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**Guideline 6-13 REQUIRES UPDATING**

## A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

# Systemic therapy for the treatment of adult patients with lower-risk myelodysplastic syndromes

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**Report Date: March 27, 2018**

**An assessment conducted in October 2019 indicated that Guideline 6-13 REQUIRES UPDATING. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).**

**Guideline 6-13 is comprised of 5 sections. You can acess the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/53186**

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**PEBC Report Citation (Vancouver Style)**: Buckstein R, Baldassarre F, Maze D, Schuh A, Cheung M, and the Myelodysplastic Syndrome Guideline Development Group. Systemic therapy for the treatment of adult patients with low-risk myelodysplastic syndromes. Toronto (ON): Cancer Care Ontario 2018 March 5 [Requires Updating 2019 Oct]. Program in Evidence-Based Care Guideline No.: 6-13 REQUIRES UPDATING.

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## GLOSSARY

| Acronym | Definition |
|---|---|
| 13 cRA | 13 cis-Retinoic acid |
| ABS | Abstract |
| AE | Adverse effects |
| AGREE | Appraisal of Guidelines for Research and Evaluation |
| AHRQ | Agency for Healthcare Research and Quality |
| AML | Acute myeloid leukemia |
| AMSTAR | A Measurement Tool to Assess Systematic Reviews |
| ASCO | American Society of Clinical Oncology |
| ASH | American Society of Hematology |
| ATG | Anti-thymocyte globulin |
| AZA | Azacytidine |
| BM | Bone marrow |
| BSC | Best supportive care |
| CALGB | Cancer and leukemia group B |
| CCO | Cancer Care Ontario |
| CG | Control group |
| CI | Confidence interval |
| CMML | Chronic myelomonocytic leukemia |
| CR | Complete response |
| CsA | Cyclosporine |
| d(s) | day(s) |
| DA | Darbepoetin alpha |
| DAC | Decitabine |
| Del(5q) | Chromosome 5q deletion syndrome |
| DVT | Deep vein thrombosis |
| ECOG | Eastern Cooperative Oncology Group |
| EFS | Event-free survival |
| EHA | European Hematology Association |
| EORTC | European Organization for Research and Treatment of Cancer |
| EPO | Epoetin alpha or Erythropoietin |
| ER | Erythroid response |
| ESA | Erythropoiesis stimulating agents |
| ESMO | European Society of Medical Oncology |
| est. | Estimate |
| FAB classification | French-American-British classification |
| FACT-An | Functional assessment of Cancer Therapy – Anemia |

| Acronym | Definition |
|---|---|
| G-CSF | Granulocyte colony-stimulating factors |
| GDG(s) | Guideline Development Group(s) |
| GFM | Groupe Francophone des Myelodysplasies |
| GI | Gastrointestinal |
| GM-CSF | Granulocyte macrophage colony-stimulating factors |
| GRADE | Grading of Recommendations, Assessment, Development and Evaluation |
| HB | Hemoglobin |
| HI | Hematologic improvement |
| hist. | Historical comparison |
| HMA | Hypomethylating agents |
| HR | Hazard ratio |
| HSCT | Hematopoietic stem cell transplant |
| ICT | Iron chelation therapy |
| IG | Intervention group |
| IMiD | Immunomodulatory drugs |
| IMRAW | International MDS Risk Analysis Workshop |
| IPSS-R | International Prognostic Scoring System (revised) |
| IQR | Interquartile range |
| ITT | Intention-to-treat |
| IU | International units |
| IV | Intravenously |
| IWG | International Working Group |
| LEN | Lenalidomide |
| LFS | Leukemia-free survival |
| M-CSF | Macrophage colony-stimulating factors |
| MDS | Myelodysplastic syndrome |
| MDS-u | Myelodysplastic syndrome, unclassifiable |
| MER | Major erythroid response |
| mos | Months |
| MPD | Myeloproliferative disorders |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NGC | National Guideline Clearinghouse |
| NICE | National Institute for Health and Care Excellence |
| NIH | National Institute of Health |
| NPM1 | Nucleophosmin |
| *nr* | Not reported |
| NS | Not significant |

| Acronym | Definition |
|---|---|
| observ. | Observational |
| OIR | Overall improvement rate |
| OMHLTC | Ontario Ministry of Health and Long-Term Care |
| OR | Odds ratio |
| ORR | Overall response rate |
| OS | Overall survival |
| p.o. | Orally |
| PBO | Placebo |
| PEBC | Program in Evidence-Based Care |
| PFS | Progression-free survival |
| PLT | Platelets |
| PNH | Paroxysmal nocturnal hemoglobinuria |
| PR | Partial remission/response |
| pRBC | Packed red blood cells |
| prosp. | Prospective |
| PS | Performance status |
| Pts | Patients |
| QoL | Quality of life |
| QUALMS -1 | Quality of Life in Myelodysplasia Scale |
| RA | Refractory anemia |
| RAEB | Refractory anemia with excess blasts |
| RAP | Report Approval Panel |
| RARS | Refractory anemia with ring sideroblasts |
| RBC –TI | Red blood cells transfusion-independent |
| RBC-TD | Red blood cells transfusion-dependent |
| RCMD | Refractory cytopenia with multiline age dysplasia |
| RCTs | Randomized controlled trials |
| RCUD | Refractory cytopenia with unilineage dysplasia |
| rEPO | Recombinant epoetin alfa |
| restrosp. | Retrospective |
| rHEPO | Recombinant erythropoietin |
| ROBINS-I | Risk of Bias tool for non-randomized trials |
| RR | Relative risk |
| SAGE | Standards and Guidelines Evidence Directory of Cancer Guidelines |
| SC | Subcutaneous |
| SCT | Stem cell transplant |
| SD | Standard deviation |
| SIGN | Scottish Intercollegiate Guidelines Network |

| Acronym | Definition |
|---|---|
| SNPa | Single nucleotide polymorphism array |
| TD | Transfusion dependent |
| TFS | Transformation-free survival |
| Thal | Thalidomide |
| THPO | Thrombopoietin |
| TTP | Time to progression |
| vs. | Versus |
| WBC | White blood cells |
| WHO | World Health Organization |
| wk(s) | Week(s) |
| Yr(s) | Year(s) |

# Systemic therapy for the treatment of adult patients with lower-risk myelodysplastic syndromes

## Section 1: Recommendations

*This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.*

**GUIDELINE OBJECTIVES**

To provide guidance for the management of lower-risk myelodysplastic syndromes (MDS) using systemic therapy. Therapies include, but are not limited to:

- Hematopoiesis growth factors (i.e., erythropoiesis-stimulating agents [ESA] such as erythropoietin [EPO], granulocyte colony-stimulating factors [G-CSF], romiplostim, and eltrombopag)
- Lenalidomide in deletion 5q (del[5q]) MDS
- Lenalidomide in non-del(5q) MDS
- Hypomethylating agents (5-azacytidine [AZA] and decitabine [DAC])
- Iron chelation therapy
- Immunosuppressive therapy (i.e., cyclosporine [CsA] and anti-thymocyte globulin [ATG])

**TARGET POPULATION**

Adult patients (age ≥18 years) with lower-risk MDS, (i.e., International Prognostic Scoring System [IPSS] risk score ≤1.0, and IPSS (revised) score ≤3.5)

**INTENDED USERS**

Clinicians involved in the care of patients with MDS: hematologists, medical oncologists, oncology nurses, and oncology pharmacists.

**RECOMMENDATIONS**

**Recommendation 1: Hematopoiesis stimulating agents (ESA)**

**A. Erythropoietin (EPO)**

The Working Group recommends EPO with or without G-CSF in symptomatic anemic patients with lower-risk MDS.

Subgroups of low-risk MDS patients for which treatment with EPO is particularly recommended are: patients with MDS without excess blasts, those who have lower endogenous EPO levels, and those who are not transfusion-dependent.

The Nordic score [1] is recommended to identify patients who are unlikely to respond.

**B. G-CSF /macrophage colony-stimulating factors; romiplostim; eltrombopag**

G-CSF: The Working Group members recommend the use of G-CSF in synergy with recombinant human erythropoietin in ESA non-responders.

The subgroups of patients for whom G-CSF are particularly recommended are those with ringed sideroblasts.

Romiplostim: The Working Group members do not recommend the use of romiplostim outside

a clinical trial setting at this time.

Eltrombopag: The Working Group members do not recommend the routine use of eltrombopag outside a clinical trial setting at this time.

***Qualifying Statements for Recommendation 1A***

- The Nordic score [1] is useful at identifying patients who are unlikely to respond.
- Darbepoetin can be administered at a dose of 500 µg every two to three weeks; EPO can be given at a dose of 40,000-60,000 units weekly. A 12-week trial is recommended with dose escalation after a six-week trial in non-responders. For EPO, dose escalates from 40,000 units to 60,000 units weekly. For darbepoetin, escalate from 500 µg every three weeks, to every two weeks to every week. This dose escalation can occur along with the addition of G-CSF (see recommendation 1B below). Suggested target hemoglobin is 110 to 120 g/dL in transfusion-independent patients; in patients who are transfusion-dependent, the suggested goal of treatment is transfusion independence.

***Qualifying Statements for Recommendation 1B***

- Consider the use of G-CSF in synergy with recombinant erythropoietin after initial six to eight-week trial of EPO without adequate response.
- The dosing of G-CSF is flexible but should be given a minimum of two to three times/week and titrated to a white blood cell count of $<10\times10^9$/L.
- It is reasonable to consider eltrombopag for short-term use in patients with bleeding or prior to surgical intervention. The median daily dose to achieve a response is 50 mg (range, 50-175 mg) with a median time to response of two weeks (range, 1-15 weeks) and a median chansge in the platelet count of $124\times10^9$ /L (interquartile range 50-$217\times10^9$/L).

**Recommendation 2: Lenalidomide in del(5q)**

A. For patients with lower-risk MDS who are transfusion-dependent with or without additional cytogenetic abnormalities that have failed an ESA or are not candidates for an ESA, the Working Group recommends lenalidomide.

B. The recommended lenalidomide dose and schedule is 10 mg a day on days 1 to 21 of a 28-day cycle for a minimum of 16 weeks

C. The Working Group members do not recommend the use of lenalidomide in combination with other agents outside a clinical trial.

D. Working Group members recommend using dose reductions to manage adverse events such as neutropenia and thrombocytopenia.

E. For patients who are not transfusion-dependent, the Working Group recommends a first-line watch and wait strategy or treatment with ESA first.

***Qualifying Statements for Recommendation 2***

Patients who have symptomatic anemia but who are not transfusion-dependent were considered by the consensus panel to be candidates for lenalidomide as well.

- Patients with >1% p53 nuclear protein expression may be at higher risk of acute myeloid leukemia transformation [2]; therefore, immunohistochemical screening is a potential option for this subpopulation to guide potential intensification of therapy. Potential intensification could mean allo-transplant in younger patients, perhaps with

novel interventions post transplant, clinical trials, hypomethylating agents, other clinical trials, and closer monitoring. At the present time, p53 testing (by immunohistochemistry) requires further validation. Thalidomide was not recommended alone or in combination for any IPSS risk by Leitch et al. because the adverse effects of thalidomide have been demonstrated to be high [3], and the Working Group members agree with this recommendation.

- No evidence is available at this point to recommend lenalidomide in combination with other agents in this population.

**Recommendation 3: Lenalidomide in non-del(5q)**

It is reasonable to consider lenalidomide as a line of treatment for transfusion-dependent patients with lower risk and non-del(5q) who are ineligible or refractory to ESA.

The recommended lenalidomide regimen is 10 mg/day orally on days 1-28 of a 28-day cycle for 16 weeks.

***Qualifying Statements for Recommendation 3***

- Patients previously treated with ESA and with lower monthly transfusion need (e.g., ≤2) are most likely to reach transfusion independence when treated with lenalidomide.
- In case of adverse events, use dose reductions (refer to Recommendation 2D).

**Recommendation 4: Hypomethylating agents**

**AZA or DAC:**

AZA or DAC can be offered as options to patients with lower-risk MDS without del(5q), with clinically significant cytopenia(s).

***Qualifying Statements for Recommendation 4***

- In existing guidelines, AZA is recommended for patients who have a high or intermediate-2 IPSS score [4], but it is generally not recommended as a first-line treatment for patient with lower risk.
- There may be a subgroup of patients with lower-risk MDS that are at a higher risk of progression. Patients without del(5q) who do not respond to EPO, and who may not be candidates for further intensive therapy, may benefit from treatment with AZA or DAC.
- The preferred dose and schedule for AZA is 75 mg/m$^2$ for five days of each 28-day cycle. The preferred dose and schedule for DAC is: 20 mg/m$^2$ per day subcutaneously for three consecutive days at the beginning of every 28-day cycle.

**Recommendation 5: Immunosuppressive therapy (i.e., CsA and ATG)**

Horse ATG in combination with oral CsA: CsA can be offered as an option to selected patients with lower-risk MDS who have failed or are ineligible for ESAs if anemic, or have clinically significant cytopenia(s).

Recommended regimen: ATG at a dose of 40 mg/kg/day should be given over 4 to 6 hr for

four days. CsA should be started on day 14 at a dose of 5-12 mg/kg/day in two divided doses (every 12 hr) for 180 days with dose adjustments based on drug levels (target 200-400 ng/mL).

See qualifying statement below for adverse events.

***Qualifying Statements for Recommendation 5***

- The decision on which treatment option to use should involve a patient-centred discussion with a hematologist/medical oncologist. Patients should be aware of the higher risk of serious adverse events such as febrile transfusion reactions, and hepatic and hematologic adverse events with ATG and CsA.
- Patients who are more likely to benefit from immunosupressive treatment include: age <60 years, trisomy 8, recent transfusion dependence, paroxysmal nocturnal hemoglobinuria clones, HLA-DR15 serotype and hypocellular MDS. At the National Institute of Health, the three independent prognostic factors for response were age <60 years, HLA-DR15+, and treatment with ATG and CsA in combination.

**Recommendation 6: Iron chelation therapy**

It is reasonable to offer iron chelation to highly transfused patients with elevated ferritin (>1000 ng/mL) with lower-risk MDS.

Recommended regimen: the Working Group members recommend following recommendations for iron chelation therapy in hemoglobinopathies. The Working Group members prefer oral iron chelation over parenteral because it is more tolerable and compliance is significantly higher.

***Qualifying Statement for Recommendation 6***

- The dose and schedules used for MDS patients are based on those used for populations of patients with other hemoglobinopathies.

**Recommendation 7: Other agents**

The Working Group members do not recommend the use of ezatiostat, infliximab, amifostine, siltuximab, or topotecan outside a clinical trial setting.

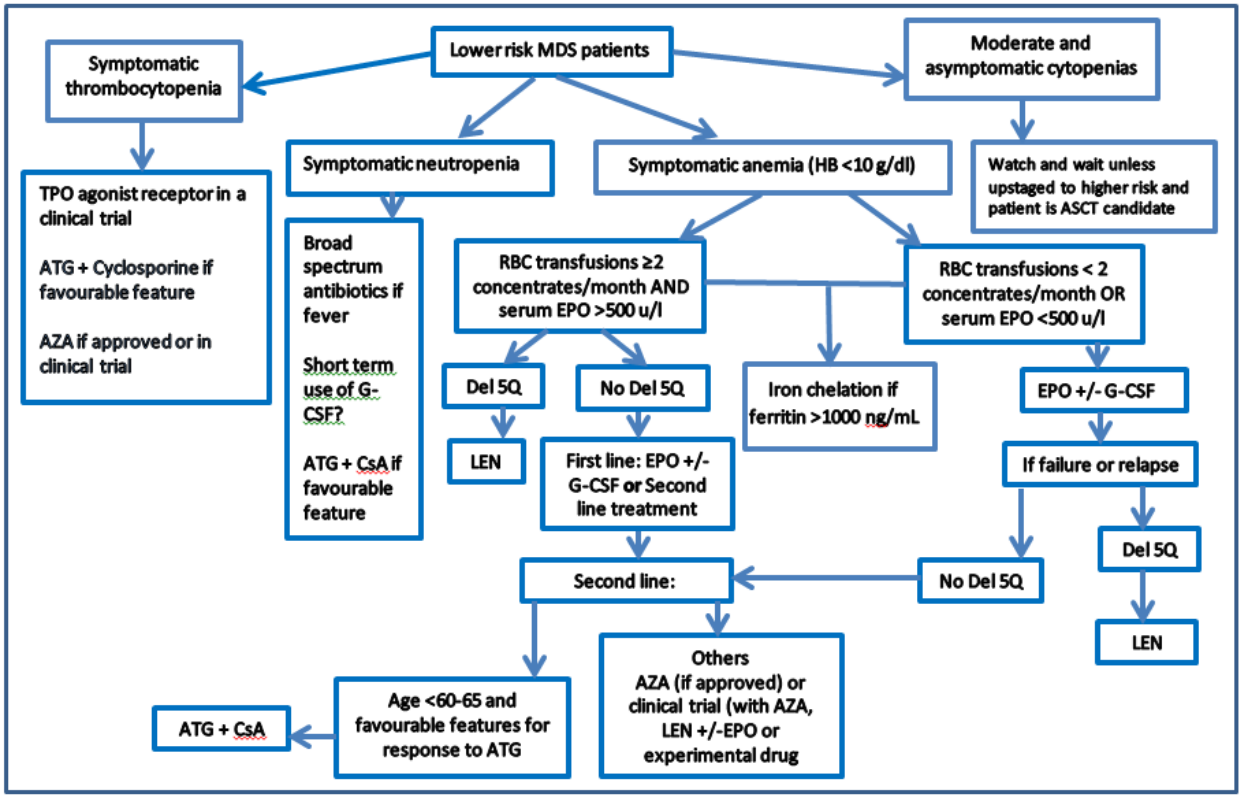


**Figure 1-1.** Treatment algorithm for the systemic treatment of lower risk myelodysplastic syndromes. Adapted from Figure 3 in: Fenaux P, et al. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 (Suppl 3): iii57–iii69 doi:10.1093/annonc/mdu180, with permission of Oxford University Press on behalf of the European Society for Medical Oncology.

# Systemic therapy for the treatment of adult patients with lower-risk myelodysplastic syndromes

## Section 2: Guideline – Recommendations and Key Evidence

**GUIDELINE OBJECTIVES**

To provide guidance for the management of lower-risk myelodysplastic syndromes (MDS) using systemic therapy. Therapies include, but are not limited to:

- Hematopoiesis growth factors (i.e., erythropoiesis-stimulating agents [ESA] such as erythropoietin [EPO], granulocyte colony-stimulating factors [G-CSF], romiplostim, and eltrombopag)
- Lenalidomide in deletion 5q (del[5q]) MDS
- Lenalidomide in non-del(5q) MDS
- Hypomethylating agents (5-azacytidine [AZA] and decitabine [DAC])
- Iron chelation therapy (ICT)
- Immunosuppressive therapy (i.e., cyclosporine [CsA] and anti-thymocyte globulin [ATG])

**TARGET POPULATION**

Adult patients (age ≥18 years) with lower-risk MDS, (i.e., International Prognostic Scoring System [IPSS] risk score ≤1.0, and IPSS-revised score ≤3.5)

**INTENDED USERS**

Clinicians involved in the care of patients with MDS: hematologists, medical oncologists, oncology nurses, and oncology pharmacists.

**RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE**

| **Recommendation 1: Hematopoiesis stimulating agents (ESA)**<br>**A. Erythropoietin (EPO)** |
|---|
| The Working Group recommends EPO with or without G-CSF in symptomatic anemic patients with lower-risk MDS.<br><br>Subgroups of low-risk MDS patients for which treatment with EPO is particularly recommended are: patients with MDS without excess blasts, those who have lower endogenous EPO levels, and those who are not transfusion-dependent.<br><br>The Nordic score [1] is recommended to identify patients who are unlikely to respond. |
| ***Qualifying Statements for Recommendation 1A*** |
| • The Nordic score [1] is useful at identifying patients who are unlikely to respond.<br>• Darbepoetin can be administered at a dose of 500 µg every two to three weeks; EPO can be given at a dose of 40,000-60,000 units weekly. A 12-week trial is recommended with dose escalation after a six-week trial in non-responders. For EPO, dose escalates from 40,000 units to 60,000 units weekly. For darbepoetin, escalate from 500 µg every three weeks, to every two weeks to every week. This dose escalation can occur along with the addition of G-CSF (see recommendation 1B below). Suggested target |

hemoglobin is 110-120 g/dL in transfusion-independent patients; in patients who are transfusion-dependent, the suggested goal of treatment is transfusion-independence.

***Key Evidence for Recommendation 1A***

In patients with lower-risk MDS, a subgroup analysis of a retrospective study [5] showed a statistically significant association between EPO plus G-CSF and overall survival (OS). Another retrospective study from the Groupe Francophone des Myélodysplasies [6] found better survival in ESA with or without G-CSF treated patients compared with an untreated cohort used to design the IPSS. The small randomized controlled trial (RCT) by Balleari et al. [7] reported a nonsignificant between-group difference in erythroid response for patients treated with recombinant EPO (rEPO) in combination with G-CSF compared with patients treated with rEPO alone (73.3% vs. 40%, p=0.065).

In patients with lower- and higher-risk MDS, the ECOG E1996, a randomized phase 3 trial by the Eastern Cooperative Oncology Group [8], reported a statistically significant better response rate for patients treated with EPO compared with patients treated with supportive care at four months follow-up (36% vs. 9.6%, p=0.002).

The ECOG E1996 [8] reported no statistically significant difference in adverse events, except for transient grade 3-4 thrombocytopenia (p<0.001) and hyperbilirubinemia (p=0.002), which occurred more frequently in patients treated with EPO compared with patients who received supportive care.

***Interpretation of Evidence for Recommendation 1A***

**Patient values:**

The Working Group members believe that patients highly value transfusion independence and increased hemoglobin.

**Certainty of the evidence:**

The certainty of the evidence for EPO in combination with G-CSF was moderate because of indirectness of the outcomes and imprecision of the data.

**Desirable effects and undesirable effects:**

Adverse events were either not detected [9], not significant [8,10], or a between-group statistical comparison was not reported [5,6,11].

**Acceptability:**

No data are available on the acceptability of this treatment to patients in Ontario.

**Generalizability:**

The majority of the patients represented in the study populations were patients with lower-risk MDS, therefore the results are generalizable to patients with these characteristics. Responses are more likely to occur if EPO < 500 IU/L and <2 units of packed red blood cells transfused per month (as per the Nordic score).

**Recommendation 1B: G-CSF/macrophage colony-stimulating factors; romiplostim; eltrombopag**

G-CSF: The Working Group members recommend the use of G-CSF in synergy with rEPO in ESA non-responders.

The subgroup of patients for whom G-CSF are particularly recommended are those with ringed sideroblasts.

Romiplostim: The Working Group members do not recommend the use of romiplostim outside a clinical trial setting at this time.

Eltrombopag: The Working Group members do not recommend the routine use of eltrombopag outside a clinical trial setting at this time.

***Qualifying Statements for Recommendation 1B***

- Consider use of G-CSF in synergy with rEPO after initial six to eight week trial of EPO without adequate response.
- The dosing of G-CSF is flexible but should be given a minimum of two to three times/week and titrated to a white blood cell count of $<10\times10^9$/L.
- It is reasonable to consider eltrombopag for short-term use in patients with bleeding or prior to surgical intervention. The median daily dose to achieve a response is 50 mg (range 50-175 mg) with a median time to response of two weeks (range1-15 weeks) and a median change in the platelet count of $124\times10^9$ /L (interquartile range 50-$217\times10^9$/L).

***Key Evidence for Recommendation 1B***

**G-CSF**:

Balleari et al. [7] in a small RCT reported a nonsignificant between-group difference in erythroid response for patients treated with rEPO in combination with G-CSF compared with patients treated with rEPO alone (73.3% vs. 40%, p=0.065). Patients received a minimum of eight weeks treatment with subcutaneous (SC) recombinant human EPO at a dose of 10,000 IU three times a week plus G-CSF (300 µg SC twice a week). This study did not report data on adverse events, and data on quality of life were not enough to provide a comparative analysis.

**Romiplostim**:

The systematic review and meta-analysis by Prica et al. [12] included four trials of romiplostim [13-16]. For bleeding events, all four trials were statistically pooled; for platelets transfusion rates, three trials were pooled [13-15]; for clinically significant thrombocytopenic events, three studies [13,14,16] were pooled; for overall response rate, three studies [13,14,16]) were pooled; for hematological improvement platelets, two trials [15,16] were pooled; and for acute myeloid leukemia (AML) progression, five trials were pooled [13-17], one of which [17] included patients treated with eltrombopag.

- *Bleeding events rates*: No statistically significant difference in bleeding events between romiplostim and control was detected when considering exposure-adjusted rates per patient-month: relative risk [RR] 0.84 (95% confidence interval [CI]: 0.57 to 1.24) [12]. One of the studies included in the Prica review [15], in a subgroup analysis, reported statistically significantly reduced bleeding events in the romiplostim group for patients who had baseline platelet counts $\geq20\times10^9$/L (p<0 .0001).
- *Platelet transfusion rates*: The pooled estimate of the proportion of patients receiving platelets transfusions did not show a significant improvement comparing romiplostim with placebo: RR, 0.70 (95% CI, 0.47 to 1.06). The pooled estimate RR of platelet transfusion rate per patient month [14-16] was significantly less with romiplostim than with placebo: RR, 0.69 (95% CI, 0.53 to 0.88) [12].
- *Clinically significant thrombocytopenic events*: no significant difference was detected between romiplostim and placebo in the pooled analysis: RR, 0.87 (95% CI, 0.69 to 1.09) [12].

- *Overall response rate*: no statistically significant increase in response rate was detected: RR, 0.94 (95% CI, 0.80 to 1.12) [12].
- *Hematological improvement, platelets:* the pooled estimate showed a significant improvement with romiplostim: RR, 0.67 (95% CI, 0.59 to 0.75); however, the heterogeneity of these trials was very high ($I^2$=92%) [12].
- *AML progression*: the pooled estimate did not reveal any statistically significant difference between treatment and placebo: RR, 1.12 (95% CI, 0.59 to 2.15). The same result persisted when a sensitivity analysis was conducted for the romiplostim trials [13-16] (RR, 1.36 (95% CI, 0.54 to 3.40). A sensitivity analysis was also conducted for population risk (higher versus lower IPSS risk), and no between-group differences were identified: $X^2$ =0, p=0.97 [12].
- *Adverse events:* The pooled analysis of three trials showed no statistically significant difference between romiplostim and placebo for chance of death: RR, 0.90 (95% CI, 0.54 to 1.50) [12].

Romiplostim in the included studies was administered at 750 µg/week in some studies [13,15], and between 500 to 750 µg in others [14,16].

**Eltrombopag**:

- *Response rate:* In the interim analysis of the eltrombopag versus placebo for low-risk MDS with thrombocytopenia (EQoL-MDS) study [18], response rate was significantly better with eltrombopag than with placebo (47% vs. 3%, p<0.0001), odds ratio (OR), 27.1 (95% CI 3.5 to 211.9, p=0.0017).
- *Disease control:* No statistically significant difference was detected in AML transformation between eltrombopag and placebo [18].
- *Adverse events*: Patients in the eltrombopag group experienced significantly more grade 3 to 4 nonhematologic adverse events than patients who received placebo (46% vs. 16%, p=0.0053) [18].

Patients received oral eltrombopag on a daily basis, starting at 50 mg and titrated up to a maximum of 300 mg [18].

***Interpretation of Evidence for Recommendation 1.B***

**Patient values**

- The Working Group members believe that patients highly value transfusion independence, decreased symptoms related to anemia and thrombocytopenia, and a reduced risk of bleeding.

**Certainty of the evidence:**

- **G-CSF:** The Working Group members considered the Balleari et al. [7] study to be at high risk of bias.
- **Romiplostim:** Although the meta-analysis by Prica et al. [12] was of very high quality, it was based on evidence of low to moderate certainty.
- **Eltrombopag:** The Oliva et al. study [18] on eltrombopag was considered to be at high risk of bias.

**Desirable effects and undesirable effects**

- Not enough evidence is available to judge the balance between desirable and undesirable effects with G-CSF.
- More evidence is needed to rule out the increase AML transformation risk with

romiplostim. Not enough data are available to evaluate eltrombopag. It may be considered for temporary use in thrombocytopenic low-risk MDS patients who are bleeding and refractory to platelets or in those who must undergo elective surgery but should not be used as a chronic growth factor.

**Acceptability**

- No data are available for the acceptability of these agents to patients in Ontario.

**Generalizability**

- Not enough evidence is available to be able to generalize to the entire population of patients with lower-risk MDS.

**Recommendation 2: Lenalidomide in patients with del(5q)**

A. For patients with lower-risk MDS who are transfusion-dependent with or without additional cytogenetic abnormalities that have failed an ESA or are not candidates for an ESA, the Working Group recommends lenalidomide.
B. The recommended lenalidomide dose and schedule is 10 mg a day on days 1 to 21 of a 28-day cycle for a minimum of 16 weeks
C. The Working Group members do not recommend the use of lenalidomide in combination with other agents outside a clinical trial.
D. Working Group members recommend using dose reductions to manage adverse events such as neutropenia and thrombocytopenia.
E. For patients who are not transfusion-dependent, the Working Group recommends a first-line watch and wait strategy or treatment with ESA first.

***Qualifying Statements for Recommendation 2***

Patients who have symptomatic anemia but who are not transfusion dependent were considered by the consensus panel to be candidates for lenalidomide as well.

- Patients with >1% p53 nuclear protein expression may be at higher risk of AML transformation [2]; therefore, immunohistochemical screening is a potential option for this subpopulation to guide potential intensification of therapy. Potential intensification could mean allo-transplant in younger patients, perhaps with novel interventions post transplant, clinical trials, hypomethylating agents, other clinical trial, and closer monitoring. At the present time, p53 testing (by immunohistochemistry) requires further validation. Thalidomide was not recommended alone or in combination for any IPSS risk by Leitch et al. [3] because the adverse effects of thalidomide have been demonstrated to be high, and the Working Group members agree with this recommendation.
- No evidence is available at this point to recommend lenalidomide in combination with other agents in this population.

***Key Evidence for Recommendation 2***

This recommendation was endorsed from an existing guideline by Letich et al. [3], and is based on the large MDS-004 RCT [19] and its corollary studies [2,20-25]. Additional evidence was identified by our review [26].

The dose and schedule of oral lenalidomide 10 mg a day on days 1 to 21 of a 28-day cycle is based on the MDS-004 RCT [19].

The Leitch et al. [3] guideline focused specifically on immunomodulatory agents. The systematic review that was the evidence base of that guideline had a methodology very

similar to our own systematic review; the authors searched for studies from 1985 to August 2010, they included studies with sample ≥20 patients, and they included non-comparative as well as comparative studies.

Among the corollary studies of the MDS 004 [19], the studies by Saft et al. [2,21] showed that patients with p53 nuclear protein expression, defined as staining in ≥1% of their bone marrow progenitors at baseline, have a shorter AML-free survival (23.9 months vs. 47.9 months, p=0.003), shorter time to AML progression (44.3 months vs. not reached, p=0.003), and that p53 positivity was strongly associated with shorter OS (p=0.01), although no statistically significant difference was noted in transfusion independence and response duration.

The study by Giagounidis et al. [22] showed that patients with lower-risk MDS and isolated del(5q) had a statistically significantly better response rate when treated with lenalidomide than with placebo (lenalidomide 5 mg: 37.2% vs. 2.2%, p=0.0001; lenalidomide 10 mg: 57.4% vs. 2.2% p<0.0001). (See numerical results of corollary studies in Appendix 6, Table 1.)

The most common grade 3 and 4 adverse events experienced by patients included in the MDS-004 study [19] were neutropenia and thrombocytopenia, and they were managed by dose reductions.

***Interpretation of Evidence for Recommendation 2***

**Patient values**

Lenalidomide can improve transfusion independence, survival, and quality of life with side effects that are controllable in these patients. The Working Group members believe that transfusion independence, survival, and quality of life are highly valued outcomes by patients in this group.

**Certainty of the evidence**

A. This was a strong recommendation with moderate certainty of evidence in Leitch et al. [3] and, in light of the new evidence, the Working Group members decided to endorse it. The MDS-004 [19] was a high-quality RCT, and evidence produced by studies of observational design [26] all points in the same direction, upgrading the certainty of this body of evidence.

B, C, and D. These recommendations were endorsed from Leitch et al. [3] and are based on evidence of low to moderate certainty.

**Desirable effects and undesirable effects**

- Patients in both the lenalidomide 10 mg and 5 mg dose groups experienced a higher transfusion independence rate than placebo (10 mg: 56.1% and 5 mg: 42.6% vs. placebo: 5.9%; both, p<0.001), a higher OS (see Table 4-4 for numerical results) and a better quality of life (see Table 4-4 for numerical results). Treatment with lenalidomide caused patients to experience higher rates of hematological adverse events, particularly neutropenia and thrombocytopenia, and these can be controlled by dose reductions (Leitch et al. [3]).

**Acceptability**

No data are available in the literature on the acceptability of lenalidomide treatment in patients with del(5q).

**Generalizability**

Patients with low-risk del(5q) and p53 expression may have a shorter OS and a higher risk of

progression so the duration of response may be shorter [2,21].

**Recommendation 3: Lenalidomide in patients with nondel(5q)**

It is reasonable to consider lenalidomide as a line of treatment for transfusion-dependent patients with lower risk and non-del(5q) who are ineligible or refractory to ESA.

The recommended lenalidomide regimen is 10 mg/day orally on days 1-28 of a 28 day cycle for 16 weeks.

***Qualifying Statements for Recommendation 3***

- Patients previously treated with ESA and with lower monthly transfusion need (e.g., ≤2*)* are most likely to reach transfusion independence when treated with lenalidomide.
- In case of adverse events, use dose reductions (refer to Recommendation 2D).

***Key Evidence for Recommendation 3***

Transfusion independence rate for eight weeks or longer was better for patients treated with lenalidomide than placebo (26.9% vs. 2.5%, p<0.001), but no statistically significant difference was seen in erythroid response rate as reported by Santini et al. [28].

No comparative data were reported for adverse events. The most common adverse events were neutropenia and thrombocytopenia [28].

The authors of the MDS-005 study [28] reported that use of ESA before study inclusion and receiving <4 units of packed red blood cells/month were independent prognostic factors for transfusion independence (respectively OR, 4.623 [95% CI, 1.324 to 16.152, p=0.016], and OR, 2.685 [95% CI, 0.95 to 7.5, p=0.06]) with lenalidomide treatment.

In the Santini et al. study [28], lenalidomide was given at a dose of 10 mg once per day in 28-day cycles until erythroid relapse, disease progression, unacceptable toxicity or consent withdrawal.

***Interpretation of Evidence for Recommendation 3***

**Patient values**

- The Working Group members believe that patients value transfusion independence highly.

**Certainty of the evidence**

- The body of evidence for this intervention was considered of moderate certainty for response, predictors of response, and adverse events: the MDS-005 study [28] was considered at low risk of bias; however, the number of patients included was fewer than 300, and this was the only study available for this population, making this body of evidence imprecise. Both the MDS-005 study [28], and the abstract report [29] were funded by the manufacturer of lenalidomide.

**Desirable effects and undesirable effects**

- The magnitude of the effect was large for transfusion independence.

**Acceptability**

- No information is available as to whether lenalidomide is acceptable to patients in the context of Ontario.

**Generalizability**

- The findings of the MDS-005 study are generalizable to patients who are transfusion-dependent with lower risk and non-del(5q), and who are ineligible or refractory to ESA.

**Recommendation 4: Hypomethylating agents**

**AZA or DAC:**

AZA or DAC can be offered as options to patients with lower-risk MDS without del(5q), with clinically significant cytopenia(s).

***Qualifying Statements for Recommendation 4***

- In existing guidelines AZA is recommended for patients who have a high or intermediate-2 IPSS score [4], but it is generally not recommended as a first-line treatment for patient with lower risk.
- There may be a subgroup of patients with lower-risk MDS that are at a higher risk of progression. Patients without del(5q) who do not respond to EPO, and who may not be candidate for further intensive therapy, may benefit from treatment with AZA or DAC.
- The preferred dose and schedule for AZA is 75 $mg/m^2$ for five days of each 28-day cycle. The preferred dose and schedule for DAC is: 20 $mg/m^2$ per day subcutaneously for three consecutive days at the beginning of every 28-day cycle.

***Key Evidence for Recommendation 4***

**A) AZA**

Among existing guidelines, Buckstein et al. [4] did not recommend AZA as first-line therapy for patients with lower-risk MDS because the authors did not locate any comparative evidence specifically in the lower-risk population.

Among studies of patients with lower-risk MDS, an abstract publication of an RCT [30] compared AZA with best supportive care in 40 patients without del(5q) or transfusion-dependent anemia, who were nonresponders to EPO and not candidate for intensive chemotherapy and transplant. There was a statistically significant between-group difference in erythroid response rate (31% vs. 5.5%, $p<0.01$), and no significant difference in OS and leukemia-free survival.

Among studies that included a mixed population of patients with low, intermediate-1, intermediate-2, or high IPSS scores, a fully published retrospective cohort by Falantes et al. [31] reported a significantly better OS for patients treated with AZA compared with the historical non-AZA cohort.

The use of AZA after lenalidomide failure in lower risk with del(5q) MDS is less studied, and our systematic review did not identify any comparative studies on this topic, although the Working Group is aware of a small, unpublished series that may show activity of AZA in this population [32].

The Lyons et al. study [33] showed that patients treated with lower AZA doses experienced less grade 3- and 4 adverse events rates (58% in the AZA 5, 77% in the AZA 5-2-5, and 84% in the AZA 5-2-2 groups, p values not reported).

**B) DAC**

The RCT by Garcia-Manero et al. [34] showed that a daily SC dose of DAC was superior to a weekly dose of the same drug. The study had an adaptive design and met the pre-determined

threshold for superiority, although overall response rate in the two groups were not statistically significantly different (see Table 4-4 in Section 4 for numerical results). Among the studies that included a population of mixed IPSS scores, the large RCT by Kantarjian et al. [35] showed a significantly better overall response rate, and quality of life with DAC than with best supportive care (see Table 4-6 in Section 4 for numerical results).

Although consensus opinion and evidence base preceeding this systematic review supports the dosing of DAC at 20 mg/m$^2$ SC for five consecutive days, a recent unpubished RCT [36] comparing AZA with decitabine in lower-risk MDS indicates that three days may be adequate for both drugs.

***Interpretation of Evidence for Recommendation 4***

**Patient values**

The Working Group members believe that patients value transfusion independence highly.

**Certainty of the evidence**

- For OS and transfusion independence with AZA the certainty of the evidence is low. The available evidence at this time comprises an abstract report of a phase II RCT [30] with a relatively small sample size (20 patients per group) which makes this body of evidence imprecise. Not enough information was provided in the abstract to evaluate its quality. Two studies, a phase II RCT [33] and a historical cohort study [31] report partially indirect evidence because the authors included patients with high, as well as low, IPSS risk scores in their samples. We considered the phase II RCT [33] of overall moderate quality because it was an open-label trial and details about the randomization process were not reported. We did not evaluate the quality of the study by Falantes et al. [31] with a formal tool. This was a cohort study with an historical control and we considered it at high risk of selection bias.
- The evidence available on DAC was moderate because of imprecision, and partial indirectness: one high-quality RCT [35] that included patients with various IPSS scores showed a significantly better overall response rate, and quality of life with DAC than with best supportive care.
- For the best DAC dose, the certainty of the evidence is moderate because of imprecision. One open-label RCT [34] showed that lower daily SC doses of DAC were more effective than weekly SC doses on overall improvement rates.
- The Working Group considered the study by Sanchez-Garcia et al. [30] to be at high risk of bias because participants and clinicians were not blinded, and because the small sample size made this body of evidence imprecise. As well, this was an abstract publication, and it was unclear whether there was a risk of selection bias, detection bias, attrition bias, and reporting bias.
- The study by Jabbour et al. [36] was identified as an abstract publication, and it is reported in Table 4-7 among the unpublished and ongoing trials. Working Group members are aware of its fully published version that appeared after the cut-off of this systematic review.

**Desirable effects and undesirable effects**

For AZA, the magnitude of the effect for response was large for transfusion independence, the outcome that Working Group members considered to be the most critical. However, there was not a statistically significant difference for OS and leukemia-free survival. Adverse events were either not reported [30,31], or a between-group comparison was not made [33]. Therefore, it was not possible to evaluate the balance between beneficial and adverse

effects.

**Acceptability**

No data are available showing AZA or DAC are not acceptable to patients.

**Generalizability**

The evidence from the abstract publication [30], and the unpublished study [36] that compares AZA with DAC applies to a specific subset of patients, those without del(5q), who had not responded to previous treatment with EPO and who were not candidate for intensive chemotherapy and transplant, which comprises the majority of patients with lower-risk MDS.

**Recommendation 5: Immunosuppressive therapy (i.e., CsA and ATG)**

Horse ATG in combination with oral CsA can be offered as an option to selected younger patients with lower-risk MDS who have failed or are ineligible for ESAs if anemic, or have clinically significant cytopenia(s).

Recommended regimen: ATG at a dose of 40 mg/kg/day should be given over 4 to 6 hr for four days. CsA should be started on day 14 at a dose of 5-12 mg/kg/day in two divided doses (every 12 hr) for a minimum of 180 days with dose adjustments based on drug levels (target 200-400 ng/mL).

See qualifying statement below for adverse events.

***Qualifying Statements for Recommendation 5***

- The decision on which treatment option to use should involve a patient-centred discussion with a hematologist/medical oncologist. Patients should be aware of the higher risk of serious adverse events such as febrile transfusion reactions, hepatic and hematologic adverse events with ATG and CsA.
- Patients who are more likely to benefit from immunosupressive treatment include: age <60 years, trisomy 8, recent transfusion dependence, presence of paroxysmal nocturnal hemoglobinuria (PNH) clones, HLA-DR15 serotype and hypocellular MDS. At the National Institute of Health (NIH), the three independent prognostic factors for response were age <60 years, HLA-DR15+, and treatment with ATG and CsA in combination

***Key Evidence for Recommendation 5***

We were unable to locate any study that focused exclusively on patients with lower-risk MDS. Among the studies that included a mixed population, Passweg et al. [37] evaluated a combination of horse ATG plus CsA versus best supportive care. Hematological response rate was statistically significantly better for the ATG-CsA combination (29% vs. 9%, p=0.02) although the dose of ATG used was only 15 mg/kg for five days. No statistically significant difference in OS was seen; although the trial was not powered to detect a survival difference, improved transformation-free survival (p=0.73) and leukemia-free survival (p=0.91) were detected (see Table 4-6 for numerical results).

The evidence for subgroups of patients that are most likely to benefit from immunosuppressive treatment is derived from a phase II study [27]

Serious adverse events were more frequent in the ATG-CsA group (35.5% [16 of 45] vs. 9.3% [4 of 43], p=0.005).

In the randomized trial [37], factors associated with response at six months in a multivariate analysis were low marrow cellularity aspirate (11 of 24 patients, 46%) versus normal/high (5 of

42 patients, 12%; p=0.009).

Dose and schedule are based on the National Comprehensive Cancer Network (NCCN) guidelines [38]. The ATG dose used in the Passweg et al. trial [37] was 15 mg/kg given intravenously over 8 to 12 hr for five consecutive days although more recent recommendations including that of NCCN [38] include 40 mg/kg intravenously over 4 to 6 hr for four days.

***Interpretation of Evidence for Recommendation 5***

**Patient values**

- The Working Group members believe that patients value transfusion independence highly.

**Certainty of the evidence**

- The certainty of the evidence for this recommendation is moderate to low because of imprecision and indirectness. We were able to identify one open-label randomized study [37] with a relatively small sample size (83 patients) that included patients with lower- and higher-risk MDS; the risk of bias of this study was considered moderate. The certainty of the evidence for subgroups of patients who are most likely to benefit is very low; however, the Working Group decided to mention it because this is a group of patients who do not have many other options.

**Desirable effects and undesirable effects**

- The treatment with these agents causes a relevant number of serious adverse events, both hematologic, and nonhematologic, as well as anaphylactic reactions. The balance between benefits and undesirable effects needs to be decided according to patient preferences after individualized discussion with the hematologist.

**Acceptability**

- No data are available on the acceptability of immunosuppressive therapy on patients in Ontario.

**Generalizability**

- This evidence is generalizable to selected patients that are more likely to respond, (i.e., age <60 years, only recently transfusion dependent, HLA-DR15 +, trisomy 8, PNH clone, hypocellular marrow). Patients with excess blasts and therapy-related MDS should not be treated with this approach.

**Recommendation 6: Iron chelation therapy (ICT)**

It is reasonable to offer ICT to highly transfused patients with elevated ferritin (>1000 ng/mL) with lower-risk MDS.

Recommended regimen: the Working Group members recommend following recommendations for ICT in hemoglobinopathies. The Working Group members prefer oral iron chelation over parenteral because it is more tolerable and compliance is significantly higher.

***Qualifying Statement for Recommendation 6***

- The dose and schedules used for MDS patients are based on those used for populations of patients with hemoglobinopathies.

***Key Evidence for Recommendation 6***

Two fully published prospective studies [39,40], and a retrospective cohort study [41] showed that patients treated with iron chelation (using deferoxamine or deferasirox) had a better OS than patients who did not receive chelation (see Table 4-4 for numerical results). Multiple analyses of iron overload reduction using ICT in lower-risk MDS have documented an association between receiving ICT and superior OS compared with patients not receiving ICT [39-45]. These studies include a matched pair analysis [45], and results include an association between dose of ICT [40,44] and effectiveness of ICT [45] and superior survival.

Two studies [39,46] reported no statistically significant between-group difference for creatinine levels and liver transaminase.

The observational study by Neukirchen et al. [45] showed a statistically significant between-group difference in OS for lower-risk patients (p=0.008), while in the subgroup of patients at higher risk the difference did not reach significance.

***Interpretation of Evidence for Recommendation 6***

**Patient values**

- The Working Group members believe that patients highly value OS and preservation of end-organ function (heart, liver). Patients would prefer oral ICT over parenteral administration.

**Certainty of the evidence**

- The certainty of this body of evidence was considered moderate. The Working Group judged the quality of the fully published studies that reported on OS [39-41], to have a moderate to serious risk of bias (see Appendix 7 C). The magnitude of the effect was large, and the fully published studies were consistent in their results. The abstract reports of unpublished studies did not provide enough information to express a judgement about their quality.

**Desirable effects and undesirable effects**

- Adverse events were reported not statistically significantly different between groups by Lyons et al. [39]. The other studies did not report on adverse events. However, the chief toxicities of deferasirox and deferoxamine, as reported in their manufacturer monographs [47,48] includes the following: 1) deferasirox: diarrhea, renal insufficiency, gatrointestinal complaints; and 2) desferoxamine: high-frequency hearing loss, retinal problems, infusional skin reactions.

**Acceptability**

- No data are available on the acceptability of ICT to patients in Ontario.

**Generalizability**

- This evidence is generalizable to all patients with lower-risk MDS who are highly tranfused.

**Recommendation 7: Other agents**

The Working Group members do not recommend the use of ezatiostat, infliximab, amifostine, siltuximab, or topotecan outside a clinical trial setting.

***Key Evidence for Recommendation 7***

Siltuximab, ezatiostat, infliximab, topotecan, and amifostine were tested in four small, phase II RCTs [49-52] of patients with lower-risk MDS. None of these agents showed statistically

significantly better outcomes than controls.

Among studies that included patients with higher and lower-risk MDS, Grinblatt et al. [53] tested the effectiveness of two doses of topotecan in an RCT. Results were not significantly different between the higher and lower dose, except for response duration (23 vs. 14 months, p=0.02) [53].

***Interpretation of Evidence for Recommendation 7***

**Patient values**

- The Working Group members believe that patients highly value transfusion independence, improvement in blood counts, symptoms, and improved survival.

**Certainty of the evidence**

- The included studies [49-51] were small, phase II studies, and the members of the Working Group rated their quality as moderate or unclear risk of bias. The members of the Working Group considered this body of evidence to be of low certainty, because of imprecision, risk of bias, and indirectness: for each intervention we identified only one study, each study had a relatively small sample, and two of the studies included patients with lower- and higher-risk MDS. Not enough evidence for each agent is available to make a recommendation for or against any of these agents.

**IMPLEMENTATION CONSIDERATIONS**

No specific issues in regard to implementation of the considered interventions became apparent during discussion. During professional consultation it was brought to the attention that some of the medications (e.g., lenalidomide in non-del[5q], AZA in low-risk refractory cytopenias, eltrombopag in selective symptomatic thrombcytopenias) are not currently covered by Cancer Care Ontario (CCO) at this time, and many patients do not have third party insurance, or may not have access to appropriate clinical trials).

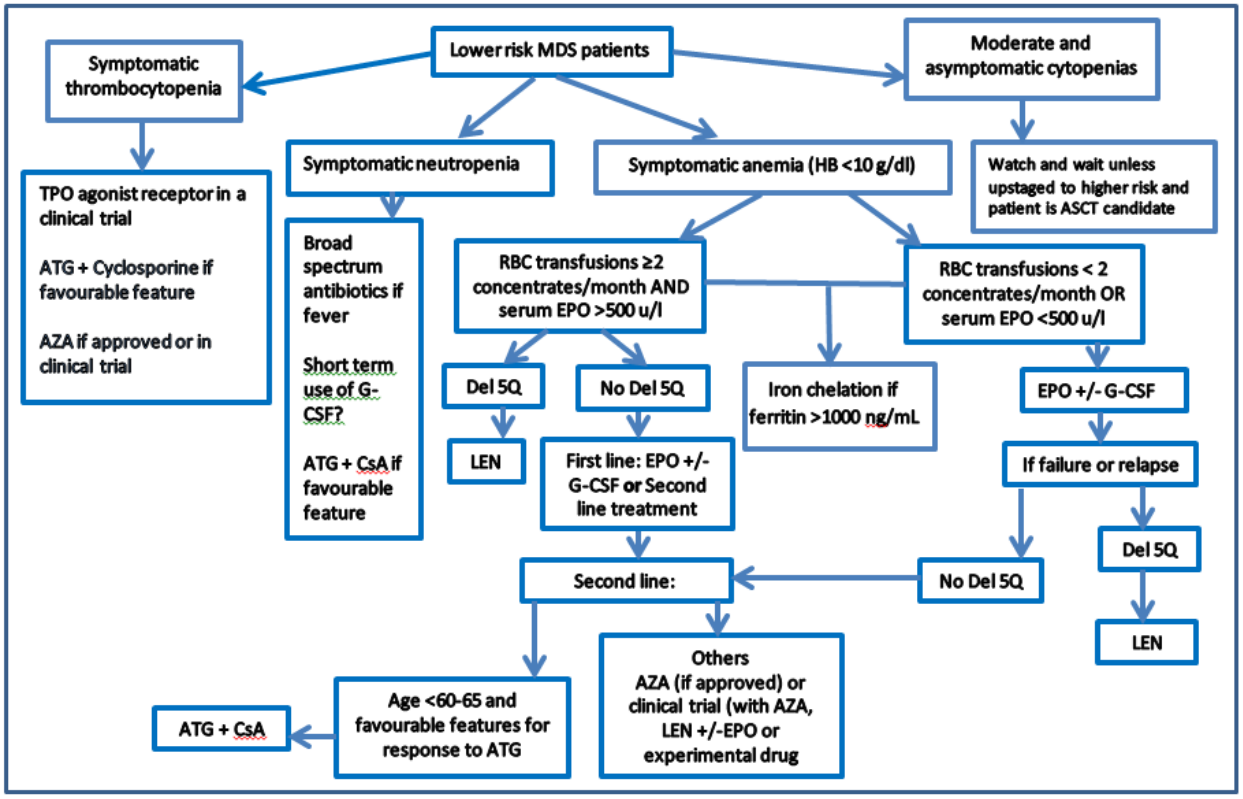


**Figure 2-1.** Treatment algorithm for the systemic treatment of lower risk myelodysplastic syndromes. Adapted from Figure 3 in: Fenaux P, et al. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 (Suppl 3): iii57–iii69 doi:10.1093/annonc/mdu180, with permission of Oxford University Press on behalf of the European Society for Medical Oncology.

**RELATED GUIDELINES**

Kouroukis CT, Rumble RB, Walker I, Bredeson C, Schuh A. Stem cell transplantation in myelodysplastic syndromes and acute myeloid leukemia. Toronto (ON): Cancer Care Ontario (CCO); 2012 Mar 29. Program in Evidence-based Care (PEBC) Recommendation Report No.: SCT-3.

Fenaux P, Haase D, Sanz GF, Santini V, Buske C, ESMO Guidelines Working Group. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii57-69.

Greenberg PL, Stone RM, Al-Kali A, Barta SK, Bejar R, Bennett JM, et al. Myelodysplastic Syndromes, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017 Jan;15(1):60-87. PubMed PMID: 28040720. Epub 2017/01/04. eng.

# Systemic therapy for the treatment of adult patients with lower-risk myelodysplastic syndromes

## Section 3: Guideline Methods Overview

*This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.*

### THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, CCO. The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

### BACKGROUND/JUSTIFICATION FOR THE GUIDELINE

Treatment for patients with lower-risk MDS is usually limited to best supportive care because patients with these characteristics live longer, and do not die from this disease. However some patients with lower risk may have a poorer prognosis, and they may benefit from treatment with drugs that are usually reserved for patients with a higher-risk profile. With this document, we would like to update the evidentiary base to ascertain what treatments are effective and safe for patients with a lower-risk profile.

The Canadian Consortium on Evidence-based Care in MDS produced a guideline for MDS in 2011 [4]. The Hematology Disease Site Group (DSG) members decided to update that guideline focussing exclusively on lower-risk MDS and to expand it by addressing therapies other than AZA.

### GUIDELINE DEVELOPERS

This guideline was developed by the MDS GDG (Appendix 1), which was convened at the request of the Hematology Disease Site Group.

The project was led by a small Working Group of the MDS GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group members had expertise in hematology and health research methodology. Other members of the MDS GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

## GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [54,55]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [56] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

### Search for Existing Guidelines

As a first step in developing this document, a search for existing guidelines was undertaken to determine whether an existing guideline could be adapted or endorsed. To this end, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse (NGC), and the Canadian Medical Assciation Infobase.
- Guideline developer websites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Health and Medical Research Council - Australia.
- Electronic databases: MEDLINE, EMBASE, and Cochrane.

We included guidelines that presented recommendations for adult patients (age ≥18 years) with lower-risk MDS, that were based on a systematic review of the evidence, and that focused on any of the agents of interest to this work.

This search, executed on October 14, 2015 and updated in July 2017, identified three guidelines [3,4,38] that used methods similar to this document. The guideline by Buckstein et al. [4] did not find any evidence for 5-AZA for patients with lower risk; therefore, the Working Group members decided to use its cut-off date as a starting date, and search for primary studies of 5-AZA after 2009. The guideline by Leitch et al. [3] provided recommendations on the use of lenalidomide in patients with del(5q), and the members of the Working Group adapted some of the recommendations from this guideline after an updated search for primary studies was conducted and the new evidence integrated. The guideline by Greenberg et al. [38] has a larger scope than the present one, and the Working Group adopted its recommendation regarding ATG dose and schedule. We also adapted the algorithm from the European Society of Medical Oncology (ESMO) guideline by Fenaux et al. [57] with two small changes. Fenaux et al. [57] recommended ATG for patients with thrombocytopenia, while we always recommend ATG in combination with CsA for first- or second-line treatment, and, unlike the ESMO authors, we do not recommend AZA for symptomatic neutropenia.

The remaining five guidelines identified by this search [58-62] were used as a source of evidence because their questions or their methods did not match those of the present systematic review.

A summary of the general characteristics is reported in Appendix 2, Table 1. An AGREE II assessment [56] of methodological rigour of guidelines based on a systematic review of the evidence [57-60] is reported in Appendix 2, Table 2.

## GUIDELINE REVIEW AND APPROVAL

### Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

### External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

## ACKNOWLEDGEMENTS

The MDS GDG would like to thank the following individuals for their assistance in developing this report:

- Melissa Brouwers, Judy Brown, Lisa Chodirker, Craig Early, Brian Leber, Sheila McNair, Duvaraga Sivajohanathan, Norma Varela, Shailendra Verma, and Karen Yee for providing feedback on draft versions.
- Ananya Nair for conducting a data audit.
- Sara Miller for copy editing.

# Systemic therapy for the treatment of adult patients with lower-risk myelodysplastic syndromes

## Section 4: Systematic Review

**INTRODUCTION**

The MDS are clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, leading to peripheral blood cytopenias, red blood cell and platelet transfusion dependence, and an increased risk of progression to AML. The median age of onset is 72 years with an incidence of 3.4 cases/100,000 [63], although most believe this is a gross underestimate of true incidence [64].

Survival and AML risk are predicted by the IPSS and newer scores such as the revised IPSS [65]. Only a minority of patients are eligible for potentially curative allogeneic stem cell transplantation [66-68].

Although disease-modifying treatments are now available for subgroups of MDS patients, including hypomethylating agents for higher-risk patients, the mainstay of treatment for lower-risk MDS is supportive care including red blood cell transfusions and hematopoietic growth factors. A small subset of patients will respond to immunosuppressive therapy, lenalidomide, and hypomethylating agents.

The Working Group of the MDS GDG developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group derived the research questions outlined below.

**RESEARCH QUESTIONS**

The Working Group stated the following research questions:

1. In patients with low-risk MDS, what is the efficacy of hematopoiesis-stimulating agents, thrombopoietin receptor agonists, immunomodulatory agents, hypomethylating agents, iron chelation, immunosuppressive agents, and other/novel agents?
2. What adverse events are associated with the use of hematopoiesis-stimulating agents, thrombopoietin receptor agonists, immunomodulatory agents, hypomethylating agents, iron chelation, immunosuppressive agents, and other/novel agents?
3. Which patients are more or less likely to benefit from treatment with hematopoiesis-stimulating agents, thrombopoietin receptor agonists, immunomodulatory agents, hypomethylating agents, iron chelation, immunosuppressive agents, and other/novel agents?
4. What are the optimal dose and schedule, and treatment duration for the aforementioned treatments?

In addition, the Group would like to create an algorithm from the data that can be used as a pathway.

## METHODS

We conducted this evidence review in two planned stages: a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

### Search for Existing Systematic Reviews

We conducted a search for systematic reviews published from 2009 to July 31, 2017 using the databases MEDLINE, EMBASE, and the Cochrane Library. The detailed search strings for systematic reviews are reported in Appendix 3A.

Identified systematic reviews were evaluated based on their clinical content and relevance. Any identified systematic reviews that addressed the research questions were assessed using A Measurement Tool to Assess Systematic Reviews (AMSTAR) [69]. The results of the AMSTAR and clinical assessment were used to determine whether or not any existing review could be incorporated as part of the evidentiary base.

### Search for Primary Literature

The systematic reviews identified did not report on all agents of interest. Their methods were often variable and their searches not always up to date; therefore, we searched for primary, comparative studies.

#### *Literature Search Strategy*

We searched the electronic databases MEDLINE, EMBASE, and the Central Registry of Clinical Trials in the Cochrane Library published from 2009, for AZA, and from 2005 to July 19, 2017 for all other agents. The detailed search strings for primary comparative studies can be found in Appendix 3B. We searched the websites of the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO), and the European Hematology Association (EHA) for relevant reports among the meeting abstracts published between 2009 and 2016. We also pulled the citations of the relevant primary studies referenced by the included systematic reviews, and added them to the primary studies retrieved from the electronic database searches.

#### *Study Selection Criteria and Process*

The detailed selection criteria can be found in Appendix 4. We included comparative studies with sample size ≥30, published in English, that examined agents used for the systemic treatment of lower-risk MDS in adult patients. Because of lack of evidence in this area of study, on November 7, 2016 the Working Group members decided to modify the selection criteria to include studies that reported outcomes of patients with lower risk together with outcomes of up to 20% of patients with higher risk and did not report separate results for the two populations. These studies will be highlighted and considered at higher risk of bias because they report at least partly indirect evidence.

The methodologist (FB) reviewed the titles and abstracts that resulted from the search, and items that warranted full-text review. Another Working Group member (DM) independently reviewed the full text of included studies.

#### *Data Extraction and Assessment of Study Quality and Potential for Bias*

The methodologist (FB) extracted data and summarized the main characteristics and summary results of included studies into tables. All extracted data were audited by an independent auditor (AN).

The methodologist (FB) assessed the quality of included, fully published, RCTs with the Cochrane Risk of Bias tool [70], and of fully published observational studies with the Cochrane

ACROBAT-NRSI tool [71]. This tool assesses the bias of comparative nonrandomized studies in relation to an ideal randomized trial, and covers seven domains through which bias can be introduced in a nonrandomized trial: 1) bias due to confounding; 2) bias in selection of participants into the study; 3) bias in measurement of interventions; 4) bias due to departures from intended interventions; 5) bias due to missing data; 6) bias in measurement of outcomes; and 7) bias in selection of the reported results. In the application of this tool it is required that the authors, at the protocol stage, identify, among the seven domains of bias, those that are expected to be more relevant to all or most studies. At the protocol stage, the authors should also identify the possible co-interventions that could have an impact on study outcomes. A second part of the tool requires the evaluation of each included study by answering specific questions.

**Synthesizing the Evidence**

Meta-analysis was not planned because not enough evidence for statistical pooling was expected. Data were summarized in a narrative manner.

**RESULTS**

**Search for Existing Systematic Reviews**

We reviewed the full text of 134 publications, and included 11 systematic reviews [12,72-81]. The flow chart of the study is presented in Appendix 5. Table 4-1 reports the characteristics of the included systematic reviews, and Table 4-2 their assessment with AMSTAR. The systematic review by Prica et al. [12] was considered to be of high quality and to use methods similar to the present document; therefore, the members of the Working Group used its content and updated the search for primary studies of thrombopoietin receptor agonists from the February 2014 search cut-off date of that review to July 31, 2017. The remaining included systematic reviews [72-80] were used as a source of evidence (i.e., we reviewed their reference lists for possible additional trials), because either their methods did not match the present review, their quality was considered low (see AMSTAR assessment reported in Table 4-2), or they did not report enough data for the present purpose (i.e., studies of interest were still ongoing at the time of review).

**Table 4-1. General Characteristics of Included Systematic Reviews Addressing Systemic Treatment of Patients with Lower-Risk MDS**

| Author, year, Country, Funding | Objectives / Focus | Population; search cut-off | Intervention | Comparison | Outcomes | Design and number of included studies Comments |
|---|---|---|---|---|---|---|
| **Hematopoiesis-stimulating agents** | | | | | | |
| **Erythropoiesis-stimulating agents** | | | | | | |
| Mundle, 2009 [75]<br><br>US<br><br>**Funding**: Centocor Ortho Biotech Services LLC | To compare EPO in monotherapy or in combination with G- or GM-CSFs; to assess ER rates in transfusion-dependent pts.<br><br>Has meta-analysis<br><br>**Focus:** EPO and G-CSFs | Studies of pts with MDS (pts with refractory anemia and pts with refractory anemia with ringed sideroblasts). Included predominantly pts with low-risk MDS. Some of the studies have mixed populations.<br><br>**Search cut-off:** 1990 to September 30, 2007 | EPO monotherapy | EPO in combination with G-/GM-CSF | ER | **Design:** NR<br>Among the full text studies included none met the selection criteria of the present review (i.e., controlled studies of pts with low-risk MDS, published on or after 2005, and focused only on the low-risk population) |
| Park, 2016 [80]<br><br>France<br><br>**Funding**: Amgen Inc. | To estimate the efficacy of DA for MDS-related anemia<br><br>**Focus:** DA as supportive care | Prospective interventional studies of MDS pts treated with DA.<br><br>**Search cut-off:** from inception to August 2015 | DA | None or different doses of DA | ER | **Design:** Nine or 10 studies included were single arm phase II studies, and one [11] was a RCT that we had incuded in this review. |
| **Granulocyte/Macrophage Colony-stimulating Factors** | | | | | | |
| Hutzschenreuter, 2016 [79]<br><br>Germany<br><br>**Funding**: University of Cologne | To assess the evidence for the effectiveness of treatment with G-CSF and GM-CSF in addition to standard therapy in newly diagnosed MDS patients<br><br>Has meta-analysis<br><br>**Focus**: Hematopoietic growth factors | Studies of all MDS pts. Pts with low risk in some of the included trials<br><br>**Search cut-off:** December 3, 2015 | G-CSF GM-CSF<br><br>**Design:** RCT | Standard therapy or standard therapy and placebo. | • OS*<br>• PFS<br>• Time to progression to AML<br>• Response<br>• Incidence of: neutropenia, infections, anemia, AE, transfusions, antibiotic treatment, hospitalization;<br>• QOL | **Design:** The authors included only RCTs and excluded cross over design. They planned to do a subgroup analysis on low vs. high-risk pts, but they could not because they did not have enough data.<br>Although their search cut-off was December 3, 2015 the included studies spanned from 1993 to 2006, and the excluded studies from 1995 to 2009.<br>Two studies were of interest of this review: Balleari et al. 2006 and Greenberg et al. 2009 [7,8]. |
| **Thrombopoietin receptor agonists** | | | | | | |
| Prica, 2014 [12]<br>Canada<br><br>Funding: None declared | To assess safety and effectiveness of adding THPO-receptor agonist to standard MDS treatment<br><br>Has meta-analysis | Studies of pts with all risk group MDS<br><br>**Search cut-off:** from inception to Feb 2014 | Romiplostin and eltrombopag<br><br>**Design:** RCT | Placebo | • Bleeding (any grade and severe)<br>• Incidence of platelet transfusions,<br>• Incidence of clinically significant thrombocytopenic | **Design:** RCT<br><br>Included 5 RCT: one of eltrombopag and 4 of romiplostim [13-16,82] |

| Author, year, Country, Funding | Objectives / Focus | Population; search cut-off | Intervention | Comparison | Outcomes | Design and number of included studies Comments |
|---|---|---|---|---|---|---|
| | **Focus:** Romiplostin and eltrombopag | | | | events (grade 3 and 4)<br>• Overall MDS response rates<br>• Incidence of leukemic transformation or increase bone marrow blasts percentage<br>• Mortality | |
| **Immunomodulatory agents** | | | | | | |
| Castelli, 2013 [77]<br><br>Italy<br><br>**Funding**: NR | To review the pharmacology, molecular action and clinical effectiveness of IMiD in MDS pts.<br><br>Does not have meta-analyis<br><br>**Focus**:<br>LEN | Studies of MDS pts of low-risk class.<br><br>**Search cut-off:** 1966 to May 2012 | IMiD | Various comparisons | Response, time to response, duration of response, prognostic factors of response, AE | **Design:** RCTs<br><br>Among the studies included seven focused on the population and intervention of interest to this review [19,83-88] |
| Lian, 2016 [81]<br><br>China<br><br>**Funding:** Governement (China) | To ascertain whether LEN improves OS and reduces progression to AML<br><br>Has meta-analysis<br><br>**Focus:** LEN | Studies of MDS pts of low-risk class.<br><br>**Search cut-off:** inception to March 2016 | LEN | Various comparators | Response, AE, OS, AML progression | **Design**: Includes all designs (RCT, comparative , single-arm studies, and pooled analyses) |
| **Hypomethylating agents** | | | | | | |
| Xie, 2015 [72]<br><br>China<br><br>**Funding**: NR | To compare efficacy of decitabine vs. 5-azacytidine.<br><br>Has meta-analysis<br><br>**Focus**:<br>HMA | Studies of pts with MDS. Pts with low-risk in one of the included studies.<br><br>**Search cut-off:** from 2000 to December 2013 | AZA | Decitabine | Treatment response (CR, PR, OR), survival, and AE | **Design:** Phase II and III clinical trials<br><br>One among the included trials examined pts with low-risk MDS: Garcia-Manero et al., 2013 [34] |
| **Immunosuppressive agents** | | | | | | |
| No systematic reviews were identified | | | | | | |
| **Iron chelation** | | | | | | |
| Meerpohl, 2014 [78]<br><br>Germany | To evaluate the effectiveness and safety of deferasirox for iron overload in pts with MDS | Studies of deferasirox compared to no therapy, placebo or other iron-chelating treatment in pts with with all types of MDS | Deferasirox | No therapy or placebo Other iron chelation therapy | • OS<br>• Reduced end-organ damage due to iron deposition (e.g., cardiac | **Design:** RCTs<br><br>The authors included 4 ongoing RCTs: Giraldo 2011, NCT02038816, NCT01868477, NCT00940602, and no |

| Author, year, Country, Funding | Objectives / Focus | Population; search cut-off | Interventio n | Comparison | Outcomes | Design and number of included studies Comments |
|---|---|---|---|---|---|---|
| **Funding**: none (Cochrane review) | Does not have meta-analysis<br><br>**Focus:** iron chelation | **Search cut-off:** from inception to 03 April 2014 | | | failure, endocrine disease, hepatic fibrosis)<br>• Measures of iron overload<br>• Measures of iron excretion over 24 hours<br>• Adverse events<br>• Participant satisfaction<br>• Cost per year | completed RCTs met the inclusion criteria.<br>The authors identified several observational trials of patients with MDS or AML among which the following are of interest of the present review: Cermak, 2013 et al. and Remacha et al., 2015 [41,46] |
| **Other** | | | | | | |
| Lucioni, 2013 [76]<br><br>Italy<br><br>**Funding**: Celgene | To examine the costs and QOL of pts with MDS<br><br>Does not have meta-analysis<br><br>**Focus: General** | Pts who were transfusion dependent and independent.<br><br>**Search cut-off:** 2003 to 2012 | Any | Any | • Cost<br>• QOL | **Design:** Reviews, and primary studies<br>The studies on cost are not of interest of this review; among the studies of QOL that are of interest are 4 conference abstracts: Pashos et al. 2011, Santini et al., 2011, Oliva et al., 2012, Filloux et al., 2011 [89-92] |
| Caocci, 2009 [73]<br><br>Italy<br><br>**Funding:** None declared | To examine existing research that measured QOL in pts with MDS<br><br>Does not have meta-analysis<br><br>**Focus:** QOL | Pts with MDS<br><br>**Search cut-off:** Jan 1980 to Jul 2008 | Various interventio ns QOL | NR | • QOL | **Design:** RCT or prospective comparative fully published reports with pt self-reported measures of QOL<br><br>4 RCTs and 5 prospective nonrandomized studies were included. Of these only 2 met the inclusion criteria of the present review Balleari, 2006 and Kantarjian, 2006 [7,35] |
| Pinchon, 2009 [74]<br><br>UK<br><br>**Funding**: NR | To identify publications on MDS that reported on QOL and describe their utility and correlation with clinical and hematological parameters.<br><br>Does not have meta-analysis<br><br>**Focus**: General | Pts with MDS: in 11 of 17 included studies pts had low-risk disease.<br><br>**Search cut-off:** NR first studies published in 2002. | Various interventio ns. | Various comparisons. | • QOL<br>• Use or red cell transfusion<br>• Hematological response | Six studies evaluation of QOL; 11 studies evaluation of effectiveness of a curative or palliative treatment.<br><br>**Design:** RCTs and no-RCTs.<br>**Comments:** 11 of 17 studies included had pts with low-risk MDS: of these, six were examining intervention of interest to this review [7,35,93-96] |

5- AZA = 5-azacytidine; AE = adverse events; AML = acute myeloid leukemia; ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; ATG = anti-thymocyte globulin; CR = complete response; DA = darbapoetin alpha; EPO = epoetin alpha; ER = erythroid response; ESAs = erythropoiesis stimulating agents; ESMO = European Society of Medical Oncology; G-CSF = granulocyte colony-stimulating factors; GM-CSF = granulocyte-macrophage colony-stimulating factors; HSCT = haematopoietic stem cell transplant; IMiD = immunomodulatory drugs; LEN = lenalidomide; MDS = myelodysplastic syndromes; NR = not reported; OS = overall survival; PFS = progression-free survival; PR = partial response; pts = patients; QOL = quality of life; RCT = randomized controlled trial; RR = response rate; Thal = thalidomide; THPO = thrombopoietin; TTP = time to progression

**Table 4-2. AMSTAR of Included Systematic Reviews Addressing Systemic Treatment of MDS:**

| Study | Intervention and population | An *a priori* design provided | Duplicate study selection and data extraction | Comprehensive literature search performed | Status of publication used as an inclusion criterion | List of studies (included and excluded) provided | Characteristics of included studies provided | Quality of included studies assessed and documented | Quality of included studies used appropriately in formulating conclusions | Methods used to combine the findings of studies appropriate | Likelihood of publication bias assessed | Conflict of interest included |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Systematic reviews from guideline publications** | | | | | | | | | | | |
| Killick, 2014 [58]; Anonymous, 2014 [97] | Management of:<br>Neutropenia, infection (G-CSF);<br>iron overload (chelation);<br>anemia (ESA, DA);<br>Immunological dysregulation (immunosuppressive agents);<br>Del(5q) syndrome (LEN, THAL)<br>Curative options (HSCT)<br>All MDS pts | **N** | **N[C]** | **N** | **N** | **Y[A]** | **N** | **N** | **N** | **N** | **N** | **Y** |
| Fenaux, 2014 [57]; Schrijvers, 2010 [61] Crawford, 2009 [62] | Management of:<br>Anemia (ESAs, DA as first line and ATG and immunosuppressants [e.g., lenalidomide])<br>Del(5q)<br>Neutropenia<br>Thrombocytopenia<br>Iron overload<br><br>Pts with MDS | **N** | **N[C]** | **N** | **N** | **Y[A]** | **N** | **N** | **N** | **N** | **N** | **Y** |
| Malcovati, 2013 [59]; Sekeres, 2013 [98] | Watchful waiting<br>Stem cell transplant<br>Low-dose chemotherapy.<br>Hypomethylating agents.<br>Hematopoietic growth factors.<br>Immunomodulatory drugs.<br>Immunosuppressive therapy.<br>Transfusion and iron chelation.<br><br>Pts with primary MDS | **Y** | **N[C]** | **N** | **N** | **Y[A]** | **N** | **N** | **N** | **N** | **N** | **Y** |
| Leitch, 2013 [3] | THAL and LEN<br><br>Pts with MDS | **Y** | **Y[B]** | **Y** | **Y** | **Y[A]** | **Y** | **N** | **Y** | **Y** | **N** | **Y** |
| Buckstein, 2011 [4] | AZA<br><br>Pts with MDS | **Y** | **Y[B]** | **Y** | **Y** | **Y[A]** | **Y** | **N** | **Y** | **Y** | **N** | **Y** |
| Rizzo, 2010 [60] | ESAs<br>Pts with cancer | **Y** | **N[C]** | **Y** | **Y** | **Y[A]** | **Y** | **N** | **N** | **Y** | **N** | **Y** |

| Study | Intervention and population | An *a priori* design provided | Duplicate study selection and data extraction | Comprehensive literature search performed | Status of publication used as an inclusion criterion | List of studies (included and excluded) provided | Characteristics of included studies provided | Quality of included studies assessed and documented | Quality of included studies used appropriately in formulating conclusions | Methods used to combine the findings of studies appropriate | Likelihood of publication bias assessed | Conflict of interest included |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Systematic reviews publications** | | | | | | | | | | | | |
| Lian, 2016 [81] | LEN | Y | Y | Y | N | Y | Y | N | N | N | Y | N |
| Park, 2016 [80] | DA | Y | Y | Y | Y | Y[A] | Y | N | N | N | Y | YT |
| Hutzschenreuter, 2016 [79] | G-CSF<br>GM-CSF<br><br>Pts with MDS | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Xie, 2015 [72] | AZA vs. Decitabine<br>Pts with MDS | Y | Y | Y | N | Y[A] | Y | N | N | N | Y | Y |
| Lucioni, 2013 [76] | Various interventions<br>Pts with MDS | Y | N | N | N | Y[A] | Y | N | N | Y | N | N |
| Castelli, 2013 [77] | IMiD<br>Pts with MDS | N | N | Y | N | Y[A] | Y | N | N | Y | N | Y |
| Pinchon, 2009 [74] | Various interventions<br><br>Pts with MDS | Y | N | Y | N | Y[A] | Y | Y | N | Y | N | N |
| Mundle, 2009 [75] | Epoetin alpha<br><br>Pts with MDS | Y | N | N | N | Y[A] | N | N | N | N | N | Y |
| Caocci, 2009 [73] | Hyopomethylating agents and G-CSF<br>Pts with MDS. | Y | Y | N[D] | Y | Y[A] | Y | Y | Y | Y | N | N |
| Prica, 2014 [12] | Thrombopoietin-receptor agonists<br>Pts with MDS | Y | Y | Y | Y | Y[A] | Y | Y | Y | Y | N | Y |
| Meerpohl, 2014 [78] | Deferasirox<br>Pts with MDS | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |

[A]No list of excluded studies is provided, and/or included studies are listed only in the reference list.
[B]Initial screening from a larger search was performed by one reviewer who divided the articles by intervention type. Subsequently two reviewers screened citations relevant to each intervention.
[C]Details on the conduct of the systematic review have not been provided in the guideline publications and the relative online appendices.
[D]The authors only searched PubMed

ATG = anti-thymocyte globulin; AZA = 5-azacytidine; DA = decitabiine; Del(5q) = deletion (5q); ESAs = erythropoiesis-stimulating agents; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; HSCT = Hematopoietic stem cell transplantation; IMiD = immunomodulatory drugs; LEN = lenalidomide; MDS myelodysplastic syndromes; N = no; pts = patients; THAL = thalidomide; Y = yes

**Search for Primary Literature**

We conducted a search for primary, comparative studies published from 2005 to July 19, 2017. The year 2009, was chosen as a cut-off date for primary studies of AZA, because the systematic review by Buckstein et al. [4] did not identify any studies for patients with lower risk prior to that date. Primary studies of other agents were searched from publication date 2005 onward.

***Literature Search Results***

The flow diagram of the primary studies section of this review is reported in Appendix 5B. The search of electronic databases and all other additional sources of evidence resulted in 2915 records that the methodologist (FB) reviewed at the title and abstract level. From these, 320 publications were selected and retrieved, and the methodologist reviewed the full text articles. After full-text review 91 were included; of these, 30 were full publications [5-8,10,11,18,19,26-28,31,33-35,37,39-41,45,46,49-53,99-102], 18 were abstract reports [9,29,30,36,42-44,103-113] of unique studies, 17 were companion publications of the main studies [2,20-25,114-123], 10 were pooled analyses of the main studies [124-133], and 16 were abstract publications of ongoing trials [134-149].

Among the included studies, six fully published trials [5-8,10,11], five abstract publications of completed studies [9,103-105,112], and an abstract publication of an ongoing trial examined hematopoiesis-stimulating agents; one fully published study [18], and a series of abstract publications of two studies [135] and Fenaux et al. [142] examined thrombopoietin receptor agonists.

Seven studies examined immunomodulatory drugs, two fully published on patients with del(5q) [19,26], and five on patients with non-del(5q) (two fully published [28,99] and three abstract publications [29,107,113]).

Twelve studies examined hypomethylating agents: five fully published [31,33-35,102], and three abstract publications of completed studies [30,36,106], and four abstract publications of ongoing studies [138,139,148,150].

Two fully published studies examined immunosuppressive agents [27,37].

Twelve studies examined ICT, six fully published [39-41,46,100,101], and five abstract reports of completed studies [42-44,108,111], and one abstract report of an ongoing trial [137].

Five fully published studies [49-53], one abstract report of a completed study [110], and three abstracts of ongoing trials [144,146,147] examined other therapeutic agents.

The general characteristics and the results of these studies are presented in Tables 4-3 and 4-4 for studies of patients with lower-risk MDS, and in Tables 4-5 and 4-6 for studies that included also patients with intermediate-2 or high-risk MDS and did not present separate results. We considered abstract reports as unpublished studies, and we reported their general characteristics and their results, along with the abstracts of interim analyses, in Table 4-7; the results of the abstract publications of completed studies are summarized in Table 4-8.

Additionally, we identified 17 companion publications of three studies [10,19,28], and 11 pooled analyses of the unique studies. The general characteristics and summary results of companion publications are summarized in Appendix 6, Tables 1, and in 2A and 2B respectively. Among the companion publications, five were fully published [2,21,22,24,25], and 12 were abstract reports [20,23,114-123]. Two of the pooled analyses were fully published [124,132], and seven were abstract reports [126-131,133]

**Table 4-3. General Characteristics of Included Comparative Studies of Patients with Lower-Risk MDS**

| Study name, Author, year, Country, Funding | Objectives / Focus / Data collection | Design Follow-up | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|---|---|
| **Hematopoiesis-stimulating agents** | | | | | | |
| **Erythropoiesis-stimulating agents** | | | | | | |
| GFM AzaEpo-2008-1 (NCT01015352)<br><br>Thepot, 2016 [102]<br><br>**Country:** France<br><br>**Funding:** Groupe Francophone des Myelodysplasies, Celgene Corporation, Roche Pharma | To report on prognostic factors of response and OS<br><br>**Data collection period:** 2009 to 2010 | RCT Phase II<br><br>**Follow-up**: 30 mos, (IQR 23 to 34) | N = 93 pts with low-risk MDS<br>**IPSS**: low- 38% (n=35), or intermediate-1 61% (n=57)<br>**Gender**: Male 70%<br>**Age** (median): 72 yrs<br>**WHO diagnosis**:<br>RA 5.3%; RARS 40.9%; RCMD 15.1%; RCMD-RS 17.2%; RAEB-1 12.9%; CMML 7.5%, MDS-u 1%<br>Time from diagnosis (median): 37.2 mos | AZA + EPO<br>beta: 75 mg/m$^2$/d for 5 ds every 28 ds for 6 cycles<br>AZA plus EPO 60000U/wk SC | AZA 75 mg/m$^2$ SC/d for 5 ds every 28 ds for 6 cycles | Predictors of OS: (mutations SF3B1, TET2, DNMT3A, ASXL1, JAK2 and 19 other genes, as well as age, gender, IPSS, IPSS cytogenetics, WHO diagnosis, time since MDS diagnosis, SNPa karyotype, duration of erythroid response)<br>OS<br>TTP<br>AE |
| GFM-LenEpo 08<br><br>Toma, 2016 [10]<br><br>**Country:** France<br><br>**Funding:** Ceelgene, Roche | To compare the efficacy of LEN with and without EPO<br><br>**Data collection period:** Jul 2010 to Jun 2012 | RCT, multicenter, open label, Phase III<br><br>**Follow-up:** *nr* | N = 132 RBC-TD pts non-responders to ESAs, non-del5q31<br>**IPSS**: Low- (n=43.5%) and Intermediate-1-risk (n=56.5%) MDS<br>**Gender**: Male 67%<br>**Age** (median, range): 73 yrs, 64-76 yrs<br>**WHO diagnosis**: RARS: 57%; RCMD-RS: 24%; RAEB1: 22%; RCMD: 15%;MDS-U:13%<br>Time from diagnosis (median): *nr* | LEN 10 mg/d for 21 ds every 28 ds + EPO 60,000 U/wk | LEN alone | *HI-Erythroid (HI-E) after 4 treatment cycles<br>Transfusion independence<br>Response duration<br>TTP<br>AE |
| Jang, 2015 [11]<br><br>**Country:** Japan and Korea<br><br>**Funding:** Kyowa Hakko Kirin Co, Ltd | To investigate the optimal initial dose of DA<br><br>**Data collection period:** *nr* | RCT multicenter, open label, Phase II<br><br>**Follow-up:** *nr* | N = 52 RBC-TD pts with hb ≤9.0 g/dL, serum EPO ≤500 mIU/mL<br>**IPSS**: Low/Intermediate-1-risk MDS<br>**Gender**: Male 61.5%<br>**Age** (median): 77 yrs (50 to 89)<br>**WHO diagnosis**:<br>RARS: 7.7%; RCMD: 59.6%; RAEB-1: 9.6%; MDS-u: 11.5%; RCUD: 7.7%<br>Time from diagnosis (median): mos | DA 240 (n=17), µg/wk for 16 wks | DA 60 (n=17), µg/week for 16 wks or DA 120 (n=18), µg/week | *Erythroid response after 16 wks, and after 48 wks<br>Hb levels<br>AE |
| Jädersten, 2008 [5]<br><br>**Country:** Multiple countries<br><br>**Funding:** Fondazione Italiana per la Ricerca sul Cancro, Italy; Fondazione Ferrata | To evaluate the effect of EPO plus G-CSF<br><br>**Data collection period:** *nr* | Retrospective cohort<br><br>**Follow-up:** *nr* | N = 358 pts with MDS<br>**IPSS**: low: 24%; Intermediate-1: 40%; Intermediate-2: 15%; high: 7%<br>**Gender**: Male IG: 54.6%, CG: 62%<br>**Age** (median): IG: yrs, range to; CG: yrs, range: to<br>**WHO diagnosis**: RA/RARS/5q-: 34%; RCMD/RCMD-RS: 30%; RAEB-1: 17%; RAEB-2: 19%<br>Time from diagnosis (median): *nr* | EPO plus G-CSF | No treatment | Association of treatment with OS in a subgroup of pts with low-intermediate-1 IPSS score |

| Study name, Author, year, Country, Funding | Objectives / Focus / Data collection | Design Follow-up | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|---|---|
| Storti, Italy; Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Pliclinico San Matteo, Italy; Cancer Society in Stockholm, Sweden, Swedish Cancer Society | | | | | | |
| **Granulocyte colony-stimulating Factors** | | | | | | |
| Balleari, 2006 [7]<br><br>**Country:** Italy<br><br>**Funding:** *nr* | To examine the effects of the front-line combination of rEPO and g-CSF compared with rEPO alone<br><br>**Data collection period:** Apr 2001 to Dec 2003 | RCT<br><br>**Follow-up:** median 28 mos | N = 30 pts<br>**IPSS**: Low-risk<br>**Gender**: Male 63%<br>**Age** (mean): 74 yrs<br>**WHO diagnosis**:<br>RA 33%; RARS 17%; RCMD 23.3%; RAEB-1 17%; 10% 5q- syndrome<br>Time from diagnosis (median): *nr* | rEPO plus G-CSF | rEPO | Hematological response<br>QOL (as measured with the FACT-An) |
| **Thrombopoietin receptor agonists** | | | | | | |
| **Romiplostim** | | | | | | |
| No comparative studies met the inclusion criteria | | | | | | |
| **Eltrombopag** | | | | | | |
| EQoL-MDS<br>Oliva 2017 [18]<br><br>Country: Multiple countries in Europe<br><br>Funding: Association QOL-ONE | To test eltrombopag<br><br>Data collection period: Jun 2011 to Jun 2016 | RCT, single blind, phase II, superiority trial - Results of only the phase I of the stsudy (interim analysis of 50% of the entire cohort)<br><br>Follow-up: 24 wks | N = 90 pts with low- or intermediate-1 MDS, with PLT<30 Gi/L, ineligible or relapsed/refractory to other treatments<br>**IPSS**: low- or Intermediate-1. (Includes also 8% of patients with high-risk MDS)<br>**Gender**: Male: 58%<br>**Age** (mean): 69 yrs (SD 12.0)<br>**WHO diagnosis**: 22 pts: refractory cytopenia with unilineage dysplasia; 9 pts: refractory anemia with ringed sideroblasts; 31 pts: refractory cytopenia with multilineage dysplasia (of which 15 with ringed sideroblasts); 6 pts: refractory anemia with excess blasts-1; 2 pts: unclassified<br>Time from diagnosis (median): *nr* | Eltrombopag | PBO | Response rate<br>Time to response<br>Frequency of PLT transfusion<br>Incidence and severity of bleeding<br>QOL (QoL EORTC QLQ-30)<br>Predictors of response<br>AE |

| Study name, Author, year, Country, Funding | Objectives / Focus / Data collection | Design Follow-up | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|---|---|
| **Immunomodulatory agents** | | | | | | |
| **Del(5q)** | | | | | | |
| **MDS 004**<br><br>Fenaux, 2011 [19]<br><br>**Countries:** UK, France, Germany, Italy, Spain, Belgium, The Netherlands, Sweden, and Israel<br><br>**Funding:** Celgene<br><br>NCT 00179621 | To assess efficacy and safety of LEN in MDS<br><br>**Data collection period:**<br>Jul 2005 to Jun 2007 | RCT, Phase III, multicenter, double blind, trial with an open label phase<br><br>**Follow-up:** median 1.55 yrs | N = 205 RBC-TD pts, 139 included in the modified ITT analysis<br>**IPSS**: Intermediate-1-risk del5q31 MDS<br>**Gender**: Male 23.7%<br>**Age** (median, range): 69, 36 to 86 yrs<br>**WHO diagnosis**:<br>RA 10.8%; RARS 2.9%; RCMD % 2.9; RAEB-1 11.5%; RAEB-2 2.9%; 5Q-syndrome 48.2%, MDS-u 18.7%<br>Time from diagnosis (median, range): 2.7, 0.2 to 17.1 mos | LEN 10 mg/d on ds 1-21 (n=69) or LEN 5 mg/d on ds 1-28 (n= 69) of 28-d cycles (the study was not powered to detect differences between LEN groups) | PBO (n=67). | *RBC-TI for ≥26 consecutive wks.<br>ER<br>Duration of RBC-TI, cytogenetic response, OS,<br>AML progression<br>AE<br>QOL[C] |
| Adès, 2012 [26]<br><br>Country: France<br><br>**Funding:** *nr* | To ascertain whether LEN can trigger AML transformation<br><br>**Data collection period:** Jan to September 2007 | Historical cohort<br><br>**Follow-up:** 4 yrs from diagnosis | N = 194 TD pts with del(5q)<br>**IPSS**: Low- and Intemediate-1 risk, IPSS score: 0 to 1<br>**Gender**: Male CG: 33% IG: 26%<br>**Age** (median, range): CG: 73 yrs, 64.9 to 81.2 yrs; IG: 70.4 yrs, 42 to 92 yrs<br>**WHO diagnosis**: RA: CG: 14%, IG: 14%; RARS/RCMD-RS: CG: 4%, IG: 14%; RCMD CG: 9% IG: 10%; RAEB-1 CG: 26%, IG: 24%; 5Q-syndrome CG: 38%, IG: 38%, CMML: CG: 1%, IG: 1%<br>Time from diagnosis (median): *nr* | LEN (n=95) 10 mg/d for 3 wks every 4 wks | No-LEN (n=99) | Incidence of AML transformation<br>OS |
| **Non-del(5Q)** | | | | | | |
| Zeidan, 2015 [99]<br><br>**Country**: US<br><br>**Funding**: *nr* | To find the optimum sequencing of LEN and AZA<br><br>**Data collection period:** ***nr*** | Retrospective analysis<br><br>**Follow-up**: *nr* | N = 63 pts with low-risk MDS for whom who ESA treatment failed<br>**IPSS**: Low- and Intemediate-1 risk, score <1.5<br>**Gender**: Male IG: 70%, CG: 69%<br>**Age** (mean): IG: 66.3 yrs, CG: 65.7 yrs<br>**WHO diagnosis**:<br>IG: RA: 11%; RARS: 24%; RCMD: 38%; RAEB-1: 14%; CMML: 5%; MDS/MPN: 8%<br>CG: RA: 15%; RARS: 27%; RCMD: 50%; RAEB-1: 4%; CMML: 4%; MDS/MPN: 0<br>Time from diagnosis (median): *nr* | LEN before AZA (fist line) (n=37) | LEN after AZA (second line) (n=26) | HI-E rate<br>OS<br>Progression to AML<br>Response rate to AZA |
| MDS 005<br><br>Santini, 2016 [28]<br><br>NCT01029262<br><br>**Country:** Multiple | To assess the efficacy and safety of LEN<br><br>**Data collection period:** Feb 2010 to Jun 2013 | RCT, Phase III, double-blind<br><br>**Follow-up:** *nr* | N = 239 pts ineligible or refractory to ESAs<br>**IPSS**: Low/Intermediate-1-risk non-del(5q) MDS<br>**Gender**: Male 67.8%<br>**Age** (median, range): 71 yrs, 43 to 87<br>**WHO diagnosis**:<br>RA:2.9%; RARS: 7.9%; RCMD/RS: 72.8%; RAEB-1: 16.3%<br>Time from diagnosis (median, range): 2.6 yrs. 0.1 to | LEN 10 mg/d in a 28-d cycle (n=160) | PBO (n=79) | *Rate of RBC-TI ≥8 wks<br>Duration of RBC-TI<br>ER<br>AML progression<br>QOL<br>AE |

| Study name, Author, year, Country, Funding | Objectives / Focus / Data collection | Design Follow-up | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|---|---|
| countries<br><br>**Funding:** Celgene | | | 29.6 yrs | | | |
| **Hypomethylating agents** | | | | | | |
| **Azacytidine** | | | | | | |
| No studies met our inclusion criteria | | | | | | |
| **Decitabine** | | | | | | |
| Garcia-Manero, 2013 [34]<br><br>**Country:** US<br><br>**Funding:** Eisai Pharmaceutical | To assess efficacy, safety and tolerability of two low-dose regimens of SC DAC<br><br>**Data collection period:** May 2008 to Oct 2009 for Schedule B; Schedule A was stopped in Dec 2009 | RCT, phase II, open-label, adaptive design<br><br>**Follow-up:** median (range) mos: Schedule A: 14.6 (0.8 to 22.2); Schedule B 15.5 (4.6 to 24.0)[B] | N = 65 pts newly treated with DAC<br>**IPSS**: low: 29%; intermediate-1: 71%<br>**Gender**: Male 69%<br>**Age** (mean ± SD): 68±13 yrs<br>**WHO diagnosis**: *nr*<br>Time from diagnosis (median): 3.6 mos | **Schedule A** (N = 43): DAC 20 mg/m$^2$ SC per d for 3 consecutive ds on ds 1, 2, and 3 every 28 ds | **Schedule B** (N = 22)**:** DAC 20 mg/m$^2$ SC per d once every 7 ds on ds 1, 8, and 15 every 28 ds | OIR*<br>HI<br>Transfusion independence (i.e., transfusion-free for 8 consecutive wks between first dose of study drug and treatment discontinuation)<br>Cytogenetic response<br>OS<br>Time to AML |
| **Immunosuppressive agents** | | | | | | |
| Sloand, 2008 [27]<br><br>**Country:** US<br><br>**Funding:** none declared | To evaluate the clinical course of pts treated with immunosuppressive therapy<br><br>**Data collection**: 1971 and 1994 | Retrosp (historical control) | N = 945 pts<br>**IPSS**: Low/Intermediate-1-risk (n=690), Intermediate-2/high (n=255) MDS (separate results are presented for the lower risk patients)<br>**Gender**: Male 61%<br>**Age**: (<60 yrs) 29%,<br>**WHO diagnosis**:<br>RA: %; RARS: %; RCMD/RS: %; RAEB-1: %<br>Time from diagnosis (median, range): *nr* | ATG +CA | **No therapy (historical control)** | Survival<br>AML progression |
| **Iron chelation** | | | | | | |
| Taher, 2017 [101]<br><br>**Country:** Multiple countries<br><br>**Funding:** Novartis Pharma | To evaluate the overall safety profile, pharmacokinetics, and patient-reported outcomes of two formulations of DFX<br><br>**Data collection period**: | RCT open-label, multicenter, phase II | N = 173 pts with transfusion-dependent thalassemia (80.9%) or very-low- (3.5%), low- (10.4%), or intermediate-risk (4.6%) MDS<br>**Gender**: Male 49%<br>**Age** (mean ± SD): 34.9±19.25 yrs<br>**WHO diagnosis**: *nr*<br>Time from diagnosis (median): *nr* | N = 87 pts film coated DFX tablet | N= 86 pts dispersion DFX tablet | Overall safety (measured by frequency and severity of adverse events and changes in laboratory values)<br>Selected GI AE (diarrhea constipation, nausea, vomiting and abdominal pain) during treatment<br>Treatment compliance<br>Pt satisfaction, and palatability |
| Leitch, 2017 [100]<br>**Country:** Canada | To analyse OS in pts receiving iron chelation therapy | Prospective, observational, registry analysis; | N=239 pts with low-risk MDS<br>**IPSS**:<br>**Gender**: Male 59% | IG: 83 pts treated with ICT: | CG: 156 not treated pts | OS<br>Leukemia-free survival<br>Causes of death |

<table>
<tr><th>Study name, Author, year, Country, Funding</th><th>Objectives / Focus / Data collection</th><th>Design Follow-up</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes</th></tr>
<tr><td>Funding: Government, Celgene</td><td>adjusting for frailty, comorbidity and disability.<br><br>Data collection period: Mar 2006 -Jul 2016.</td><td>matched pair analysis considering age, revised IPSS, transfusion dependence severity, time from MDS diagnosis</td><td>Age (median, range): IG:71 yrs, 63-76 yrs; CG: 76 yrs, 67-82<br>WHO diagnosis: RA, RARS, 5q, MDS-U, Unclassified, RCUD-A, RCUD-T: IG: 44.6%; CG: 39.1%<br>RCMD/RCMD-RS: IG: 42.2%; CG: 35.3%<br>CMML, MDS/MPD: IG: 4.8%; CG: 10.3%<br>RAEB-1: IG: 8.4%; CG:15.4%<br>RARS/RARS-T/RCMD-RS: IG: 28.9%; CG: 12.8%<br>Time from diagnosis (months: median, range): IG: 18, 2-46; CG: 6, 1-17</td><td>deferasirox (n = 63, 75.9%), deferoxamine (n = 7, 8.43%) and deferoxamine followed by deferasirox, (n = 13, 15.7%).</td><td></td><td></td></tr>
<tr><td>Remacha, 2015 [41]<br><br>Country: Spain<br><br>Funding: none declared</td><td>To evaluate the evolution of iron overload<br><br>Data collection period: Mar 2010 to Mar 2011</td><td>Retrospective cohort</td><td>N = 263 pts<br>IPSS: Low-: 82.9%; Intermediate-1: 0 Missing data: 17.1%<br>Gender: Male: 57%<br>Age (mean±SD): 71.9±10.5 yrs<br>WHO diagnosis: RA: 14.8 %; RARS: 36.1%; RCMD: 24%; RCMD-RS: 9.9%; del 5q: 7.2%; RAEB-I: 2.7%; CMML 3.4%; MDS-u: 1.1%<br>Time from diagnosis (median): nr</td><td>Iron chelation</td><td>No chelation</td><td>OS<br>Leukemia-free survival<br>Cardiac EFS<br>Predictors of OS</td></tr>
<tr><td>Lyons, 2014 [39]<br><br>Country: US<br><br>Funding: Novartis Pharmaceutical Corporation</td><td>To evaluate the association between chelation and clinical outcomes<br><br>Data collection period: starting on Dec 2010</td><td>Prospective observational (registry data)<br><br>Follow-up: 24 mos</td><td>N = 600 pts<br>IPSS: low: IG: 44.1%, CG: 49.3%; intermediate-1: IG: 55.9%, CG: 66.3%;<br>Gender (male): IG: 76.3%; CG: 70.4%<br>Age (median, range): IG: 75 yrs, 21 to 94 yrs; CG: 77 yrs, 47 to 99 yrs<br>WHO diagnosis:<br><table><tr><th></th><th>IG</th><th>CG</th></tr><tr><td>RA</td><td>16.7%</td><td>33.9%</td></tr><tr><td>RARS</td><td>51.3%</td><td>30.4%</td></tr><tr><td>RCMD</td><td>15.4%</td><td>17.9%</td></tr><tr><td>RCMDrs</td><td>9%</td><td>7.1%</td></tr><tr><td>del(5q)</td><td>7.7%</td><td>10.7%</td></tr></table>Time from diagnosis (median, range): varying</td><td>Iron chelation</td><td>No chelation</td><td>OS<br>Number of RBC units transfused<br>Time to progression to AML<br>Death rate</td></tr>
<tr><td>Cermak, 2013 [46]<br><br>Country: Czech Republic<br><br>Funding: Ministry of Health of Czech Republic</td><td>To compare the outcomes of deferiprone and deferasirox<br><br>Data collection period: nr</td><td>Retrospective cohort</td><td>N = 113<br>IPSS: Low-: IG:32%; CG: 24.7%; Intermediate-1: IG: 25.6%; CG: 17.6%<br>Gender: Male: IG:52.3%; CG:58.3%<br>Age (mean, range): IG: 64.9 yrs, 29 to 84; CG: 66.8 yrs, 29 to 84 yrs<br>WHO diagnosis:<br><table><tr><th></th><th>IG</th><th>CG</th></tr><tr><td>RARS</td><td>12.2%</td><td>23%</td></tr><tr><td>RCMD /RCMDrs</td><td>44.5%</td><td>35.2%</td></tr><tr><td>RAEB-I</td><td>4.8%</td><td>0</td></tr></table></td><td>Deferasirox 10-40 mg/kg</td><td>Deferiprone 40-90 mg/kg</td><td>Decrease in serum ferritin of >25%<br>Decrease of serum ferritin >50%</td></tr>
</table>

| Study name, Author, year, Country, Funding | Objectives / Focus / Data collection | Design Follow-up | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|---|---|
| | | | Time from diagnosis (median): *nr* | | | |
| Rose, 2010 [40]<br><br>**Country:** France<br><br>**Funding:** *nr* | To assess the effect of iron chelation<br><br>**Data collection period:** May 15 to Nov 15, 2007 | Prospective cohort, multicentre<br><br>**Follow-up** (median) 2.5 yrs | N = 97 pts regularly transfused<br>**IPSS**: low- 46.4% or intermediate -1 risk 53.6%<br>**Gender**: Male 59.7%<br>**Age** (mean): 72 yrs<br>**WHO diagnosis**:<br>RA: 12.2%; RARS: 28%; RCMD 4.9%; RCMD-RS: 6.1%; RAEB-1: 24.4%; del(5q):9.8% MDS-u: 14.6%, Missing: 15%<br>Time from diagnosis (median, range): 23 mos, 3 to 192 mos | Iron chelation (deferoxamine 40 mg/kg/d or deferiprone 30-75 mg/kg/d) | No chelation | OS<br>Progression to AML<br>Causes of death |
| **Other agents** | | | | | | |
| Garcia-Manero, 2014 [49]<br><br>**Country:** US<br><br>**Funding:** *nr* | To test the efficacy of siltuximab in reducing RBC transfusions requirement and to assess its safety and tolerability<br><br>**Data collection period:** Nov 2011 to Jul 2012 | RCT, double-blind, multicenter, Phase II<br><br>Stopped early for futility | N = 76 transfusion-dependent pts, with ECOG performance status 0 to 2<br>**IPSS**: all low- Intermediate-1 (IPSS score of 0, 0.5, or 1.0)<br>**Gender**: Male 58%<br>**Age** (median, range): 72 yrs, 50 to 85 yrs<br>**WHO diagnosis**:<br>RA: 5%; RARS: 20%; RCMD: 36%; RCMD-RS: 20%; RAEB-1 11%; RAEB-2 0%; del5q 0%; MDS-u 4%<br>Time from diagnosis (median): *nr* | Siltuximab 15 mg/kg$^{-1}$ every 4 wks+best supportive care (n=26) | PBO + best supportive care for 12 wks (n=26) | Reduction in RBC transfusions<br>Change in hemoglobin<br>AE |
| Raza, 2012 [52]<br><br>**Country:** US<br><br>**Funding:** Telik, Inc. | To evaluate 2 exended dose schedules of oral ezatiostat<br><br>**Data collection period:** *nr* | RCT, Phase II<br><br>**Follow-up:** *nr* | N = 73 heavily pretreated pts with ECOG performance status 0 to 1<br>**IPSS**: low- (32%) or intermediate-1 (69%)<br>**Gender**: Male 51%<br>**Age** (median, range): 73, 48 to 89 yrs<br>**WHO diagnosis**:<br>RA: 12%; RARS: 15%; RCMD: 33%; RCMD-RS: 19%; RAEB-1: 6%; MDS/MPD-U: 3%; MDS-u: 6%; MDS del 5q 6%; Unknown 1%<br>Time from diagnosis (median): *nr* | Ezatiostat dose schedule 1: 1500 mg p.o., twice/d for 2 wks, and 1-wk rest period | Ezatiostat dose schedule 2:<br>1000 mg p.o. twice/d for 3 wks, and 1-wk rest period | HI rates for erythroid, neutrophils, platelets<br>AE |
| EORTC 0623<br>Baron, 2012 [50]<br><br>**Country:** Multiple countries Europe<br><br>**Funding:** National Cancer Institute (Bethesda, MD, USA) and Fonds Cancer, Belgium | To assess efficacy and safety of 2 dosages of infliximab<br><br>**Data collection period:** *nr* | RCT, Phase II, adaptive design (Simon 2-stage design)<br><br>**Follow-up:** *nr* | N = 46 pts<br>**IPSS**: Low- risk: 24%; Intermediate-1: 59%; Intermediate-2: 11%<br>**Gender**: Male 46%<br>**Age** (median, range): IG: 65.5 yrs, 50 yrs to 83 yrs; CG: 66 yrs, 39 yrs to 91 yrs<br>**WHO diagnosis**: *nr*<br>Time from diagnosis (median, range): IG: 2.5 yrs, 0.1 to 18 yrs; CG: 2.8 yrs, 0.3 to 15 yrs | Infliximab 3 mg/kg, i.v. on ds 1 and 15 and then every 4 wks for 6 mos (8 infusions) (n=22) | Infliximab 5 mg/kg, i.v. on ds 1 and 15 and then every 4 wks for 6 mos (8 infusions) (n=21) | Response rate<br>PFS<br>OS<br>AE |

| Study name, Author, year, Country, Funding | Objectives / Focus / Data collection | Design Follow-up | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|---|---|
| | | | | | | |
| Schanz, 2009 [51]<br><br>**Country:** Germany<br><br>**Funding:** Essex-Pharma, Germany | To examine the effectiveness of amifostine<br><br>**Data collection period:** *Jan 2000 to May 2003* | RCT, multicentre, Phase II<br><br>**Follow-up:** 52 wks | N = 44 pts<br>**IPSS**:low: 34%, Intermediate-1: 66%<br>**Gender**: Male 61%<br>**Age** (mean±SD): 67 yrs ± 9.3 yrs<br>**WHO diagnosis**:<br>RA: 50%; RARS: 39%; RAEB: 7%; CMML: 5%<br>Time from diagnosis (mean±SD): 15.8±24.2mos | Amifostine | Best supportive care | HI (improvement of Hb)<br>Disease progression<br>Induction of cytogenetic remission |

*primary outcome
[A] The authors' hospital classification
[B] The study was terminated early for benefit. Protocol defined superiority of Schedule A over Schedule B (posterior probability of more than 95%)
[C] As measured with the *Functional Assessment of Cancer Therapy-Anemia (FACT-An)*
[D] Two patients with IPSS score 1.5 were allowed to enter the study despite protocol violation

A = anemia; AE = adverse events; AML = acute myeloid leukemia; ATG = antithymocyte globulin; CA = cyclosporine; CG = control group; CMML = chronic myelomonocytic leukemia; d(s) = day(s); DA = darbapoetin alpha; DAC = decitabine; del(5q) = chromosome 5q deletion syndrome; COG = Eastern Cooperative Oncology Group; EFS = event-free survival; EORTC = European Organization for Research and Treatment of Cancer; EPO = erythropoetin; ER = erythroid response; ESAs = erythropoiesis stimulating agents; FACT-An = Functional assessment of Cancer Therapy - Anemia; G-CSF = granulocyte colony stimulating factors; Hb = hemoglobin; HI = hematologic improvement; IG = intervention group; IPSS = International Prognostic Scoring System; ITT = intention-to-treat; IU = international units; i.v. = intravenously; LEN = lenalidomide; MDS = myelodysplastic syndromes; MDS-u = myelodysplastic syndrome, unclassifiable; mos = months; MPD = myelo-proliferative disorders; *nr* = not reported; OIR = overall improvement rate, which includes complete remission, partial remission, marrow complete response or hematologic improvement measured at the end of each cycle by using each patient's best response; OS = overall survival; PBO = placebo; PFS = progression-free survival; PLT = platelets; p.o. = orally; PR = partial remission; prosp = prospective; Pts = patients; QOL = quality of life; RA: refractory anemia; RAEB-1 = refractory anemia with excess blasts with: 1. Bone marrow aspirate blast count (of at least 500 cells), 2. Peripheral blood blast count (of at least 200 cells), and 3. No Auer rods; RARS = refractory anemia with ring sideroblasts; RBC = red blood cells; RBC-TD = red-blood-cells transfusion-dependent; RBC-TI = red-blood-cells transfusion-independent; RCMD = refractory cytopenia with multilineage dysplasia; RCMD-RS = refractory cytopenia with multilineage dysplasia and ringed sideroblasts; RCT = Randomized controlled trial; RCUD = refractory anemia with unilineage dysplasial; rEPO = recombinant epoetin alpha, beta or darpoetin; SC = sub cutaneous; SD = standard deviation; T = thrombocytopenia; TD = transfusion –dependent; TTP = timet progression; yrs = years; WHO: World Health Organization; wk(s) = week(s).

**Table 4-4. Results of Included Comparative Studies of Patients with Lower Risk MDS**

| Author, year, Country, Funding | Design | Intervention Control | Survival | Disease control (e.g., EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|---|
| **Hematopoiesis-Stimulating Agents** | | | | | | | |
| **Erythropoiesis-stimulating agents** | | | | | | | |
| GFMAzaEpo-2008-1<br>Thepot, 2016 [102] | RCT | AZA + EPO beta vs. AZA | OS (median): 2.5 yrs vs. 42.2 mos, p=0.69 | *nr* | **Erythroid response**<br>after 4 courses: 31% vs. 37.5%, p=0.82<br>After 6 courses: 24% vs 35%, p=1.00 | *nr* | **Predictors of OS:**<br>Univariate analysis: None of the predictors tested significantly predicted treatment response after 4 or 6 courses<br>Multivariate analysis: time since MDS diagnosis (HR=0.97, 95% CI: 0.95 to 0.99) and abnormal SNPa karyotype (HR=2.92, 95% CI: 1.07-8.01) were prognostic of worse survival. |
| GFM-LenEpo 08<br><br>Toma, 2016 [10] | RCT | LEN + EPO 60,000 U/wk vs. LEN alone | *nr* | Response duration (median): 18.1 (95% CI: 7.6 to NA) mos, vs. 15.1 (95% CI: 10.5 to NA), p=0.64<br><br>Time to response: NS<br><br>TTP: *nr* | *HI-Erythroid*<br>39.4% (95% CI 27.6 to 52.2) vs. 23.1% (95% CI 13.5to 32.2), p=0.044. RR=1.7, p=0.043<br>*Transfusion independence*<br>24.6% (16 pts) vs. 14.1% (9 pts), Relative Risk=1.7, p=0.13 | NS | *Predictors of better response rate:*<br>Baseline serum EPO level below 100 UI/L (OR= 3.3, 95% CI: 1.35-7.9; p=0.0087);<br>presence of the G allele at CRBN rs1672753 (OR= 2.6, 95%CI: 1.09-6.3; p=0.032) |
| Jang, 2015 [11] | RCT | DA 60 vs. DA 120 vs. DA 240 | OS rates: no comparative data provided<br>AML-free survival rates: no comparative data provided | *nr* | ER rate: 64.7% vs. 44.4% vs. 66.7%, p = NS<br>Major ER at 16 wks: 17.6% vs.16.7% vs. 33.3%<br>Hb levels (range): (7.6 to 8.1 g/dL) vs. (8.1 to 8.4 g/dL) vs. (8.6 to 9.1 g/dL) | *No comparative data were reported* | *nr* |
| Jädersten, 2008 [5] | Cohort Retrosp | EPO + G-CSF vs.<br>No treatment | *nr* | *nr* | *nr* | *nr* | *Sub-group of low-risk IPSS score:*<br>Association of treatment with OS: HR, 0.45, 95%CI, 0.21 to 0.94, p=0.033 |

| Author, year, Country, Funding | Design | Intervention Control | Survival | Disease control (e.g., EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|---|
| **Granulocyte Colony-stimulating Factors** | | | | | | | |
| Balleari, 2006 [7] | RCT | rEPO + G-CSF vs. rEPO | *nr* | Progression to AML, NS | ER: 73.3% vs. 40%, p=0.065) | *nr* | QOL: not enough data for comparative analysis |
| **Romiplostim** | | | | | | | |
| No comparative studies met the inclusion criteria | | | | | | | |
| **Eltrombopag** | | | | | | | |
| EQoL-MDS Oliva 2017 [18] | RCT | Eltrombopag vs. PBO | *nr* | AML transformation: 7% vs. 3%, p=0.83 | Response rate 47% vs. 3%, p<0.0001, OR 27.1 (95% CI 3.5 to 211.9, p=0.0017)<br><br>Incidence and severity of bleeding 14% vs. 42%, p=0.0025 | Treatment-related deaths: 0<br>Nonhematologic AE, grade 3 to 4: 46% vs. 16%, p=0.0053<br>Discontinuation due to drug toxicity: 14% in the eltrombopag group. | QOL<br>No significant between group changes were detected<br><br>*Predictors of response*<br>Hb concentration, OR 1.38; 95% CI: 1.12 to 1.70, p=0.0024 |
| **Immunomodulatory agents** | | | | | | | |
| **Deletion (5q)** | | | | | | | |
| **MDS 004**<br><br>Fenaux, 2011 [19]; | RCT | LEN 10 mg or LEN 5 vs. PBO | **OS (median, range)**:<br>LEN 10 mg: 36.9 mos, 0.4 to 57.7 mos<br>LEN 5 mg: 35.5 mos, 1.9-59.4 mos<br>Placebo: 35.9 mos, 2.1-56.5 mos<br><br>**OS median rates:**<br>LEN 10 mg: 44.5 mos (95% CI, 35.5 to not reached)<br>LEN 5 mg: ≥35.5 mos (95% CI, 24.6 to not reached),<br><br>Placebo: 42.4 mos (95% CI, 31.9 to not reached) | **Disease progression**: Duration of follow-up for AML progression (median, range):<br>LEN 10 mg: 36.1 mos, 0.4 to 57.7 mos<br>LEN 5 mg: 31.8 mos, 0.8 to 59.4 mos<br>Placebo: 30.9 mos, 2.1 to 56.5 mos | **Erythroid response at ≥26 wks**:<br>LEN 10 mg: 55.1% (95% CI 42.6% to 67.1%)<br>LEN 5 mg: 34.8% vs.<br>PBO: 6.0%; p<0.001 vs. both LEN groups<br>**Transfusion independence:**<br>LEN 10 mg: 56.1% vs.<br>LEN 5 mg: 42.6% vs. PBO 5.9%; both *p* <0.001). | **Grade 3 or 4 AE:**<br><br>LEN 10mg / LEN 5mg / PBO<br>*Pts with ≥1 AE*: 94.20% / 89.9▫% / 4▫.3▫%<br>*Neutropenia*: 7▫▫40 % / 73.90% / 14.90%<br>▫*Thrombocytopenia*: 40.▫▫% / 33.30 / 1.▫0%<br>*Leukopenia*: 8.70% / 13.0% / 0<br>▫*Anemia*: 2.90% / 5.80 / 9%<br>*DVT*: ▫.80% / 1.4▫% / 1.5% | **Subgroups**<br>LEN 10 mg vs. LEN 5 mg: RBC-TI≥26 wks<br><br>Wks / LEN 10mg<br>50 / 84.9<br>100 / 62.5<br>150 / 5741<br><br>**Predictors of ER (multivariate analysis):**<br>LEN treatment 10 mg vs placebo: p<0.0001<br>LEN treatment 5 mg vs placebo: p=0.0004<br>Higher baseline PLT count ≥150x109/L: p=0.003<br>Longer time since MDS diagnosis: >2 yrs, p=0.05<br><br>**QOL**[B]<br>Mean change from baseline at wk 12:<br>LEN 10 mg vs. placebo: |

| Author, year, Country, Funding | Design | Intervention Control | Survival | Disease control (e.g., EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|---|
| | | | | | | | 5.8 vs. −2.5; F=4.25, p<0.05<br>LEN 5 mg vs. placebo: 5.9 vs. −2.5; F=4.18, p<0.05 |
| Adès, 2012 [26] | Cohort historical | LEN vs. no-LEN | OS (median) after diagnosis:<br>150 mos vs. 78 mos, HR 0.47, 95% CI 0.23 to 1.01, p=0.06 | **Incidence of AML transformation:**<br>9% vs. 15.7%,HR .87, 95% CI 0.27 to 2.82, p=0.82 | *nr* | *nr* | *nr* |
| **Nondeletion (5q)** | | | | | | | |
| Zeidan, 2015 [99] | Retrosp analysis | LEN first-line after ESA failure vs. LEN second line after AZA | OS: NS | Progression to AML: NS | HI-E: 38% vs. 12%, p=0.04<br><br>Responsee rate to AZA: NS | *nr* | ***nr*** |
| **MDS-005**<br><br>Santini, 2016 [28] | RCT | LEN vs. PBO | Not reached | Duration of RBC-TI (median):<br>30.9 wks (95% CI, 20.7 to 59.1) vs. not estimable<br><br>AML progression (median, range):<br>1.6 yrs , (0 to 3.6) yrs vs. 1.3 yrs, (0 to 4 yrs) | TI≥8 wks rate:<br>26.9% vs. 2.5%, (Fisher exact p<0.001)<br>TI ≥ 24 wks rate:<br>17.5% vs. 0 (Fisher exact p<0.001)<br>ER rate:<br>36.5% vs. 19.5%, p=NS | Rates of grade 3 and 4 AE:<br>Neutropenia: 61.9% vs 12.7%<br>Thrombocytopenia: 35.6% vs. 3.8%<br>Infection: 14.4% vs 3.8%<br>Bleeding: 1.9% vs. 0<br>Discontinuation rate due to AE: 31.9% vs. 11.4%<br>Death rate during treatment: 2.5% vs. 2.5%<br>Rate of dose reductions due to treatment: 39.4% vs. 5.1%<br>(p values *nr*) | **Predictors of response:**<br>Average baseline 28-d transfusion burden (low vs. high)[E]:<br>OR: 2.685 (95% CI, 0.955 to 7.551), p=0.061<br>Prior ESA use (yes vs. no):<br>OR: 4.623 (95% CI, 1.324 to 16.152), p=0.016<br>**QOL**<br>At wk 12 NS<br>At wk 24 At week 24,: fatigue, dyspnea, physical functioning,<br>global quality of life: NS<br>emotional functioning: 0.8 vs. 27.1, p=0.047 |

| Author, year, Country, Funding | Design | Intervention Control | Survival | Disease control (e.g., EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|---|
| **Hypomethylating agents** | | | | | | | |
| **Azacytidine** | | | | | | | |
| No studies met our inclusion criteria | | | | | | | |
| **Decitabine** | | | | | | | |
| Garcia-Manero, 2013, [34] | RCT | **Schedule A:** Daily dose: 20 mg/m$^2$ SC per d for 3 consecutive ds on ds 1, 2, and 3 every 28 ds vs.<br><br>**Schedule B:** Weekly dose: 20 mg/m$^2$ SC per d once every 7 ds on ds 1, 8, and 15 every 28 ds | OS median: not reached, HR, 1.5; 95% CI, 0.5 to 4.5, p=NS | Time to AML: NS | OIR: 23% vs. 23% (95% CI for difference: -21.1 to 22.1)<br>HI: 7% vs. 14% p=NS<br>(However protocol-defined superiority was reached and the study was terminated early) | All pts experienced at least 1 drug related AE<br>Grade ≥3 AE:<br>Anemia: 14% vs. 18%<br>Leukopenia: 7% vs. 14%<br>Neutropenia: 28% vs. 32%<br>Pancytopenia: 0 vs. 5%<br>Thrombocytopenia: 12% vs. 23%<br>Death: 19% vs. 27% | Subgroups: (according to age, IPSS risk assessment, time from MDS diagnosis, type of MDS, receipt or not of prior MDS therapy, baseline cytogenetic abnormalities, or ECOG PS<br><br>No relevant between-group differences were detected in OIR when patients were classified by subgroups. |
| **Immunosuppressive agents** | | | | | | | |
| Sloand, 2008 [27] | Retrosp | Immunosuppressive therapy (IST) with ATG or in combination with CA, or CA alone | Comparative data *nr* | Comparative data *nr* | For int-1 IPSS pts, RR to ATG+CA vs.: 54% vs. 29% (p=0.004). | No comparative data provided | Separate results for lower risk patients are not reported |
| **Iron chelation** | | | | | | | |
| Leitch, 2017 [100] | Matched pair analysis prosp | Chelation vs. no chelation | OS (median): 5.2 yrs vs. 2.1 yrs, p<0.0001<br>By multivariate analysis: HR for death: 2.0, p=0.03<br><br>Causes of death: NS | NS | *nr* | *nr* | *nr* |

| Author, year, Country, Funding | Design | Intervention Control | Survival | Disease control (e.g., EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|---|
| Remacha, 2015 [41] | Cohort retrosp | Chelation vs. no chelation | OS: median not reached vs. 153 mos (95% CI, 78.0 to 228), p<0.001 | Leukemia-free survival: not reached vs. not reached, p=0.007<br>Cardiac EFS: 137 mos (95% CI 108.5 to 165.5), vs. 96 mos (95% CI 84.1 to 107.9) p=0.017 | *nr* | *nr* | *Predictors of OS[E]:*<br>Age: p=0.011<br>IPSS: p<0.001<br>Chelation treatment: p=0.015<br>*Predictors of leukemia-free survival[E]:*<br>transfusion frequency: p=0.001<br>IPSS: p=0.014<br>*Predictors of cardiac EFS[E]:*<br>Chelation treatment: p=0.04<br>Sorror comorbidity index: p=0.039 |
| Lyons, 2014 [39] | Observ prosp | Chelation vs. no chelation | OS [median, (25th, 75th percentile)]: 99.3 mos (54.1 mos, not reached) vs. 52.2 mos (24 mos to 136.2 mos), p<0.0001<br>Death rate: 40.7% vs. 50.7% | Time to progression to AML (mean [SD]): 40.6 mos [25.3] vs. 27.3 [20.3], p=NS | Number of RBC units transfused (median, range): 39 , 0 to 620 vs.20 (0 to 250) | Creatinine levels: NS<br>Liver transaminase: NS | *Subgroups:*<br>OS in low-risk group (median, range): 98.7 mos (12.8 to 103.8 mos) vs. 53.6 mos (4.1 to 66.3 mos) |
| Cermak, 2013 [46] | Cohort retrosp. | Deferasirox vs. Deferiprone | *nr* | *nr* | *nr* | NS | Decrease in serum ferritin of >25%:<br>61.5% vs. 27.1%<br>Decrease of serum ferritin >50%: 27.7% vs. 0 |
| Rose, 2010 [40] | Cohort prosp. | Iron chelation vs. no chelation | OS (median): 124 vs. 53 mos, p<0.0003<br>Causes of death: NS | Progression to AML rate: 17% vs. 34%, p=0.087 | *nr* | *nr* | *Prognostic factors of response[E]:*<br>Adequate chelation: HR 0.302; 95% CI 0.16 to 0.58, p=0.0003,<br>Transfusion requirement >3 PRBC/mo: HR 2.516, 95% CI 1.37 to 4.61, p=0.0028<br>IPSS>0: HR 1.929, 95% CI 1.02 to 3.63, p=0.042<br>Age>72 HR 0.678, 95% CI 0.37 to 1.23, p=0.2004<br>Comorbidities>3:<br>HR 1.288, 95% CI 0.59 to 2.83, p=0.527 |

| Author, year, Country, Funding | Design | Intervention Control | Survival | Disease control (e.g., EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|---|
| **Other agents** | | | | | | | |
| Garcia-Manero, 2014 [49] | RCT | Siltuximab + best supportive care vs. PBO + best supportive care | *nr* | *nr* | Reduction in RBC transfusion rate 12% vs. 3.84% showed a reduction, p=0.271 | Grade ≥3 AE 24% vs 31%, NS | *Hb improvement at wk 13* 8% vs. 4%, NS |
| Raza, 2012 [52] | RCT | Ezatiostat high dose vs. ezatiostat lower dose | *nr* | *nr* | HI rates: Erythroid: 21%, 95% CI 9% to 38% vs. 17%, 95% CI 6% to 33% Neutrophils: 8%, 95% CI 0 to 39% vs. 23%, 95% CI 5% to 54 % Platelets: 6%, 95% CI 0 to 27% vs. 0, 95% CI 0 to 15 % | 11 treatment-related serious AE (not presented by group) | *Subgroups:* Effect of prior therapy: Pts who had prior LEN but were HMA-free (n=15): HI- erythroid rate: 40%, 95% CI, 16 to 68 Prior HMA treatment was associated with a 6-fold decrease in the odds for HI- ER to subsequent ezatiostat (p=0 .027). (OR = 0.16; 95% CI, 0.03 to 0.81) Transfusion-independent rate of pts with prior LEN treatment compared with pts with no prior LEN treatment: 4 of 18, 22%, 95% CI, 6 to 48 vs. 0%, 95% CI, 0 to 17% |
| Baron, 2012 [50] | RCT | Infliximab 3 mg/kg vs. Infliximab 5 mg/kg | *nr* | *nr* | Response rate (only IPSS Intermediate-1 or low-risk): 10%,95% CI, 1.2%-31.7% vs. (0%; 95% CI, 0-18.5%) | Grade 3 to 5 infections 41% vs. 19% Treatment-related deaths: 9.5% vs. 4.5% | *nr* |
| Schanz, 2009 [51] | RCT | Amifostine vs. best supportive care | OS median: 162 wks vs. 254 wks p NS | PFS NS | HI rates all cell lines: 18.2% vs. 13.6%, NS HI rates PLT: 9.1% vs.4.5%, NS HI rates erythrocytes: 18.2% | AE grade ≥3: Hemorrhages: 18% vs. 41%, p NS Infections: 36% vs. 64%, p=0.021 | *nr* |

| Author, year, Country, Funding | Design | Intervention Control | Survival | Disease control (e.g., EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|---|
| | | | | | vs. 13.6%, NS<br>HI rates neutrophil:<br>0 vs.4.5%, NS | | |

[A] No results are reported for this outcome in the subgroup of patients with low- intermediate-1 risk category.
[B] Data for QOL outcomes are available for 71% of randomized patients.
[C] Data available on 26 patients in the LEN 5 mg group, 26 patients in the Placebo group and 37 patients in the LEN 10 mg groups
[D] Only data from the double-blind phase of the trial were used because after that patients were allowed to cross over.
[E] In multivariate analysis.
[F] In a Cox model with sex, age, percentage of blasts, French-American-British, karyotype, and rEPO treatment as covariates.
[G] Adjusted for interim analysis
[H] Results refer only to pts with low- intermediate IPPS risk
[I] ≥50% relative decrease and a ≥2-unit absolute decrease in RBC transfusions during the 8 weeks before unblinding at Week 13 compared with RBC transfusions during the 8 weeks before the date of informed consent.

AE = adverse events; AML = Acute myeloid leukemia; AZA = 5-azacytidine; AE = adverse events; CI = confidence interval; DA = darbapoetin alpha; DFX = deferasirox; DVT = deep vein thrombosis; ECOG PS = Eastern Cooperative Oncology Group performance status; EFS = event-free survival; EPO = erythropoetin; ER = erythroid response; ESAs = erythropoiesis stimulating agents; G-CSF = granulocyte colony stimulating factors; Hb = haemoglobin; HI = hematologic improvement; HMA = hypomethylating; HR = hazard ratio; IPSS = International Prognostic Scoring System; LEN = lenalidomide; MDS = myelodysplastic syndromes; mos = months; *nr* = not reported; NS = not significant; Observ. = observational; OIR = overall improvement rate; OR = odds ratio; OS = overall survival; PBO = placebo; PFS = progression-free survival; PLT = platelets; PRBC = packed red blood cells; prosp. = prospective; pts = patients; QOL = quality of life; RBC = red blood cells; RBC-TI = red blood cells transfusion independence; RCT =randomized controlled trial; rEPO = recombinant epoetin alpha, beta or darpoetin; Retrosp = retrospective; SC = subcutaneously; SD = standard deviation; TI = transfusion independence; TTP = time to progression; wk(s) = week(s).

**Table 4-5. General Characteristics of Included Studies of Patients with Lower-, and Higher-Risk MDS that Did Not Report Separate Results**

| Study name, Author, year, Country, Funding | Objectives / Focus / Data collection | Design Follow-up | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|---|---|
| **Hematopoiesis-stimulating agents** | | | | | | |
| **Erythropoiesis-stimulating agents** | | | | | | |
| ECOG E1996<br>Greenberg, 2009 [8]<br><br>Country: US, Canada<br><br>Funding: National Cancer Institute, National Institutes of Health, and the department of Health and Human Services | To test efficacy and safety of EPO and G-CSF and examine predictors of OS<br><br>Data collection period: Dec 1997 - Jun 2004 | RCT, Phase III, multicentre<br><br>Follow-up: median 5.8 yrs (range 0.8 to 9.6 yrs) | N = 110 anemic pts with low-risk MDS<br>**IPSS**: low- Intermediate 1: 83%, Intermediate 2 or high-risk: 17%,<br>**Gender**: Male 63%<br>**Age** (median):73 yrs<br>**WHO diagnosis**: nr<br>Time from diagnosis (median): nr | EPO 150 U/Kg SC with G-CSF (for non-responders) and supportive care (n=53) | Supportive care alone (n=57) | RR<br>QOL (as measured with the FACT-G)<br>OS<br>Incidence of transformation in AML<br>Predictors of survival and response<br>AE |
| **Granulocyte colony-stimulating factors** | | | | | | |
| GFM<br>Park, 2008 [6]<br><br>Country: France and Belgium<br><br>Funding: *nr* | To confirm prognostic factors of response to rEPO with or without G-CSF<br><br>Data collection period: nr | Cohort (historical comparison with the IMRAW cohort [n=475] pts)<br><br>Follow-up: 26 mos | N = 403 pts requiring transfusions<br>Historical cohort: 816 pts International MDS Risk Analysis Workshop [IMDSRAW]<br>**IPSS**: Low- Intermediate 1 risk: 75%, Intermediate-2: 8%, high risk: 2%, IPSS not available 14%<br>**Gender**: Male 56%<br>**Age** (median): 74 yrs<br>**WHO diagnosis**:<br>RA: 15%; RARS: 21%; RCMD: 17%; RCMD-RS: 14.1%; RAEB-1: 23%; RAEB-2: 6.5%, del 5q- syndrome: 4.5%<br>Time from diagnosis (median): 6 mos | rEPO + G-CSF | rEPO alone<br>Untreated (IMDSRAW historical cohort) | Predictive factors or response<br>Time to AML |
| **Romiplostim** | | | | | | |
| No new fully published new studies identified | | | | | | |
| **Eltrombopag** | | | | | | |
| No new fully published new studies identified | | | | | | |
| **Immunomodulatory agents** | | | | | | |
| No new fully published new studies identified | | | | | | |
| **Hypomethylating agents** | | | | | | |
| **Azacytidine** | | | | | | |
| Falantes, 2015 [31]<br><br>Country: Spain | To assess efficacy of AZA in pts treated who had a lower-risk IPSS | Historical cohort<br><br>Follow-up: | N = 88 pts<br>**IPSS**: low- Intermediate-1 risk MDS: IPSS score 0: 3.4%; IPSS score 0.5: 50%; IPSS score 1: 46.6% | AZA cohort: N= 27<br>AZA 75 mg/m$^2$/d, every 4 wks | Non-AZA, historical cohort: N = 61 (i.e., BSC [n=46] or BSC plus | ORR (CR/PR/HI)<br>OS<br>Progression to AML |

| Study name, Author, year, Country, Funding | Objectives / Focus / Data collection | Design Follow-up | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|---|---|
| Funding: nr | profile, but presented adverse clinical features<br><br>Data collection period: nr | (median) 17 mos | **Gender**: *nr*<br>Age (median, range ): 71, 48-86 yrs<br>**WHO diagnosis**:<br>RA/RARS: 17%; RCMD/RS: 38.6%; RAEB-1: 33%; CMML: 11.4%<br>Time from diagnosis (median): *nr* | | ESAs, [n=15]) | |
| Lyons 2009 [33]<br><br>**Country:** US<br><br>**Funding:** *nr* | To evaluate three alternative AZA dosing schedules that avoid week-end dosing<br><br>Data collection period: | RCT Phase II multicentre open-label | N = 151 pts<br>**IPSS**: *nr. Pts with lower risk FAB were included.*<br>**Gender** (male):<br>AZA 5: 66%<br>AZA 5-2-2: 56%<br>AZA 5-2-5: 73%<br>**Age** (median, range ):<br>AZA 5: 76 yrs, 47 to 93 yrs<br>AZA 5-2-2: 73 yrs, 37 to 88 yrs<br>Aza 5-2-5: 76 yrs, 54 to 91yrs<br>**FAB classification**:<br>AZA 5: RA:44%; RARS: 14%; RAEB: 28%; RAEB-T: 4%; CMML: 10%<br>AZA 5-2-2: RA:44%; RARS: 14%; RAEB:28%; RAEB-T: 2%; CMML: 12%<br>Aza 5-2-5: RA:41%; RARS: 14%; RAEB: 33%; RAEB-T: 2%; CMML:10%<br>Time from diagnosis (median): mos | 6 cycles of:<br>AZA 5-2-2: AZA 75 mg/m$^2$/d SC for 5 ds + 2 ds of break + AZA 75 mg/m$^2$/d SC for 2 ds (total dose 525 mg/m$^2$)<br><br>vs.<br><br>AZA 5-2-5:<br>AZA 50 mg/m$^2$/d SC for 5 ds (total dose 500 mg/m$^2$) | 6 cycles of:<br>AZA 5:<br>AZA 75 mg/m$^2$/d SC for 5 ds (total dose 375 mg/m$^2$) | HI<br>Transfusion independence rates<br>AE |
| **Decitabine** | | | | | | |
| Kantarjian, 2006 [35]<br><br>Country: US<br><br>Funding: *nr* | To evaluate the efficacy of DAC in pts with MDS<br><br>Data collection period:<br>Jul 2001 to Jan 2004 | RCT, open label, Phase III, trial<br><br>Follow-up: nr | N = 170 pts<br>**IPSS**:<br>Intermediate-1: 31% (n=52)<br>Intermediate-2: 44% (n=74);<br>hi-risk: 25% (n=44)<br>**Gender**: Male 68%<br>Age (median, range): IG: 70 yrs, 65 to 76 yrs; CG: 70 yrs, 62 to 74 yrs<br>**WHO diagnosis**:<br>nr for the subgroup at low-intermediate-1 risk pts<br>Time from diagnosis (median): nr for the subgroup at low- intermediate-1 risk pts | DAC n=89; in the low- intermediate-1 risk subgroup: n=28 | BSC; n=81; in the low-intermediate-1 risk subgroup: n=24 | ORR*<br>HI<br>Time to AML transformation* Death[A]<br>AE[A]<br>QOL |
| **Immunosuppressive agents** | | | | | | |
| Passweg, 2011 [37]<br><br>Country: Swiss, Germany, the Netherlands | To evaluate the impact of immunosuppressio n | RCT, Phase III open label<br><br>Follow-up: median | N = 83 pts who were transfusion dependent<br>**IPSS**: Low: 18%; Intermediate 1: 56%; Intermediate-2: 14%; high 1%; Not evaluable: 11% | Horse ATG 15 mg/kg + CsA | BSC | *RR at 6 mos<br>Transfusion requirement<br>Transformation<br>OS |

| Study name, Author, year, Country, Funding | Objectives / Focus / Data collection | Design Follow-up | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|---|---|
| Funding: none declared | Data collection period: 2000 to 2006 | (range) 2.3 yrs (0 to 6.5 yrs). | **Gender**: Male 68%<br>**Age** (median):IG: 62 yrs (range, 23 to 75 yrs) and 65 yrs (range, 24 to 76 yrs)<br>**WHO diagnosis:**<br>RA 44.3%; RAS 16%; RAEB-1 22.7%; RAEB-II 2%; hypoplastic 14.7%<br>Time from diagnosis (median): mos | | | |
| **Iron chelation** | | | | | | |
| Neukirchen, 2012 [45]<br><br>**Country**: Germany<br><br>**Funding**: Novartis Pharma | To test whether iron chelation improves survival<br><br>**Data collection period**: 1975 to 2008 | Retrospective matched-pair analysis of the Düsseldorf registry<br><br>**Follow-up:** *nr* | N = 188 pts<br>**IPSS**: low 37%; intermediate-1 46% Intermediate-2: 14%; high: 3%,<br>**Gender** (male): IG: 52%; CG: 58%<br>**Age** (median, range): IG: 64 yrs, 18 to 82 yrs; CG: 67 yrs, 33 to 89 yrs<br>**WHO diagnosis**: RA: 6%; RARS :10%; RCMD: 43%; RAEB-1: 9%; RAEB-2: 4%; del(5q): 23%, CMML: 5%<br>Time from diagnosis (median, range): 21 mos, 0 to 212 mos | Iron chelation (56% deferoxamine, 44% deferasirox) | No chelation | OS<br>AML transformation |
| **Other agents** | | | | | | |
| CALGB 198034<br>Grinblatt, 2009 [53]<br><br>Country: US<br><br>Funding: Glaxo-Smith-Kline | To test the effectiveness of two different doses of topotecan<br><br>Data collection period: nr | RCT, Phase II<br><br>Follow-up: *nr* | N = 90 transfusion-dependent pts<br>**IPSS**: low: 8%; Intermediate-1: 29%; Intermediate-2: 26%; high: 12%; missing: 26%<br>It included pts with different IPSS scores but reported data for the low-Intermediate1 group, however not in a comparative fashion<br>**Gender**: Male 64%<br>**Age** (median, range): 70 yrs, 32 yrs to 85 yrs<br>WHO diagnosis: nr<br>Time from diagnosis (median): mos | Topotecan, p.o. 1.2 mg/m$^2$ twice/d for 5 ds, every 21 ds for ≥ 2 cycles (n=46) | Topotecan, p.o. 1.2 mg/m$^2$ once/d for 10 ds, every 21 ds for ≥ 2 cycles (n=44) | Response<br>OS<br>Time to AML or death<br>AE were not reported for low and intermediate-1 risk |

* Primary end point

13-cis-retinoic acid = cRA; ABS = abstract; AE = adverse events; AML = Acute myeloid leukemia; ATG = anti-thymocyte globulin; AZA = 5-azacytidine; BSC = best supportive care; CG = control group; CI = confidence interval; CMML = chronic myelomonocytic leukemia; CR = complete response; CsA = cyclosporine A;); DAC = decitabine; del 5q = chromosome 5q deletion syndrome; ECOG = Eastern Cooperative Oncology Group performance status; EPO = erythropoetin; ESAs = erythropoiesis stimulating agents; FAB classification = French-American-British classification of AML; FACT-G = Functional Assessment of Cancter Therapy; G-CSF = granulocyte colony stimulating factors; GFM = Groupe Francophone des Myélodysplasies; HI = hematologic improvement; IG = intervention group; IMRAW = International MDS risk analysis workshop; IPSS = International Prognostic Scoring System; mos = months; *nr* = not reported; NS = not significant; ORR = overall response rate; OS = overall survival; p.o. = by mouth; PR = partial response; pts = patients; QOL = quality of life; RA = refractory anemia; RAEB-1 = refractory anemia with excess blasts with: 1. Bone marrow aspirate blast count (of at least 500 cells), 2. Peripheral blood blast count (of at least 200 cells), and 3. No Auer rods; RARS = refractory anemia with ring sideroblasts; RCMD = refractory cytopenia with multilineage dysplasia; RCMD-RS = refractory cytopenia with multilineage dysplasia and ringed sideroblasts; RCT = randomized controlled trial; rEPO = recombinant epoetin alpha, beta or darpoetin; RR = response rate; SC = subcutaneous; SD = standard deviation; vs. = versus; wk(s) = weeks(s); WHO = World Health Organization; yrs = years.

**Table 4-6. Results of Included Studies that Included Patients with Lower- and Higher-Risk MDS and Did Not Report Separate Results**

| Author, year, Country, Funding | Design | Intervention Control | Survival | Disease control (e.g. EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|---|
| **Hematopoiesis-Stimulating Agents** | | | | | | | |
| **Erythropoiesis-stimulating agents** | | | | | | | |
| ECOG E1996 Greenberg, 2009 [8] | RCT | EPO + G-CSF (only non-responders) vs. supportive care | OS median: 3.1 yrs vs. 2.6 yrs, NS | Incidence of transformation to AML: 7.5% vs. 10.5%, NS | Response rate: 36% vs. 9.6% (at the initial treatment step – 4 mos evaluation point), p=0.002 | EPO vs. supportive care:<br>Transient grade3-4 thrombocytopenia: p<0.001<br>Transient hyperbilirubini8emia p=0.002<br>Other AE: NS | *Predictors of survival:*<br>Erythroid responders:<br>OS: 5.5 yrs vs. 2.3 yrs, p=0.004<br>*QOL (n=84):* NS. |
| **Granulocyte colony-stimulating factors** | | | | | | | |
| Park, 2008 [6] | Cohort (histor) | rEPO + G-CSF vs. rEPO alone | *nr* | *nr* | *nr* | *nr* | *Prognostic factors of response:*<br>EPO level ≤200 iU/L, OR 2 (95% CI 1.2 to 3.5)<br>Absence of transfusion requirement OR 0.4 (95% CI 0.2 to 0.6)<br>Low and intermediate-1 IPSS score OR 2.5 (95% CI 1 to 6.4)<br>*Subgroups*<br>*Responders to rEPO:*<br>OS: 64% vs. 39%, p<0.001<br>*Non-responders:*<br>OS: NS |
| **Romiplostim** | | | | | | | |
| No additional studies were identified | | | | | | | |
| **Eltrombopag** | | | | | | | |
| No additional studies were identified | | | | | | | |
| **Immunomodulatory agents** | | | | | | | |
| No additional studies were identified | | | | | | | |
| **Hypomethylating agents** | | | | | | | |
| **Azacytidine** | | | | | | | |
| Falantes, 2015 [31] | Cohort hist | AZA cohort: 75 mg/m$^2$/d, every 4 wks vs.<br>Non-AZA cohort: BSC or BSC plus ESAs | OS:<br>actuarial at 1 yr: 62% vs 25.4%<br>actuarial at 2 yrs: 45% vs. 11%, p=0.0001<br>Est. OS rate at 12 mos: 62.4% vs. 31.5%<br>Est. OS rate at 24 mos: 45.1% vs. 5.7% | Progression to AML rate: 14.8% vs. 24.6%, p=0.19 | ORR: AZA: 40.7% (CR: 20%, PR: 8%, HI:12%)<br>Non-AZA*: nr* | Hematological toxicity: not assessed<br>Death (drug-related): 0 | *Predictors of survival (multivariable analysis):*<br>BM blast%, neutropenia, thrombocytopenisa and AZA treatment were not significant predicotrs HR = 1.502, 95% CI, 0.258 to 3, p=0.258<br>Severe thrombocytopenia (<50x10$^9$L$^{-1}$) had a negative impact on OS: HR=1.690, 95% CI 1.036 to 2.756, |

| Author, year, Country, Funding | Design | Intervention Control | Survival | Disease control (e.g. EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|---|
| | | | | | | | p=0.03 |
| Lyons 2009 [33][B] | RCT | AZA 5 vs. AZA 5-2-2 vs. AZA 5-2-5 | *nr* | Duration of transfusion independence (median):<br>AZA 5: 387 ds<br>AZA 5-2-2: 473 ds<br>AZA 5-2-5: not reached | Transfusion independence:<br><br>AZA 5: 16 (64%, 95% CI, 43 to 82)<br>AZA 5-2-2: 12 (50%,95% CI 29 to 71)<br>AZA 5-2-5: 12 (55% ,95% CI 32 to 76) | Rates (number) of pts who discontinued or delayed treatment during the first 6 cycles due to an AE:<br>AZA 5: 34% (17 of 50)<br>AZA 5-2-2: 68% (34 of 50)<br>AZA 5-2-5: 63% (30 of 48)<br>**AE:**<br>Hematologic disorders:<br>AZA 5: 34%<br>AZA 5-2-2:66%<br>AZA 5-2-5: 50%<br>Infections:<br>AZA 5: 10%<br>AZA 5-2-2: 22%<br>AZA 5-2-5: 29%<br>Serious AE % (N):<br>AZA 5: 30% (15)<br>AZA 5-2-2: 54% (27)<br>AZA 5-2-5: 40% (19) | *Subgroups: Pts with lower FAB risk:*<br>HI (major or minor) rates (number):<br>AZA 5: 50% (16 of 32)<br>AZA 5-2-2: 49% (16 of 33)<br>AZA 5-2-5: 41% (12 of 29)<br>Pts who achieved transfusion independence:<br>AZA 5: 69%<br>AZA 5-2-2: 75%<br>AZA 5-2-5: 50%<br><br>*Predictors of transfusion independence:*<br>Absence of baseline neutropenia ($\geq 1.5x10^9/L$)<br>Absence of thromobocytopenia ($\geq 100x10^9/L$)<br>Lower transfusion requirements (≤2 units/56 ds)<br>Comparison among the 3 dose schedules NS |
| **Decitabine** | | | | | | | |
| Kantarjian, 2006 [35] | RCT | DAC vs. BSC | OS: 14 mos vs. 14.9 mos, p=0.636 | Median time to AML 12.1 mos vs 7.8, p=0.16 | ORR:17% vs. 0%, p<0.001<br>HI: 13% vs. 7% p values *nr* | Death: 14% vs 22%<br>Serious AE: 69% vs. 56% (neutropenia, thrombocytopenia, anemia, pyrexia, hyperbilirubinemia, and pneumonia) | *Subgroups*<br>Treatment-naïve pts: Time to AML or death: 12.3 mos vs. 7.3 mos, p=0.08<br>IPSS score intermediate-2/High: 12 mos vs 6.8 mos, p=0.03<br>DAC responders vs. non responders: OS 23.5 vs. 13.7 mos p=0.007<br>*QOL*<br>Global health status p<0.05 at the end of cycles 2 and 4<br>Fatigue p<0.05 at the end of cycles 2,4,5,6<br>Dyspnea p<0.05 at the end of all cycles |
| **Immunosuppressive agents** | | | | | | | |
| Passweg, 2011 [37] | RCT | Horse ATG + CsA vs. Best supportive care | OS estimate at 2 yrs: 49% (95% CI, 31% to 66%) vs. 63% (95% CI, 42% to 78%), p=0.828 (The trial was not powered to detect | TFS at 2 yrs: 46% (95% CI, 28% to 62%) vs 55% (95% CI, 34% to 70%), p=0.73<br>LFS at 2 yrs: | Hematological response rate at 6 mos: 29% vs. 9%, p=0.0156[C] | Deaths: 38% vs. 31%<br>Serious AE:<br>40% vs. 10%, p=0.005 | *Transfusion requirement (medical resource use)*<br>RBC transfusion units (median number):<br>28 (range, 0 to 148; n=42) and 16.5 (range, 0 to 205; n=40); |

| Author, year, Country, Funding | Design | Intervention Control | Survival | Disease control (e.g. EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|---|
| | | | survival differences) | 51% (95% CI, 31% to 67%) vs.62% (95% CI, 41% to 78%), p=0.91 | | | Platelet transfusion units (median number):<br>3.5 (range, 0 to 85; n=42) and 0 (range, 0 to 97; n=40) |
| **Iron chelation** | | | | | | | |
| Neukirchen, 2012 [45] | Observ retrosp | Iron chelation vs. No chelation | OS (median): 75 mos vs. 49 mos, p=0.002 | AML transformation risk: NS | *nr* | *nr* | *Subgroups:*<br>OS median: high-risk pts: NS; low-risk pts p=0.008 |
| **Other agents** | | | | | | | |
| CALGB 198034 Grinblatt, 2009 [53] | RCT | Topotecan, p.o. 1.2 mg/m$^2$ twice/d for 5 ds vs. Topotecan, p.o. 1.2 mg/m$^2$ once/d for 10 ds | OS (median): 17 mos (95% CI 13 to 22 mos) vs. 12 mos (95% CI 7 to 18), p=0.53 | Response duration:<br>23 mos (95% CI 15 to 29 mos) vs. 14 mos (95% CI 8 to 17 mos), p=0.02<br><br>Time to AML or death: 17 mos vs. 11 mos, p=0.3 | ORR: 33% vs. 27%, p=0.91 | NS | *Subgroups: IPSS score*<br>OS median (95% CI):<br>Low: 18.3 mos (10 to 28.1 mos)<br>Intermediate-1 score: 18.3 mos (13.2 to 33.1 mos)<br>Intermediate-2 score: 14.9 mos (7.7 to 18.1 mos)<br>High score: 6.5 mos (3.6 to 11.6 mos)<br>Unknown: 13.0 mos (6.2 to 16.7)<br>p=0.004 (for differences among groups) |

[A] In this study no formal hypothesis testing was planned for all comparisons because of the small sample size in each group.
[B] This trial was not designed to achieve statistically significant results or formal hypothesis testing among the three alternative regimens
[C] Adjusted for interim analysis.

13cRA = 13-cis-retinoic acid; ABS = abstract; AE = adverse events; AML = Acute myeloid leukemia; ATG = anti-thymocyte globulin; AZA = 5-azacytidine; CALGB = Cancer and leukemia group B; BM= bone marrow; BSC = best supportive care; CI = confidence interval; CsA = cyclosporine A; DA = darbapoetin alpha; DAC = decitabine; d(s) = day(s); ECOG = Eastern Cooperative Oncology Group performance status; EPO = erythropoetin; est = estimate; FAB classification = French-American-British classification of AML; G-CSF = granulocyte colony stimulating factors; GM-CSF = granulocyte-macrophage colony-stimulating factors; HI = hematologic improvement; hist = historical comparison; HR = hazard ratio; IPSS = International Prognostic Scoring System; LFS = leukemia-free survival; mos = months; *nr* = not reported; NS = not significant; OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; pts = patients; QOL = quality of life; RBC = red blood cells; rEPO = recombinant epoetin alpha, beta or darpoetin; TFS = transformation-free survival; vs. = versus; wk(s) = weeks(s); yrs = years.

***Study Design and Quality***

Among the studies that included only or that reported separate results for patients with lower-risk MDS 15 were RCTs [7,10,11,18,19,28,30,34,49-52,101,102,151] and 17 were observational studies [5,26,27,29,39-41,43,46,99,100,106,108,111-113].

Thirteen of the included RCTs [7,10,11,18,19,28,34,49-52,101,102] and nine of the observational studies [5,26,27,39-41,46,99,100] were fully published articles, and the remainder were abstract reports of conference proceedings. General characteristics and results of the abstract reports are presented in Tables 4-7 ad 4-8 among the unpublished and ongoing trials. We did not measure the quality of abstract reports because not enough information was available to conduct a consistent judgement.

The quality of included, fully published, RCTs, as measured with the Cochrane Risk of Bias Tool [70] is summarized in the graphs presented in Figure 4-1A, and 4-1B. The judgement for the quality of each individual study and its justification is reported in Appendix 7A and B. Among the RCTs of patients with lower risk, two trials, the MDS004 [19], and MDS005 [28], were considered to be of high quality; the others were considered to be of variable quality.

Among the RCTs of patients with lower, and intermediate-2 or high IPSS risk that did not present separate results for the lower risk population, one study was considered to be of higher quality [35], and the others [8,33,37,53] to be of variable quality. The certainty of the evidence from these studies was downgraded because of indirectness.

Our search also identified four additional randomized trials [13-16]. These trials were included in the systematic review by Prica et al. [12], and we endorsed the reviewers' judgement about their quality (the trials were judged to be of high quality), and their results. Therefore, these trials do not appear in our tables, and in the flow diagram.

The summary judgements about the quality of the non-randomized, fully published, observational studies of patients with lower-risk MDS [5,26,27,39-41,46,99,100], performed with the Cochrane Risk of Bias in Non Randomized Studies – of Interventions [71], are reported in Appendix 7C. Three of these observational cohort studies were prospective and their risk of bias has been considered moderate [40,100], and serious [39]. The other studies [5,26,27,39-41,46,99] were retrospective and their risk of bias was considered serious [5,26,41,99], or critical [46].

The observational studies that reported on a population of patients with lower- and intermediate-2 IPSS risk [6,31,42,45,110], and did not present separate results for the lower-risk population were considered at high risk of bias because the evidence reported was at least partially indirect, and quality assessment was not conducted.

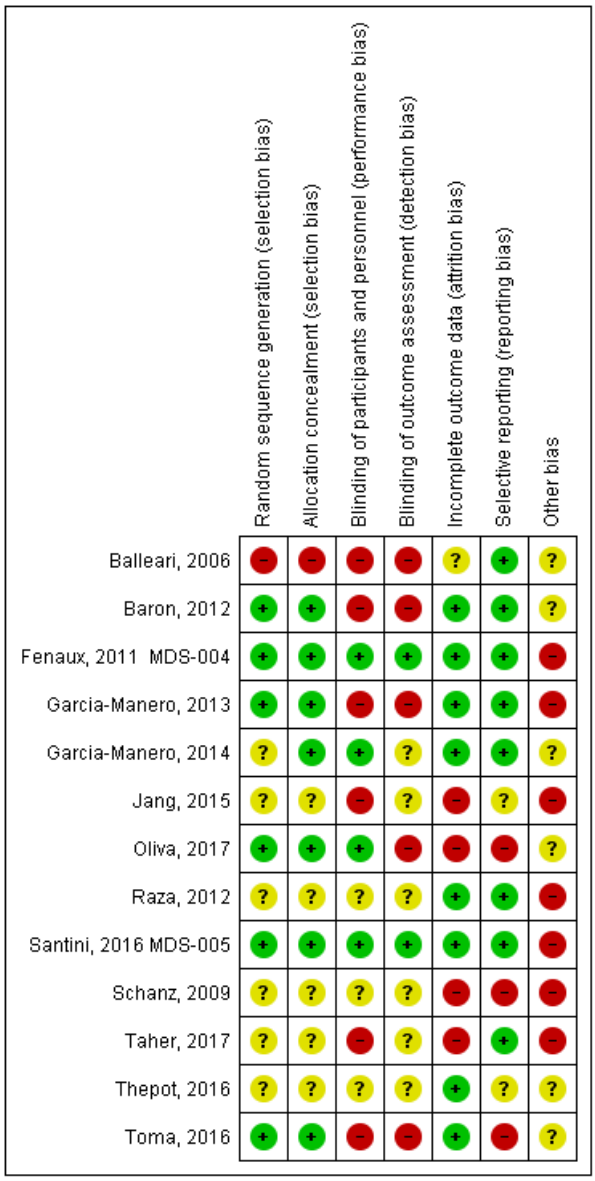


Figure 4-1A. Risk of bias summary [70] for randomized controlled trials of systemic treatment of patients with lower risk myelodysplastic syndromes: review authors' judgements about each risk of bias item for each included study. : Low risk of bias; : Unclear risk of bias; : high risk of bias.

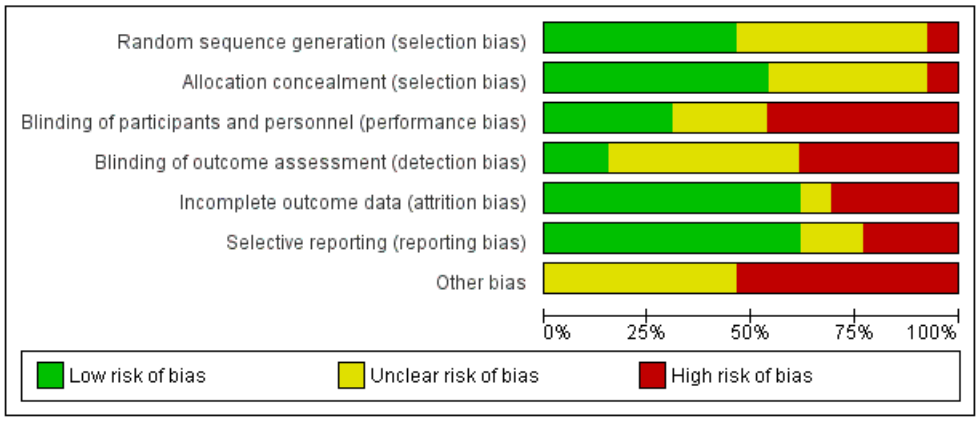


Figure 4-1B. Risk of bias graph [70]: review authors' judgements about each risk of bias item presented as percentages across all included randomized controlled trials of systemic treatment of patients with lower-risk myelodysplastic syndromes.

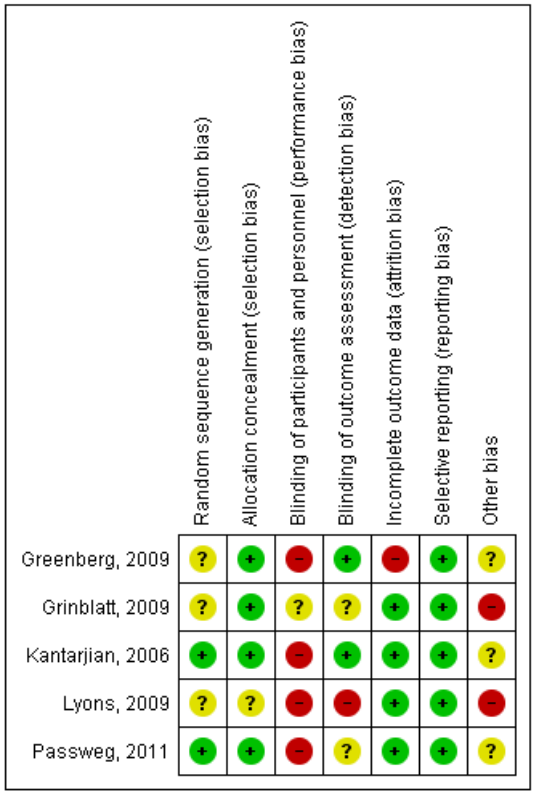


Figure 4-1C. Risk of bias summary [70] for randomized controlled trials of systemic treatment of patients with lower, and up to 15% of patients with intermediate-2/high International Prognostic Scoring System risk myelodysplastic syndromes: review authors' judgements about each risk of bias item for each included study. : Low risk of bias; : Unclear risk of bias; : high risk of bias.

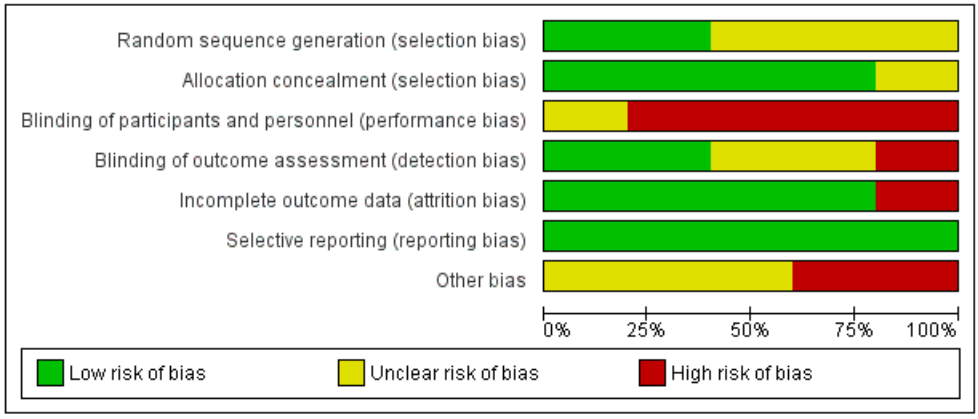


Figure 4-1D. Risk of bias graph [70]: review authors' judgements about each risk of bias item presented as percentages across randomized controlled trials of systemic treatment of patients with lower, and up to 15% of patients with intermediate-2/high International Prognostic Scoring System risk myelodysplastic syndromes.

**OUTCOMES**

The members of the Working Group agreed that the critical outcome for this population is response rate and, consesquently, freedom from transfusion.

**HEMATOPOIESIS-STIMULATING AGENTS**

**EPO and G-CSF**

The body of evidence for this group of agents in patients with lower risk is composed of four RCTs [7,10,11,102], and one retrospective historic cohort study considered at serious risk of bias [5]. Among the RCTs, one is a phase II trial [11] that investigated the optimal dose of darbapoetin; another [10] compared the efficacy of lenalidomide with or without EPO; the third [7] compared EPO plus G-CSF with supportive care, and the fourth [102] compared AZA plus EPO with AZA alone (Tables 4-3 and 4-4).

Among the studies that included both patients with lower and higher IPSS risk MDS, and therefore reported at least partially indirect evidence, the body of evidence is composed of the ECOG E1996 trial [8], a phase III RCT that compared EPO plus G-CSF with supportive care, and by a retrospective historic cohort trial by Park et al. [6] (Tables 4-5 and 4-6).

The body of evidence for EPO plus G-CSF was considered to be of moderate to low certainty because of the risk of bias and indirectness of the included studies.

Among the unpublished trials, four completed RCTs [9,103-105], and the abstract of a retrospective observational study [112], met our inclusion criteria. These trials compared EPO with placebo [105]; lenalidomide plus EPO with lenalidomide alone [103]; biosimilar EPO alpha with EPO alpha [9]; darbapoetin with placebo [104]; and EPO alpha with no treatment [112] (Tables 4-7 and 4-8).

The Nordic score [1] is derived from research published prior to the cut-off for this systematic review.

Evidence from the systematic review by Mundle et al. [75] that included trials preceding this systematic review cut-off (<2009) and expert opinion support the suggested dosing.

Jang et al. [11], a randomized dose-finding study that included 52 patients in three groups, did not report any statistically significant difference for erythroid hematologic improvement among doses of darbepoetin alpha of 60 µg/wk, 120 µg/wk, and 240 µg/wk, and did not report any statistical comparisons for adverse effects.

Among the ongoing trials, seven RCTs compared epoetin alpha with placebo (NCT01381809), darbapoetin alpha with filgrastim and with red blood cell transfusion (NCT01196715), recombinant epoetin with recombinant epoetin combined with vitamins (NCT00804050), epoetin alpha with placebo (NCT00695396), two doses and schedules of epoetin alpha (NCT00446602), lenalidomide with EPO and G-CSF with lenalidomide alone [136], an observational cohort study compared epoetin alpha with amifostine trihydrate (NCT00003681), and a case control study compared ESA with transfusional support (NCT01739452) (More information about these trials can be found in Tables 4-7, 4-8, and in Appendix 8).

The included studies tested various ESA agents alone [8,9,11,105,109,112], in combination with lenalidomide [10], and with AZA [102]. Two studies tested G-CSF in combination with EPO [5,7].

***Efficacy***

*Response rate*

Studies of patients with lower-risk disease (Tables 4-3 and 4-4)

Toma et al. [10] reported a statistically significant erythroid benefit for patients treated with lenalidomide plus EPO compared with patients treated with lenalidomide alone: hematological improvement 39.4% versus 23.1% (RR, 1.7, p=0.043); and transfusion independence: 24.6% versus 14.1% (RR, 1.7, p=0.13).

Thepot et al. [102] did not find any statistically significant difference between patients treated with AZA and EPO compared with AZA alone.

Balleari et al. [7] reported a nonsignificant between-group difference in erythroid response for patients treated with rEPO in combination with G-CSF compared with patients treated with rEPO alone (73.3% vs. 40%, p=0.065).

Unpublished trials of patients with lower risk disease (Tables 4-7 and 4-8)

The abstracts of two randomized trials [104,105] reported a favourable erythroid response rate for EPO compared with placebo (31.8% vs. 4.4%, p<0.001, and 14.7% vs. 0%, p=0.016, respectively).

The abstract publication by List et al. [103] reported a better response rate for EPO in combination with lenalidominde compared with lenalidomide alone (25.6% vs. 9.9%, p=0.015).

Studies of patients of lower- and higher-risk MDS (Tables 4-5 and 4-6)

The ECOG E1996 [8] reported a statistically significant benefit for patients treated with EPO compared with patient treated with supportive care at four months follow-up (36% vs. 9.6%, p=0.002).

*Survival outcomes*

Studies of patients with lower risk disease (Tables 4-3 and 4-4)

Thepot et al. [102]did not find any statistically significant difference in OS between AZA with EPO and AZA alone.

Jädersten et al. [5] in their retrospective study found an association of treatment with OS for the subgroup of low-risk patients who received EPO plus G-CSF compared with patients who received supportive care (HR, 0.45; 95% CI, 0.21 to 0.94; p=0.033).

Studies of patients of lower- and higher-risk MDS (Tables 4-5 and 4-6)

The ECOG E1996 RCT [8] found no statistically significant difference in OS and incidence of AML transformation.

*Disease control outcomes*

Studies of patients with lower-risk disease (Tables 4-3 and 4-4):

Toma et al. [10] found a nonsignificant difference in time to progression and response duration between patients treated with lenalidomide and EPO combination and patients treated with lenalidomide alone.

Balleari et al. [7] reported a nonsignificant between-group difference in progression to AML between patients treated with EPO and G-CSF or EPO alone.

Studies of patients of lower- and higher-risk MDS (Tables 4-5 and 4-6)

The ECOG E1996 RCT [8] found no between-groups statistically significant difference in incidence of AML transformation.

*Adverse events*

Studies of patients of lower- and higher-risk MDS (Tables 4-5 and 4-6)

The ECOG E1996 [8] reported a statiscally significant difference in transient grade 3-4 thrombocytopenia ($p<0.001$) and hyperbilirubinemia ($p=0.002$) in patients treated with EPO compared with patients who received supportive care. Toma et al. [10] did not find any statistical significant difference in adverse events between lenalidomide with EPO and lenalidomide alone.

Unpublished trials of patients with lower risk disease (Tables 4-7 and 4-8)

Adverse events were either not reported, not detected, or not significant in the abstract publications of completed trials.

*Subgroups*

Studies of patients with lower-risk disease (Tables 4-3 and 4-4):

The abstract report of an observational study [112] showed that patients who were not transfusion dependent, and had hemoblobin levels between 8 and 10 g/dL had a better OS when treated with EPO than with placebo (median 216 months vs. 99 months, $p=0.002$).

***Predictors of outcome***

Toma et al. [10] showed that polymorphisms in the *CRBN* gene, and baseline serum EPO level below 100 UI/L was associated with hematologic improvement (erythroid) (respectively, OR, 2.6; 95% CI, 1.09 to 6.3; $p=0.032$, and OR, 3.3; 95% CI, 1.35 to 7.9; $p=0.0087$). Thepot et al. showed that time since MDS diagnosis (HR, 0.97; 95% CI, 0.95 to 0.99) and abnormal SNPa karyotype (HR, 2.92; 95% CI, 1.07 to 8.01) were prognostic of worse survival [102].

Studies of patients of lower- and higher-risk MDS (Tables 4-5 and 4-6)

The ECOG E1996 RCT [8] reported that patients who were erythroid responders had a significantly better OS (5.5 years vs. 2.3 years, $p=0.004$); in this study, having a baseline EPO <200 mU/mL, and belonging to the subgroup with refractopry anemia with excess blasts were also predictors of response ($p=0.002$, and $p=0.006$, respectively).

Park et al. [6] reported in an retrospective cohort trial that baseline EPO level ≤200 IU/L, absence of transfusion requirement, and low- and intermediate-1 IPSS score were prognostic factors of response to treatment with rEPO and G-CSF (See Table 4-6 for numerical results).

***Dose and schedule:***

Studies of patients with lower-risk disease (Tables 4-3 and 4-4)

Jang et al. [11] found a similar erythroid response rate for patients who received 60, 120, or 240 µg/week of darbepoetin as an initial dose. The major erythroid response rate was declared higher in the higher dose group (17.6% vs.16.7% vs. 33.3%, p values not reported).

EPO was administered subcutaneously at 60000 U/week [10,102], or 40000 U/week [9].

Studies of patients of lower- and higher-risk MDS (Tables 4-5 and 4-6)

EPO was administered at 150 U/kg daily SC [8].

***Other outcomes:***

Studies of patients of lower- and higher-risk MDS (Tables 4.5 and 4-6)

The ECOG E1996 [8] reported a nonsignificant difference in quality of life between patients treated with EPO versus supportive care (data provided on 84 of 110 patients).

**THROMBOPOIETIN RECEPTOR AGONISTS**

The systematic review and meta-analysis by Prica et al. [12] included five RCTs; four, fully published, examined romiplostim [13-16] mostly in patients with lower-risk MDS and one, available as an abstract publication [17], examined eltrombopag in high-risk MDS patients. Therefore, we considered only the results regarding romiplostim from this review. Among the studies included in the Prica et al. review [12], the Working Group members considered the study by Giagounidis et al. [15] at high risk of bias, because the authors did not report details about the randomization procedures, and because the study was stopped early for benefit and perceived harm. The study by Wang et al. [14] was at moderate risk of bias, because it was a small study that presented a per-protocol analysis, did not report details on some of the randomization procedures, and funded by the manufacturer of romiplostim. The study by Kantarjian et al. [16] was at moderate risk of bias because the authors did not provide data on the randomization procedure; the sample of this study was very small, and the study was unblinded after completing the treatment phase. The Greenberg et al. study [13] was a very small study including 29 patients, and would not have met the inclusion criteria of our review. These studies included 384 patients randomized from October 2006 to Febraury 2011 that compared thrombopoietin-receptor agonists to placebo.

The updated search for this systematic review included an additional full report of an interim analysis of a phase II RCT of eltrombopag versus placebo by Oliva et al. [18], and an abstract report of the final, five-year follow-up [117] of one of the RCTs [15] included in the Prica et al. [12] systematic review. The Oliva et al. study [18] was considered at high risk of bias because of its small sample size, lack of blinding of outcome assessors (i.e., the investigator was able to see, directly from the completed case report form, which group the patients was assigned to), incomplete outcome bias (i.e., missing data were not imputed), and selective reporting bias (i.e., because what is available is the full-text report of a planned interim analysis, outcomes presented differ from what specified in the analysis section). Details of the follow-up study are reported in Appendix 6, Table 1.

This body of evidence was considered of moderate certainty for all outcomes because of inprecision: the total number of events was low (i.e., <300) and the confidence intervals were wide.

**Romiplostim**

***Efficacy***

*Response rate:*

Bleeding events rates (four trials [13-16])

Prica et al. [12] did not detect any statistically significant difference in bleeding events between romiplostim and control when considering exposure-adjusted rates per patient-month (RR, 0.84; 95% CI, 0.57 to 1.24).

Platelet transfusions rates (three trials [13,14,16])

Prica et al. [12] showed a nonsignificant improvement comparing romiplostim with placebo (RR, 0.70; 95% CI, 0.47 to 1.06) in the pooled estimate of the proportion of patients receiving platelet transfusions. The pooled estimate RR of platelet transfusion rate per patient month [14-16] was significantly less with romiplostim than with placebo (RR, 0.69; 95% CI, 0.53 to 0.88) [12].

Clinically significant thrombocytopenic events (three studies [13,14,16])

Prica et al. [12] did not detect any significant difference between romiplostim and placebo in the pooled analysis (RR, 0.87; 95% CI, 0.69 to 1.09).

Overall response rate (three studies [13,14,16])

Prica et al. [12] did not detect any statistically significant increase in response rate (RR, 0.94; 95% CI, 0.80 to 1.12).

Hematological improvement, platelets (two trials [15,16])

The pooled estimate by Prica et al. [12] showed a significant improvement with romiplostim (RR, 0.67; 95% CI, 0.59 to 0.75); however, the heterogeneity of these trials was very high ($I^2$=92%).

***Survival outcomes***

*AML progression*

The pooled estimate by Prica et al. [12] did not reveal any statistically significant difference between treatment and placebo (five trials [13-17] (RR, 1.12; 95% CI, 0.59 to 2.15). The same result persisted when the authors conducted a sensitivity analysis for the romiplostim trials [13-16] (RR, 1.36; 95% CI, 0.54 to 3.40). A sensitivity analysis was also conducted for population risk (higher versus lower IPSS risk), and no between-group differences were identified ($X^2$ =0; p=0.97).

*Dose and schedule*

Romiplostim in the included studies was administered at 750 mcg/week [13,15]; 500 or 750 mcg [14,16].

Adverse events

Death

The pooled analysis of three trials [13,15] showed no statistically significant differenced between romiplostim and placebo for chance of death (RR, 0.90; 95% CI, 0.54 to 1.50).

**Eltrombopag**

***Efficacy (studies of patients with lower risk disease [Tables 4-3 and 4-4])***

*Response rate:*

In the interim analysis of the EQoL-MDS [18] response rate was significantly better with eltrombopag than with placebo (47% vs. 3%, p<0.0001; OR, 27.1; 95% CI, 3.5 to 211.9; p=0.0017).

*Disease control*

There was no statistically significant difference in AML transformation between eltrombopag and placebo [18].

*Adverse events*

Patients in the eltrombopag group experienced significantly more grade 3 to 4 nonhematologic adverse events than patients who received placebo (46% vs. 16%, p=0.0053) [18].

*Dose and schedule*

Patients received oral eltrombopag on a daily basis, starting at 50 mg and up to 300 mg [18].

**Unpublished and ongoing trials**

Among the unpublished and ongoing trials, we identified an abstract publication of the interim anlaysis of an extension study of romiplostim [143] (Table 4-7).

Additionally, by searching the registry clinicaltrials.gov, we identified two ongoing RCTs (NCT00321711, NCT00418665) and an observational trial of romiplostim (NCT0233526), and five RCTs (NCT02928419, NCT02912208, NCT02912208, NCT02158936, NCT01440374) and one observational study of eltrombopag (NCT01772420). Detailed characteristics of these studies and results are reported in Appendix 8.

**IMMUNOMODULATORY AGENTS**

Included studies of immunomodulatory agents included only patients with lower-risk disease. Authors of fully published studies examined lenalidomide in patients with del(5q) [19,26], and in patients with non-del(5q) [28,99] (see Tables 4-3 and 4-4 for general characteristics and summary results of these studies). Authors of abstract publications of comparative, non-randomized trials, reported on lenalidomide used in combination with AZA in patients with non-del(5q) [29,107] (Tables 4-7, an 4-8).

**Lenalidomide in del(5q)**

The body of evidence for lenalidomide in patients with lower-risk and chromosome 5Q deletion syndrome is composed of the Leitch et al. guideline [3], that includes MDS-004 study [19]; of the MDS-004 eight corollary studies [2,20-25,118]; and of a historical cohort study [26]. The MDS-004 trial is a phase III, low risk of bias, RCT that compared effectiveness and safety of lenalidomide 10 mg/day or 5 mg/day with placebo in 205 transfusion-dependent patients with intermediate-risk MDS and del(5q). The corollary studies were an open label extension study [20], two analyses of the prognostic value of p53 immunohistochemistry [2,21], a study of patients with isolated del(5q) [22], a study assessing subgroups of patients with different 5Q breakpoints [23], a study of health-related quality of life [24], a subgroup analysis according to baseline EPO levels and prior ESA use [25], and an analysis of the timing and management of hematologic adverse events linked to the use of lenalidomide [118].

Details of the included studies are in Tables 4-3 and 4-4, and of corollary studies in Appendix 6, Table 1.

The cohort study [26] compared 95 transfusion-dependent patients with del(5q) treated with lenalidomide with an historical cohort of 99 patients who had not received lenalidomide to ascertain whether treatment with lenalidomide may trigger AML (Tables 4-3 and 4-4).

The body of evidence for this intervention was considered of moderate certainty for response and adverse events, and of low certainty for OS. The MDS-004 study [19] was at low risk of bias; however, the number of patients included in the intention-to-treat analysis was relatively low (n=139), thus making the evidence imprecise. The Adès et al. study [26] reported on OS; this was a retrospective cohort study, and it was considered at serious risk of bias.

***Efficacy (studies of patients with lower risk disease [Tables 4-3 and 4-4])***

*Response rate*

In the MDS-004 [19], the rate of transfusion independence ≥26 weeks (intention-to-treat population) was as follow: lenalidomide 10 mg, 55.1% (95% CI, 42.6 to 67.1); lenalidomide 5 mg, 34.8% (95% CI, 23.7 to 47.2); and placebo, 6% (95% CI, 1.7 to 14.6), p<0.001 for each intervention group versus placebo.

*Survival outcomes*

Disease progression and OS (median and rates) data for the MDS-004 study [19] are reported in Table 4.4 (p values not reported). In the Adès et al. study [26], the incidence of AML transformation at the four-year follow-up (estimated), and OS were similar for patients treated with lenalidomide and controls (respectively, 9% vs. 15.7%, HR, 0.87; 95% CI, 0.27 to 2.82, for AML transformation; and 150 vs. 78 months; HR, 0.47; 95% CI, 0.23 to 1.01 for OS, [see Table 4-4]).

*Dose and schedule*

In a subgroup analysis of lenalidomide 10 mg/day versus 5 mg/day, including 45 patients with baseline EPO level >500 mIU/mL, red blood cells transfusion independence rate was 76.2% versus 33.3%, (p=0.004) [19].

*Adverse events*

In the MDS-004 [19], 94.2% of patients in the lenalidomide 10 mg group experienced one or more grade 3 or 4 adverse events compared with 89.9 in the lenalidomide 5 mg and 43.3% in the placebo group (p values not reported). The most common grade 3 and 4 adverse event with lenalidomide was myelosuppression (see Table 4-4 for numerical data). Lenalidomide dose reduction (in the safety population) was necessary in 55.1% and 52.2% of patients in the 10 mg/day and 5 mg/day treatment groups, respectively; dose interruptions were reported in 46.4% and 29% of patients, respectively. Median time to dose reduction or interruption was 27 days (range 10 to 269 days) and 43 days (range 7 to 215 days).

*Other outcomes*

In a multivariate analysis, the authors of the MDS-004 trial [19] showed that in the combined lenalidomide groups, transfusion independence for ≥8 weeks was associated with 42% reduction in RR of AML progression or death, (p=0.048), and a 47% reduction in RR of death (p=0.021). Higher baseline ferritin levels, older age, and higher transfusion burden were associated with a significant increased risk of AML progression (AML-free survival: HR, 1.01; 95% CI, 1 to 1.02; p=0.02 for baseline ferritin; HR 1.04; 95% CI, 1.01 to 1.06; p=0.011 for

older age; and HR, 1.08; 95% CI, 1 to 1.16; p=0.055 for high transfusion burden, respectively), or death (OS: HR 1.01; 95% CI, 1 to 1.02; p=0.019 for baseline ferritin; HR, 1.04; 95% CI, 1.01 to 1.07; p=0.003 for older age; and HR, 1.09; 95% CI, 1.02 to 1.17; p=0.011 for high transfusion burden, respectively).

**Lenalidomide in non-del(5q)**

The body of evidence for lenalidomide in patients with lower MDS risk without chromosome 5Q deletion is composed of the MDS-005 trial [28], and by a retrospective analysis by Zeidan et al. [99]. The MDS-005 [28] is a phase III RCT that compared effectiveness and safety of leanlidomide in 239 patients without del(5q) who were refractory or resistant to ESAs. The analysis by Zeidan et al. [99] explored the efficacy of lenalidomide given before or after AZA, in patients who were refractory to or had failed ESAs (Tables 4-3 and 4-4). Six corollary studies of the MDS-005 [28], published in abstract form, explored factors associated with response [123], changes in quality of life [122], the relationship between lenalidomide and clinically meaningful measures of response [120], the relationship between lenalidomide exposure, including dose reductions, and duration of treatment, and the clinical benefit [116], and described frequency, timing, and management of treatment-emergent adverse events [119].

The body of evidence for this intervention was considered to be of moderate certainty for response, predictors of response, and adverse events. The MDS-005 study [28] was at low risk of bias; however, fewer than 300 patients were included, and this was the only study available for this population, making this body of evidence imprecise.

***Efficacy***

*Response rate*

Transfusion independence rate for eight weeks or longer was better for patients treated with lenalidomide than placebo (26.9% vs. 2.5%; p<0.001), but no statistically significant difference was seen in erythroid response rate [28]. Red blood cell transfusion independence (RBC-TI) ≥24 weeks was achieved in 28 (17.5%) patients in the lenalidomide group and in no patients in the placebo group (Fisher exact *p*<0.001) (Table 4-4).

*Survival outcomes*

Median duration of response was 30.9 weeks for patients in the lenalidomide group versus not estimable (Table 4-4). Median OS was not reached [28].

*Adverse events*

The most common adverse events were neutropenia and thrombocytopenia. No comparative data were reported [28].

*Dose and schedule*

Zeidan et al. [99] found a statistically significant difference in favour of giving lenalidomide before AZA (erythroid response rate 38% vs. 12%; p=0.04).

***Other outcomes***

*Prognostic factors of transfusion independence*

Santini et al. [28] reported that low baseline transfusion burden (<4 units over 28 days; OR, 2.685; 95% CI, 0.955 to 7.55; p=0.061) and use of ESA before study inclusion (OR, 4.623; 95% CI, 1.324 to 16.152; p=0.016] were prognostic factors for transfusion independence.

*Quality of life*

At 12 and 24 weeks no statistically significant difference was found for fatigue, dyspnea, physical functioning and global quality of life between patients taking lenalidomide and those taking placebo. Emotional functioning was statistically significant better in the lenalidomide group at 24 weeks, but the authors [28] did not perform any adjustment for multiplicity. In a post hoc analysis, achievement of RBC-TI ≥8 weeks was associated with significant improvements ($p<0.01$) in all five preselected health-related quality of life domains.

**Lenalidomide in combination with other agents**

Two small unpublished studies of patients with non-del(5q) were identified that tested lenalidomide in combination or in sequence with hypomethylating agents [29,107]. Their characteristics and results are reported in Tables 4-7 and 4-8.

**HYPOMETHYLATING AGENTS**

The body of evidence for this group of agents in patients with lower risk is composed of an existing guideline [4], and an open label phase II RCT with Bayesian adaptive design [34] that investigated safety and tolerability of DAC administered with two different doses and schedules: subcutaneous DAC 20 mg/m$^2$ for three consecutive days in a cycle of 28 days compared with DAC 20 mg/m$^2$ every seven days in a cycle of 28 days. Detailed characteristics of this study and results are reported in Tables 4-3 and 4-4.

The Buckstein et al. guideline [4] did not recommend AZA as first-line therapy for patients with lower-risk MDS because the authors did not locate any evidence for this in the lower-risk population.

Among the studies that included both patients with lower and higher IPSS risk MDS, the phase II, open-label RCT by Lyons et al. [33] compared three doses and schedules of AZA; the historical cohort study by Falantes et al. [31] compared efficacy outcomes in patients treated with AZA with patients who did not receive AZA; and the unblinded, phase III RCT by Kantarjian et al. [35] compared DAC with best supportive care. Detailed characteristics and results of these studies are reported in Tables 4-5 and 4-6.

The use of AZA after lenalidomide failure in lower-risk patients with del(5q) MDS is less studied, and our systematic review did not identify any comparative studies on this topic, although the Working Group is aware of a small, unpublished series (excluded from this review) that may show activity of AZA in this population [32].

We also identified the abstract publications of a retrospective study of AZA [106], and of two RCTs of DAC [30,36]. Their characteristics and results are reported in Tables 4-7 and 4-8.

We considered the body of evidence for this intervention of moderate certainty for response rate, and for dose and schedule outcomes because of indirectness and imprecision. The study by Kantarjian et al. [35] included patients with lower and higher-risk MDS; it had a relatively small sample size, and it was the only study available to report on response rate. The study by Garcia-Manero et al. [34] included patients with lower MDS risk; however, it was an open label trial, had a relatively small sample size, and it was the only study available reporting on dose and schedule outcomes.

**AZA and DAC**

***Efficacy***

*Response rate and survival*

*Studies of patients with lower risk disease (Tables 4-3 and 4-4)*

An abstract publication of an RCT [30] compared AZA with best supportive care in 40 patients without del(5q) or transfusion-dependent anemia, who were nonresponders to EPO and not candidate for intensive chemotherapy and transplant. There was a statistically significant between-group difference in erythroid response rate (31% vs. 5.5%; p<0.01), and no significant difference in OS, and leukemia-free survival.

*Response rate and survival*

Studies of patients of lower- and higher-risk MDS (Tables 4-5 and 4-6)

Kantarjian et al. [35] showed a statistically significantly better overall response for patients treated with DAC compared with those treated with best supportive care (17% vs. 0%; p<0.001). Falantes et al. [31] did not report comparative data on response rate.

*Survival*

Studies of patients of lower- and higher-risk MDS (Tables 4-5 and 4-6)

No statistically significant difference in OS was detected [35] between patients treated with DAC and those who received best supportive care.

Similar results were reported by the abstract publications by Sanchez-Garcia et al. [30] and Jabbour et al. [36].

Falantes et al. [31] in their observational sudy reported a better OS in the AZA cohort than in the best supportive care cohort at one and two years; (respectively, 62% vs. 25.4%, and 45% vs. 11%; p=0.0001). Similar results were reported in the abstract report of the observational study by Sohn et al. [106].

*Disease control*

Studies of patients of lower- and higher-risk MDS (Tables 4-5 and 4-6)

No statistically significant difference in time to AML was detected [35] between patients treated with DAC and those who received best supportive care. As well, Falantes et al. [31] did not detect between-groups difference in progression to AML.

***Adverse events:***

Studies of patients of lower- and higher-risk MDS (Tables 4-5 and 4-6)

Most patients experienced a drug-related adverse event [34]. These events were mostly haematological, and they were transient. No treatment-related deaths were reported. No difference in adverse events between AZA and DAC were noted in the systematic review by Xie et al. [72], and in the abstract report by Jabbour et al. [36]. No comparative data are available from the other included trials [31,33,35]. The Lyons et al. study [33] showed that patients treated with lower AZA doses experienced less grade 3 and 4 adverse event rates (58% in the AZA 5, 77% in the AZA 5-2-5, and 84% in the AZA 5-2-2 groups; p values not reported).

***Dose and schedule***

Studies of patients with lower-risk disease (Tables 4-3 and 4-4)

The study of DAC by Garcia-Manero et al. [34] was terminated early because the pre-defined threshold for superiority was met; that is, the posterior probability of more than 95% that the objective reponse for patients who received DAC 20 mg/m$^2$ SC, per day for three consecutive days in a cycle of 28 days was superior to that of patients who received

decitabine 20 mg/m$^2$ every seven days on days 1, 8, and 15 in a cycle of 28 days. The randomized phase 2 study by Jabbour et al. [36], using Baysian adaptive design, randomized 113 patients with lower-risk MDS to three days of AZA 75 mg/m$^2$ SC daily (n=40) or three days of DAC 20 mg/m$^2$ SC daily (n=73). The overall response raterwas 70% versus 49% for DAC and AZA respectively (p=0.03). Thirty-two percent of patients treated with DAC became transfusion independent compared with 16% treated with AZA (p=0.2).

***Subgroups***

DAC responders had a statistically significantly better median OS than non-responders (23.5 months compared with 13.7 months; p=0.007) [35].

Falantes, et al. [31] did not find any statistically significant difference in progression rate to ANL between the group treated with AZA and the group that received best supportive care in patients with adverse clinical features (p=0.19) (Table 4-6).

**IMMUNOSUPPRESSIVE AGENTS**

No studies of patients with lower-risk disease treated with immunosuppressive agents met our inclusion criteria. The body of evidence for this group of agents is composed of one good-quality, phase III, open-label RCT with a group sequential two-stage design [37], and one observational retrospective trial [27] at serious risk of bias. Passweg et al. [37] evaluated the impact of immunosuppression in 83 transfusion-dependent patients with low, intermediate-1, intermediate-2, and high IPSS risk, treated with horse ATG combined with CsA compared with best supportive care. Sloand et al. [27] compared ATG alone or in combination with CsA, and compared their institutional cohort with an historical cohort.

We considered the body of evidence for this intervention of moderate certainty because of indirectness and imprecision. Passweg et al. [37] included patients with higher- as well as with lower-risk MDS, and had a relatively small sample. Twenty-seven per cent of the patients included by Sloand et al. [27] had higher-risk disease, and not all results for all comparisons were presented separately for lower-risk patients.

**Efficacy (studies of patients of lower- and higher-risk MDS [Tables 4-5 and 4-6])**

***Response rate***

Patients in the immunosuppressive treatment group showed a hematologic response (complete plus partial response) rate statistically significantly better than patients in the best supportive care group at six months (29% vs. 9%; p=0.0156) [37].

***Survival outcomes***

The study by Passweg et al. [37] was not powered to detect a between-group difference in survival.

***Disease control***

No statistically significant difference was detected in transformation-free survival (p=0.73) and leukemia-free survival (p=0.91) at two years [37].

***Adverse events***

Statistically significant greater adverse event rates were reported in the immunosuppressive treatment group compared with best supportive care (40% vs. 10%, p=0.005). In the immunosuppressive group, adverse events included major hemorrhage (12.5%), cardiac events (12.5%), serum sickness/fever (12.5%), thrombosis (12.5%), severe infections (25%), and other complications (25%) [37].

***Subgroups***

No data on patient subgroups are available [37].

**Dose and schedule**

Patients received ATG at a dose of 15 mg/kg for five days in combination with oral CsA for 180 days.

**IRON CHELATION**

We did not identify any RCTs comparing iron chelation with no chelation. Among the studies of patients with lower-risk disease three prospective studies [39,40,100] and two retrospective cohort studies [41,46] met our inclusion criteria.

Among the studies with patient population including lower- as well as higher-risk groups one retrospective cohort study met our inclusion criteria [45] (Tables 4-5 and 4-6).

We considered the body of evidence for this intervention to be of moderate certainty for OS because of high risk of bias, with a large effect that was consistent across studies. We considered the certainty of this body of evidence to be low for all other outcomes.

We also identified one prospective [44] and three retrospective cohort studies [43,108,111] published in abstract form; their characteristics and results are reported in Tables 4-7 and 4-8.

**Studies of patients with lower risk disease (Tables 4-3 and 4-4)**

***Efficacy***

*Response rate*

No statistically significant difference in the number of red blood cell units transfused beween chelated and non-chelated patients were reported by Lyons et al. [39]. Other studies of patients with lower risk did not report on this outcome.

*Survival outcomes*

All three studies that reported on OS [39-41] showed a statistically significant better outcome for patients on chelation therapy compared with no chelation (see numerical results in Table 4-4).

*Disease control*

Three included studies [39-41] reported inconsistent results on disease control outcomes (see numerical results in Table 4-4).

***Adverse events***

The two studies that reported on this outcome [39,46] reported a nonsignificant difference between chelated and non-chelated patients.

***Dose and schedule***

In the included studies, patients were given three chelating agents at dosages that varied from 40 mg/kg/day for deferoxamine, to 10 to 40 mg/kg/day for deferasirox, to 30 to 90 mg/kg/day for deferiprone.

**Studies of patients of lower- and higher-risk MDS (Tables 4-5 and 4-6)**
***Efficacy***
*Response rate*

None of the included studies reported on this outcome.

*Survival outcomes*

The observational study by Neukirchen et al. [45] showed a statistically significant advantage in OS for patients treated with iron chelation compared with no chelation (see numerical results in Table 4-6).

*Disease control*

The observational study by Neukirchen et al. [45] showed no statistically significant differences between groups.

*Adverse events*

Lyons et al. [39] reported that there were no statistically significant differences in adverse events between groups. The main adverse events of deferasirox and deferoxamine reported in the manufacturer monographs [47,48] are diarrhea, renal insufficiency, and gastrointestinal complaints for deferasirox, and high frequency hearing loss, retinal problems, and infusional skin reactions for deferoxamine.

*Subgroups*

The observational study by Neukirchen et al. [45] showed a statistically significant between-group difference in OS for lower-risk patients, while in the subgroup of patients at higher risk the difference did not reach significance.

**OTHER INTERVENTIONS**

Four randomized phase II trials with a population of patients with lower-risk MDS [49-52], a randomized, phase II trial [53] that included patients with lower- and higher-risk population met our inclusion criteria, and an abstract report of an unpublished retrospective cohort study [110]. The included studies examined six different interventions: siltuximab [49], ezatiostat [52], infliximab [50], amifostine [51], topotecan [53], and 13-cis-retinoic acid with alpha tocopherol [110].

We considered this body of evidence to be of low certainty, because of imprecision, risk of bias, and indirectness; for each intervention we identified only one study, each study had a relatively small sample of patients, and two of the studies included patients with lower- and higher-risk MDS.

Among the unpublished trials, we identified the abstract publication of a retrospective analysis that examined the efficacy of 13-cis-retinoic acid and alpha tocopherol (see Tables 4-7 and 4-8 for general characteristics and results).

**Studies of patients with lower risk disease (Tables 4-3 and 4-4):**
***Efficacy***
*Response rate*

Siltuximab did not reduce the need for red blood cells transfusion better than placebo and supportive care [49]. Ezatiostat and infliximab at a higher dose did not result in a statistically significantly better response rate than ezatiostat and infliximab at a lower dose [50,52]. Amifostine did not show a statistically significantly better response than supportive care [51] (see Tables 4-3 and 4-4 for numerical results).

*Survival outcomes*

Survival data were available only for amifostine, and no statistically significant difference between the intervention and control group was detected.

*Disease control*

No statistically significant difference was detected for progression-free survival between amifostine and best supportive care [51] (see Tables 4-3 and 4-4 for numerical results).

***Adverse events***

Patients treated with siltuximab did not experience statistically significantly more grade ≥3 adverse events than patients treated with placebo and best supportive care [49]. Comparisons for adverse events for infliximab and ezatiostat and their relative comparison groups were not reported. Patients treated with amifostine experienced significantly fewerinfections than patients on supportive care (see Tables 4-3 and 4-4 for numerical results).

**Studies of patients of lower- and higher-risk MDS (Tables 4-5 and 4-6)**

***Efficacy***

*Response rate*

No statistically significant differences in overall response rate were detected between patients treated with higher- versus lower-dose topotecan [53].

*Survival outcomes*

No statistically significant differences in median OS were detected between patients treated with higher- versus lower-dose topotecan [53].

*Disease control*

A statistically significant difference was detected in favour of higher-dose topotecan treatment for response duration (23 months: 95% CI, 15 to 29 months vs. 14 months: 95% CI, 8 to 17 months; p=0.02) [53].

***Adverse events***

Adverse events were similar for higher- and lower-dose topotecan [53].

**Ongoing, Unpublished, or Incomplete Studies**

Table 4-7 reports a summary of unpublished or ongoing studies that were identified.

**Table 4-7. Unpublished or Ongoing trials: General Characteristics**

| Study name, Author, year, Country, Funding Identification number | Objectives / Focus / Data collection | Design | Population | Intervention/ Comparison | Outcomes |
|---|---|---|---|---|---|
| **Hematopoiesis-stimulating agents** | | | | | |
| E2905 Intergroup Study<br><br>List, 2016 [103] ABS<br><br>**Country:** US<br><br>**Funding:** Government | To test whether LEN may overcome resistance to rhu-EPO<br><br>**Focus:** Combination of LEN with EPO<br><br>**Data collection:** April 2009 and May 2016<br><br>Stopped early on July 2015 because it met the predefined stopping criteria | RCT Phase III | N = 195 randomized, 163 analyzed (because stopped early) pts with lower – risk MDS who were refractory or not candidates for treatment with rhu-EPO, and had serum EPO >500 mU/mL<br>**IPSS**: low- 39%, intermediate-1 55%<br>**Gender**: Male 55%<br>**Age** (median, range): 74 yrs, 47-89 yrs<br>**WHO diagnosis**:<br>RA 15%; RARS 14%; RCMD 44%; del(5q) 9%; RAEB-1 16%; MDS-u 2%<br>Time from diagnosis (median): *nr* | LEN 10 mg/d × 21ds every 4 wks+ EPO alpha 60,000U SC/wk vs. LEN | Major erythroid response after 4 cycles<br>Response biomarkers<br>AE |
| ARCADE (20090160)<br><br>Platzbecker, 2016 [104] ABS<br>**Country:** Multiple countries, Europe<br><br>**Funding:** Amgen | To evaluate the efficacy and safety of DAR alfa (DAR).<br><br>**Data collection period:** Dec 2011 - Aug 2014 | RCT phase 3<br><br>**Follow-up:** 48 wk | N=147 anemic pts with low- or intermediate-1 MDS, with no previous treatment with ESAs and serum EPO ≤500 mU/mL.<br>**IPSS**: low- 50.7%, intermediate-1 49.3%<br>**Gender**: Male 55%<br>**Age** (median): 74 yrs<br>**WHO diagnosis**:<br>RA 15%; RARS 14%; RCMD 44%; del(5q) 9%; RAEB-1 16%; MDS-u 2%<br>Time from diagnosis (median): *nr* | 24 wks of SC DAR 500 µg vs. PBO every 3 wks | Transfusion incidence from weeks 5-24 and<br><br>Eythroid response (HI E) |
| Fenaux, 2016 ABS [105] | To evaluate the efficacy of epoetin-a in improving anemia<br><br>**Data collection period:** ***nr*** | RCT phase III double blind<br><br>**Follow-up:** *nr* | N = 130 pts<br>**IPSS**: Low- and Intermediate-1-risk MDS<br>**Gender**: Male: EPO group: 54.6%<br>**Age** (median): EPO Group: 75 yrs<br>**WHO diagnosis**: *nr*<br>Time from diagnosis (median): *nr* | EPO-a 450IU/kg (n=85) vs. PBO | Erythroid response<br>Erythroid response duration<br>Time to first transfusion |
| Messa, 2013 ABS [112]<br><br>**Country:** Italy<br><br>**Funding:** *nr* | To assess which group of pts could benefit more from ESA treatment<br><br>**Data collection period:** *nr* | Retrospective observational<br><br>**Follow-up:** *nr* | N = 1110 pts enrolled in Italian MDS registries<br>**IPSS**: low- or Intermediate-1<br>**Gender**: *nr*<br>**Age** (median): *nr*<br>**WHO diagnosis**: *nr*<br>Time from diagnosis (median): *nr* | EPO alpha (n=356) vs. No treatment (n=754) | OS |

| Study name, Author, year, Country, Funding Identification number | Objectives / Focus / Data collection | Design | Population | Intervention/ Comparison | Outcomes |
|---|---|---|---|---|---|
| Giordano, 2012 ABS [9]<br><br>**Country:** Italy<br><br>**Funding:** *nr* | To verify non-inferiority between biosimilar EPO alpha and EPO alpha<br><br>**Data collection period:** *nr* | RCT<br><br>**Follow-up:** *nr* | N = 86 pts with RA<br>**IPSS**: low- or Intermediate-1<br>**Gender**: Male IG: 35%, CG: 56%<br>**Age** (median): IG: 64 yrs, range 60 to 70; CG: 70 yrs, range: 63 to 73<br>**WHO diagnosis**: RA 100%<br>Time from diagnosis (median): *nr* | Biosimilar EPO alpha 40,000 IU/wk, SC<br>vs.<br>EPO alpha 40,000 IU/wk, SC | AE<br>Response (Hb level increase) |
| Van De Loosdrecht, 2016 [136] ABS ONGOING<br><br>**Country:** *nr*<br><br>**Funding:** *nr* | To assess the efficacy of LEN with EPO and G-CSF | RCT Phase II | N= 200 pts with low or Intermediate-1 MDS refractory to EPO and G-CSF<br>**IPSS**: low- or Intermediate-1<br>**Gender**: Male 55%<br>**Age** (median, range ): 71 yrs, 38 to 89 yrs<br>**WHO diagnosis**: *nr*<br>Time from diagnosis (median): *nr* | LEN+ EPO and G-CSF vs. LEN alone | HI-E rate<br>Time to response<br>OS<br>PFS<br>Predictors of response and survival<br>AE |
| **Romiplostim** | | | | | |
| Fenaux, 2010, 2011 ABS ONGOING [141-143,149]<br><br>**Country:** France<br>**Funding:** *nr* | To test romiplostim | Open label extension study of 3 previous trials: (1) romiplostim only for up to 52 wks [Kantarjian JCO 2009], (2) romiplostim or PBO plus decitabine for >4 cycles [Greenberg ASH 2009], and (3) romiplostim or PBO plus LEN for >4 cycles [Lyons ASH 2009] | MDS pts who had completed a prior romiplostim study and had platelets <50 × $10^9$/L with no evidence of disease progression | Romiplositm | *AE incidence<br>Bleeding events incidence<br>PLT transfusions<br>PLT response duration |
| Lee, 2016 [135] ABS ONGOING<br><br>**Country:** South Korea<br>**Funding:** *nr* | To determine an optimal initial dose of romiplostim for patients with aplastic anemia refractory to immunosuppressive therapy | RCT, multicenter, open-label, parallel, comparative, dose-finding | N=35 pts with aplastic anemia refractory to ATG | Romiplostim SC at three different doses: 1, 3, 6, or 10 µg/kg once weekly for 8 wks | RR: Proportion of subjects achieving a hematological response (any of the platelet response, erythroid response, and neutrophil response) at Week 27 |

| Study name, Author, year, Country, Funding Identification number | Objectives / Focus / Data collection | Design | Population | Intervention/ Comparison | Outcomes |
|---|---|---|---|---|---|
| NCT02094417 | | | | | |
| **Immunomodulatory agents** | | | | | |
| **Non-5Q deletion** | | | | | |
| Komrokji, 2016 ABS [107]<br><br>**Country:** *nr*<br><br>**Funding:** *nr* | To assess the best order of LEN and HMA in optimizing response potential in lower-risk MDS<br><br>**Data collection period:** *nr* | Retrospective cohort<br><br>**Follow-up:** *nr* | N = 144 pts who received both HMA and LEN as first or second line therapy after ESA failure<br>**IPSS**: Low/Intermediate-1-risk non-del(5q) MDS<br>**Gender**: Male LEN 1st: 74% vs. LEN 2nd 80%<br>**Age** (mean, range): LEN 1st: 67 yrs (62 to 74 yrs)<br>LEN 2nd: 70 yrs (66 to 77)<br>**WHO diagnosis**: *nr*<br>Time from diagnosis (median): *nr* | LEN 1st line followed by AZA (n=80) vs. LEN 2nd line after AZA (n=64) | * HI Erythroid |
| Rollison, 2014 [113] ABS<br><br>**Country:** US<br><br>**Funding:** *nr* | To investigate the association of LEN treatment and AML transformation<br><br>**Data collection period:** 2004 to 2012 | Retrospective cohort with nested case-control<br><br>**Follow-up:**30 mos | N=1248 pts with non-del(5q) MDS | LEN vs. no LEN | AML transformation |
| Corrales-Yepez, 2013 ABS [29]<br><br>**Country:** *nr*<br><br>**Funding:** Celgene | To evaluate the best sequence of LEN (as first line after ESAs or after AZA failure)<br><br>**Data collection period:** *nr* | Retrospective cohort<br><br>**Follow-up:** *nr* | N = 63 pts<br>**IPSS**: Low/Intermediate-1-risk non-del(5q) MDS<br>**Gender**: Male 70%<br>**Age** (mean): 66 yrs<br>**WHO diagnosis**:<br>RA 13%; RARS 25%; RCMD 43%; RAEB-1 10%; CMML 5%, MDS-u 5%<br>Time from diagnosis (median): *nr* | LEN 1st line followed by AZA (n=37) vs. LEN 2nd line after AZA (n=26) | *Erythroid HI<br>OS<br>AML transformation<br>Response to AZA |
| **Hypomethylating agents** | | | | | |
| **Azacytidine** | | | | | |
| Sohn, 2014 ABS [106]<br><br>**Country:** *nr*<br><br>**Funding:** *nr* | To evaluate long-term outcomes of front-line HMA compared with supportive care in pts with low-risk MDS.<br><br>**Data collection period:** Oct 1992 to Jul 2013 | Retrospective cohort and Case control<br><br>**Follow-up:** 5 yrs | N = 353 pts<br>**IPSS**: Low/Intermediate-1- MDS<br>**Gender**: *nr*<br>**Age** (mean): *nr*<br>**WHO diagnosis**: *nr*<br>Time from diagnosis (median): *nr* | HMA (n=243) vs. BSC (n=110) | Prognostic factors of OS |
| QUAZAR | To investigate the efficacy and | RCT, phase III | N = planned 386 pts transfusion dependent | CC-486 (oral AZA) 300 | Transfusion independence |

| Study name, Author, year, Country, Funding Identification number | Objectives / Focus / Data collection | Design | Population | Intervention/ Comparison | Outcomes |
|---|---|---|---|---|---|
| AZA-MDS-003 Garcia-Manero, 2016, 2015 ABS ONGOING [145,148] **Country:** US<br><br>**Funding:** Celgene NCT01566695 | safety of CC-486 (an oral formulation of AZA) for the treatment of patients with IPSS lower-risk MDS with poor prognostic features | | and thrombocytopenic<br>**IPSS**: Low/Intermediate-1- MDS<br>**Gender**: Male<br>**Age** (mean): yrs<br>**WHO diagnosis**:<br>Time from diagnosis (median): *nr* | mg/d<br>vs.<br>PBO for 21 ds of repeated 28-d cycles | Time to transfusion independence<br>Progression to AML<br>TTP<br>Hematologic response<br>Clinically significant bleeding events<br>safety<br>QOL<br>Healthcare resource utilization. |
| Sanchez-Garcia, 2013 [150] ONGOING ABS | To test AZA | RCT, phase II | Pts with low-risk MDS without del(q5) | AZA vs. support treatment | HI Erythroid |
| De Miguel Llorente, 2011, 2010 [139,140] ONGOING ABS | To evaluate the efficacy and safety of AZA in all MDS groups and secondary AML patients, noncandidates to aggressive therapy | Retrospective cohort | 13 pts with low/intermediate-1 IPSS risk MDS, 10 pts as high/int-2 IPSS risk MDS and 4 secondary AML diagnosed pts. | High risk MDS and AML pts received AZA dose of 75mg/sqm/d subcutaneously during ds 1-7, in a 28-day cycle; and low-risk received same schedule by 5 ds. | Grade 3-4 AE<br>Response rate<br>Response duration<br>Progression |
| GFMAzaEpo-2008-1 Boehrer, 2010 [138] ONGOING ABS NCT01015352 | To test AZA in ESA-resistant pts | RCT, phase II An interim analysis was planned after 49 of 98 planned patients were evaluable for response after 6 courses | Pts with IPSS low or int-1 MDS resistant to ESA | AZA 75mg/$m^2$/d for 5 ds every 28 ds for 6 cycles (AZA arm) vs. AZA+EPO beta 60000 U/week | *HI-Erythroid major responses after 6 courses.<br>Overall IWG 2000 HI-E, including major and minor, after 4 and 6 courses,<br>Response duration,<br>IPSS progression,<br>OS, and<br>toxicity |
| **Decitabine** | | | | | |
| Kropf, 2016 ABS ONGOING [134] | To test the effectiveness of DAC alone or in combination with arsenic trioxide ± carboplatin | RCT phase II (adaoptive randomization design) | Pts with MDS or chronic myelomonocytic leukemia IPSS risk intermediate-1 | DAC 20 mg/$m^2$ ds 1-5, (DAC);<br>DAC as above and Carboplatin AUC 5 on d 8 (DAC/Carbo);<br>or DAC as above and | *Composite RR (CR: complete response, mCR: marrow complete response and CRi: complete response with incomplete blood count recovery)<br>OS |

| Study name, Author, year, Country, Funding Identification number | Objectives / Focus / Data collection | Design | Population | Intervention/ Comparison | Outcomes |
|---|---|---|---|---|---|
| | | | | ATO 0.15 mg/kg ds 1-5 (DAC/ATO). | Safety |
| Sanchez-Garcia 2015 ABS [30]<br><br>**Country:** Spain<br><br>**Funding:** *nr* | To test the effectiveness of AZA<br><br>**Data collection period:** *nr* | RCT Phase II, open-label<br><br>**Follow-up:** *nr* | N = 40 pts without del(5q), with transfusion-dependent anemia, who had not responded to previous treatment with EPO and who were not candidates for intensive chemotherapy and transplant<br>**IPSS**: low- Intermediate-1 risk MDS<br>**Gender**: *nr*<br>**Age** (median, range ): 76.2 yrs, 45 to 90 yrs<br>**WHO diagnosis**: *nr* | AZA 75 mg/m$^2$ for 5 ds of each 28 d cycle for 9 cycles vs.<br>Best supportive care | Erythroid response |
| Jabbour , 2016 ABS [36], | To compare low-dose DAC with low-dose AZA<br><br>**Data collection period:** Nov 2012 to Feb 2016 | RCT phase II with a Bayesian design<br><br>**Follow-up** (median): 20 mos (range, 2 to 42 mos). | N= 113 pts with low- or intermediate-1 risk MDS<br>**IPSS**: low: 19%; intermediate-1: 81%<br>**Gender:** *nr*<br>**Age** (median, range ): 70 yrs, 44-88 yrs<br>**WHO diagnosis:** *nr* | Low-dose DAC vs. low-dose AZA<br>DAC: 20 mg/m$^2$ IV over the course of an hour for 3 consecutive ds<br>AZA: 75 mg/m$^2$ IV over the course of 1 hour or subcutaneously daily for 3 ds. | Overall improvement rate<br>AE<br>Cytogenetic response<br>Conversion to transfusion independence<br>EFS<br>OS |
| **Immunosuppressive agents** | | | | | |
| No studies met the inclusion criteria | | | | | |
| **Iron chelation** | | | | | |
| Parmar, 2015 ABS [108]<br><br>**Country:**Canada<br><br>**Funding:** *nr* | To compare characteristics and clinical outcomes of lower-risk TD MDS patients who received ICT with those who did not, adjusting for MDS and patient-related factors. | Cohort retrospective<br><br>**Follow-up** (median): 2.7 yrs (IQR 2.2 to 3.3) from diagnosis | N = 219 pts<br>**IPSS**: low-risk (n=69) and intermediate-1 risk (n-=149)<br>**Gender (male)**: 60%<br>**Age** (mean [IQR]): 73 yrs [65 to 80 yrs]<br>**WHO diagnosis**: *nr*<br>Time from diagnosis until TD (median, IQR): 7 mos [1 to 28] | ICT vs. no chelation | Predictive factors for OS |
| Langemeijer, 2016 ABS [44]<br><br>**Country:** multiple countries, Europe | To assess the efficacy of iron chelation and counteract the effects of iron overload<br><br>**Data collection period:** *nr* | Observational, prospective, registry study<br><br>**Follow-up:** | N = 768<br>**IPSS**: low-risk<br>**Gender (male)**: 69%<br>**Age** (mean [SD]): 69 [9]<br>**WHO diagnosis**: *nr*<br>Time from diagnosis (median, range): IG: 6 mos, 1 to 30 mos; CG: 6 mos, 1 to 32 mos | N= 195<br>Deferasirox (n=149)<br>Deferoxamine (n=36)<br>Deferiprone (n=10)<br>vs.<br>No chelation (573) | OS |

| Study name, Author, year, Country, Funding Identification number | Objectives / Focus / Data collection | Design | Population | Intervention/ Comparison | Outcomes |
|---|---|---|---|---|---|
| **Funding:** *nr* | | | | | |
| Delforge, 2012 ABS [42]<br><br>Country: Belgium<br><br>Funding: *nr* | To examine the effects of iron chelation<br><br>Data collection period: *nr* | Retrospective cohort<br><br>Follow-up: *nr* | N = 186 pts<br>**IPSS**: low-intermediate1: 68%<br>Intermediate 2-high: 9%, IPSS score not available: 23%<br>**Gender**: *nr*<br>**Age** (mean±SD): 77±9 yrs<br>**WHO diagnosis**: nr<br>Time from diagnosis (median): 3.6 yrs | Iron chelation vs. No chelation | OS<br>AML-free survival<br>AML progression |
| Francis, 2012 ABS [111]<br><br>**Country:** UK<br><br>**Funding:** *nr* | To test if iron chelation leads to improvement in survival and reduction of infections<br><br>**Data collection period:** *nr* | Retrospective cohort<br><br>**Follow-up:** *nr* | N = 61 pts<br>**IPSS**: *nr*<br>**Gender**: Male 60.7%<br>**Age** (mean): 68.7 yrs<br>**WHO diagnosis**: *nr*<br>Time from diagnosis (median): *nr* | Iron chelation (n=12) vs.<br>No chelation (transfusion only: n=30, no transfusion and no chelation: n=19) | Leukemia-free<br>OS<br>Reduced infection risk |
| Komrokji, 2011 ABS [43]<br><br>**Country:** *nr*<br><br>**Funding:** Novartis | To examine the impact of iron chelation therapy at an individual centre<br><br>**Data collection period:** Jul 2001 to Jul 2009 | Retrospective cohort<br><br>**Follow-up** (median) 85.7 mos | N = 97 pts with MDS and serum ferritin level ≥ 1000 ng/mL<br>**IPSS**: low- or Intermediate-1 risk<br>**Gender**: Male IG:73.3%, CG: 63.5%<br>**Age** (median): *nr*<br>**WHO diagnosis**:<br>RA 23%; RARS 22%; RCMD 32%; del 5q 3%; RAEB-I 15%; RAEB-II 3%; CMML 1%, MDS-u 1%<br>Time from diagnosis (median): *nr* | Iron chelation (n=45): 35 pts received deferasirox and 10 pts received deferoxamine vs.<br>No chelation (n=52) | OS<br>AML transformation |
| Lyons, 2013 ABS ONGOING [137]<br><br>**Country:** US<br><br>**Funding:***nr* | 36 mos interim analysis of registry<br><br>**Data collection period:** 5 yrs | Retrospective cohort<br><br>**Follow-up** (median) 36 mos | N = 600 pts with iron overload<br>**IPSS**: low- (38.6%) or Intermediate-1 risk (61.4%)<br>**Gender**: Male 57.8%<br>**Age** (median): 76 yrs (range, 21 to 99 yrs),<br>**WHO diagnosis**: *nr*<br>Time from diagnosis (median): *nr* | Iron chelation vs. no chelation | OS<br>time to AML transformation |
| **Other agents** | | | | | |
| Besa, 2011 ABS [110]<br><br>Country: US<br><br>Funding: nr | To examine the efficacy of 13cRA and alpha tocopherol<br><br>Data collection period: nr | Retrospective analysis<br><br>Follow-up: | N = 49 pts<br>**IPSS**: low- (41%), intermediate-1 (49%), and intermediate-2 (10%),<br>**Gender**: Male 55%<br>**Age** (median): IG = 69.6 yrs; CG = 66.2<br>**WHO diagnosis**: nr | Low-dose, long term maintenance low dose 13cRA + alpha tocopherol (n=20) vs.<br>Hi-dose 13cRA, short | ORR<br>Disease progression<br>Response<br>AML transformation<br>OS |

| Study name, Author, year, Country, Funding Identification number | Objectives / Focus / Data collection | Design | Population | Intervention/ Comparison | Outcomes |
|---|---|---|---|---|---|
| | | | Time from diagnosis (median): nr | term (n=29) + alpha tocopherol | |
| Komrokji, 2015 [147] ONGOING ABS NCT01736683 | To test different doses of sotatercept (ACE011) | RCT, phase II, open label, dose-finding study | Pts with lower-risk MDS or non-proliferative chronic myelomonocytic leukemia (CMML) and anemia requiring transfusion. | SC sotatercept at 0.1, 0.3, 0.5, or 1.0 mg/kg every 3 wks | HI Erythroid |
| PACE-MDS Giagounidis, 2015 [146] ONGOING ABS | To test luspatercept | RCT phase II multicenter, open label extension study | Pts with low- intermediate-1 risk MDS | Luspatercept vs. | Erythroid response (reduction of RBC transfusions) |
| Raza, 2013 [144] ONGOING ABS | To test graphic rigorsertib | RCT phase II | Pts with low- or intermediate-1 MDS that were transfusion-dependent | Rigorsertib administered intermittently vs. rigosertib administered continuosly | AE (urinary) |

13cRA = 13-cis-retinoic acid; ABS = abstract; AE = adverse events; AML = Acute myeloid leukemia; AZA = 5-azacytidine; CG = control group; CMML = chronic myelomonocytic leukemia; d(s) = day(s); DA = darbapoetin alpha; DAC = decitabine; del 5q = chromosome 5q deletion syndrome; EFS = event-free survival; EPO = erythropoetin; ESAs = erythropoiesis stimulating agents; GFM = Groupe Francophone des Myélodysplasies; Hb = hemoglobin; HI = hematologic improvement; HMA = hypomethylating agents; ICT = iron chelation therapy; IG = intervention group; IPSS = International Prognostic Scoring System; IQR = inter-quartile range; IWG = international working group; LEN = lenalidomide; mos = months; MDS = myelodysplastic syndromes; MDS-u = MDS unclassified; *nr* = not reported; Observ = observational; ORR = overall response rate; OS = overall survival; PBO = placebo; PLT = platelets; pts = patients; QOL = quality of life; RA = refractory anemia; RAEB-1 = refractory anemia with excess blasts with: 1. Bone marrow aspirate blast count (of at least 500 cells), 2. Peripheral blood blast count (of at least 200 cells), and 3. No Auer rods; RARS = refractory anemia with ring sideroblasts; RBC = red blood cells; RCMD = refractory cytopenia with multilineage dysplasia; RCMD-RS = refractory cytopenia with multilineage dysplasia and ringed sideroblasts; RCT = randomized controlled trial; rEPO = recombinant epoetin alpha, beta or darpoetin; rhu-EPO = recombinant human EPO; Retrosp = retrospective; SC = subcutaneous; SD = standard deviation; TD = transfusion dependency; TTP = time to progression; vs. = versus; wk(s) = weeks(s); WHO = World Health Organization; yrs = years.

**Table 4-8. Results of Unpublished Studies**

| Author, year | Design | Intervention Control | Survival | Disease control (e.g. EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|---|
| **Hematopoiesis-stimulating agents** | | | | | | | |
| **Erythropoiesis-stimulating agents** | | | | | | | |
| List, 2016 [103] | RCT | EPO+ LEN vs. LEN alone | *nr* | Response duration: not reached vs. 25.4 mos, p value = *nr* | Major erythroid response rate after 4 cycles:<br>14.3% vs. 33.3% (116 evaluable pts), p=0.018<br>ITT analysis: 25.6% (n=21) vs. 9.9% (n=8) (p=0.015) | NS | Response biomarkers:<br>Between-group comparisons *nr* |
| Platzbecker, 2016 [104] ABS | RCT | DAR vs. PBO | *nr* | *nr* | HI-E:<br>DAR:14.7% (11 of 75 evaluable) vs PBO:0% (0 of 35 evaluable), p=0.016 | *nr* | *nr* |
| Fenaux, 2016 ABS [105] | RCT | EPO vs. PBO | *nr* | Erythroid response duration: no comparative data reported<br><br>Time to first transfusion: p=0.046 | Erythroid response:<br>31.8% vs. 4.4%, p<0.001. | *nr* | *nr* |
| Messa, 2013 ABS [112] | Observ retrosp | EPO alpha vs. no treatment | *nr* | *nr* | *nr* | *nr* | Subgroups:<br>Pts not transfusion dependent with 8 g/dL<Hb<10 g/dL:<br>OS median: 216 mos vs. 99 mos, p=0.002<br>Pts with hb<8 g/dL or hb>10 g/dL: NS |
| Giordano, 2012 ABS [9] | RCT | Biosimilar EPO alpha vs.<br>EPO alpha | *nr* | *nr* | IG: Hb level increased by 1 g/dL in 3.5 wks (range3 to 8) vs. 5 wks (range 4-9) | No AE detected in either group | *nr* |
| ARCADE (20090160) Platzbecker, 2016 ABS [109] | RCT | Darbapoetin vs. PBO | *nr* | *nr* | HI Erythroid:<br>Double blind period (evaluable pts): 14.7% (11/75) vs. 0% (0/35), (p=0.016) | NS | *nr* |
| **Romiplostim** | | | | | | | |
| No definitve results | | | | | | | |
| **Eltrombopag** | | | | | | | |
| No definitive results | | | | | | | |
| **Immunomodulatory agents** | | | | | | | |
| **Non-5Q deletion** | | | | | | | |
| Komrokji, 2016 ABS [107] | Cohort retrosp | LEN 1st line followed by AZA vs. | OS (median): 79 mos vs. 61 mos, p=0.4 | AML transformation: 9% vs. 22% (p=0.03) | HI Erythroid: 20% (16/80) vs. 11% (7/64) (p=0.046) | *nr* | *nr* |

| Author, year | Design | Intervention Control | Survival | Disease control (e.g. EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|---|
| | | LEN 2nd line after AZA | AML-survival: 78 mos vs. 61 mos (p=0.4) | | | | |
| Rollison, 2014 ABS [113] | Cohort retrosp with nested case-control | LEN vs. no LEN | *nr* | Association of AML transformation with LEN treatment after adjustment for prognostic factors: OR: 0.44, 95% CI: 0.10 to 1.94 | *nr* | *nr* | *nr* |
| Corrales-Yepez, 2013 ABS [29] | Cohort retrosp | LEN 1st line vs. LEN 2nd line (as 1st line after ESAs or 2nd line after AZA failure) | OS rate: NS<br>OS median: 104 mos vs. 87 mos, p=0.55 | AML transformation rate: 5.4% vs. 11%, p=0.33 | Erythroid HI rate: 38% vs. 12%, p=0.04<br><br>Response rate to AZA: 38% vs. 35%, p=0.69 | *nr* | *nr* |
| **Hypomethylating agents** | | | | | | | |
| **Azacytidine** | | | | | | | |
| Sohn, 2014 ABS [106] | Cohort retrosp and Case control | HMA vs. BSC | OS rate (5-year): 41.0±7.4 vs. 62.5±10.8% (p=0.049) | *nr* | *nr* | *nr* | Factors associated with worse OS (multivariable analysis):<br>• ECOG-PS 2-3 (HR 5.036, p<0.001),<br>• IPSS blast ≥0.5% (HR 2.157, p=0.035)<br>• First-line HMA therapy (HR 2.213, p=0.026) |
| **Decitabine** | | | | | | | |
| Sanchez-Garcia 2015 ABS [30] | RCT | AZA vs. best supportive care | OS: NS<br>Leukemia-free survival: NS | *nr* | Erythorid response rate: 31% transfusion independence vs. 5.5%, p<0.01 | *nr* | *nr* |
| Jabbour , 2016 ABS [36] | RCT | Low-dose DAC vs. low-dose AZA | OS rate: 84% vs. 87%, p=0.80 | EFS rate (1-year): 73% vs. 57, p=0.15<br><br>Progression to AML: 8% vs. 13%, p values = *nr* | *nr* | Infection and neutropenic fever: 7% vs. 5%, p=*nr*<br>No grade 4 AE in either group | *nr* |
| **Immunosuppressive agents** | | | | | | | |
| No studies met inclusion criteria | | | | | | | |
| **Iron chelation** | | | | | | | |
| Parmar, 2015 ABS [108] | Cohort retrosp | ICT vs no chelation | OS (median): 8.62 yrs vs. 4.38 yrs, p=0.0005 | *nr* | *nr* | *nr* | Factors predictive of OS (multivariate analysis):<br>ICT: HR 1.821 (95% CI, 1.122 to |

| Author, year | Design | Intervention Control | Survival | Disease control (e.g. EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|---|
| | | | | | | | 2.953), p=0.0152<br>Age: HR 1.025 (95% CI, 1.005 to 1.045), p=0.0125<br>IPSS-R at time of TD: p=0.0018 |
| Langemeijer, 2016 ABS [44] | Observ retrosp | Chelation vs. no chelation | OS[E]: HR 1.5 (95% CI 1.1 to 2), p=0.01 | *nr* | *nr* | *nr* | *Subroups:*<br>OS for pts on deferasirox vs. not chelated pts: HR: 1.6 9(5% CI 1.2 to 2.3, p=0.006<br>OS for pts on deferasirox vs. pts on deferoxamine[E] : HR 1.9 (95% CI 1.1 to 3.3) |
| Delforge, 2012 ABS [42] | Cohort retrosp | Iron chelation vs. No chelation | OS (median): 126 vs. 37 mos, p<0.001 | AML-free survival: NS | *nr* | *nr* | *Subgroups:*<br>Pts with low IPSS score: OS: 171 vs. 37 mos, p<0.001<br>Pts with intermediate-1 IPSS score:<br>OS: 126 vs. 37 mos, p=0.002 |
| Francis, 2012 ABS [111] | Cohort retrosp | Iron chelation vs. no chelation | OS<br>Values not reported, NS for pts belonging to the same IPSS group, p=0.16<br>Leukemia-free survival: NS when pts in the same IPSS score were compared, p=0.7 | *nr* | *nr* | Infective epidsodes: NS for number of positive urine bacteriology, blood cultures or abnormal CSR | *nr* |
| Komrokji, 2011 ABS [43] | Cohort retrosp | Iron chelation vs. no chelation | OS (median)<br>59 mos (95% CI, 22 to 48 mos) vs. 33.7 mos (95% CI, 38 to 80 mos).<br>In multivariable analysis iron chelation was associated with better OS: HR 0.52, 95% CI, 0.31 to 0.87, p=0.013 | AML transformation: 15.6% vs. 21.2%, p=0.33 | *nr* | *nr* | *nr* |
| **Other agents** | | | | | | | |
| Besa, 2011 ABS [110] | Cohort retrosp | Low-dose, long term maintenance low dose 13cRA + | *nr* | AML transformation rate:<br>15% vs. 13.7% | ORR: 75% vs. 44.8% | *nr* | *nr* |

| Author, year | Design | Intervention Control | Survival | Disease control (e.g. EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|---|
| | | alpha tocopherol vs. Hi-dose 13CRA, short term (n=29) + alpha tocopherol | | | | | |

13cRA = 13-cis-retinoic acid; ABS = abstract; AE = adverse events; AML = Acute myeloid leukemia; AZA = 5-azacytidine; BSC = best supportive care; CG = control group; CI = confidence interval; DAC = decitabine; COG = Eastern Cooperative Oncology Group performance status; EFS = event-free survival; EPO = erythropoetin; ESAs = erythropoiesis stimulating agents; GFM = Groupe Francophone des Myélodysplasies; HI = hematologic improvement; HMA = hypomethylating agents; HR = hazard ratio; ICT = iron chelation therapy; IG = intervention group; IPSS = International Prognostic Scoring System; ITT = intention to treat; LEN = lenalidomide; mos = months; MDS = myelodysplastic syndromes; *nr* = not reported; NS = not significant; Observ = observational; ORR = overall response rate; OS = overall survival; PBO = placebo; PFS = progression-free survival; pts = patients; Retrosp = retrospective; QOL = quality of life; RCT = randomized controlled trial; RR = response rate; TD = transfusion dependency; vs. = versus; wk(s) = weeks(s); yrs = years.

## DISCUSSION AND CONCLUSIONS

The majority of patients with lower-risk MDS are elderly, and two-thirds to three-quarters of patients are considered 'low-risk' using conventional prognostic scores. Because of their age and comorbidities, curative therapy is typically unavailable to this patient group even if they are very symptomatic. Goals of therapy are improved quality of life, avoidance of or decreased transfusion dependence, and improved overall and/or leukemia-free survival. For these reasons, we have been broad in our inclusion criteria, and we included comparative studies as well as randomized trials. We also included studies that combined lower- with higher-risk populations and did not report outcomes separately. Therefore, the recommendations are sometimes weak as they were based on evidence that was at times partially indirect and of moderate to low certainty.

For Ontario, we decided to adapt the algorithm presented by the ESMO guideline [57], with two small modifications (Figure 4-2). This algorithm is germane to our practice, and to the evidence presented herein. Patients may present with moderate and asymptomatic anemia, or suffer from symptomatic anemia, thrombocytopenia, neutropenia, and, if subject to long-term transfusion therapy, they may suffer end-organ damage caused by iron overload.

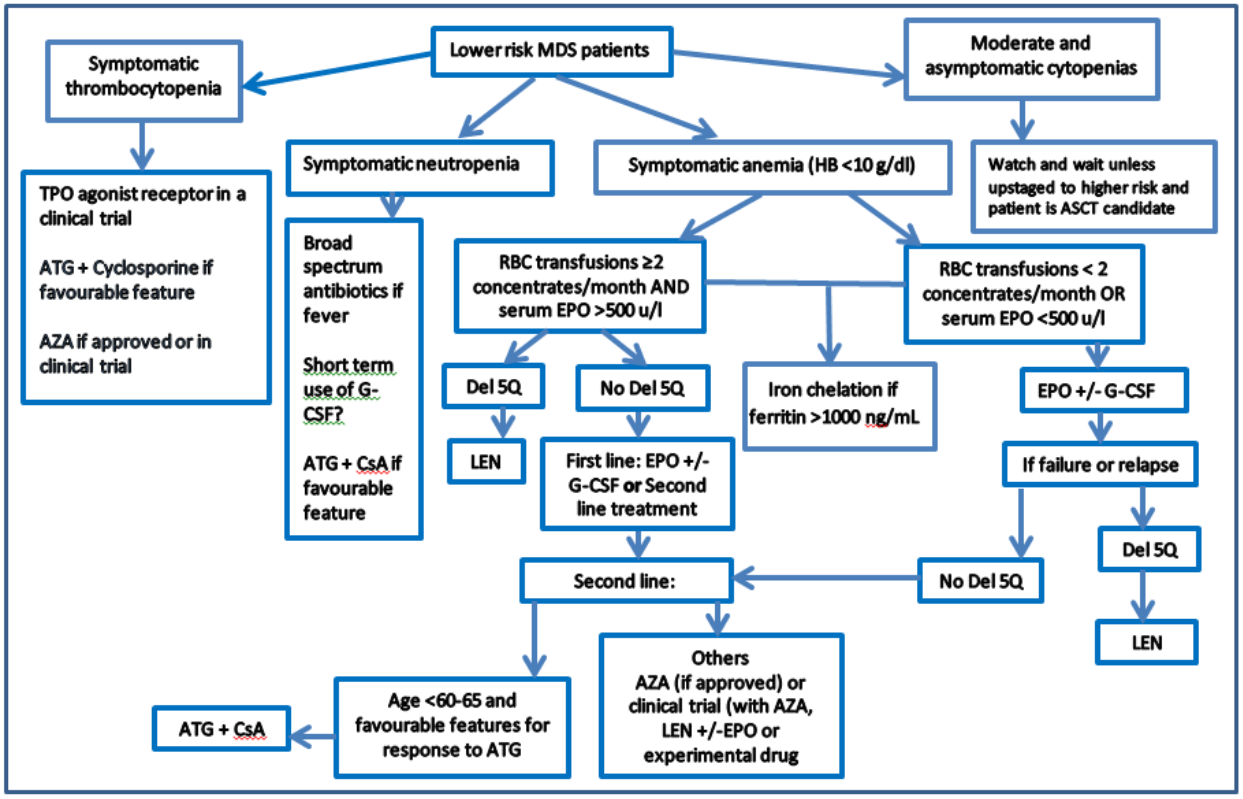


**Figure 4-2.** Treatment algorithm for the systemic treatment of lower-risk myelodysplastic syndromes. Adapted from Figure 3 in: Fenaux P, et al. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 (Suppl 3): iii57–iii69 doi:10.1093/annonc/mdu180, with permission of Oxford University Press on behalf of the European Society for Medical Oncology.

**Patients with moderate and asymptomatic anemia**

For this population of patients, we agreed to a watch and wait approach unless the patients are upstaged to higher-risk disease and they are candidate for an allogeneic stem cell transplant (Recommendation 2D).

**Patients with symptomatic anemia**

We recommended EPO with or without G-CSF (Recommendations 1A, 1B). This recommendation is consistent with previous consensus [60,61], and evidence-based guidelines [57].

The synergistic effect of G-CSF with EPO had been shown by a randomized trial by Casadevall et al. [152], which was published prior to the cut-off date of our systematic review. Additionally, objective response rate was improved when G-CSF was added to to EPO in non-responders in the noncomparative Step 3 and Step 4 of the ECOG E1996 trial [8]. In this review we found abundant evidence in support of the use of ESAs in anemic and/or transfusion-dependent patients with lower endogenous erythropoietin levels and transfusion need. There is no clear superiority of erythropoietin over darbepoetin with the key message that high doses are needed to achieve erythroid responses, and that responses can usually be observed within 16 weeks of therapy. The addition of G-CSF to the ESA may augment responses particularly in the subytpes with ring sideroblasts, although this has not been observed in all studies.

We recommended lenalidomide in patients with del(5q) as a second-line treatment after ESA has failed (Recommendations 2A, 2B, and 3). The evidence that we included in this

systematic review confirmed our clinical experience that this treatment may lead to transfusion independence in most patients. Adverse events are transient and can be managed with dose reductions (Recommendation 2C).

For the subpopulation of patients with p53 nuclear protein expression, who are at heightened risk for AML transformation, we suggested immunohistochemical screening as a potential option to guide therapy intensification (Recommendation 2). This suggestion is based on a corollary study [2] of the trial MDS 004 [19], which showed how positivity for p53 was strongly associated with risk of AML progression.

Not enough evidence is available at this time to recommend lenalidomide in combination with other agents outside of a clinical trial.

For patients without del(5q) who are refractory or ineligible to ESA we suggested a line of treatment with lenalidomide (Recommendation 3). For those who do not respond to EPO, and who are not candidates for intensive chemotherapy and transplant, we suggested an option of treatment with hypomethylating agents (AZA or DAC) (Recommendation 4).

For all patients with transfusional hemosiderosis, we suggested ICT.

**Patients with thrombocytopenia or neutropenia**

The body of evidence at this time is not mature enough to recommend romiplostim and eltrombopag outside of a clinical trial setting (Recommendation 1B). However, this field is evolving rapidly, and, among our included trials is a recent unpublished five-year follow-up data [117] companion of a randomized trial [15] of romiplostim that was included in the review by Prica et al. [12]. In the original trial [15], romiplostim had to be stopped because of concerns about increased risk of excess blasts and AML transformation. The long-term follow-up has shown that romiplostim reduced bleeding and did not increase leukemia or shorten survival [117].

For selected patients who have failed or are ineligible to take ESAs, we suggested an option of treatment with immunosuppressive therapy (ATG and CsA) (Recommendation 5).

**Patients with iron overload**

At this time, it is incompletely understood whether there is a different physiology of iron in any of the MDS subgroups, so it is unclear whether any particular subgroups are prone to benefit more than others from iron chelation. No RCT data have been published thus far on the efficacy of iron chelation to improve survival in the MDS population. We are aware of the ongoing TELESTO trial (NCT00940602); at its completion, and with an update of this guideline, this section will be made more useful.

The major strength of this work is that we we comprehensively reviewed the comparative data related to hematopoietic growth factors, lenalidomide, iron chelation, and hypomethylating agents from 2009 to 2017, and from 2005 to 2017 for all other agents, and we integrated these data with clinical expertise to form our recommendations for patients in Ontario. Among the limitations of our work, we were unable to find any evidence regarding the acceptability of the recommended interventions to our patients. In the Buckstein et al. guideline [4] studies that included a mixed population of patients with low, intermediate-1 and intermediate-2 or high IPSS scores were not included, so in this review a small number of studies belonging to this group and published before 2009 may have been missed.

We based our judgement about which outcomes were critical and very important to patients on the expertise of the members of the Working Group and on the opinion of one patient representative who is a member of our Expert Panel. This is certainly another limitation of our work. However, during our searches we also identified nine studies that explored patients' perspectives on MDS and its treatment options [153-161]. As we did not specifically search for these studies, we excluded them from our systematic review. However,

they bring anecdotal testimony of what is important to patients undergoing the treatments we propose, and confirm our choices.

# Systemic therapy for the treatment of adult patients with lower-risk myelodysplastic syndromes

## Section 5: Internal and External Review

**INTERNAL REVIEW**

The guideline was evaluated by the GDG Expert Panel and the PEBC RAP (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

**Expert Panel Review and Approval**

Of the 24 members of the GDG Expert Panel, 20 members cast votes for a total of 83% response in November 2017. Of those that cast votes, 19 approved the document (95%) and one abstained (0.05%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

**Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.**

| Comments | Responses |
|---|---|
| Editorial changes | We corrected typos, and clarified sentences in the Target Population paragraph, thoughout the document sections. |
| Asked to check on lenalidomide dose (Recommendation 2B) | We checked and confirmed dose and schedule. |
| Asked to change "low-, intermediate risk" to "lower-risk" | We have modified throughout the document, including the title. |
| Recommendation 4: asked to add: AZA for patients with lower risk who have severe cytopenias | We deleted the sentence: "AZA is not recommended as a first-line treatment for patients with low- and intermediate-1 IPSS risk MDS." from the recommendation, and we added that AZA or DAC can be offered to patients with clinically significant multiple cytopenias. |

**RAP Review and Approval**

Three RAP members, including the PEBC Director, reviewed this document in September/October 2017. The RAP conditionally approved the document on October 2, 2017. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

**Table 5-2. Summary of the Working Group's responses to comments from RAP.**

| Comments | Responses |
|---|---|
| Readability would improve if the level of detail in Section 2 would be thinned out. Details can be displayed in Section 4 with the systematic review data. (APPROVE) | We moved some very detailed paragraphs from the Key evidence in Section 2 to Section 4. |
| The guideline is structured around when to use specific tools, as opposed to what to do in particular clinical situations. As a non- | We adapted Figure 3 from the ESMO guideline [57] and reproduced here with permission. The Figure has been placed at the end of Section 1, |

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| content expert I found it to be one of the more difficult guidelines to follow…. I looked up the ESMO guideline that the authors say they adapted for their recommendations. Figures 2 and 3 are very useful. Could an Ontario version of those be added to this? (APPROVE) | Section 2, and Section 4.<br><br>The suggested approach has been followed in the discussion section that summarizes the content of the guideline from a clinical situation perspective. |
| 1. I think the inclusion of studies that combine low-intermediate risk with higher-risk population where outcomes are not separately reported is justified, but does weaken the conclusions. I think this should be emphasized in the discussion. The lack of RCT data and reliance on secondary tier evidence should also be emphasized.<br>2. The only issue I have is with Recommendation 5 where weak evidence seems to have been inferred for the use of immunosuppressive therapy in the target population. Prefer this to be stated frankly and that the recommendation is 'weak'.<br>3. A complex document and the authors must be congratulated. The changes I suggest are relatively minor. (CONDITIONALLY APPROVE) | 1. We modified the discussion section to emphasize the weakness of the conclusions: Goals of therapy are improved quality of life, avoidance of, or decreased transfusion dependence, and improved overall and/or leukemia-free survival. For these reasons, we have been broad in our inclusion criteria, and we included comparative studies as well as randomized trials. We also included studies that combined lower- with higher-risk populations and did not report outcomes separately. Therefore, the recommendations are sometimes weak as they were based on evidence that was at times partially indirect, and of moderate to low certainty.<br>2. Recommendation 5 is a weak recommendation, ("…can be offered as an option") with a suggestion to involve the patient in a discussion with the hematologist/oncologist.<br>**3.** Does not require any changes. |

## EXTERNAL REVIEW
## External Review by Ontario Clinicians and Other Experts

### *Targeted Peer Review*

Three targeted peer reviewers from Ontario who are considered to be clinical and/or methodological experts on the topic were identified by the Hematology GDG and the MDS Working Group. All agreed to be the reviewers (Appendix 1), and responses were received from all. Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

**Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.**

| | **Reviewer Ratings (N=3)** | | | | |
|---|---|---|---|---|---|
| **Question** | Lowest Quality (1) | (2) | (3) | (4) | Highest Quality (5) |
| **1. Rate the guideline development methods.** | | | | 1 | 2 |
| **2. Rate the guideline presentation.** | | | | 1 | 2 |
| **3. Rate the guideline recommendations.** | | | | 2 | 1 |
| **4. Rate the completeness of reporting.** | | | | 1 | 2 |
| **5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?** | | | | 1 | 2 |
| **6. Rate the overall quality of the guideline report.** | | | | | |
| | Strongly Disagree (1) | (2) | Neutral (3) | (4) | Strongly Agree (5) |
| **7. I would make use of this guideline in my professional decisions.** | | | | 1 | 2 |
| **8. I would recommend this guideline for use in practice.** | | | | 1 | 2 |
| **9. What are the barriers or enablers to the implementation of this guideline report?** | | | | | |

## Table 5-4. Responses to comments from targeted peer reviewers.

| Comments | Responses |
|---|---|
| **1. Question 1 comments.**<br>I would consider adding eprex dosing up front in the recommendation boxes so the clinician does nott have to search below | No changes made |
| **2. Question 2 comments.**<br>Figure 1-1: recommendation that if EPO > 500 and receiving >2 units would still give eprex. I'm not sure that this is standard of care or based on evidence. According to the Nordic Score chance of response would be 7% so would not be offered by all clinicains | This is standard of care worldwide. Not offering ESA in a very low response (predicted) group is standard of care among MDS experts. |
| **3. Question 3 comments** Comprehensive and forward-looking.<br>These recommendations are consistent with my practice, but there are limitations in implementing this routinely for all patients (see response to question 6). The authors should be commended for developing this guideline. However, it is a dense document to peruse and there is variability with the strength of the recommendations based on the quality of the evidence (e.g., lower with immunosuppressive therapy and iron chelation). | Some of the limitations in implementation have been mentioned in the IMPLEMENTATION CONSIDERATIONS section, at the end of Section 2. |
| a. In Section 1, Qualifying Statements for Recommendation 1A (bullet 2, page 2) – it states that "…EPO can be given at a dose of 40,000-60,000 units weekly…A 12-week trial is recommended with dose escalation after an initial eight-week trial in nonresponders. For EPO, dose escalates from 40,000 units to 60,000-80,000 units weekly." Should the "…40,000-60,000 units…" be changed to "…40,000-80,000 units…" to keep this consistent? For guidance, is there much evidence for increasing to 80,000 units as opposed to 60,000 units? Can any comment be made about trying higher doses, eg 100,000 units? Where does the initial trial period of 8 weeks (at the lower dose come from, as opposed to 6 weeks then escalate)? | Bullet 2 of the Qualifying statement of recommendation 1A has been changed to: "Darbepoetin can be administered at a dose of 500 µg every two to three weeks; EPO can be given at a dose of 40,000-60,000 units weekly. A 12-week trial is recommended with dose escalation after an six-week trial in non-responders. For EPO, dose escalates from 40,000 units to 60,000 units weekly. For darbepoetin, escalate from 500 µg every three weeks, to every two weeks to every week. This dose escalation can occur along with the addition of G-CSF (see recommendation 1B below). Suggested target hemoglobin is 110-120 g/dL in transfusion-independent patients; in patients who are transfusion-dependent, the suggested goal of treatment is transfusion-independence." 80,000 has been removed to be consistent with the cited literature, and left it at 60,000. There is no real evidence for 80,000 units/week- ,but just clinician experience (anecdotal). The precedent for raising the dose after 6-8 weeks comes from clinical trials where this was done (some at 6 weeks, others at 8). I would be comfortable using 6 weeks as the time point to dose escalate. |
| b. In Section 2, Interpretation of Evidence for recommendation 1A, Generalizability (page 3) – should there be a statement that responses are more likely to occur if EPO level < 500 IU/L and <2 units of packed red blood cells transfused per month (as per the Nordic score)? | A line with this statement has been added to the Generalizability statement in the ***Interpretation of Evidence for Recommendation 1A*** section. |
| c. In Section 1, Qualifying Statements for Recommendation 2 (bullet 1, page 2) – it states "..therefore, immunohistochemical screening is a potential option for this subpopulation to guide potential intensification of therapy. At the present time, p53 testing requires further validation." Please clarify what the "potential intensification of therapy" means (eg allotransplantation [which does not work very well either], closer monitoring, clinical trial, etc). | This sentence was added to the Qualyfing statement in Section 1 and in Section 2: Potential intensification could mean allo-transplant in younger patients, perhaps with novel interventions post transplant, clinical trials (e.g., with cenersen), hypomethylating agents, other clinical trial, and closer monitoring. |
| d. In Section 2, Recommendation 3: Lenaldiomide in nondel(5q) (pages 7 & 8) – it recommends "lenalidomide regimen is 10 mg/day on days 1-21 of a 28 day cycle". However, in the phase 3 MDS-005 trial (Santini et al. J Clin Oncol 2016; 34(25):2988-2996), the dosing schedule used was 10 mg po daily (days 1-28 of a 28 day cycle). The recommendation for the 10 mg/day on days 1-21 of a 28-day cycle dosing scheduled is extrapolated from the phase 3 MDS-004 trial (Fenaux et al. Blood 2011; 118(14):3765-76). Therefore, the decision to use the 21/28 dosing schedule in this nondel(5q) population needs to be explained/justified. | Change made. |

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| e. In Section 1, Recommendation 4: Hypomethylating agents (page 3) – it states that "AZA or DAC can be offered as options to patients with lower-risk MDS without del(5q), with clinically significant cytopenia(s), and who are not candidates for intensive chemotherapy and transplant, and to patients with multiple clinically significant cytopenias". I am not sure I understand all the points being raised here, can the phrase simply be shortened to "AZA or DAC can be offered as options to patients with lower-risk MDS without del(5q), with clinically significant cytopenia(s)"? | Change made.<br>Recommendation 4 now reads in Sections 1 and 2:<br>"AZA or DAC can be offered as options to patients with lower-risk MDS without del(5q), with clinically significant cytopenia(s)" . |
| f. In Section 2, Key Evidence for Recommendation 4, A) AZA (but 1, page 9) – it states that "Among existing guidelines, Buckstein et al. [4] did not recommend AZA as first-line therapy for patients with lower-risk MDS because the authors did not locate any comparative evidence specifically in the lower-risk population". In the Buckstein et al. guideline, we did not breakdown studies that included a mixed population of patients with low, intermediate-1 and intermediate-2 or high IPSS scores, such as the Silverman et al. trial (Silverman et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the Cancer and Leukemia Group B. J Clin Oncol 2002;20(10):2429-40; Silverman et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: Studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol 2006;24(24):3895-903). IPSS score were available for 81 of 191 patients enrolled onto the 9221 study (9% low risk and 45% intermediate-1 risk; so at least 44 of the patients had lower-risk MDS). However, in the current CCO gudieline under review, these types of studies were included. So you may be missing some (probably a small number other than the Silverman papers) primary studies concerning azacitidine if the AZA search was restricted to 2009 and later. | We cannot look at noncompartive AZA trials in this guideline because our methodology would be violated.<br>We added the sentence:<br>"In the Buckstein et al. guideline [4] studies that included a mixed population of patients with low, intermediate-1 and intermediate-2 or high IPSS scores were not included, so in this review a small number of studies belonging to this group and published before 2009 may have been missed." to the limitations in the Discussion section. |
| g. In Section 1, Qualifying Statements for Recommendation 4 (bullet 3, page 3) – it states that the "…preferred dose and schedule for AZA is 75 mg/$m^2$ for three days of each 28-day cycle. The preferred dose and schedule for DAC is 20 mg/$m^2$ per day SC for three consecutive days at the beginning of every 28-day cycle." I don't agree with this dose/schedule recommendation. Forty patients received AZA and 73 patients received DAC. Ovearall response rate was 70% and 49% (P=0.03) for patients treated with DAC and AZA, respectively. 32% (12/38) of the patients receiving DAC became transfusion independent (TI) compared with only 16% (3/19) of patients treated with AZA (P=0.2). The number of patients treated are small and rates of transfusion independence extremely low, so why is AZA 75 mg/$m^2$/d SC or IV for 3 consecutive days better than the standard 75 mg/$m^2$/d SC or IV for 7 consecutive days which more patients, even lower risk have received (Silverman et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the Cancer and Leukemia Group B. J Clin Oncol 2002;20(10):2429-40; Silverman et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: Studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol 2006;24(24):3895-903) or 75 mg/m2/d sc or IV for five consecutive days (Lyons et al. Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. J Clin Oncol 2009;27(11):1850-6)? Why would you choose AZA over DAC if the overall response rate and transfusion independence is better with DAC (if one is prepared to accept this small trial as how to treat lower risk MDS pateints with HMAs)? And mechanistically, why would DAC given for 3 days | This is the only comparative study restricted to lower-risk MDS patient so we cited the doses and schedules used. Higher doses of HMAs (or more days of) are associated with greater cytotoxicity and appropriate for higher-risk disease. The standard dose/schedules of decitabine (20 mg/$m^2$ /day × 5 days) and azacitidine (75 mg/$m^2$ /day × 7 days) that are commonly used for patients with higher-risk MDS tend to be myelosuppresive and may have a less favorable risk-benefit balance in patients with lower-risk MDS. Several studies have previously suggested that low doses of HMAs administered using shorter treatment schedules are active in lower-risk MDS. Low-dose decitabine (20 mg/$m^2$ daily x 3 days) showed promising results in a small trial [35], with an objective response rate of 23% and transfusion independency rate of 67%.1<br><br>The Lyons study [33] gave 5 or 7 or 5 2 5 schedules of AZA in a mixed population of lower- and higher risk disease. Maybe 5-7 days is better than 3 in lower risk disease but we have no comparative data.<br><br>The Qualifying statement for Recommendation 4 has been changed:<br>I agree with you - DAC should be used over AZA based on this study in lower risk MDS but it is not marketed in Canada (YET). So we advocated for the HMA that is available and used the dose of the comparative study. I would be comfortable changing to 5 days (re AZA) given that it was found to be comparable to 7 days in the Lyons study which enrolled a good number of low risk patients.<br><br>BTW: in the discussion of the Jabbour [162] (DEC versus AZA study), this is mentioned: A larger multicenter study assessing the benefit of early intervention is ongoing. This study |

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| instead of the standard 5 days be considered comparable to AZA given for 3 days instead of the standard 7 days (especially when other studies have examined at least a 5-day dosing schedule of AZA)? | will address the role of early intervention (HMA therapy versus supportive care only) and the best schedule of HMA therapy (3 days of decitabine versus 3 days of azacitidine versus 5 days of azacitidine) |
| h. In Section 2, Interpretation of Evidence for Recommendation 5, Generalizability (page 12) – it states "This evidence is generalizable to selected patients that are more likely to respond, (i.e., age <60 years, only recently transfusion dependent, HLADr15 +, trisomy 8, PNH clone)…" What about hypocellular marrow, which was a predictor of response in the Passweg et al. phase 3 trial (J Clin Oncol 2011;29(3):303-9) and which was included in the Section 1, Qualifying Statements for Recommendation 5 (bullet 2, page 4)? Was this omitted in error? | Change made. Hypocellular marrow was added as an additional predictor. This was omitted in error |
| i. In the guidelines, there is no mention about the role of allogeneic stem cell transplant for patients with lower risk MDS who are thrombocytopenic and platelets transfusion dependent and/or neutropenic with recurrent infections? | The focus is on drug therapy and not cellular therapy and we have no comparative data to cite regarding allogeneic stem cell transplant. In all my years treating MDS, I have never had to do that. such a patient is usually found to have higher risk disease anyway (eg using the IPSS-R) and would qualify for this. |
| j. In Section 1, Figure 2-1 (page 1), why (a) is a TPO agonist or AZA in clinical trial listed as option for symptomatic thrombocytopenia, but other agents (e.g oral decitabine/ IV decitabine) are not listed? Is it better to say clinical trial (e.g., TPO agonist, hypomethylating agent, etc)?; (b) are clinical trials not listed as a option for symptomatic neutropenia?; (c) is the role for allogeneic stem cell transplant (other than for disease progression to higher risk MDS) not listed in the algorithm? | The algorithm was reproduced with permission and minimally adapted from Figure 3 in: Fenaux, et al. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 (Suppl 3): iii57–iii69 doi:10.1093/annonc/mdu180, with permission of Oxford University Press on behalf of the European Society for Medical Oncology. . |
| 4. **Question 4 comments**: Extremely thorough. Excellent source of curated and graded evidence. | No need for comments. |
| 5. **Question 5 comments**:<br>a. Does the guideline pertain to patients with de novo MDS or also to patients with secondary or therapy-related MDS? It is only specifies that patients with therapy-related MDS should not be treated with IST (Section "Interpretation of Evidence for Recommendation 5", subsection "Generalizability", page 12). | This guideline is applicable to de-novo MDS. The clinical trials we cite are mostly in de-novo MDS. Nevertheless, an older non-transplant eligible patient with secondary MDS could be treated with ESA's, lenalidomide etc., since there are no other options. I think we do need to qualify that this is for de-novo MDS. Therapy-related-MDS is generally higher risk and should be referred for allogeneic stem cell transplant consideration. |
| b. In Section 1, Recommendation 3: Lenalidomide in nondel(5q) (page 3) – there is no minimum duration of therapy specified unlike the recommendatiosn for ESAs (12 weeks), lenalidomide in del(5q) MDS (16 weeks), and ATG and CSA. | Change made in Section 1 and Section 2. In MDS-005 it was 16 weeks; accordingly, we added 16 weeks. |
| c. In Section 1, Recommendation 4: Hypomethylating agents (page 3) – there is no minimum duration of therapy specified unlike the recommendations for ESAs (12 weeks), lenalidomide in del(5q) MDS (16 weeks), and ATG and CSA. | Minimum duration of therapy is 24 weeks in higher risk MDS- this is extrapolated from the MDS001 study. In the Jabbour comparative study [162] (JCO) of decitabine versus AZA, patients stayed on treatment for as long as they benefited and the median number of cycles cycles was 9 (range, 1-41). |
| 6. Question 6 comments: Access to medications that are currently not covered by CCO, e.g., G-CSF in EPO failures; lenolidomide in non-del(5q) ASA in low-risk retractory cytopenias, eltrombog in selective symptomatic thrombocytopena.<br>Recommendations will be hard to implement as most patients do not have third-party insurance to pay for medications (and may or may not have access to appropriate clinical trials). | Funding is out of scope for this guideline. A line has been added in the implementation considerations section at the end of Section 2. |
| a. G-CSF is not CCO funded for administration in combination with ESAs for MDS patients with symptomatic anemia. | Funding is out of scope for this guideline. A line has been added in the implementation considerations section at the end of Section 2. |

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| b. ESAs are CCO funded for a 12 week period for new applicants. Patients who do not demonstrate a response to ESAs will not get an extension of Exceptional Access Programme approval for ESAs. Therefore, if one of the recommendations is to increase the dose of for eg epoietin from 40,000U after 8 weeks without a response to 60,000U for another 4 weeks (total 12 weeks) and there is still no response, it will be imposiible to use the combination of ESA and G-CSF without third party coverage. | Funding is out of scope for this guideline. A line has been added in the implementation considerations section at the end of Section 2. |
| c. EPO is not CCO funded for patients with EPO levels >500 IU/L. | Funding is out of scope for this guideline. A line has been added in the implementation considerations section at the end of Section 2. |
| d. Eltrombopag is not CCO funded for this indication. It will be hard to obtain "eltrombopag for short-term use in patients with bleeding or prior to surgical intervention.." (Section 1, Qualifying Statements for Recoemmendation 1B, bullet 3, page 2) as most hospitals will not pay for the drug in these scenarios and the insurance companies may or may not pay for drug especially, if not approved for the indication and if administered in a hospital. | Funding is out of scope for this guideline. A line has been added in the implementation considerations section at the end of Section 2. |
| e. Lenalidomide is not approved for the treatment of lower-risk non-del(5q) MDS patients wih transfusion dependent anemia (and Celgene is not planning to seek Health Canada or FDA approval for this indication), so it is not CCO funded and may or may not be funded by third-party insurance. | Funding is out of scope for this guideline. A line has been added in the implementation considerations section at the end of Section 2. |
| f. AZA is not Health Canada approved for this indication and hence, not CCO funded and hence, unlikely to be funded by insurance companies. Furthermore, insurance companies have not been reimbursing/paying for drugs administered in hospital. | Funding is out of scope for this guideline. A line has been added in the implementation considerations section at the end of Section 2. |
| g. DAC is not Health Canada approved for this indication or for higher-risk MDS, as the pharmaceutical company has not sought Health Canada approval. | Funding is out of scope for this guideline. A line has been added in the implementation considerations section at the end of Section 2. |
| h. It is diffcult to obtain CCO approval for oral iron chelating agents and older patients are often reluctant to or refuse to receive parenteral iron chelating agents. | Funding is out of scope for this guideline. A line has been added in the implementation considerations section at the end of Section 2. |
| Question 7 commen ts<br>Extremely well done – congratulations!<br>Minor points: this is not direct comparison of EPO vs lenolidomide in low transfusion border del(5q); in as much as lenalidomide is disease-modifying but EPO likely is not . Choice of LEN up-front rather than only in EPO failure entirely reasonable if listed and benefits discussed with patients. | No change is needed |
| Some minor comments:<br>a. In the Section "Recommendation 1: Hematopoiesis stimulating agents (ESA)", subsection "G-M-CSF/macrophage colony-stimulating factors…" (page 1) – were any articles pulled describing use of GM-CSF in this population or just G-CSF? If just G-CSF, would change the title to "G-CSF/granulocyte colony stimulating factors…" | The title was not changed because of future updates may include GM-CFS (we searched for it). Perhaps add a sentence that no evidence was located for the use of GM-CSF. |
| b. In the Section "Key Evidence for Recommendation 4", subsection "A) AZA" (bullet 3, page 9) – the "…studies that included a mixed population of patients with low intermediate-1 and intermediate-2 or high IPSS scores,.." should be changed to "…studies that included a mixed population of patients with low, intermediate-1, and intermediate-2 or high IPSS scores,.." | Change made |
| c. In the Section "Interpretation of Evidence for Recommendation 5", subsection "Generalizability" (page 12) – the "…only recently transfusion dependent, HLADr15 +, trisomy 8, PNH clone…" should be changed to "only recently transfusion dependent, HLA-DR15 +, trisomy 8, PNH clone…" | Change made |

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| d. In Section "The Program in Evidence-Based Care" (paragraph 3, page 17) – the "..from the OMHLTC" should be changed to "..from the MOHLTC" | Change made |
| e. In the Section "Guideline Developers" (paragraph 1, page 17) – the "…at the request of the Hematology Disease Site Group" should be changed to "…at the request of the Hematology Disease Site Group" | Change made |
| f. In "Table 4-3. General Characteristics of Included Comparative Studies…" (row 7, column 2, page 31) – the "To find the optiman sequencing of LEN and AZA" should be changed to "To find the optimum sequencing of LEN and AZA" | Change made |
| g. In the Section "Predictors of outcome" (page 54) – the "..EPO level below 100 UI/L were…" should be changed to "..EPO level below 100 IU/L were…" | Change made |
| h. In the Section "Iron Chelation", subsection "Dose and schedule" (page 63) – it states "…to 10 to 40 mg/kg/day for deferasirox,.." Since both Exjade and Jadenu are available with the active ingredient being deferasirox, but have different dosages (given better bioavailability of Jadenu), it may be prudent to indicate this (in case someone not familiar with the studies give an incorrect higher dose of Jadenu). | No change needed. |
| i. In "Table 4-7. Unpublished or Ongoing trials: General Characteristics" (row 6, page 67) – why is the study by Lee et al which is trying "to determine an optimal initial dose of romiplostim for patients with aplastic anemia refractory to immunosuppressive therapy" included (as it does not deal with patients with lower risk MDS)? | This is an ongoing trial, and it may include patients with lower-risk MDS when published fully. |
| j. In "Table 4-7. Unpublished or Ongoing trials: General Characteristics" (row 5, column 2, page 68) – the font color for "To assess the best order of LEN and HMA in optimizing response potential in lower risk MDS" needs to be changed to black. | Change made |
| k. In "Table 4-7. Unpublished or Ongoing trials: General Characteristics" (row 4, page 69) – why is the retrospective study by De Miguel Llorente et al included since there are only 27 patients in this retrospective cohort study? | This is an ongoing trial and the number of included patients may change when fully published. |
| l. In "Table 4-7. Unpublished or Ongoing trials: General Characteristics" (row 4, page 72) – the objectives/focus/data collection of the PACE-MDS study needs to be clarified, as well as the intervention/comparison. | Not enough information was available in these abstracts to be more specific. |
| m. In "Table 4-7. Unpublished or Ongoing trials: General Characteristics" (row 5, page 72) – the objectives/focus/data collection of the Raza et al. rigosertib study needs to be clarified | |

***Professional Consultation***

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All hematologists, medical oncologists, radiation oncologists, pharmacists, nurse practitioners, and family physiciansin the PEBC database were contacted by email to inform them of the survey. Three hundred thirty professionals working in Ontario were contacted, and 19 responded (0.6%). Thirty-four practitioners stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 19 people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

**Table 5-5. Responses to four items on the professional consultation survey.**

| | Number 19 (0.6%) | | | | |
|---|---|---|---|---|---|
| **General Questions: Overall Guideline Assessment** | Lowest Quality (1) | (2) | (3) | (4) | Highest Quality (5) |
| **1. Rate the overall quality of the guideline report.** | | | | 8 (42%) | 11 (58%) |
| | Strongly Disagree (1) | (2) | (3) | (4) | Strongly Agree (5) |
| **2. I would make use of this guideline in my professional decisions.** | 2 (10.5%) | | 1 (5%) | 7 (37%) | 9 (47.4%) |
| **3. I would recommend this guideline for use in practice.** | 1 (5%) | | 1 (5%) | 3 (16%) | 14 (74%) |
| **4. What are the barriers or enablers to the implementation of this guideline report?** | Barriers<br>• Availability of medications because of approval/financial coverage. Expensive treatments taken for chronic periods of time present a huge challenge to our system.<br>• Recognition of the clinical entity by non-hematologist/internist - referral in timely manner; funding of treatment<br>• Availability of staff and subspecialty expertise for initiation and supervision of therapy.<br>• Length of report.<br>• Availability of medications.<br>• The lack of discussion around indications for transplant in low-risk, heavily transfusion-dependent MDS.<br>• p53 testing by immunohistochemistry does not likely have widespread uptake at this time.<br>• Lack of awareness of guideline.<br>Enablers<br>• Algorithm helpful.<br>• Wide distribution of guideline to potential users.<br>• Buy-in from the physicians group; incorporate recommendations into oncology nursing education (high level) to promote better understanding among staff that hopefully translates into better patient care (follow-up and education). | | | | |

**Table 5-6. Modifications/Actions taken/Responses regarding main written comments from professional consultants.**

| Comments | Responses |
|---|---|
| First of all, thank you for this guideline! I do have a few minor things....not sure if this was the time and place.... For (1) recommendation 1A/1B: - these two recommendations are not titled as such in Section 1...please add "1A" and "1B" labels - do we want to suggest a maximum rate of escalation of HB for the ESAs (e.g., 10g/L every two weeks, etc)? –<br>(2) specifying G-CSF = filgrastim and NOT pegfilgrastim may make things a little more clear - Is it your intention to include GM-CSF to provide guidance outside of Canada? If so, it is not clear what the intention of inclusion is because of the way you state G/M-CSF in the headers, but never talk about it in the body of the recommendations. Thus, I'm not clear if you are demonstrating preference for G-CSF by excluding GM-CSF from the actual recommendation (for those countries that actually have access to GM-CSF)? Or is it to INCLUDE GM-CSF as being equal to G-CSF? If the latter scenario is your goal, you should be using "G-CSF or GM-CSF" or "G/M-CSF" throughout your document<br>(3) recommendation 4: - Perhaps it is because I am out of touch with this realm, but can you confirm that the SC route is your preferred route over the IV route? Is that why it is the only drug to have the route specified in Section 1? I am wondering if you are preferring SC over IV for reasons other than convenience/logistics? Perhaps consider a brief explanation to make this clearer?<br>(4) recommendation 5: - Recommended regimen should be stated as "CsA should be started on day 14 at a dose of 5-12 mg/kg/DAY in two divided doses (every 12 hr) FOR 180 DAYS with dose adjustments based on drug levels (target 200-400 ng/mL)." [ADD THE "PER DAY" into the dose]<br>(5)TREATMENT ALGORITHM: -Why is there a question mark after G-CSF in the symptomatic neutropenia flow? -What happens to patients with EPO =500 u/L? This is not explicitly stated in the algorithm.<br>(6) KEY EVIDENCE FOR RECOMMENDATION 7 (page 13): What does the "NOT FOR DISTRIBUTION" mean? | (1) 1A and 1B labels have been added; I don't think we need to specify a max rate of Hb increase.<br>(2) GM-CSF was included in the heading/document as this was searched for; however, there was no evidence base to support recommending GM-CSF specifically.<br>(3) Recommendation 4 – yes SC is the preferred route. Based on the trials.<br>(4) Recommendation 5 –change has been made<br>(5) The algorithm has been adopted from the ESMO guideline with very few modifications.<br>(6) The "NOT FOR DISTRIBUTION" phrase has been deleted |
| The reviewers have done an excellent job of reviewing the literature and making recommendations for treatment | No changes needed |
| I was not entirely certain of the meaning of 'acceptability' of recommendations under the interpretation of evidence section. | No changes needed |

**CONCLUSION**

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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**Appendix 1: Affiliations and Conflict of Interest Declarations**

| Name | Affiliation | Declarations of interest |
|---|---|---|
| **Working group** | | |
| Dr. Rena Buckstein | Odette Cancer Centre at Sunnybrook Health Sciences Centre, 2075 Bayview Ave., Toronto, ON | Declared that received grants or research support either as principal or co-investigator of more than $10,000 a year; has been principal investigator of a clinical trial on the object of this study; published editorials or commentaries or opinion papers on the topic object of this study; has managerial responsibility for an organization that has received >$5,000 a year from a relevant business entity; has published an editorial on eltrombopag in MDS. |
| Dr. Matthew Cheung | Odette Cancer Centre at Sunnybrook Health Sciences Centre, 2075 Bayview Ave., Toronto, ON | Declared to have received $8,000 or more in a single year to act in a consulting capacity by Gilead |
| Dr. Dawn Maze | Princess Margaret Hospital, 610 University Ave., Toronto, ON | Declared no conflict of interest |
| Dr. André Schuh | Princess Margaret Hospital, 610 University Ave., Toronto, ON | Declared no conflict of interest |
| Ms. Fulvia Baldassarre | McMaster University<br>Program in Evidence-based Care, Cancer Care Ontario, McMaster University, Juravinski Hospital<br>G Wing 2nd Floor Room 220<br>1280 Main St. West<br>Hamilton, ON | Declared no conflict of interest |
| **Expert panel** | | |
| Dr. Lisa Hicks | St. Michael's Hospital, 30 Bond St., Toronto, ON | Declared no conflict of interest |
| Dr. Yael Zaretsky | Sunnybrook Health Sciences Centre, 2075 Bayview Ave., Toronto, ON | Declared no conflict of interest |
| Dr. Ivan Tyono | Odette Cancer Centre at Sunnybrook Health Sciences Centre, 2075 Bayview Ave., Toronto, ON | Declared no conflict of interest |
| Dr. Irwin Walker | McMaster University Medical Centre, 1200 Main St. | Declared to have received other financial or |

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|---|---|---|
| | W, Hamilton, ON | material support exceeding $5,000 in a single year |
| Dr. Nicole Laferriere | Thunder Bay Regional Health Sciences Centre, 980 Oliver Rd., Thunder Bay, ON | Declared no conflict of interest |
| Dr. Jill Dudebout | Cancer Centre of Southeastern Ontario, 25 King St. W, Kingston, ON | Declared no conflict of interest |
| Dr. David Robinson | Patient Representative | Declared no conflict of interest |
| Dr. Mitchell Sabloff | The Ottawa Hospital, 501 Smyth Rd., Ottawa, ON | Declared to have received other financial or material support exceeding $5,000 in a single year |
| Dr. Micael Crump | Princess Margaret Hospital, 610 University Ave., Toronto, ON | Declared no conflict of interest |
| Dr. Patricia Disperati | Toronto East General Hospital, 825 Coxwell Ave., East York, ON | Declared no conflict of interest |
| Dr. Sindu Kanjeekal | Windsor Regional Hospital, 2220 Kildare Rd, Windsor, ON | Declared no conflict of interest |
| Dr. Tom Kouroukis | Juravinski Cancer Centre, 699 Concession St., Hamilton, ON | Declared no conflict of interest |
| Dr. Graeme Fraser | Juravinski Cancer Centre, 699 Concession St., Hamilton, ON | Declared no conflict of interest |
| Dr. Anca Prica | Princess Margaret Hospital, 610 University Ave., Toronto, ON | Declared to have received grants or other research support from a relevant buiseness entity |
| Dr. Chris Bredeson | The Ottawa Hospital, 501 Smyth Rd., Ottawa, ON | Declared to have had managerial responsibility for an organization or department that has received $5,000 or more in a single year by a relevant business entity |
| Dr. Jordan Herst | Northeastern Ontario Regional Cancer Centre, Sudbury Regional Hospital, 41 Ramsey Lake Rd., Sudbury, ON | Declared no conflict of interest |
| Dr. Janet MacEachern | Grand River Regional Cancer Centre, 835 King St. W, Kitchener, ON | Declared no conflict of interest |
| Dr. David Hodgson | Princess Margaret Hospital, 610 University Ave., Toronto, ON | Declared no conflict of interest |

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| Dr. Robert Stevens | Grand River Regional Cancer Centre, 835 King St. W, Kitchener, ON | Declared no conflict of interest |
| Dr. Jonathan Sussman | Juravinski Cancer Centre, 699 Concession St., Hamilton, ON | Declared no conflict of interest |
| Dr. Anthony Woods | Lakeridge Health, 1 Hospital Court, Oshawa, ON | Declared no conflict of interest |
| Dr. Chai W. Phua | London Health Sciences Centre, 800 Commissioners Rd E, London, ON N6A 5W9 | Declared no conflict of interest |
| Dr. Rebecca McClure | Health Sciences North (HSN), 41 Ramsey Lake Rd. Sudbury, ON Canada, P3E 5J1 | Declared no conflict of interest |
| Dr. Lee Mozhessohn | Sunnybrook Health Sciences Centre, 2075 Bayview Ave., Toronto, ON Canada, M4N 3M5 | Declared no conflict of interest |
| Dr. Anna Nikonova | Princess Margaret Cancer Centre, University Health Network, 610 University Ave., Toronto, ON Canada, M5G 2M9 | Declared no conflict of interest |
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| **Targeted Peer Reviewers** | | |
| Dr. Karen Yee | Princess Margaret Hospital<br>610 University Ave., Toronto, ON | Declared to have received grants or other research support either as a principal or co-investigator, imn any amount, from Celgene, Astex, and Novartis. Declared to have been a principal investigator for a clinical trial involving any of the objects of study. |
| Dr. Lisa Chodirker | Sunnybrook Health Sciences Centre | |

| | | |
|---|---|---|
| | 2075 Bayview Ave., Toronto, ON | |
| Dr. Brian Leber | Juravinski Cancer Centre, 699 Concession St., Hamilton, ON | Declared to have received financial support exceeding $5,000 in a single year as member of the advisory board for Novartis and Celgene. |

NB: Conflict of interest (COI) requirements for authors Buckstein and Cheung were waived by the PEBC Director per the PEBC COI Policy.

## Appendix 2: Existing Guidelines

### Table 1. Systemic treatment of patients with low-risk MDS: General characteristics of guidelines

| Author, year, Country, Funding | Objectives / Focus | Population; search cut-off | Intervention | Design of included studies | Comments/ Use |
|---|---|---|---|---|---|
| **General diagnosis and treatment** | | | | | |
| Greenberg, 2017 [38]<br><br>US<br><br>**Funding:** | General diagnosis and management of MDS<br><br>Has algorithm for low-risk MDS management. | Pts with MDS<br><br>**Search cut-off:** *nr* | Interventions are: EPO, ATG, G-CSF, AZA | *nr* | This is NCCN guideline, it presents evidence blocks, but the methods are not available online or in the journal publication. |
| Killick, 2014 [58]<br><br>UK<br><br>**Funding:** British Society for Haematology | General diagnosis and management of MDS<br><br>Has algorithm for low-risk MDS management. | Low- and High-risk MDS<br><br>**Search cut-off:** Up to Dec 2012 | Interventions are:<br>• Erythropoiesis stimulating agents (ESAs)<br>• Immunosuppressive therapy<br>• Allogeneic transplant<br>• LEN in del 5q<br>Additional interventions are examined for:<br>• Neutropenia and infection<br>• Thrombocytopenia and bleeding<br>• Spiritual/emotional health needs<br>• Iron overload | Used GRADE for quality assessment.<br><br>RCTs and observational comparative studies (assumed) | No mention of the inclusion criteria in regard to design. According to the grading of recommendations one can assume that the included studies were comparative. Search ends in 2012. |
| Fenaux, 2014 [57]<br><br>Europe<br><br>**Funding:** ESMO | General diagnosis, treatment and follow-up.<br><br>Has algorithm for low-risk MDS management | Pts with low- and high-risk MDS<br><br>**Search cut off:** not stated. | General diagnosis treatment and follow-up. Interventions are:<br>• TPO agonist<br>• Allogeneic SCT<br>• Chemotherapy<br>• Hypomethilating agents<br>• Hematopoietic growth factors<br>• Immunomodulatory drugs<br>• Immunosuppressive therapy<br>• Iron chelation<br>• Watchful waiting | Not able to assess | ESMO guidelines are not based on a systematic review of the evidence |
| Malcovati, 2013 [59]<br><br>Europe<br><br>**Funding:** European Leukemia Net | Recommendations on the diagnosis, prognosis and treatment<br><br>Has algorithm for low-risk MDS management<br>Has algorithm for intermediate1-risk | Adult pts with primary MDS<br><br>**Search cut off:** 1985-2012 | General diagnosis and treatment. Interventions are:<br>• Watchful waiting<br>• Allogeneic SCT<br>• Chemotherapy<br>• Hypomethilating agents<br>• Hematopoietic growth factors<br>• Immunomodulatory drugs<br>• Immunosuppressive therapy<br>• Iron chelation | Studies of ≥10 pts<br><br>Levels of evidence according to the SIGN criteria | It is a wide scope guideline, search ends in 2012 |

| Author, year, Country, Funding | Objectives / Focus | Population; search cut-off | Intervention | Design of included studies | Comments/ Use |
|---|---|---|---|---|---|
| | MDS management | | • Platelet transfusion | | |
| **Erythropoietic stimulating agents** | | | | | |
| Rizzo, 2010 [60]<br><br>US<br><br>**Funding:** ASCO | To provide an update of a previous ASCO/ASH guideline on ESAs in pts with cancer | Pts with cancer<br><br>**Search cut-off:** Jan 1, 2007 to Jan 31, 2010 | General on ESA in cancer; has one rec for low risk MDS. | Practice guidelines, systematic reviews, meta-analyses, and RCTs | This guideline has only a very short recommendation for patients with low-risk MDS |
| Schrijvers, 2010 [61]<br><br>Europe<br><br>**Funding:** ESMO | To provide a guideline for the use of ESAs | Pts with cancer and anemia<br><br>**Search cut-off:** not stated | Erythropoieis stimulating agents | Not able to assess | ESMO guidelines are not based on a systematic review of the evidence |
| **Hematopoietic growth factors** | | | | | |
| Crawford, 2009 [62]<br><br>Europe<br><br>**Funding:** ESMO | To provide recommendations on the use of hematopoietic growth factors | Pts with cancer<br><br>**Search cut-off:** not stated | Hematopoietic growth factors | Not able to assess | ESMO guidelines are not based on a systematic review of the evidence |
| **Immunomodulatory agents** | | | | | |
| Leitch, 2013 [3]<br><br>Canada<br><br>**Funding:** Aplastic Anemia and Myelodysplasia Association of Canada | Provide guidance for the use of IMiD in pts with MDS | Pts with MDS<br><br>**Search cut-off:** 1985 to June 17, 2009 updated only through Pubmed on Aug 9 2010 only limited to IMiD. | IMiD (i.e., LEN and thalidomide) | Phase 2-3 clinical trials with ≥20 pts per arm | Companion of Buckstein et al., 2011 [4] (same search, updated)<br>Uses GRADE system to develop recommendations |
| **Hypomethylating agents** | | | | | |
| Buckstein, 2011 [4]<br><br>Canada<br><br>**Funding:** Aplastic Anemia and Myelodysplasia Association of Canada | To provide recommendations for the use of 5-AZA in MDS | All pts with MDS<br><br>**Search cut-off:** 1985 to June 17, 2009 | AZA compared with any agent (alone or in combination), placebo or standard of care | Comparative studies. The review is based on 6 studies (2 RCTs) | Methods same as PEBC.<br>Does not recommend AZA as first line therapy for pts with low-, intermediate1 MDS.<br>This review did not locate any evidence for the low-intermediate-1 risk population.<br>Search up to 2009. |
| **Immunosuppressive agents** | | | | | |
| No guidelines found | | | | | |
| **Iron chelation** | | | | | |
| No guidelines found | | | | | |

5-AZA = 5-azacytidine; ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; ESAs = Erythropoietic stimulating agents; ESMO = European Society of Medical Oncology; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; IMiD = immunomodulatory agents; MDS = myelodysplastic syndromes; NICE = National Intstitute for Health and Care Excellence; Pts = patients; RCTs = randomized controlled trials; SCT = stem cell transplant; SIGN = Scottish Intercollegiate Guidelines Network Grading Review Group

**Table 2. Guidelines for the diagnosis and management of adult myelodysplastic syndromes: Assessment with AGREE II [56]**

| Section | Killick [58] | | Fenaux [57] | | Malcovati [59] | | Leitch [3] | | Rizzo [60] | | Buckstein [4] | | Greenberg [43] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rating | Comment | Rating | Comment | Rating | Comment | Rating | Comment | Rating | Comment | Rating | Comment | Rating | Comment |
| 1. Scope and Purpose: Overall objectives specifically described? | 5 | Title only says what it is. | 3 | only stated in title | 7 | page 2943 | 7 | | 7 | | 6 | | 6 | This is a NCCN guideline |
| 2. Scope and Purpose: Health questions specifically described? | 2 | No description except for title stating objectives | 1 | nr | 6 | p 2944 | 7 | | 7 | | 7 | | 5 | |
| 3. Scope and Purpose: Population to whom recommendation apply specifically described? | 6 | individual recommendations say what type of patients they are for. | 4 | Subtitles according to pt subpopulations | 7 | in adult patients with primary MDS | 7 | | 7 | | 7 | | 7 | |
| 4. Stakeholder Involvement: The guideline development group includes individuals rom all relevant professional groups? | 6 | page 519 | 1 | nr | 7 | it comprised physicians with specific areas of expertise who are experienced in MDSs and active in both care of patients and clinical research. | 6 | Authors are all hematologists. | 5 | | 6 | | 7 | |
| 5. Stakeholder Involvement: Views and preferences of the target population have been sought? | 1 | NR | 1 | nr | 1 | nr | 1 | nr | 1 | | 1 | | 1 | |
| 6. Stakeholder Involvement: the target users of the guideline | 2 | ONe could assume physicians treating pts with mds, but not stated | 2 | one can assume it treating physicians | 5 | in the discussion end of column 1 | 4 | end of p 164. the sr and companion practice guidelines are intended to promote evidence- | 6 | | 6 | | 5 | |

| Section | Killick [58] | | Fenaux [57] | | Malcovati [59] | | Leitch [3] | | Rizzo [60] | | Buckstein [4] | | Greenberg [43] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| are clearly defined? | | | | | | | | based practice in Canada. One can assume users are physicians in Canada. | | | | | | |
| 7. Rigour of Development: Systeamtic methods were used to search for evidence? | 5 | Databases searched and keyword used reported. No selection criteria nor tables | 1 | nr | 6 | | 7 | | 7 | | 7 | | 4 | |
| 8. Rigour of Development: The criteria for selecting the evidence are clearly described | 2 | no selection criteria, the authors say they used the GRADE nomenclature. | 1 | | 6 | | 7 | p 165 | 1 | | 7 | | 1 | |
| 9. Rigour of Development: The strength and limitations of the body of evidence are clearly described? | 1 | nr | 1 | | 2 | nothing more than evidence comes from rcts and non rcts | 6 | study design | 6 | | 7 | | 1 | |
| 10. Rigour of Development: The methods for formulating the recommendation are clearly described | 6 | see page 519 | 1 | | 1 | | 7 | they used GRADE | 4 | | 1 | | 1 | |
| 11. Rigour of Development:The health benefits, side effects have been considered | 5 | | 2 | there is a discussion but not systematically for all | 2 | | 7 | page 184 | 6 | | 6 | | 2 | |
| 12. Rigour of Development: There is an explicit link between the recommendation and the supporting evidence | 4 | Not always.See p. 509 use of g-CSF is not supported by reference. | 3 | Citations in text | 7 | | 7 | | 7 | | 6 | | 5 | Evidence blocks |

| Section | Killick [58] | | Fenaux [57] | | Malcovati [59] | | Leitch [3] | | Rizzo [60] | | Buckstein [4] | | Greenberg [43] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 13. Rigour of Development: the guideline has been externally reviewed prior to its publication | 7 | | 1 | | 2 | | 7 | | 2 | | 1 | | 7 | The J Natl Compr Canc Netw is a peer reviewed journal |
| 14. Rigour of Development: a procedure for updating the guideline is provided | 7 | Annual review | 1 | | 1 | | 1 | nr | 1 | | 1 | | 7 | See NCCN web site https://www.nccn.org/professionals/physician_gls/guidelines-development.asp |
| 15. Clarity of Presentation: The recommendations are specific and unambiguous | 7 | | 6 | algorhithm | 6 | | 7 | | 7 | | 7 | | 7 | algorithm |
| 16. Clarity of Presentation: The different options for the management of the condition are clearly presente | 7 | | 6 | discussion of personalized medicine | 6 | | 7 | | 7 | | 5 | | 7 | algorithm |
| 17. Clarity of Presentation: key recommendations are clearly identifieable | 7 | | 2 | they are embedded in text | 5 | | 6 | | 7 | | 7 | | 7 | algorithm |
| 18. Applicability: The guideline describes facilitators and barriers to its application | 1 | | 1 | nr | 1 | | 2 | | 2 | | 2 | | 1 | |

| Section | Killick [58] | | Fenaux [57] | | Malcovati [59] | | Leitch [3] | | Rizzo [60] | | Buckstein [4] | | Greenberg [43] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 19. Applicability: Advice and tool to put the guideline in practice are provided | 1 | | 1 | | 1 | | 1 | | 2 | | 1 | | 7 | algorithm |
| 20. Applicability: the potential resource implications of applying the recommendation have been considered | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| 21. Applicability: The guideline presents monitoring or auditing criteria | 6 | | 1 | | 1 | | 1 | | 1 | | 1 | | 7 | In the NCCN web site |
| 22. Editorial Independence: The views of the funding body have not influenced the guideline | 4 | conflict of interest are declared, but not sure whether the funding bodies influenced the gl | 2 | Cannot tell | 6 | | 7 | | 7 | | 1 | | 6 | In the NCCN web site |
| 23. Editorial Independence: Competing interests of guideline development group members have been recorded and addressed | 7 | | 6 | | 7 | | 7 | | 7 | | 7 | | 7 | |

## Appendix 3: Search strategies

### A) Search strategies for systematic reviews

Database(s): Ovid MEDLINE(R) without Revisions, Ovid MEDLINE(R) Daily Update, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1996 to July 31, 2017

Search Strategy:

| # | |
|---|---|
| 1 | (systematic adj (review: or overview:)).mp. |
| 2 | (meta-analy: or metaanaly:).mp. |
| 3 | (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp. |
| 4 | (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw. |
| 5 | (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab. |
| 6 | (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab. |
| 7 | or/1-6 |
| 8 | (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab. |
| 9 | (stud: adj1 select:).ab. |
| 10 | (8 or 9) and review.pt. |
| 11 | 7 or 10 |
| 12 | (guideline or practice guideline).pt. |
| 13 | exp consensus development conference/ |
| 14 | consensus/ |
| 15 | (guideline: or recommend: or consensus or standards).ti. |
| 16 | 12 or 13 or 14 or 15 |
| 17 | 11 or 16 |
| 18 | (comment or letter or editorial or note or erratum or short survey or news or newspaper article or case report or historical article).pt. |
| 19 | 17 not 18 |
| 20 | myelodysplastic syndromes.mp. or exp Myelodysplastic Syndromes/ |
| 21 | MDS.mp. |
| 22 | preleukemia.mp. or Preleukemia/ |
| 23 | 20 or 21 or 22 |
| 24 | 19 and 23 |
| 25 | limit 24 to (english language and yr="2009 -Current") |

Database: Embase <1996 to 2015 Week 41>
Search Strategy:

| # | Searches |
|---|---|
| 1 | exp practice guidelines/ |
| 2 | guideline?.tw,pt,sh. |
| 3 | (practice guideline or guideline?).mp,pt. |

4 consensus.sh,tw,pt.

5 (systematic adj (review: or overview:)).mp.

6 (meta-analy: or metaanaly:).mp.

7 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.

8 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.

9 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.

10 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.

11 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.

12 (stud: adj1 select:).ab.

13 (11 or 12) and review.pt.

14 or/5-10

15 13 or 14

16 consensus development conference/

17 practice guideline/

18 *consensus development/ or *consensus/

19 *standard/

20 (guideline: or recommend: or consensus or standards).kw.

21 (guideline: or recommend: or consensus or standards).ti.

22 or/16-21

23 (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/

24 (15 or 22) not 23

25 1 or 2 or 3 or 4

26 24 or 25

27 myelodysplastic syndromes.mp. or exp myelodysplastic syndrome/

28 MDS.mp.

29 preleukemia.mp. or exp preleukemia/

30 27 or 28 or 29

31 26 and 30

32 limit 31 to (english language and yr="2009 -Current")

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2005 to September 2015, EBM Reviews - Database of Abstracts of Reviews of Effects 2nd Quarter 2015
Search Strategy:

| # | Searches |
|---|---|
| 1 | myelodysplastic syndromes.mp. [mp=ti, ot, ab, tx, kw, ct] |
| 2 | preleukemia.tw. |
| 3 | 1 or 2 |
| 4 | from 3 keep 1-31 |

B) Search strategies for primary studies

Database: Ovid MEDLINE(R) without Revisions, Ovid MEDLINE(R) Daily Update , Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1996 to July week 2, 2017>, >

Search Strategy:
---
1 myelodysplastic syndrome:.mp. or exp myelodysplastic syndrome/
2 MDS.mp.
3 preleukemia.mp. or exp preleukemia/
4 1 or 2 or 3
5 exp Randomized Controlled Trial/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ or ((exp Clinical Trial/ or Prospective Study/ or Prospective Studies/) and Random$.tw.) or exp Randomized Controlled Trials as topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or exp "Randomized Controlled Trial (Topic)"/ or "Phase 3 Clinical Trial (Topic)"/ or "Phase 4 Clinical Trial (Topic)"/ or ((exp Clinical Trials as Topic/ or exp "Clinical Trial (Topic)"/) and random$.tw.) or Random Allocation/ or Randomization/ or Single-Blind Method/ or Double-Blind Method/ or Single Blind Procedure/ or Double Blind Procedure/ or Triple Blind Procedure/ or Placebos/ or Placebo/ or ((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).tw. or (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or (placebo? or (allocat$ adj2 random$)).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp.
6 4 and 5
7 limit 6 to english language
8 animal/ not (exp human/ or humans/)
9 7 not 8
10 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article)
11 9 not 10

Database: Embase <1996 to 2016 Week 19>
Search Strategy:
Search Strategy:
---
1 myelodysplastic syndrome:.mp. or exp myelodysplastic syndrome/
2 MDS.mp.
3 preleukemia.mp. or exp preleukemia/
4 1 or 2 or 3
5 exp Randomized Controlled Trial/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ or ((exp Clinical Trial/ or Prospective Study/ or Prospective Studies/) and Random$.tw.) or exp Randomized Controlled Trials as topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or exp "Randomized Controlled Trial (Topic)"/ or "Phase 3 Clinical Trial (Topic)"/ or "Phase 4 Clinical Trial (Topic)"/ or ((exp Clinical Trials as Topic/ or exp "Clinical Trial (Topic)"/) and random$.tw.) or Random Allocation/ or Randomization/ or Single-Blind Method/ or Double-Blind Method/ or Single Blind Procedure/ or Double Blind Procedure/ or Triple Blind Procedure/ or Placebos/ or Placebo/ or ((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).tw. or (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or (placebo? or (allocat$ adj2 random$)).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp.
6 4 and 5
7 limit 6 to english language
8 animal/ not (exp human/ or humans/)

9 7 not 8
10 (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
11 7 not 10

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <July 2017>
Search Strategy:
---
1 myelodysplastic syndrome:.mp.
2 exp Myelodysplastic Syndromes/
3 MDS.mp.
4 preleukemia.mp.
5 Preleukemia/
6 1 or 2 or 3 or 4 or 5

## Appendix 4: Selection criteria for systematic reviews, guidelines, and primary studies

**INCLUDED**

**Systematic reviews:**

Systematic reviews, and guidelines with a systematic review that included studies of patients ≥18 years of age with low-risk MDS (i.e., IPSS-R risk score ≤4.5 or IPSS score of <=1.0) published after 2009. At a Working Group meeting held on November 7, 2016, it was decided to expand the selection criteria to include studies that analyzed a minority of patients (i.e., ≤15%) with intermediate-2 or high IPSS risk and did not provide separate results for the lower and higher risk population. This change was made because of the scarsity of evidence found with the criteria set in the first place.

Treatments of interest include:

- **Hematopoiesis-stimulating agents**
- **Lenalidomide in del(5q) MDS**
- **Lenalidomide in non-del(5q) MDS**
- **Hypomethylating agents (5-azacytidine and decitabine)**
- **Immunosuppressive therapy antithymocyte globulin (ATG) and cyclosporine**
- **Iron chelation therapy**
- **Other/novel agents**

Comparisons of interest are alternate treatment of supportive care alone.

Studies reporting on response rate, response duration, disease control, survival, quality of life, and adverse events were sought.

Studies published in English

**Primary studies**

- Comparative studies of patients ≥18 years of age with low- or intermediate-risk MDS (i.e., IPSS-R risk score ≤4.5 or IPSS score of ≤1.0)) or a combination of a majority (>80%) of patients with low- intermediate-1 risk MDS and a minority (≤20%) of patients with higher-risk MDS.
- Studies published from 2009 onward for hypomethylating agents, and from 2005 onward for other interventions
- Treatments of interest include: same as for systematic reviews
- Comparisons of interest are alternate treatment of supportive care alone
- Outcomes of interest are survival, quality of life, disease control, response duration, response rate, and adverse events
- Studies published in English
- Studies with a sample size ≥30 patients

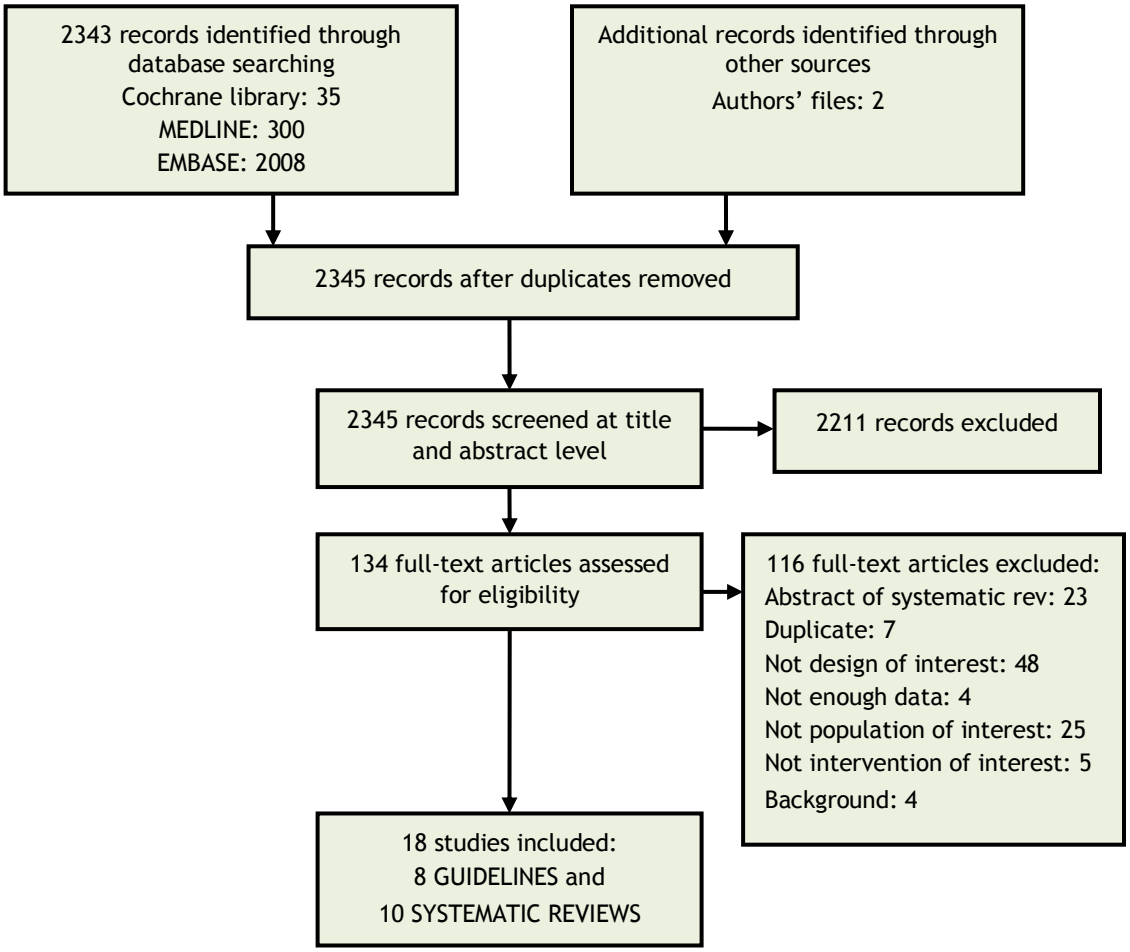
**EXCLUDED**

- Studies published prior to the cut-off limit
- Studies that do not report on the population of interest (i.e., pediatric studies, other cancers)
- Studies that do not have the design of interest (i.e., narrative reviews, surveys, case studies, single-arm studies, and publications types such as letters, comments, notes, consensus guidelines, narrative reviews, or editorials)

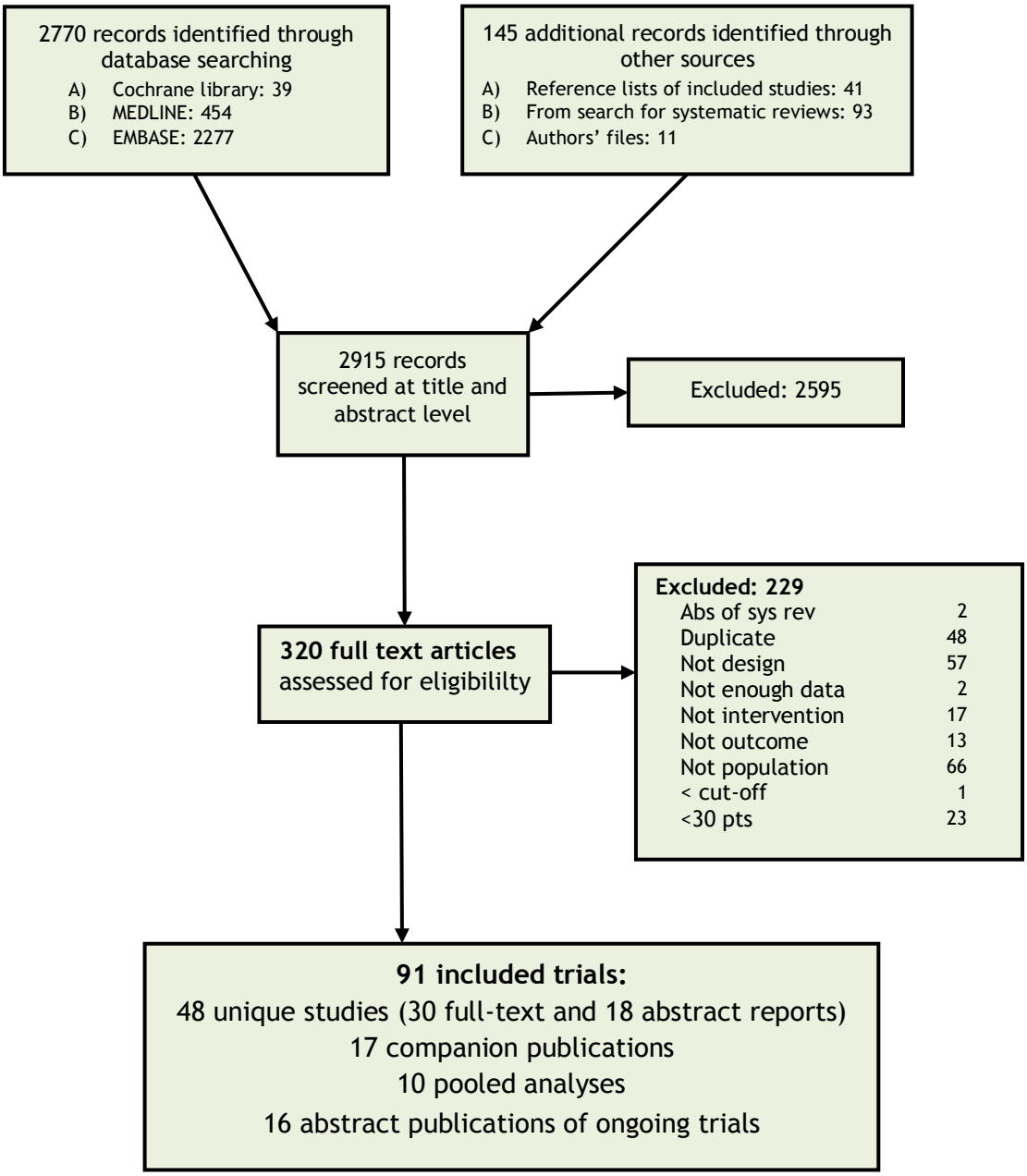
- Studies that do not report of the interventions of interest (i.e., studies of transfusion therapy and antibiotic therapy, and of management strategies other than listed)
- Studies that do not report on the outcomes of interest (e.g., economic studies)
- Studies that do not report enough data (e.g., protocol of systematic review, abstracts of systematic reviews, abstracts of interim analyses of comparative studies)
- Comparative studies with sample size <30
- Studies in which the higher-risk MDS patients results could not be distinguished from those of patients with lower-risk or AML
- Duplicate publications

## Appendix 5: PRISMA Flow Diagram

### A) Systemic treatment of MDS in adult, low-risk patients. Flow Chart: Systematic reviews



B) **Systemic treatment of MDS in adult, low-risk patients. Flow Chart: Primary studies**



## Appendix 6. Companion publications of included studies

### Table 1. Secondary analyses of comparative studies of patients with low-risk MDS

| Primary publication, Study name, Author, yr and objectives | Additional analysis: Author, yr and objectives | Summary results of additional publications |
|---|---|---|
| **MDS 004**<br><br>Fenaux, 2011 [19]<br><br>**Objectives:**<br>To assess efficacy and safety of LEN in MDS<br><br>**Population:**<br>205 RBC-TD pts with Intermediate-1 IPSS risk and del5q MDS<br><br>**Intervention/ Comparison:**<br>LEN vs. PBO | Fenaux, 2010 ABS [20]<br><br>**Objectives:**<br>Open label extension phase of original study<br>**Population:**<br>54 pts who had completed 52 wks of at least 1 dose of therapy with LEN 5 mg or 10 mg in main study<br>**Intervention:**<br>LEN 5 mg and LEN 10 mg combined<br>**Outcome:** survival, prognostic factors<br>**Design:** Cohort (open label extension phase of original study)<br>**Follow-up:** median, range 36 mos, 0.4 to 59.4 mos | **Survival:**<br>OS (median, 95% CI):<br>3.68 yrs, 2.93 to not-estimable.<br>OS rate: 56%<br>Death rate: 48%<br>**Prognostic factors**:<br>(multivariate analysis)<br>Achieving RBC-TI≥26 wks was associated with a 45% and 51% reduction in the risk of AML progression p=0.022 and death, p=0.008 |
| | Saft, 2014a [21]<br><br>**Objectives:**<br>Retrospective analysis to evaluate the prognostic value of adding p53 immunohistochemistry to IPSS-R to predict OS and AML progression<br>**Population:**<br>N = 61 pts (n = 42 LEN n = 19 Placebo) from MDS 004<br>**Intervention:**<br>p53+ vs. p53-<br>**Outcome:** survival, disease control, response<br>**Design:** Retrospective analysis<br>**Follow-up:** *nr* | **Survival:** AML-free survival (median): 23.9 mos vs 47.9 mos, p=0.003<br>OS(median): 27.0 vs. 50.6 mos, p=0.005<br>**Disease control:** Time to AML progression (median): 44.3 mos vs. not reached, p=0.003<br>**Other:** Among p53+: IPSS-R very low/Low, Intermediate and High/very High: 29%, 47%, and 63%, p=0.050.<br>The 3 IPSS-R risk groups significantly predicted AML-free survival and OS, (log-rank p<0.001 for both AFS and OS) but not time to AML progression , p=0.335.<br>**Subgroups:** IPSS-R Very Low/ Low (n=38):<br>AML-free survival (median):20.1 mos vs. 63.1 mos, p=0.011<br>OS (median): 28.4 mos vs. 76.8 mos, p=0.031<br>Time to AML progression (median):65.2 mos vs. not reached, p=0.014<br><br>IPSS-R Intermediate, and High/very high (n=23): NS |
| | Saft, 2014b [2]<br><br>**Objectives:** To assess the association between p53 protein expression by immunohistochemistry in pts with low-risk del(5q) MDS treated with LEN and its correlation with clinical outcomes<br>**Population:** N = 137 pts from MDS 004 who had isolated del(5q)<br>**Intervention:** p53 protein expression:<br>strongly positive (+++) vs. negative (-), faintly positive (+), moderately positive (++)<br>**Outcome:** survival, disease control, response<br>**Design:** Retrospective analysis<br>**Follow-up:** *nr* | **Survival:** p53+++ was strongly associated with shorter OS, p=0.0104<br>**Disease control:** p53+++ was strongly associated with higher risk of progression to AML, p=0.0003<br>**Response**: No association of p53+++ with transfusion independence, p=0.636, or response duration, p=0.4421<br>p53+++ was strongly associated with CyR:<br>CyR: 51% for p53-negative, 14% for p53 positive, p=0.009<br>**Subgroups:**<br>Pts treated with LEN 10 mg: CyR: 13% in p53+ and 84% in p53- |
| | Giagounidis, 2014 [22] | **Survival: OS** (Median): LEN 10 mg: 4.0 yrs (95% CI, 2.5 to NR), |

<table>
<tr><th>Primary publication, Study name, Author, yr and objectives</th><th>Additional analysis: Author, yr and objectives</th><th>Summary results of additional publications</th></tr>
<tr><td></td><td>Objectives: To evaluate outcomes in pts with low-Intermediate-1 MDS and isolated del(5q)<br>Population: N=135 pts from MDS 004 who had isolated del(5q)<br>Intervention: LEN 10 mg (n=47), LEN 5 mg (n=43) and PBO (n=45)<br>Outcome: survival, disease control, response<br>Design: Retrospective post hoc analysis<br><br>Follow-up: nr</td><td>LEN 5 mg: 3.5 yrs (95% CI, 1.7 to 4.8) Placebo: 2.9 yrs (95% CI, 2.2 to 4.2)<br>Disease control: AML progression at 2 yrs<br>LEN 10 mg: 12.6% (95% CI, 5.4 to 27.7),<br>LEN 5 mg: 17.4% (95% CI, 8.7 to 33.3)<br>Placebo: 16.7% (95% CI, 8.3 to 32.0)<br>Response: RBC-TI≥182 ds<br>LEN 5 mg vs. Placebo<br>37.2% vs. 2.2%, p=0.0001<br>LEN 10 mg vs. Placebo<br>57.4% vs.2.2%, p<0.0001<br>Median duration: not reached, p=0.8783<br>CyR[C]<br>Major + minor response<br>LEN 5 mg vs. Placebo: 23.1% vs. 0, p=0.0299<br>LEN 10 mg vs. Placebo<br>56.8% vs. 0, p<0.0001<br>Response: RBC-TI≥182 ds: LEN 5 mg vs. Placebo: 37.2% vs. 2.2%, p=0.0001; LEN 10 mg vs. Placebo: 57.4% vs.2.2%, p<0.0001<br>Median duration: not reached, p=0.8783<br>CyR[C]<br>Major + minor response<br>LEN 5 mg vs. Placebo: 23.1% vs. 0, p=0.0299<br>LEN 10 mg vs. Placebo<br>56.8% vs. 0, p<0.0001<br>Safety:
<table>
<tr><th></th><th>LEN 10mg</th><th>LEN 5mg</th><th>PBO</th></tr>
<tr><td>AE led to dose reductions</td><td>59.60%</td><td>58.10%</td><td>nr</td></tr>
<tr><td>AE led to drug discontinuation:</td><td>6.40%</td><td>16.30%</td><td>4.40%</td></tr>
<tr><td>Grade 3-4 AE:</td><td></td><td></td><td></td></tr>
<tr><td>Neutropenia</td><td>74.50%</td><td>76.70%</td><td>15.60%</td></tr>
<tr><td>Thrombocytopenia</td><td>38.30%</td><td>37.20%</td><td>2.20%</td></tr>
<tr><td>Deep vein thrombosis</td><td>6.40%</td><td>0%</td><td>2.20%</td></tr>
<tr><td>Hemorrhage</td><td>25.50%</td><td>20.90%</td><td>15.60%</td></tr>
<tr><td>Infection</td><td>63.80%</td><td>58.10%</td><td>28.90%</td></tr>
</table></td></tr>
<tr><td></td><td>Göhring, 2013 [23] ABS<br>Objectives: To retrospectively assess outcomes at ≥26 wks according to the 5q breakpoints to ascertain if the proximal level of the breakpoints influences OS, AML progression, or the RBC-TI response</td><td>Survival: OS: NS, log rank test p=0.6533; (median) 3.8 yrs (95% CI 2.5 to not evaluable) vs. 4.4 yrs (95% CI 2.3 to not evaluable)<br>Disease control: Time to AML progression: 5 yrs rates: 37.3% (95% CI 23.7% to 50.9%) vs. 34.5% (95% CI 13.6% to 55.3%), NS<br>Response: RBC-TI rates: NS</td></tr>
</table>

| Primary publication, Study name, Author, yr and objectives | Additional analysis: Author, yr and objectives | Summary results of additional publications |
|---|---|---|
| | **Population:** N=91 pts with isolated del(5q) treated with LEN<br>**Intervention:** Most frequent breakpoint (q14q34, [64.2 %]) n=59 vs. All other breakpoints (q13q34 [6.6%],q15q34 [2.2%], q21q34 to q31q34 [26.3%], and q31q35 [0.7%]) n=32<br>**Outcomes:** survival, disease control, response<br>**Design:** Retrospective analysis<br>**Follow-up:** *nr* | |
| | Revicki, 2013 [24]<br>**Objectives:** To evaluate the effects of LEN vs. Placebo on HRQOL outcomes every 12 wks<br>**Population:** N=167 RBC-TD pts from MDS 004 who had isolated del(5q)<br>**Intervention:** LEN 10 mg (n=58), LEN 5 mg (n=54) vs. PBO (n=55)<br>**Outcome: QOL**<br>**Design:** Randomized, double blind with an open label phase<br>**Follow-up:** *nr* | **QOL:** HRQOL change in FACT-An score at 12 wks: LEN 10 mg: 5.7; LEN 5 mg: 5.7; PBO: -2.8<br>**Subgroups:**<br>Mean baseline to 12 week changes in FACT-An Total scores improved with LEN 5 and 10 mg (+5.7 and +5.7, respectively) vs. PBO (−2.8) (both $p < 0.05$). Clinically important changes in HRQL from baseline were observed at weeks 12, 24, 36, and 48 among RBC-TI ≥26 wk responders in both treatment groups. LEN treatment may be effective in improving HRQL outcomes. |
| | Fenaux, 2010 [25]<br>**Objectives:** To examine RBC-TI according to baseline EPO levels and prior ESA use in pts treated with LEN, and the effect of LEN dose used in these pts subgroups<br>**Population:** N = 87 pts treated with LEN 10 mg (n=41) and with LEN 5 mg (n=46)<br>**Intervention:** a) Pts with EPO≤500mIU/mL vs. EPO>500 mIU/mL (all pts)<br>b) In pts with EPO>500 mIU/mL: LEN 10 mg vs. LEN 5 mg<br>c) In pts with EPO≤500 mIU/mL: LEN 10 mg vs. LEN 5 mg<br>d) prior ESA vs. no prior ESA (all pts)<br>e) In pts with prior ESA: LEN 10 vs. LEN5 mg<br>f) In pts without prior ESA: LEN 10 vs. LEN5 mg<br>g) In all pts: Pts with EPO level >500 mIU/mL or received prior ESA vs. ≤500mIU/mL and no prior ESA use<br>h) LEN 10 mg vs. LEN 5 mg in pts with EPO >500 mIU/mL or who and prior ESA<br>i) LEN 10 mg vs. LEN 5 mg in pts with EPO≤500 mIU/mL and no prior ESA<br>**Outcome:** response<br>**Design:** post hoc subgroup analysis<br>**Follow-up:** *nr* | **Response:**<br>RBC-TI<br>a) 48% vs. 51%, p=0.81<br>b) 76% vs 29%, p=0.0016<br>c) 43% vs. 54%, p=0.57<br>d) 36% vs. 63%, p=0.01<br>e) 42% vs. 30%, p=0.42<br>f) 76% vs. 52%, p=0.12<br>g) 42% vs. 80%, p=0.025<br>h) 51% vs. 33%p=0.12<br>i) 80% vs. 80%, p=1.0 |
| | Fenaux, 2010 ABS [118]<br>**Objectives:** To describe frequency, timing and management of hematologic AE associated with LEN<br>**Population:** N=138<br>**Intervention:** LEN 10 mg (n=69), LEN 5 mg (n=69) **Outcome:** hematologic AE | Median (range) exposure duration: 50 wks (1 to 56 wks) vs. 18 wks (2 to 53 wks) (higher response LEN 10 mg group: G3-4 neutropenia most common in cycles 1 (45%) and 2 (46%), decreasing with additional cycles (29%, 29%, 11%, 7% for cycles 3-6). G3-4 thrombocytopenia rates were 28%, 27%, 12%, 10%, 13%, and 2% in cycles 1-6.<br>LEN 5 mg: neutropenia (cycles 1-6: 46%, 47%, 25%, 22%, 11%, 15%) and thrombocytopenia (cycles 1-6: 19%, 19%, 14%, 8%, 2%, 6%). |

| Primary publication, Study name, Author, yr and objectives | Additional analysis: Author, yr and objectives | Summary results of additional publications |
|---|---|---|
| | **Design:** Randomized, double blind with an open label phase<br>**Follow-up:** *nr* | Infection: 12% vs.9%<br>Febrile neutropenia: 1% vs.3%<br>G3-4 bleeding: 0%<br>Hematologic AEs requiring dose reduction:<br>Neutropenia: 38% vs. 28%<br>Thrombocytopenia: 23% vs. 12%)<br>Hematologic AEs requiring discontinuation:<br>Neutropenia: 1% vs. 6%) |
| GFM-LenEpo 08<br><br>Toma, 2016 [10]<br><br>**Objectives:** To compare the efficacy of LEN with and without EPO<br>**Population:** 132 RBC-TD pts non-responders to ESAs, non-del5q31<br>**Intervention/ Comparison:** LEN+ EPO vs. LEN alone | Chesnais, 2014 ABS [121]<br>**Objectives:** To investigate biomarkers of response to LEN<br>**Population:** 99 RBC-TD pts non-responders to ESAs, non-del5q31 including 41% responders and 59% non-responders<br>**Intervention:** LEN Responders vs. LEN Non-responders<br>**Outcome:** Predictors of response<br>**Design:** Cohort<br>**Follow-up:** *nr* | *Predictors of erythroid HI:*<br><br>A A>G polymorphism in the 5'UTR region of CRBN gene (rs1672753): 41.5% vs. 22.4%, p=0.048.<br>A low expression level of NPM1 before treatment predicted LEN resistance, p<0.001 (sensitivity: 86.7 %, specificity 92.8%). |
| MDS 005<br><br>Santini, 2016 [28]<br><br>NCT01029262<br>**Objectives:** To assess the efficacy and safety of LEN<br><br>**Population:** 239 pts inelidgible | Santini, 2015 ABS [123]<br>**Objectives:** To evaluate RBC-TI according to different clinical variables<br>**Population:** 160 pts treated with LEN (subgroup of 155 analyzed)<br>**Intervention:** EPO ≤500mU/mL (n=97) vs. EPO>500mU/mL (n=58)<br>**Outcome:** Rates of RBC-TI for ≥8 wks according to baseline EPO levels prior to randomization (≤500 mU/mL and >500mU/mL<br>**Design:** cohort<br>**Follow-up:** *nr* | Factors associated with response:<br>EPO level RBC-TI rates ≥8 wks:<br>>500 15.5%<br>500-200 ¤3.3%<br>200-100 33.3%<br>≤100 42.5%<br>p=0.02¤* |

<table>
<tr><th>Primary publication, Study name, Author, yr and objectives</th><th>Additional analysis: Author, yr and objectives</th><th>Summary results of additional publications</th></tr>
<tr><td>or refractory to ESAs with low/intermediate-1-risk non-del(5q) MDS<br>Intervention/ Comparison: LEN/PBO</td><td>Santini, 2015 ABS [122]<br>Objectives: To evaluate changes in QOL<br>Population: Same as in main study<br>Intervention: LEN vs. PBO<br>Outcome: QOL (fatigue, dyspnea, physical functioning, emotional functioning and global quality of life at wks 12 and 24<br>Design: post hoc analysis<br>Follow-up: 24 wks</td><td>QOL:<br>At wk 12: NS<br>At wk 24: benefit for Emotional Functioning (p=0.047)</td></tr>
<tr><td></td><td>Garcia-Manero, 2016 ABS [120]<br>Objectives: To evaluate the relationship between LEN and clinically meaningful measures of response in pts from MDS-005<br>Population: Same as in main study<br>Intervention: LEN 10 mg/d (n = 160) vs. PBO (n = 79)<br>Outcome: RBC-TI ≥ 8 wks, or transfusion reduction of ≥ 4 units packed RBCs (pRBCs) ≥ 8 wks, or hemoglobin (Hb) increase ≥ 1.5 g/dL at 8 wks (IWG 2006), or Cytologic response<br>Design: RCT<br>Follow-up: same as in main study</td><td><table>
<tr><th>Response, n (□)</th><th>LEN (n = 160)</th><th>PBO (n = 79</th><th>O□ (95% CI)</th></tr>
<tr><td>Clinical benefit</td><td>51 (31.9)</td><td>3 (3.8)</td><td>11.85 (3.57-39.38)</td></tr>
<tr><td>RBC-TI ≥ 8 wks</td><td>43 (26.9)</td><td>2 (2.5)</td><td></td></tr>
<tr><td>Transfusion reduction ≥ 4 pRBC units ≥ 8 wks[1]</td><td>34 (21.3)</td><td>0</td><td></td></tr>
<tr><td>Hb increase ≥ 1.5 g/dL (IWG 2006)</td><td>31 (19.4)</td><td>2 (2.5)</td><td></td></tr>
<tr><td>CyR</td><td>9 (5.□)</td><td>0</td><td></td></tr>
</table></td></tr>
<tr><td></td><td>Garcia-Manero, 2016 ABS [116]<br>Objectives: to evaluate the relationship between LEN exposure, including dose reductions, and duration of treatment, and the clinical benefit to pts with lower-risk, non-del(5q) MDS in pts from MDS-005<br>Population: Same as in main study<br>Intervention: LEN 10 mg/d (n = 160) vs. PBO (n = 79)<br>Outcome: RBC-TI ≥ 8 wks, or transfusion reduction of ≥ 4 units packed RBCs (pRBCs) ≥ 8 wks, or hemoglobin (Hb) increase ≥ 1.5 g/dL at 8 wks (IWG 2006), or Cytologic response<br>Design: post hoc analysis of main study<br>Follow-up: same as in main study</td><td>Pts undergoing ≥ 1 LEN dose reduction compared with pts with no dose reductions had:<br>longer duration of treatment (172 ds [interquartile range 140 to 391 ds] vs. 92 days [IQR 46 to 168 ds]).<br>Pts undergoing ≥ 1 LEN dose reduction compared with pts with no dose reductions were more likely to achieve<br>RBC-TI rate: (39% vs 16%; odds ratio [OR] 3.44 [95% CI: 1.63 to 7.26]).<br>Clinical benefit rate (composite endpoint):(47% vs 18%; OR 3.98 [95% CI: 1.94 to 8.15]).</td></tr>
<tr><td></td><td>Almeida, 2016 ABS [119]<br>Objectives: To describe frequency, timing, and management of treatment-emergent AE in pts from MDS-005<br>Population: Same as in main study</td><td>Grade 3 and 4 treatment emergent AE were reported in 86.3% of pts<br>Grade 3 and 4 AEs:<br>Neutropenia: 61.9%<br>Thrombocytopenia: 35.6%</td></tr>
</table>

| Primary publication, Study name, Author, yr and objectives | Additional analysis: Author, yr and objectives | Summary results of additional publications |
|---|---|---|
| | **Intervention:** LEN 10 mg/d (n = 160) vs. PBO (n = 79)<br>**Outcome:** treatment-emergent AE<br>**Design:** cohort of patients treated with LEN<br>**Follow-up:** same as in main study | Anemia: 5.6%<br>Pneumonia: 5.6%<br>deep vein thrombosis: 1.9%<br>Grade 3 and 4 neutropenia and thrombocytopenia generally occurred in cycles 1–4.<br>*Due to treatment-emergent AEs*<br>Dose interruptions: 54.4%<br>Dose reductions: 6.3%<br>Dose interruptions with subsequent reduction: 42.5%<br>Time to first dose interruption or reduction (median, range): 57 days (6 to 504). |
| | Santini, 2016 ABS [115]<br>**Objectives:** To investigate the relationship between somatic gene mutations, response, and OS in lower-risk non-del(5q) MDS pts treated with LEN in the MDS-005 study<br>**Population:** 198 pts<br>**Intervention:** Same as in main study<br>**Outcome:** Association between mutations and OS, response<br>**Design:** post hoc analysis<br>**Follow-up (median, range):** *nr* | Somatic mutations in genes recurrently mutated in myeloid cancers were detected in 87% of pts. SF3B1 mutations (alone or in combination) (59%) were not associated with response to LEN (p=0.101).<br>TET2 (33%)<br>ASXL1 (23%)<br>DNMT3A (14%)<br>ASXL1 mutant pts had a significantly lower LEN response rate vs wildtype pts, whereas DNMT3A mutant pts had a trend for improved LEN response.<br>Median OS was influenced by mutations (higher number of mutations associated with worse OS, p=0.0005), but not significantly modified by LEN. |
| | Garcia-Manero, 2016 [114]<br>**Objectives**: To evaluate the relationship between LEN and clinically meaningful measures of response.<br><br>**Population:** Same as in original study<br><br>**Intervention:** LEN 10 mg/d vs. PBO<br><br>**Outcome**: composite endpoint of: RBC-TI ≥8 wks, or transfusion reduction of ≥4 units packed RBCs (pRBCs) ≥8 wks, or hemoglobin (Hb) increase ≥1.5 g/dL at 8 wks (IWG 2006), or cytogenetic response (CyR).<br><br>**Follow-up (median, range):** Same as in original study | Clinical benefit was higher in the LEN group than in the PBO. |

| Primary publication, Study name, Author, yr and objectives | Additional analysis: Author, yr and objectives | Summary results of additional publications |
|---|---|---|
| Giagounidis, 2014 [15] (included in Prica, 2014 [12]<br><br>**Objectives:** To test the effectiveness and safety of romiplostim in monotherapy<br><br>**Population:** 250 low- or intermediate-1 MDSpts with thrombocytopenia and history of bleeding<br><br>**Intervention/ Comparison:** romiplostim 750 µg/wk SC | Kantarjian, 2016 [117]<br>**Objectives:** to provide a final, 5-yr follow-up to the Giagoudinis, 2014 study [15]<br>**Population:** Same as in main study<br>**Intervention:** supportive care after romiplostim was stopped<br>**Outcome:** Disease progression to AML<br>**Design:** cohort<br>**Follow-up (median, range):** 27.5 mos (10.8 to 58.7 mos) | *Romiplostim vs. PBO:*<br>Death: 1.03 (95% CI: 0.72 to 1.47)<br>AML progression: 1.06 (95% CI: 0.48 to 2.33) |

* Fisher Exact test
[C] Data available on 26 patients in the LEN 5 mg group, 26 patients in the Placebo group and 37 patients in the LEN 10 mg group

Table 2A. Pooled analyses of studies of systemic treatment of patients with MDS: general characteristics

| Author, year, Country, Funding | Objectives / Focus / Data collection | Design Follow-up | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|---|---|
| **MDS004 AND MDS003 POOLED ANALYSES** | | | | | | |
| Fenaux, 2017 [124]<br><br>**Country:** multiple countries<br><br>**Funding:** Celgene | To assess the effect of age on clinical characteristics and outcomes in LEN-treated MDS patients with del(5q) from the MDS-003, and MDS-004 trials.<br><br>**Data collection period:** *nr* | Poled analysis<br><br>**Follow-up:** *nr* | N=286 pts treated with LEN from MDS-003 AND MDS-004 trials<br><br>**IPSS**: Low/Intermediate-1-risk del(5q) MDS<br><br>**Gender**: *nr*<br><br>**Age** (median): 69 years ( <65 years: 33.9%; ≥65 to <75 years: 34.3%; and ≥75 years: 31.8% )<br><br>**WHO diagnosis**: *nr*<br><br>Time from diagnosis: *nr* | Age groups: <65 years, and %; ≥65 to <75 years | Age group: ≥75 years | Association of age with outcomes |
| Sekeres, 2015 ABS [133]<br><br>**Country:** multiple countries<br><br>**Funding:** Celgene | To evaluate the impact of LEN exposure including induction-type dosing in Cycle 1 and subsequent dose reductions<br><br>**Data collection period:** Same as original studies for MDS-003, 004 | Pooled analysis<br><br>**Follow-up:** *nr* | N = 286 pts from MDS-003 AND MDS-004 trials<br><br>**IPSS**: Low/Intermediate-1-risk del(5q) MDS<br><br>**Gender**: *nr*<br><br>**Age** (median): *nr*<br><br>**WHO diagnosis**: *nr*<br><br>Time from diagnosis: *nr* | LEN 10 mg or LEN 5 mg for a total of >210 mg in Cycle 1 | LEN 10 mg or LEN 5 mg for a total of ≤210 mg | AML-free survival<br>OS |
| Giagounidis, 2014 ABS [131]<br><br>**Country:** multiple countries<br><br>**Funding:** *nr* | To describe the prevalence and clinical impact of the most common cytogenetic abnormalities in pts with del(5q) from MDS-003 and MDS-004<br><br>**Data collection period:** *nr* | Pooled analysis<br><br>**Follow-up:** *nr* | N = 281 pts from MDS-003 AND MDS-004 trials<br>**IPSS**: *nr*<br><br>**Gender**: *nr*<br><br>**Age**: *nr*<br><br>**WHO diagnosis**: *nr*<br><br>Time from diagnosis (median): mos | Pts with abnormalities +21 | Pts with abnormalities +8<br>Pts with other abnormalities | Prevalence of cytogenetic abnormalities<br>AML progression<br>OS |

| Author, year, Country, Funding | Objectives / Focus / Data collection | Design Follow-up | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|---|---|
| Kuendgen, 2013 [132]<br><br>**Country:** multiple countries<br><br>**Funding:** Celgene | a) To compare outcomes in pts treated with LEN in studies MDS-003 and MDS-004 with untreated pts from a registry<br>b) To identify potential risk factors for2786<br>AML progression and mortality<br><br>**Data collection period:** Same as original studies for MDS-003, 004 and from 1982 for the untreated cohort | Retrospective cohort<br><br>**Follow-up** (median, range)**:** 4.3 yrs, 0.02 to 6.8 yrs from first dose for LEN treated pts<br>4.6 yrs, 0.06 to 19.0 yrs from diagnosis for control group | **N**= 295 RBC-TD pts treated with LEN from MDS-003 and MDS-004 and 125 untreated RBD-TD pts from a registry who had isolated del(5q)<br><br>**IPSS:** Low/Intermediate-1-risk del5q31 MDS<br><br>**Gender:** 24.6% male<br><br>**Age:** mean (range): 67.1 yrs, 36to 86<br><br>**WHO diagnosis:** *nr*<br><br>**WHO diagnosis**:<br>RA 73.2% vs. 76.8%; RARS 7.1% vs. 8%; RAEB-1 18.3% vs. 15.2%; Other or missing 0.7% vs. 0<br><br>**Time from diagnosis** (median, range): 2.7 yrs, 0.1 to 29.2 yrs for the LEN group | LEN 10 mg (MDS-003) or LEN 10 mg or 5 mg (MDS-004) | BSC = best supportive care | *2-yr AML progression<br>*OS |
| Benettaib, 2013 ABS [126] | To estimate the impact of LEN on long-term mean survival based on MDS003 and MDS004 trial data and published literature.<br><br>**Data collection period:** Same as in main studies | Pooled analysis<br><br>**Follow-up:** *nr* | N = 122 RBC-TD pts<br><br>**IPSS**: low and int-1 risk MDS del5q<br>**Gender**: Male %<br><br>**Age** (median): yrs<br><br>**WHO diagnosis**: *nr*<br><br>Time from diagnosis (median): *nr* | LEN | BSC | Long-term OS<br>RBC-TI |
| List, 2013 ABS [128]<br><br>**Country:** multiple countries<br><br>**Funding:** *nr* | To evaluate response to treatment, progression to AML and OS by proportion of del(5q) metaphases in patients with isolated del(5q) from the MDS-003 and 004<br><br>**Data collection period:** *nr* | Retrospective analysis<br><br>**Follow-up:** *nr* | N = 194 pts from MDS-003 and MDS-004<br><br>**IPSS**: low and int-1 risk MDS with isolated del(5q)<br><br>**Gender**: *nr*<br><br>**Age**: *nr*<br><br>**WHO diagnosis**: *nr*<br><br>Time from diagnosis (median): *nr* | Proportion of del(5q) metaphases or interphases ≤ 60% (n = 21) | Proportion of del(5q) metaphases or interphases > 60% (n = 173) | RBC-TI ≥ 26 wks<br>Time to AML progression<br>OS |
| List, 2011 ABS [129] | To evaluate the predictive factors for durable RBC-TI in LEN-treated pts in MDS-003/- | Retrospective analysis | N = 286 pts from MDS-003 and MDS-004<br><br>**IPSS**: low and int-1 risk MDS with | LEN | PBO | Predictors of RBC-TI |

| Author, year, Country, Funding | Objectives / Focus / Data collection | Design Follow-up | Population | Intervention | Comparison | Outcomes |
|---|---|---|---|---|---|---|
| **Country:** multiple countries<br><br>**Funding:** *nr* | 004<br><br>**Data collection period:** *nr* | **Follow-up:** median 166 wks(MDS-003) and 156 (MDS-004) wks | isolated del(5q)<br><br>**Gender**: *nr*<br><br>**Age**: *nr*<br><br>**WHO diagnosis**: *nr*<br>Time from diagnosis (median): *nr* | | | |
| Giagounidis, 2011 ABS [127]<br><br>**Country:** multiple countries<br><br>**Funding:** *nr* | To investigate the effect of additional cytogenetic abnormalities on OS and AML progression, and interaction of treatment-associated RBC-transfusion independence (RBC-TI) in MDS-003/-004<br><br>**Data collection period:** Same as in main studies | Retrospective analysis<br><br>**Follow-up:** median 38.4 mos for MDS-003 and 36.0 mos for MDS-004 | N = 274 pts from MDS-003 and MDS-004<br><br>**IPSS**: low and int-1 risk MDS with isolated del(5q)<br><br>**Gender**: 31% male<br><br>**Age**: (median) 69 yrs, range 36 to 95<br><br>**WHO diagnosis**: *nr*<br>Time from diagnosis (median, range): 2.7 yrs, 0.1 to 29.2 | LEN 5 mg or 10 mg | NA | According to cytogenetic complexity:<br>OS<br>AML progression |
| Sekeres, 2011 ABS [130]<br><br>**Country:** multiple countries<br><br>**Funding:** *nr* | To identify predictors of OS and AML progression in MDS-003/-004<br><br>**Data collection period:** Same as in main studies | Retrospective pooled analysis<br><br>**Follow-up:** Median 38.4 mos (range 0.3 to 81.9) for MDS-003 and 36.1 mos (range 0.4 to 59.4) for MDS-004 | **N**= 286 RBC-TD pts<br>**IPSS**: low and int-1 risk MDS with del(5q)<br><br>**Gender**: 30% male<br><br>**Age**: (median) 69 yrs, range 36 to 95<br><br>**French-American-British (FAB) classification**: RA/RARS: 63%; RAEB/CMML: 19%; Other or missing: 19%<br>Time from diagnosis (median, range): *nr* | LEN 5 mg or 10 mg | NA | Predictors of OS and of AML progression |

**Table 2B. Pooled analyses of studies of systemic treatment of patients with MDS: summary results**

| Author, year, Country, Funding | Intervention Control | Survival | Disease control (e.g. EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|
| **MDS 004 AND MDS 003 POOLED ANALYSES** | | | | | | |
| Fenaux, 2017 [124] | Age groups: <65 years, and % vs. ≥65 to <75 years vs. ≥75 years | OS (adjusted for life expectancy): NS | Age <65 years was associated higher rates of AML progression (Gray's test, p = 0.013) | **RR**: Age <65 years was associated with less favorable IPSS risk and additional cytopenias at baseline versus older age groups, significantly lower cytogenetic response rates (p=0.022 vs. ≥65 to <75 yrs; p=0.047 vs. ≥75 yrs).<br><br>**Transfusion independence:** ≥26 weeks: NS | NS | |
| Kuendgen, 2013 [132] | LEN vs. BSC | OS rates:<br>2-yrs: 89.9%, (95% CI 84.1 to 96.0) vs. 74.4%, (95% CI 66.1 to 83.7)<br>5-yrs: 53.7%, (95% CI 46.6 to 61.9) vs. 40.5% (95% CI 30.9 to 53.1)<br>OS median from diagnosis:<br>5.2 yrs (95% CI 4.5 to 5.9) vs. 3.8 (95% CI 2.9 to 4.8) | Cumulative AML incidence<br>2-yrs: 6.9%, (95% CI 3.3 to 13.9) vs. 12.1%, (95% CI 7.0 to 20.3)<br>5-yrs: 22.8%, (95% CI 17.1 to 30.3) vs. 19.9% (95% CI 12.9 to 30.0) | *nr* | *nr* | **Subgroups:**<br>Pts with isolated del(5q):<br>Cumulative AML incidence:<br>2-yrs: 6.6% (95% CI 2.5 to 16.7) vs. 7.4% (95% CI 3.1 to 16.9)<br>5-yrs: 18.1% (95% CI 11.3 to 28.1) vs. 16.9% (95% CI 9.4 to 29.4)<br>Median time to AML:<br>Not reached vs. not reached<br><br>OS rates:<br>2-yrs: 93.5%, (95% CI 87.5 to 99.9) vs. 76.1%, (95% CI 66.4 to 87.1)<br>5-yrs: 60.2%, (95% CI 51.1 to 71.0) vs. 44.4% (95% CI 32.8 to 60.3)<br>OS median:<br>6.1 yrs (95% CI 5.1 to 6.8) vs. 4.6 yrs (95% CI 3.2 to 6.1), p=0.87<br>**Predictors of AML progression:**<br>Del(5q) and >1 additional abnormality vs. isolated del(5q), HR 3.555, (95% CI 1.576 to 8.022) p=0.002<br>Bone marrow blast count 5-10% vs. <5%, HR 2.158, (95% CI 1.133 to 4.098) p=0.0019<br>Higher RBC transfusion burden, HR 1.090, (95% CI 1.003 to 1.0185) p=0.041 |

| Author, year, Country, Funding | Intervention Control | Survival | Disease control (e.g. EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|
| Sekeres, 2015 ABS [133] | LEN 10 mg or LEN 5 mg for a total of >210 mg in Cycle 1 vs. LEN 10 mg or LEN 5 mg for a total of ≤210 mg | OS<br>Longer for LEN >210 mg dose in Cycle 1 than for control, p=0.0002<br>[E]Higher LEN dose was associated with improved OS: HR 0.97, p=0.036<br><br>LEN dose reduction was associated with improved OS, HR 0.56 (95% CI 0.40 to 0.80), p<0.001 | AML-free survival<br>Longer for LEN >210 mg dose in Cycle 1 than for control, p=0.0005<br>[E]Higher LEN dose was associated with improved AML-free survival: HR 0.97, p=0.033<br>LEN dose reduction was associated with improved AML-free survival, HR 0.54 (95% CI 0.39 to 0.77), p<0.001 | *nr* | *nr* | *nr* |
| Giagounidis, 2014 ABS [131] | LEN 10 mg or 5 mg vs. PBO | Median OS<br>Pts with 8+: 4.1 yrs (95% CI 0.9–5.3)<br>Pts with 21+: 3.0 yrs (95% CI 1.1–4.9)<br>Other: 3.4 yrs (95% CI 2.6–6.5) (P = 0.423) | AML progression (median time to progression):<br>Pts with +21:<br>(2.6 yrs, 95% CI 1.2 to 4.8)<br>Pts with +8:<br>(4.8 yrs, 95% CI 1.6 to not estimable)<br>Pts with other abnormalities: (7.5 yrs, 95% CI 4.1 to 7.5), p=0.0143<br>AML progression rates at 5 yrs:<br>Pts with +21: 85.7% (95% CI 53.5–99.3),<br>Pts with +8: 68.8% (95% CI 26.6–98.7),<br>Pts with other abnormalities: 36.3% (95% CI 19.2–61.3) | *nr* | *nr* | *Prevalence of cytogenetic abnormalities:*<br>+8, +21, del(11Q), del(20Q), and t(2;11) accounted for 50% of abnormalities |
| Benettaib, 2013 ABS [126] | LEN vs. BSC | OS (mean):<br>5.7 yrs vs 4.6 yrs<br>OS (median):<br>4.7 yrs vs.4.5 yrs | *nr* | RBC-TI rates:<br>60.9% vs. 8.4% | *nr* | *nr* |
| List, 2013 ABS [128] | Proportion of del(5q) metaphases or interphases ≤ 60% vs. proportion of del(5q) metaphases or | OS rates:<br>longer in the > 60% versus the ≤ 60% group, p= 0.0436;<br><br>OS (median) 3.7 yrs (95% CI, 3.0 to 4.2) vs. 2.4 yrs (95% CI, 1.5 to 4.9) | Time to AML progression, 2-yr rates: 22.2% (95% confidence interval [CI]: 7.7–54.5%) vs.14.6% (95% CI: 9.9–21.2%), p=0.9802 | RBC-TI rates:<br>Similar, p=0.6515 | *nr* | *nr* |

| Author, year, Country, Funding | Intervention Control | Survival | Disease control (e.g. EFS, PFS, etc.) | Response | AE | Other |
|---|---|---|---|---|---|---|
| | interphases > 60% | | | | | |
| List, 2011 ABS [129] | LEN vs. PBO | *nr* | *nr* | *nr* | *nr* | Predictors of RBC-TI≥26 wks<br>*Positive predictors:*<br>Total cycle 1 dose received, x 10 mg OR 1.070 p=0.0014<br>Platelets ≥150 vs. <150 x $10^9$/L: 1.662, p=0.0955<br><br>*Negative predictors:*<br>Transfusion burden, units/8 wks: 0.861, p=0.0022<br>Del(5q) (+≥1 abnormality isolated) 0.532, p=0.0375 |
| Giagounidis, 2011 ABS [127] | LEN | OS (median):<br>del(5q)+≥2: 19.4 mos<br>del(5q)+1: 53.4 mos<br>iso-del(5q):47.5 mos, log rank p=0.0016<br>At 1 yr:<br>Similar OS across al cytogenetic groups | *nr* | *nr* | *nr* | Variables associated with reduced AML risk[E]:<br>Cytogenetic complexity, HR 1.942, p=0.0014 |
| Sekeres, 2011 ABS [130] | LEN | NA | NA | NA | NA | *Predictors of OS:*<br>Age: RR, 1.0465, p<0.001<br>FAB (RAEB/CMML vsRA/RARS): RR, 1.6260, p=0.012<br>Transfusion burden, units/8 wks: RR, 1.0643, p=0.013<br>Platelet count, per 100x$10^9$/L: RR, 0.5713, p=0.026<br>RBC-TI ≥26 wks: RR0.3584, p<0.001<br>*Predictors of AML progression:*<br>Transfusion burden: RR1.1255, p<0.001<br>del(5q) plus ≥1additional abnormality vs isolated): RR, 2.1205, p=0.606 |

ABS = abstract; AE = adverse eveents; AML = acute myeloid leukemia; BSC = best supportive care; CCI = confidence interval; Del(5q) = deletion (5q); EFS = event-free survival; HR = hazard ratio; LEN = lenalidomide; NS = not significant; OS = overall survival; PBO = placebo; PFS = progression-free survival; Pts = patients; RBC = red blood cells; RR = response rate; TI = transfusion independence; vs. = versus; yrs = years

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## Appendix 7. Quality of included primary studies.
## A) Application of the Cochrane Risk of Bias tool to individual randomized controlled studies of patients with low- and intermediate-1 IPSS risk MDS

### Balleari, 2006 [7];

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | p. 175: Patients were randomly divided in a 1:1 fashion |
| Allocation concealment (selection bias) | High risk | No mention |
| Blinding of participants and personnel (performance bias) | High risk | no mention |
| Blinding of outcome assessment (detection bias) | High risk | no mention |
| Incomplete outcome data (attrition bias) | Unclear risk | Analysis per protocol but it is not stated |
| Selective reporting (reporting bias) | Low risk | Same outcomes listed in methods are reported in the results. However, they did not report on overall survival which most other studies did |
| Other bias | Unclear risk | I could not see any |

### Baron, 2012 [50];

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Appendix methods central randomization |
| Allocation concealment (selection bias) | Low risk | Central randomization |
| Blinding of participants and personnel (performance bias) | High risk | no blinding |
| Blinding of outcome assessment (detection bias) | High risk | no blinding |
| Incomplete outcome data (attrition bias) | Low risk | ITT analysis |
| Selective reporting (reporting bias) | Low risk | However, for the population of interest not all data are available |
| Other bias | Unclear risk | I could not see |

### Fenaux, 2011 MDS-004 [19]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Multicentre |
| Allocation concealment (selection bias) | Low risk | Central allocation |
| Blinding of participants and personnel (performance bias) | Low risk | Double blind |
| Blinding of outcome assessment (detection bias) | Low risk | Central review |
| Incomplete outcome data (attrition bias) | Low risk | ITT analysis |
| Selective reporting (reporting bias) | Low risk | Same outcomes in protocol and report |
| Other bias | High risk | Study director from Celgene (manufacturer of LEN) |

### Garcia-Manero, 2013 [34]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Central generation of random sequence |

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | Central allocation |
| Blinding of participants and personnel (performance bias) | High risk | Open label |
| Blinding of outcome assessment (detection bias) | High risk | Open label |
| Incomplete outcome data (attrition bias) | Low risk | ITT |
| Selective reporting (reporting bias) | Low risk | Same outcomes in protocol and report |
| Other bias | High risk | Funded by manufacturer of drug |

## Garcia-Manero, 2014 [49]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Low risk | Multicentre |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blinded |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias) | Low risk | ITT |
| Selective reporting (reporting bias) | Low risk | Same outcomes in protocol and report |
| Other bias | Unclear risk | I could not see |

## Jang, 2015 [11]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias) | High risk | Open label |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias) | High risk | Per protocol analysis |
| Selective reporting (reporting bias) | Unclear risk | Not reported |
| Other bias | High risk | Funded by manufacturer |

## Oliva, 2017 [18]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Generated by means of the RAND function of the EXCEL ...The sequence was uploaded to a protected database |
| Allocation concealment (selection bias) | Low risk | Secure sockets layer certificated on a server's web interface guaranteeingallocation concealment |
| Blinding of participants and personnel (performance bias) | Low risk | Patients were masked to the allocation (single-blinded design) |
| Blinding of outcome assessment (detection bias) | High risk | The investigator was able to see, directly from the ompleted case report form which group the patients was assigned to |
| Incomplete outcome data (attrition bias) | High risk | Missing data were not imputed page 4 |
| Selective reporting (reporting bias) | High risk | Different outcomes are presented than what specified in the analysis section |

| | | |
|---|---|---|
| Other bias | Unclear risk | This is a report of an interim analysis |

## Raza, 2012 [52]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not reported |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias) | Low risk | ITT |
| Selective reporting (reporting bias) | Low risk | Same outcomes in methods section and results |
| Other bias | High risk | Funded by manufacturer |

## Santini, 2016 MDS-005 [28]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Centrally randomized |
| Allocation concealment (selection bias) | Low risk | Centrally randomized |
| Blinding of participants and personnel (performance bias) | Low risk | Double blind |
| Blinding of outcome assessment (detection bias) | Low risk | The primary end point was assessed in a blind fashion by an independent response committee and reported by using independent response committee data. |
| Incomplete outcome data (attrition bias) | Low risk | ITT analysis |
| Selective reporting (reporting bias) | Low risk | Same outcomes in methods section as in results |
| Other bias | Unclear risk | Funded by manufacturer |

## Schanz, 2009 [51]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not reported |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias) | High risk | Per protocol analysis |
| Selective reporting (reporting bias) | High risk | They report more outcomes in the Results section than in the Methods |
| Other bias | High risk | Funded by manufacturer |

## Taher, 2017 [101]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not described |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel | High risk | Open label |

| | | |
|---|---|---|
| (performance bias) | | |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias) | High risk | Did not do an ITT analyis |
| Selective reporting (reporting bias) | Low risk | Report all the outcomes that stated in methods / could not see protocol |
| Other bias | High risk | Study sponsored by pharma |

## Thepot, 2016 [102]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not described it's a phase II |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not described |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias) | Low risk | They did an ITT analysis |
| Selective reporting (reporting bias) | | Cannot determine |
| Other bias | Unclear risk | Unclear |

## Toma, 2016 [10]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Used computerized lists based on permutation blocks stratified by centers. |
| Allocation concealment (selection bias) | Low risk | Centralized randomization |
| Blinding of participants and personnel (performance bias) | High risk | Open label |
| Blinding of outcome assessment (detection bias) | High risk | Not reported |
| Incomplete outcome data (attrition bias) | Low risk | Exclusion of one patient because of withdrawal of consent from IIT analysis |
| Selective reporting (reporting bias) | High risk | Results for time to progression were not reported |
| Other bias | Unclear risk | Unclear |

## B) Application of the Cochrane Risk of Bias tool to individual randomized controlled studies of patients with low- and intermediate-1 and up to 20% Intermediate-2/high IPSS risk MDS

### Greenberg, 2009 [8]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Low risk | It was a multicenter trial with central randomization |
| Blinding of participants and personnel (performance bias) | High risk | The study was unblinded because the responders were asked to stay on treatment |
| Blinding of outcome assessment (detection bias) | Low risk | Central pathology review |
| Incomplete outcome data (attrition bias) | High risk | p. 2394: After central pathology review, 7 patients, on step 1 (4 on arm A, 3 on arm B) either withdrew or died before the initial 4-month response evaluation time point and were determined to be ineligible. One patient on step 1 (arm A) never started treatment. Three patients at step 2, 4 at step 3, and 1 at step 4 were ineligible and one did not receive treatment at step 3. These patients were included for evaluation of survival and leukemic transformation but not for erythroid response. |
| Selective reporting (reporting bias) | Low risk | Same outcomes in the methods section and in the results and in clinicaltrials.gov file |
| Other bias | Unclear risk | I could not see |

### Grinblatt, 2009 [53]:

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Low risk | Patient registration and data collection were managed by the CALGB Statistical Center. |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not reported |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias) | Low risk | The intent-to-treat approach was adopted. |
| Selective reporting (reporting bias) | Low risk | Same outcomes in the methods section and in the results and in clinicaltrials.gov file |
| Other bias | High risk | Funded by manufacturer |

### Kantarjian, 2006 [35]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Centralized call-in process. |
| Allocation concealment (selection bias) | Low risk | Centralized call-in process. |
| Blinding of participants and personnel (performance bias) | High risk | Open label |
| Blinding of outcome assessment (detection bias) | Low risk | p. 1795 a blinded central review of all bone marrow aspirates and biopsies was performed by an expert hematomorphologist (J.M.B.) to determine each patient's best hematologic response per the MDS IWG criteria (centrally reviewed dataset). |
| Incomplete outcome data (attrition bias) | Low risk | ITT analysis |

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | Same endpoints in methods and results - I was not able to locate the protocol because it is an old study |
| Other bias | Unclear risk | I could not see |

## Lyons, 2009 [33]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Cannot tell |
| Allocation concealment (selection bias) | Unclear risk | Cannot tell |
| Blinding of participants and personnel (performance bias) | High risk | Open label |
| Blinding of outcome assessment (detection bias) | High risk | Open label |
| Incomplete outcome data (attrition bias) | Low risk | ITT analysis |
| Selective reporting (reporting bias) | Low risk | Same outcomes in Methods as in Results |
| Other bias | High risk | Funded by manufacturer |

## Passweg, 2011 [37]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | It was a multicentre with central randomization procedures |
| Allocation concealment (selection bias) | Low risk | Multicentre study with centralized randomization |
| Blinding of participants and personnel (performance bias) | High risk | It was open label - info from clinicaltrials.gov |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias) | Low risk | Analysis was carried out both as ITT and per protocol |
| Selective reporting (reporting bias) | Low risk | Same outcomes in methods protocol (NCT00004208) and results. |
| Other bias | Unclear risk | I could not see |

**C) Application of the Cochrane Risk of Bias tool for nonrandomized trials (ROBINS-I) [71] to individual nonrandomized trials of patients with low-, and Intermediate-1 IPSS risk MDS. Studies of patients with lower as well as higher risk populations were considered at critical risk of bias because they presented at least partially indirect evidence.**

| Study author, year (ref) | Intervention vs. comparison | Risk of bias judgement | Comment |
|---|---|---|---|
| **Prospective Studies** | | | |
| Leitch, 2017 [100] | Iron chelation vs. no chelation | Moderate | The study was at risk of bias in selection of the reported results. |
| Lyons, 2014 [39] | Iron chelation vs. no chelation | Serious | The study was at risk for confounding (no adjustment made); chelation was decided based on clinical status; patients had different follow-up times and different duration of chelation. pts started interventions at different points from diagnosis. |
| Rose, 2010 [40] | Iron chelation vs. no chelation | Moderate | The study was at risk of selection bias, although the authors performed a Cox proportional hazards regression with all the parameters that were unbalanced between groups and bias in classification of interventions. No information was given about missing data. |
| **Retrospective Studies** | | | |
| Zeidan, 2015 [99] | LEN before AZA vs. LEN after AZA | Critical | This was a retrospective study; the authors did not control for confounding variables, and the risk for selection bias is high. |
| Remacha, 2015 [41] | Iron chelation vs. no chelation | Serious | This is a retrospective study; the authors controlled appropriately in analysis for possible confounders. However missing data were not considered in the analyses. Over 30% of pts withdrew from assigned intervention and no analysis was conducted to account for this. |
| Cermak, 2013 [46] | Iron chelation vs. no chelation | Critical | This was a retrospective study; the authors did not control for confounding variables. Patients had different follow-up times, and different duration of chelation. (confounding domain) Patients were not followed-up from the start of interventions (selection bias domain) |
| Adès, 2012 [26] | Immunomodulatory agents: LEN vs. no LEN | Serious | This was a retrospective cohort study. The authors used appropriate analyses to control for confounding. However, this was not done when estimating the treatment effect. |
| Jädersten, 2008 [5] | Hematopoiesis growth factors vs. no treatment | Serious | This is a retrospective cohort study. However the authors controlled for all variables that could have affected outcome, and an intention-to-treat analysis was conduceted. |
| Sloand, 2008 [27] | Immunosuppressive therapy | Serious | This is a retrospective cohort study. However the authors controlled for all variables that could have affected outcome, and an intention-to-treat analysis was conduceted. |

## Appendix 8. Ongoing trials. Results of the search of the registry Clinicaltrials.gov executed on January 13, 2017. Search terms were: "Myelodysplastic syndromes" and "Low": 350 hits

| Interventions, design | Official title | Status | Protocol ID | Completion Date | Last updated |
|---|---|---|---|---|---|
| **HEMATOPOIESIS STIMULATIN-AGENTS** | | | | | |
| **ESAs** | | | | | |
| Darbepoetin alfa vs.Placebo<br><br>RCT phase 3 | A Multicenter, Randomised, Double-blind, Placebo-controlled Study of Darbepoetin Alfa for the Treatment of Anaemic Subjects With Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) | **Ongoing, but not recruiting participants** | NCT01362140 | Aug 2017 | Dec 2016 |
| Group 2: Placebo vs.<br>Group 1: Epoetin alfa<br><br>RCT, phase 3, double blind | A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Evaluating Epoetin Alfa Versus Placebo in Anemic Patients With IPSS Low- or Intermediate-1-Risk Myelodysplastic Syndromes | **Completed** | NCT01381809 | Jan 2016 | Mar 2016 |
| Darbepoetin alpha vs.<br>Filgrastim vs. Blood Red Cell Transfusion<br><br>RCT phase 3 | REGIME: A Randomised Controlled Trial of Prolonged Treatment With Darbepoetin Alpha, With or Without Recombinant Human Granulocyte Colony Stimulating Factor, Versus Best Supportive Care in Patients With Low-risk Myelodysplastic Syndromes (MDS). | **Unknown** | NCT01196715 | Nov 2015 | Mar 2012 |
| ESAs vs. transfusional support<br><br>Case control | National Registry of Patients Diagnosed With Low-risk Myelodysplastic Syndromes According to the Criteria of the WHO / French-American-British Classification System (FAB) and IPSS and Treated With Erythropoietic Agents. | **Completed** | NCT01739452 | Sep 2014 | Apr 2015 |
| Infusion A: rEPO vs. Infusion B: rEPO combined with vitamins pills<br><br>RCT phase 3 open label | Comparison Between Erythropoietin and Erythropoietin Associated to Differentiating Therapy With Acid 13-cis-retinoic and Dihydroxyvitamin D3 in Myelodysplastic Syndromes Without Excess of Blasts | **Terminated** | NCT00804050 | Mar 2010 | Jun 2011 |
| Placebo vs. Epoetin alpha<br><br>RCT phase 3 double blind | A Randomized, Double Blind, Placebo Controlled, Multicenter Study Evaluating Epoetin Alfa Initiated at 40,000 IU Every Week or 80,000 IU Every Week Versus Placebo in Subjects With IPSS Low- or Intermediate-1 Risk Myelodysplastic Syndromes at Risk For Transfusion | **Terminated**<br>**Has Results** | NCT00695396 | Jan 2010 | Oct 2012 |
| Epoetin alpha (2 schedules)<br><br>RCT phase 2 | A Phase 2, Randomized, Open-Label Study To Assess The Safety And Efficacy Of Weekly (QW) Or Once Every Two Week (Q2W) Dosing Of Epoetin Alfa (PROCRIT) in Anemic Subjects With Low- or Intermediate-1 Risk Myelodysplastic Syndromes (MDS) | **Withdrawn** (*company decision to focus resources on a larger, controlled study)* | NCT00446602 | Aug 2009 | Jun 2011 |
| Epoetin alpha vs. amifostine trihydrate<br><br>Observational cohort phase 2 | Phase II Multicenter Study of Amifostine in Patients With Myelodysplastic Syndromes at Relatively Low Risk of Developing Acute Leukemia | **Active, not recruiting** | NCT00003681 | Not reported | May 2009 |
| **G-CSF** | | | | | |
| G-CSF vs.Plerixafor vs.Azacitidine<br>Non-RCT Phase 1 open label | A Phase I Trial Evaluating the Effects of Plerixafor (AMD3100) and G-CSF in Combination With Azacitidine (Vidaza) for the Treatment of MDS | **Ongoing, but not recruiting participants** | NCT0106512 | Nov 2013 | Jun 201 |
| **Romiplostim** | | | | | |
| Drug: N-Plate vs. romiplostim | Prospective validation of a predictive model of response to | **Recruiting** | NCT0233526 | Sep 2020 | Aug 2015 |

| Interventions, design | Official title | Status | Protocol ID | Completion Date | Last updated |
|---|---|---|---|---|---|
| Observational Phase 2 | romiplostim in patients with ipss low or intermediate-1 risk myelodysplastic syndrome (mds) and thrombocytopenia - the europe-trial | | | | |
| Placebo vs. AMG 531 (Romiplostim) vs. Azacitidine vs. Decitabine<br><br>RCT phase 2 | A Randomized, Double Blind, Placebo Controlled Study Evaluating the Efficacy and Safety of Romiplostim (AMG 531) Treatment of Subjects With Low or Intermediate Risk Myelodysplastic Syndrome (MDS) Receiving Hypomethylating Agents | **Completed Has Results** | NCT00321711 | Oct 2010 | Jul 2013 |
| Romiplostim vs.Placebo<br><br>RCT | A Randomized, Double Blind, Placebo Controlled Study Evaluating the Efficacy and Safety of AMG 531 Treatment of Subjects With Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) Receiving Lenalidomide. | **Completed Has Results** | NCT00418665 | Oct 2010 | Jan 2011 |
| **Eltrombopag** | | | | | |
| Eltrombopag/Revolade vs. Placebo vs. Lenalidomide<br><br>RCT phase 2 | Efficacy of Eltrombopag Plus Lenalidomide Combination Therapy in Patients With IPSS Low and Intermediate-risk Myelodysplastic Syndrome With Isolated del5q: a Multicenter, Randomized, Double-blind, Placebo Controlled Study - QOL-ONE Rev2MDS | **Recruiting** | NCT02928419 | May 2021 | Oct 2016 |
| Eltrombopag/Revolade vs. Placebo<br><br>RCT phase 2 | Eltrombopag for the Treatment of Thrombocytopenia Due to Low- and Intermediate Risk Myelodysplastic Syndromes (EQol-MDS) | **Recruiting** | NCT02912208 | Jun 2019 | Sept 2016 |
| Eltrombopag vs. Hypomethylating Agent (HMA)<br><br>RCT phase 2 | Phase II Study of Eltrombopag With or Without Continuation of Hypomethylating Agent After Hypomethylating Agent Failure For Patients With Myelodysplastic Syndrome (MDS) | **Ongoing, but not recruiting participants** | NCT02912208 | Oct 2019 | Nov 2016 |
| Eltrombopag Olamine vs. Laboratory Biomarker Analysis vs. Lenalidomide<br><br>Observational Phase 2 | Phase II Study of Lenalidomide and Eltrombopag in Patients With Symptomatic Anemia in Low or Intermediate I Myelodysplastic Syndrome (MDS) | **Recruiting** | NCT01772420 | Oct 2017 | Jan 2016 |
| Eltrombopag vs.Azacitidine vs. Placebo<br><br>RCT phase 3 double blind | A Randomized, Double-blind, Placebo-controlled, Phase III, Multi-centre Study of Eltrombopag or Placebo in Combination With Azacitidine in Subjects With IPSS Intermediate-1, Intermediate 2 and High-risk Myelodysplastic Syndromes (MDS) SUPPORT: A StUdy of eltromboPag in myelodysPlastic SyndrOmes Receiving azaciTidine | **terminated** | NCT02158936 | Apr 2016 | Jul 2016 |
| Eltrombopag vs.placebo<br><br>RCT phase 2 | A Three-part Study of Eltrombopag in Thrombocytopenic Subjects With Myelodysplastic Syndromes or Acute Myeloid Leukemia (Part 1: Open-label, Part 2: Randomized, Double-blind, Part 3: Extension) | **Completed Has Results** | NCT01440374 | Dec 2015 | May 2016 |
| **IMMUNOMODULATORY AGENTS** | | | | | |
| Lenalidomide vs placebo<br><br>RCT phase 3 | Multicenter, Randomized, Double-blind, Phase III Study of REVLIMID (Lenalidomide) Versus Placebo in Patients With Low Risk Myelodysplastic Syndrome (Low and Intermediate-1 IPSS) With Alteration in 5q- and Anemia Without the Need of Transfusion. | **Recruiting** | NCT01243476 | Jan 2022 | Apr 2016 |
| Lenalidomide vs. Placebo<br><br>RCT phase 3 | A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study To Compare The Efficacy And Safety of Lenalidomide (Revlimid®) Versus Placebo In Subjects With Transufsion-Dependent Anemia Due to IPSS Low Or Imtermidate-1 Risk | **Ongoing, but not recruiting participant** | NCT01029262 | Jun 2018 | Nov 2016 |

| Interventions, design | Official title | Status | Protocol ID | Completion Date | Last updated |
|---|---|---|---|---|---|
| | Myelodysplastic Syndromes Without Deletion 5Q(31) And Unresponsive Or Refractory To Erthropoiesis-Stimulating Agents | | | | |
| Epoetin Alfa vs. Laboratory Biomarker Analysis vs. Lenalidomide<br><br>RCT phase 3 | Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment With Lenalidomide (Revlimid®) Alone and in Combination With Epoetin Alfa (Procrit®) in Subjects With Low- or Intermediate-1 Risk MDS and Symptomatic Anemia<br>List A (author) | **Ongoing, but not recruiting participants** | NCT00843882 | Apr 2017 | Jan 2017 |
| Lenalidomide vs.Recombinant human erythropoietin<br><br>Observational Phase 1 and phase 2 | A Pharmacokinetic And Pharmacodynamic Study Of Oral Lenalidomide (Revlimid) In Subjects With Low-Or Intermediate-1-Risk Myelodysplastic Syndromes | **Completed<br>Has Results** | NCT00910858 | May 2009 | Jul 2013 |
| **5Q deletion** | | | | | |
| No new studies identified | | | | | |
| **Non-5Q deletion** | | | | | |
| Lenalidomide vs. Epoetin beta | A Phase II Study Evaluating the Efficacy/Safety of Lenalidomide With or Without Epoetin Beta in Transfusion-dependent ESA-resistant Patients With IPSS Low- and Intermediate-1 Risk Myelodisplastic Syndromes Without Chromosome 5 Abnormality. | **Completed** | NCT01718379 | Jun 2016 | Nov 2016 |
| **HYPOMETHYLATING AGENTS** | | | | | |
| **AZACYTIDINE** | | | | | |
| Oral Azacitidine vs. Placebo<br><br>RCT phase 3 | A Phase 3, Multicenter, Randomized, Double-blind Study to Compare the Efficacy and Safety of Oral Azacitidine Plus Best Supportive Care Versus Placebo Plus Best Supportive Care in Subjects With Red Blood Cell Transfusion-dependent Anemia and Thrombocytopenia Due to IPSS Lower-risk Myelodysplastic Syndromes. | **Recruiting** | NCT01566695 | Oct 2021 | Dec 2016 |
| CC-486 (oral azacitidine) vs. Durvalumab<br><br>RCT phase 2 open label | A Phase 2, International, Multicenter, Randomized, Open-label, Parallel Group to Evaluate the Efficacy and Safety of Cc-486 (Oral Azacitidine) Alone in Combination With Durvalumab (MEDI4736) in Subjects With Myelodysplastic Syndromes Who Fail to Achieve an Objective Response to Treatment With Azacitidine for Injection or Decitabine | **Recruiting** | NCT02281084 | Jan 2019 | Dec 2016 |
| Decitabine vs. Azacitidine<br><br>RCT phase 2 | Phase II Randomized Study of Lower Doses of Decitabine (DAC; 20 mg/m2 IV Daily for 3 Days Every Month) Versus Azacitidine (AZA; 75 mg/m2 SC/IV Daily for 3 Days Every Month) in Myelodysplastic Syndrome (MDS) Patients With Low and Intermediate-1 Risk Disease | **Ongoing, but not recruiting participant** | NCT01720225 | Nov 2017 | Feb 2016 |
| Azacitidine 5-day vs. 7-day<br><br>RCT phase 2 open label | 5 Day Versus 7 Day Azacitidine in Lower Risk Myelodysplastic Syndrome. | **Recruiting** | NCT01652781 | Dec 2016 | Nov 2015 |
| Azacitidine vs. Entinostat vs. Laboratory Biomarker Analysis<br><br>RCT phase 2 | A Randomized Phase II Trial of Azacitidine With or Without the Histone Deacetylase Inhibitor Entinostat for the Treatment of Myelodysplastic Syndrome, Chronic Myelomonocytic Leukemia (Dysplastic Type), and Acute Myeloid Leukemia With Multilineage Dysplasia | **Ongoing, but not recruiting participants.** | NCT00313586 | Apr 2016 | Jan 2016 |

| Interventions, design | Official title | Status | Protocol ID | Completion Date | Last updated |
|---|---|---|---|---|---|
| Azacitidine vs. best supportive care<br><br>RCT phase 2 | Multicentre, Open-label, Randomized Phase II Study of Vidaza (Azacitidine) Versus Support Treatment in Patients With Low Risk Myelodysplastic Syndrome (Low and Intermediate-1 International Prognostic Scoring System(IPSS )) Without the 5q Deletion and Transfusion Dependent Anaemia | **Completed** | NCT01338337 | Dec 2015 | Jan 2016 |
| Azacitidine vs. Epoetin beta<br><br>RCT phase 2 | A Phase II Study of Azacitidine (Vidaza®) Combined to Epoetin Beta (NeoRecormon®) in IPSS Low-risk and Intermediate-1 MDS Patients, Resistant to ESA | **Completed** | NCT01015352 | Mar 2014 | Nov 2009 |
| Azacitidine vs. Beta Erythropoietin<br><br>Non-RCT phase 2 | A Multicenter, Non-Randomized, Open-Label Study to Evaluate Efficacy and Safety of Azacitidine and Beta Erythropoietin Treatment in Patients With Myelodysplastic Syndrome Red Cell Transfusion Dependent With Low or Intermediate -1 Risk. | **Terminated** | NCT00495547 | Jun 2011 | Apr 4, 2014 |
| Aza-5: vs. Aza-5-2-2: vs. Aza-5-2-5: vs.Maintenance Aza<br><br>RCT phase 2, open label | A Multicenter, Randomized, Open-Label Study Comparing Three Alternative Dosing Regimens of Subcutaneous Azacitidine Plus Best Supportive Care for the Treatment of Myelodysplastic Syndromes | **Completed Has Results** | NCT00102687 | Aug 2008 | Jun 2010 |
| Azacitidine vs. Erythropoietin vs Azacitidine (Monotherapy)<br><br>RCT phase 2 | Phase II Randomized Trial With A Modified Dose & Schedule of Subcutaneously Administered Azacitidine & Erythropoietin v Azacitidine Alone in Patients With Low-Risk Myelodysplastic Syndromes (Less Than 11% Marrow & Peripheral Blood Blasts) | **Terminated** | NCT00379912 | Dec 2008 | Feb 2016 |
| Lirilumab vs. Nivolumab vs. Azacitidine<br><br>Cohort | Phase II Combination of Lirilumab and Nivolumab With 5-Azacitidine in Patients With Myelodysplastic Syndromes (MDS) | **Recruiting** | NCT02599649 | Not reported | Aug 2016 |
| **DECITABINE** | | | | | |
| Decitabine (ultra-low dose vs low dose<br><br>RCT | Prospective, Open, Multi-center, Double Arm Clinical Trial Evaluating the Efficacy of Ultra Low Dose of Decitabine in Myelodysplastic Syndromes (MDS) | **Recruiting** | NCT02779569 | Feb 2018 | May 2016 |
| Decitabine Injection 20 $mg/m^2/d*5d$, IV> 1h, one cycles per 4 weeks<br>vs.<br>Decitabine Injection $12mg/m^2/d*8d$, IV> 1h, one cycles per 4 weeks.<br><br>RCT phase IV | A Randomized, Controlled, Multi-center Collaborative Phase Ⅳ Study to Evaluate the Safety and Efficacy of Decitabine in Myelodysplastic syndrome | **Unknown** | NCT02013102 | Dec 2015 | Dec 2013 |
| Decitabine vs. Valproic Acid<br><br>RCT phase 2 | Phase II Randomized Study of Low-Dose Decitabine (5-AZA-2'-Deoxycytidine) With or Without Valproic Acid in Myelodysplastic Syndrome (MDS) and Acute Myelogenous Leukemia -"SPORE" | **Completed** | NCT00414310 | May 2015 | Jul 2015 |
| Decitabine at 15 $mg/m^2$ vs. Decitabine at 20 $mg/m^2$<br><br>RCT phase 3b, open label | An Open-label, Multi-center, Phase IIIb Study for Decitabine in Patients With Myelodysplastic Syndrome (MDS) | **Completed** | NCT01751867 | Apr 2013 | Apr 2016 |

| Interventions, design | Official title | Status | Protocol ID | Completion Date | Last updated |
|---|---|---|---|---|---|
| Azacitidine vs. decitabine<br><br>Observational, retrospective cohort | Head to Head Comparison of Azacitidine and Decitabine in Myelodysplastic Syndrome: Retrospective, Multicenter Study | **Completed** | NCT01409070 | Dec 2011 | Oct 2012 |
| Decitabine (3 schdules)<br><br>RCT phase 2 | Phase II Randomized Study of Three Different Schedules of Low-Dose Decitabine (5-AZA-2'-Deoxycytidine) in Myelodysplastic Syndrome (MDS) | **Completed**<br>**Has Results** | NCT00067808 | May 2009 | Aug 2012 |
| Decitabine vs. supportive care<br><br>RCT phase 3 | Intravenous Low-Dose Decitabine Versus Supportive Care in Elderly Patients With Primary Myelodysplastic Syndrome (MDS) (>10% Blasts or High-Risk Cytogenetics), Secondary MDS or Chronic Myelomonocytic Leukemia (CMML) Who Are Not Eligible for Intensive Therapy: An EORTC-German MDS Study Group Randomized Phase III Study | **Unknown** | NCT00043134 | May 2008 | Apr 2008 |
| Azacitidine (AZA) Days 1 – 3 vs. Decitabine (DAC) vs. Best Supportive Care (BSC) vs. Azacitidine (AZA) Days 1 – 5<br><br>RCT phase 2 | Phase II Randomized Study of Lower Doses of Decitabine (DAC; 20 mg/m2 IV Daily for 3 Days Every Month) Versus Azacitidine (AZA; 75 mg/m2 SC/IV Daily for 3 Days Every Month) Versus Azacitidine (AZA; 75 mg/m2 SC/IV Daily for 5 Days Every Month) in MDS Patients With Low and Intermediate-1 Risk Disease Transfusion-Dependent Versus Best Supportive Care (BSC) in MDS Patients With Low and Intermediate-1 Risk Disease Transfusion-Independent | **Recruiting** | NCT02269280 | Not reported | Dec 2016 |
| **IMMUNOSUPPRESSIVE AGENTS** | | | | | |
| ATG + CsA vs. Supportive care<br><br>RCT, phase 3, factorial design | Antithymocyte Globulin (ATG) and Cyclosporine (CsA) to Treat Patients With Myelodysplastic Syndrome (MDS). A Randomized Trial Comparing ATG + CsA With Best Supportive Care | **Completed** | NCT00004208 | Oct 2011 | Mar 2015 |
| Daclizumab vs.ATG | A Randomized Trial of Recombinant Humanized Anti-IL-2 Receptor Antibody (Daclizumab) Versus Antithymocyte Globulin (ATG) to Treat the Cytopenia of Myelodysplastic Syndrome (MDS) | **Completed** | NCT00072969 | Aug 2005 | Mar 2008 |
| Biological: anti-thymocyte globulin<br><br>RCT, phase 2B | An Open Label, Prospective, Stratified, Randomized, Controlled, Multi-Center, Phase IIB Study of the Impact of Thymoglobulin Therapy on Transfusion Needs of Patients With Early Myelodysplastic Syndrome (MDS) | **Unknown** | NCT00017550 | Not reported | Feb 2009 |
| **IRON CHELATION** | | | | | |
| Deferasirox vs. Placebo<br>TELESTO trial<br>RCT double blind phase 2 | A Multi-center, Randomized, Double-blind, Placebo-controlled Clinical Trial of Deferasirox in Patients With Myelodysplastic Syndromes (Low/Int-1 Risk) and Transfusional Iron Overload | **Active, not recruiting** | NCT00940602 | Jan 2018 | Sep 2016 |
| Erythropoietin alpha vs. Deferasirox<br><br>RCT Phase 2 | An Open-label, Phase II, Randomized, Pilot Study to Assess the Effect in Term of Erythroid Improvement of Deferasirox Combined With Erythropoietin Compared to Erythropoietin Alone in Patients With low- and Int-1-risk Myelodysplastic Syndrome. | **Recruiting** | NCT01868477 | May 2017 | Nov 2016 |
| Core Study: Deferasirox; vs. Deferoxamine;<br>Extension: deferoxamine to deferasirox;<br>deferasirox to deferoxamine;<br>Deferasirox; Deferoxamine<br><br>RCT | A Multicenter, Randomized, Open-label Phase II Trial Evaluating Deferasirox Compared With Deferoxamine in Patients With Cardiac Iron Overload Due to Chronic Blood Transfusions | **Completed**<br>**Has Results** | NCT00600938 | Mar 2013 | Aug 2014 |
| Drug: Deferasirox 2 schedules | A Multicenter, Randomized, Comparative Study of Different | **Terminated** | NCT01326845 | Sept 2012 | Apr 2016 |

| Interventions, design | Official title | Status | Protocol ID | Completion Date | Last updated |
|---|---|---|---|---|---|
| RCT Phase 4 | Deferasirox Administration Regimens on Gastrointestinal (GI) Tolerability in Low or Intermediate (Int-1) Risk MDS Myelodysplastic Syndrome Patients With Transfusional Iron Overload. | **Has Results** | | | |
| **OTHER AGENTS** | | | | | |
| Nivolumab vs. Ipilimumab vs. 5-azacitidine<br><br>Observational phase 2 (MD Anderson) | Combination of Nivolumab and Ipilimumab With 5-azacitidine in Patients With Myelodysplastic Syndromes (MDS) | **Recruiting** | NCT02530463 | Sep 2021 | Jan 2017 |
| Imetelstat vs. Placebo<br><br>RCT phase 3 | A Study to Evaluate Imetelstat (JNJ-63935937) in Transfusion-Dependent Subjects With IPSS Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) That is Relapsed/Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment | **Recruiting** | NCT02598661 | Apr 2020 | Nov 2016 |
| Best Supportive Care vs. BI 836858<br><br>RCT phase 2 | A Phase I/II, Multicentre, Open-label, Dose Escalation and Randomized Trial of BI 836858 in Patients With Low or Intermediate-1 Risk Myelodysplastic Syndromes | **Recruiting** | NCT02240706 | Nov 2019 | Jan 2017 |
| Luspatercept vs. Placebo<br><br>RCT phase 3 | A Phase 3, Double-blind, Randomized Study to Compare the Efficacy and Safety of Luspatercept (ACE-536) Versus Placebo for the Treatment of Anemia Due to the IPSS-R Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes in Subjects With Ring Sideroblasts Who Require Red Blood Cell Transfusions. | **Recruiting** | NCT02631070 | Jun 2019 | Dec 2016 |
| Ascorbic acid<br><br>Observational phase 4 | Kinetics of the Plasmatic Concentration of L-Ascorbic Acid in Patient With Myelodysplastic Syndromes and Control Subjects | **This study is not yet open for participant recruitment** | NCT02809222 | Mar 2019 | Jun 2016 |
| Talacotuzumab vs. Daratumumab<br><br>RCT, phase 2 | A Phase 2 Proof-of-Concept Study to Separately Evaluate the Activity of Talacotuzumab (JNJ-56022473) or Daratumumab in Transfusion-Dependent Subjects With Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS) Who Are Relapsed or Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment | **Not yet recruiting** | NCT03011034 | Jan 2019 | Jan 2017 |
| Guadecitabine vs. Treatment Choice<br><br>RCT phase 3 | A Phase 3, Multicenter, Randomized, Open-Label Study of Guadecitabine (SGI-110) Versus Treatment Choice in Adults With Myelodysplastic Syndromes (MDS) or Chronic Myelomonocytic Leukemia (CMML) Previously Treated With Hypomethylating Agents | **Recruiting** | NCT02907359 | Dec 2018 | Jan 2017 |
| Either Wait and See, vs. Supportive Treatment, vs. Active Treatment at physician discretion<br><br>Observational cohort | Post-authorization, Observational Study to Assess the Evolution in the Normal Clinical Practise of Patients With Recent Diagnosis of Myelodysplastic Syndrome (MDS) or Chronic Myelomonocytic Leukemia (CMML), Depending on the Time of Active Treatment Initiated | **Ongoing, but not recruiting participants** | NCT02085798 | Aug 2018 | Sept 2016 |
| Sotatercept (different doses)<br><br>RCT phase 2 | An Open-label, Randomized, Phase 2, Parallel, Dose-Ranging, Multicenter Study of Sotatercept for the Treatment of Patients With Anemia and Low or Intermediate-1 Risk Myelodysplastic Syndromes or Non-proliferative Chronic Myelomonocytic Leukemia (CMML) | **Ongoing, but not recruiting participants.** | NCT01736683 | Jul 2018 | Dec 2016 |
| ON 01910.Na<br>RCT phase 3 | Phase III MultiCenter Randomized Controlled Study to Assess Efficacy and Safety of ON 01910.Na 72-Hr Continuous IV Infusion in MDS | **Ongoing, but not recruiting** | NCT01241500 | Jul 2017 | Nov 2016 |

| Interventions, design | Official title | Status | Protocol ID | Completion Date | Last updated |
|---|---|---|---|---|---|
| | Patients With Excess Blasts Relapsing After or Refractory to or Intolerant to Azacitidine or Decitabine | **participants** | | | |
| Rigorsertib (3 doses)<br><br>RCT phase 1 | A Randomized Phase I Study to Assess the Pharmacokinetics, Tolerability, Efficacy and Pharmacodynamics of Three Dosing Schedules of Oral Rigosertib in Transfusion-dependent, Low, Intermediate 1, or Intermediate-2 Myelodysplastic Syndrome Patients Based on the International Prognostic Scoring System | **This study has suspended participant recruitment.** *(Study suspended before enrollment and treatment of any patients; study potentially will resume after evaluation of results from other studies)* | NCT02075034 | Apr 2017 | Apr 2016 |
| LY2157299 vs. Placebo<br><br>RCT phase 2, phase 3 | Phase 2/3 Study of Monotherapy LY2157299 Monohydrate in Very Low-, Low-, and Intermediate-Risk Patients With Myelodysplastic Syndromes | **Active, not recruiting** | NCT02008318 | Mar 2017 | Aug 2016 |
| SGI-110<br><br>RCT phase 1, 2 | A Phase 1-2, Dose Escalation, Multicenter Study of Two Subcutaneous Regimens of SGI-110, a DNA Hypomethylating Agent, in Subjects With Intermediate or High-Risk Myelodysplastic Syndromes (MDS) or Acute Myelogenous Leukemia (AML) | **This study is ongoing, but not recruiting participants.** | NCT01261312 | Mar 2016 | Jan 2016 |
| Platelet Transfusion<br><br>RCT pilot | Outpatient Platelet Transfusions in Myelodysplastic Syndromes and Leukemia: The OPTIMAL Pilot | **Terminated** | NCT01615146 | Jun 2015 | Sept 2015 |
| BSC vs. HIDRA/VPA<br><br>RCT phase 2 | Phase II Clinical Trial for Treatment of Myelodysplastic Syndromes Comparing Hydralazine / Ac.Valproico and Supportive Care in Patients Not Candidates, Refractory and / or Intolerant to Intensive Chemotherapy | **Unknown** | NCT01356875 | Jan 2015 | May 2011 |
| INCB047986<br><br>RCT phase 1 and phase 2 | A Randomized, Open-Label, 2-Stage Study of INCB047986 Administered Orally to Subjects With Primary Myelodysplastic Syndrome (MDS) Refractory to or Unlikely to Respond to Erythropoiesis-Stimulating Agents (ESAs) | **Terminated** | NCT02093429 | Sep 2014 | Feb 2015 |
| KRN321<br><br>RCT phase 2<br>Study name: KRN321-401 | A Phase 2, Randomized, Open-Label, Parallel, Comparative, Dose-Response Study to Evaluate the Efficacy and Safety of KRN321 in Adult Subjects With Low- or Intermediate-1-Risk Myelodysplastic Syndrome | **Completed** | NCT01497145 | Feb 2014 | Mar 2015 |
| Human umbilical cord-derived MSCs vs. cyclosporine A (CsA)<br><br>RCT phase 2 | Phase II Study of Umbilical Cord/Placenta-Derived Mesenchymal Stem Cells to Treat RA and RARS of MDS | **Unknown** | NCT01129739 | May 2013 | May 2010 |
| Siltuximab vs. Placebo vs. Best supportive care (BSC)<br><br>RCT | A Phase 2, Randomized, Double-blind, Placebo-controlled, Multicenter Study Comparing Siltuximab Plus Best Supportive Care to Placebo Plus Best Supportive Care in Anemic Subjects With International Prognostic Scoring System Low- or Intermediate-1-Risk Myelodysplastic Syndrome | **Terminated** *(stopped after the interim analysis based on* | NCT01513317 | Sep 2012 | Sep 2014 |

| Interventions, design | Official title | Status | Protocol ID | Completion Date | Last updated |
|---|---|---|---|---|---|
| | | *lack of sufficient efficacy. No safety concerns.)* | | | |
| Ezatiostat Hydrochloride (2 schdules)<br><br>RCT phase2 | Phase 2 Randomized Study Comparing Two Dose Schedules of Ezatiostat Hydrochloride (Telintra™, TLK199 Tablets) in Low to Intermediate-1 Risk Myelodysplastic Syndrome (MDS) | **Completed** | NCT00700206 | Jul 2011 | Aug 2011 |
| Panobinostat (2 doses)<br><br>Non-RCT phase 2 | A Phase II Trial of LBH589 in Refractory Myelodysplastic Syndromes (MDS) Patients | **Terminated**<br>**Has Results** | NCT00594230 | Mar 2011 | Oct 2015 |
| SCIO-469<br><br>RCT phase 2 | A Randomized, MultiCenter, Open-Label, Modified Dose-Ascension, Parallel Study of the Safety, Tolerability, and Efficacy of Oral SCIO-469 in Patients With Myelodysplastic Syndromes | **Completed** | NCT00113893 | Dec 2007 | Oct 2013 |
| Infliximab (2 doses)<br><br>RCT phase 2 open label | Randomized Phase II Trial With Infliximab (Remicade) in Patients With Myelodysplastic Syndrome and a Relatively Low Risk of Developing Acute Leukemia | **Completed** | NCT00074074 | Dec 2006 | Jul 2012 |
| Pracinostat vs. Placebo vs Azacitidine<br><br>RCT phase 2 double blind | A Phase 2 Randomized Double-Blind Placebo-Controlled Study of Pracinostat in Combination With Azacitidine in Patients With Previously Untreated International Prognostic Scoring System (IPSS) Intermediate Risk-2 or High-Risk Myelodysplastic Syndrome(MDS) | **Active, not recruiting** | NCT01873703 | Not reported | Apr 2016 |
| Gemtuzumab ozogamicin (2 doses and schedules)<br><br>RCT phase 2 | A Randomized Study Of The Safety And Efficacy Of Two Dose Schedules Of Gemcituzumab Ozogamicin In Patients With Intermediate-2 Or High-Risk Myelodysplastic Syndromes | **Unknown** | NCT00022321 | Not reported | Dec 2013 |
| PR1 leukemia peptide vaccine vs. incomplete Freund's adjuvant vs. sargramostim<br><br>Observational phase 2 | Phase 2 Study of Proteinase 3 PR1 Peptide Mixed With Montanide ISA 51 VG Adjuvant and Administered With GM-CSF inLow Risk and Intermediate-1 MDS | **Active, not recruiting** | NCT00513578 | Not reported | Jan 2014 |
| QUALMS-1 Questionnaire vs. FACT-An Questionnaire<br><br>Cohort | Interventional Validation of an MDS-Specific Measure of Quality of Life: Assessing the Responsiveness of the Quality of Life in Myelodysplasia Scale (QUALMS-1) to Different Hypomethylating Agent Regimens for Low and Intermediate Risk Disease | **Recruiting** | NCT02378701 | Not reported | Nov 2016 |
| Red blood cell transfusions<br><br>RCT | Red Blood Cell Transfusion Thresholds and QOL in MDS (EnhanceRBC): a Pilot, Feasibility Study | **Unknown** | NCT02099669 | Not reported | Mar 2014 |
| Darbepoetin and Filgrastim vs. Darbepoetin<br><br>RCT Phase 2, Phase 3 | A Randomised Controlled Trial of Prolonged Treatment With Darbepoetin Alpha With or Without Recombinant Human Granulocyte Colony Stimulating Factor (G-CSF) Versus Best Supportive Care in Patients With Low-Risk Myelodysplastic Syndromes | **Active, not recruiting** | NCT00234143 | Not reported | Mar 2009 |

## Appendix 9 – Excluded studies

### List of articles excluded after full-text review by reason for exclusion

#### 1: Abstract of systematic review

1. Park S, Fenaux P, Greenberg P, Mehta B, Callaghan F, Kim C, et al. Efficacy and safety of darbepoetin alfa (DA) in patients with myelodysplastic syndromes (MDS): A systematic review and meta-analysis. Blood. 2015;126 (23):5236.
2. Wang X, Liang X, Zeng D, Zhang C, Zhang X, Liao J, et al. A meta-analysis of hypomethylating agents as bridging therapy to hematopoietic stem cell transplantation in patients with myelodysplastic syndromes. Bone Marrow Transplant. 2016;51:S509.

#### 2: Duplicate publications

1. Almeida A, Fenaux P, Garcia-Manero G, Giagounidis A, Goldberg S, Gropper S, et al. Treatment-emergent adverse events in lenalidomide-treated low/int-1-risk myelodysplastic syndromes patients without del(5q) ineligible for or refractory to erythropoiesis stimulating agents. Haematologica. 2016;101:502.
2. Besa EC. A retrospective analysis using 13-cis retinoic acid (13CRA) and alpha tocopherol (AT) in MDS patients to prevent progression. Leuk Res. 2011;35:S82.
3. Brandenburg N, Fu T, Revicki D, Knight R, Muus P, Fenaux P. Impact of lenalidomide on health-related quality of life in patients with RBC transfusion-dependent low- or int-1-risk myelodysplastic syndromes with DEL5Q: A randomized phase 3 study (MDS-004). Haematol. 2010;95:127.
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7. Fenaux P, Giagounidis A, Beyne-Rauzy O, Mufti G, Mittelman M, Muus P, et al. Prognostic factors of long-term outcomes in low- or int-L-risk MDS with del5q treated with lenalidomide (LEN): Results from a randomized phase 3 trial (MDS-004). Blood Conference: 52nd Annual Meeting of the American Society of Hematology, ASH. 2010;116(21).
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**3: Not design of interest**

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