Pharmacokinetic/Pharmacodynamic Analysis of Elritercept in Phase 2 Studies Shows Efficacy in Anemia Treatment for Lower-Risk Myelodysplastic Neoplasms and Myelofibrosis

MDS-951

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*At the time of data collection.

Question What is the relationship between elritercept exposure and clinical response to treatment among patients with lower-risk (very low, low, or intermediate) myelodysplastic neoplasms (LR-MDS) or myelofibrosis (MF)?

Methods

Data from two phase 2 clinical studies: NCT04419649 (LR-MDS) and NCT05037760 (MF) Part 1: dose escalation; Part 2: dose confirmation

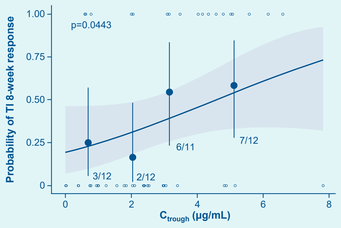
Elritercept RP2D: 3.75 mg/kg (titrating up to 5.0 mg/kg based on clinical response)

Pharmacodynamic (PD) assessments: Effects of elritercept on hemoglobin (Hb), reticulocyte levels, and efficacy as measured by overall erythroid response, hematologic improvement-erythroid (HI-E), and transfusion independence (TI)

This analysis: Characterization of pharmacokinetics (PK) and PK/PD profiles of elritercept and exposure– response (E–R) relationship in patients with LR-MDS or MF

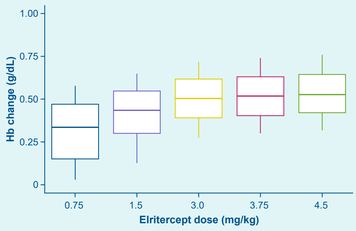
Results

A) Elritercept E–R relationship: TI 8-week response (LR-MDS)



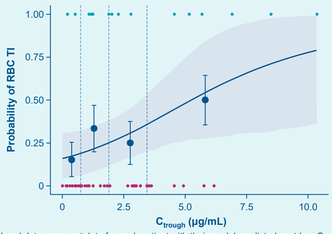
Small dots represent data for each patient with their model-predicted post-hoc C_{trough} value (x values) and whether they achieved the response of interest (y values: yes=1, no=0). Median is represented by the large blue dots with 95% confidence intervals (CI). The blue solid line is the regression line; light shading indicates the standard error around the regression line.
C_{trough}, trough concentration.

B) Elritercept dose–PK/PD relationship: Hb change (MF)



Changes over a 12-week pre- and post-treatment period shown. The bottom and top of each box represent the 25th and 75th percentiles, respectively; the whiskers represent the 10th and 90th percentiles; the line within the box represents the median.

C) Elritercept C_{trough} correlation with RBC TI (MF)



Colored dots represent data for each patient with their model-predicted post-hoc C_{trough} value (x values) and whether they achieved the response of interest (y values: yes=1 [green], no=0 [pink]). Larger blue dots with vertical lines are the mean and standard error for PK cohorts generated using the 25th, 50th, and 75th percentiles of the data; the blue line is the logistic regression model fit, and the shaded region is the 95% confidence interval. Red blood cell (RBC) TI is defined as TI over ≥12 weeks.

Key conclusions

- Elritercept demonstrated dose-dependent improvements in anemia-related outcomes in patients with LR-MDS and MF, with higher doses correlating with enhanced efficacy
- An adaptive dosing regimen of 3.75 mg/kg every 4 weeks (Q4W), with the option to titrate to 5.0 mg/kg Q4W, is recommended for further evaluation of the benefit-risk profile of elritercept in patients with LR-MDS and MF

Statement of Purpose

- MDS and MF are distinct hematological disorders that affect multi-lineage blood cell production[1,2]
- Elritercept is an investigational, modified activin receptor type IIA/IgG1 fusion protein designed to bind and block downstream signaling of select transforming growth factor-beta (TGF-β) superfamily ligands, including activin A/B and growth differentiation factors 8/11[3–6]
- Elritercept rebalancing of TGF-β superfamily signaling has the potential to restore functional hematopoiesis and ameliorate anemia, leading to durable TI[6]
- In a phase 1 study in 48 healthy postmenopausal women, elritercept was well tolerated with no dose-limiting toxicities observed at doses up to 4 mg/kg Q4W[6]
- The safety, tolerability, PK, and PD of elritercept are being evaluated in two ongoing phase 2 clinical trials in patients with LR-MDS (NCT04419649) and MF (NCT05037760)
- This analysis characterizes the PK and PK/PD profiles of elritercept and examines its E–R relationship in patients with LR-MDS and MF

Methods

- NCT04419649 (n=71) and NCT05037760 (n=49) are phase 2, open-label, ascending dose studies of elritercept (**Figure 1**)

Figure 1. NCT04419649 and NCT05037760 study designs

NCT04419649 (LR-MDS)

Part 1: dose escalation
Elritercept monotherapy: 0.75 to 5.0 mg/kg

NCT05037760 (MF)

Part 1: dose escalation
Arm A: Elritercept monotherapy: 0.75 to 4.5 mg/kg
Arm B: Elritercept (0.75 mg/kg to 4.5 mg/kg) in combination with ruxolitinib

Part 2: dose confirmation
RP2D 3.75 mg/kg SC Q4W* for up to 24 cycles

PK sampling
- Cycle 1, Days 1, 8, 15, and 22
- Cycle 2–6, Days 1 and 15
- Cycle 6+, Day 1

*Option to titrate up to 5.0 mg/kg based on clinical response.
RP2D, recommended phase 2 dose; SC, subcutaneous.

Population PK analysis

- Nonlinear mixed-effects modeling was used for the Population PK analyses
- Simulations to derive exposure metrics for the subsequent E–R analysis were conducted using 'R'
  - Covariates tested were body weight, formulation, and anti-drug antibody (ADA) status
- Goodness-of-fit plots and prediction-corrected visual predictive checks (pcVPC) confirmed model adequacy

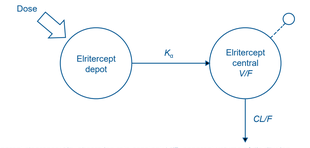
E–R analysis

- Exposure metrics (area under the concentration-time curve over 672 hours [AUC_{0-672h}], maximum concentration [C_{max}], and trough concentration [C_{trough}]) were derived from individual post-hoc estimates using the final PK model
- Logistic regression models were developed to evaluate the relationship between exposure and binary efficacy endpoints:
  - LR-MDS: overall erythroid response (defined as either HI-E or TI over any 8-week period overall and by RS status), HI-E per Modified International Working Group 2006 criteria, and TI 8-week response
  - MF: RBC TI and overall anemia response, defined as ≥12 consecutive weeks of post-baseline evaluations of RBC transfusion(s) or RBCs either achieving a 50% reduction in transfusion burden (RBC units/12 weeks) or achieving a mean increase from baseline in Hb of ≥1.0 g/dL over a 12-week period
- Improvement of clinical response was estimated by a logistic regression model describing the probability of overall best response as a responder versus a non-responder for the respective efficacy endpoint
- Continuous measures of response using reticulocyte counts and Hb time-series were calculated as follows: for each patient, the difference in mean PD value over an 8-week period pre- versus post-treatment (LR-MDS) or 12-week pre- and post-treatment period (MF); these were then used as a dependent variable within a univariable linear regression analysis
- Simulations were conducted to compare predicted efficacy outcomes for 3.75 mg/kg and 5.0 mg/kg Q4W dosing regimens. Exposure metrics were simulated for a typical patient (70 kg, ADA-negative), and 1,000 parameter vectors were sampled from the variance-covariance matrix of the logistic models to estimate 95% CIs for predicted response rates
- Only patients with both PK and PD data were included in the analyses; any PK measurements below limit of quantification were considered censored

Results

- NCT04419649 (LR-MDS) Part 1 only:
  - As of the data cutoff of April 14, 2022, PK and PD data were collected from 31 patients
    - 0.75 mg/kg (n=6), 1.5 mg/kg (n=6), 2.25 mg/kg (n=6), 3.75 mg/kg (n=6), 5.0 mg/kg (n=7)
- NCT05037760 (MF):
  - As of the data cutoff of April 3, 2024, PK and PD data were collected from 49 patients
    - Monotherapy: 0.75 mg/kg (n=6), 1.5 mg/kg (n=6), 3.0 mg/kg (n=5), 3.75 mg/kg (n=1), 4.5 mg/kg (n=4)
    - Combination: 0.75 mg/kg (n=6), 1.5 mg/kg (n=5), 3.0 mg/kg (n=5), 3.75 mg/kg (n=7), 4.5 mg/kg (n=4)
- The PK analysis indicated that elritercept follows a one-compartment model with first order absorption and elimination (**Figure 2**). The PK/PD relationship remained consistent across both indications, and exposure data supported alignment of the RP2D across both indications

Figure 2. Schematic of the PK model

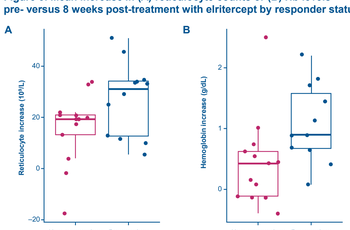


CL/F, apparent clearance; Kα, absorption rate constant; V/F, apparent volume of distribution.

LR-MDS

- In PK/PD modelling, both CL/F and steady-state C_{trough} were found to be predictors of early change in reticulocyte counts (CL/F: p=0.009; C_{trough}: p=0.042) or Hb (CL/F: p=0.046; C_{trough}: p=0.004)
- Patients with an increase in reticulocyte counts >20 x10⁹/L were more likely to respond to treatment with elritercept versus those without; patients with an increase in Hb >0.6 g/dL were more likely to respond versus those without (**Figure 3**)

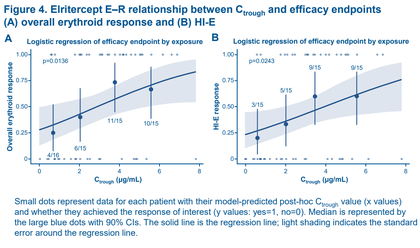
Figure 3. Mean increase in (A) reticulocyte counts or (B) Hb levels pre- versus 8 weeks post-treatment with elritercept by responder status



The bottom and top of each box represent the 25th and 75th percentiles, respectively; the whiskers represent the 10th and 90th percentiles; the line within the box represents the median.
Responders were defined as HI-E or TI per Modified International Working Group 2006 criteria.

- The E–R analyses showed no significant relationship between the exposure metrics and the efficacy endpoints; however, there was a positive correlation between higher C_{trough}, and in HI-E (**Figure 4**) and TI (**Summary Panel A**)

Figure 4. Elritercept E–R relationship between C_{trough} and efficacy endpoints (A) overall erythroid response and (B) HI-E



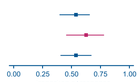
Small dots represent data for each patient with their model-predicted post-hoc C_{trough} value (x values) and whether they achieved the response of interest (y values: yes=1, no=0). Median is represented by the large blue dots with 90% CIs. The solid line is the regression line; light shading indicates the standard error around the regression line.

- Model-based simulation indicated that dose escalation from 3.75 to 5.0 mg/kg increased the probability of achieving an erythroid response (**Figure 5**). Thus, the starting dose of elritercept in patients with LR-MDS was established at 3.75 mg/kg, with up-titration to 5.0 mg/kg (beginning at cycle 3) based on predefined response criteria and safety/tolerability assessments

Figure 5. Model-predicted proportion of patients with (A) overall erythroid response, (B) HI-E response, and (C) TI response by exposure metric following 8-week treatment with elritercept 3.75 mg/kg or 5.0 mg/kg Q4W

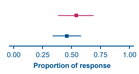
A) Overall erythroid response

Exposure metric	Dose (mg/kg)	Predicted proportion of patients with overall erythroid response (95% CI)
C_{max}	5.0	0.552 (0.372, 0.709)
	3.75	0.513 (0.389, 0.637)
AUC_{672h}	5.0	0.617 (0.431, 0.780)
	3.75	0.535 (0.397, 0.658)
C_{trough}	5.0	0.626 (0.453, 0.781)
	3.75	0.538 (0.404, 0.673)



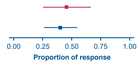
B) HI-E

Exposure metric	Dose (mg/kg)	Predicted proportion of patients with HI-E response (95% CI)
C_{max}	5.0	0.493 (0.323, 0.661)
	3.75	0.445 (0.318, 0.574)
AUC_{672h}	5.0	0.540 (0.360, 0.716)
	3.75	0.454 (0.328, 0.595)
C_{trough}	5.0	0.542 (0.382, 0.691)
	3.75	0.460 (0.335, 0.585)



C) TI 8-week response

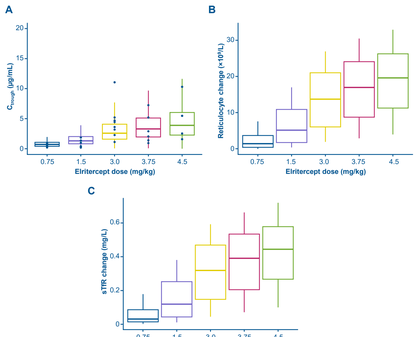
Exposure metric	Dose (mg/kg)	Predicted proportion of patients with TI 8-week response (95% CI)
C_{max}	5.0	0.374 (0.206, 0.577)
	3.75	0.384 (0.25, 0.527)
AUC_{672h}	5.0	0.455 (0.253, 0.667)
	3.75	0.402 (0.263, 0.549)
C_{trough}	5.0	0.492 (0.307, 0.674)
	3.75	0.407 (0.266, 0.552)



MF

- In PK/PD analysis, C_{trough} was consistently correlated with PD changes, defined as the difference in means between pre- and 12 weeks post-treatment for reticulocytes, Hb, soluble transferrin receptor (sTfR), and platelets
- In patients with MF, PK/PD analyses demonstrated enhanced PD effects at doses equal to or higher than 3.0 mg/kg versus lower doses, with improvements in anemia-related outcomes, including increases in Hb levels (**Summary Panel B**) and reductions in transfusion burden (**Figure 6**)

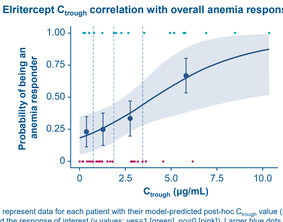
Figure 6. Model-predicted elritercept dose–PK/PD relationship for (A) C_{trough}, (B) reticulocyte change, and (C) sTfR change over a 12-week period pre- and post-treatment for each dose



A shows the distribution of model-predicted C_{trough}, with patient data overlaid (panel A – points). The bottom and top of each box represent the 25th and 75th percentiles, respectively; the whiskers represent the 10th and 90th percentiles; the line within the box represents the median.

- Logistic regression analysis demonstrated that C_{trough} was a significant predictor of clinical response (p<0.05) including RBC TI (**Summary Panel C**) and overall anemia response (**Figure 7**) over the course of the study

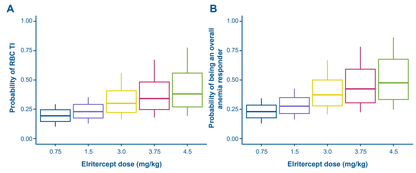
Figure 7. Elritercept C_{trough} correlation with overall anemia response



Colored dots represent data for each patient with their model-predicted post-hoc C_{trough} value (x values) and whether they achieved the response of interest (y values: yes=1 [green], no=0 [pink]). Larger blue dots with vertical lines are the means and standard errors for PK cohorts generated using the 25th, 50th, and 75th percentiles of the data; the blue line is the logistic regression model fit, and the shaded region is the 95% CI. Overall anemia responders are defined as a patient in the anemia response-evaluable population (includes all patients in the PD population with ≥12 consecutive weeks of post-baseline evaluations of RBC transfusion(s) or RBCs either achieving a 50% reduction in transfusion burden (RBC units/12 weeks) or achieving a mean increase from baseline in Hb of ≥1.0 g/dL over a 12-week period.

- The maximum effect was achieved at doses equal to or higher than 3.0 mg/kg, indicating that increasing the dose is likely to result in a significant increase in the proportion of patients achieving RBC TI and/or overall anemia response (**Figure 8**)

Figure 8. Model-predicted probability of response by dose of elritercept for (A) TI and (B) overall anemia response



RBC TI was defined as TI over ≥12 weeks. Overall anemia responders were defined as a patient in the anemia response-evaluable population (includes all patients in the PD population with ≥12 consecutive weeks of post-baseline evaluations of RBC transfusion[s] or RBCs) who either achieved a 50% reduction in transfusion burden (RBC units/12 weeks) or a mean increase from baseline in Hb of ≥1.0 g/dL over a 12-week period.

Conclusions

- Elritercept demonstrated dose-dependent improvements in anemia-related outcomes in patients with LR-MDS and MF, with higher doses correlating with enhanced efficacy
- Based on predefined response criteria and safety/tolerability assessments, an adaptive dosing regimen of 3.75 mg/kg Q4W, with the option to titrate to 5.0 mg/kg Q4W, aims to optimize therapeutic efficacy while minimizing the risk of dose delays or treatment interruptions
  - Further evaluation of the benefit-risk profile of an adaptive dosing regimen of elritercept in patients with LR-MDS and MF is recommended

References

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Disclosures

X. Zhou is an employee of and holds stocks and shares from Takeda. C. Materna, D. Grayson, and J. Salstrom are former employees of Keros Therapeutics.

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