Update from the phase 2 RESTORE trial of elritercept in patients with myelofibrosis receiving ruxolitinib

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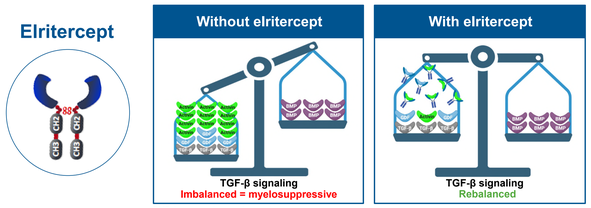
Background and Methods

- Dysregulated signaling of transforming growth factor β (TGF-β) superfamily ligands contributes to bone marrow dysfunction and bone marrow fibrosis[1,2]
- Anemia affects 35−38% of patients with myelofibrosis (MF) at the time of diagnosis,[3] and over 80% beyond one year of diagnosis[3–5]
  - Anemia in MF is associated with fatigue, transfusion dependence, reduced quality of life, and reduced survival[3]
- Janus kinase (JAK) inhibitors, such as ruxolitinib, are effective in reducing spleen size and symptoms in patients with MF, but are associated with anemia and thrombocytopenia[6]
  - This can limit their use, leading to suboptimal dosing and reduced clinical benefit
- There is a need for therapies that rebalance the bone marrow microenvironment and restore functional hematopoiesis, in addition to reducing spleen size and symptoms
- Elritercept is a modified activin receptor type IIA/IgG1 fusion protein that selectively binds and potently blocks downstream signaling of the TGF-β superfamily ligands activin A and B and growth differentiation factors 8 and 11[7]



BMP, bone morphogenetic protein.

- Preclinical data with RKER-050 (preclinical version of elritercept used for *in vivo* testing) have demonstrated induced erythropoiesis in a mouse model of MF,[8] reversed ruxolitinib-associated reductions in hemoglobin (Hgb), hematocrit, and red blood cell (RBC) count,[9] and increased platelet counts[10]
- RESTORE is an ongoing phase 2 study investigating elritercept as a monotherapy and in combination with ruxolitinib in patients with MF (**Summary Panel**)
- The dose escalation phase of the study is complete, and the recommended phase 2 dose (RP2D) of elritercept was determined to be 3.75 mg/kg, with the option to up-titrate to 5 mg/kg, administered once every four weeks (Q4W)
- Here, we present results from the elritercept plus ruxolitinib arm of the dose expansion phase of the study, in which 38 patients have been enrolled as of the data cut-off date of July 21, 2025

Results

Patients and BL characteristics

- Patients have been enrolled in seven countries across Europe, Asia, Australia, and South America
- MF diagnosis was a mix of primary, post-essential thrombocytosis (ET), and post-polycythemia vera (PV)
- Patients had severe anemia; 60.5% were transfusion-dependent (TD)
- Notable splenomegaly was observed despite ongoing ruxolitinib treatment, with >70% of patients having spleen volume ≥450 cm^3
- At the time of data cut-off, study treatment was ongoing in 28/38 patients (73.7%); median treatment duration was 47.4 weeks

Characteristic	Elritercept plus ruxolitinib (N=38)
Age in years, median (range)	71.0 (45–80)
≥65 years, n (%)	28 (73.7)
Male, n (%)	24 (63.2)
Years since MF diagnosis, median (range)	2.3 (0.4–18.0)
Duration of prior ruxolitinib in weeks, median (range)	44.0 (18–631)
Ruxolitinib total daily dose in mg on C1D1, median (range)	20 (5–50)
Diagnosis classification, n (%)	
Primary MF	22 (57.9)
Post-PV MF	6 (15.8)
Post-ET MF	10 (26.3)
Hematologic parameters	
Hgb in g/dL, median (range)	8.5 (4.4–10.0)
Platelet count per 10^9/L, median (range)	120.7 (45–416)
Baseline RBC transfusion units per 12 weeks, median (range)	4.0 (0–17.0)
TD*, n (%)	23 (60.5)
NTD†, n (%)	15 (39.5)
DIPSS risk category, n (%)	
Intermediate-1	4 (10.5)
Intermediate-2	26 (68.4)
High	8 (21.1)
Spleen volume in cm^3, median (range)	948.5 (244.1–6,961.5)
<450 cm^3, n (%)	11 (28.9)
≥450 cm^3, n (%)	27 (71.1)

*Received ≥3 RBC units/12 weeks; †received 0–2 RBC units/12 weeks.
C1D1, cycle 1 Day 1; DIPSS, Dynamic International Prognostic Scoring System; NTD, non-transfusion dependent.

RESTORE study overview

Primary MF, post-ET, or post-PV MF with anemia

Part 1: dose escalation 0.75 mg/kg to 4.5 mg/kg Q4W	Part 2: dose expansion RP2D (3.75 mg/kg Q4W)
Monotherapy: JAK inhibitor relapsed, refractory, intolerant or ineligible	Monotherapy: JAK inhibitor relapsed, refractory, intolerant or ineligible
Elritercept plus ruxolitinib*	Elritercept plus ruxolitinib*

Population
- Patients with anemia and primary MF, post-ET MF, or post-PV MF
- On ruxolitinib for ≥8 weeks, stable dose for ≥4 weeks
- TD: received ≥3 RBC units/12 weeks
- NTD: 0–2 RBC units/12 weeks
- Baseline Hgb <10 g/dL, with or without transfusions and platelet count ≥25 x 10^9/L

Endpoints
- **Primary**: Safety
- **Secondary/exploratory**: Transfusion independence (TI); ≥50% reduction in RBC transfusion; spleen volume; progression to accelerated MF and acute myeloid leukemia; symptom score (MPN-SAF TSS); PROMIS short form − Fatigue 7a; *JAK2 V617F* VAF

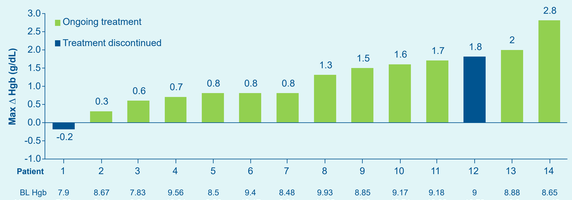
Study status
- Part 1 (dose escalation) enrollment is complete
- **RP2D was identified as 3.75 mg/kg Q4W, with option to up-titrate to 5 mg/kg Q4W**
- Part 2 (dose expansion): 38 patients enrolled in the elritercept plus ruxolitinib arm (23 TD, 15 NTD)

*Patients continued to take their pre-study dose of ruxolitinib; dose increases were not permitted during the first 12 weeks after C1D1 of elritercept treatment.

Key results

Anemia response among NTD patients

Mean change from baseline* Hgb in NTD patients over any 12 weeks



*Baseline was defined as the mean of all evaluable Hgb values within 12 weeks prior to and including C1D1 (if the pre-dose Hgb on C1D1 was evaluable).

Transfusion response in TD patients

Maximum RBC transfusion reduction in TD patients, from baseline* up to Week 24

*Baseline was defined as the total number of RBC units/12 weeks.

Key take away

Overall, findings support elritercept as a differentiated therapy in the treatment of patients with anemia and MF (whether due to underlying disease, treatment with ruxolitinib, or both) and warrant further clinical development of elritercept in this indication

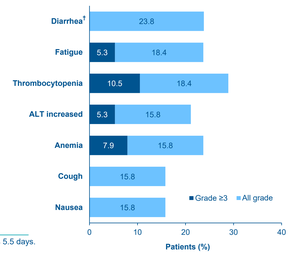
Safety overview and most frequent adverse events

- Overall, elritercept was well tolerated when given with ruxolitinib, with no grade ≥3 diarrhea and low rates of grade ≥3 treatment-emergent adverse events (TEAEs)

	Elritercept plus ruxolitinib (N=38)
Elritercept exposure in months, median (range)	10.9 (1.2–20.6)
Doses of elritercept received, median (range)	11.0 (1.0–22.0)
Patients with elritercept up-titration, n (%)	21 (55.3)
Any TEAEs, n (%)	38 (100)
Grade ≥3	23 (60.5)
TESAEs, n (%)	13 (34.2)
Any TEAE related to study drug	22 (57.9)
Grade ≥3	9 (23.7)
TEAEs leading to, n (%)	
Elritercept dose reduction	1 (2.6)
Elritercept dose interruption	7 (18.4)
Elritercept discontinuation	2 (5.3)
Ruxolitinib dose reduction	7 (18.4)
Ruxolitinib dose interruption	1 (2.6)
Ruxolitinib discontinuation	1 (2.6)
On-study death,* n (%)	1 (2.6)

*Not deemed related to either ruxolitinib or elritercept. †Median duration of diarrhea was 5.5 days.
ALT, alanine aminotransferase; TESAE, treatment-emergent serious adverse event.

Most frequent TEAEs (≥15% of patients, all grades) with elritercept plus ruxolitinib



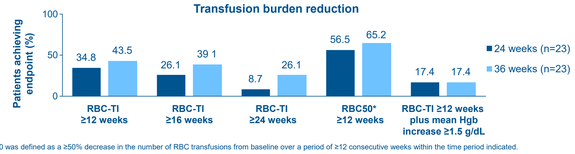
Anemia response (Summary Panel)

- In NTD patients, 35.7% (five of 14) and 50.0% (seven of 14) achieved mean Hgb increases of ≥1.5 g/dL and ≥1.0 g/dL, respectively, over any 12-week period

RBC transfusion responses (Summary Panel)

- In TD patients, at the Week 36 assessment:
  - 43.5% of patients achieved RBC-transfusion independence (TI) ≥12 weeks
  - 39.1% of patients achieved long responses with RBC-TI ≥16 weeks
  - 65.2% of patients achieved at least a 50% reduction in RBC transfusions

Transfusion burden reduction

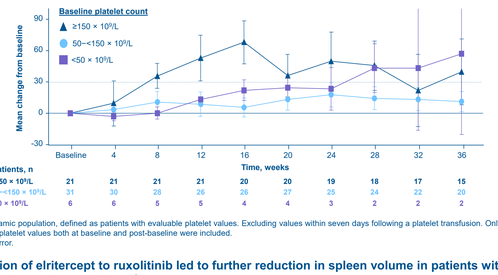


*RBC50 was defined as a ≥50% decrease in the number of RBC transfusions from baseline over a period of ≥12 consecutive weeks within the time period indicated.

Improvement in platelet counts following treatment with all doses of elritercept plus ruxolitinib

- Of all TD and NTD patients, 39.7% (23/58) achieved a mean platelet count increase of ≥30 × 10^9/L over any consecutive 12-week period within the first 24 weeks
- Of the TD and NTD patients who had <150 × 10^9/L platelets at baseline, 21.6% (8/37) achieved a mean increase of ≥30 × 10^9/L over any consecutive 12-week period within the first 24 weeks

Mean (±SE) change in platelet counts from Baseline to Week 36*

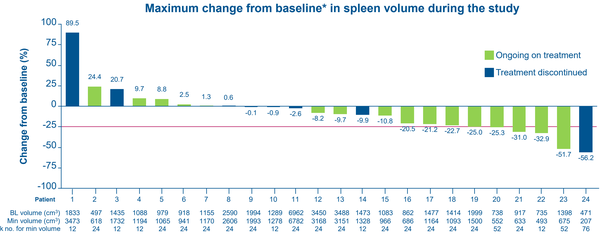


*Pharmacodynamic population, defined as patients with evaluable platelet values. Excluding values within seven days following a platelet transfusion. Only patients with evaluable platelet values both at baseline and post-baseline were included.
SE, standard error.

The addition of elritercept to ruxolitinib led to further reduction in spleen volume in patients with baseline spleen volume ≥450 cm^3

- Throughout the study, 5 of 24 evaluable patients (20.8%) achieved a maximum spleen volume reduction (SVR) of ≥25%; 2 of 24 (8.3%) achieved a maximum SVR of ≥35%

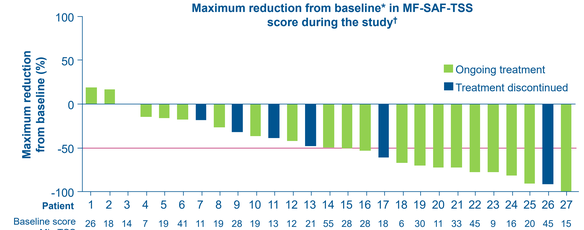
Maximum change from baseline* in spleen volume during the study



*Baseline was defined as the last available, valid, non-missing assessment prior to elritercept dosing on C1D1.
BL, baseline; min, minimum.

Further reduction in MF-SAF-TSS following treatment with elritercept plus ruxolitinib

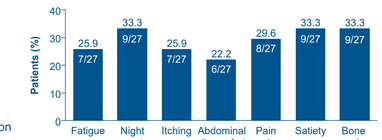
Maximum reduction from baseline* in MF-SAF-TSS score during the study†



MF-SAF-TSS, Myelofibrosis Symptom Assessment Form Total Symptom Score. *Baseline was defined as the last available, valid, non-missing assessment prior to elritercept dosing on C1D1. †Symptom Response TSS7 evaluable population (includes patients in the safety population who had ≥2 symptoms with an average score ≥3 or an average total score ≥10 in MF-SAF-TSS questionnaire v4.0 over the 7-day recall period at baseline, and who had ≥1 post-baseline assessment of MF-SAF-TSS).

Among TD and NTD patients:
- 88.9% (24/27 evaluable patients) achieved a reduction in MF-SAF-TSS during the study, including 48.1% (13/27 evaluable patients) who achieved ≥50% reduction
- 18.8% of patients 6/32 evaluable patients) experienced ≥5-point improvements in Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue T score by Week 24

Proportion of patients with a ≥50% reduction in individual MF-SAF-TSS items from baseline* at Week 24†



*Baseline was defined as the last available, valid, non-missing assessment prior to elritercept dosing on C1D1.
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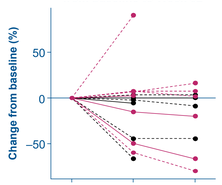
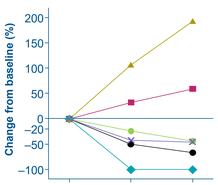
Changes in *JAK2 V617F* VAF following treatment with elritercept plus ruxolitinib

Changes in *JAK2 V617F* VAF, from baseline to Week 52



Case study – responder



Anemia response: Responder; Non-responder
Transfusion status: TD; NTD
Parameters: HgB; *JAK2* VAF; TSS; RBC transfusion; Platelet counts; Spleen volume

Data cut-off date: October 2025.
VAF, variant allele frequency.

- Of 35 evaluable patients at baseline, 10 had a *CALR* mutation, two had a *MPL* mutation, and 22 had a *JAK2 V617F* mutation
  - Median *JAK2 V617F* VAF was 47% (range, 1–91%)
  - Twenty-one patients had a *JAK2 V617F* mutation VAF ≥5%
- *JAK2 V617F* VAF reduction of ≥50% was observed in three of 19 evaluable patients at Week 24, with sustained reductions observed at Week 52
  - One of the three patients responded to treatment, demonstrating clinically meaningful changes in Hgb, MF-SAF-TSS, platelet counts, and spleen volume
- For the majority of patients with available longitudinal data, the VAF remained largely unchanged at Weeks 24 and 52

Conclusions

- Elritercept at the RP2D, in combination with ruxolitinib, given to patients with MF with poorer prognoses (89.5% classified as DIPSS intermediate-2 or high risk), demonstrated:
  - Robust efficacy, including anemia improvement, reduction of RBC transfusions, and increasing Hgb and platelets
  - Further reduction in spleen volume and MF-SAF-TSS in patients already maintained on a stable dose of ruxolitinib
  - An acceptable and manageable safety profile with mild (grade 1–2), transient diarrhea, and low rates of drug-related grade ≥3 TEAEs
- These results suggest that elritercept has potential effects on clonal architecture and hematopoietic restoration, consistent with its proposed mechanism of action

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