A Systematic Literature Review of the Clinical Efficacy and Safety Evidence Associated with Treatment of Patients with Higher-Risk Myelodysplastic Syndrome

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Key Findings

- Survival and response outcomes were poor for patients with higher-risk myelodysplastic syndrome (HR-MDS) receiving current treatment options, with median overall survival (OS) ranging from 7.3 to 28.2 months[1–17]
- Hypomethylating agent (HMA) monotherapy and combination therapies tended to have better outcomes compared with best supportive care (BSC) and chemotherapy, with combinations demonstrating the greatest benefit[1–29]
- Time to acute myeloid leukaemia (AML) progression ranged from 2.0 to 19.3 months[16,17,21,30,31]
- Treatment-related adverse events (TRAEs) were experienced by ≥50% of patients[4,21,32]

Conclusions

- Current clinical outcomes of treatments for patients with HR-MDS are poor and there is variation in outcomes within the patient population
- Patients with HR-MDS not only suffer a significant burden from the disease, but also due to the adverse events (AEs) they experience from the treatments they receive
- There remains an unmet medical need for novel targeted therapies with tolerable safety profiles that delay AML progression across the patient population

Introduction

- HR-MDS is a spectrum of heterogenous disorders where the bone marrow produces dysfunctional blood cells. It is associated with poor survival outcomes due to cytopenias and progression to AML[33]
- Stem cell transplant (SCT) is the only potential curative option for MDS; however, there are limitations in patient eligibility and donor availability. Non-SCT treatments, such as HMA, aim to extend survival and manage MDS by improving blood production and slowing down disease progression, whilst BSC aims to help with the symptoms of chronic cytopenias[33,34]

Objective

- To conduct a systematic literature review (SLR) to identify clinical efficacy and safety evidence associated with HR-MDS treatments

Methods

- Database and hand-searches were conducted in October 2022. Articles were screened for eligibility based on pre-specified PICOS criteria **(Table 1)**
- All articles were assessed for inclusion by two independent reviewers at title/abstract and full-text review. Disagreements were resolved through discussion between the reviewers and consultation with a third independent reviewer
- Included studies were extracted by one reviewer and checked by a second reviewer

Table 1. PICOS criteria

Characteristics	Inclusion Criteria
Population	Adult patients with HR-MDS
Intervention	Azacitidine, sabatolimab, magrolimab, decitabine, lenalidomide, luspartacept, cytarabine-containing regimens, hydroxyurea, clofarabine, topotecan, IDH inhibitors, high intensity/AML-like intensive chemotherapy, and/or BSC (as monotherapy or combination treatment)
Comparator	Placebo, SoC, or above interventions
Outcomes	Clinical efficacy outcomes, including but not limited to, survival, remission, response, time to progression to AML, proportion of patients with transfusion dependency, proportion of patients that were eligible for and received a transplant after treatment with the intervention Safety outcomes, including but not limited to AEs and mortality
Study design	RCTs, non-randomised interventional studies or observational studies
Publication type	Original peer reviewed research, conference abstracts published in or after 2020
Other	Any location, human subjects, English language

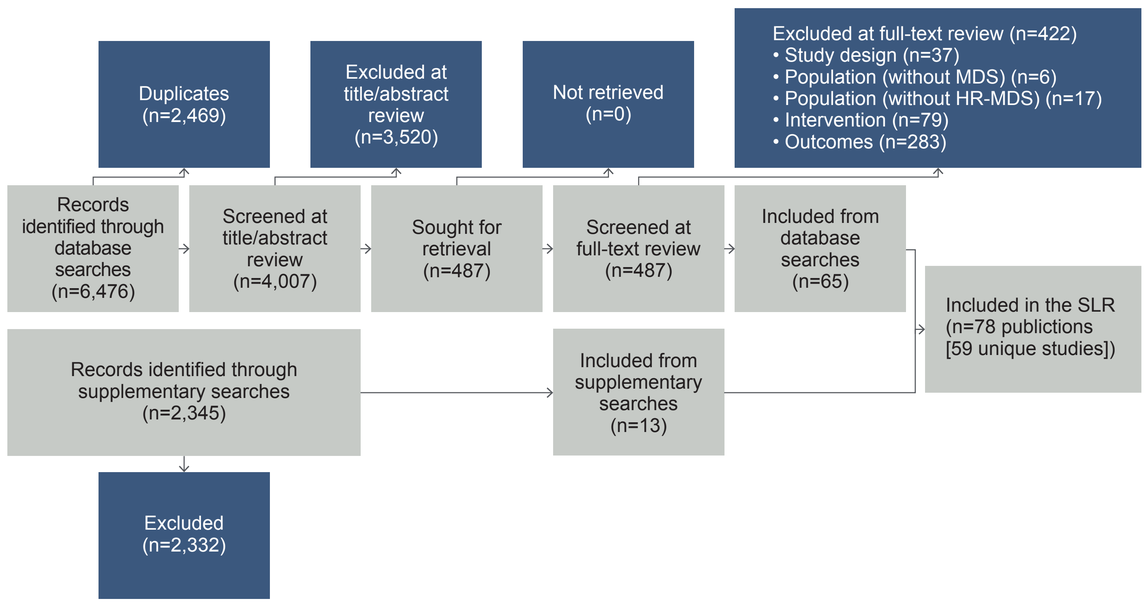
Abbreviations: AEs: adverse events; AML: acute myeloid leukaemia; BSC: best supportive care; HR-MDS: higher-risk myelodysplastic syndrome; IDH: isocitrate dehydrogenase; RCT: randomised controlled trial; SoC: standard of care.

Results

Included Studies

- Of 8,821 records retrieved, 59 unique studies were included **(Figure 1)**
- Twenty-four of the included studies exclusively enrolled patients with HR-MDS, the remaining 35 studies included patients with HR-MDS as a subgroup
- Baseline characteristics were representative of the real-world MDS population, with the greatest proportion of patients being 50–82 years old, white and male
- Most studies assessed HMA monotherapies (n=34 studies, 23 assessing azacitidine), and HMA + venetoclax (n=10 studies, 5 assessing azacitidine + venetoclax)

Figure 1. PRISMA flow diagram



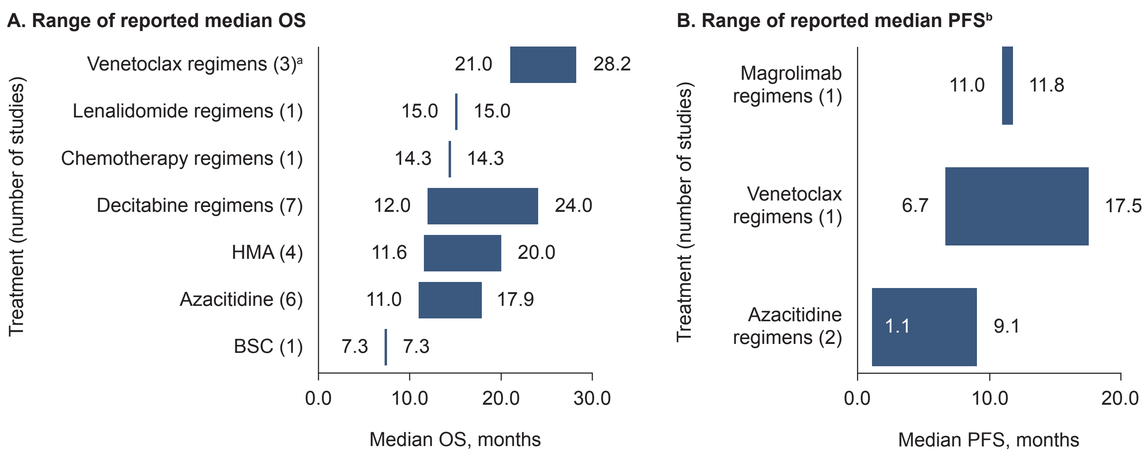
Abbreviations: (HR)-MDS: (higher-risk) myelodysplastic syndrome; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR: systematic literature review.

Results (continued)

Survival

- Median OS, reported in 17 studies, ranged from 7.3 to 28.2 months **(Figure 2A)**.[1–17] Of seven studies that performed statistical comparisons between treatment arms, the only statistically significant improvement in median OS was azacitidine compared with BSC (16.9 versus 7.3 months, p=0.039, n=1 study)[1]
- Progression-free survival (PFS), reported in four studies, ranged from 1.05 to 17.5 months **(Figure 2B)**[8,24,35–37]
- Higher risk classifications of MDS tended to have reduced OS (n=12 studies)[1–3,6,11,12,14,16,19,25,37–39]

Figure 2. Summary of reported survival outcomes

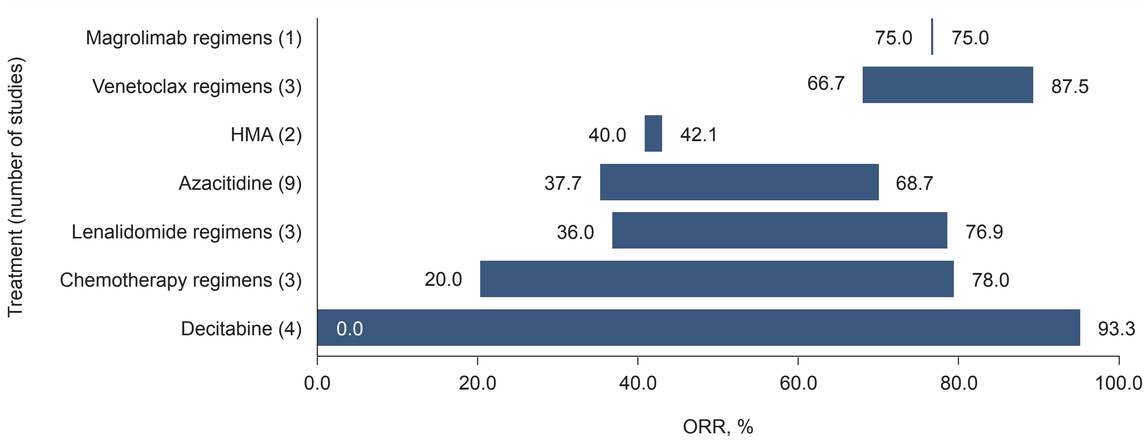


Footnote: [a]In Azizi 2020, median OS was not reached; [b]The studies reporting median PFS for patients receiving magrolimab and venetoclax regimens, and one study reporting median PFS for patients receiving azacitidine regimens, reported PFS in different subgroups of patients with HR-MDS, defined by their risk group. **Abbreviations:** BSC: best supportive care; HMA: hypomethylating agents; OS: overall survival; PFS: progression-free survival.

Response

- Objective response rate (ORR), reported in 23 studies, ranged from 0% to 93.3% **(Figure 3)**[1-11,18-29]
- Generally, combination HMA therapies tended to have the highest response rates[1-11,18-29]

Figure 3. Range of reported ORR

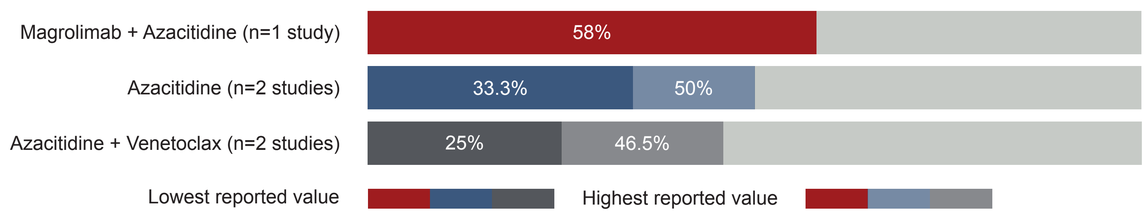


Abbreviations: HMA: hypomethylating agents; ORR: objective response rate.

Transfusion Independence

- The proportion of patients who became transfusion independent following treatment varied by treatment received (n=5 studies) **(Figure 4)**[4,40–43]

Figure 4. Range of reported transfusion independence following treatment



Progression to AML

- Median time to AML progression, reported in five studies, ranged from 2 to 19.3 months **(Table 2)**.[16,17,21,30,31] Only one study reported a statistically significant difference between treatments in time to AML progression, with decitabine delaying time to progression compared with BSC (12.0 versus 6.8 months; p=0.03)[31]

Table 2. Range of reported median time to AML progression

Treatment	Number of Studies[a]	Median Time to AML Progression (months)
Azacitidine	1	3.7–10.6
Decitabine	1	9.3–12.0
HMA	2	8.2–19.3
BSC	2	2.0–6.8

Footnote: [a]The studies reporting median time to AML progression in patients receiving azacitidine and decitabine, and one study reporting time to AML progression in patients receiving BSC, reported median time to AML progression in different subgroups of patients with HR-MDS, defined by their risk group. **Abbreviations:** AML: acute myeloid leukaemia; BSC: best supportive care; HMA: hypomethylating agents.

AEs

- TRAEs were reported by 50–100% of patients across three studies, with neutropenia (including febrile neutropenia) and thrombocytopenia being the most reported TRAEs across venetoclax regimens and azacitidine treatment[4,21,32]
- Across five studies, 0–14.4% of patients discontinued treatment as a result of AEs[8,18,21,24,26]

Strengths and limitations of the SLR

- The SLR followed guidance from the Cochrane Handbook for Systematic Reviews of Interventions to conduct an exhaustive search of the literature across a variety of sources, with steps taken to minimise selection bias and the risk of errors
- Limitations of the SLR were only reviewing publications in English and interpreting data via crude qualitative analyses, resulting in the pooling of results from populations with different baseline characteristics, including HR-MDS classification and intensity of treatment received

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Disclosures: Papadakis-Sali A, Radford M, Sabate Estrella EJ and Asukai Y are employed by Gilead Sciences Inc. Radford M and Sabate Estrella EJ own stock in Gilead Sciences, Inc. Asukai Y owns stock in Gilead Sciences, Inc, GSK and Haleon. Bobrowska A and Shaw S are consultants to Gilead Sciences, Inc.

References: References for the poster are accessible through the QR code.

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