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Dynamic and Time-to-event Analyses Demonstrate Marked Reduction in Transfusion Requirements for JAKi–naïve Myelofibrosis Patients Treated With Momelotinib Compared Head To Head With Ruxolitinib

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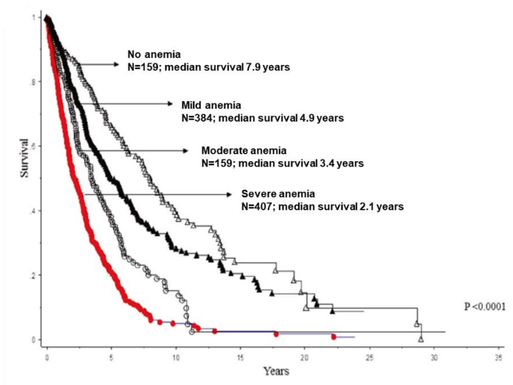
Background

Anemia is a Critical Prognostic Hallmark of Myelofibrosis

- Approximately 60% of patients with myelofibrosis (MF) are anemic and 45% are transfusion dependent (TD) within 1 year of diagnosis (Tefferi 2014), with most progressing to transfusion dependency over time.
- Transfusion dependency and moderate/severe anemia are acknowledged to be critical negative prognostic factors in myelofibrosis (Elena 2011, Nicolosi 2018) (Figure 1).
- Accordingly, the burden of receiving transfusions as supportive care, as well as the complexities and complications of transfusions, have a significant impact on both quality of life and overall survival in myelofibrosis.

Tefferi et al, Mayo Clin Proc. 2014; Elena et al, Haematologica 2011; Nicolosi M et al; Leukemia 2018

Figure 1: Anemia Predicts Poor Survival in Myelofibrosis



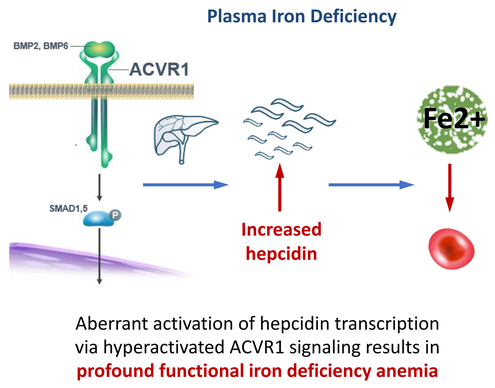
Momelotinib's Mechanism of Action

Momelotinib Inhibits JAK1, JAK2 *and* ACVR1

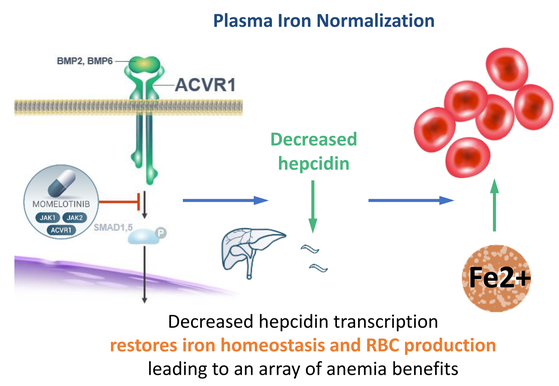
- Momelotinib (MMB) is a potent inhibitor of JAK1, JAK2 *and* ACVR1 (Figure 2) providing potential benefits on all three hallmarks of MF: constitutional symptoms, anemia and splenomegaly, without the myelosuppressive properties of approved JAK inhibitors (JAKi).
- The complex and inter-related drivers of anemia in MF include bone marrow fibrosis fundamental to the disease, splenic sequestration of red blood cells (RBCs), and anemia of inflammation, including the inflammatory cytokine-mediated inhibition of residual erythropoietic bone marrow capacity.
- Anemia of inflammation is a complex disorder, driven through both the direct and indirect effects of cytokines and increased synthesis of the iron regulatory hormone hepcidin controlled via ACVR1-directed SMAD signaling.
- Increased hepcidin leads to iron sequestration in monocytes and macrophages, resulting in perturbed iron homeostasis and a characteristic iron-restricted anemia (Ganz 2013, Langdon 2014).

Ganz et al, Physiol Rev. 2013; Langdon at al, Am J Hematol. 2014

Figure 2: Inhibits ACVR1 Leading to Positive Anemia Benefits



Aberrant activation of hepcidin transcription via hyperactivated ACVR1 signaling results in **profound functional iron deficiency anemia**



Decreased hepcidin transcription **restores iron homeostasis and RBC production** leading to an array of anemia benefits

Standard Analyses of the SIMPLIFY-1 Data Demonstrate Momelotinib's Anemia Benefits vs Ruxolitinib

- SIMPLIFY 1 (S1) was a Phase 3, head-to-head comparison of MMB vs ruxolitinib (RUX) in JAKi treatment naïve myelofibrosis patients with a 24-week double-blind treatment period.
- Relevant baseline characteristics were well balanced, including median hemoglobin levels (10.5 g/dL and 10.3 g/dL) and percentages of TD and TI patients (25% and 24%; and 68% and 70%) for the MMB and RUX groups, respectively.
- The primary objective of non-inferiority (NI) for splenic response rate was met, however, the study did not meet the objective of NI for MFSAF Total Symptom Score (TSS).
- A variety of standard analyses of anemia benefit were conducted in S1, demonstrating consistently positive benefits in favor of MMB. These endpoints were tested hierarchically following TSS, and as a result, outcomes with p<0.05 are considered 'nominally' significant.

	MMB	RUX	p-value
% TI at Week 24	67	49	< 0.001
% TD at Week 24	30	40	0.019
% TD → TI (rolling 12-week)	49	29	0.0455

Methods and Results

Novel Dynamic Analyses of Transfusion Burden

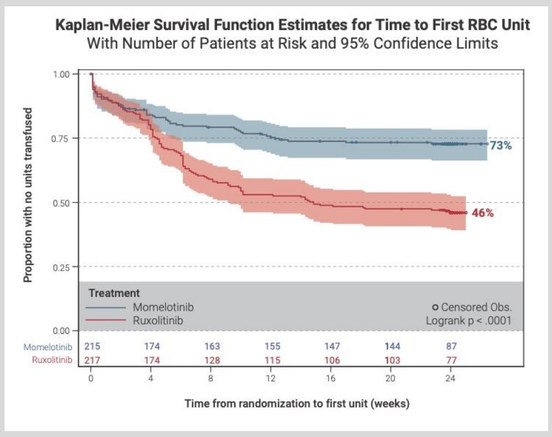
- Landmark or other "static" analyses alone do not completely describe the patient burden of transfusions or fully elucidate the differences in therapeutic options for clinicians.
- Retrospective analyses of S1 data were performed using a variety of novel dynamic anemia benefit endpoints to explore the relative burden of transfusions in patients treated with MMB vs RUX.

Time-to-Transfusion Method

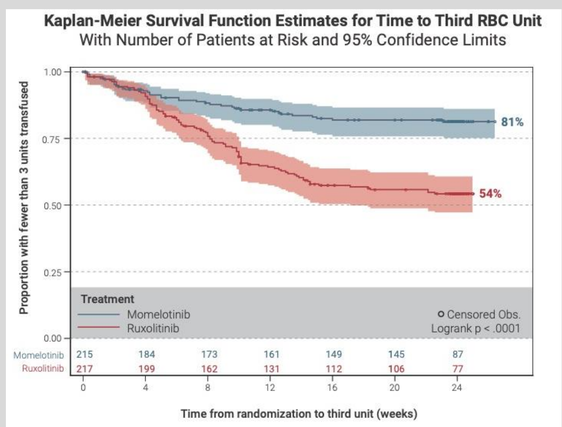
Kaplan-Meier (KM) estimates of time-to-first, time-to-third, and time-to-fifth RBC unit(s) transfused were employed to determine and compare relative 'transfusion events' between groups:

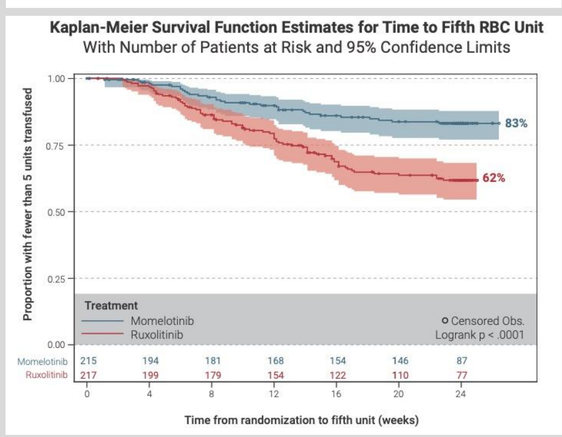
- The first RBC unit transfused provides an alternate relative assessment of the proportion of patients who are transfusion free over the course of treatment (Figure 4A).
- When greater than zero, the number of RBC units transfused can be considered to represent 'transfusion events'; assuming two units of RBCs per typical transfusion, the third and fifth RBC units transfused represent the second and third 'transfusion event' respectively (Figure 4B and 4C).

Figure 4A: More Patients Require No Transfusions on Momelotinib



Figures 4B and 4C: Immediate and Sustained Reduction in Transfusion Burden on Momelotinib





The KM time-to-first RBC unit transfused analysis indicated an **immediate and sustained MMB treatment effect** compared to RUX (log-rank p < 0.0001).

In this model, patients randomized to MMB were more likely to receive no transfusions (73%) compared to patients randomized to RUX (46%). The odds of receiving no transfusions during treatment was **3.2 times higher** on MMB than on RUX.

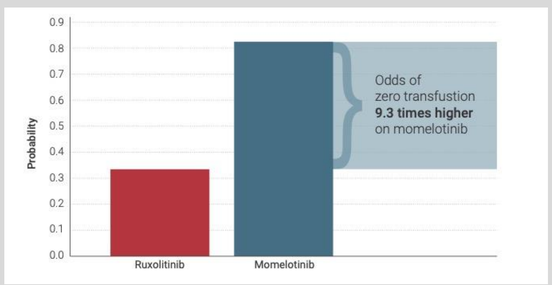
Similar results were observed when examining a burden of fewer than three and fewer than five RBC units transfused to Week 24. In both cases a strong treatment effect was noted, demonstrating that the proportion of patients with fewer transfusions was greater in the MMB arm compared with RUX:

- Odds of receiving fewer than three transfusions **was 3.7 times higher** on MMB (81%) compared to RUX (54%, p < 0.0001).
- Odds of receiving fewer than five transfusions was **3.0 times higher** on MMB (83%) compared to RUX (62%, p < 0.0001).

Zero-Inflated Negative Binomial Methods

- To further analyze transfusion burden in S1, a zero-inflated negative binomial (ZINB) model, encompassing baseline covariates, was fit to the transfusion data.
- This ZINB model was employed to compare the proportions of patients with zero transfusion burden (ie, transfusion free) and the mean transfusion rates between treatment groups (Figure 5).
- Zero-inflated models are useful when a large proportion of individuals has zero events, as is the case for patients in S1, while other individuals have counts ranging to several dozen over the same time period.
- There are two components to the distribution of counts: the "zero" component and the "non-zero" component. Such distributions require the zero and non-zero components to be modeled separately.

Figure 5: ZINB Model Demonstrates Increased Odds of Zero Transfusions on Momelotinib



The outcomes of the covariate* ZINB model demonstrate that a typical patient in S1 had an 82% chance of receiving no transfusions when receiving MMB vs only a 33% chance when receiving RUX.

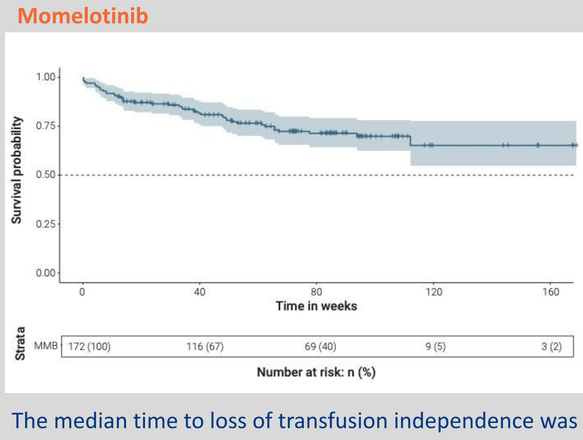
The odds of zero RBC units transfused were **9.3 times higher** on MMB than on RUX (p < 0.0001).

* Covariates were disease diagnosis (PMF, post-PVMF, post-ET MF), bone marrow fibrosis grade, and number of RBC units transfused in the eight weeks prior to randomization (0, 1-3, >4).

Time-to-Loss of Transfusion Independence Methods

- The duration of TI response in S1 was determined by a KM analysis of time to loss of TI (Figure 7).
- 'Loss of TI' was defined by the requirement for RBC transfusion or hemoglobin < 8.5 g/dL at any time.

Figure 7: Transfusion Independence is Durable on Momelotinib



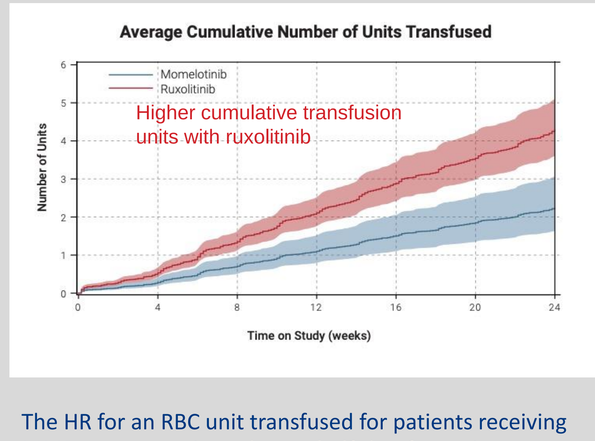
The median time to loss of transfusion independence was not reached in this analysis.

Mean Cumulative Function Methods

A proportional hazards recurrent events model analyzing recurrent data was employed to assess the relative cumulative transfusion burden between groups in a dynamic model across the duration of treatment:

- Transfusions of RBC units were considered as recurrent events, examined with and without patients' baseline characteristics as covariates.
- The model focused on the hazard, or risk, of undergoing an RBC unit transfused.
- The outcome from this recurrent events model is a hazard ratio (HR) comparing one treatment to the other and a "mean cumulative function" (MCF) that describes the average cumulative number of events (RBC unit transfusions) for patients in each group (Figure 6).

Figure 6: An Average Patient Received Twice as Many RBC Units on Ruxolitinib at Any Timepoint



The HR for an RBC unit transfused for patients receiving MMB was approximately **one-half** that for patients on RUX (HR = 0.522; p < 0.0001) for models both with and without patients' baseline characteristics as covariates.

Conclusions

- Uniquely amongst the JAKi in development, MMB potently inhibits JAK1, JAK2 *and* ACVR1, resulting in a significant mechanistically-driven range of potential MF benefits, including an array of positive anemia outcomes.
- Current approaches to analyzing anemia benefit in MF have relied on assessments of transfusion dependence and transfusion independence by landmark analysis.
- The novel dynamic and time-to-event methods described here support MMB as a potential preferred treatment option for patients with myelofibrosis, demonstrating significant anemia benefits including substantively reduced transfusion burden compared directly with RUX, specifically:
  - Immediate and sustained benefit manifests in an overall reduced transfusion burden on MMB.
  - Patients receiving MMB had a significantly reduced chance of receiving one transfusion, two "transfusion events" (≥ 3 RBC units) or three "transfusion events" (≥ 5 RBC units).
  - Odds of receiving zero transfusions, in a covariate ZINB model, were more than nine times higher on MMB.
  - At any given time, the mean cumulative number of RBC units received for a typical patient receiving MMB is approximately half of that for patients receiving RUX (HR = 0.522). Thus, for patients on MMB half as many RBC units are transfused at any time as compared to RUX.
  - A sustained and durable period of TI was maintained over long-term treatment on MMB.
- Importantly, these meaningful anemia benefits reported from the SIMPLIFY-1 Phase 3 trial were achieved while also providing improvements in constitutional symptoms and demonstrating non–inferior splenic response when compared directly to RUX.

MOMENTUM Phase 3 Clinical Trial

- Momelotinib's suite of anemia benefits are being further evaluated in MOMENTUM, a Phase 3 clinical trial in anemic patients who have previously received a JAKi. This ongoing trial is intended to support potential registration of momelotinib for the treatment of patients with myelofibrosis.
- In addition to assessments of constitutional symptoms, landmark anemia rates (i.e. transfusion independence) and splenomegaly, MOMENTUM will provide an opportunity to further evaluate associations between anemia benefit, transfusion burden and patient reported measures of clinical benefit.

Acknowledgements

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