Treatment recommendations of Polish Adult Leukemia Group (PALG) for management of myelodysplastic syndromes (MDS) and other MDS-related conditions in Poland

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Abstract

Myelodysplastic syndromes (MDS) comprise a heterogeneous group of malignant hematopoietic stem cell disorders that are characterized by ineffective blood cell production and a variable risk of transformation into acute myeloid leukemia. In recent years, significant progress in MDS biological research has allowed the addition of new drugs to the few existing therapeutic options.

This article presents the recommendations of MDS experts of the Polish Adult Leukemia Group for the treatment of myelodysplastic syndromes, and for the management of conditions that are particularly common in patients with MDS i.e. infections, iron overload, and disease recurrence after hematopoietic cell transplantation. The aim of this study was to present a clear therapeutic algorithm to facilitate decision-making in everyday practice.

Key words: myelodysplastic syndromes, treatment, recommendations
Introduction

The choice of treatment for patients with myelodysplastic syndromes (MDS) is determined by the level of risk of transformation into acute myeloid leukemia (AML), as well as by the predicted overall survival time according to the prognostic scoring systems International Prognostic Scoring System (IPSS) and Revised International Prognostic Scoring System (IPSS-R):

- the lower-risk group (MDS-LR) consists of patients with low and intermediate-1 risk according to IPSS, or very low, low, and intermediate risk with scores ≤3.5 according to IPSS-R;
- the higher-risk group (MDS-LR) consists of patients with intermediate-2 or high risk according to IPSS, or intermediate with scores ≥4.0, high, or very high risk according to IPSS-R [1, 2].

The goal of treatment in lower-risk patients is to obtain hematological improvement, and the quality of life (QoL) improvement that comes with that. Taking into account the relatively favorable prognosis, and the toxicity of therapy, aggressive treatment is not usually used in this population (Figure 1).

In higher-risk patients, depending on their general condition and the biological characteristics of the underlying disease, palliative or disease-modifying treatments (i.e. hypomethylating agents, chemotherapy) are used with the intention of prolonging survival and improving QoL or even as curative treatment [e.g. allogeneic hematopoietic stem cell transplantation (allo-HSCT)] (Figure 2).

Treatment response criteria

Treatment response is assessed according to the International Working Group (IWG) 2006 criteria, modified in 2018 for MDS-LR patients. Such responses include increases in blood cell count, reductions in the number of transfusions or transfusion independence, and reductions in bone marrow blasts percentages (Tables I and II) [3, 4].

Treatment of lower-risk patients

Blood product transfusions

Red blood cell (RBC) transfusions are given to prevent the serious complications of anemia, including heart failure and myocardial infarction. Chronic persistence of anemia, with hemoglobin (Hb) levels <9 g/dL in men and <8 g/dL in women, contributes to an increased risk of death and cardiovascular events [5, 6]. However, there is no data on the optimal time at which to start transfusions in MDS-LR patients, and the decision to transfuse RBC is based on clinical symptoms and Hb level.

Although the severity of anemia has a significant impact on the QoL of MDS patients, the Hb level at which RBC should be transfused has not been determined [7]. The only randomized study in MDS-LR patients comparing two thresholds for transfusion e.g. restrictive (8.0 g/dL, maintaining Hb level 8.5–10.0 g/dL) versus liberal (10.5 g/dL, maintaining Hb level 11.0–12.5 g/dL) favored the liberal versus the restrictive policy in relation to improvements in the five main QoL components [8].

The concept of RBC transfusion dependence (TD) is not clearly defined. The consensus is that patients who require two RBC concentrate units/month are transfusion-dependent. According to the 2018 IWG criteria, patients with red blood cell transfusion dependency (RBC-TD) are those who require a transfusion of ≥3 units/16 weeks [4]. RBC-TD is associated with shorter survival and faster transformation into AML [9]. However, an European MDS Registry (EU-MDS Registry) analysis found that even transfusion <3 units/16 weeks was associated with an increased risk of MDS progression [10]. Accordingly, it may be that we should consider all patients receiving regular transfusions as TD. Recommendations for transfusion of RBC and platelet concentrates (PC) are set out in Tables III [11–14] and IV [15–21]. Recommended platelets (PLT) level when performing invasive procedures are presented in Table V.

Erythropoiesis-stimulating agents

Erythropoiesis-stimulating agents (ESAs) are recommended as first-line treatment in MDS-LR patients with symptomatic anemia and Hb levels below 10 g/dL [2, 15]. Erythropoietin alpha has been registered in the European Union in this indication, and darbepoetin (approved only in the United States) is widely used in Poland and other European countries [22, 23]. The use of ESAs in patients with symptoms of anemia and higher Hb levels depends on individual clinician decision. Appropriate patient qualification determines the success of treatment. The validated and preferred predictive response model is the Nordic index.

The benefits of ESA treatment have been observed in patients with erythropoietin (EPO) levels below 500 U/L and a transfusion requirement of less than 2 RBC units/month (see Table VI) [24]. However, the greatest benefit is derived from starting ESA treatment before the patient becomes dependent on RBC transfusions. Initiating ESA treatment within 6 months of diagnosis improves response rates and delays the need for transfusion [25, 26].

Detailed information on the dosing and treatment regimen of ESA is provided in Figure 3. Treatment failure should only be considered after 24 weeks of ESA administration, with or without granulocyte colony-stimulating factor (G-CSF).

The response rate to ESA treatment is 38–60%, median time to response to ESA is 2–3 months, and median duration of response is 18–24 months [22–24, 27]. For non-responders,
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Figure 1. Therapeutic algorithm in patients with low-risk myelodysplastic syndromes (MDS); allo-HSCT — allogeneic hematopoietic stem cell transplantation; CsA — cyclosporine; ATG — anti-thymocyte globulin; ESA — erythropoiesis stimulating agent; G-CSF — granulocyte colony-stimulating factor; Hb — hemoglobin level; IPSS — International Prognostic Scoring System; IPSS-R — Revised International Prognostic Scoring System; MDS-LR — low-risk myelodysplastic syndrome; MDS-RS — MDS with ring sideroblasts; RBC-TD — red blood cell transfusion dependency

Increasing the ESA dose and adding G-CSF allows a response to be obtained in an additional c.20% of patients [28, 29]. Patients who achieve complete (Hb >11.5 g/dL) or partial (Hb elevation >1.5 g/dL and RBC independence but Hb <11.5 g/dL) RBC response should continue treatment at the lowest dose needed to maintain the response [24].

There is no clinical data describing the management of only a minor RBC response according to IWG 2018 (reduction in the number of RBC transfusions by half). However, it seems justified to continue treatment at the current doses or, if possible, with increased ESA doses or in combination with G-CSF.
Although the risk of thromboembolic complications in MDS patients treated with ESA is less than 2%, it seems appropriate to temporarily discontinue treatment if a rapid increase in hematocrit is observed, or if Hb level increases above 12 g/dL [22, 23, 30]. ESA can be re-started in a reduced dose, and responses should be carefully monitored [15].

The Polish Adult Leukemia Group (PALG) MDS working group’s indications for the treatment of ESA ± G-CSF are as follows in MDS LR group according to IPSS with:

■ symptomatic anemia (regardless of RBC-TD although it is optimal to start treatment before RBC transfusion demand is ≥2 units/month) and

■ EPO level <500 U/L

In non-responding patients or after loss of response to ESA some efficacy is shown by: lenalidomide, immunosuppressants, hypomethylating agents (HMA), luspatercept, and allogeneic hematopoietic stem cell transplantation (allo-HSCT) in selected cases.

**Thrombopoietin receptor agonists**

Thrombopoietin receptor agonists (TPO-RAs), romiplostim and eltrombopag are not approved for the treatment of thrombocytopenia in MDS-LR patients. Romiplostim at a dose of 500 to 1,500 µg weekly has increased platelet count in 36–65% of patients [31–33]. Eltrombopag at a dose of 150–300 mg/day has increased platelet count in 47% of MDS LR patients [34]. The use of both drugs allows for a significant reduction in the frequency of bleeding complications, and a reduction in the number of platelet transfusions. Some concerns have been raised by the impact of TPO-RA on the increased risk of transformation into AML. A transient increase in blasts percentage that resolves after drug discontinuation has been observed in 15% of patients, and a long-term follow-up did not confirm a higher transformation risk or increased mortality in patients receiving romiplostim [35]. The efficacy and safety of TPO-RA has not been confirmed in phase III studies, and therefore these drugs should be used with caution in clinical trials in patients with a blast percentage below 5%.

No phase III study has been conducted so far that would confirm the efficacy and safety of TPO-RA, and these drugs have not been approved for the treatment of patients with myelodysplastic syndromes in either the United States or Europe. Therefore they are not recommended by Polish experts in routine clinical practice.

It is worth noting however that TPO-RA may be a valuable therapeutic option in MDS-LR patients with severe...
Table I. 2006 International Working Group (IWG) myelodysplastic syndrome (MDS) response criteria (based on [3])

<table>
<thead>
<tr>
<th>Category</th>
<th>Response criterion (must last at least 4 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission (CR)</td>
<td>Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines</td>
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<tr>
<td></td>
<td>Persistent dysplasia permissible</td>
</tr>
<tr>
<td>Partial remission (PR)</td>
<td>Hb: ≥11 g/dL, platelets: ≥100 G/L, neutrophils: ≥1.0 G/L, blasts: 0%</td>
</tr>
<tr>
<td>Marrow complete remission (mCR)</td>
<td>All CR criteria if abnormal before treatment, except bone marrow blasts decreased by ≥50% over pretreatment but still &gt;5%</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>Bone marrow: ≤5% myeloblasts and decreased by ≥50% over pretreatment regardless of peripheral blood response</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>Failure to achieve CR and PR, but no evidence of progression for &gt;8 weeks</td>
</tr>
<tr>
<td></td>
<td>For patients with:</td>
</tr>
<tr>
<td></td>
<td>• less than 5% blasts: 50% increase in blasts to 5% blasts</td>
</tr>
<tr>
<td></td>
<td>• 5–10% blasts: 50% increase to 10% blasts</td>
</tr>
<tr>
<td></td>
<td>• 10–20% blasts: 50% increase to 20% blasts</td>
</tr>
<tr>
<td></td>
<td>• 20–30% blasts: 50% increase to 30% blasts</td>
</tr>
<tr>
<td></td>
<td>Any of the following:</td>
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<tr>
<td></td>
<td>• at least 50% decrement from maximum remission/response in granulocytes or platelets</td>
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<tr>
<td></td>
<td>• reduction in Hb by 2 g/dL</td>
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<td></td>
<td>• transfusion dependence</td>
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<tr>
<td>Relapse after CR or PR</td>
<td>At least one of the following:</td>
</tr>
<tr>
<td></td>
<td>Return to pretreatment bone marrow blast percentage</td>
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<tr>
<td></td>
<td>Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets</td>
</tr>
<tr>
<td></td>
<td>Reduction in Hb concentration by ≥1.5 g/dL or transfusion dependence</td>
</tr>
<tr>
<td>Hematological improvement (HI)</td>
<td>Response criteria (responses must last at least 8 weeks):</td>
</tr>
<tr>
<td>Erythroid response (HI-E)</td>
<td>• Hb increase by ≥1.5 g/dL</td>
</tr>
<tr>
<td>(pretreatment, &lt;11 g/dL)</td>
<td>• relevant reduction of units of RBC transfusions by ≥4 RBC transfusions/8 weeks</td>
</tr>
<tr>
<td>Platelet response (HI-PLT)</td>
<td>• absolute increase of ≥30 G/L for patients starting with &lt;20 G/L platelets</td>
</tr>
<tr>
<td>(pretreatment PLT &lt; 100 G/L)</td>
<td>• increase from &lt;20 G/L to ≥20 G/L and by at least 100%</td>
</tr>
<tr>
<td>Neutrophil response (HI-G)</td>
<td>• at least 100% increase and an absolute increase &gt;0.5 G/L</td>
</tr>
</tbody>
</table>

Hb — hemoglobin level; RBC — red blood cells

Table II. Revised International Working Group (IWG) 2018 hematological response criteria in patients with myelodysplastic syndrome (MDS) (based on [4])

<table>
<thead>
<tr>
<th>Line</th>
<th>Pretreatment criteria</th>
<th>Response criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI-E</td>
<td>NTD = (0 RBC in 16 weeks) [1] Transfusion independent anemia:</td>
<td>Hi-E response:&lt;br&gt; at least 2 consecutive Hb measurements with increase of ≥1.5 g/dL for minimum of 8 weeks in observation period of 16–24 weeks&lt;br&gt; Hi-E response:&lt;br&gt; TRSFN independence for minimum of 8 weeks in an observation period of 16–24 weeks&lt;br&gt; Major Hi-E response:&lt;br&gt; TRSFN independent over a period of a minimum of 8 weeks in an observation period of 16–24 weeks&lt;br&gt; Minor Hi-E:&lt;br&gt; reduction by at least 50% of RBC over a minimum of 16 weeks&lt;br&gt; Absolute increase of ≥30 G/L&lt;br&gt; Increase to &gt;20 G/L and by at least 100%&lt;br&gt; At least 100% increase and absolute increase &gt;0.5 G/L</td>
</tr>
<tr>
<td></td>
<td>LTB:&lt;br&gt; 0 RBC in 16 weeks</td>
<td></td>
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<tr>
<td></td>
<td>3–7 RBC in 16 weeks in at least 2 TRSFN episodes&lt;br&gt; max 3 in 8 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HTB:&lt;br&gt; ≥8 RBC in 16 weeks&lt;br&gt; ≥4 in 8 weeks</td>
<td></td>
</tr>
<tr>
<td>Platelet response</td>
<td>20 G/L &lt; PLT &lt; 100 G/L&lt;br&gt; 0 &lt; PLT &lt; 20 G/L</td>
<td>Absolute increase of ≥30 G/L&lt;br&gt; Increase to &gt;20 G/L and by at least 100%</td>
</tr>
<tr>
<td>Neutrophil response</td>
<td>NEU &lt; 1.0 G/L</td>
<td>At least 100% increase and absolute increase &gt;0.5 G/L</td>
</tr>
</tbody>
</table>

Hb — hemoglobin level; HI-E — hematological improvement-erythroid response; HTB — high transfusion burden; LTB — low transfusion burden; NEU — neutrophils; NTD — not transfusion dependent; PLT — platelet count; RBC — red blood cells; TRSFN — transfusion
Table III. Recommendations for red blood cell (RBC) transfusion in patients with low-risk myelodysplastic syndrome (MDS-LR) (based on [11–14])

Hb threshold for RBC transfusion should be individualized depending on:
• comorbidities
• symptoms at a given Hb level
• observed clinical benefits after previous transfusions
• patient preferences

No specific Hb level can be recommended as a threshold for RBC transfusion. But in asymptomatic patients with chronic anemia, Hb transfusion should be considered when Hb level is <8 g/dL.

No single target Hb level can be recommended, but it should be taken into account that chronic anemia with Hb <8–9 g/dL significantly increases risk of cardiovascular disease and death.

No limit on frequency or total number of units transfused lifelong into MDS patient.

Frequency of transfusions should reflect duration of clinical benefit between transfusions.

Routine RBC phenotypic selection is not recommended for all MDS patients treated with transfusions, but may be considered for patients with little improvement after RBC transfusions.

Multiple recipients should be transfused with leukocyte-depleted preparations.

Table IV. Recommendations for platelets (PLT) transfusion in patients with low-risk myelodysplastic syndrome (MDS-LR) (based on [15–21])

Prophylactic PLT transfusion is not recommended in asymptomatic patients not receiving MDS modifying therapy.

Preventive PLT transfusions (routinely transfuse only one PLT package (1 unit/10 kg bw):
• in patients receiving intensive chemotherapy/hypomethylating drugs or undergoing allo-HSCT to maintain PLT levels ≥10 G/L, even without clinically significant bleeding (grade 0–1 and not requiring invasive procedures)
• in patients in serious condition/seriously ill, even if there is no active bleeding or no invasive procedure planned
• individual assessment of patients with chronic bleeding of WHO grade ≥2 according to symptoms severity and establishing strategies for prophylactic PLT transfusions, e.g. twice a week

In patients with bleeding, use of anti-fibrinolytic agents such as tranexamic acid should be considered [21].

Table V. Recommended platelets (PLT) level when performing invasive procedures [17–20]

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Recommended PLT level [G/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placement of central catheters:</td>
<td>&gt;20–30</td>
</tr>
<tr>
<td>• tunneled</td>
<td></td>
</tr>
<tr>
<td>• non-tunneled</td>
<td></td>
</tr>
<tr>
<td>Major surgery</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>≥40</td>
</tr>
<tr>
<td>Epidural catheter insertion/removal</td>
<td>≥80</td>
</tr>
<tr>
<td>Percutaneous liver biopsy</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Ophthalmic surgery for posterior segment of eye</td>
<td></td>
</tr>
</tbody>
</table>

Table VI. Predictive model of response to erythropoiesis-stimulating agents (ESA) treatments

<table>
<thead>
<tr>
<th>Need for transfusions, point</th>
<th>EPO level [IU/L], point</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 RBC unit/month, 0</td>
<td>&lt;500, 0</td>
</tr>
<tr>
<td>≥2 RBC unit/month, 1</td>
<td>≥500, 1</td>
</tr>
</tbody>
</table>

Anticipated response to ESA treatment:
• score 0 = 74%, score 1 = 23%, score 2 = 7%

Granulocyte colony-stimulating factors

Neutropenia occurs in 15–20% of MDS-LR patients [36]. Although the use of G-CSFs increases the number of neutrophils in 60–75% of patients with neutropenia, chronic use of G-CSF is not recommended because it does not prolong survival in these patients. In addition, the possibility of transformation into AML, or progression to more advanced MDS, in patients treated with G-CSF has not been absolutely ruled out [37, 38]. G-CSFs are currently recommended in MDS LR patients with dominant neutropenia, but only with recurrent or severe infections [2, 39].

Lenalidomide

Lenalidomide at a dose of 10 mg for 21 days in 28-day cycles is recommended in MDS-LR patients with del5(q) who have lost a response or who are not candidates for ESA treatment [4, 5]. Erythroid response is achieved after 4–5 weeks in 61–76% of patients, RBC independence in 56–67% of patients, and 50–73% of patients achieve a cytogenetic response, including 29–45% of complete responses [40, 41]. Median overall survival in lenalidomide-treated patients is 3.5–4 years, and 5.7 years in patients who achieved transfusion independence.
Figure 3. Algorithm of treatment with erythropoiesis stimulating proteins in patients with myelodysplastic syndromes (MDS); CBC — complete blood count; DAR — darbepoetin; EPO — erythropoietin; Fe — ferrum; G-CSF — granulocyte colony-stimulating factor; GFR — glomerular filtration rate; Hb — hemoglobin level; HI-E according to IWG 2018 — hematological improvement-erythroid response according to revised International Working Group (IWG) 2018 hematological response criteria; MDS-LR — low-risk myelodysplastic syndrome; MLD — multilineage dysplasia; N — normal level; PER — partial erythroid response; RS — ring sideroblasts; sEPO — serum erythropoietin; SLD — single lineage dysplasia; TIBC — total iron binding capacity; WBC — white blood cells

Before treatment:
- CBC
- creatinine/GFR
- sEPO before transfusion
- ferritin
- Fe/TIBC
- blood pressure

MDS-LR (SLD, MLD, MDS 5q)
- EPO 30,000–40,000 IU/week
- or 
- DAR 150–300 μg/14 days or 500 μg/3 weeks

Response assessment after 8 weeks

Complete erythroid response (CER):
- Hb ≥11.5 g/dL
- transfusion independency

Maintenance dose of EPO 30,000 IU/L/week
- DAR 300 μg/1–3 weeks or 500 μg/3 weeks

Partial erythroid response (PER):
- Hb level increase of 1.5 g/dL
- transfusion independency

Maintenance treatment with EPO/DAR in previous dose until response persists

No response (at least PER) or no HI E acc. to IWG 2018

MDS-LR (RS-SLD, RS-MLD)
- EPO 30,000–40,000 IU/week
- or 
- DAR 150–300 μg/14 days or 500 μg/3 weeks

±
- G-CSF 1–2 μg/kg/2–3 × per week (300 μg)
- (WBC 6–10 G/L) up to max dose 3 × 300 μg/week

No response (at least PER) after next 8 weeks

MDS-LR (SLD, MLD, MDS 5q)
- EPO 60,000–80,000 IU/week
- Aranesp 300–500 μg/2 weeks

±
- G-CSF 1–2 μg/kg/2–3 × per week (300 μg)
- (WBC 6–10 G/L) up to max dose 3 × 300 μg/week

No response (at least PER) after next 8 weeks or HI E according to IWG 2018

MDS-LR (RS-SLD, RS-MLD)
- Therapy discontinuation

The most common side effects of lenalidomide are neutropenia (75%) and thrombocytopenia (40%), with 70% of patients requiring drug discontinuation in the first month of treatment and subsequent dose reduction to 5 mg when restarted [42]. In recurrent neutropenia, 1–2 injections of G-CSF weekly should be considered. In cases of renal failure, the dose of lenalidomide should be reduced to a minimum of 2.5 mg every other day. Due to the increased risk of thromboembolic events with lenalidomide, it is reasonable to use anticoagulation prophylaxis, especially when additional risk factors are present.

In Poland, lenalidomide is reimbursed only in patients with an isolated del5(q) and RBC dependence, although the National Comprehensive Cancer Network (NCCN) recommends the use of lenalidomide before the need for transfusion and in patients with an isolated chromosome
5 deletion. According to the European LeukemiaNet (ELN) guidelines, patients may have an additional cytogenetic aberration except chromosome 7 disorder or deletion 17. The TP53 gene mutation is found in c.20% of MDS patients with del5q and is a negative prognostic and predictive factor for response to lenalidomide, although the chance of RBC independence is comparable to that in patients without TP53 gene mutation.

In patients without del5(q) and transfusion dependence treated with lenalidomide, hematological improvement (HI-E) is achieved in 43% of patients, and RBC independence in 27% of patients, with a response duration of 8 months [43]. Treatment with lenalidomide in combination with ESA does not significantly alter treatment outcomes: HI-E is achieved by 39% of patients, and RBC independence in 24% of patients with a response duration of 15 months [44]. Lenalidomide is not approved for the treatment of anemia in patients without del(5q), and its use is associated with the possibility of developing or worsening of neutropenia and thrombocytopenia.

Indications for lenalidomide treatment (all criteria must be met):
- low-risk or intermediate-low-risk MDS according to IPSS;
- isolated del5 (+ possibly an additional abnormality except chromosome 7 disorder or del 17);
- symptomatic anemia and RBC independence (Hb 8–10 g/dL): dose of 5 mg or patients with RBC-TD: dose of 10 mg.

**Luspatercept**

Luspatercept was registered in 2020 in the European Union (EU) based on MEDALIST, a randomized phase III trial for the treatment of patients with (myelodysplastic syndrome with ring sideroblasts) MDS-RS subtype with RBC-TD who failed or were not eligible for ESA treatment. Luspatercept, a transforming growth factor beta (TGF-β) receptor inhibitor, unblocks the proper erythroblasts for response to lenalidomide, although the chance of RBC independence is comparable to that in patients without TP53 gene mutation.

**Immunosuppressive treatment**

Immunosuppressive therapy (IST) can be used in MDS-LR patients with symptomatic cytopenia, with thrombocytopenia or neutropenia even in the first line [37], and in the case of anemia only after the failure of first and/or second line treatment. Although hypocellular bone marrow, the presence of HLA-DR 15, age less than 60 years, normal karyotype or trisomy 8, the presence of paroxysmal nocturnal hemoglobinuria (PNH) clone, and short RBC dependence duration are often considered to be predictors of a favorable response to IST, a study by Sloand et al. [47], and Stahl et al. [48] showed that none of these factors had predictive value for achieving ed blood cell transfusion dependency (RBC-TD), except for hypocellular bone marrow <20%.

Anti-thymocyte globulin (ATG) with or without cyclosporin is used for IST; horse ATG (h-ATG) is more effective, but it is only available in the United States [49]. A meta-analysis of trials with IST in MDS-LR patients showed 42% of responses and 33% of RBC independence. In the elderly, cyclosporine can be used as monotherapy, and the chances of achieving overall response (OR), HI-E, and transfusion independence (TI) are 47%, 50%, and 45%, respectively [48].

**Other agents**

HMA are not approved in the EU for use in MDS-LR patients, although 20–30% of ESA and/or lenalidomide failures achieve response [50, 51]. In patients with MDS LR, the use of 5-day treatment regimens allows for comparable efficacy as the 7-day courses, and with less toxicity [52]. Patients who have failed treatment with ESA and/or lenalidomide should be offered available clinical trials with new drugs whenever possible.

**Iron chelating agents**

Iron overload resulting from RBC transfusions (1 unit contains 200–250 mg of iron), and significant hyperferritinemia associated with e.g., ineffective iron metabolism, adversely affect overall survival in MDS patients [53–55]. Ferritin levels should be measured in MDS-LR patients every 12 weeks [15]. Chelation therapy should be started after an infusion of 20–25 units of RBC concentrate or when ferritin levels exceed 1,000 μg/L with the proviso that the patient’s non-MDS-related life expectancy exceeds 3 years, and always in HSCT candidates with iron overload regardless of IPSS risk score [56–58].

Deferoxamine is used at a dose of 30–40 mg/kg/day in infusions lasting many hours (e.g. 10–12 h) (subcutaneously or intravenously), at least 5 days a week, until the ferritin level drops below 1,000 μg/L. Deferasirox at a dose of 20–30 mg/kg can be used to obtain a ferritin concentration below 500 μg/L, but this drug is not reimbursed in Poland in adult patients.
In the prospective, randomized TELESTO [Myelodysplastic Syndromes (MDS) Event Free Survival With Iron Chelation Therapy] study, oral deferasirox (20–30 mg/kg) prolonged (2:1) the time to onset of hepatic and heart failure compared to a placebo [59]. Phlebotomy should be considered in patients after allogeneic hematopoietic cell transplantation who are still iron overloaded and no longer anemic. The Polish experts recommend the use of iron chelators in patients with MDS with low or intermediate-1 risk score according to IPSS and:
- with serum ferritin level >1,000 µg/L and/or
- who received over 25 units of RBC concentrate;
- with two patient-related factors (not related to MDS) that could shorten survival to less than 3 years.

Treatment of higher risk MDS patients

Chemotherapy (intensive and low-dose)

Anthracyclines and cytarabine-based intensive chemotherapy (IC) in high-risk myelodysplastic syndrome (MDS-HR) patients has limited indications due to low efficacy and high toxicity. The complete remission (CR) rate is 36–60%, and is particularly low in patients with unfavorable prognostic karyotype. The duration of remission is short (10–12 months), and prolonged periods of aplasia are more common than in AML patients [60, 61].

Low doses of cytarabine, e.g. 20 mg/m²/day for 14–21 days in 4-week cycles, make it possible to achieve CR/partial remission (PR) in 15–20% of patients, although their use is associated with a shorter overall survival compared to HMA, and therefore this treatment regimen is not recommended.

Intensive chemotherapy is recommended in patients:
- with MDS-HR (>10% bone marrow blasts) without severe comorbidities, up to 65–69 years without unfavorable prognostic cytogenetics according to IPSS and IPSS-R and/or TP53 mutations/deletions
- and who
- are candidates for allo-HSCT (for remission).

The use of IC in patients who do not have a donor, or do not agree to allo-HSCT, is debatable.

Hypomethylating agents

Patients at higher risk according to IPSS who are not eligible for allo-HSCT are candidates for azacitidine treatment according to the Summary of Product Characteristics (SmPC). It should be noted however that some patients qualified for an allo-HSCT procedure may benefit from azacitidine as first-line treatment. According to the SmPC, the use of azacitidine in this group of patients is possible because at the time of commencing this drug the patient may not be eligible for allo-HSCT due to high MDS activity, and after several treatment cycles remission could be achieved, allowing for the transplantation. The dose of azacitidine is 75 mg/m² administered subcutaneously for 7 days on/21 days off (28-day cycle). For organizational reasons, the drug can be administered within a 5-day schedule with a 2-day break (weekend) and then two consecutive days of drug administration (i.e. 5 + 2 + 2). The treatment results are similar to those of the 7-day regimen.

In patients treated with azacytidine, CR rate is 17%, PR rate 12%, and hematological improvement (HI) including possible CR and PR is 49%.

The median time to response is four treatment cycles, so it is important that the patient is able to receive at least three; 24–37% of patients receive up to three [62]. The response duration is 9–15 months, but much shorter (4 months) in patients with complex karyotype [63]. Patients who have achieved CR, PR, or hematological response (e.g. RBC, PLT transfusion independence) should receive the drug until disease progression or unacceptable toxicity. Discontinuation of azacitidine treatment leads to rapid progression.

The most common adverse reactions are grade 3–4 peripheral cytopenias: neutropenia (84%), thrombocytopenia (74%), anemia (54%), and grade 3–4 infections (30–60%). It is worth noting that, if possible, doses/intervals should not be modified due to hematological toxicity during the first three treatment cycles.

Decitace increases progression-free survival (PFS) but does not extend overall survival compared to best supportive care (BSC), so is not approved in the EU.

The prognosis of patients after the failure of azacitidine treatment is poor, with median survival of c.6 months. Indications for treatment with azacitidine:
- intermediate-2 and high-risk myelodysplastic syndromes according to the IPSS in patients not eligible for IC;
- chronic myelomonocytic leukemia (CMML) with 10–29% bone marrow blasts without myeloproliferative disorder (WBC <13 G/L), in patients not eligible for IC;
- acute myeloid leukemia with 20–30% blasts with multi-lineage dysplasia, according to World Health Organization (WHO) classification, in patients not eligible for IC;
- AML with >30% bone marrow blasts according to WHO classification, in patients not eligible for IC;
- bridging therapy in selected patients prior to allo-HSCT (in patients with unfavorable karyotype or aged >65);
- higher-risk patients who have undergone allo-HSCT as relapse treatment, pre-treatment, or maintenance treatment.
Allogeneic hematopoietic stem cells transplantation in treatment of MDS

Despite the undoubted progress in the treatment of patients with MDS in recent years, allo-HSCT remains the only potentially curative method [64]. Patient-related and disease-related factors should be taken into account in the decision-making process of qualifying an MDS patient for allo-HSCT [56, 64–66]. Patient-related factors include: age, performance status according to Karnofsky performance scale (KPS), comorbidities (according to the augmented HCT-CI scale), psychosocial status, and patient preferences. The mean age of developing MDS is c.70, so it is particularly important to consider the qualification of some patients >65 years to allo-HSCT. Currently, it is believed that the chronological age (previously accepted upper age limit 65–75) is slightly less important than the biological age [assessment based, among others, on Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI), KPS, geriatric scales] [67].

‘Fit’ patients, i.e., those in whom an allo-HSCT procedure can be performed, are defined by the following parameters: KPS ≥70–80 and HCT-CI ≤3 (ELN 2020) [56].

High-risk patients with bone marrow blasts <10% and no medical contraindications for transplantation should be eligible for allo-HSCT as first-line therapy provided they have an available donor. Best long-term results were achieved when pre-transplant blasts <5%. Conversely, when bone marrow blasts are 10% or greater, the patient should receive cytoreduction therapy prior to transplantation. The clinical outcomes of the use of azacitidine or intensive chemotherapy as cytoreduction are comparable [68].

Hematopoietic stem cells transplantation is a potential option for ‘fit’ patients from the higher risk group according to IPSS or IPSS-R, and in lower risk (IPSS) or moderate/low risk (IPSS-R) patients with:

- unfavorable cytogenetic disorders;
- a 50% increase in blasts or bone marrow blasts >15%;
- life-threatening cytopenias defined as:
  - absolute neutrophil count (ANC) <0.3 G/L,
  - PLT <30 G/L,
  - RBC-TD of at least 2 units/month for 6 months.

The long-term outcome of allo-HSCT in MDS patients and the peri-transplant risk have been assessed in several prognostic indices, among which the predictive model by Della Porta et al. (based on age, HCT-CI, karyotype, IPSS-R and response to induction chemotherapy) and the so-called European Group for Blood and Marrow Transplantation (EBMT) transplant-specific risk score for MDS, are the most widely used [65, 69].

When qualifying an MDS patient for a transplant procedure, the optimal preparation method should be considered, i.e. conditioning. The choice of myeloablative conditioning (MAC) versus reduced intensity conditioning (RIC) depends primarily on the patient’s age and the presence of comorbidities. In the randomized, multicenter EBMT clinical trial, the results of RIC versus MAC use were comparable, with 2-year survival rates of 76.3% and 63.2%, respectively [70]. In this study, patients >60 years accounted for only 4%. The decision to select specific conditioning regimens is generally based on site preferences and experience [70–73]. In recent years, a fludarabine/treosulfan regimen with relatively low toxicity has been successfully used. In Wedge et al.’s study [74], 3-year overall survival rate after fludarabine/treosulfan-based conditioning was 71%. In the group receiving the standard MAC regimen [total body irradiation (TBI)/cyclophosphamide or busulfan/cyclophosphamide] it was 52.8%, and in the group receiving RIC it was 62% (p = 0.075) [74].

Today, for the vast majority of patients, it is possible to match a donor of hematopoietic cells: the first choice is a related donor fully matched with human leukocyte antigen (HLA) antigens, the second choice is a fully matched or other acceptable unrelated donor, and the next best is a haploidentical donor.

Azacitidine in patients after allo-HSCT

The most common cause of allo-HSCT failure in patients with MDS and AML is disease relapse (30–70% of patients) [75]. Survival rate in patients with relapse after allo-HSCT is low, e.g. 2-year survival rate below 10–20%.

Recent reports indicate that in a selected population of MDS patients with relapse after transplantation, the treatment strategy may be even more important for overall survival than pre-transplant cytoreduction [76].

Due to the genetic heterogeneity of AML/MDS and the risk of clonal evolution after transplantation, it is helpful to simultaneously use several assessment methods for remission monitoring. Standard recommendations regarding optimal minimal residual disease (MRD) measurement intervals after transplantation have not yet been established.

The following are relapse definitions [77–81]:

- cytometric, according to ELN AML 2017, is defined at MRD cut-off level >0.1%;
- molecular: an increase in MRD level of ≥1 log10 between 2 positive samples in a previously negative patient;
- hematological relapse of MDS after alloHSC: bone marrow blasts 5–20% and/or reappearance of myelodysplastic features associated with cytopenia or autologous regeneration in chimerism testing;
- hematological relapse of MDS with progression to AML: bone marrow blasts exceeding 20%;
- hematological relapse of AML after allo-HSC: bone marrow blasts equal to or greater than 5%, peripheral blood blasts or extramedullary leukemia.

Complete chimerism (CC) and mixed chimerism (MC) means >95% and ≤95, respectively, of donor cells in the selected fraction of tested cells [82]. Currently, the most
commonly used treatments of MDS/AML relapse after allo-HSCT are hypomethylating agents, especially azacitidine, often in combination with donor lymphocyte infusions (DLI). The principles of maintenance treatment, pre-treatment and relapse treatment are summarized in Table VII [83–92].

### Hypoplastic myelodysplastic syndromes

Decreased bone marrow cellularity is found in 10–20% of MDS patients, and this is the basis for the diagnosis of the hypoplastic form of this disease [hypoplastic MDS (h-MDS)]. To date, no precise definition of h-MDS has been developed, but the usual borderline value is bone marrow cellularity below 20–30%. According to the WHO classification, h-MDS is not a separate subtype of myelodysplastic syndrome. Patients with h-MDS are younger, with less severe anemia, but with deeper neutropenia and thrombocytopenia compared to patients with normo-/hypercellular bone marrow. The distribution of particular prognostic groups according to IPSS does not differ depending on the marrow cellularity. The clinical course of this disease is characterized by greater effectiveness of immunosuppressive treatment and a better prognosis compared to typical MDS.

Primarily, aplastic anemia (AA) should be considered in the differential diagnosis [93, 94].

### Myelodysplastic syndrome with bone marrow fibrosis

According to the WHO 2016 classification, myelodysplastic syndrome with bone marrow fibrosis (MDS-F) is not a separate subtype of MDS, although a provisional subtype has
been distinguished: myelodysplastic syndromes with excess of blasts and fibrosis, known as MDS-EB-F or MDS-F [95]. Most patients with MDS-F have an increased percentage of bone marrow blasts. Unlike primary myelofibrosis, patients with MDS-F usually do not have splenomegaly or leukoerythroblastosis. MDS-F includes patients with grade 2 or more fibrosis (10–15% of MDS).

The presence of advanced fibrosis worsens the prognosis, increases mortality [96] and shortens the time to transformation into AML [97]. Due to the difficulties in obtaining a reliable bone marrow for cytological examination, trephine biopsy is a valuable supplementary test in assessing the percentage of blasts. It has been shown that in MDS-F, grade 3 fibrosis correlates with an increased percentage of blasts, increased lactate dehydrogenase (LDH) activity, lower number of platelets, greater RBC dependence, multilinear dysplasia, complex karyotype, and the presence of molecular disorders (in TP53, SETBP1 genes). JAK2 gene mutation has not been found to be more frequent, which may help differential diagnosis.

Advanced fibrosis (BMF 3) has been shown not to worsen the response to hypomethylating agents and lenalidomide, but it has not yet been established whether their use in low-risk groups reduces fibrosis [96].

Fibrosis worsens transplantation outcomes by delaying cell reconstitution and increasing the risk of graft failure. The probability of 3-year overall survival in MDS patients with stage 3 fibrosis is only 21%, compared to 40–49% in patients with grade 0–2 fibrosis. Fibrosis does not influence the risk and course of graft-versus-host disease (GvHD) [98].

Therapy-related myelodysplastic syndromes

Therapy-related myelodysplastic syndromes (t-MDS) are a group of diseases that are a late complication after chemo- and/or radiotherapy used in the treatment of neoplastic and non-neoplastic diseases [95]. t-MDS accounts for c.10–20% of all myelodysplastic syndromes [99]. Among neoplastic diseases, 70% of newly diagnosed t-MDS are preceded by therapy of solid tumors, and 30% by treatment of hematological malignancies [95]. The incidence of t-MDS after treatment with conventional chemotherapy is 0.8–6.3% over 20 years, and after high-dose chemotherapy with autologous hematopoietic stem cell transplantation (auto-HSCT) is 1.1–24.3% over 5 years [100]. The prognosis in patients with t-MDS is worse than in patients with pMDS, with overall survival of 5–34 months [101].

Therapy of t-MDS includes hypomethylating agents, conventional chemotherapy, adjuvant therapy, and allo-HSCT, which remains the only potentially curative form of therapy [102].

Prevention and treatment of infections in myelodysplastic syndromes

The risk of infections in MDS patients is the result of immune disorders occurring in the course of disease, general condition, comorbidities and treatment complications [103–106]. Infectious complications account for 30–38% of all death causes [107].

The most common infectious complications in the course of MDS are febrile neutropenia (36–47%), pneumonia (21–50%) and sepsis (14%) [108, 109]. The most common is bacterial etiology, accounting for 80% of infections (caused by both Gram-positive and Gram-negative bacteria), but they are usually diagnosed clinically, and microbiological confirmation is achieved only in c.30% of patients.

In recent years, attention has turned to the increased incidence of invasive mycoses, including mucormycosis, in this group of patients. Viral infections [except for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] are rare in conventionally treated patients, although influenza can have a severe course in patients with myelodysplastic syndromes.

The risk of infection depends on the severity of the underlying disease; in MDS-LR patients treated with azacitidine, the risk of grade 3–4 infections is c.9.5–26% and is significantly lower than in MDS-HR patients (43–71%) [110, 111]. Infections most often occur within the first three treatment cycles of azacitidine (66% of all infections).

Based on a retrospective analysis of 298 patients performed by the PALG MDS Working Group, a model of infection risk in patients treated with azacitidine has been developed with the following risk factors identified: RBC-TD, neutropenia <0.8 G/L, thrombocytopenia <50 G/L, hypoalbuminemia <3.5 g/dL, and Eastern Co-operative Oncology Group Performance Status (ECOG PS) ≥2.

Patients with three, four, or all five of the abovementioned factors had a significantly higher risk of infection (73%) compared to patients with 0–2 risk factors (25%) [108]. In this study, mortality in patients with sepsis, pneumonia, and febrile neutropenia was 45%, 26%, and 15%, respectively. Based on preliminary data, SARS-CoV-2 infection in MDS patients is associated with a very high risk of death, reaching 42–47% [112].

Although there is no clear indication for pharmacological prophylaxis in all patients treated with azacitidine, it should be considered in specific risk groups [113]. The efficacy of fluoroquinolone-based antibacterial prophylaxis has been confirmed in patients treated with decitine [114]. It remains unclear which antifungal agents should be used in this group of patients, and in particular whether to use azoles with proven efficacy against molds [115]. Recommendations regarding the prevention of infection in MDS patients for whom treatment is planned are set out in Table VIII.
New agents in myelodysplastic syndrome treatment

In recent years, many clinical trials with the use of new molecules have been conducted in patients with myelodysplastic syndromes. After many years without new effective drugs, the latest results of phase II and III studies are generating optimism regarding the addition of new agents to what is still a relatively modest armamentarium (Table IX).

Authors’ contributions
Conception and design: KM, JDT. Manuscript writing, final approval of the manuscript: all authors.

Conflict of interest
None.

Financial support
None.

Ethics
The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to Biomedical journals.

Table VIII. Recommendations for infection prophylaxis in myelodysplastic syndrome (MDS) patients with planned treatment

<table>
<thead>
<tr>
<th>Infection type</th>
<th>Diagnostic tests</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B, C</td>
<td>HBsAg, anti-HCV</td>
<td>HBsAg, anti-HCV</td>
</tr>
<tr>
<td>HIV</td>
<td>Anti-HBc, (HBV DNA), anti-HBsAg, (HCV RNA)</td>
<td>— optionally</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>HIV combi</td>
<td>— optionally</td>
</tr>
<tr>
<td>Colonization with MRB</td>
<td>IGRA, tuberculin test — optional</td>
<td>— optional</td>
</tr>
<tr>
<td>(ESBL, VRE, MBL)</td>
<td>Outpatient — no</td>
<td>— optional</td>
</tr>
<tr>
<td>Invasive mycoses</td>
<td>Hospitalized — yes (rectal swab with culture)</td>
<td>Only in patients treated with IC-posaconazole</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Galactomannan antigen</td>
<td>In patients undergoing allo-HSCT: same procedure as in other transplant patients</td>
</tr>
<tr>
<td>Immunization</td>
<td></td>
<td>Primary: only at high risk Secondary: quinolones</td>
</tr>
<tr>
<td>HSV, CMV, EBV, parvovirus B19</td>
<td>Routinely not</td>
<td>G-CSF: to be considered only when infection with neutropenia</td>
</tr>
</tbody>
</table>

HBsAg — hepatitis B surface antigen; anti-HBV — antibodies against hepatitis B virus; anti-HBc — antibodies against core antigen of hepatitis B virus; HBV DNA — hepatitis B virus deoxyribonucleic acid; HCV RNA — hepatitis C virus ribonucleic acid; HIV — human immunodeficiency virus; IGRA — gamma interferon secretion tests; MRB — multiresistant bacteria; ESBL — extended-spectrum beta-lactamase; VRE — vancomycin-resistant enterococci; MBL — metallo-beta-lactamase; IC — intensive chemotherapy; allo-HSCT — allogeneic hematopoietic stem-cell transplantation; G-CSF — granulocyte colony-stimulating growth factors; SARS-CoV-2 — severe acute respiratory syndrome coronavirus 2; HSV — herpes simplex virus; CMV — cytomegalovirus; EBV — Epstein–Barr virus
Table IX. Clinical trials with selected new agents for myelodysplastic syndrome (MDS) treatment

<table>
<thead>
<tr>
<th>Agent</th>
<th>MoA</th>
<th>Studied cohort</th>
<th>Phase</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imetelstat</td>
<td>Telomerase inhibitor</td>
<td>LR-MDS</td>
<td>II</td>
<td>RBC-TI 42% (HI-E 68%)</td>
<td>[116]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RBC-TD, r/r ESA or EPO &gt;500 U/L</td>
<td>III</td>
<td>Ongoing (2023)</td>
<td></td>
</tr>
<tr>
<td>Roxadustat</td>
<td>Inhibition of HIFα degradation</td>
<td>LR-MDS</td>
<td>III (OL)</td>
<td>RBC-TI 38% (HI-E 63%)</td>
<td>[117]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RBC-TD LTB, non-del 5q, EPO &lt;400 U/L</td>
<td>III</td>
<td>Ongoing (2021)</td>
<td></td>
</tr>
<tr>
<td>Venetoclax</td>
<td>BCL-2 inhibitor</td>
<td>HR MDS: venetoclax + AZA (l line)</td>
<td>lb</td>
<td>OR 79% (CR 39.7%)</td>
<td>[118, 119]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HMA r/r</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venetoclax + AZA (ll line)</td>
<td>III</td>
<td>OR 39% (CR 7%)</td>
<td>[120, 121]</td>
</tr>
<tr>
<td>Pevonledistat</td>
<td>Neddylation inhibitor</td>
<td>HR-MDS</td>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HMA r/r</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pevonledistat + AZA</td>
<td></td>
<td>OR 42% (CR, mCR, HI)</td>
<td></td>
</tr>
<tr>
<td>Magrolimab</td>
<td>CD47 inhibitor</td>
<td>Pevonledistat + AZA (l lline)</td>
<td>III</td>
<td>OR 79% (CR, PR, HI)</td>
<td>[122]</td>
</tr>
<tr>
<td>Eprenetapopt</td>
<td>Restoring p53 function</td>
<td>MDS-HR (l line)</td>
<td>lb</td>
<td>OR 100% (CR 53%)</td>
<td></td>
</tr>
<tr>
<td>APR-246</td>
<td></td>
<td>Magrolimab + AZA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>III</td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td>Rigosertib</td>
<td>RAS pathway affector inhib.</td>
<td>HR MDS with TP53 mutation (+ AZA)</td>
<td>II</td>
<td>OR 92% (CR 34%)</td>
<td>[124]</td>
</tr>
<tr>
<td></td>
<td>PI3K and PLK</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>HR MDS Rigosertib + AZA (l line)</td>
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<tr>
<td></td>
<td></td>
<td>HMA r/r</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rigosertib ± AZA (l line)</td>
<td>III</td>
<td>OR 54% (CR 4%)</td>
<td></td>
</tr>
</tbody>
</table>

AZA — azacitidine; CCR — complete cytogenetic response; CR — complete response; EPO — erythropoietin; ESA — erythropoiesis-stimulating agent; HI-E — hematological improvement erythropoiesis; HIFα — hypoxia inducible factor; HMA — hypomethylating agent; HR — high-risk; LR — low-risk; LTB — low transfusion burden (1–4 red blood cell units/8 weeks); mCR — marrow complete remission; MoA — mechanism of action; OL — open label; OR — overall response; PI3K — phosphoinositide 3-kinase; PLK — polo-like kinase; PR — partial remission; RBC-TD — red blood cell transfusion dependency; RBC-TI — red blood cell transfusion independence; r/r — relapsed/refractory.

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