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Myelodysplastic Syndromes

IMETELSTAT RESTORES ERYTHROID MATURATION IN RESPONDING LOW RISK MDS PATIENTS

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Background: Imetelstat is a first-in-class human telomerase (hTERT) inhibitor, decreasing the upregulated telomerase activity of neoplastic hematopoietic stem and progenitor cells (HSPCs). By suppressing hTERT, Imetelstat selectively eliminates dysplastic clones, enabling restoration of normal hematopoiesis. Recently approved by the FDA for the treatment of red blood cell transfusion–dependent (RBC-TD) lower-risk myelodysplastic syndromes (LR-MDS) patients after erythropoiesis-stimulating agent (ESA) failure, its precise mechanism of action remains unclear. We provide the first *in vivo* evidence that Imetelstat enhances erythroid maturation by alleviating ineffective erythropoiesis and reducing bone marrow (BM) clonal burden in responding LR-MDS patients.
Methods: Comprehensive erythroid flow cytometry (FC) and targeted next-generation sequencing (t-NGS) analyses were performed on BM samples from LR-MDS patients enrolled in the phase III *IMerge trial* (. NCT02598661). FC analysis included total $CD71^+$ erythroid cells (Ery_{tot}), early $CD34^+/CD117^+$, and late $CD117^-$ erythroid precursors. The erythroid ratio (ER) was defined as the ratio of late to early precursors. BM erythroid indices and variant allele frequency (VAF) of driver somatic mutations were longitudinally assessed at baseline, +6 and +12 months after Imetelstat initiation; extended FC data were available at +24 months for one ongoing responder.
Results: Four representative cases were analyzed: (a) a long responder (>1 year RBC transfusion independence), (b) a transient responder (<1 year RBC-TI), (c) a non-responder, and (d) a placebo-treated patient. The sustained responder displayed marked and persistent decreases in Ery_{tot} population (29%→11% at 24 months) accompanied by increased ER (2.36→7.33), consistent with enhanced erythroid maturation (**Figure 1a**). The transient responder exhibited a similar pattern during response (Ery_{tot} 17%→2%, ER 3→6.14 at 6 months) but relapsed by 12 months, with Ery_{tot} expansion (30%) and ER reduction (2.22). No significant changes were observed in non-responder or placebo cases. Clonal dynamics mirrored erythroid trends: BM VAFs of driver mutations decreased during hematologic response (22%→4.7% in the ongoing responder at 12 months, 32.9% →4.3% in the short responder at 6 months) and re-expanded at relapse (4.3%→22.6% in the transient responder at 12 months, **Figure 1b**). As for erythroid populations, BM VAF did not change significantly over time in both the non-responder and the placebo-treated patient.
Conclusions: Imetelstat treatment in LR-MDS promotes erythroid maturation and reduces BM clonal burden during clinical response, supporting a dual mechanism of action that combines telomerase-mediated clonal suppression with restoration of effective erythropoiesis. These findings provide *in vivo* mechanistic insight into how telomerase inhibition reverses ineffective erythropoiesis in MDS and underpin the durable clinical responses observed in the *IMerge* trial.

MYELODYSPLASTIC SYNDROMES