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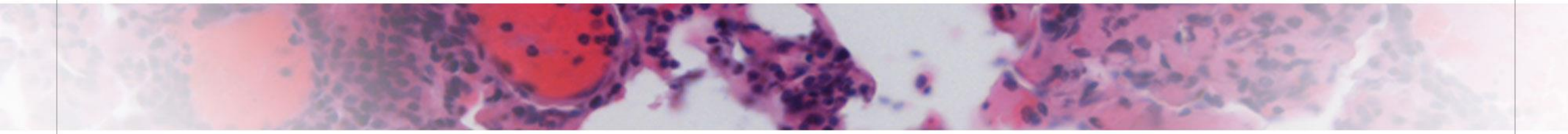

Bone Marrow Fibrosis Changes Do Not Correlate with Efficacy Outcomes in Myelofibrosis: Analysis of More Than 300 JAK Inhibitor-Naïve Patients Treated with Momelotinib or Ruxolitinib

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Background

Bone marrow fibrosis (BMF) is a primary pathological and diagnostic feature of MF[1-3]

Several studies associated increasing BMF with poor prognosis[3,4]

Recent studies report BMF improvement as evidence of disease modification.[5-7] Limited clinical data exists on associations of treatment-related BMF changes with efficacy outcomes

Objective: To investigate the impact of 2 differentiated JAK inhibitors, momelotinib (MMB), and ruxolitinib (RUX), on BMF, and assess correlations between BMF changes and clinical outcomes among JAK inhibitor-naïve patients with MF in the phase 3 SIMPLIFY-1 study

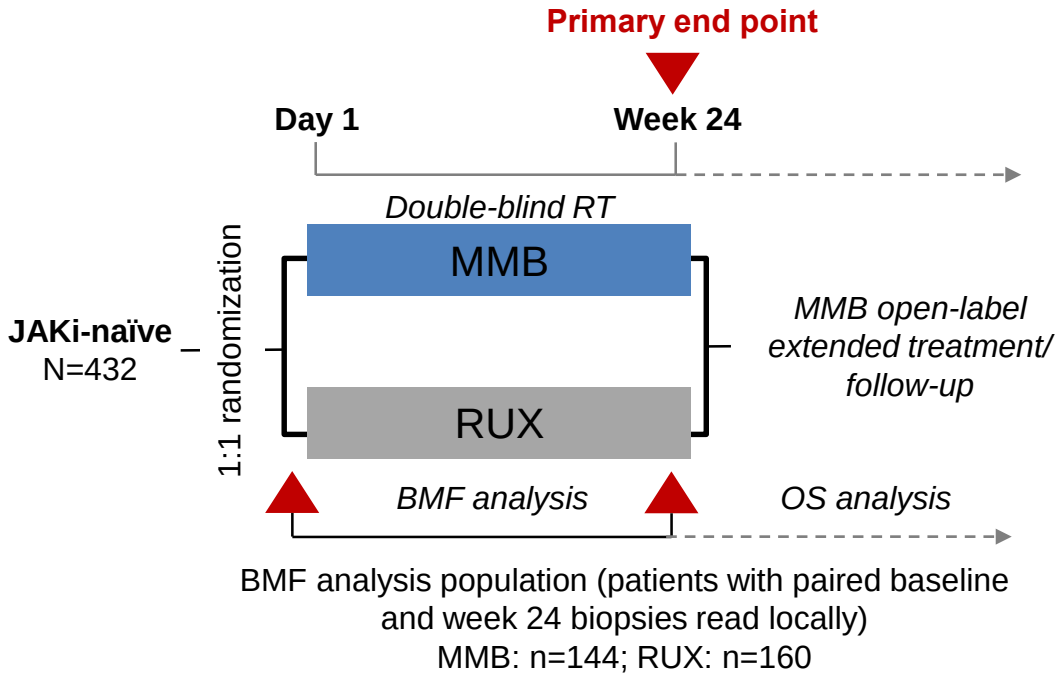
BMF, bone marrow fibrosis; JAK, Janus kinase; MF, myelofibrosis; MMB, momelotinib; RUX, ruxolitinib.

1. Zahr AA, et al. *Haematologica*. 2016;101(6):660-671. 2. O'Sullivan JM, Harrison CN. *Clin Adv Hematol Oncol*. 2018;16(2):121-131. 3. Li B, et al. *Blood Cancer J*. 2016;6(12):e505. 4. Guglielmelli P, et al. *Am J Hematol.* 2016;91(9):918-922. 5. Harrison CN, et al. *J Clin Oncol*. 2022;40(15):1671-1680. 6. Pemmarau N, et al. *Lancet Haematol*. 2022;9(6):e434-e444. 7. Kremyanskaya M, et al. Abstract presented at: 63rd American Society of Hematology Annual Meeting & Exposition; December 10-14, 2021; Atlanta, GA. Abstract 141.

SIMPLIFY-1 Was a Randomized, Head-to-Head, Double-Blind, Phase 3 Study of Momelotinib Versus RUX in Over 400 JAKi-Naïve Patients With MF[1]

Methods

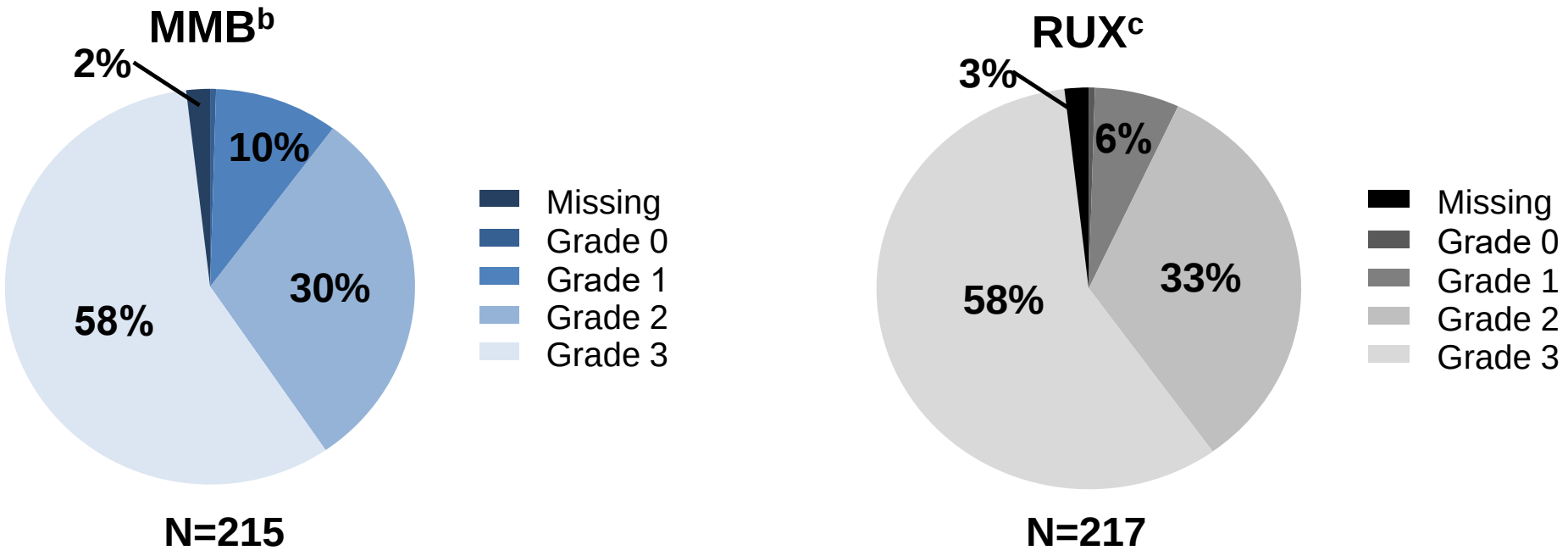
- BMF biopsies were collected pretreatment and after 24 weeks of momelotinib or RUX RT from >300 patients
- Grading was performed locally using an updated WHO scale from grade 0 (normal BM) to grade 3 (diffuse and dense increase in reticulin, etc)
- The JAKi-naïve setting minimized prior treatment confounders
- The impact of RUX and momelotinib on BMF and MF-associated clinical outcomes were analyzed
- Other efficacy assessments made throughout the study included:
  - MFSAF symptom scoring (during RT period only)
  - Spleen volume imaging
  - TI status and Hgb levels



BM, bone marrow; BMF, bone marrow fibrosis; Hgb, hemoglobin; JAKi, Janus kinase inhibitor; MFSAF, Myelofibrosis Symptom Assessment Form; MMB, momelotinib; OS, overall survival; RT, randomized treatment; RUX, ruxolitinib; TI, transusion independence; WHO, World Health Organization.

1. Mesa RA, et al. *J Clin Oncol.* 2017; 35:844–3850.

A Total of 58% of the JAKi-Naïve Patients[a] in SIMPLIFY-1 Had Grade 3 BMF at Baseline



[a]N=432. [b]211/215 randomized MMB patients had baseline BMF assessment. [c]213/217 randomized RUX patients had baseline BMF assessment.
BMF, bone marrow fibrosis; JAKi, Janus kinase inhibitor; MMB, momelotinib; RUX, ruxolitinib.

Ruxolitinib and Momelotinib Have a Similar Effect on ≥1 Grade Improvement in BMF in Assessment of Paired Biopsies

SIMPLIFY-1: MMB Patients With Baseline and Week 24 Paired Biopsy

Baseline grade improvement	Week 24 Grade 0	Week 24 Grade 1	Week 24 Grade 2	Week 24 Grade 3	Total
Grade 0	1	0	0	0	1
Grade 1	2	6	4	2	14
Grade 2	2	7	22	15	46
Grade 3	1	4	15	63	83
Total	6	17	41	80	144

SIMPLIFY-1: RUX Patients With Baseline and Week 24 Paired Biopsy

Baseline grade improvement	Week 24 Grade 0	Week 24 Grade 1	Week 24 Grade 2	Week 24 Grade 3	Total
Grade 0	0	0	0	0	0
Grade 1	2	2	3	3	10
Grade 2	1	10	24	24	59
Grade 3	0	3	20	68	91
Total	3	15	47	95	160

≥1 grade improvement

BMF stable

≥1 grade worsening

MMB Cohort

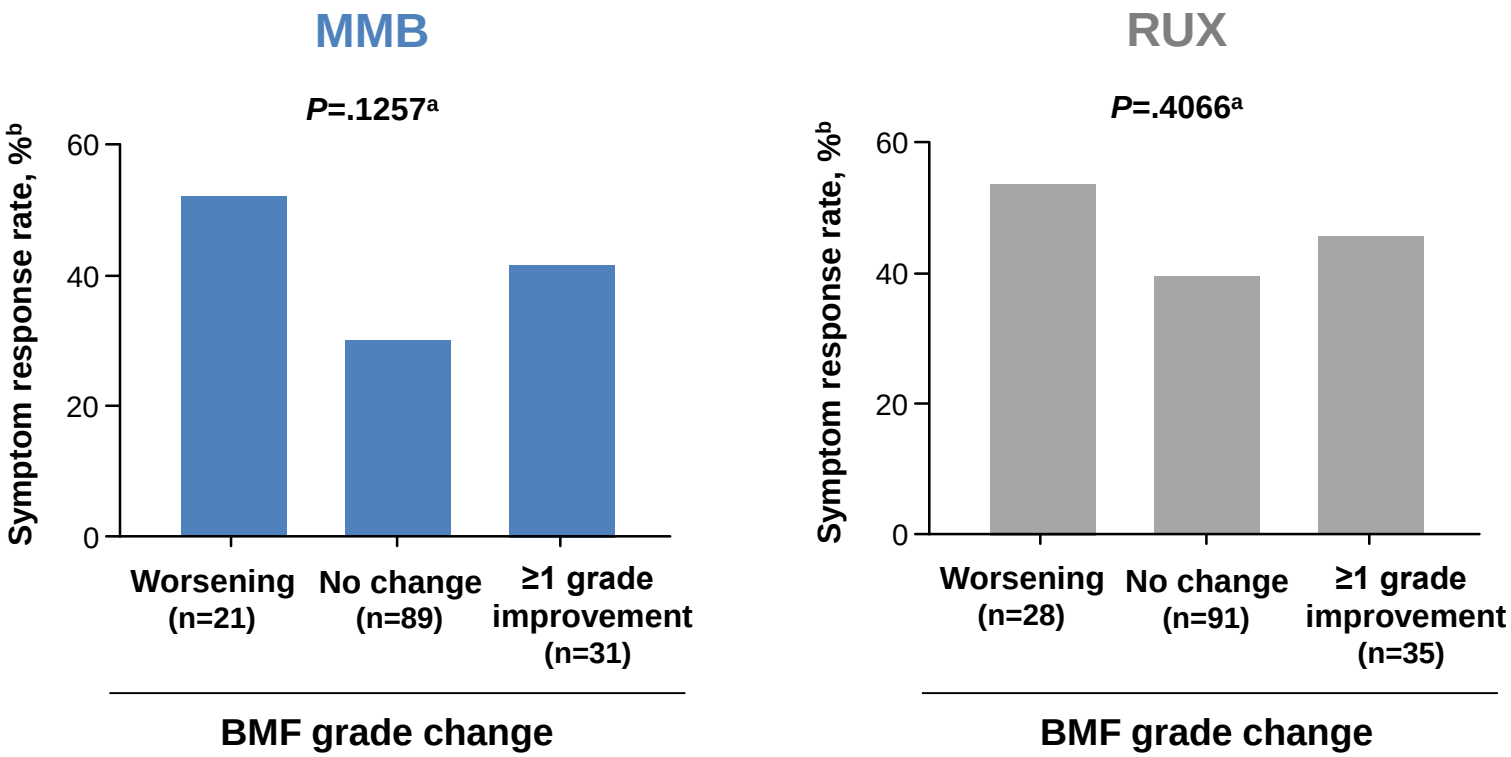
- **21.5% (31/144) had ≥1 grade improvement in BMF**
- 85% (123/144) had stable or improved BMF over the 24-week period

RUX Cohort

- **22.5% (36/160) had ≥1 grade improvement in BMF**
- 81.2% (130/160) had stable or improved BMF over the 24-week period

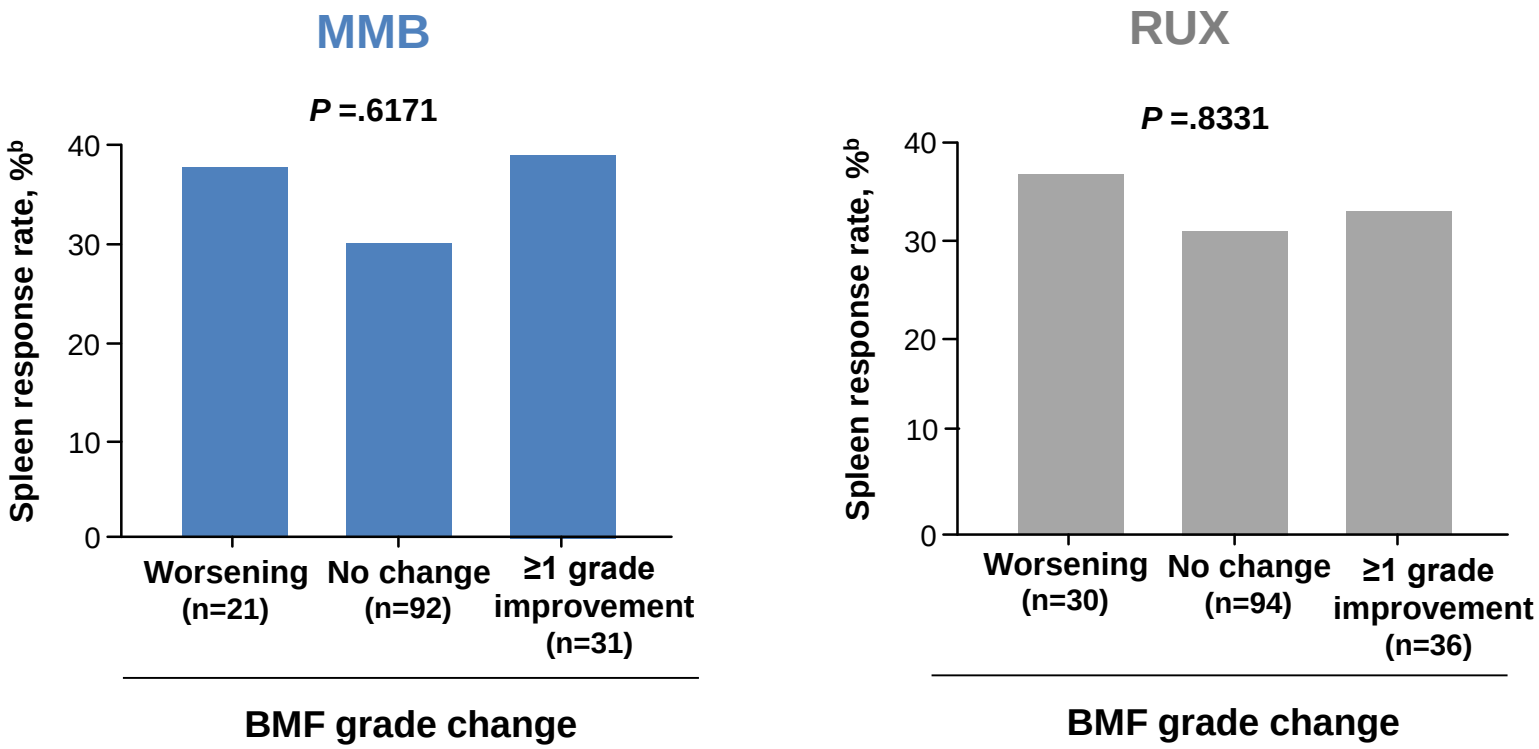
BMF, bone marrow fibrosis; MMB, momelotinib; RUX, ruxolitinib.

No Associations Between BMF Changes and Week 24 Symptom Response for Either Momelotinib or Ruxolitinib



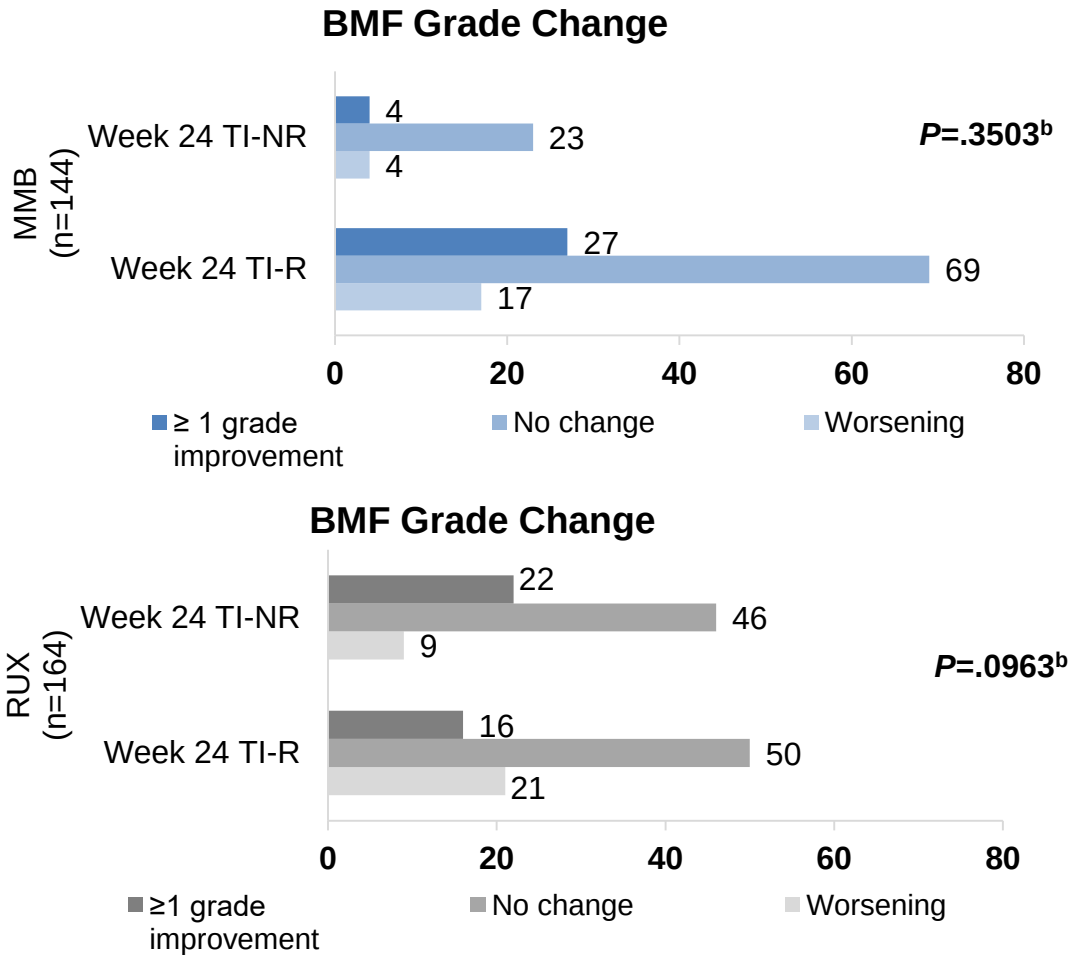
[a]*P* value was calculated using a chi-square test. [b]Symptom response is defined as achieving ≥50% reduction in MFSAF TSS over the 28 days immediately before the end of week 24 compared with baseline. Percentage is calculated using the BMF change category as denominator (ie, ≥1 grade improvement, no change, or worsening).
BMF, bone marrow fibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MMB, momelotinib; RUX, ruxolitinib; TSS, total symptom score.

No Associations Between BMF Changes and Week 24 Spleen Response for Either Momelotinib or Ruxolitinib



[a]*P* value was calculated using a chi-square test. [b]Spleen response is defined as achieving a ≥25% or ≥35% reduction in spleen volume from baseline. Percentage is calculated using the BMF change category as denominator (ie, ≥1 grade improvement, no change, or worsening).
BMF, bone marrow fibrosis; MMB, momelotinib; RUX, ruxolitinib.

No Associations Between BMF Changes and Week 24 TI-R[a] for Either Momelotinib or Ruxolitinib

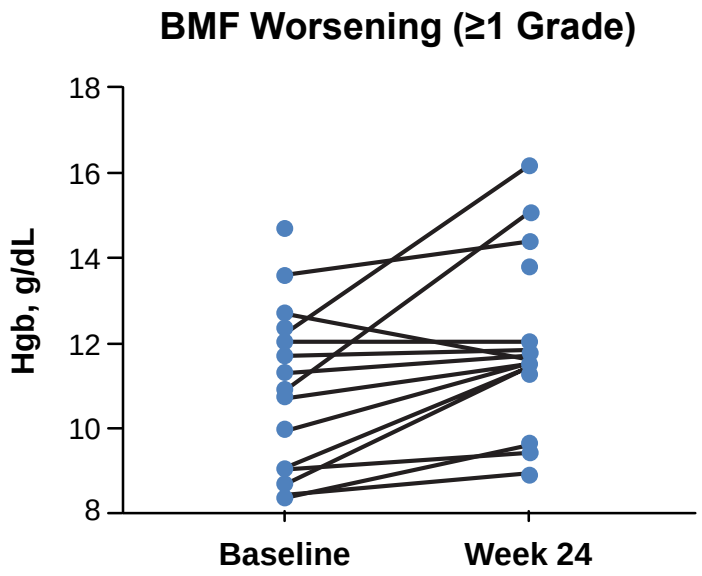


- Overall, 78% of patients achieved week 24 TI-R on momelotinib versus 53% on ruxolitinib
- Twice as many patients on momelotinib with ≥1 grade BMF improvement achieved week 24 TI-R compared with ruxolitinib
- Similar TI-R was seen with both momelotinib and ruxolitinib with worsening BMF
- There is no consistent trend in TI responses across BMF groups within each treatment group
- In momelotinib-treated patients, TI responses were achieved regardless of BMF changes, suggesting the anemia benefit of momelotinib is a feature of its JAK1-, JAK2-, and ACVR1-mediated mechanism of action, which is not reciprocated by ruxolitinib

[a]TI-R was defined as absence of RBC transfusions and no Hgb levels <8 g/dL in the 12 weeks before week 24. [b]*P* value was calculated using a chi-square test.
ACVR1, activin A receptor type 1; BMF, bone marrow fibrosis; Hgb, hemoglobin; MMB, momelotinib; RBC, red blood cell; RUX, ruxolitinib; TI, transfusion independence; TI-NR, transfusion independence nonresponse; TI-R, transfusion independence response.

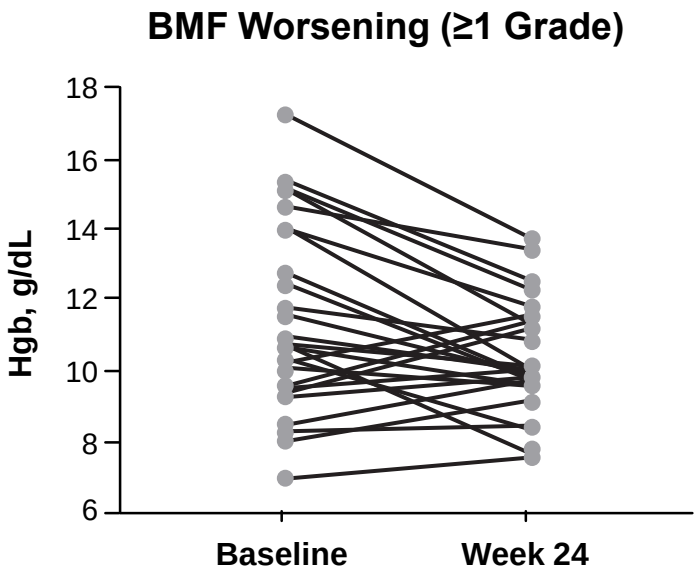
Despite BMF Worsening at Week 24, Hgb Generally Increased on Momelotinib but Decreased on RUX

MMB



Mean baseline Hgb[a]	Mean week 24 Hgb
10.7	11.7

RUX

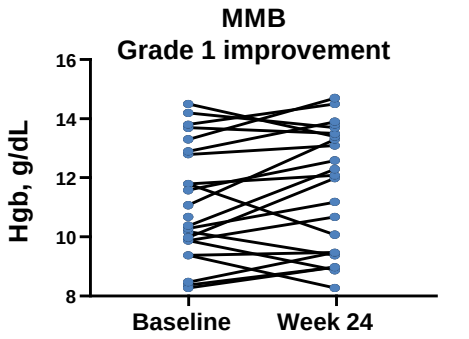


Mean baseline Hgb[b]	Mean week 24 Hgb
11.3	10.3

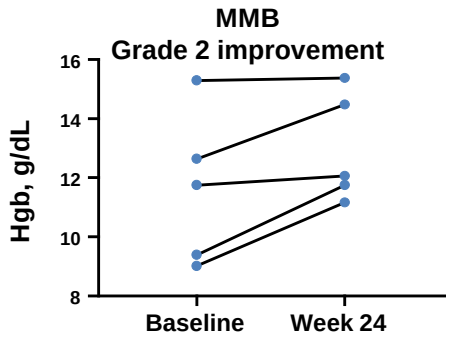
[a]A total of 3/21 patients missing week 24 Hgb measurement. [b]A total of 2/30 patients missing week 24 Hgb measurement.
BMF, bone marrow fibrosis; Hgb, hemoglobin; MMB, momelotinib; RUX, ruxolitinib.

Hgb Levels Increased on Momelotinib but Decreased on RUX Regardless of BMF Improvement Or Worsening at Week 24

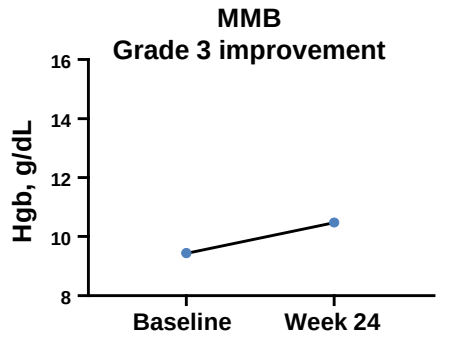
MMB



Mean baseline Hgb	Mean week 24 Hgb
11	11.7

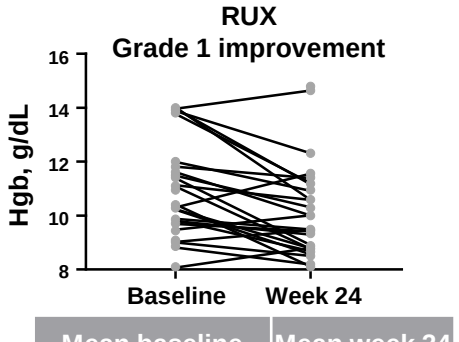


Mean baseline Hgb	Mean week 24 Hgb
11.3	12.4

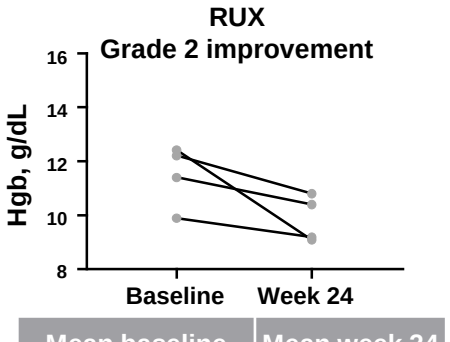


Mean baseline Hgb	Mean week 24 Hgb
9.5	10.5

RUX



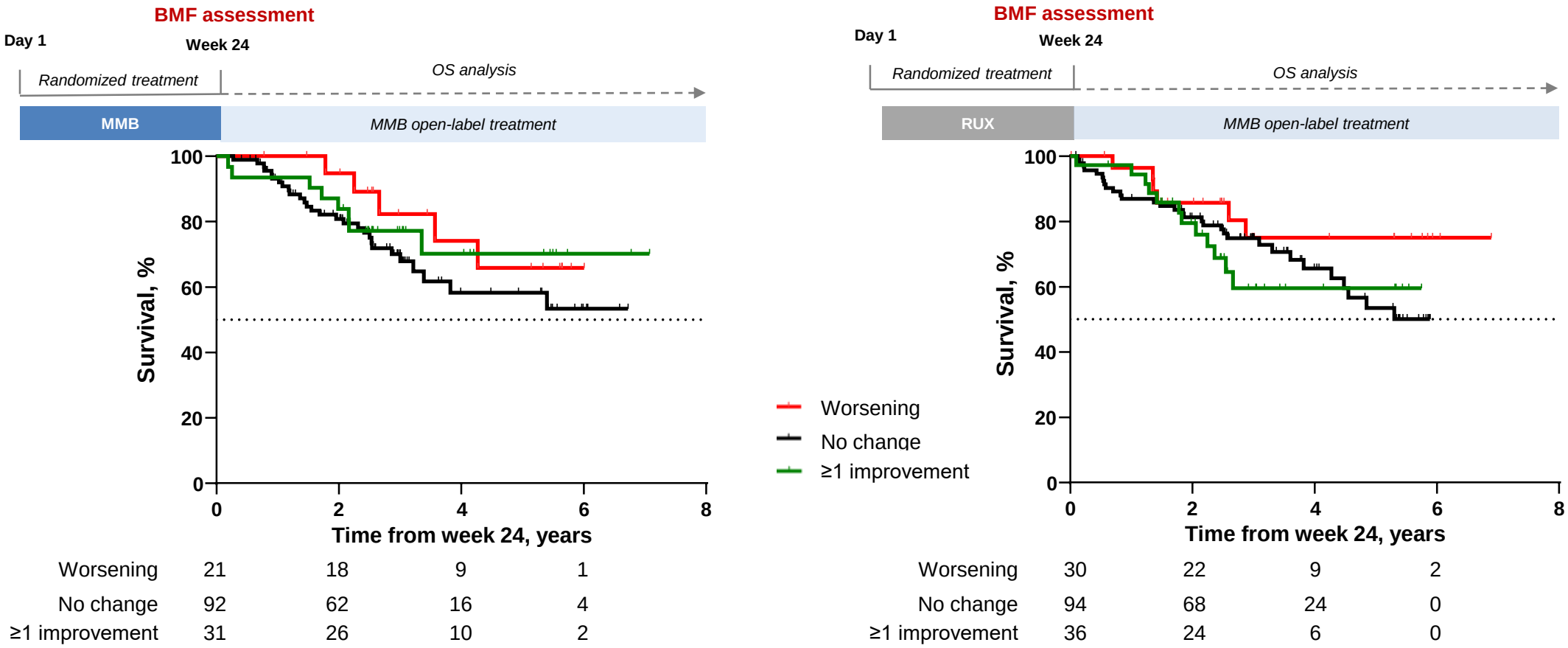
Mean baseline Hgb	Mean week 24 Hgb
10.6	9.6



Mean baseline Hgb	Mean week 24 Hgb
11.5	9.9

BMF, bone marrow fibrosis; Hgb, hemoglobin; MMB, momelotinib; RUX, ruxolitinib.

BMF Changes Were Not Associated With OS



Worsening	21	18	9	1
No change	92	62	16	4
≥1 improvement	31	26	10	2

Worsening	30	22	9	2
No change	94	68	24	0
≥1 improvement	36	24	6	0

BMF, bone marrow fibrosis; MMB, momelotinib; OS, overall survival; RUX, ruxolitinib.

Conclusions and Implications

These data represent the most extensive BMF assessment in patients with MF to date (>300 paired biopsies and mature clinical data across distinct JAKi in treatment-naïve patients)

Approximately 20% of JAKi-naïve patients experienced ≥1 grade BMF improvement within 24 weeks of either momelotinib or ruxolitinib treatment

However, BMF changes from baseline to week 24 did not correlate with week 24 symptom or spleen response, anemia improvement, or long-term OS

Given the lack of association with OS, these findings indicate the need to better understand BMF changes by week 24 as a surrogate for clinical benefit and disease modification

BMF, bone marrow fibrosis; JAKi, Janus kinase inhibitor; MMB, momelotinib; MF, myelofibrosis; OS, overall survival; RUX, ruxolitinib.

Acknowledgments

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