-controlled trial (COMFORT-I). The objective of this analysis was to evaluate the efficacy of ruxolitinib across patient (pt) subgroups in COMFORT-I.

Methods: Pts with MF were randomized to start placebo or ruxolitinib at a dose of 15 mg or 20 mg PO BID depending on baseline platelet count (100-200 $X10^9$/L or >200 $X10^9$/L, respectively). The dose was optimized for efficacy and safety during treatment. SV change was measured by MRI; MF symptoms were assessed using a daily diary (modified Myelofibrosis Symptom Assessment Form [MFSAF] v2.0) over 1 wk prior to dosing and throughout the 24 wks of dosing. The percent changes from baseline to wk 24 in SV and MFSAF Total Symptom Score (TSS, a measure of combined scores for abdominal discomfort, pain under ribs on left side, early satiety, itching, night sweats, and bone/muscle pain) were compared for ruxolitinib and placebo pts across the following subgroups: MF disease subtype, age, International Prognosis Scoring System (IPSS) risk group, presence/absence of JAK2V617F mutation, baseline hemoglobin, baseline spleen size (palpable spleen length), and baseline TSS. Survival was estimated by Kaplan-Meier method.

Changes in SV and TSS Across Subgroups: 309 pts were randomized: 155 to ruxolitinib and 154 to placebo. Ruxolitinib demonstrated consistent benefit compared with placebo in both SV and TSS across all subgroups evaluated (Table).

Mean Percent Change From Baseline to Wk 24 ± SD

Subgroup	SV		TSS	
	Ruxolitinib	Placebo	Ruxolitinib	Placebo
Primary MF	-29.9±17.5	+8.5±16.7	-38.5±54.3	+41.7±92.0
Post-Polycythemia Vera MF	-37.3±20.9	+5.9±14.5	-54.9±41.5	+27.2±105
Post-Essential Thrombocythemia MF	-27.0±17.4	+11.1±11.2	-49.9±45.1	+73.7±112
High Risk	-30.9±19.5	+7.7±15.8	-41.5±52.2	+48.7±94.8
Intermediate-2 Risk	-32.8±18.4	+9.1±14.5	-53.5±43.2	+28.8±107
Age ≤65	-31.1±18.8	+12.7±15.6	-48.1±46.6	+28.6±73.0
Age >65	-32.2±19.3	+6.3±14.9	-45.0±50.6	+47.7±109
V617F Positive	-34.6±19.8	+8.1±16.5	-52.6±44.9	+42.8±98.6
V617F Negative	-23.8±14.2	+8.4±8.5	-28.1±55.5	+37.2±105

Baseline Palpable Spleen Length ≤10 cm	-26.8±19.1	+13.0±11.7	-28.5±56.6	+39.1±116
Baseline Palpable Spleen Length >10 cm	-32.9±18.9	+6.9±15.9	-51.1±45.4	+42.4±95.5
Baseline Hb ≥10 g/dL	-33.4±18.7	+7.6±16.1	-47.0±49.6	+27.2±99.7
Baseline Hb <10 g/dL	-28.3±19.2	+8.9±14.3	-45.6±47.1	+63.8±95.6

The impact of symptom severity on response was evaluated by baseline TSS quartiles (maximum score for TSS = 60). Ruxolitinib pts with baseline TSS of <8.5, 8.5-<16.5, 16.5-<25.5 and ≥25.5 had mean percent changes in SV of -28.0, -31.4, -31.7 and -34.8, respectively, vs +8.1 for all placebo pts combined. The mean percent change in TSS for these same subgroups was -40.5, -47.2, -48.1 and -48.2 vs +41.8 for all placebo pts combined. These data indicate that pts with modest to marked symptoms all benefit from ruxolitinib therapy in terms of both SV and TSS.

Survival Analysis: 13 ruxolitinib and 24 placebo pts died during the study or during extended follow-up (median follow-up of 52 and 51 wks, respectively), representing a hazard ratio (95% CI) of 0.499 (0.254, 0.98) (p=0.0395). For ruxolitinib- and placebo-treated pts, respectively, the probability of survival (95% CI) >48 wks was 0.98 (0.92, 0.99) and 0.90 (0.81, 0.95) for pts with baseline hemoglobin values ≥10 g/dL and 0.84 (0.72, 0.91) and 0.77 (0.63, 0.86) for pts with baseline hemoglobin <10 g/dL.

Conclusions: Pts receiving ruxolitinib had higher response rates than placebo based on reductions in SV and improvements in TSS at wk 24 regardless of baseline subgroup: MF disease subtype, age (≤65 or >65 y), IPSS risk group (intermediate-2 or high-risk), presence or absence of JAK2V617F mutation, hemoglobin level (≥10 g/dL or <10 g/dL), palpable spleen length (≤10 cm or >10 cm), and symptom severity (TSS quartile). In addition, the overall survival analysis suggested a benefit with ruxolitinib therapy over placebo.