Red Blood Cell Transfusion Independence Status Is an Independent Predictor of Survival: A Post Hoc Time-Dependent Analysis of the Phase 3 SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM Trials

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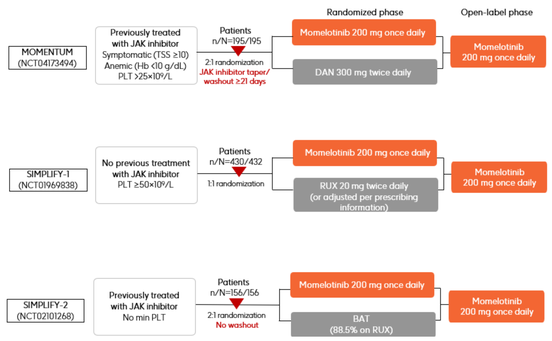
Introduction

- The management of anemia in myelofibrosis (MF), a chronic progressive myeloproliferative neoplasm, remains an ongoing medical need as it is present in approximately 30% of patients at diagnosis and >50% after 1 year, contributing to negative impacts such as fatigue, medical complications, and poor quality of life[1-3]
  - Anemia and resulting transfusion need are independent predictors of poor prognosis and associated with shorter overall survival (OS)[4]
- Momelotinib is a Janus kinase (JAK) 1/JAK2/activin A receptor type 1 inhibitor that has demonstrated spleen, symptom, and anemia benefits, including increases in hemoglobin and reduction or elimination of red blood cell (RBC) transfusion requirements in patients with MF[5-7]
  - Results from the MOMENTUM and SIMPLIFY-1 trials led to the September 2023 US Food and Drug Administration approval of momelotinib for the treatment of intermediate- or high-risk MF, including primary or secondary MF, in adults with anemia[8]
- Data from the phase 3 MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2 studies have shown an association between transfusion independence at week 24 and prolonged OS with momelotinib[9,10]
- Because these analyses did not adjust for additional prognostic factors or effect modifiers nor potential longitudinal changes in transfusion status over time, the impact of transfusion status on OS has not been fully characterized
- Here, we describe an analysis investigating the prognostic influence of RBC transfusion status over time and other covariates on OS from the MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2 studies irrespective of the treatment received

Methods

- These treatment-agnostic OS analyses incorporated data from the safety populations of 3 multicenter, international, randomized trials investigating momelotinib vs an active comparator (**Figure 1**)

Figure 1. **Study Design for MOMENTUM,[5] SIMPLIFY-1[6], and SIMPLIFY-2[7]**



Methods

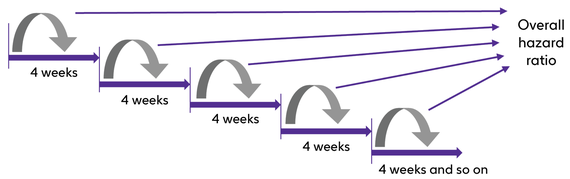
- In the current analysis, time-dependent covariates and fixed baseline covariates were evaluated to determine their prognostic impact on OS (**Table 1**)

Table 1. **Time-Dependent and Fixed Baseline Covariates**

Time-dependent covariates
RBC transfusion status (assessed every 4 weeks) • TI: absence of RBC transfusion and no Hb level <8 g/dL in the prior 12 weeks • Non-TI: not satisfying the criteria for TI
Fixed baseline covariates
Demographics • Age (<65, ≥65 years) • Sex (female, male)
Disease status • MF subtype (primary MF, post–polycythemia vera, post–essential thrombocythemia) • *JAK2* mutation (positive, negative, unknown)
Clinical characteristics • ECOG performance status (0, 1, 2) • TSS (< median, ≥ median) • IPSS score for SIMPLIFY-1 and DIPSS score for SIMPLIFY-2 and MOMENTUM (intermediate-1, intermediate-2, high) • Platelet count (< median, ≥ median) • Spleen volume (< median, ≥ median)

- An extended Cox model was used to generate an overall hazard ratio (HR) using all available follow-up time until the end of each trial, and independent variables were retained if a backward variable selection method determined that they were significantly associated with OS (**Figure 2**)

Figure 2. **Extended Cox Proportional Hazards Model**



Results

- Significant covariates associated with survival across the 3 trials are presented in **Table 2**, with RBC transfusion status over time remaining a consistent prognostic variable significantly associated with survival in all 3 trials
  - In MOMENTUM, no other covariate was significantly associated with OS
  - In SIMPLIFY-1, baseline age, baseline platelet count, and baseline spleen volume were also significantly associated with OS
  - In SIMPLIFY-2, additional significant covariates were baseline age, baseline spleen volume, and baseline Dynamic International Prognostic Scoring System (DIPSS) score

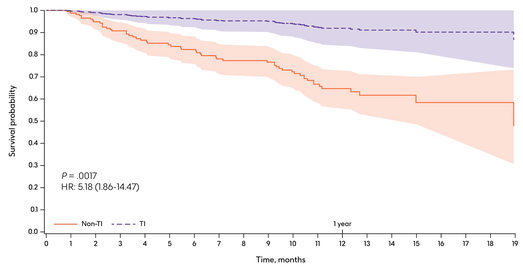
Table 2. **Estimates of Relative OS by Adjusted Covariates**

Covariate, reference vs comparator	HR (95% CI)[a]	*P* value[b]
MOMENTUM		
RBC transfusion status, TI[c] vs non-TI	5.18 (1.86-14.47)	.0017
SIMPLIFY-1		
RBC transfusion status, TI[c] vs non-TI	3.32 (2.31-4.78)	<.0001
BL age, <65[c] vs ≥65 years	2.40 (1.59-3.64)	<.0001
BL platelet count, ≥100[c] vs <100×10⁹/L	1.97 (1.17-3.32)	.0109
BL spleen volume, < median[c] vs ≥ median	1.81 (1.25-2.62)	.0015
SIMPLIFY-2[d]		
RBC transfusion status, TI[c] vs non-TI	1.87 (1.07-3.29)	.0287
BL age, <65[c] vs ≥65 years	2.71 (1.44-5.09)	.0020
BL spleen volume, < median[c] vs ≥ median	2.55 (1.55-4.20)	.0002
BL DIPSS, intermediate-1[c] vs high risk	2.97 (1.27-6.91)	.0118
BL DIPSS, intermediate-2[c] vs high risk	2.66 (1.47-4.82)	.0013

[a] For all covariates, HR >1 suggests longer OS with the reference category (TI, age <65 years, platelet count ≥100×10⁹/L, spleen volume < median, or lower DIPSS risk score) than the comparator category (non-TI, age ≥65 years, platelet count <100×10⁹/L, spleen volume ≥ median, or higher DIPSS risk score). [b] P value <.05 indicates statistical significance. [c] Indicates reference category for each covariate. [d] In the SIMPLIFY-2 analysis, the result for BL DIPSS, intermediate-1 vs intermediate-2 risk, was not significant (P=.7597).

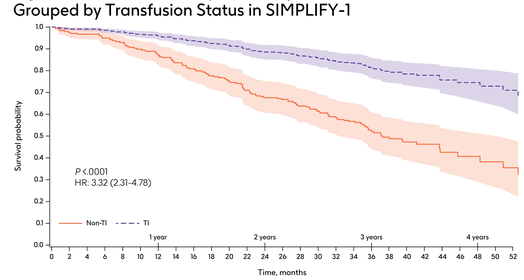
- Results from MOMENTUM demonstrate a strong and significant relationship between transfusion status over time and OS (HR, 5.18; 95% CI, 1.86-14.47; *P*=.0017), suggesting that patients who were non–transfusion independent (TI) have a higher risk of all-cause mortality more than 5 times that of patients who remain TI (**Table 2**)
- Similar results with respect to the survival benefits of TI status over time were observed in both SIMPLIFY-1 (HR, 3.32; 95% CI, 2.31-4.78; *P*<.0001) and SIMPLIFY-2 (HR, 1.87; 95% CI, 1.07-3.29; *P*=.0287) (**Table 2**)
- Predictive models depicting potential relative survival over time demonstrate the significance of transfusion status on OS in MOMENTUM (**Figure 3**), SIMPLIFY-1 (**Figure 4**), and SIMPLIFY-2 (**Figure 5**)
  - The separation of curves between the TI and non-TI populations over time indicates an increased risk of death for the non-TI population

Figure 3. **Estimate of OS by Mean Adjusted Covariates Over Time Grouped by Transfusion Status in MOMENTUM**



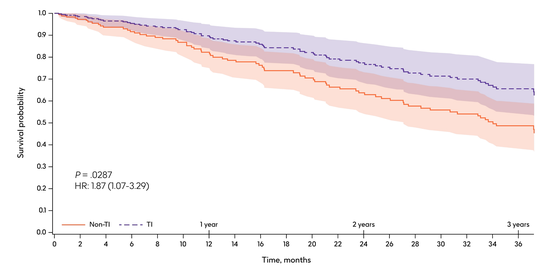
Shaded area indicates 95% CI. Estimations are based on multivariate analysis.

Figure 4. **Estimate of OS by Mean Adjusted Covariates Over Time Grouped by Transfusion Status in SIMPLIFY-1**



Shaded area indicates 95% CI. Estimations are based on multivariate analysis.

Figure 5. **Estimate of OS by Mean Adjusted Covariates Over Time Grouped by Transfusion Status in SIMPLIFY-2**



Shaded area indicates 95% CI. Estimations are based on multivariate analysis.

Conclusion

- These data demonstrate that when accounting for differences in known prognostic factors and effect modifiers as well as changes in RBC transfusion status over time, a consistent and statistically significant relationship was observed between transfusion independence and OS across all 3 phase 3 momelotinib trials
- Consistent with inclusion of transfusion status in DIPSS-plus risk assessment,[11] these data support maintenance or achievement of TI status as a clinically relevant and meaningful endpoint that is prognostic for survival in JAK inhibitor–naive and –experienced disease settings, irrespective of other covariates
- While factors such as sample size and follow-up that vary across trials impact the observed probability estimates for survival, the differing magnitudes of the separation between the TI and non-TI populations in each trial suggest that earlier initiation of momelotinib (eg, the JAK inhibitor–naive setting of SIMPLIFY-1) to maintain TI status or achieve it earlier may lead to more pronounced effects on OS
- A limitation of these analyses is that evaluation of any potential differential impacts of these covariates on OS between momelotinib and comparator arms was not possible due to the crossover design of all 3 trials; all patients who remained in the trial after week 24 received momelotinib, confounding assessment of survival by treatment arm
- Sensitivity analyses incorporating other time-dependent variables (eg, ferritin levels, platelet counts) and subgroup analyses (eg, baseline transfusion status) are being explored and may identify additional longitudinal changes that, along with transfusion status, impact OS in patients with MF

Abbreviations

BAT, best available therapy; BL, baseline; DAN, danazol; DIPSS, Dynamic International Prognostic Scoring System; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; HR, hazard ratio; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MF, myelofibrosis; OS, overall survival; PLT, platelet count; RBC, red blood cell; RUX, ruxolitinib; TI, transfusion independent; TSS, Total Symptom Score.

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