Analysis of Duration of Response, Exposure-Adjusted Safety and Progression to Acute Myeloid Leukemia (AML) for Patients with Lower-Risk Myelodysplastic Syndromes (LR-MDS) Receiving Luspatercept in the MEDALIST Study

Authors: Uwe Platzbecker, Valeria Santini, Rami S. Komrokji, Amer M. Zeidan, Guillermo Garcia-Manero, Rena J. Buckstein, Shelonitda Rose, Shannon Fabre, Dimana Miteva, Jennie Zhang, Aylin Yucel, Christina Hughes, Pierre Fenaux

Introduction:
Patients with LR-MDS who are refractory or ineligible for treatment with erythropoiesis-stimulating agents (ESAs) have limited treatment options for anemia. Luspatercept is a first-in-class erythroid maturation agent that enhances late-stage erythropoiesis, and is approved by the US FDA for the treatment of anemia in adult patients with LR-MDS with ring sideroblasts (RS) or MDS/myeloproliferative neoplasm with RS and thrombocytosis after ESA failure. In the randomized, double-blind, phase 3 MEDALIST study, luspatercept significantly reduced transfusion burden versus placebo in patients with LR-MDS (NCT02631070; Fenaux P, et al. *N Engl J Med* 2020;382:140-151).

Here we report additional analyses from the final data cut of the MEDALIST study, including: duration of treatment and red blood cell transfusion independence (RBC-TI) response; the number of responses per patient; exposure-adjusted rates of treatment-emergent adverse event (TEAE); and time to progression to AML.

Methods:
Eligible patients were ≥ 18 years of age; had IPSS-R-defined Very low-, Low-, or Intermediate-risk MDS with RS; were refractory, intolerant, or unlikely to respond to ESAs (serum erythropoietin > 200 U/L); and required regular RBC transfusions. Patients were randomized 2:1 to luspatercept (starting dose 1.0 mg/kg, with titration up to 1.75 mg/kg) or placebo, administered subcutaneously every 3 weeks (wk). The primary endpoint was achievement of RBC-TI ≥ 8 wk during the first 24 wk of treatment. The duration of treatment in wk was calculated by (1 + the number of days between first dose and end of treatment) / 7. End of treatment date was either the last dose date plus 20 days, the study discontinuation date, or the death date, whichever was earlier. Duration of response was defined as the longest duration of RBC-TI response during the entire treatment period for patients who achieved RBC-TI ≥ 8 wk during wk 1-24 or wk 1-48. Exposure-adjusted incidence rates were calculated per 100 patient-years for TEAEs (any grade) in ≥ 5% of patients in any treatment group. Time to AML progression was defined as the time between the randomization date and the date of first AML diagnosis.

Results:
As of November 26, 2020, the median duration of treatment for patients randomized to luspatercept was 50.9 wk (range 6-207) versus 24.0 wk (range 7-103) for placebo. Patients randomized to luspatercept received a median of 17 doses (range 2-66) of treatment versus

8 doses (range 3-34) for placebo. Overall, 58 of 153 (37.9%) patients who received luspatercept achieved RBC-TI during any consecutive 8-wk period during wk 1-24, versus 10 of 76 (13.2%) for placebo. Of those achieving a response (RBC-TI ≥ 8 wk) during wk 1-24, the median duration of RBC-TI was 30.2 wk (range 8.1-201.1) for patients randomized to luspatercept versus 13.6 wk (range 9.1-66.4) for placebo, and 29.9 wk (range 8.1-201.1) for patients randomized to luspatercept versus 17.4 wk (range 9.1-66.4) for placebo, for those who responded during wk 1-48. Among patients who responded during wk 1-24 in the luspatercept arm, 17 (29.3%), 13 (22.4%), and 16 (27.6%) patients experienced 2, 3, or ≥ 4 separate RBC-TI ≥ 8-wk response events during the entire treatment period, versus 3 (30%) and 1 (10%) patients in the placebo arm, who experienced 2 or 3 response events. The only TEAEs with exposure-adjusted incidence rates ≥ 5 per 100 person-years higher in patients randomized to luspatercept versus placebo were: diarrhea (25.8 versus 18.4); dizziness (19.2 versus 8.9); nausea (20.1 versus 13.7); bronchitis (10.7 versus 2.2); vertigo (5.8 versus 0); and influenza (5.3 versus 0). Four of 153 (2.6%) patients randomized to luspatercept experienced progression to AML versus 3 of 76 (3.9%) patients randomized to placebo. The median time from randomization to AML progression for patients randomized to luspatercept was 61.7 months (range 56.7-223.6) versus 32.7 months (range 30.1-60.4) for placebo.

Conclusions:

Up through wk 48, patients randomized to luspatercept in the MEDALIST study remained on treatment longer and had more durable and repeated episodes of RBC-TI response events than placebo. Luspatercept had a tolerable safety profile when adjusted for exposure and patients receiving luspatercept had a longer time to AML progression than placebo. Luspatercept demonstrated durable responses over a longer time period in patients with anemia who have limited treatment options.