A pooled analysis of overall survival in COMFORT-I and COMFORT-II, 2 randomized phase III trials of ruxolitinib for the treatment of myelofibrosis

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Supplemental Methods

Study Design

Patients in COMFORT-I were required to be resistant or refractory to, intolerant of, or in the investigator's opinion not candidates for available therapies; patients in COMFORT-II could not be candidates for stem cell transplant but could have failed previous therapies. Eligible patients were required to have a life expectancy of ≥ 6 months.

Efficacy Analysis

A Cox proportional hazards model was used for the analysis, providing HRs with 95% CI. Wald *P* values are provided unless specified otherwise; the level of significance was considered as *P* = .05. In addition to the ITT analysis of OS, a time from study discontinuation until death was estimated in patients who discontinued randomized treatment due to disease progression or for any reason. This analysis included all ruxolitinib randomized patients who permanently discontinued treatment and all control arm patients who permanently discontinued treatment with placebo or BAT without subsequently crossing over to ruxolitinib.

The proportion of patients who achieved a spleen response at week 24 was the key secondary endpoint in COMFORT-II. The proportion of patients who achieved a ≥ 50% improvement from baseline in symptoms, as assessed using the Myelofibrosis Symptom Assessment Form—Total Symptom Score, was a key secondary endpoint specific to COMFORT-I and was not evaluated here.

Reverse Kaplan-Meier Analysis

Reverse Kaplan-Meier estimation and log-rank tests were used to analyze the intensity of censoring between the 2 arms of each of the studies. Time to censoring was evaluated with deaths treated as censored events; patients with gaps of > 180 days between the last known date to be alive and the database cutoff date were considered lost to follow-up and were censored at the last date known to be alive.

RPSFT Accounting for Crossover

The crossover-corrected treatment effect was estimated using an RPSFT model.[17,18] The RPSFT method (see **Supplemental Figure 1**) maintains the original randomized group definitions and thus preserves the validity of between-group comparisons. RPSFT provides a randomization-based estimate of treatment effect corrected for the bias introduced by crossover. The main assumption for the method is treatment affects survival by multiplying survival time by a given factor once the patient starts receiving ruxolitinib (structural and thus untestable assumption). OS time was determined for the (1) observed time for patients randomized to ruxolitinib, (2) observed time for patients randomized to control, and (3) observed time for control arm patients who did not cross over and the reconstructed survival time for patients who crossed over to ruxolitinib. The crossover-corrected HR was obtained from a Cox regression model with the original ruxolitinib and reconstructed control arms. The reconstructed control arm used the original OS time for patients who did not cross over and the corrected time for crossover patients. The symmetrical Wald test–based 95% CI were obtained by inflating the standard error of the log-HR to preserve the ITT *P* value.

Spleen Size Reduction and OS

Categories for degrees of spleen volume reduction at week 24 were < 10% or no assessment (including patients who had increases in spleen volume), ≥ 10% to < 25%, ≥ 25% to < 35%, ≥ 35% to < 50%, and ≥ 50%. Categories for spleen length changes at week 24 were increased spleen length, no change to a < 25% reduction, and reductions of ≥ 25% to < 50%, ≥ 50% to < 75%, and ≥ 75% to no longer palpable. A multivariate proportional hazards model was fit for each treatment arm separately to evaluate the impact of the degree of spleen volume reduction, whereas the prognostic baseline covariates were adjusted as described below. HRs were calculated using patients who achieved a < 10% reduction as a reference group for spleen volume and < 25% reduction as a reference group for spleen length.

Evaluation of Baseline Covariates

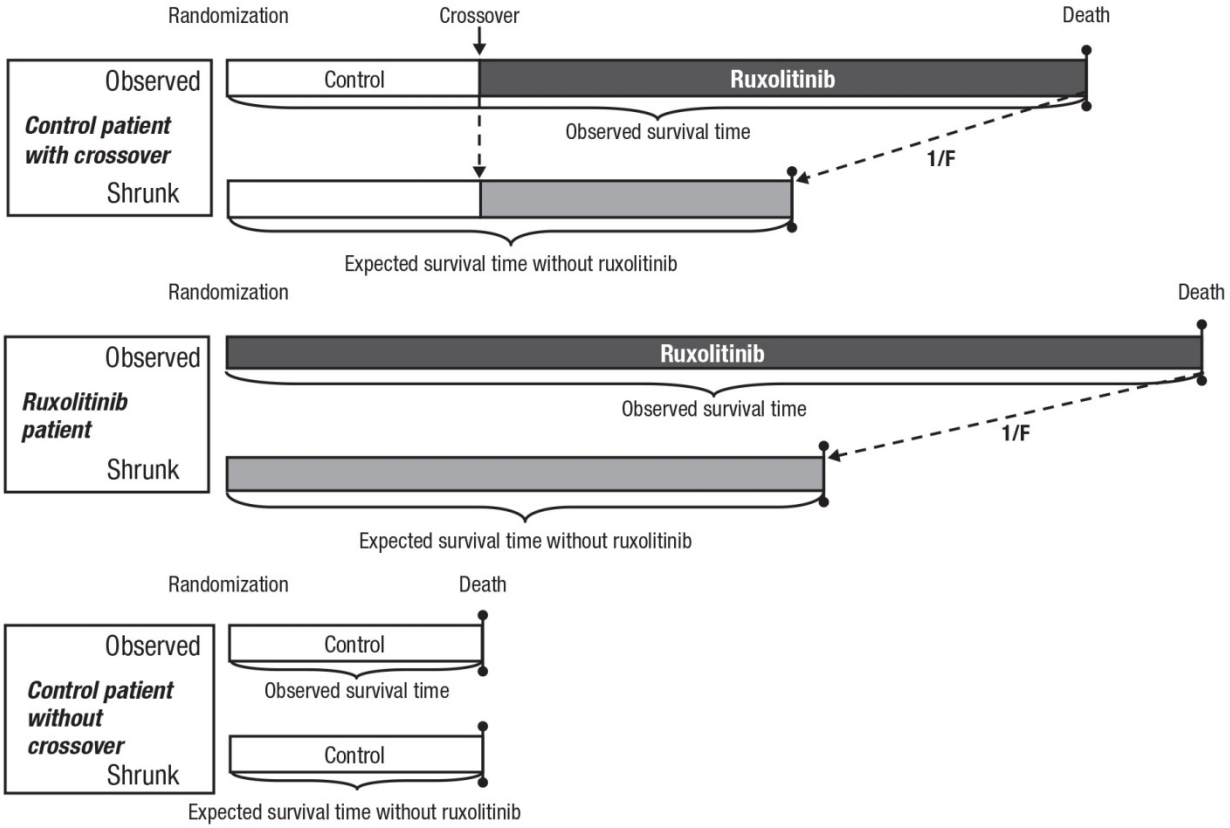
The following baseline factors were evaluated as prognostic for OS, irrespective of treatment: age (years), age > 65 years (yes/no), sex (male/female), MF subtype (PMF/secondary MF), IPSS risk category (Int-2/high risk; as collected on the clinical report form in COMFORT-I and as randomization strata in COMFORT-II), *JAK2* V617F mutation status (positive/negative), baseline palpable spleen length (per cm below left costal margin), baseline spleen volume (per 5 dL), baseline Hb (g/L), Hb < 10 g/dL (yes/no), baseline WBC (g/L), WBC > 25 g/L (yes/no), baseline platelet count ($\times 10^9$/L), presence of constitutional symptoms (yes/no), and presence of circulating blasts (yes/no). The initial selection of covariates was based on experts' knowledge; for further feature selection, an exhaustive set of Cox models was fitted to the data with 1 to n covariates at a time.[29] Covariates that assessed the same parameter on a continuous or discrete scale were not included in the same model (eg, either baseline Hb as continuous [g/L] or binary [< 10 g/dL, yes/no] but not together). Goodness of fit was evaluated with the AIC, and the models were ordered according to minimizing AIC.[30] The covariates most often included in the top 1000 models were considered for the final model, and treatment effect was estimated with adjustments for these covariates. The covariates considered were those identified as potential sources of bias or known to have an impact on MF prognosis.

Supplemental Table 1. Summary of Baseline Characteristics by Overall Survival Lost to Follow-up Status in the BAT Arm

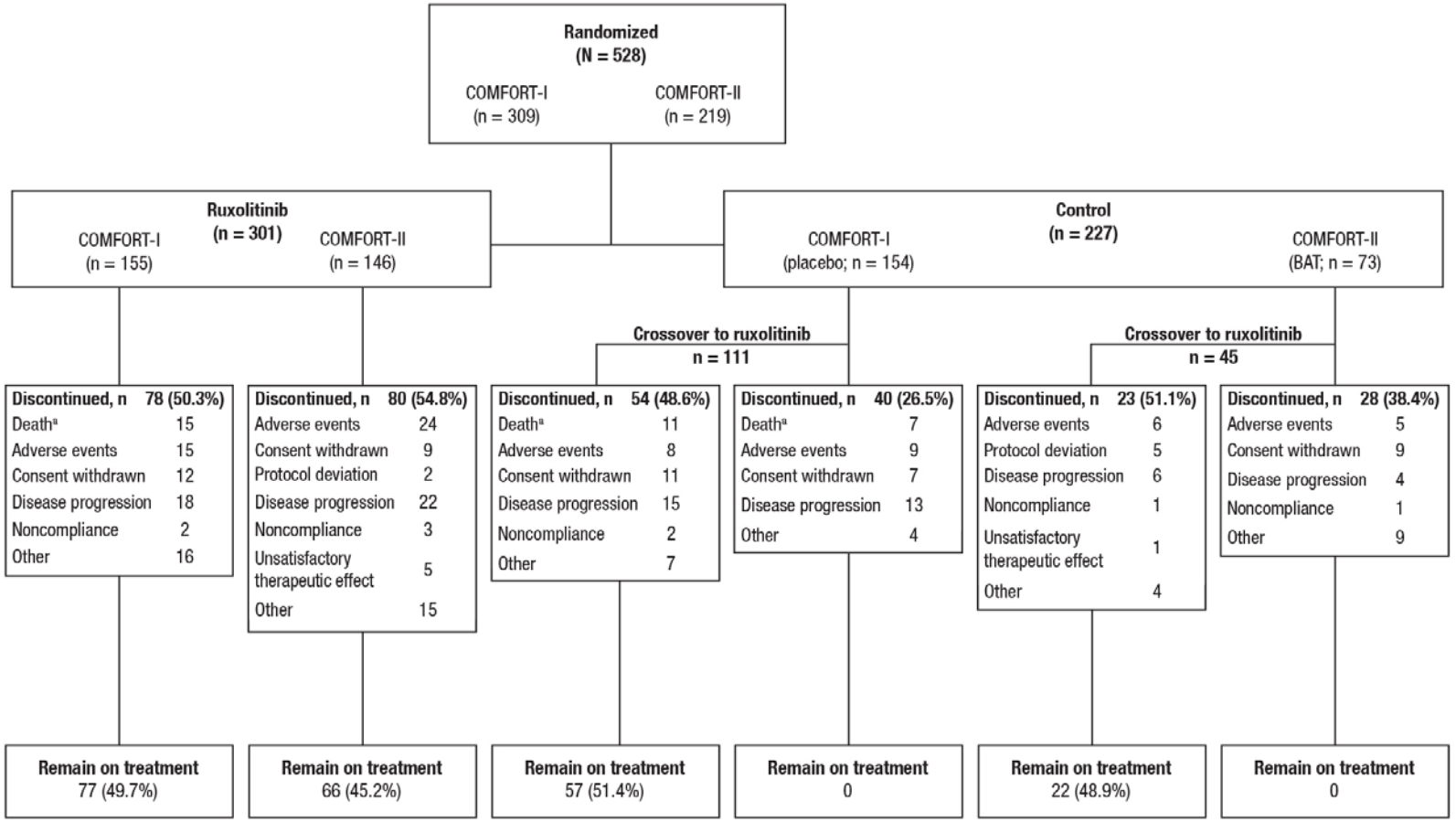
Baseline characteristics, n (%)	**Not lost to follow-up (n = 53)**	**Lost to follow-up (n = 20)**
Risk category		
Int-2	30 (57)	7 (35)
High	23 (43)	13 (65)
Age ≥ 65 years	28 (53)	12 (60)
Primary MF subtype	27 (51)	12 (60)
ECOG performance status		
0	19 (36)	7 (35)
1	28 (53)	9 (45)
2	5 (9)	4 (20)
3	1 (2)	0
JAK2 V617F mutation status		
Positive	40 (75)	9 (45)
Negative	11 (21)	9 (45)
Missing	2 (4)	2 (10)
Platelet count, median (range), $\times 10^9$/L	239.0 (104-850)	206.5 (102-1049)
Hemoglobin, median (range), g/L	105 (54-154)	99 (70-118)
Crossover to ruxolitinib, n (%)		
No	12 (23)	16 (80)
Yes	41 (77)	4 (20)

BAT, best available therapy; ECOG, Eastern Cooperative Oncology Group; JAK2, Janus kinase 2; MF, myelofibrosis.

Supplemental Figure 1. RPSFT Accounting for Crossover

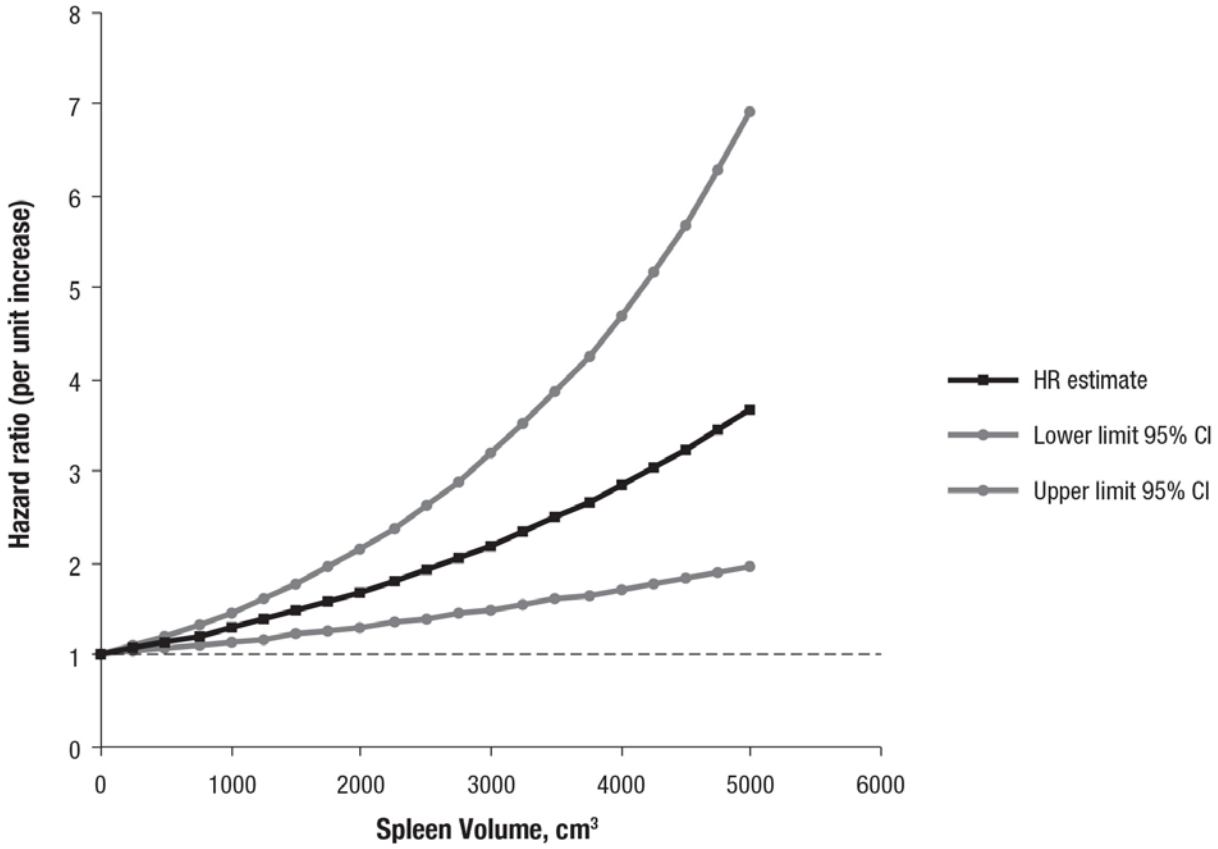


Supplemental Figure 4. Patient Disposition



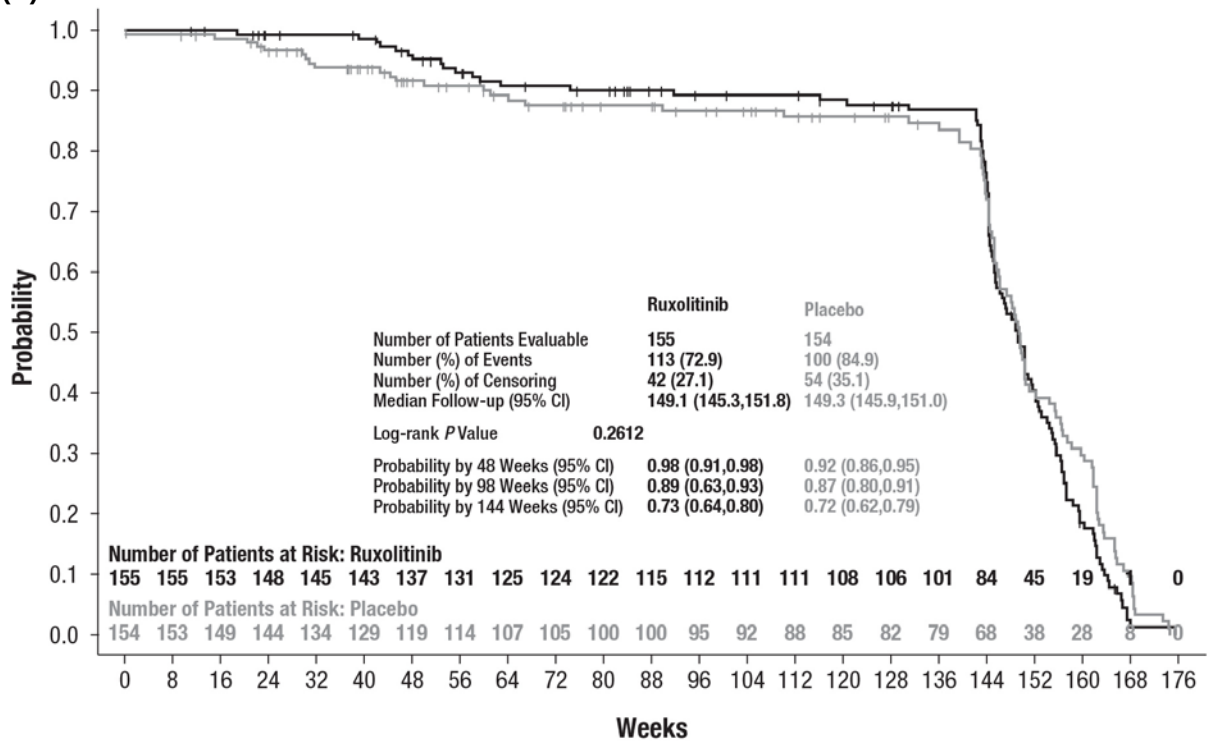
[a] In COMFORT-I, death was considered as a reason for discontinuation if the death date was the same as the discontinuation date while the primary reason of discontinuation was recorded on the case report form as due to an AE

Supplemental Figure 3. Relationship Between Spleen Volume and Survival (based on multivariate model with adjustments for other covariates)



Supplemental Figure 4. Kaplan-Meier Analysis of the Risk of Being Censored for Survival Data in (A) COMFORT-I and (B) COMFORT-II

(A)



(B)