

Optimizing Frontline LR-MDS Treatment: EHA 2026 Data Review

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Lower-risk myelodysplastic syndromes (LR-MDS) present a clinical challenge in balancing disease progression risk with quality of life, particularly concerning anaemia and transfusion dependence. New data presented at EHA 2026 provide further clarity on optimal frontline therapeutic strategies, emphasizing agents that improve erythroid response and transfusion independence.¹

KEY TAKEAWAYS

- **The Pivot:** Frontline treatment selection for LR-MDS should prioritize agents demonstrating sustained erythroid response and transfusion independence.
- **The Data:** Specific agents achieved transfusion independence rates of 40-50% in transfusion-dependent, lower-risk MDS patients.
- **The Action:** Clinicians should consider patient-specific factors, including SF3B1 mutation status and baseline transfusion burden, when selecting initial therapy.

Lower-risk myelodysplastic syndromes (LR-MDS) are characterized by ineffective haematopoiesis, leading to cytopenias, most commonly anaemia. The primary goals of treatment in LR-MDS are to improve quality of life, reduce transfusion dependence, and delay progression to higher-risk MDS or acute myeloid leukaemia (AML).¹ Current guidelines recommend risk stratification using tools such as the Revised International Prognostic Scoring System (IPSS-R) to guide therapeutic decisions.² Patients classified as lower-risk (Very Low, Low, or Intermediate IPSS-R scores) often experience significant morbidity due to anaemia, necessitating regular red blood cell transfusions.³ Transfusion dependence is associated with iron overload, increased infection risk, and reduced overall survival.⁴ Therefore, effective frontline therapies that achieve sustained erythroid response and transfusion independence are critical. The global incidence of MDS is estimated to be between 3 and 5 cases per 100,000 people per year, with LR-MDS constituting a substantial proportion of these cases, particularly in older adults. The median age at diagnosis typically ranges from 70 to 75 years. This demographic often presents with multiple comorbidities, further complicating treatment selection and management.

Evaluating Frontline Therapeutic Strategies

A comprehensive review of data presented at EHA 2026 focused on the efficacy and safety of various frontline treatment options for LR-MDS patients. The analysis included studies evaluating erythropoiesis-stimulating agents (ESAs), lenalidomide, and luspatercept, among others. Patient cohorts typically included transfusion-dependent individuals with LR-MDS, often defined by a requirement of at least 2 units of red blood cells over 8 weeks.⁵ Key endpoints assessed

were erythroid response (ER), defined as a haemoglobin increase of at least 1.5 g/dL or reduction in transfusion burden, and transfusion independence (TI), defined as no red blood cell transfusions for a specified period, typically 8 or 12 weeks.⁶ The studies reviewed employed rigorous methodologies, including randomized controlled trials and prospective observational studies, to ensure robust data collection and analysis. Eligibility criteria often included specific IPSS-R scores, bone marrow blast percentages below 5%, and absence of prior disease-modifying therapy, ensuring a focus on frontline treatment settings.

For patients with LR-MDS and serum erythropoietin (EPO) levels below 500 U/L, ESAs remain a standard initial approach. Studies consistently show that ESAs can achieve an erythroid response in approximately 40-50% of patients and transfusion independence in 20-30%.⁷ The duration of response, however, can be variable, with many patients eventually becoming refractory.⁸ ESAs work by stimulating erythroid progenitor cells in the bone marrow, mimicking the action of endogenous erythropoietin.

Lenalidomide has demonstrated particular efficacy in LR-MDS patients with isolated del(5q) cytogenetic abnormality. In this specific subgroup, lenalidomide can achieve transfusion independence rates of 50-60%, with a median duration of response often exceeding 2 years.⁹ For LR-MDS patients without del(5q), lenalidomide's efficacy is lower, with TI rates around 20-30%.¹⁰ Lenalidomide's mechanism of action in del(5q) MDS involves selective cytotoxicity to del(5q) clones and immunomodulatory effects.

Luspatercept, a recombinant fusion protein that modulates TGF- β signalling, has emerged as an important option, particularly for patients with ring sideroblasts (RS) and SF3B1 mutations. Data presented at EHA 2026 reinforced its role, showing that in transfusion-dependent LR-MDS patients with RS, luspatercept achieved transfusion independence for at least 8 weeks in 38% of patients and for at least 12 weeks in 28%.¹¹ The median duration of TI was approximately 30 weeks.¹¹ These responses were observed regardless of prior ESA failure, positioning luspatercept as a viable option after ESA failure or as a frontline alternative in specific contexts.¹² Luspatercept acts by inhibiting aberrant SMAD2/3 signaling, thereby promoting erythroid maturation.

The safety profiles of these agents were also reviewed. ESAs are generally well-tolerated, with common adverse events including hypertension and thrombotic events, though these are infrequent.¹³ Lenalidomide is associated with myelosuppression (neutropenia and thrombocytopenia), fatigue, and rash.¹⁴ Luspatercept's most common adverse events include fatigue, nausea, and musculoskeletal pain, generally mild to moderate in severity.¹⁵ While these treatments offer significant benefits, limitations exist, including the potential for primary or secondary resistance, the need for continuous monitoring, and the financial burden associated with long-term therapy. Future research aims to identify biomarkers for even more precise patient selection and to develop novel combination therapies.

The data underscore the importance of patient stratification based on prognostic markers, including cytogenetics and molecular mutations such as SF3B1. For instance, the presence of an SF3B1 mutation strongly predicts response to luspatercept.¹⁶ Conversely, patients with very low serum EPO levels and no SF3B1 mutation may still benefit from ESAs.¹⁷ The choice of frontline therapy must therefore be individualized, considering the patient's specific disease characteristics, transfusion burden, and comorbidities. The goal is to achieve early and durable transfusion independence to mitigate the complications associated with chronic transfusions and improve patient quality of life.¹⁸

For a comprehensive overview of haematological conditions, including myelodysplastic syndromes and their management, consult the indispensable Oxford Handbook of Clinical Haematology.

CLINICAL IMPLICATIONS

The EHA 2026 data on LR-MDS frontline treatment reinforce the need for precise patient stratification. It is no longer sufficient to treat all lower-risk patients uniformly. Clinicians must integrate molecular and cytogenetic profiling, specifically SF3B1 mutation status and del(5q), into their initial diagnostic workup. The evidence strongly suggests that a 'one-size-fits-all' approach with ESAs will leave a significant proportion of patients suboptimally managed, prolonging transfusion dependence and its associated morbidities. The availability of agents like luspatercept for SF3B1-mutated patients, and lenalidomide for del(5q) cases, means that delaying these targeted therapies in favour of a potentially less effective, broader approach is increasingly difficult to justify.

From an industry perspective, the continued development of targeted therapies for LR-MDS is critical. The market for these agents is expanding, driven by improved diagnostic capabilities and a clearer understanding of disease biology. Pharmaceutical companies investing in novel agents that address specific molecular subsets of MDS will see their products integrated rapidly into clinical practice, provided the efficacy data, particularly for sustained transfusion independence, are compelling. The economic burden of chronic transfusions also provides a strong argument for the cost-effectiveness of therapies that achieve durable TI, which should be a focus for health economic evaluations.

For patients, these advancements translate to a more personalized and potentially more effective treatment pathway. The prospect of achieving and maintaining transfusion independence significantly improves quality of life, reducing hospital visits, iron overload complications, and the psychological burden of chronic illness. However, access to advanced molecular diagnostics and newer, often more expensive, targeted therapies remains a concern. Healthcare systems and guideline bodies, such as NICE or ESMO, will need to evaluate these data carefully to ensure equitable access to optimal frontline treatments, moving beyond older, less effective strategies when superior, evidence-based alternatives are available.

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