

Transfusion Independence is Associated With Improved Overall Survival in Myelofibrosis Patients Receiving Momelotinib

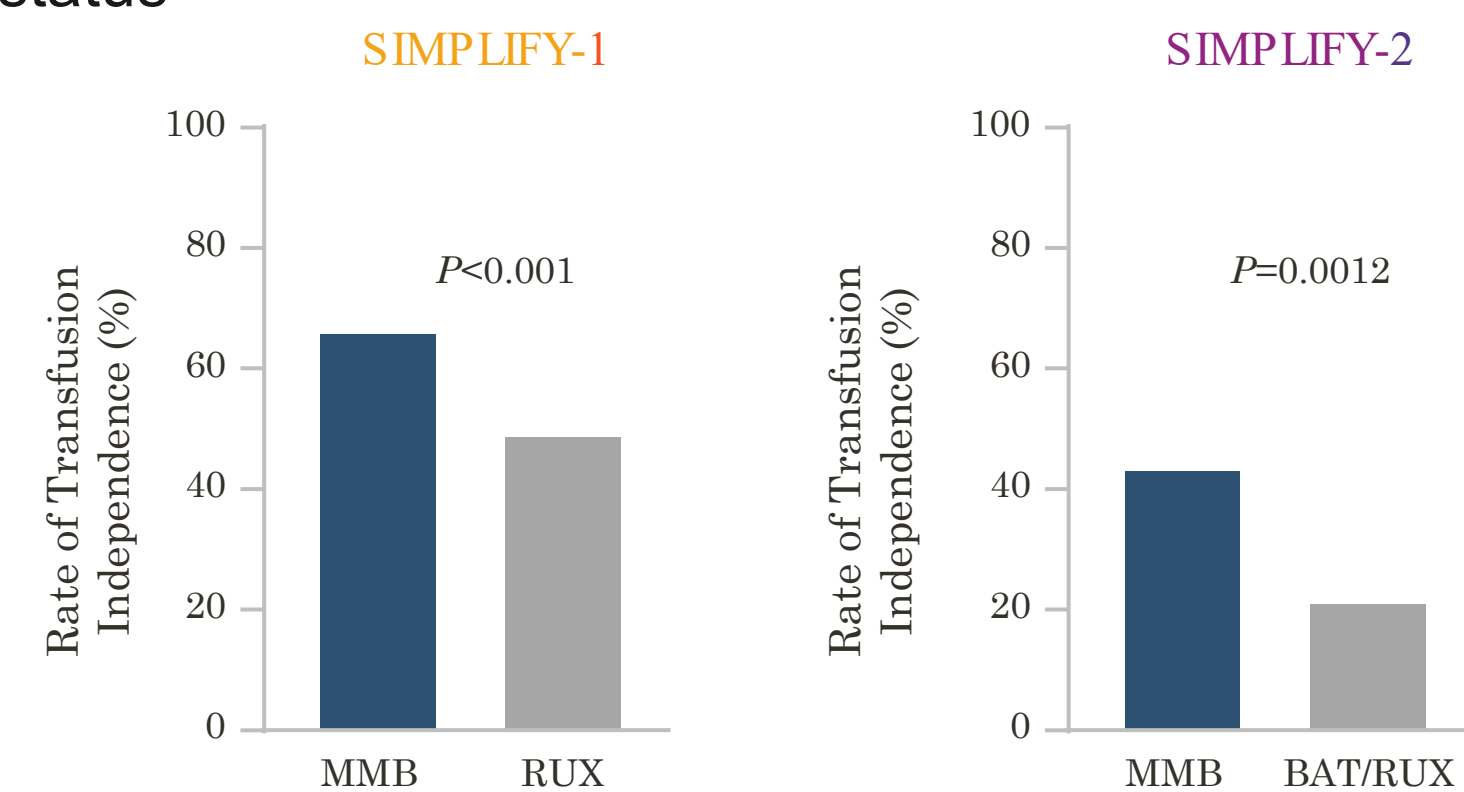


Ruben Mesa¹, Stephen T. Oh², Aaron T. Gerds³, Vikas Gupta⁴, John Catalano⁵, Francisco Cervantes⁶, Timothy Devos⁷, Marek Hus⁸, Jean-Jacques Kiladjian⁹, Ewa Lech-Maranda¹⁰, Donal McLornan¹¹, Jeanne Palmer¹², Uwe Platzbecker¹³, Jacek Trelinski¹⁴, Kazuya Shimoda¹⁵, Rafe Donahue¹⁶, Bryan Strouse¹⁶, Mark Kowalski¹⁶, and Srdan Verstovsek¹⁷

¹UT Health San Antonio Cancer Center, San Antonio, TX; ²Washington University, St. Louis, MO; ³Cleveland Clinic Department of Hematology and Medical Oncology, Avon, OH; ⁴Princess Margaret Cancer Centre, Toronto, ON, Canada; ⁵Monash University & Frankston Hospital, Frankston, Australia; ⁶Hematology Department, Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Spain; ⁷Department of Hematology, University Hospitals Leuven Department of Microbiology and Immunology, Laboratory of Molecular Immunology (Rega Institute), KU Leuven, Leuven, Belgium; ⁸Department Hemato-Oncology and Bone Marrow Transplantation, Medical University of Lublin, Lublin, Poland; ⁹Saint-Louis Hospital (AP-HP), Paris, France; ¹⁰Department of Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland; ¹¹Guy's and Saint Thomas' NHS Foundation Trust, London, United Kingdom; ¹²Mayo Clinic Hospital, Phoenix, AZ, USA; ¹³Leipzig University Hospital, Leipzig, Germany; ¹⁴Medical University of Lodz, Lodz, Poland; ¹⁵University of Miyazaki, Miyazaki, Japan; ¹⁶Sierra Oncology Inc., Vancouver, Canada; ¹⁷The University of Texas MD Anderson Cancer Center, Houston, TX

Background

- Myelofibrosis (MF) is a highly heterogenous disease that remains incurable beyond hematopoietic stem cell transplantation
- About 60% of patients with MF are anemic and 45% are RBC transfusion requiring within 1 year of diagnosis, with most progressing to transfusion dependency (TD) over time. Both TD and anemia are critical negative prognostic factors in MF and are inversely correlated with quality of life
- Approved JAK inhibitors (JAKi) provide spleen and symptom improvements but are generally myelosuppressive and do not address TD
- Momelotinib (MMB) is a potent JAK1, JAK2, and ACVR1/ALK2 inhibitor with clinical activity against anemia, constitutional symptoms, and splenomegaly in MF. These findings were demonstrated in the previously conducted Phase 3 SIMPLIFY-1 & -2 (S1 and S2; NCT01969838 and NCT02101268) trials comparing MMB to ruxolitinib (RUX) in JAKi-naïve patients and to best available therapy (BAT; RUX in 88% of patients) in patients with prior RUX therapy, respectively
- Preclinical and clinical translational studies have demonstrated the ability of MMB to address anemia and TD through inhibition of ACVR1/ALK2
- Previously published data demonstrate Week 24 (W24) transfusion independence (TI) rates were higher in the MMB arms of S1 (67% vs 49%) and S2 (43% vs 21%)
- Additionally, as shown in ASCO 2021 abstract #e19039, the W24 TI rate in S1 was higher in patients receiving MMB vs RUX, irrespective of the degree of baseline anemia, or the baseline platelet (PLT) count or transfusion status



SIMPLIFY-1 Baseline Characteristic	MMB W24 TI Response	RUX W24 TI Response
Hgb < 8 g/dL	29%	18%
Hgb < 10 g/dL	47%	27%
Hgb < 12 g/dL	62%	37%
Hgb ≤ 14 g/dL	67%	46%
Hgb > 14 g/dL	64%	89%
PLTs < 150 × 10 ⁹ /L	62%	43%
PLTs < 300 × 10 ⁹ /L	68%	48%
PLTs ≥ 300 × 10 ⁹ /L	63%	51%
Transfusion independent	81%	62%
Transfusion requiring	53%	31%
Transfusion dependent	30%	17%

Methods

- To explore the relationship between efficacy outcomes and overall survival (OS), subgroup analyses were performed for patients randomized to MMB in S1 and S2. Subgroups were defined as follows:
 - W24 TI response: no RBC transfusion for ≥ 12 weeks, with hemoglobin (Hgb) ≥ 8 g/dL
 - W24 spleen response: ≥ 35% spleen volume reduction vs baseline (BL)
 - W24 symptom response: ≥ 50% reduction in Myelofibrosis Symptom Assessment Form total symptom score vs BL
- Survival was estimated using Kaplan-Meier (K-M) analysis with descriptive log-rank tests for comparison applied (all *P* values are descriptive). Hazard ratios (HRs) were computed using proportional hazard regression

Results

OS for TI Responders vs Nonresponders

- In S1, W24 TI responders randomized to MMB had an OS advantage, with median OS not reached and a 3-year survival rate of 80% (HR=0.30; *P*<0.0001) compared with MMB TI nonresponders, who had a median OS of 3 years (3-year survival rate, 50%)
- In S2, W24 TI responders randomized to MMB show a trend toward better OS vs MMB TI nonresponders (HR=0.57; *P*=0.0652)
- To adjust for the time to response bias, OS from W24 was also calculated and compared with OS calculated from randomization presented here. These analyses demonstrated consistent results

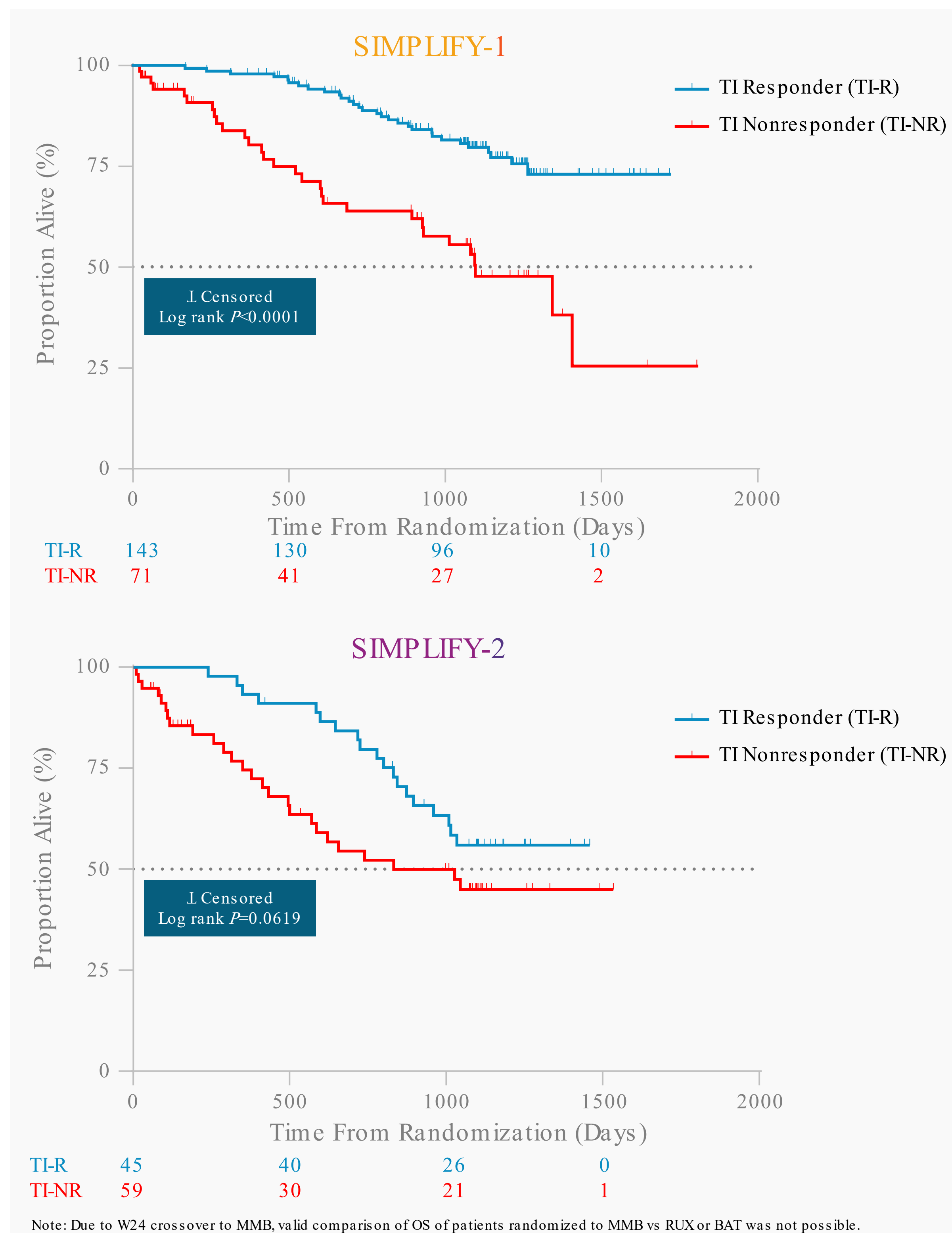
Spleen and Symptom Responders vs Nonresponders

- Similar K-M analyses for the subgroups of patients with spleen and symptom response at W24 in both S1 and S2 were performed
- HRs in S1 for MMB responders vs nonresponders for spleen and symptoms were 0.59 (*P*=0.0904) and 0.66 (*P*=0.1657), respectively, suggesting a trend toward improved OS in responders for these endpoints. These relationships were not statistically significant
- Similarly, in S2 no statistically significant difference in OS was observed between spleen and symptom responders and nonresponders (HR=2.06; *P*=0.1004 and HR=0.67; *P*=0.2513)

Clinical Relevance and Conclusions

- Momelotinib has been shown to provide anemia benefit, resulting in higher rates of transfusion independence compared with ruxolitinib, regardless of degree of baseline anemia, baseline platelet count, or transfusion status
- These new subgroup analyses of overall survival (OS) in patients with myelofibrosis randomized to momelotinib suggest patients who are transfusion independent (TI) at Week 24 predicts for a clinically relevant improvement in OS compared with patients who were not TI at Week 24
- In JAKi-naïve patients randomized to momelotinib, Week 24 TI was found to be a significant predictor of improved OS (HR=0.30; *P*<0.0001)
- Week 24 endpoints such as reduction in spleen volume and symptomatic improvements are commonly used to evaluate treatment-related clinical benefit; however, no significant association of these endpoints with OS was observed
- The findings presented here suggest the clinical benefit of TI may predict improved OS in myelofibrosis, supporting the clinical relevance of momelotinib's pro-erythropoietic ACVR1/ALK2 inhibition
- Week 24 transfusion independence is associated with improved overall survival in patients with myelofibrosis randomized to momelotinib**

Poster previously presented at virtual ASCO June 4-8, 2021



Note: Due to W24 crossover to MMB, valid comparison of OS of patients randomized to MMB vs RUX or BAT was not possible.