TREATMENT WITH IMETELSTAT PROVIDES DURABLE TRANSFUSION INDEPENDENCE (TI) IN HEAVILY TRANSFUSED NON-DEL(5Q) LOWER RISK MDS (LR-MDS) RELAPSED/REFRACTORY (R/R) TO ERYTHROPOIESIS STIMULATING AGENTS (ESA)

Author(s): Uwe Platzbecker, Pierre Fenaux, David P. Steensma, Koen Van Eygen, Azra Raza, Ulrich Germing, Patricia Font, Maria Diez-Campelo, Sylvain Thepot, Edo Vellenga, Mrinal M. Patnaik, Jun Ho Jang, Helen Varsos, Esther Rose, Jacqueline Bussolari, Fei Huang, Laurie Sherman, Faye Feller, Souria Dougherty, Libo Sun, Ying Wan, Aleksandra Rizo, Valeria Santini

Background

Patients (pts) with LR-MDS who are red blood cell (RBC) transfusion dependent (TD) and have ESA-R/R disease have limited treatment options. Imetelstat is a first-in-class telomerase inhibitor that targets cells with short telomeres and active telomerase, characteristics observed in MDS pts across all disease stages. IMerge (MDS3001; NCT02598661) is a Phase 2/3 global study of imetelstat for TD pts with ESA-R/R LR-MDS. Phase 2 results indicate that imetelstat achieves durable TI in induces durable TI in LR-MDS pts (Steensma ASH 2018, Fenaux EHA 2019).

Aims

We report long term efficacy, safety, and biomarker updates in 38 LR non-del(5q) TD ESA R/R MDS pts, all lenalidomide and hypomethylating agent naïve, from the open-label, single-arm Phase 2 portion of IMerge.

Methods

During Phase 2, pts received imetelstat 7.5 mg/kg IV every 4 weeks (w). Long term efficacy includes ≥8-w RBC TI rate, ≥24-w TI rate, ≥1-year (y) TI rate, longest and cumulative duration of ≥8-w TI, duration of hematologic improvement-erythroid (HI-E), and major/minor response per updated International Working Group (IWG) 2018 guidelines. Exploratory biomarker evaluations were performed.

Results

Per IWG 2018, all pts had high transfusion burden (≥8 units [u] RBCs/16 w, ≥4 u/8 w) and 84% had ≥6 u/8 w with a median of 8 u/8 w. 89% received prior ESAs and 32% had EPO level >500 U/L; 71% had ringed sideroblasts (RS) World Health Organization subtypes.

As of 4 Feb 2020, median follow-up was 24 months (mo) for the 38 pts. In these pts, 16 (42%) had ≥8-w TI, of whom 12 showed a hemoglobin rise ≥3.0 g/dL during the transfusion-free interval vs the pretreatment level. Furthermore, 12 (32%) pts achieved ≥24-w TI, and 11 (29%) pts, who had a median transfusion burden of 6 u/8 w, were transfusion free for ≥ 1 y. Kaplan-Meier (KM) median TI duration was 88 w (20 mo) and the longest TI is 2.7 y. KM median

cumulative duration of ≥8 w TI (sum of all periods of TI ≥8 w) was 92 w (21 mo). Per IWG 2018, clinically meaningful major (16-w TI) and minor response (50% transfusion reduction/16 w) was achieved by 37% and 55% of pts, respectively. HI-E was achieved by 26 (68%) pts, with KM median duration of 93 w (21 mo). Most frequently reported adverse events were manageable and reversible grade ≥3 cytopenias.

Five of 6 pts (83%) with IPSS-R intermediate or poor cytogenetic risk achieved ≥8-w TI, all with RS WHO subtypes; 3 had ≥1-y TI. Cytogenetic and mutational malignant clone reduction in some pts indicates disease modifying activity of imetelstat. On-target imetelstat activity was demonstrated by ≥50% reduction of telomerase activity post imetelstat dosing in 23.1% (3/13) of pts and of human telomerase reverse transcriptase (hTERT) RNA level in 54.3% (19/35) of pts. Compared to pts without TI, a significantly higher proportion of pts had ≥50% hTERT expression reduction when achieving ≥8-w TI (80% [12/15] vs 35% [7/20]; p=0.0155) and ≥24-w TI (91.7% [11/12] vs 34.8% [8/23]; p=0.0016), indicating a correlation between inhibiting the telomerase target with imetelstat and clinical benefit.

Conclusion

Imetelstat achieved an 8-w TI rate of 42% for a median duration of 20 mo, the longest so far reported with any agent in non-del 5q LR-MDS, and 29% of pts achieved TI ≥ 1 y. Furthermore, a high and durable HI-E rate (68% for median of 21 mo) was also achieved in this population of heavily RBC TD, ESA-R/R LR-MDS. Enrollment is ongoing in the Phase 3 portion of IMerge, a placebo-controlled trial of the efficacy and safety of imetelstat, including potential predictive biomarkers of response.

Session topic: 10. Myelodysplastic syndromes - Clinical

Keyword(s): Clinical trial, Myelodysplasia, Telomerase