MODULATION OF TGF-β SUPERFAMILY SIGNALING TO TREAT MYELOFIBROSIS AND MITIGATE JAK INHIBITOR TOXICITY: A REPORT ON THE PHASE 2 STUDY OF KER-050 IN PARTICIPANTS WITH MYELOFIBROSIS

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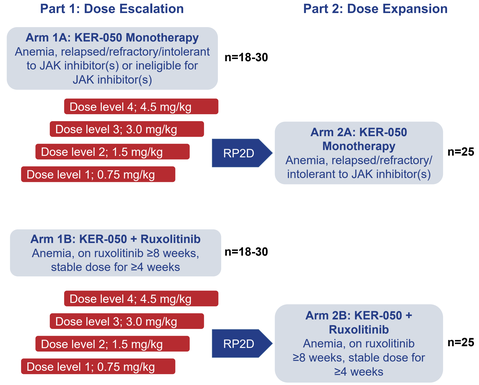
INTRODUCTION

- Myelofibrosis (MF) is a disorder characterized by unrestrained proliferation of myeloid precursors and dysfunctional Janus kinase (JAK) signaling[1]
  - Hyperplastic/dysplastic megakaryocyte expansion releases inflammatory cytokines which disrupt the osteohematopoietic niche, leading to ineffective hematopoiesis, bone remodeling, and a hostile microenvironment, all of which are exacerbated by iron overload resulting from transfusion[1,2]
  - JAK inhibitors, such as ruxolitinib, have been shown to improve symptoms, but are associated with dose-limiting cytopenias, reducing their utility for many patients[3]
- KER-050 is an investigational modified activin receptor type IIA ligand trap that is designed to inhibit TGF-β superfamily ligands (activins A and B, growth and differentiation factors 8 and 11) to restore balance to the osteohematopoietic niche and promote differentiation of erythroid and megakaryocytic precursors
  - Preclinical studies demonstrated that KER-050 restored erythropoiesis, increased platelet counts, improved bone mass, prevented fibrosis, and reversed ruxolitinib-associated anemia[4-6]
  - Accumulated clinical data have demonstrated that KER-050 stimulated erythropoiesis and thrombopoiesis in healthy postmenopausal women and myelodysplastic syndrome participants with ineffective hematopoiesis[7]
- Here we present data from the first clinical study investigating KER-050 in participants with MF (NCT05037760; EudraCT 2021-003227-15)

METHODS

- This ongoing, phase 2, open-label, 2-part study is evaluating KER-050 administered with or without ruxolitinib in participants with MF who have anemia (hemoglobin ≤10 g/dL or receiving transfusions)
- Part 1 involves parallel dose-escalation arms (1A: monotherapy, 1B: combination with ruxolitinib) to evaluate the safety and tolerability of KER-050 and identify the dose(s) of KER-050 to be evaluated in Part 2 (**Figure 1**)
- This study will evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, efficacy, and exploratory biomarkers to evaluate the potential for KER-050 to impact key aspects of the MF disease state and mitigate ruxolitinib-associated cytopenias and related dose reductions

Figure 1. Study Design Schema



JAK: Janus kinase; RP2D: recommended Part 2 dose(s).

RESULTS Based on 1-Oct-2022 data cutoff date

Baseline Characteristics

- This study enrolled an elderly population with advanced MF: 75.0% had primary MF and 66.7% had a Dynamic International Prognostic Scoring System risk category of high risk; mutation status was 33.3% *JAK2*, 25.0% *CALR*, 8.3% *MPL*, and 1 (8.3%) triple-negative participant enrolled
- 41.7% of participants were transfusion dependent (TD) with a mean transfusion burden of 9.8 units of red blood cell (RBC) transfusion in the 12 weeks prior to cycle 1 day 1
- The median baseline ruxolitinib dose in Arm 1B was 12.5 mg twice daily, indicating that most participants were unable to sustain maximum permissible ruxolitinib dose intensity

Table 1. Baseline Characteristics

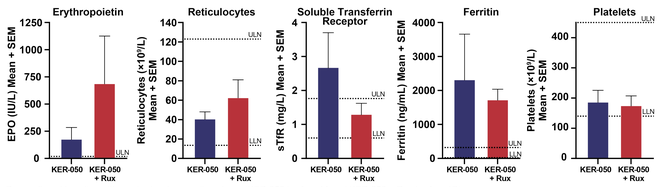
Parameters	KER-050 0.75 mg/kg n=6	KER-050 0.75 mg/kg + Rux n=6	Total N=12
Median age, years (range)	72.0 (60-85)	75.5 (69-86)	75.0 (60-86)
Male sex, n (%)	3 (50.0)	6 (100.0)	9 (75.0)
RBC transfusion status			
TD,[a] n (%)	1 (16.7)	4 (66.7)	5 (41.7)
RBC units, mean (SD)	10.0 (NA)	9.8 (1.5)	9.8 (1.3)
Non-TD,[b] n (%)	5 (83.3)	2 (33.3)	7 (58.3)
RBC units, mean (SD)	2.2 (2.3)	4.5 (0.7)	2.9 (2.2)
Iron chelation therapy usage, n (%)			
TD, n (%)	1 (16.7)	1 (16.7)	2 (16.7)
Non-TD, n (%)	0	1 (16.7)	1 (8.3)
Ruxolitinib doses (mg BID)			
Median (range)	NA	12.5 (5-20)	12.5 (5-20)
WHO classification diagnosis, n (%)			
Primary MF	5 (83.3)	4 (66.7)	9 (75.0)
Post-PV MF	1 (16.7)	0	1 (8.3)
Post-ET MF	0	2 (33.3)	2 (16.7)
DIPSS risk category, n (%)			
Low/intermediate-1	0	0	0
Intermediate-2	3 (50.0)	1 (16.7)	4 (33.3)
High risk	3 (50.0)	5 (83.3)	8 (66.7)
Mutation status, n (%)			
JAK2 present	2 (33.3)	2 (33.3)	4 (33.3)
CALR present	1 (16.7)	2 (33.3)	3 (25.0)
MPL present	0	1 (16.7)	1 (8.3)
Triple negative	1 (16.7)	0	1 (8.3)
Missing data	2 (33.3)	1 (16.7)	3 (25.0)

[a]TD defined as a participant having received ≥6 units transfusion for MF-related anemia in the 12 weeks preceding C1D1 and at least 1 unit transfusion in the 28 days preceding C1D1. [b]Non-TD defined as any participant not characterized as TD.
BID: twice daily; C1D1: cycle 1 day 1; *CALR*: calreticulin; DIPSS: Dynamic International Prognostic Scoring System; *JAK2*: Janus kinase 2; MF: myelofibrosis; *MPL*: myeloproliferative leukemia virus oncogene; NA: not applicable; post-ET: post-essential thrombocythemia; post-PV: post-polycythemia vera; RBC: red blood cell; Rux: ruxolitinib; TD: transfusion dependent; WHO: World Health Organization.

Baseline Laboratory Values

- All participants had high erythropoietic drive as indicated by elevated erythropoietin (EPO); 3 (25%) had markedly elevated EPO in excess of 500 U/L
- Despite largely normal reticulocyte counts, soluble transferrin receptor (sTfR) levels indicated variable erythropoietic activity, especially in the monotherapy population
- All participants had elevated ferritin and 7 (58.3%) had markedly elevated ferritin in excess of 1000 ng/mL, indicating iron overload
- 4 (33.3%) participants, 2 in each arm, exhibited baseline thrombocytopenia

Figure 2. Baseline Laboratory Values



Preenrollment baseline with x-axis showing enrollment arm (KER-050 for Arm 1A and KER-050 + Rux for Arm 1B).
EPO: erythropoietin; LLN: lower limit of normal; Rux: ruxolitinib; sTfR: soluble transferrin receptor; ULN: upper limit of normal.

Safety and Exposure

- 1 participant received 11 doses of KER-050 in the monotherapy arm (1A) and is ongoing on study therapy; more than half of participants (Arms 1A + 1B) have received ≥3 doses
- No participants have dose reduced KER-050 or ruxolitinib while on study therapy; 1 participant (8.3%) discontinued study therapy for an unrelated adverse event (AE)
- There were no grade 4 or 5 AEs experienced and there were no severe (grade 3) or serious AEs (SAEs) deemed related to KER-050; there have been no dose-limiting toxicities (DLTs) observed
  - 3 participants (25%) experienced SAEs; these events were COVID-19, catheter site cellulitis, bone pain (due to disease progression), and transient ischemic attack, all of which were grade 3
  - 2 participants (16.7%, 1 of whom also experienced a SAE) had nonserious grade 3 AEs of anemia and asthenia, both of which worsened from a grade 2 baseline condition
- The most common (occurring in ≥2 participants) AEs observed were diarrhea (n=3, 25.0%), COVID-19 (n=2, 16.7%), dyspnea (n=2, 16.7%), and fatigue (n=2, 16.7%)

Table 2. Treatment-Emergent Adverse Events

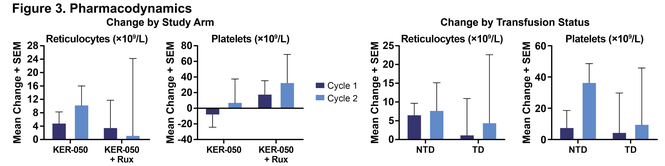
	KER-050 0.75 mg/kg n=6	KER-050 0.75 mg/kg + Rux n=6	Total N=12
TEAE, any grade, n (%)	4 (66.7)	5 (83.3)	9 (75.0)
Grade 1	1 (16.7)	0	1 (8.3)
Grade 2	2 (33.3)	2 (33.3)	4 (33.3)
Grade 3	1 (16.7)	3 (50.0)	4 (33.3)
Grade 4	0	0	0
Grade 5	0	0	0
Serious TEAE	1 (16.7)	2 (33.3)	3 (25.0)
DLT	0	0	0

DLT: dose-limiting toxicity; Rux: ruxolitinib; TEAE: treatment-emergent adverse event.

Pharmacodynamics

- Although variability was observed, treatment with KER-050 at the lowest dose level in this study (dose level 1, 0.75 mg/kg) resulted in increased reticulocytes and platelets on aggregate, both as monotherapy and in combination with ruxolitinib, regardless of transfusion status

Figure 3. Pharmacodynamics

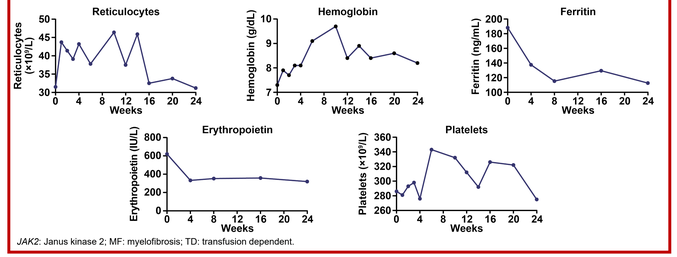


NTD: non-transfusion dependent; Rux: ruxolitinib; TD: transfusion dependent.

Participant Profiles and Biomarkers

- In 1 non-TD participant who received KER-050 monotherapy, a robust increase in reticulocytes was observed after a single dose and was followed by a sustained increase in hemoglobin and decrease in ferritin and EPO with continued dosing; an increase in platelets was also observed (**Figure 4**)
  - This participant achieved an erythroid response defined as mean hemoglobin increase of ≥1.5 g/dL from baseline over a period of >12 consecutive weeks within the first 24 weeks of study

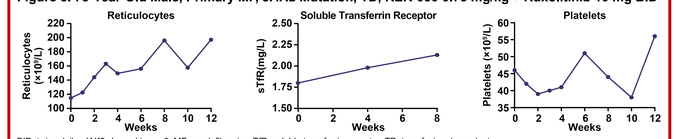
Figure 4. 60-Year-Old Female, Primary MF, *JAK2* Mutation, Non-TD, KER-050 0.75 mg/kg Monotherapy



JAK2: Janus kinase 2; MF: myelofibrosis; TD: transfusion dependent.

- In 1 TD participant with grade 3 thrombocytopenia at baseline who received KER-050 in combination with ruxolitinib, robust and sustained increases in reticulocytes and sTfR were observed after a single dose, with subsequent improvement in platelets evident after the second and third doses (**Figure 5**)
  - RBC transfusion burden 9 units/12 weeks pretreatment to 6 units/12 weeks posttreatment

Figure 5. 75-Year-Old Male, Primary MF, *JAK2* Mutation, TD, KER-050 0.75 mg/kg + Ruxolitinib 10 mg BID



BID: twice daily; *JAK2*: Janus kinase 2; MF: myelofibrosis; sTfR: soluble transferrin receptor; TD: transfusion dependent.

CONCLUSIONS

- This ongoing phase 2 study enrolled an intermediate-2 to high-risk MF population with significant disease burden, including substantially elevated baseline EPO and ferritin
- KER-050 was generally well tolerated with no DLTs and no treatment-related dose reductions as of the data cutoff date of 1-Oct-2022
- KER-050 treatment led to increased reticulocytes and platelets on aggregate, consistent with previously reported data[4-7] on the pharmacodynamic effect of KER-050; collectively, these data indicate that KER-050 could potentially promote differentiation of erythroid and megakaryocytic precursors and ameliorate anemia and thrombocytopenia in patients with MF
- Upon analysis of individual study participants, the following was observed:
  - A non-TD participant receiving KER-050 monotherapy experienced a sustained increase in reticulocytes and mean hemoglobin (≥1.5 g/dL over baseline) and corresponding decrease in ferritin and EPO over 24 weeks of study; an increase in platelets was also observed
  - A TD and thrombocytopenic participant receiving KER-050 + ruxolitinib experienced increased reticulocytes, sTfR, and platelets over 12 weeks
- KER-050 is an investigational modified activin receptor type IIA ligand trap that is designed to inhibit TGF-β superfamily ligands to restore balance to the osteohematopoietic niche and promote multilineage hematopoietic differentiation
  - KER-050 therefore has potential to impact multiple aspects of the MF disease state and data presented herein provide a promising early look at KER-050 monotherapy and in combination with ruxolitinib for the treatment of MF

Study update: enrollment into cohort 2 (1.5 mg/kg) has been initiated for both Arms 1A and 1B

REFERENCES

1. Vainchenker W, et al. *Blood*. 2017;129(6):667-679.
2. Tanaka H, et al. *Cells*. 2019;8(3):226.
3. Harrison C, et al. *Ther Adv Hematol*. 2012;3(6):341-354.
4. Nathan R, et al. *Blood*. 2021;138(Supplement 1):934.
5. Feigenson M, et al. *Blood*. 2021;138(Supplement 1):2068.
6. Materna C, et al. Presented at: ASBMR; Sep 9-12, 2022; Austin, TX. Poster SUN-623.
7. Tan S, et al. Presented at: EHA; June 9-13, 2022; Vienna, Austria. Poster P776.

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