Reduction in red blood cell transfusion burden: a novel longitudinal time-dependent analysis in patients with transfusion-dependent myelofibrosis treated with momelotinib

Claire Harrison,[1] Ruben Mesa,[2] Moshe Talpaz,[3] Vikas Gupta,[4] Aaron T. Gerds,[5] Barbara Klencke,[6] Catherine Ellis,[7] Jun Kawashima,[6] Rafe Donahue,[6] Bryan Strouse,[6] Stephen Oh[8]

[1]Guy's and St Thomas' NHS Foundation Trust, London, UK; [2]Wake Forest University School of Medicine, Winston-Salem, NC, USA; [3]University of Michigan Health, Ann Arbor, MI, USA; [4]University of Toronto, Toronto, ON, Canada; [5]Cleveland Clinic Taussig Cancer Center, Cleveland, OH, USA; [6]Sierra Oncology, San Mateo, CA, USA; [7]GSK plc, Philadelphia, PA, USA; [8]Washington University School of Medicine, St Louis, MO, USA

Introduction

- Anemia, defined by hemoglobin (Hb) levels below the lower limit of normal, is a key hallmark of myelofibrosis (MF) that often progresses over time, representing a high medical need[1-3]
  - Anemia is associated with negative quality of life in patients with MF and is included as a negative prognostic factor for survival in all MF risk assessment tools[1,4-6]
- Red blood cell (RBC) transfusions are a mainstay of anemia management in MF but are associated with further detriment to quality of life and survival and impose a substantial healthcare resource burden[5,7-9]
  - Cytopenias, primarily anemia, are associated with lower spleen and symptom responses and shorter overall survival in patients with MF treated with ruxolitinib, and prognostic modeling highlights the negative impact of RBC transfusion requirements during the initial 6 months of ruxolitinib treatment[10,11]
  - Thus, reduction of transfusion burden represents an important clinical consideration in MF
- Momelotinib is an oral inhibitor of JAK1, JAK2, and activin A receptor type 1 (ACVR1) that has demonstrated consistent spleen, symptom, and anemia benefits across 3 phase 3 clinical trials in patients with JAK inhibitor–naive and JAK inhibitor–experienced MF (SIMPLIFY-1, SIMPLIFY-2, MOMENTUM)[12-14]
  - The phase 3 clinical trial program was supported by a phase 2 translational biology study in patients with transfusion-dependent (TD) MF, linking the anemia benefits of momelotinib to ACVR1-mediated regulation of hepcidin and iron homeostasis[15]
- Across momelotinib clinical trials, anemia benefit was assessed via a strict, prespecified definition of transfusion independence response (TI-R), defined in the phase 3 trials as no RBC transfusions for ≥12 weeks immediately preceding the end of week 24, with all Hb levels ≥8 g/dL[12-14]
  - However, this binary response/nonresponse endpoint may not fully characterize the treatment effect on overall RBC transfusion burden in patients with MF, as reductions that do not meet the threshold for transfusion independence may nevertheless be meaningful

Objective

- To evaluate the effects of momelotinib on the RBC transfusion burden of the total study population in a phase 2 trial, using novel analyses of time-dependent transfusion intensity

Methods

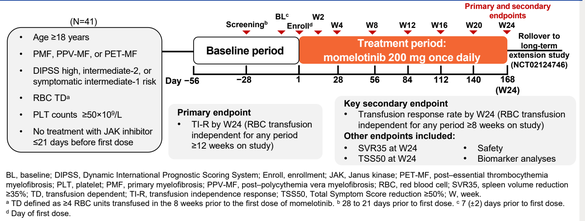
Phase 2 Study (Figure 1)[15,16]

- This was an open-label, phase 2, translational biology study (NCT02515630) of momelotinib (200 mg once daily) in TD (≥4 RBC units in the 8 weeks prior to first dose) patients with intermediate-risk or high-risk MF across 13 sites in the US and Canada
- Patients were treated for up to 24 weeks, at which time they discontinued or entered an open-label extension study (NCT02124746)
- Clinic visits were at screening, baseline, enrollment (first dose), and weeks 2, 4, 8, 12, 16, 20, and 24; RBC transfusions were recorded at every visit, laboratory values were recorded at all on-treatment visits, and samples for biomarker evaluation were collected up to 6 hours post dose at each visit
- The primary endpoint was TI-R by week 24 (defined as no RBC transfusions for any period ≥12 weeks on study); additional endpoints included transfusion response rate, splenic response rate, Total Symptom Score response rate, safety, and exploratory biomarker analyses, and all have been previously reported[15]
  - Of 41 TD patients enrolled, 14 (34%) achieved the primary endpoint of TI-R by week 24[15]

Time-Dependent Transfusion Burden

- Time-dependent transfusion burden (number of RBC units administered per 28 days) was tracked for every patient, with corresponding mean baseline-period (56 days prior to enrollment) and treatment-period (up to 168 days on treatment for most patients) intensities per patient
  - Baseline-period vs treatment-period intensity for each patient was illustrated via scatterplot, and cumulative distribution functions were generated
  - For additional visualization of shifts in RBC transfusion burden on treatment, patients were grouped jointly based on baseline- and treatment-period intensities per 28 days into ordinal bins based on the number of RBC units transfused: exactly 0 units, >0 to 1 unit, >1 to 2 units, >2 to 3 units, >3 to 4 units, and >4 units
- Summary measures for the total study population, including mean change in RBC transfusion intensity from baseline, were also calculated

Figure 1. Study Design (NCT02515630)[15,16]



BL, baseline; DIPSS, Dynamic International Prognostic Scoring System; Enroll, enrollment; JAK, Janus kinase; PET-MF, post–essential thrombocythemia myelofibrosis; PLT, platelet; PMF, primary myelofibrosis; PPV-MF, post–polycythemia vera myelofibrosis; RBC, red blood cell; SVR35, spleen volume reduction ≥35%; TD, transfusion dependent; TI-R, transfusion independence response; TSS50, Total Symptom Score reduction ≥50%; W, week.
[a] TD defined as ≥4 RBC units transfused in the 8 weeks prior to the first dose of momelotinib. [b] 28 to 21 days prior to first dose. [c] 7 (±2) days prior to first dose. [d] Day of first dose.

Results

- Baseline characteristics, as previously reported, are summarized in **Table 1**[15]
- 35 of 41 patients (85%) had a numeric reduction in RBC transfusion intensity on treatment (**Figure 2**; noted by increase in lighter shading during the treatment period)
  - Transfusion intensity of 0 during the treatment period correlated well with TI-R (primary endpoint)
- When patients with similar baseline-period transfusion intensities were grouped using ordinal bins (**Figure 3**), 90% (37/41) showed improved (26/41) or stable (11/41) intensity on treatment, including 9 patients (22%) who became RBC transfusion-free for the entire treatment period
  - This is consistent with the individual baseline-period vs treatment-period RBC transfusion intensities per patient (**Figure 4**); 35 patients (85%) fell below the diagonal, indicating reduced transfusion intensity on treatment, while 6 patients had modest increases in transfusion intensity on treatment (2 with marginal increases were counted as "stable" using the ordinal bins in Figure 3)
- The mean RBC transfusion requirement of 3.2 units per 28 days during the baseline period (range, 1.5-6.0 units) was reduced to 1.7 units per 28 days (range, 0.0-6.0 units) on treatment (**Table 2**)
- Improvement in RBC transfusion burden during the treatment period was also evident in the leftward shift of the cumulative distribution function curve compared with the baseline-period curve, reflecting an overall lower distribution of transfusion intensities on treatment (**Figure 5**)

Table 1. Baseline Characteristics[15]

Baseline characteristics	(N=41)
Age, mean (SD), years	70 (9.0)
Male, n (%)	26 (63.4)
White, n (%)	36 (87.8)
Type of MF, n (%)	
PMF	32 (78.0)
PPV-MF/PET-MF	9 (22.0)
DIPSS risk, n (%)	
Intermediate-1	5 (12.2)
Intermediate-2	22 (53.7)
High	14 (34.1)
JAK inhibitor naive, n (%)	36 (87.8)
Time since MF diagnosis, mean (SD), years	3.3 (2.8)
RBC TD, n (%)[a]	40 (97.6)[b]
RBC units transfused ≤8 weeks prior to enrollment, mean (SD)	6 (2.3)
Hb, mean (SD), g/dL	8.3 (1.0)
Hb <8 g/dL, n (%)	12 (29.3)
PLT count, mean (SD), ×10⁹/L	181 (129.9)
Spleen volume, mean (SD), cm³	2057.1 (1299.8)
TSS, mean (SD)	20.73 (14.7)
***JAK2*V617F mutation positive, n (%)**	28 (68.3)
BMF grade 3, n (%)	30 (73.2)
EPO, mean (SD), mIU/mL	444 (770)
Ferritin, mean (SD), ng/mL	1328 (1324)
Hepcidin (morning), mean (SD), nM	36.9 (24.1)

BMF, bone marrow fibrosis; DIPSS, Dynamic International Prognostic Scoring System; EPO, erythropoietin; Hb, hemoglobin, JAK, Janus kinase; MF, myelofibrosis; PET-MF, post–essential thrombocythemia myelofibrosis; PLT, platelet; PMF, primary myelofibrosis; PPV-MF, post–polycythemia vera myelofibrosis; RBC, red blood cell; TD, transfusion dependent; TSS, Total Symptom Score.
[a] Defined as ≥4 RBC units in the 8 weeks prior to first dose. [b] One patient enrolled without a confirmed transfusion history and was categorized as a nonresponder at week 24.

Table 2. Summary Measures of RBC Transfusion Intensity

Intensity per 28 days, RBC units	Baseline period	Treatment period
Mean (SD)	3.2 (1.5)	1.7 (1.5)
Minimum	1.5	0.0
25th percentile	2.0	0.2
50th percentile	3.0	1.6
75th percentile	4.0	2.7
Maximum	6.0	6.0
Change in intensity per 28 days from baseline period to treatment period, RBC units[a]		
Mean (SD)	−1.5 (1.3)	
Minimum	−4.7	
25th percentile	−2.5	
50th percentile	−1.9	
75th percentile	−0.6	
Maximum	1.0	

RBC, red blood cell.
[a] Negative numbers indicate improvement (reduction) in RBC transfusion burden.

Baseline Period

- 75% of patients had transfusion needs ≥2 RBC units per 28 days
- All patients needed ≥1.5 RBC units per 28 days
- The mean transfusion need was 3.2 RBC units per 28 days

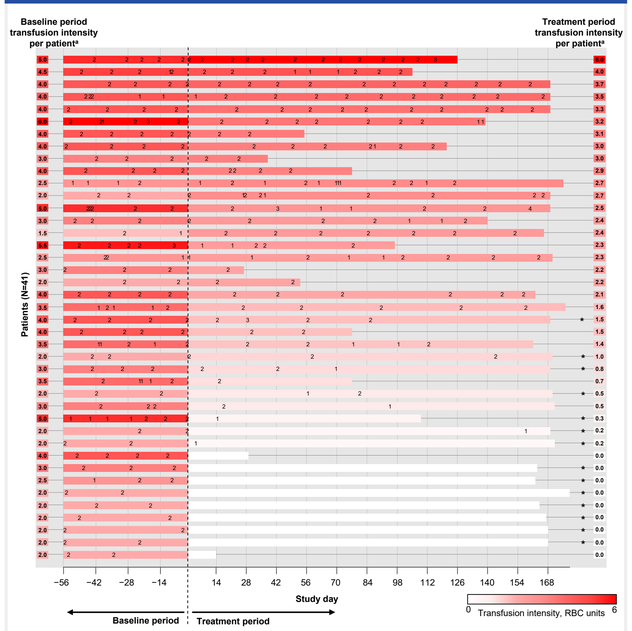
Treatment Period

- 50% of patients had transfusion needs <1.6 RBC units per 28 days
- Some patients needed 0 RBC transfusions
- The mean transfusion need was 1.7 RBC units per 28 days

Change From Baseline

- On average, transfusion need on treatment was reduced by 1.5 RBC units per 28 days
- Given the mean baseline-period intensity of 3.2 RBC units per 28 days, this represents a reduction of ≈50%

Figure 2. RBC Transfusions Per Patient Throughout the Baseline and Treatment Periods



Patients are sorted from highest to lowest treatment-period RBC transfusion intensity. Numerals along each bar indicate the number of RBC units transfused on each day on which a transfusion occurred.
RBC, red blood cell; TI-R, transfusion independence response.
* indicates patients who met the primary endpoint (TI-R).[b]
[a] RBC transfusion unit intensity for the baseline period (56 days; left of dashed line) and treatment period (up to 168 days for most patients, indicated by length of bars; right of dashed line). Shading indicates intensity over the entire baseline or treatment period, from the minimum of 0 to the maximum of 6 RBC units transfused per 28 days. [b] Defined as 0 RBC units transfused for any period ≥12 weeks on study.

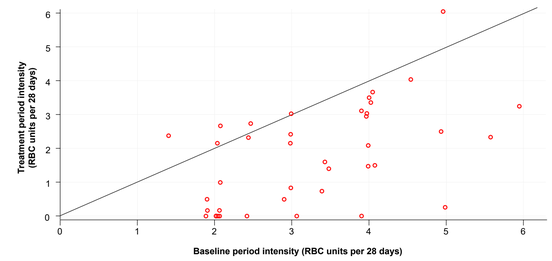
Figure 3. Shift Table of Change in RBC Transfusion Intensity

Left of diagonal = improvement/reduction
Right of diagonal = worsening/increase

Baseline transfusion intensity (RBC units per 28 days) \ Transfusion intensity during the treatment period[b] (RBC units per 28 days)	0	>0 to 1	>1 to 2	>2 to 3	>3 to 4	>4	Total (baseline):
n (%)[a]							
0							n=0
>0 to 1							n=0
>1 to 2	6 (46)	4 (31)		3 (23)			n=13
>2 to 3	2 (22)	2 (22)		4 (44)	1 (11)		n=9
>3 to 4	1 (8)	1 (8)	4 (31)	2 (15)	5 (38)		n=13
>4		1 (17)		2 (33)	1 (17)	2 (33)	n=6
Total (during treatment):	n=9	n=8	n=4	n=11	n=7	n=2	N=41

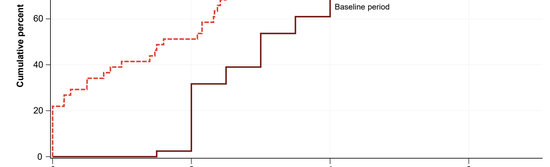
RBC, red blood cell.
[a] Percentage of baseline transfusion intensity category. [b] Rounding was applied to place patients in each ordinal bin/category; as a result, changes in intensity during treatment that did not result in a change in ordinal bin from baseline may not be apparent.

Figure 4. Scatterplot of Individual Baseline-Period vs Treatment-Period RBC Transfusion Intensities



Each circle corresponds to a patient. Circles below the diagonal indicate reduced transfusion intensity on treatment; circles above the diagonal indicate increased transfusion intensity on treatment.
RBC, red blood cell.

Figure 5. Cumulative Distribution Function for RBC Transfusion Intensity



RBC, red blood cell.

Conclusions

- In a phase 2 study of 41 RBC TD patients treated with momelotinib, 85% (35/41) achieved a numeric reduction in RBC transfusion requirements on treatment compared with baseline
- Using ordinal bins to group patients based on baseline-period and treatment-period intensity of RBC units transfused per 28 days, 90% (37/41) experienced a decline or stabilization of transfusion requirements on treatment; no patients were RBC transfusion-free at baseline, but 9 (22%) had no RBC transfusions over the entire treatment period
- Mean change in transfusion intensity from baseline was −1.5 RBC units per 28 days, a decrease from baseline of ≈50%
- Overall, these novel transfusion burden analyses demonstrate that binary transfusion independence response/nonresponse (34% transfusion independence responders in this study) may not fully capture the anemia benefits of momelotinib, which was associated with reduced RBC transfusion burden in the majority of patients (85%)
- The RBC TD population and frequent assessments in this phase 2 study were advantageous to the present analysis, but limitations include the small sample size and lack of a comparator arm
  - With this phase 2 study providing proof of concept for the novel RBC transfusion burden analyses described here, similar analyses in the larger, randomized controlled phase 3 studies of momelotinib are ongoing

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Corresponding author email address: claire.harrison@gstt.nhs.uk

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