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 (ESAS)

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Background
There are limited treatment options for red blood cell (RBC) transfusion dependent (TD) LR (IPSS Low/Int-1) MDS patients who are relapsed/refractory to ESAs. Imetelstat is a first-in-class telomerase inhibitor that targets cells with short telomeres and active telomerase, characteristics observed in some MDS patients across all disease stages. Preliminary results show that imetelstat is effective treatment in LR-MDS patients inducing durable TI (Steensma et al ASH 2018 Abstr463).

Aims
We report updated efficacy data with a median follow-up of 12.1 months in 38 LR non-del(5q) MDS patients, R/R to ESA and LEN/HMA naive from the open-label, single-arm Part 1 of IMerge, an ongoing phase 2/3 study (NCT02598661).

Methods

Part 1 of the IMerge study included patients with LR MDS, who were heavily transfused (≥4U/8wks), were R/R to ESA or had sEPO >500 mU/mL. Imetelstat 7.5 mg/kg was administered IV every 4 weeks. The primary endpoint was 8-week TI rate; key secondary endpoints included 24-week TI rate, safety, duration of TI, and hematologic improvement (HI) rate. Among the initially enrolled patients, higher 8-week TI rate was observed in the non-del5q, LEN/HMA naive patients. Therefore, the study was amended to subsequently enroll only these patients. From a total of 57 patients enrolled in Part 1, 38 were non-del(5q), LEN/HMA naïve patients (13 in the initial and 25 in the expansion cohort). Here we report long-term efficacy, safety and biomarker data from these 38 patients.

Results

Median baseline RBC transfusion burden was 8U/8weeks (range 4-14), 37% of the patients had IPSS Int-1; 71% had WHO 2001 RARS or RCMD-RS subtype and 32% with evaluable sEPO levels had baseline level >500 mU/mL.

As of 23 January 2019, median follow-up was 12.1 months for the 38 patients, representing 30.4 and 11.6 months for the initial 13 and additional 25 patients, respectively. The 8-week TI rate was 45% (17/38) and median TI duration was 8.5 months (range 1.8-32.4). Of the 17 responding patients, 10 (59%) remained transfusion free for over 24 weeks. The 8-week TI rate did not differ based on the

presence of ring sideroblasts or baseline sEPO levels. The 24-week TI rate was 26% (10/38). Erythroid HI, defined as transfusion reduction by at least 4 units /8 weeks (IWG2006), was achieved in 68% (26/38) of the patients. The most frequently reported adverse events were manageable and reversible grade ≥3 cytopenias. 6/38 patients had IPSS-R intermediate/poor cytogenetic risk. All 6 patents achieved 8-week TI; 2/6 patients achieved partial cytogenetic response. Post treatment decrease in telomerase hTERT RNA level was observed in 25/34 (73.5%) patients with available sample. Among 7 patients with pre- and post-treatment mutation analyses, six had SF3B1 mutations at baseline, and a decrease in the mutation VAF was observed in 2 patients that had longest TI duration on study.

Conclusion

In high RBC transfusion burden patients with non-del(5q) LR-MDS R/R to ESA and naive to LEN/HMA, single-agent imetelstat yielded 8-week TI rate of 45%, with a median duration of 8.5 months (range 1.8-32.4). The 24-week TI rate was 26%. HI-E rate was 68%. All patients with IPSS-R intermediate and poor cytogenetic risk responded. Biomarker analyses of telomerase activity and mutation allele burden indicate an effect on the malignant mutant clone. These data support Part 2 of IMerge, Phase 3 placebo-controlled, randomized portion of the study, expected to open mid-2019.