Survival Benefit and Resource Utilization of First-line (1L) Treatment with Luspatercept vs. 1L Erythropoiesis-stimulating Agents (ESAs) for Lower-risk Myelodysplastic Syndromes (LR-MDS): Results of Model Simulation

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Introduction

- Patients with myelodysplastic syndromes (MDS) often require regular red blood cell (RBC) transfusions to manage anemia, the most prevalent cytopenia associated with ineffective hematopoiesis in MDS.[1,2] Patients with lower risk (LR) MDS who are RBC-transfusion dependent (TD) experience decreased overall survival and quality of life (QoL) compared with those who are transfusion independent (TI).[1-6]
- Until recently, the standard of care in the first-line (1L) setting was erythropoiesis-stimulating agents (ESAs) in combination with best supportive care (BSC), which includes RBC transfusions.[7] However, more than half of patients who receive ESAs do not achieve response, and durability of response is sub-optimal (6–18 months).[3,8-10]
- In August 2023, luspatercept received expanded approval by the US FDA to include the 1L treatment of adult patients with LR-MDS, based on the Phase III COMMANDS trial (NCT03682536).[11-13] In COMMANDS, 58.5% of patients treated with luspatercept in 1L achieved TI for ≥12 weeks and experienced an increase in hemoglobin of ≥1.5 g/dL compared with 31.2% of patients who received an ESA (epoetin alpha) in the first 24 weeks of treatment. The approval expands on the second line (2L) indication for luspatercept, i.e., patients with LR-MDS who had an unsatisfactory response to or are ineligible for ESAs based on the Phase III MEDALIST trial (NCT02631070).[14]
- Among patients with LR-MDS, the recently approved imetelstat is another option for 2L treatment, as well as BSC.[2,14-15] Imetelstat received FDA approval in June 2024 based on results of the Phase III IMerge study.[16]

Objective

- **To predict the clinical and healthcare resource use (HCRU) outcomes associated with two treatment pathways: 1L use of luspatercept and 1L use of ESA.**

Methods

- A patient simulation model (patients at baseline represent those in COMMANDS[11]) was developed to compare outcomes between treatment pathways starting in 1L for a patient's lifetime (**Figure 1**).
  - 1L luspatercept: Luspatercept in 1L followed by imetelstat or BSC in 2L and BSC in 3L
  - 1L ESA: ESA in 1L followed by luspatercept, BSC, or imetelstat in 2L and BSC in 3L.

Model Approach

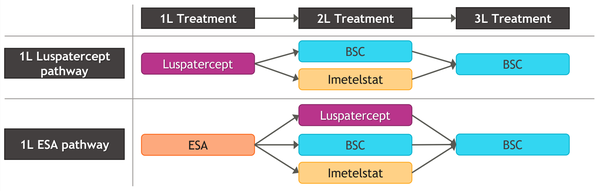
- In each line of treatment, some patients can achieve TI response (**Figure 2**). Those who do not respond move to the next line of treatment. TI patients can lose TI response and move to the next line of treatment. Response probabilities and duration of response were based on the observed data from the trials (**Figure 1**).
  - To align with the endpoints in the trials, 1L response was defined as ≥12 weeks RBC-TI and 2L response was defined as ≥8 weeks RBC-TI within the first 24 weeks of treatment for both. For patients who receive imetelstat, an assumption is made that most patients who achieved response in IMerge did so within the first 24 weeks even though the trial did not specifically apply that restriction.
- QoL, risk of complications, and HCRU are also impacted by TI and TD status (**Table 1**), as are survival and progression to acute myeloid leukemia (AML) (*see next two sections*).
- The choice of treatment in 2L was informed by market share distributions, data on file.
- The model and analyses reported herein expand upon previous analyses[17,18,19] by including a market basket of treatments available in 2L.

Overall Survival

- Survival was modeled using a combination of data from trials and published literature, where survival depends on patient TI/TD status. In 1L, OS data from COMMANDS stratified by TI response and non-response was applied, pooling treatment arm data.[11] (Note: the COMMANDS trial was not powered to detect survival difference by treatment).
  - For 2L treatment, TI patient survival is based on published data,[20] and TD patients experience an increased mortality relative to TI (hazard ratio [HR] of 2.732[4])

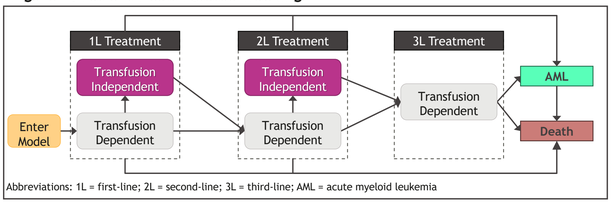
Figure 1. Treatment Pathway

Transition	1L Source	2L Source	3L Source
Response	COMMANDS[11]	MEDALIST[11] and IMerge[16]	N/A
Loss of Response	COMMANDS[11]	MEDALIST[11] and IMerge[16]	N/A
Survival*	COMMANDS[11]	Literature[4,20]	Literature[4,20]



Abbreviations: 1L = first-line; 2L = second-line; 3L = third-line; BSC = best supportive care; ESA = erythropoiesis-stimulating agent; *Survival varies depending on whether the patient is TI or TD

Figure 2. Patient Health Status Tracking



Abbreviations: 1L = first-line; 2L = second-line; 3L = third-line; AML = acute myeloid leukemia

Acute Myeloid Leukemia

- Patients in any line of treatment are at risk of progression to AML, which was sourced from published data[20] with a higher risk (HR of 1.76) for TD patients vs. TI patients.[21] Upon onset of AML, patients experience an increased risk of death.[22,23]

Clinical Complications, HCRU, and Utilities

- Model inputs included rates of complications associated with LR-MDS (**Table 1**).
- Survival adjusted for QoL was calculated in the model by applying health utility values to survival, where a value of 1 is considered perfect health (**Table 1**).
- Treatment received in each line of therapy influences patient health status (e.g., TI/TD), which impacts complication rates and QoL.

Table 1. Model Inputs: Annual Rates[a] of Complications, HCRU, and Utilities

Health status	Cardiac events[24]	Infection[25]	Bleeding[25]	Hospitalization[25]	ER visits[25]	Utility value
TI	0.01[b]	0.61	0.23	3.60	3.30	0.85[26]
LTB	0.076[b]	1.57	0.64	6.40	5.60	0.77[26]
HTB						0.65[26]
AML						0.65[27]

Abbreviations: AML = acute myeloid leukemia; ER = emergency room; HTB = high transfusion burden (≥4 units/8 weeks); LTB = low transfusion burden; TI = transfusion independent; **Clinical Complications footnotes:** [a]Incidence per person-year.[24-25] [b]Estimated via visual inspection of presented Kaplan-Meier plots.[24] TI - TI rate reported across all countries,[25] LTB/HTB - transfusion-dependent rate reported across all countries,[25] AML assumed equal to transfusion dependence; **Utility footnotes:** reference 26 is a time trade-off study; TI - TI utility reported,[26] LTB assumed to align with the reduced transfusion burden utility reported,[26] HTB - transfusion-dependent utility reported,[26] AML - utility for induction phase assumed[27]

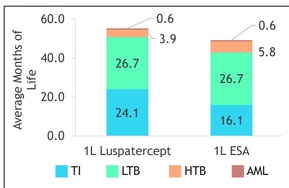
Analysis

- The model simulates the disease course of individual patients and averages their outcomes across each treatment pathway (1L luspatercept vs. 1L ESA)
- In addition to the primary analysis, an analysis was conducted to compare outcomes for patients that respond to luspatercept in 1L vs. 2L .

Results

- The model estimated that patients who received 1L luspatercept lived 6.0 (55.3 vs. 49.2) months longer than patients who received 1L ESA (**Figure 3**) and experienced 5.5 (43.9 vs. 38.4) more quality-adjusted months of life.
- Patients in the 1L luspatercept pathway vs. 1L ESA pathway required fewer RBC units and experienced fewer clinical complications (**Table 2**).

Figure 3. Months of Life



Interpretation

- Patients receiving 1L luspatercept instead of 1L ESA are predicted to experience an additional 8 months more time spent TI, and 1.9 months less time with a high transfusion burden
- As a result, patients receiving luspatercept in 1L are expected to experience a better QoL compared with those receiving ESA in 1L.

Abbreviations: 1L = first-line; 2L = second-line; AML = acute myeloid leukemia; ESA = erythropoiesis-stimulating agent; HTB = high transfusion burden; LTB = low transfusion burden; TI = transfusion independent

Table 2. Results

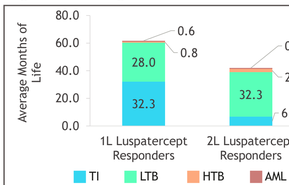
Outcome	1L Luspatercept	1L ESA	Difference
RBC Units per 8 Weeks	**1.77**	**2.08**	**-0.31 (-14.8%)**
Annual Infections	**1.18**	**1.29**	**-0.11 (-8.6%)**
Annual Bleeding Events	**0.47**	**0.52**	**-0.05 (-9.2%)**
Annual Hospitalizations	**1.27**	**1.44**	**-0.18 (-12.2%)**
Annual ED Visits	**1.15**	**1.27**	**-0.13 (-9.9%)**

Abbreviations: 1L = first-line; ED = emergency department; ESA = erythropoietin-stimulating agent
Results reflect a lifetime analysis, i.e., from 1L initiation until death; *Numbers may not add up due to rounding

Luspatercept Responders in 1L vs. 2L Results

- Patients who achieved response to luspatercept in 1L vs. 2L, had substantial benefits, with a gain of 19.7 (61.7 vs 41.9) months of life and 17.4 (49.9 vs. 32.5) quality-adjusted months of life, primarily due to the more than 3.5-times increase in total time spent TI for 1L luspatercept responders (**Figure 4**).
- Patients who achieved response to luspatercept in 1L vs. 2L required fewer RBC units and experienced fewer clinical complications (**Table 3**).

Figure 4. Average Months of Life and Transfusion Burden



Interpretation

- Patients responding to luspatercept in 1L instead of 2L are predicted to experience an additional 25.5 more months of time spent in TI and 1.5 months less time with a high transfusion burden
- 1L response to luspatercept has a longer duration than that observed for 2L response

Abbreviations: 1L = first-line; 2L = second-line; AML = acute myeloid leukemia; HTB = high transfusion burden; LTB = low transfusion burden; TI = transfusion independent

Table 3. Results

Outcome	1L Luspatercept	2L Luspatercept	Difference
RBC Units per 8 Weeks	**1.55**	**2.72**	**-1.16 (-42.8%)**
Annual Infections	**1.08**	**1.47**	**-0.39 (-26.6%)**
Annual Bleeding Events	**0.43**	**0.60**	**-0.17 (-27.8%)**
Annual Hospitalizations	**1.12**	**1.73**	**-0.61 (-35.5%)**
Annual ED Visits	**1.04**	**1.48**	**-0.44 (-29.8%)**

Abbreviations: 1L = first-line; ED = emergency department; ESA = erythropoietin-stimulating agent; RBC = red blood cell
Results reflect a lifetime analysis, i.e., from 1L initiation until death; *Numbers may not add up due to rounding

- To assess the sensitivity of the model results, scenario analyses were tested. The 1L luspatercept pathway resulted in greater life years and quality-adjusted life years and a lower RBC transfusion burden per 8 weeks compared with the 1L ESA pathway across these various scenarios.
- The following inputs were tested: imetelstat response and duration of response (to assess the impact of inconsistencies in the IMerge response definition and population compared with MEDALIST and COMMANDS), which resulted in incremental months of life ranging from 4.8–6.0 in scenarios, survival and duration of response extrapolations with incremental months of life ranging from 5.3–8.3 in scenarios, and market share distributions in 2L with incremental months of life ranging from 4.2–6.0 in scenarios.

Limitations and Assumptions

- The limitations and assumptions associated with this analysis are similar to those of prior analyses[17-19] in that alternative data sources were considered for the model (e.g., survival) but the sources identified did not align with the model population and/or model outcomes (e.g., TI/TD status). There was also uncertainty in extrapolating data beyond the observed period in the studies, but this is mitigated by testing scenarios around these inputs.
- There are differences in the populations in the COMMANDS, MEDALIST, and IMerge trials.
  - Patients in COMMANDS and IMerge were older and were diagnosed with MDS later in life than patients in MEDALIST. COMMANDS and IMerge did not restrict to ring sideroblast (RS)-positive patients (73% and 62% RS+, respectively) while MEDALIST excluded RS-negative. Patients in COMMANDS had a lower transfusion burden at baseline than MEDALIST and IMerge, with patients in IMerge with the highest on average.
  - Due to these differences and potential survival bias for patients who enrolled in MEDALIST and IMerge, survival data from these studies was not used in the model.
- The patient populations evaluated from the model data sources may not be generalizable to patients treated in clinical practice.

Conclusions

- **Our model predicts that for patients with TD LR-MDS, a treatment pathway that starts with luspatercept in 1L (compared with ESA) results in benefits to survival, quality-adjusted survival, resource use, and disease burden.**
- **Moreover, there are greater health and resource use benefits of achieving response to luspatercept early in the disease pathway (1L vs. 2L).**

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Disclosures

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