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637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Net Clinical and Quality of Life Benefit of Luspatercept in Transfusion-Dependent MDS: A Win Ratio Analysis Using Data from the Phase 3 MEDALIST Study

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Background: Patients with transfusion-dependent (TD) myelodysplastic syndromes (MDS) often experience various anemia-related symptoms and functional impairments. Treatments reducing red blood cell (RBC) transfusion burden could impact these symptoms and/or functions to varying degrees depending on patients' conditions at baseline and warrants the use of composite endpoints, including both clinical outcomes and patient-reported outcomes (PROs) to fully capture these benefits. However, conventional statistical approaches may not satisfactorily assess composite outcomes, especially when the components of the composite outcomes have different types of scales and/or degrees of importance to stakeholders. The win ratio (WR) approach, one of the generalized pairwise comparison methods commonly used for assessing treatments in cardiovascular diseases, offers hierarchical structure, statistical power, and flexibility to address these challenges.
Objective: This exploratory analysis used the WR approach to assess the net benefit of luspatercept vs. placebo on composite clinical/PRO endpoints using data from the MEDALIST study.
Methods: Four different WR scenarios were performed, in each of which every possible patient-to-patient pair between the luspatercept and placebo arms was compared on a set of relevant clinical/PRO endpoints in a pre-specified order of assumed priority from patients' perspectives, accompanied with a pre-determined rule to assign a win, loss, or tie for luspatercept in each pairwise comparison on each endpoint. If a win or loss could not be determined on a given endpoint, then the next endpoint in the hierarchy was evaluated until a win or loss occurred. Otherwise, if all pre-specified endpoints were evaluated, a tie was assigned. The scenarios considered two clinical endpoints: RBC-transfusion independence [TI] ≥8 weeks over Weeks 1-24 and RBC-TI over Weeks 1-24. PRO endpoints included changes from baseline to the end of Week 24 in five key domains of the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), categorized as improvement (≥10-point improvement), stable (10 > change >-10), or worsening (≥10-point worsening). Improvement was considered a better outcome than stable and worsening, and stable was considered better than worsening when determining a win or loss for luspatercept on each of the PRO endpoints. The four different scenarios of composite clinical/PRO endpoints and their order of priority, shown in the **Table** were pre-specified for assessment **.** The WR (nominal 95% CI, p-value) for luspatercept on each scenario of the composite clinical/PRO endpoints was calculated as the total number of pairs with a win divided by the total number of pairs with a loss. A WR >1 indicates that luspatercept is more favorable than placebo.
Results: 153 patients randomized to the luspatercept arm were compared to 76 patients randomized to the placebo arm, for a total of 11,628 pairwise comparisons within each WR analysis. In all four scenarios, WRs were nominally statistically significantly in favor of luspatercept (**Table**). Most wins favoring luspatercept were attributed to wins on the clinical endpoint. Among those pairs who tied on the clinical endpoint, the luspatercept arm experienced more wins (or tied) in almost all of the five PRO endpoints. WRs were similar whether PRO endpoints were prioritized over others or not.
Conclusions: The analysis findings indicate that, for two randomly selected patients with low-risk TD MDS, the odds that the patient treated with luspatercept would have a better outcome (if not tied) than the patient with placebo, is significantly higher than 1, ranging between 1.51 to 1.90. The analysis also shows that when multiple clinical and PRO endpoints, especially with

different importance to stakeholders, are considered to provide a comprehensive treatment benefit, WR can be a useful and valuable approach for making this evaluation.

Disclosures Oliva: *Grande Ospedale Metropolitano BMM:* Current Employment; *Daiichi:* Consultancy, Honoraria; *Ryvu:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Alexion:* Consultancy, Honoraria, Speakers Bureau; *Novartis:* Honoraria, Speakers Bureau; *Amgen:* Honoraria, Speakers Bureau; *Sobi:* Honoraria, Speakers Bureau; *Servier:* Patents & Royalties; *Bristol Myers Squibb:* Consultancy, Honoraria, Speakers Bureau. **Pelligra:** *Evidera, a Thermo Fisher Scientific business:* Current Employment. **Lord-Bessen:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Guo:** *Evidera Inc.:* Current Employment; *Bristol Myers Squibb:* Consultancy. **Sieluk:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Glassberg:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company, Research Funding. **Miteva:** *Bristol Myers Squibb:* Current Employment. **Yucel:** *Bristol Myers Squibb:* Current Employment, Current holder of *stock options* in a privately-held company.

Table. Results of WR Analyses

Composite Clinical/PRO Endpoints and Priority	WR (95% CI), p-value
1: RBC-TI ≥8 Weeks over Weeks 1-24, global QoL, PF, FA, DY, EF	1.86 (1.28, 2.72), 0.001
2: RBC-TI ≥8 Weeks over Weeks 1-24, (global QoL, PF, FA, DY, EF)*	1.90 (1.29, 2.81), 0.001
3: RBC-TI Weeks 1-24, global QoL, PF, FA, DY, EF	1.51 (1.02, 2.22), 0.038
4: RBC-TI Weeks 1-24, (global QoL, PF, FA, DY, EF)*	1.55 (1.04, 2.29), 0.030

*Equal priority among the PRO domains was assumed and a win for luspatercept was assigned if net wins across domains was ≥1.

Abbreviations: CI=confidence interval; DY=dyspnea, EF=emotional functioning, FA=fatigue, PF=physical functioning, QoL=quality of life, RBC-TI = red blood cell transfusion independence

Figure 1

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