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Dodillet H, Kreuzer KA, Monsef I, Skoetz N.
Thrombopoietin mimetics for patients with myelodysplastic syndromes.
Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD009883.
DOI: [10.1002/14651858.CD009883.pub2](https://doi.org/10.1002/14651858.CD009883.pub2).

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
BACKGROUND	6
OBJECTIVES	7
METHODS	8
Figure 1.	10
RESULTS	12
Figure 2.	14
Figure 3.	15
Figure 4.	16
Figure 5.	17
Figure 6.	18
DISCUSSION	19
AUTHORS' CONCLUSIONS	20
ACKNOWLEDGEMENTS	21
REFERENCES	22
CHARACTERISTICS OF STUDIES	26
DATA AND ANALYSES	49
Analysis 1.1. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 1 Mortality during study - all.	54
Analysis 1.2. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 2 Mortality during study - all (sensitivity analysis, FE model).	54
Analysis 1.3. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 3 Mortality during study - different types of thrombopoietin mimetics.	55
Analysis 1.4. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 4 Mortality during study - different types of additional agents.	55
Analysis 1.5. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 5 Mortality during study - different types of MDS risk groups.	56
Analysis 1.6. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 6 Mortality during study - full-text versus abstract publication.	57
Analysis 1.7. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 7 Transformation to AML - all.	57
Analysis 1.8. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 8 Transformation to AML - all (sensitivity analysis, FE model).	58
Analysis 1.9. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 9 Transformation to AML - different types of thrombopoietin mimetics.	58
Analysis 1.10. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 10 Transformation to AML - different types of additional agents.	59
Analysis 1.11. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 11 Transformation to AML - different types of MDS risk groups.	60
Analysis 1.12. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 12 Incidence of bleeding events - all.	60
Analysis 1.13. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 13 Incidence of bleeding events - all (sensitivity analysis, FE model).	61
Analysis 1.14. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 14 Incidence of bleeding events - $\geq$ grade 3 versus all bleeding events.	61
Analysis 1.15. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 15 Incidence of bleeding events - different types of thrombopoietin mimetics.	62
Analysis 1.16. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 16 Incidence of bleeding events - different types of additional agents.	62
Analysis 1.17. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 17 Incidence of bleeding events - different MDS risk groups.	63
Analysis 1.18. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 18 Transfusion requirement - all.	64

Analysis 1.19. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 19 Transfusion requirement - all (sensitivity analysis, FE model).	64
Analysis 1.20. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 20 Transfusion requirement - different types of additional agents.	64
Analysis 1.21. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 21 All adverse events - all.	65
Analysis 1.22. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 22 All adverse events - all (sensitivity analysis, FE model).	65
Analysis 1.23. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 23 All adverse events - different types of thrombopoietin mimetics.	66
Analysis 1.24. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 24 All adverse events - different types of additional agents.	66
Analysis 1.25. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 25 All adverse events - different MDS risk groups.	67
Analysis 1.26. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 26 Adverse events $\geq$ grade 3 - all.	68
Analysis 1.27. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 27 Adverse events $\geq$ grade 3 - all (sensitivity analysis, FE model).	68
Analysis 1.28. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 28 Adverse events $\geq$ grade 3 - different types of thrombopoietin mimetics.	69
Analysis 1.29. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 29 Adverse events $\geq$ grade 3 - different types of additional agents.	69
Analysis 1.30. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 30 Adverse events $\geq$ grade 3 - different MDS risk groups.	70
Analysis 1.31. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 31 Serious adverse events - all.	71
Analysis 1.32. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 32 Serious adverse events - all (sensitivity analysis, FE model).	71
Analysis 1.33. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 33 Serious adverse events - different types of additional agents.	71
ADDITIONAL TABLES	72
APPENDICES	75
CONTRIBUTIONS OF AUTHORS	78
DECLARATIONS OF INTEREST	78
SOURCES OF SUPPORT	79
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	79
NOTES	79
INDEX TERMS	79

[Intervention Review]

Thrombopoietin mimetics for patients with myelodysplastic syndromes

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ABSTRACT

Background

Myelodysplastic syndrome (MDS) is one of the most frequent haematologic malignancies of the elderly population and characterised by progenitor cell dysplasia with ineffective haematopoiesis and a high rate of transformation to acute myeloid leukaemia (AML). Thrombocytopenia represents a common problem for patients with MDS, ranging from mild to serious bleeding events and death. To manage thrombocytopenia, the current standard treatment includes platelet transfusion, unfortunately leading to a range of side effects. Thrombopoietin (TPO) mimetics represent an alternative treatment option for MDS patients with thrombocytopenia. However, it remains unclear, whether TPO mimetics influence the increase of blast cells and therefore to premature progression to AML.

Objectives

To evaluate the efficacy and safety of thrombopoietin (TPO) mimetics for patients with MDS.

Search methods

We searched for randomised controlled trials in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (January 2000 to August 2017), trials registries (ISRCTN, EU clinical trials register and clinicaltrials.gov) and conference proceedings. We did not apply any language restrictions. Two review authors independently screened search results, disagreements were solved by discussion.

Selection criteria

We included randomised controlled trials comparing TPO mimetics with placebo, no further treatment or another TPO mimetic in patients with MDS of all risk groups, without gender, age or ethnicity restrictions. Additional chemotherapeutic treatment had to be equal in both arms.

Data collection and analysis

Two review authors independently extracted data and assessed the quality of trials, disagreements were resolved by discussion. Risk ratio (RR) was used to analyse mortality during study, transformation to AML, incidence of bleeding events, transfusion requirement, all adverse events, adverse events $\geq$ grade 3, serious adverse events and platelet response. Overall survival (OS) and progression-free survival (PFS) have been extracted as hazard ratios, but could not be pooled as results were reported in heterogeneous ways. Health-related quality of life and duration of thrombocytopenia would have been analysed as standardised mean differences, but no trial reported these outcomes.

Main results

We did not identify any trial comparing one TPO mimetic versus another. We analysed six eligible trials involving 746 adult patients. All trials were reported as randomised and double-blind trials including male and female patients. Two trials compared TPO mimetics (romiplostim or eltrombopag) with placebo, one trial evaluated eltrombopag in addition to the hypomethylating agent azacitidine, two

trials analysed romiplostim additionally to a hypomethylating agent (azacitidine or decitabine) and one trial evaluated romiplostim in addition to the immunomodulatory drug lenalidomide. There are more data on romiplostim (four included, completed, full-text trials) than on eltrombopag (two trials included: one full-text publication, one abstract publication). Due to small sample sizes and imbalances in baseline characteristics in three trials and premature termination of two studies, we judged the potential risk of bias of all included trials as high.

Due to heterogenous reporting, we were not able to pool data for OS. Instead of that, we analysed mortality during study. There is little or no evidence for a difference in mortality during study for thrombopoietin mimetics compared to placebo (RR 0.97, 95% confidence interval (CI) 0.73 to 1.27, N = 6 trials, 746 patients, *low-quality evidence*). It is unclear whether the use of TPO mimetics induces an acceleration of transformation to AML (RR 1.02, 95% CI 0.59 to 1.77, N = 5 trials, 372 patients, *very low-quality evidence*). Thrombopoietin mimetics probably improve the incidence of all bleeding events (RR 0.92, 95% CI 0.86 to 0.99, N = 5 trials, 390 patients, *moderate-quality evidence*). This means that in the study population, 713 out of 1000 in the placebo arm will have a bleeding event, compared to 656 of 1000 (95% CI 613 to 699) in the TPO mimetics arm. There is little or no evidence for a difference that TPO mimetics significantly diminish the rate of transfusion requirement (RR 0.83, 95% CI 0.66 to 1.05, N = 4 trials, 358 patients, *low-quality evidence*). No studies were found that looked at quality of life or duration of thrombocytopenia.

There is no evidence that patients given TPO mimetics suffer more all adverse events (RR 1.01, 95% CI 0.96 to 1.07, N = 5 trials, 390 patients, *moderate-quality evidence*). There is uncertainty whether the number of serious adverse events decrease under therapy with TPO mimetics (RR 0.89, 95% CI 0.54 to 1.46, N = 4 trials, 356 patients, *very low-quality evidence*).

We identified one ongoing study and one study marked as completed (March 2015), but without publication of results for MDS patients (only results reported for AML and MDS patients together). Both studies evaluate MDS patients receiving eltrombopag in comparison to placebo.

Authors' conclusions

No trial evaluated one TPO mimetic versus another.

Six trials including adult patients analysed one TPO mimetic versus placebo, sometimes combined with standard therapy in both arms. Given the uncertainty of the quality of evidence, meta-analyses show that there is little or no evidence for a difference in mortality during study and premature progress to AML. However, these assumptions have to be further explored. Treatment with TPO mimetics resulted in a lower number of MDS patients suffering from bleeding events. There is no evidence for a difference between study groups regarding transfusion requirement. Enlarged sample sizes and a longer follow-up of future trials should improve the estimate of safety and efficacy of TPO mimetics, moreover health-related quality of life should be evaluated. As two ongoing studies currently investigate eltrombopag (one already completed, but without published results), we are awaiting results for this drug.

PLAIN LANGUAGE SUMMARY

Thrombopoietin mimetics for patients with myelodysplastic syndromes

Background

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematopoietic stem cell disorders associated with anaemia, bleedings or infections as a result of peripheral cytopenias and a premature progress to acute myeloid leukaemia (AML). Patients mainly suffer at an elderly age. Bone marrow transplantation remains the only curative option. Thrombocytopenia represents a life-threatening complication in the course of illness and alternative treatment options to platelet transfusion are limited. The introduction of TPO mimetics (raising platelet counts by imitating the effect of human TPO) in the treatment of MDS may extend the range of therapy.

Review question

With this review we aimed to take a closer look at TPO mimetics in the treatment of MDS patients. We intended to focus on changes of overall survival, mortality during study, transformation to AML, incidence of bleeding events, transfusion requirement, health-related quality of life, all adverse events, and serious adverse events to explore the effect of TPO mimetics.

Study characteristics

We searched medical databases such as Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, conference proceedings and study registries (January 2000 to August 2017). No trial evaluated one TPO mimetic (romiplostim or eltrombopag) versus another. We found eight eligible trials (six included, two ongoing, one of which is completed but without final results for MDS patients) and we included 746 adult patients in our review. The trials were randomised, double-blinded and used either romiplostim or eltrombopag versus placebo. In four trials hypomethylating agents or immunomodulatory drugs were administered in combination to romiplostim or eltrombopag. Only adults were included.

Key results

A meta-analysis of overall survival data was not possible, since data were too heterogeneous to pool. Instead of that, we analysed mortality data. There was no evidence for a difference between TPO mimetics and placebo in terms of mortality during study, transformation to AML, transfusion requirement, adverse events and serious adverse events. Thrombopoietin mimetics probably decrease the number of patients having bleeding events. In the study population, 713 out of 1000 in the placebo arm had a bleeding event, compared to 656 of 1000 (95% confidence interval (CI) 613 to 699) in the TPO mimetics arm. No trial evaluated health-related quality.

Quality of evidence

The quality of evidence for the outcomes incidence of bleeding events and all adverse events is moderate due to high risk of bias (small sample sizes and imbalances in baseline characteristics in three trials, premature closure of two trials, selective reporting in one trial, industrial sponsorship). The quality of evidence for the outcomes mortality during study and transfusion requirements is low, due to imprecision through small number of events and high risk of bias. It is very low for the outcomes transformation to AML and serious adverse events, because of very small number of events, high risk of bias and heterogeneity between trials.

Conclusion

Although this systematic review reveals a potential patient-relevant benefit regarding decreasing bleeding events for evaluated adult patients, future trials should focus on outcomes referring to safety, efficacy and quality of life aspects of TPO mimetics to test their everyday usage. The assumption of premature progress to AML could not be clearly verified. Because of the low number of included trials and small sample sizes, uncertainties of the findings in this review exist and demand further investigation with more trials and participants and longer follow-up periods.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Thrombopoietin mimetics compared to placebo for patients with myelodysplastic syndromes

Thrombopoietin mimetics compared to placebo for patients with myelodysplastic syndromes

Patient or population: Adult patients with myelodysplastic syndromes and thrombocytopenia

Setting: Inpatient or outpatient. The duration of studies ranged from four 28-day cycles to 6 months and > 58 weeks

Intervention: Thrombopoietin mimetics or thrombopoietin plus standard therapy; thrombopoietin mimetics:

- romiplostim: 500 µg or 750 µg
- eltrombopag: 200 mg/day (100 mg/day for East Asians), adjusted by 100 mg increments (50 mg for East Asians) to a maximum 300 mg/day (150 mg/day in East Asians) or 50 mg daily initial dose, adjusted every 2 weeks based on platelet response up to a maximum of 300 mg once daily (150 mg for East Asian patients) for 6 months as an oral tablet

Comparison: Placebo or placebo plus standard therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Thrombopoietin mimetics				
Overall survival	see comment	see comment		282 (2 studies)		As Platzbecker 2015 did not provide 95% CI, data could not be meta-analysed. Giagounidis 2014 : OS 58-weeks follow up: 18% of romiplostim patients died and 20.5% of placebo patients (HR 0.86, 95% CI 0.48 to 1.56). Platzbecker 2015 : median OS: 34 weeks for eltrombopag patients and 15.4 weeks for placebo-treated patients (HR 0.70, CI not provided)
Mortality during study	Study population		RR 0.97 (0.73 to 1.27)	746 (6 RCTs)	⊕⊕⊕⊕ LOW 1; 2	
	249 per 1.000	242 per 1.000 (182 to 316)				
Transformation to AML	Study population		RR 1.02 (0.59 to 1.77)	372 (5 RCTs)	⊕⊕⊕⊕ VERY LOW 2, 3	
	110 per 1.000	112 per 1.000 (65 to 195)				

Incidence of bleeding events	Study population		RR 0.92 (0.86 to 0.98)	390 (5 RCTs)	⊕⊕⊕⊖ MODERATE ²
	713 per 1.000	656 per 1.000 (613 to 699)			
Transfusion re-quirement	Study population		RR 0.83 (0.66 to 1.05)	358 (4 RCTs)	⊕⊕⊖⊖ LOW ^{1, 2}
	508 per 1.000	422 per 1.000 (335 to 534)			
Health-related quality of life			not reported		
All adverse events	Study population		RR 1.01 (0.96 to 1.07)	390 (5 RCTs)	⊕⊕⊕⊖ MODERATE ²
	912 per 1.000	921 per 1.000 (875 to 976)			
Serious adverse events	Study population		RR 0.89 (0.54 to 1.46)	356 (4 RCTs)	⊕⊖⊖⊖ VERY LOW ^{1, 2, 4}
	387 per 1.000	344 per 1.000 (209 to 564)			

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Small number of events (<200) resulting in downgrading 1 point due to imprecision

² High risk of bias due to small sample sizes and imbalances in baseline characteristics in three trials, premature closure of two trials, selective reporting in one trial, and industrial sponsorship

³ Very small number of events (<50) resulting in downgrading 2 points due to imprecision

⁴ Heterogeneity between studies resulting in downgrading in 1 point

BACKGROUND

Description of the condition

Epidemiology of myelodysplastic syndromes (MDS)

Myelodysplastic syndromes (MDS) are a heterogeneous group of haematological diseases that are characterised by a uni- or multilineage dysplasia of haematological stem cells. MDS is a rare disease of the elderly population. The overall incidence of the disease is about 4 to 7 per 100,000 people, whereas 20 to 50 per 100,000 people over the age of 70 years are affected ([Della Porta 2010](#); [Greenberg 2011](#); [Sekeris 2011b](#)). Approximately 85% of all patients with MDS are over 60 years when first diagnosed ([Goldberg 2010](#)). In general, MDS is characterised by myeloid, erythroid or megakaryocytic dysplasia, or a combination of dysplasias, associated with ineffective haematopoiesis and a high rate of transformation to acute myeloid leukaemia (AML) in approximately 20% of patients with MDS ([Nimer 2008](#); [Vardiman 2009](#)).

Classification of MDS

Two systems are commonly used to define haematopoietic malignancies. The French-American-British classification, introduced in 1976, is based on morphological and cytochemical methods ([Bennett 1976](#)). It subcategorises MDS into five entities and sets the threshold between high-grade MDS and AML at 30% blasts in the bone marrow. The World Health Organization (WHO) classification, introduced in 1999 and revised in 2008, uses morphology and newer prognostic factors such as karyotype and clinical features to define the different entities ([Harris 1999](#); [Vardiman 2009](#)). It distinguishes between five entities and 11 subtypes of MDS, and the threshold for the diagnosis of AML has been lowered to > 20% blasts ([Harris 1999](#); [Vardiman 2009](#)).

Prognosis of MDS

The International Prognostic Scoring System (IPSS) is the most widely used risk assessment system to evaluate the prognosis of MDS. The tool is based on the percentage of blasts in the bone marrow, the number of cytopenias and the karyotype, and categorises newly diagnosed patients into the following four groups: low, intermediate-1, intermediate-2 and high risk ([Greenberg 1997](#)). These prognostic groups are associated with a median survival of 5.7 years (low risk), 3.5 years (intermediate-1 risk), 1.2 years (intermediate-2 risk) and 0.4 years (high risk) ([Greenberg 1997](#)).

Clinical presentation focusing on thrombocytopenia

Clinical symptoms of patients with MDS are related to the occurring cytopenias (anaemia, neutropenia (decrease in white blood cells, specifically neutrophils), and thrombocytopenia (decrease in the number of blood platelets)) that arise from the ineffective haematopoiesis. Often patients present with symptoms of anaemia such as fatigue, asthenia and dyspnoea, accompanied by infections due to neutropenia and prolonged bleeding time or bleeding events because of thrombocytopenia ([Nimer 2008](#)).

In 2007 Kantarjian and colleagues performed a systematic review to summarise the available information regarding the incidence and impact of thrombocytopenia in patients with MDS. It demonstrated that thrombocytopenia (defined as platelet count < 100 x 10⁹/L) is a common clinical problem in MDS patients with a prevalence of 65% (range 23% to 93%) in untreated patients at baseline ([Kantarjian](#)

[2007](#)). An additional problem is the iatrogenically-induced thrombocytopenia through currently available therapeutics in the treatment of MDS such as hypomethylation agents (i.e. azacitidine, decitabine), or lenalidomide ([Kantarjian 2006](#); [List 2006a](#)). Randomised studies reported thrombocytopenia grade 3 or 4 in 70% to 74% of the patients receiving azacitidine ([Fenaux 2009](#); [Santini 2010](#)), 85% of the patients with decitabine ([Kantarjian 2006](#)) and 54.7% of the patients with lenalidomide ([List 2006a](#)).

The most important clinical complications caused by thrombocytopenia are bleeding events and death. The reported incidence of bleeding in MDS patients ranges from 3% to 53% ([Kantarjian 2007](#)). These bleeding complications might be less severe such as petechiae, gingival bleeding (bleeding from the gums) or haematoma, but can also be serious if gastrointestinal, intracranial, pulmonary or retinal haemorrhages occur ([Dayyani 2010](#); [Neukirchen 2009](#)). The frequency of haemorrhagic deaths in patients with MDS ranges from 14% to 24% ([Kantarjian 2007](#)).

Description of the intervention

General treatment approaches of MDS

Patients with clinically relevant cytopenia can be stratified into two major risk groups, the relatively lower-risk patients (IPSS: low risk, intermediate-1-risk) and the higher-risk patients (IPSS: high risk, intermediate-2-risk) ([Bowen 2003](#); [Greenberg 2011](#)). In lower-risk patients with MDS, supportive care, meaning red blood or platelet transfusion, antibiotics and hematopoietic growth factors, is the main treatment option, but the administration of additional treatment with hypomethylation agents or immunosuppressive therapy might be considered ([Fey 2010](#); [Gotze 2010](#); [Greenberg 2011](#); [Santini 2010](#)). Higher-risk patients with MDS should receive allogeneic stem cell transplantation (alloSCT), which is the only curative treatment for MDS patients. If they are not eligible for allogeneic stem cell transplantation (due to patient's age, performance status and presence of major comorbid conditions) or lacking an available donor, there are different recommended alternatives that include hypomethylation agents, other low-intensive chemotherapeutics and high-intensive chemotherapy regimens, with or without autologous stem cell transplantation ([Fey 2010](#); [Gotze 2010](#); [Greenberg 2011](#); [Santini 2010](#)).

Treatment options focusing on thrombocytopenia

In general, clinical practice guidelines recommend platelet transfusion to manage severe thrombocytopenia or thrombocytopenic bleeding ([Fey 2010](#); [Greenberg 2011](#); [Santini 2010](#)). Furthermore, aminocaproic acid or other antifibrinolytic agents may be considered for bleeding refractory to platelet transfusion or profound thrombocytopenia ([Greenberg 2011](#)).

Although platelet transfusions are effective to increase platelet counts, they are associated with a range of risks including transfusion-related fever, allergic reactions, infections with bacteria or viruses, pulmonary disease or alloimmunisation ([Kantarjian 2009](#); [McCullough 2000](#); [Melchert 2008](#)). Platelet alloimmunisation occurs when a patient has formed antibodies against donor platelets. It leads to refractoriness of platelet transfusion with a significantly lower platelet count after transfusion than expected. After multiple platelet transfusions 5% to 15% of the patients become refractory ([Rebulla 2005](#)).

Alternative treatment options to platelet transfusion are limited. Clinical studies evaluated different approaches including immunosuppressive agents such as cyclosporine (Sloand 2005) and antithymocyte globulin (Deeg 2004). Due to the limited efficacy of these agents, clinical practice guidelines mention immunosuppressive therapy as a treatment option only for patients with refractory severe thrombocytopenia (Fey 2010; Greenberg 2011). Currently, thrombopoietin mimetics (i.e. romiplostim and eltrombopag) are in the focus of clinical research.

How the intervention might work

Thrombopoietin is a glycoprotein, primarily synthesised by the liver and kidney. It is the major regulator of both megakaryocytopoiesis and thrombopoiesis. After binding to the thrombopoietin receptor (that is expressed at the pluripotential stem cells, early progenitor cells, the megakaryocyte colony-forming cells and early megakaryocyte progenitors) thrombopoietin launches a number of signal transduction processes that initiate cell proliferation, ramp up cell differentiation and stimulate an anti-apoptotic cascade (Kaushansky 2006; Kuter 2007).

Romiplostim

Romiplostim (synonym: AMG 53) is a thrombopoietin peptide mimetic that stimulates the megakaryocytopoiesis and generates increases in platelet counts by binding to the human thrombopoietin receptor (Kuter 2009; Stasi 2010). Romiplostim is available as a lyophilised, powdery agent and is usually dissolvable in sterile water. It is syringed subcutaneously once a week at doses of 1 µg/kg to 10 µg/kg (Kantarjian 2009; Sekeres 2011a). Single intravenous or subcutaneous injections in healthy people showed a dose-responsive platelet production with an apparently linear relationship between platelet response and dose and a peak platelet count on days 12 to 16 without clinically significant adverse events (Wang 2004).

Small non-randomised trials examining the administration of romiplostim in thrombocytopenic patients with lower-risk MDS have shown platelet responses (defined as eight consecutive weeks independent of platelet transfusions) in 46% to 57% of participants (Kantarjian 2009; Sekeres 2011a). However, treatment-related serious adverse events such as osteonecrosis, febrile neutropenia, thrombocytopenia and blast cell count increase were reported in five of 44 patients (11%) (Kantarjian 2009). Furthermore, the European Medicines Agency recommended the use of romiplostim for the treatment of patients with MDS only in clinical trials, because cases of transient increases in blast cell counts were observed and cases of MDS disease progression to AML were reported (EMA 2011). In addition, thromboembolic complications (i.e. portal vein thrombosis) have been reported in patients with chronic liver disease receiving romiplostim (AMGEN 2011).

Eltrombopag

Eltrombopag, a non-peptide mimetic, also activates the thrombopoietin receptor by binding to it (Kuter 2007; Stasi 2010). It is available as an orally administered drug, available as 25 mg, 50 mg or 75 mg tablets and should be taken daily and continuously on an empty stomach (Kuter 2007; Stasi 2010). In healthy volunteers receiving eltrombopag for 10 days at doses of 5 mg, 10 mg, 25 mg, 30 mg, 50 mg and 75 mg platelet counts increased in a dose-dependent manner. There were no differences in the incidence

or severity of adverse events between eltrombopag and placebo (Jenkins 2007).

So far, the effects of eltrombopag have only been researched on bone marrow mononuclear cells from patients with MDS and AML, healthy participants or laboratory animals in preclinical or phase I studies (Jenkins 2007). Ex vivo trials show that eltrombopag increases megakaryocytopoiesis in bone marrow mononuclear cells and does not influence the proliferation of malignant blasts. Adverse effects like headache, abdominal pain, sore throat and tiredness were not dose-related and did not differ among treatment groups (Jenkins 2007; Will 2009).

Romiplostim and eltrombopag, experiences from their use in chronic idiopathic thrombocytopenic purpura (ITP)

Thrombopoietin mimetics (i.e. romiplostim and eltrombopag) have been approved for clinical use by the US Food and Drug Administration (FDA) for the treatment of chronic idiopathic thrombocytopenic purpura (ITP) (Ikeda 2009). A Cochrane review investigating the use of romiplostim and eltrombopag for chronic ITP was published in 2011 by Zeng and colleagues (Zeng 2011). It included six trials with 808 patients (five studies compared thrombopoietin mimetics with placebo). Overall survival (OS) was not studied by these randomised controlled trials and despite significantly increased platelet response, there was no evidence to demonstrate that thrombopoietin mimetics compared to placebo or standard care improved significant bleeding events in chronic ITP. In summary, there is currently no evidence that supports the efficiency of these substances compared to placebo or other treatment options in patients with chronic ITP (Zeng 2011).

Why it is important to do this review

Thrombocytopenia is a common clinical problem in patients with MDS and alternative treatment options to platelet transfusion are limited. Thrombopoietin mimetics (i.e. romiplostim and eltrombopag) currently, are the focus of clinical research (e.g. Greenberg 2009; Kantarjian 2010a; Lyons 2009). They have been tested in MDS patients with thrombocytopenia and might be an effective treatment option for MDS patients (Jenkins 2007; Kantarjian 2009; Sekeres 2011a). Nevertheless, the evidence of clinical efficacy of romiplostim and eltrombopag has not been assessed systematically. It is still uncertain whether thrombopoietin (TPO) mimetics can induce a meaningful clinical benefit in patients with MDS. Furthermore, it remains unclear whether they influence the increase of blast cells leading to premature progression to AML (EMA 2011; Kantarjian 2009).

As far as we know at this stage one systematic review has been published, investigating safety and efficacy of thrombopoietin-receptor (TPO-R) agonists in MDS patients (Prisca 2014). We are aiming to obtain more evidence regarding the clinical benefit (overall survival (OS), progression-free survival (PFS), quality of life) and the therapy-related risks (treatment-related mortality, adverse events), by systematically analysing the reliability and validity of the data and by considering only randomised controlled trials for our review.

OBJECTIVES

To evaluate the efficacy and safety of thrombopoietin (TPO) mimetics for patients with myelodysplastic syndromes (MDS).

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised controlled trials as primary studies in this review and meta-analysis. We included both full-text and abstract publications. Randomisation is the best way to prevent systematic differences between baseline characteristics of participants between the two relevant intervention groups in terms of both known and unknown (or unmeasured) confounders (O'Connor 2011). We did not include cross-over studies or quasi-randomised trials.

Types of participants

Participants had to be diagnosed with MDS. We included studies concerning all risk groups, without gender, age or ethnicity restrictions. If trials consisted of patients with different haematological malignancies, we only used data from the MDS subgroup. If subgroup data for MDS patients were not provided after contacting the author of the trial, we excluded the trial if less than 80% of patients had MDS.

Types of interventions

We considered the following interventions:

- Experimental intervention: Thrombopoietin (TPO) mimetics
- Comparator intervention:
 - * Placebo or no treatment
 - * Another TPO mimetic

We considered the following comparisons:

- TPO mimetic versus placebo or no treatment in MDS patients with thrombocytopenia
- TPO mimetic 1 versus TPO mimetic 2 in MDS patients with thrombocytopenia
- TPO mimetic versus placebo or no treatment in patients with MDS (thrombocytopenia is not described as an inclusion criteria of the study)
- TPO mimetic 1 versus TPO mimetic 2 in patients with MDS (thrombocytopenia is not described as an inclusion criteria of the study)

We included trials comparing different dosages or time schedules of TPO mimetics.

We evaluated only the first comparison as we identified only trials randomising thrombocytopenic patients to TPO mimetics or placebo.

Additional chemotherapeutic treatment had to be equal in both arms except for the use of TPO mimetics.

Types of outcome measures

Primary outcomes

- Overall survival (OS), defined as the time interval from random treatment assignment/entry into the study to death from any cause or to last follow-up.
- Mortality during study

Secondary outcomes

We assessed the following secondary outcomes for all considered comparisons.

- Transformation to acute myeloid leukaemia (AML)
- Incidence of minor bleedings (analysed as incidence of bleeding events)
- Incidence of major bleedings (analysed as incidence of bleeding events)
- Transfusion requirement
- Health-related quality of life was summarised, if available and measured with reliable and valid instruments. In the case that different questionnaires were used, we reviewed the concept of measurement of these instruments to compare, and if possible meta-analyse, their content
- Adverse events (i.e. all adverse events of World Health Organization (WHO) grade III or IV; serious adverse events)
- Tumour control outcomes such as time to progression (e.g. progression-free survival (PFS) (defined as time from randomisation to first evidence of progressive disease or death), or similar outcomes)

We assessed the following secondary outcome only in trials that included thrombocytopenic patients with MDS.

- Platelet responses (we aimed to extract the increase of thrombocytes by at least 30,000/mm³ or transfusion independence)

We would have assessed the following secondary outcomes in trials that included patients with MDS (thrombocytopenia was not described as an inclusion criteria of the study), but did not identify any of these trials.

- Incidence of thrombocytopenia
- Duration of thrombocytopenia

Search methods for identification of studies

Electronic searches

We adapted search strategies from those suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). No language restriction was applied to reduce the language bias.

We searched the following databases of medical literature and started the search in 2000, as the intervention of interest (thrombopoietin mimetics) was mentioned the first time in 2000, in a trial in dogs (Case 2000):

- Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library 2017, Issue 7 (Appendix 1).
- MEDLINE (2000 to 01 August 2017) (Appendix 2)

Searching other resources

We searched the following conference proceedings from January 2000 to May 2017, if they were not included in CENTRAL.

- American Society of Hematology (ASH)
- American Society of Clinical Oncology (ASCO)
- European Hematology Association (EHA)

- European Society of Medical Oncology (ESMO)

We electronically searched in the database of ongoing trials up to 05 May 2017.

- ISRCTN: <http://www.isrctn.com>
- EU clinical trials register: <https://www.clinicaltrialsregister.eu/ctr-search/search>
- Clinicaltrials.gov: <https://clinicaltrials.gov/>

In addition, we looked for studies in reference lists of relevant publications and at the European Group for Bone and Marrow Transplantation (available at: <http://www.ebmt.org/>).

Data collection and analysis

Selection of studies

After the first review of all titles and abstracts of the identified studies from the above sources, two review authors independently

rejected all studies that were clearly ineligible. We assessed selected studies by using an eligibility form regarding study design and compliance with inclusion criteria. The forms contained the following questions.

- Was the study described as randomised?
- Were the participants previously untreated?
- Were the patients diagnosed with MDS?
- Were the patients in the intervention group treated with TPO mimetics?
- Were the patients in the control group treated with placebo or no treatment or with a TPO mimetic?

In case of doubt we included full-text analysis and discussed eligibility with both review authors to finalise a decision (preferably including studies rather than losing relevant data). According to PRISMA we used a flow diagram to show numbers of identified records, excluded articles and included studies ([Figure 1](#)) ([Moher 2009](#)).

Figure 1. Study flow diagram.

Data extraction and management

Two review authors (HD, NS) independently extracted data according to Chapter Seven of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b) by using a standardised data extraction form containing the following items.

- **General information:** Author, title, source, publication date, country, language, duplicate publications.
- **Quality assessments:** Sequence generation, allocation concealment, blinding (participants personnel outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias.
- **Study characteristics:** Trial design, aims, setting and dates, source of participants, inclusion/exclusion criteria, comparability of groups, subgroup analysis, statistical methods, power calculations, treatment cross-overs, compliance with assigned treatment, length of follow-up, time point of randomisation.
- **Participant characteristics:** Age; gender; number of participants recruited, allocated, evaluated; participants lost to follow-up; stage of disease; type of International Prognostic Scoring System (IPSS); type of MDS.
- **Interventions:** TPO mimetics (treatment and control arm), best supportive care (treatment and control arm).
- **Outcomes:** OS, mortality, transformation to AML, transfusion requirements, incidence of minor bleedings, incidence of major bleedings, adverse events (i.e. all adverse events of WHO grade III or IV; serious adverse events), health-related quality of life, platelet responses, tumour control outcomes such as time to progression (e.g. progression-free survival, event-free survival or disease-free survival), incidence of thrombocytopenia, duration of thrombocytopenia.

Assessment of risk of bias in included studies

To assess the methodological quality and the risk of bias we used a questionnaire according to the recommendations in Chapter Eight of the *Cochrane Handbook for Systematic Reviews of Interventions* for the following criteria (Higgins 2011c).

- Sequence generation
- Allocation concealment
- Blinding (participants, personnel, outcome assessors)
- Incomplete outcome data
- Selective outcome reporting
- Other sources of bias

The judgement of the review authors involved an answer for each criterion, based on a three-point scale (low risk of bias, high risk of bias or unclear) and a summary description.

Measures of treatment effect

For binary outcomes we calculated risk ratios (RR) with 95% confidence intervals (CIs) for each trial. We planned to calculate continuous outcomes as standardised mean difference (SMD), but no trial reported specific outcomes. For time-to-event outcomes we extracted the hazard ratio (HR) from published data according to Parmar 1998 and Tierney 2007.

Dealing with missing data

As suggested in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), there were many potential sources of missing data that had to be taken into account: at study level, at outcome level, at summary data level, at individual level and at study-level characteristics (e.g. for subgroups analysis). It was important to differentiate between "missing at random" and "not missing at random".

If data were assumed to be missing at random, we analysed only the available data (i.e. ignoring the missing data).

In the case data were assumed not to be missing at random, we imputed the missing data with replacement values, and treated these as if they were observed (e.g. last observation carried forward, imputing an assumed outcome such as assuming all were poor outcomes, imputing the mean, imputing based on predicted values from a regression analysis).

Assessment of heterogeneity

We assessed heterogeneity of treatment effects between trials by using a χ^2 test with a significance level at $P < 0.1$. We used the I^2 statistic to quantify possible heterogeneity ($30\% < I^2 < 75\%$: moderate heterogeneity, $75\% < I^2$: considerable heterogeneity) (Deeks 2011).

We accomplished subgroups by tests for interaction.

Assessment of reporting biases

As we did not conduct meta-analyses with at least 10 trials, we were not able to explore the potential publication bias by generating a funnel plot. In future updates we will test potential publication bias with a linear regression test and considering $P < 0.1$ as significant for this test (Sterne 2011).

Data synthesis

We performed analyses according to the recommendations of Chapter Nine of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We used aggregated data for analysis. For statistical analysis, we entered data into the Cochrane statistical package Review Manager (RevMan) 5. One review author entered data into the software and a second review author checked it for accuracy. As the trials were heterogenous in terms of clinical characteristics (e.g. concomitant medication), we performed meta-analyses using a random-effects model (e.g. the generic inverse variance method for survival data outcomes and Mantel-Haenszel method for dichotomous data outcomes). We used the fixed-effect model in terms of sensitivity analyses.

We created a 'Summary of findings' table on absolute risks with the help of GRADE. We summarised the evidence of mortality during study, transformation to AML, incidence of bleeding events, transfusion requirement, health-related quality of life, all adverse events, and serious adverse events in [Summary of findings for the main comparison](#).

Subgroup analysis and investigation of heterogeneity

We assessed heterogeneity of treatment effects between trials by using a χ^2 test with a significance level at $P < 0.1$. We used the I^2 statistic to quantify possible heterogeneity. We performed subgroup analyses on the following characteristics.

- Different types of TPO mimetics
- Different types of additional agents (e.g. no other additional agent versus other chemotherapeutics)
- Different types of MDS risk groups

Sensitivity analysis

We performed sensitivity analyses on the following characteristics.:

- Fixed-effect modelling versus random-effects modelling
- We performed sensitivity analysis regarding full-text publications versus abstract only publication

RESULTS

Description of studies

For study details please see: [Included studies](#); [Excluded studies](#)

Results of the search

We identified 679 potentially relevant references through database searches and handsearching. Of these, we excluded 653 at the initial stage of screening because they did not fulfil our predefined inclusion criteria. We checked the remaining 26 publications for detailed evaluation. Of these, we excluded nine publications. Finally, we included six eligible trials (in 17 publications) with 812 patients in this review. A total of 746 patients entered the meta-analysis, as 66 patients in the [Platzbecker 2015](#) trial were analysed with AML and therefore excluded in this review.

The overall number of trials screened, identified, selected, excluded and included was documented with reasons according to PRISMA flow diagram (see [Figure 1](#)).

Included studies

We included six trials ([Dickinson 2016](#); [Giagounidis 2014](#); [Greenberg 2013](#); [Kantarjian 2010](#); [Platzbecker 2015](#); [Wang 2012](#)) in this review. We extracted data from full-text publications for five trials ([Giagounidis 2014](#); [Greenberg 2013](#); [Kantarjian 2010](#); [Platzbecker 2015](#); [Wang 2012](#)), one trial was published as an abstract ([Dickinson 2016](#)). All studies were published in English. We included a total of 746 MDS patients who fulfilled our predefined criteria.

Details of the methods, participants, interventions and outcome measures of individual studies are summarised in [Characteristics of included studies](#).

Design

All studies were reported to be randomised, double-blind and placebo-controlled trials. Of all the included trials, four trials were two-armed randomised controlled trials ([Dickinson 2016](#); [Giagounidis 2014](#); [Greenberg 2013](#); [Platzbecker 2015](#)) and two trials were three-armed randomised controlled trials ([Kantarjian 2010](#); [Wang 2012](#)). With the exception of [Dickinson 2016](#), all trials were reported to be multicentre studies.

Sample size

Sample sizes ranged from 29 patients ([Greenberg 2013](#)) to 356 patients ([Dickinson 2016](#)).

Location

Three included trials were carried out in the USA ([Greenberg 2013](#); [Kantarjian 2010](#); [Wang 2012](#)) and the other three trials were performed by an international study group ([Dickinson 2016](#); [Giagounidis 2014](#); [Platzbecker 2015](#)).

Participants

We included a total of 746 male and female patients. Of these, 236 patients were randomised to romiplostim, 227 patients were randomised to eltrombopag and 283 patients were randomised to placebo. For all trials, patients from 18 years of age and older were enrolled. The median age of participants was 68 years (range 52 to 84) ([Greenberg 2013](#)), 70 years (range 24 to 89) ([Dickinson 2016](#)), 70 years (range 61 to 77) ([Giagounidis 2014](#)), 71 (range 56 to 86) ([Kantarjian 2010](#)), 71 years (range 40 to 91) in the placebo group and 73 years (range 29 to 88) in the eltrombopag group ([Platzbecker 2015](#)) and 74 years (range 39 to 90) ([Wang 2012](#)). Four trials included low- and intermediate-1 risk MDS patients ([Giagounidis 2014](#); [Greenberg 2013](#); [Kantarjian 2010](#); [Wang 2012](#)), one trial included intermediate-1, intermediate-2 and high-risk MDS patients ([Dickinson 2016](#)), and one trial included advanced MDS and AML patients ([Platzbecker 2015](#)). However, from this trial only patients diagnosed with MDS were included in the current review.

Interventions

Four trials analysed the thrombopoietin (TPO) mimetic romiplostim ([Giagounidis 2014](#); [Greenberg 2013](#); [Kantarjian 2010](#); [Wang 2012](#)). In two trials patients received the TPO mimetic eltrombopag ([Dickinson 2016](#); [Platzbecker 2015](#)). In two trials a dose of 750 µg romiplostim was evaluated versus placebo ([Giagounidis 2014](#); [Greenberg 2013](#)). Two trials assessed two different dose schedules (750 µg or 500 µg) of romiplostim and were analysed as three-armed trials with the different doses included as one arm versus placebo ([Kantarjian 2010](#); [Wang 2012](#)). In four trials, patients concurrently received the hypomethylating agents azacitidine ([Dickinson 2016](#); [Kantarjian 2010](#)) or decitabine ([Greenberg 2013](#)) or the immunomodulatory drug lenalidomide ([Wang 2012](#)). The duration of studies ranged from four 28-day cycles ([Dickinson 2016](#); [Greenberg 2013](#); [Kantarjian 2010](#); [Wang 2012](#)), six months ([Platzbecker 2015](#)) to > 58 weeks ([Giagounidis 2014](#)). No trial drew a comparison between two different kinds of TPO mimetics.

Primary outcome measure

We elaborated overall survival (OS) in two trials ([Giagounidis 2014](#); [Platzbecker 2015](#)), however as [Platzbecker 2015](#) did not report 95% confidence intervals (CIs), data could not be meta-analysed.

Due to absence of applicable data referring to OS we used "mortality during study" as a new primary outcome. This outcome was reported by all trials.

Secondary outcome measures

Transformation to AML was reported in five studies ([Giagounidis 2014](#); [Greenberg 2013](#); [Kantarjian 2010](#); [Platzbecker 2015](#); [Wang 2012](#)). Data with regard to minor and major bleeding events were summarised as incidence of bleeding events and reported by five trials as follows: all bleeding events ([Giagounidis 2014](#); [Greenberg 2013](#); [Kantarjian 2010](#); [Wang 2012](#)) and grade ≥ three haemorrhages ([Platzbecker 2015](#)). Four trials ([Giagounidis 2014](#);

Greenberg 2013; Kantarjian 2010; Wang 2012) assessed transfusion requirement. Progression-free survival (PFS) was assessed by Platzbecker 2015 as median PFS in weeks. Giagounidis 2014 reported PFS as AML-free survival. Five trials reported all adverse events (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012); $\geq$ grade 3 adverse events were reported by Greenberg 2013, Kantarjian 2010, Platzbecker 2015 and Wang 2012. Four trials published data regarding serious adverse events (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Wang 2012). As platelet response was only assessed in trials that included thrombocytopenic patients with MDS, only Platzbecker 2015 provided information regarding this outcome. No trial mentioned duration of thrombocytopenia or health-related quality of life.

Due to insufficient data or variable definition of the outcome, we only included mortality during the study, transformation to AML, transfusion requirement, incidence of bleeding events, all adverse events, adverse events $\geq$ grade 3, and serious adverse events in the meta-analysis.

Conflict of interest

All trials disclosed their conflict of interest and were supported by the pharmaceutical industry as follows.

- **Dickinson 2016:** All authors were either employee, consultant, participant in speakers' bureau or received funding or honoraria from GlaxoSmithKline, Celgene Corporation, Janssen-Cilag, Novartis, Astex, TEVA Pharmaceutical Industries, Pfizer or Roche
- **Giagounidis 2014:** All authors were either employee, consultant, equity owner, advisory committee member or received funding or honoraria from Amgen, Alexion, Bristol Myers Squibb, GlaxoSmithKline, Celgene, Roche, Janssen Cilag or Celgene Corp.
- **Greenberg 2013:** five of eight authors were either employee, spokesman, consultant, equity owner, advisory committee member or received funding from Novartis, Eisai, Genentech, Celgene or Amgen Inc..
- **Kantarjian 2010:** All authors were either employee, consultant or advisor of Amgen.
- **Platzbecker 2015:** 10 of 11 authors were either advisory board member, employee, consultant or received funding or honoraria from Amgen, GlaxoSmithKline, Novartis or were participants in speakers' bureau for Astellas Pharma, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Covidien, GlaxoSmithKline, Hospira, Leo Pharma and Novartis.

- **Wang 2012:** All authors were either employee, spokesman, consultant, equity owner or received funding or honoraria from GlaxoSmithKline, Johnson&Johnson, Celgene or Amgen Inc.

Excluded studies

A total of six studies (eight articles) were excluded after detailed evaluation of full-text publications. The main reasons for exclusion were:

- one review
- six publications of non-randomised controlled trials
- one study included patients with different haematological malignancies; data from the MDS subgroup were not reported

For information on excluded trials see [Characteristics of excluded studies](#), where reasons for the exclusion are listed.

Ongoing studies (one already completed awaiting final results)

Currently there are two ongoing trials.

NCT01440374 is a three-part (part 1: open-label, part 2: randomised, double-blind, part 3: extension) worldwide, multicentre study, also sponsored by GlaxoSmithKline. It started in September 2011 and finally included 162 patients. Participants with MDS or AML who have thrombocytopenia due to bone marrow insufficiency from their underlying disease or prior chemotherapy have been enrolled. In part 2 of this study; MDS patients were randomised to receive eltrombopag in comparison to placebo. Study completion date was September 2015, but no final results for MDS patients have been published, only data for AML and MDS patients together.

Oliva 2017 is a phase II, multicentre, prospective, placebo-controlled single-blind study. An interim report based on data of 90 patients has been reported, 174 patients will be included in this trial. Eligible participants receive eltrombopag in comparison to placebo; study completion is planned for 2019.

Detailed information regarding these trials is summarised under [Characteristics of ongoing studies](#).

Risk of bias in included studies

Overall the potential risk of bias of included trials is high. The judgement is graphically summarised in [Figure 2](#) and [Figure 3](#). For more information see risk of bias table of included trials in [Characteristics of included studies](#).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dickinson 2016	?	+	+	+	+	-	-
Giagounidis 2014	+	+	+	+	+	+	-
Greenberg 2013	+	+	+	+	+	+	-
Kantarjian 2010	+	+	+	+	+	+	-
Platzbecker 2015	+	+	+	+	+	-	+
Wang 2012	+	+	+	+	+	+	-

Allocation

Four trials (Giagounidis 2014; Greenberg 2013; Platzbecker 2015; Wang 2012) reported allocation concealment using an interactive voice response system (IVRS) for randomisation. We supposed that Kantarjian 2010 also used IVRS for randomisation as it is part A of the Greenberg 2013 trial. We judged allocation concealment for these trials as low risk. As Dickinson 2016 provided insufficient data according allocation we judged this study to have an unclear risk. For all included trials sequence generation was judged to be low risk.

Blinding

All trials reported to be double-blind, but provided insufficient information regarding this item. Nevertheless, we judged the risk of performance bias for these trials as low risk as we assume it was adequate.

Incomplete outcome data

There was no suggestion of incomplete outcome data in all trials. Therefore we judged low risk for all trials.

Selective reporting

Study protocols were available for all trials. All of the studies' pre-specified primary and secondary outcomes that are of interest in the review were reported by four trials (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Wang 2012); we judged risk of selective reporting as low for these trials. Dickinson 2016 was judged as high risk for selective reporting as fewer outcomes than the protocol-predefined outcomes have been published. We judged Platzbecker 2015 to be high risk as only a subgroup analysis for MDS patients was published as an abstract publication (this may have influenced the outcome of transformation to AML). More importantly, there has been no full report of the total MDS population.

Other potential sources of bias

Due to small sample sizes and imbalances in baseline characteristics (e.g. mismatch within arms regarding severity of the MDS disease, enrolment of patients with diverging baseline platelet counts, no individually-adjusted TPO-mimetic doses to bring platelets into a target range), we judged high risk in three trials (Greenberg 2013; Kantarjian 2010; Wang 2012). Giagounidis 2014 was discontinued earlier due to concerns regarding the potential for transient increases in blast cell counts and the risk for progression to or treatment for AML. Therefore, we also judged this trial to be at high risk. As the Dickinson 2016 trial was prematurely stopped, because outcomes crossed the predefined futility threshold and for safety reasons we also judged high risk of bias for this item. We did not identify other risk of bias for the Platzbecker 2015 trial, therefore we judge as low risk of potential bias.

All trials were funded by the pharmaceutical industry.

Effects of interventions

See: [Summary of findings for the main comparison Thrombopoietin mimetics compared to placebo for patients with myelodysplastic syndromes](#)

We did not identify any trial evaluating one thrombopoietin (TPO) mimetic versus another. The following results are for the comparison of one TPO mimetic versus placebo or in addition

to standard therapy compared to standard therapy only. All trials included thrombocytopenic patients, therefore all trials were analysed in one meta-analysis.

Primary outcome: Overall survival (OS)

Data of overall survival (OS) were available from Giagounidis 2014 and Platzbecker 2015 with a total of 282 (TPO mimetic/placebo: 185/97) patients. This outcome was defined as OS within a predefined period (Giagounidis 2014) and as OS in weeks (Platzbecker 2015).

In Giagounidis 2014, OS was assessed during the 58-week study period and included the time to follow-up for participants who discontinued the study drug earlier. There was no evidence for a difference between treatment groups with 18% of romiplostim patients dying and 20.5% of placebo patients (hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.48 to 1.56).

Platzbecker 2015 reported a median OS of 34 weeks for eltrombopag-treated patients in comparison to 15.4 weeks for placebo-treated. The HR was 0.70 without evidence for a difference ($P = 0.38$). As Platzbecker 2015 did not provide 95% CI, data could not be meta-analysed.

Subgroup and sensitivity analysis were not performed, because the identified studies were not meta-analysed.

Primary outcome: Mortality during study

All trials released information regarding mortality during study with a total of 746 (TPO mimetic/placebo: 433/313) patients.

With regards to mortality during study, there is little or no evidence for a difference in the pooled analysis (RR 0.97, 95% CI 0.73 to 1.27, $P = 0.80$; six trials, 746 patients; low-quality evidence; Analysis 1.1; Figure 4). The same is true for the subgroup analysis for different types of TPO mimetic, different types of additional agents and different types of MDS risk groups (Analysis 1.3; Analysis 1.4; Analysis 1.5). By comparing fixed-effect modelling (FE) versus random-effects modelling (RE) in the sensitivity analysis, there was also no evidence for a difference between both models (Analysis 1.2).

Figure 4. Forest plot of comparison: 1 Thrombopoietin mimetics versus placebo, outcome: 1.1 Mortality during study - all.

In the original analysis from June 2011, Giagounidis 2014 reported that 18% of patients in the romiplostim and 20.5% of patients in the placebo group died (HR 0.86, 95% CI 0.48 to 1.56). These data were used for the meta-analysis on mortality during the study. The trial was discontinued early, due to a potentially increased risk of

AML caused by romiplostim. We did not use the long-term follow-up data as the patients did not receive the study drug any longer during this period.

Greenberg 2013 documented the death of three patients. One death caused by neutropenic sepsis was considered to be related to the hypomethylating agent decitabine. Kantarjian 2010 mentioned two patients who died in the placebo group from fungal pneumonia and from endocarditis. Platzbecker 2015 provided information regarding five eltrombopag-treated and six placebo-treated patients dying on therapy or < 30 days from the last drug administration. There were 57 cases of death (32%) in the eltrombopag arm and 51 cases of death (29%) in the placebo arm in Dickinson 2016. Within 30 days after end of treatment, 33 events of death (19%) were reported in the eltrombopag group and 29 events of death (16%) were reported in the placebo group. More than 10% of all deaths were caused by diseases under study treatment and sepsis. In Wang 2012, one patient in the 750 µg romiplostim group died of intestinal obstruction in the extension period without any relation to romiplostim treatment.

Secondary outcome: Transformation to Acute myeloid leukaemia (AML)

Data regarding transformation to AML were available from five trials (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012) with a total of 390 (TPO mimetic/placebo: 254/136) patients.

There was no evidence for a difference concerning transformation to AML (RR 1.02, 95% CI 0.59 to 1.77, $P = 0.94$; five trials, 372 patients; very low-quality evidence; Analysis 1.7; Figure 5). There was no evidence for subgroup differences in the analyses of different types of TPO mimetics, different types of additional agents and different types of MDS risk groups (Analysis 1.9; Analysis 1.10; Analysis 1.11). By comparing fixed-effect modelling (FE) versus random-effects modelling (RE) in the sensitivity analysis, we could not identify any relevant difference between both models (Analysis 1.8).

Figure 5. Forest plot of comparison: 1 Thrombopoietin mimetics versus placebo, outcome: 1.7 Transformation to AML - all.

In 2011, Giagounidis 2014 detected a non-statistically significant increased risk of transformation to AML with HR 2.51, (95% CI 0.55 to 11.47, $P = 0.23$). Due to concerns of premature AML progression, these results led to early withdrawal of the study. However, two romiplostim-treated patients with increasing peripheral blast cell counts achieved treatment for AML without having a bone marrow puncture four weeks after discontinuation of romiplostim. These patients were counted as AML-progressed patients. In addition, in both arms there were more patients with RAEB-1/RAEB-2 (refractory anaemia with excess blasts) among those developing AML. Long-term follow-up analyses regarding this issue from 2011 were well balanced for both arms (HR 1.15, 95% CI 0.47 to 2.85). Updated follow-up results from 2012 again presented balanced numbers of AML-progression for both arms (HR 1.14, 95% CI 0.49 to 2.62). Finally, five-year long-term follow-up from December 2016 confirmed all previous follow-up data (HR 1.06, 95% CI 0.48 to 2.33) with 20 (11.9%) patients developing AML in the romiplostim arm and 9 (11.0%) patients developing AML in the placebo arm.

Secondary outcome: Incidence of bleeding events

We meta-analysed data of all reporting trials with a total of 390 patients (TPO mimetic/placebo: 254/136). Analysable data with regard to bleeding events were reported by five trials as follows: all number of bleeding events (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Wang 2012) and grade ≥ 3 bleeding events (Platzbecker 2015).

Comparing these trials, treatment with TPO mimetics resulted in a statistically significant lower incidence of all bleeding events compared to placebo (RR 0.92, 95% CI 0.86 to 0.98, $P = 0.02$; Analysis 1.12; five trials, 390 patients; moderate-quality evidence see Figure 6). There was no evidence for a difference for the subgroup analyses of different types of TPO mimetics, different types of additional agents, different MDS risk groups and grade ≥ 3 versus all bleeding events (Analysis 1.14; Analysis 1.15; Analysis 1.16; Analysis 1.17). Moreover, we could not identify any significant difference between fixed-effect model and random-effects model (Analysis 1.13).

Figure 6. Forest plot of comparison: 1 Thrombopoietin mimetics versus placebo, outcome: 1.12 Incidence of bleeding events - all.

Secondary outcome: Transfusion requirement

Four trials (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Wang 2012) with a total of 358 (TPO/placebo: 236/122) patients provided informations regarding transfusion requirement.

Regarding transfusion requirement, there was no evidence for a difference between patients treated with TPO mimetic or placebo (RR 0.83, 95% CI 0.66 to 1.05, P = 0.11; four trials, 358 patients; low-quality evidence; Analysis 1.18). There was no evidence for a difference in the subgroup analysis of different types of additional agents (Analysis 1.20) and no relevant difference between fixed-effect and random-effects model (Analysis 1.19).

Kantarjian 2010 reported a higher need of platelet transfusions in patients with intermediate-2 risk (86%) in comparison to patients with low- or intermediate-1 risk (38%) MDS. Unfortunately, due to missing data regarding different MDS risk groups, we had to we were unable to carry out this subgroup analysis. Subgroup analysis in terms of "different types of thrombopoietin mimetics" was also not performed, because the identified studies showed no differences or presented insufficient data regarding these study characteristics.

Secondary outcome: Health-related quality of life

No trial provided sufficient data to interpret health-related quality of life.

Secondary outcome: Duration of thrombocytopenia

None of the trials reported duration of thrombocytopenia.

Secondary outcome: All adverse events

Five trials with a total of 390 (TPO mimetic/placebo: 254/136) patients reported total number of patients affected by adverse events (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012).

Concerning this outcome, there was no evidence for a difference (RR 1.01, 95% CI 0.96 to 1.07, P = 0.67; five trials, 390 patients; moderate-quality evidence; Analysis 1.21). There was also no evidence for a difference in the subgroup analyses of different types of TPO mimetics, different types of additional agents and different MDS risk groups (Analysis 1.23; Analysis 1.24; Analysis 1.25) and in the sensitivity analysis (Analysis 1.22).

All adverse events reported in this trial are presented in Table 1.

Secondary outcome: Adverse events >= grade 3

Adverse events >= grade 3 were reported by five trials (Dickinson 2016; Giagounidis 2014; Kantarjian 2010; Platzbecker 2015; Wang 2012) with a total of 494 patients (TPO mimetic/placebo: 267/227). Four trials were meta-analysed regarding this outcome (Giagounidis 2014; Kantarjian 2010; Platzbecker 2015; Wang 2012).

The analysis of adverse events >= grade 3 showed no evidence for a difference (RR 0.98, 95% CI 0.74 to 1.31, P = 0.91; four trials, 138 patients; Analysis 1.26). All subgroup analyses and the sensitivity analysis confirmed this finding (Analysis 1.28; Analysis 1.29; Analysis 1.30; Analysis 1.27).

Dickinson 2016 reported 195 adverse events >= grade 3 in the eltrombopag arm and 137 adverse events >= grade 3 in the placebo arm. As in this trial the number of adverse event were counted, instead of the number of patients, this trial could not be added to the meta-analysis.

Secondary outcome: Serious adverse events

Four trials including 358 patients (thrombopoietin mimetic/placebo: 236/122) reported this outcome (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Wang 2012).

Regarding serious adverse events there was no evidence for a difference between arms (RR = 0.89, 95% CI 0.54 to 1.46, P = 0.64; four trial, 356 patients; very low-quality evidence; Analysis 1.31).

In the subgroup analysis of different types of additional agents Giagounidis 2014, the only trial solely treating with romiplostim monotherapy, showed a statistically significant advantage for the placebo arm (RR = 1.51, 95% CI 1.01 to 2.27, P = 0.04). Wang 2012, substituting a combination therapy of romiplostim and the immunomodulatory drug lenalidomide, showed a statistically significant advantage for the TPO arm (RR 0.48, 95% CI 0.24 to 0.98, P = 0.04). The test for differences between subgroups for different types of additional agents was statistically significant (P = 0.010) (Analysis 1.33). However, due to the very low number of patients included in the Wang 2012 trial, certainty in this effect estimate is very low.

Secondary outcome: Progression-free survival (PFS)start here

Two trials with a total of 282 patients (thrombopoietin mimetic/placebo: 185/97) reported this outcome. Progression-free survival (PFS) was reported as AML-free survival in two different ways: Giagounidis 2014 published data about patient numbers reaching this outcome. Platzbecker 2015 defined this outcome as time span

of weeks. Due to different outcome definitions this item did not undergo a meta-analysis.

At the time of study discontinuation in February 2011 [Giagounidis 2014](#) reported similar rates of AML-free survival between treatment arms (HR 0.86, 95% CI 0.49 to 1.51). 33 (19.8%) of the romiplostim-treated patients and 19 (22.9%) of placebo-treated patients had an AML-free survival. However, two romiplostim-treated patients with increasing peripheral blast cell counts achieved treatment for AML without having a bone marrow puncture four weeks after discontinuation of romiplostim. These patients were counted as AML-progressed patients. In addition, in both arms there were more patients with RAEB-1/RAEB-2 among those developing AML. Follow-up results in 2012 (data beyond 58 weeks) documented a HR of 1.11 (95% CI 0.72 to 1.70) with 66 (39.5%) of the romiplostim-treated patients and 32 (38.6%) of placebo-treated patients. In November 2013 updated follow-up results confirmed these results (HR 1.14, 95% CI 0.49 to 2.62). Final five-year long-term follow-up data from December 2016 again reinforced the non-impact of romiplostim on PFS (HR 1.04, 95% CI 0.73 to 1.48). Due to missing data regarding the P value we were not able to make a statement regarding statistical significance.

[Platzbecker 2015](#) presented a median PFS of 16.1 weeks for eltrombopag patients compared to 7.7 weeks for placebo patients with a HR of 0.61. With $P = 0.1531$ this result was not statistically significant.

Subgroup and sensitivity analysis were not performed, because the identified studies were not meta-analysed.

Secondary outcome: Platelet response

As mentioned in [Methods](#), this outcome was only assessed in trials that included thrombocytopenic patients with MDS. Only one trial with a total of 32 patients (TPO mimetic/placebo: 18/14) provided information regarding this outcome ([Platzbecker 2015](#)).

[Platzbecker 2015](#) defined this outcome as proportion of subject with baseline platelet count < 20 Gi/L and an increase to > 20 Gi/L and at least 2 x baseline or a baseline platelet count ≥ 20 Gi/L and an increase to ≥ 50 Gi/L and at least 2x baseline at any time during treatment with study medication.

Ten out of 34 (29%) placebo-treated patients and 18 out of 64 (28%) eltrombopag-treated patients showed a platelet response.

As these data included both, MDS and AML patients and unfortunately results solely for MDS patients were not reported, thus these findings could not be included.

Secondary outcome: Incidence of thrombocytopenia

As thrombocytopenia represents a common symptom for MDS patients and may also occur as a drug-induced side effect, we judged this outcome as meaningless and therefore did not analyse incidence of thrombocytopenia.

DISCUSSION

In the context of Myelodysplastic syndromes (MDS) disease, thrombocytopenia, due to illness or iatrogenically induced, represents a potential life-threatening condition. Thrombopoietin (TPO) mimetics like romiplostim or eltrombopag might represent a curative option to platelet transfusions, at present considered as

the common treatment of thrombocytopenia. Before using these agents outside of clinical trials, it is necessary to illustrate the role and impact of TPO mimetics in the treatment of MDS patients. For that reason we performed this systematic review.

Summary of main results

Our meta-analysis including six trials and 746 patients results in the following conclusions.

- No meta-analysis was performed for overall survival (OS), our primary outcome, as insufficient data were available.
- There is little or no evidence for a difference regarding our primary outcome of mortality during study and our secondary outcomes transformation to acute myeloid leukaemia (AML), transfusion requirement, all adverse events and $\geq$ grade 3 adverse events and serious adverse events.
- There is a statistically significance for subgroup differences for serious adverse events when comparing different types of additional agents. Serious adverse events occur more frequently in patients treated with romiplostim monotherapy in comparison to placebo. Serious adverse events were observed less frequently when TPO mimetics were combined with immunomodulatory agents. However, as the number of included patients in the trial giving immunomodulatory agents is very low, certainty of this result remains very low.
- Treatment with TPO mimetics results in a statistically significant lower incidence of bleeding events compared to placebo.
- Due to different outcome definitions progression-free survival (PFS) was not meta-analysed. Platelet response was not meta-analysed because no MDS-subgroup data were available.
- None of the trials reported health-related quality of life or duration of thrombocytopenia.

Overall completeness and applicability of evidence

Six studies, five published in full-text publications and one published as an abstract, addressed the use of TPO mimetics for MDS patients and included adult patients between 18 and 90 years of age with IPSS low-, intermediate-1, intermediate-2 risk or high-risk MDS. Except health-related quality of life and duration of thrombocytopenia, the included trials reported our previously specified protocol outcomes. OS and PFS were only reported in some trials, but could not be included in the meta-analysis, due to missing data and different outcome definition. The outcome "mortality during study" was analysed as an additional primary outcome.

Due to small sample sizes (e.g. [Greenberg 2013](#) $N = 29$; [Kantarjian 2010](#) $N = 40$; [Platzbecker 2015](#) $N = 32$; [Wang 2012](#) $N = 39$;) the included studies do not have adequate power to detect small differences. Moreover, a poor information content of these trials hampered the evaluation of differences in subgroup analyses and therefore a potential heterogeneity in detail. The trials provided sufficient informations in terms of therapy-related risks (e.g. transformation to AML, transfusion requirement, incidence of bleeding events), but adequate data on the clinical benefit (e.g. OS, AML-free survival, health-related quality of life) were lacking. Reported follow-up were short for some trials: four weeks ([Greenberg 2013](#); [Wang 2012](#)), six months ([Platzbecker 2015](#); [Kantarjian 2010](#)), 19 months ([Greenberg 2013](#)) and five years ([Giagounidis 2014](#)). Due to the premature study closure of two

studies (Dickinson 2016; Giagounidis 2014), overestimates are imaginable and publication bias might be present, but we have no evidence for this.

Currently, there is one ongoing study and one already completed trial, focusing on eltrombopag for patients with MDS. The ongoing study will be completed in 2019; the other trial was completed in 2015, but no results for MDS patients have been published yet. Both trials could help to shed light on the value of eltrombopag in the treatment of MDS patients, as this drug is under-represented in the meta-analysis.

Quality of the evidence

Overall, the potential risk of bias of the six included trials with 746 patients is high. All trials were reported to be randomised, double-blinded and placebo-controlled and all had a registered protocol. Five trials suggested using an interactive voice response system (IVRS) for random sequence generation. Although there was a lack of information regarding allocation concealment and blinding procedures, we did not expect any selection or performance bias. However, three trials were very small, baseline imbalances were reported for two trials. In addition, two studies were stopped prematurely, because outcomes crossed the predefined futility threshold or due to concerns regarding a transient increase in blast cell counts, and as a result the risk for a premature progression to AML. Less outcomes than protocol-predefined were published in one trial. In summary, this could lead to selection bias and other sources of bias. All trials were sponsored by the pharmaceutical industry. Furthermore, Amgen, the manufacturer of romiplostim, funded four included trials.

The quality of evidence for the outcomes number of bleeding events and adverse events is moderate due to high risk of bias and downgraded by one point (small sample sizes and imbalances in baseline characteristics in three trials, premature closure of two trials, selective reporting in one trial). The quality of evidence for the outcomes mortality during study (measured instead of OS) and transfusion requirements is low, due to imprecision through small number of events (downgraded one point) and high risk of bias (downgraded one point). It is very low for the outcomes transformation to AML and serious adverse events, because of very small number of events (downgraded two points), high risk of bias and heterogeneity between trials (downgraded one point). Quality of life was not reported in any of the included trials.

Potential biases in the review process

To avoid potential biases within the review, only randomised controlled trials were observed and the entire processing was edited by two review authors. All conference proceedings (ASH, ASCO, EHA, ESMO) and study registries were searched until May 2017. We expect, that all appropriate studies were identified, all essential data could be acquired and the processing of this meta-analysis did not introduce bias into this review.

As less than 10 trials were included in this meta-analysis, we were not able to evaluate publication bias and therefore did not generate a funnel plot. By searching all relevant databases and study registries (ISRCTN, EU clinical trials register, Clinicaltrials.gov), we identified one ongoing trial with an estimated completion date in 2019 and one which has already been completed (September 2015), but without publishing results for MDS patients. This may indicate

an unexciting result and hence a lack of incentive to publish, but we are awaiting further results of this trial soon.

Agreements and disagreements with other studies or reviews

Prisca 2014 and colleagues analysed the value of TPO mimetics compared to placebo in patients with MDS, Desborough 2016 and colleagues evaluated alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure. Both reviews included five trials for the comparison TPO mimetics versus placebo for MDS patients or patients with chronic bone marrow failure. We included the same trials, but due to our updated search strategy also the trial by Dickinson 2016 and colleagues. Our results are in line with these reviews, also less bleeding events and pointing out the unclear risk of potentially more patients with transformation to AML caused by these agents. As the focus of the Desborough 2016 review was on alternative agents to platelet transfusions, they assessed different outcomes and also included patients with AML. Moreover, the authors planned a network meta-analysis, which they were not able to perform, due to huge inconsistency between trials.

AUTHORS' CONCLUSIONS

Implications for practice

No study evaluated one thrombopoietin (TPO) mimetic versus another.

Six trials in adult patients evaluated one TPO mimetic versus placebo or in addition to standard therapy compared to standard therapy only. At this stage there is little or no evidence to provide, that TPO mimetics represent an effective therapeutical option for myelodysplastic syndrome (MDS) patients with thrombocytopenia in everyday practice. Due to the uncertainty, given the quality of the evidence at present, there is little or no evidence for a difference for a prolonged overall survival (OS) or a lower mortality rate when treated with TPO mimetics compared to placebo. Although this meta-analysis did not show statistically significant results that TPO mimetic treatment leads to premature AML-progression, this might be the case and requires further investigations. Compared to placebo-treated patients, less bleeding events occurred under therapy with TPO mimetics. The use of romiplostim or eltrombopag might reduce the requirement of platelet transfusion and therefore lower all, partly fatal transfusion-associated risks. There might be more serious adverse events when romiplostim is solely administered without any concomitant agents, whereas a combination of TPO mimetics and immunomodulatory agents e.g. lenalidomide seem to reduce the incidence of serious adverse events.

Implications for research

More studies with longer follow-up periods and a larger number of participants are needed to produce solid results and therefore determine the effect of TPO mimetics. We have to acquire more evidence in terms of the safety, efficacy and quality of life aspects of these agents. Especially the impact of TPO mimetics regarding the potential of influencing premature AML transformation should be further investigated, as AML progression represents a dreaded event for MDS patients. It is a fact that hypomethylating agents also cause haematologic improvement. Therefore, single-agent

trials focusing on TPO mimetics alone should be performed to explore the individual benefit of these agents regarding platelet response, bleeding events and transfusion requirements. As long as TPO mimetics are not proven to provide any benefit compared to placebo or no treatment only, head-to-head comparisons are not necessary.

ACKNOWLEDGEMENTS

We are grateful to the following people for their comments and improving the protocol and review.

Guido Schwarzer, Sue Richard, Mohamed Haendawi, Celine Fournier and the members of the Cochrane Haematological Malignancies Group Editorial Base. Moreover, we thank Heather Maxwell for copy-editing.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Dickinson 2016

Methods	<u>Randomisation</u> <ul style="list-style-type: none"> A phase 3, randomised, double-blind, placebo-controlled study with two arms: 1. arm: eltrombopag & azacitidine, 2. arm: placebo & azacitidine <u>Allocation ratio</u> <ul style="list-style-type: none"> 1:1 <u>Recruitment period</u> <ul style="list-style-type: none"> No information provided <u>Median follow-up time</u> <ul style="list-style-type: none"> No information provided
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> Age ≥ 18 years (for participants in Taiwan age > 20 years)

Dickinson 2016 (Continued)

- MDS by WHO or FAB-classification
- Intermediate-1, intermediate-2 or high-risk MDS by IPSS
- At least one platelet count < 75 Gi/L
- ECOG status 0-2
- Adequate baseline organ function defined by the criteria below: total bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN) except for Gilbert's syndrome or cases clearly not indicative or inadequate liver function (i.e. elevation of indirect [haemolytic] bilirubin in the absence of alanine aminotransferase [ALT] abnormality); ALT $\leq 2.5 \times$ ULN; creatinine $\leq 2.5 \times$ ULN
- Participants with a correct QT interval (QTc) < 450 msec or 480 msec for participants with bundle branch block. The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF), machine or manual overread. For participant eligibility and withdrawal, QTcF will be used. For purposes of data analysis, QTcF will be used. The QTc should be based on single or average QTc values of triplicate electrocardiograms (ECGs) obtained over a brief recording period.
- Participant is able to understand and comply with protocol requirements and instructions
- Participant has signed and dated informed consent
- Women must be either of non-child bearing potential, or women with child-bearing potential and men with reproductive potential must be willing to practice acceptable methods of birth control during the study
- Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days of first dose of study treatment and agree to use effective contraception during the study and for 3 months following the last dose of study treatment.
- Men with female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception from time of randomisation until 16 weeks after the last dose of study treatment.
- French participants: In France, a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

Exclusion criteria

- Previous treatment with hypomethylating agent or induction chemotherapy for MDS
- Proliferative type chronic myelomonocytic leukaemia with white blood cell count >12 Gi/L at any time during the 28 days before day 1
- History of treatment with eltrombopag, romiplostim or other thrombopoietin receptor (TPO-R) agonists
- Previous allogeneic stem-cell transplantation
- Known thrombophilic risk factors. Exception: participants for whom the potential benefits of participating in the study outweigh the potential risks of thromboembolic events, as determined by the investigator
- Treatment with an investigational drug within 30 days or 5 half-lives preceding the first dose of investigational product (eltrombopag/placebo)
- Active and uncontrolled infections, including hepatitis B or C
- Human Immunodeficiency Virus (HIV)
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to eltrombopag or its excipient, or azacitidine, that contraindicates the participant's participation
- Pregnant or lactating female
- Any serious and/or unstable pre-existing medical condition (including any advanced malignancy other than the disease under study), psychiatric disorders, or other conditions that could interfere with participant's safety, obtaining informed consent or compliance with the study procedures
- French participants: The French participant has participated in any study using an investigational drug during the previous 30 days

Patients recruited (n = 356)

- Eltrombopag: n = 179
- Placebo: n = 177

Median age, years

Dickinson 2016 (Continued)

Total: 70 years (range 24, 89)

IPSS score (eltrombopag / placebo / total)

- Intermediate-1: 64 / 61 / 125
- Intermediate-2: 77 / 83 / 160
- High risk: 38 / 33 / 71

Gender

- Both genders

Participating centres

- Worldwide

Interventions	<p><u>Arm 1</u></p> <ul style="list-style-type: none">• Eltrombopag: 200 mg/day (100 mg/day for East Asians), adjusted by 100 mg increments (50 mg for East Asians) to a maximum 300 mg/day (150 mg/day in East Asians) for as long as patients receive azacitidine• Azacitidine: 75 mg once daily for 7 days every 28 days for at least 6 cycles <p><u>Arm 2</u></p> <ul style="list-style-type: none">• Placebo: 200 mg/day (100 mg/day for East Asians), adjusted by 100 mg increments (50 mg for East Asians) to a maximum 300 mg/day (150 mg/day in East Asians) for as long as patients receive azacitidine• Azacitidine: 75 mg once daily for 7 days every 28 days for at least 6 cycles
Outcomes	<p><u>Outcomes and time-points reported</u></p> <ul style="list-style-type: none">• Overall survival• Adverse events
Notes	<ul style="list-style-type: none">• <u>Disclosures</u>: Dickinson: <i>GlaxoSmithKline</i>: Consultancy, research funding. Fenaux: <i>Celgene, Janssen, Novartis, Astex, Teva</i>: Research funding; <i>Celgene, Novartis, Teva</i>: Honoraria. Mittleman: <i>Celgene, Novartis, Janssen</i>. Speakers bureau; <i>Novartis, Pfizer, Janssen, Roche</i>: Consultancy. Portella: <i>Novartis</i>: Employment. Burgess: <i>Novartis</i>: Employment. Platzbecker: <i>Celgene Corporation</i>: Honoraria, Research funding; <i>TEVA Pharmaceutical Industries</i>: Honoraria, Research funding; <i>Amgen</i>: Honoraria, Research funding; <i>Janssen-Cilag</i>: Honoraria, Research funding; <i>Novartis</i>: Honoraria, Research funding.• The trial was registered with ClinicalTrials.gov (NCT02158936)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	<p><u>Quote</u>: "[...] patients [...] were randomised [...]".</p> <p><u>Comment</u>: The method of concealment was not reported, but we assume it was adequate.</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p><u>Quote</u>: "[...] a randomised, double blind, placebo-controlled trial [...]".</p> <p><u>Comment</u>: Unlikely that the blinding was broken</p>
Blinding of outcome assessment (detection bias)	Low risk	<p><u>Quote</u>: "[...] a randomised, double blind, placebo-controlled trial [...]".</p> <p><u>Comment</u>: Unlikely that the blinding was broken</p>

Dickinson 2016 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	<u>Comment:</u> No hint of incomplete outcome data
Selective reporting (reporting bias)	High risk	A study protocol is available (ClinicalTrials.gov: NCT02158936). Due to the premature study closure less outcomes (primary and secondary) than prespecified in the study protocol have been reported
Other bias	High risk	<ul style="list-style-type: none"> The trial was prematurely stopped, because outcomes crossed the predefined futility threshold and for safety reasons The study was funded by <i>GlaxoSmithKline, Teva, Celgene Corporation, Amgen, Novartis & Janssen-Cilag</i>.

Giagounidis 2014

Methods	<u>Randomisation</u> <ul style="list-style-type: none"> A randomised, multicentre, double-blind, placebo-controlled study with two arms: 1. arm: 750 µg romiplostim versus 2. arm: placebo <u>Allocation ratio</u> <ul style="list-style-type: none"> 2:1 <u>Recruitment period</u> <ul style="list-style-type: none"> No information provided <u>Median follow-up time</u> <ul style="list-style-type: none"> No information provided
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> Adults Both genders Patients diagnosed with MDS according to the World Health Organization (WHO) criteria International Prognostic Scoring System (IPSS) classification of low risk or intermediate-1 risk MDS Platelet counts of $\leq 20 \times 10^9/L$ or $\geq 20 \times 10^9/L$ with a history of bleeding <u>Exclusion criteria</u> <ul style="list-style-type: none"> Any MDS disease-modifying treatments or haematopoietic growth factors within 4 weeks of the study's start <u>Patients enrolled (n = 250)</u> <ul style="list-style-type: none"> Romiplostim 750 µg: n = 167 Placebo: n = 83 <u>Mean age, years</u> <ul style="list-style-type: none"> Romiplostim 750 µg: 71 years (range 62 to 77) Placebo: 69 years (range 61 to 76) Total: 70 years (range 61 to 77) <u>Gender, men (%)</u>

Giagounidis 2014 (Continued)

- Romiplostim 750 µg: 95 (56.9)
- Placebo: 53 (63.9)
- Total: 148 (59.2)

Ethnic group, Caucasians (%)

- Romiplostim 750 µg: 156 (93.4)
- Placebo: 79 (95.2)
- Total: 235 (94)
- No further informations about other ethnic groups provided

Median platelets, ($\times 10^9/L$)

- Romiplostim 750 µg: 19.7 (range 13.3 to 31.3)
- Placebo: 17.7 (range 11.0 to 28.7)
- total: 19.3 (range 12.5 to 30.3)

Median MDS duration, years

- Romiplostim 750 µg: 0.39 (range 0.13 to 1.74)
- Placebo: 0.58 (range 0.16 to 1.86)
- Total: 0.44 (range 0.13 to 1.74)

Subtypes of MDS, based on World Health Organization classification system (Romiplostim, placebo, total), (%)

- Refractory anaemia (RA): 6 (3.6), 5 (6), 11 (4.4)
- Refractory anaemia with ring sideroblasts (RARS): 2 (1.2), 0 (0), 2 (0.8)
- Refractory cytopenia with multilineage dysplasia (RCMD): 114 (68.3), 55 (66.3), 169 (67.6)
- Refractory anaemia with multilineage dysplasia & ring sideroblasts (RCMD-RS): 4 (2.4), 2 (2.4), 6 (2.4)
- Refractory anaemia with excess blasts (RAEB) -1: 24 (14.4), 9 (10.8), 33 (13.2)
- Refractory anaemia with excess blasts (RAEB) -2: 1 (0.6), 0 (0), 1 (0.4)
- Unclassified myelodysplastic syndrome (MDS-U): 16 (9.6), 12 (14.5), 28 (11.2)
- Del 5q: 0 (0), 0 (0), 0 (0)

International Prognostic Scoring System status, (romiplostim, placebo, total), (%)

- Low: 40 (24), 23 (27.7), 63 (25.2)
- Intermediate-1: 120 (71.9), 58 (70), 178 (71.2)
- Intermediate-2: 1 (0.6), 0 (0), 1 (0.4)
- Missing: 6 (3.6), 2 (2.4), 8 (3.2)

IPSS cytopenias (romiplostim, placebo, total), (%)

- 1: 63 (37.7), 31 (37.3), 94 (37.6)
- 2: 61 (36.5), 32 (38.6), 93 (37.2)
- 3: 43 (25.7), 20 (24.1), 63 (25.2)

IPSS cytogenetics (romiplostim, placebo, total), (%)

- Good: 131 (78.4), 63 (75.9), 194 (77.6)
- Intermediate: 26 (15.6), 18 (21.7), 44 (17.6)
- Poor: 4 (2.4), 0 (0), 4 (1.6)
- Unknown: 5 (3), 1 (1.2), 6 (2.4)
- Missing: 1 (0.6), 1 (1.2), 2 (0.8)

Prior MDS therapy (romiplostim, placebo, total), (%)

- No: 133 (79.6), 70 (84.3), 203 (81.2)

Giagounidis 2014 (Continued)

- Yes: 34 (20.4), 13 (15.7), 47 (18.8)

Participating centres

- 109 sites in the USA, Canada and Europe

Interventions

Arm 1

- 750 µg romiplostim, weekly, subcutaneous

Arm 2

- Volume matched placebo

Procedure

- The romiplostim dose could be adjusted in 250-µg increments (from 250 µg every other week to 1000 µg weekly) or volume-matched placebo on the basis of platelet counts. Doses were withheld when the platelet count was $> 450 \times 10^9/L$ and were reinitiated at a reduced dose when the platelet count was $< 200 \times 10^9/L$; if patients were receiving 250 µg, then the dose was re-initiated every other week. If the platelet count was $< 50 \times 10^9/L$ for the first 3 consecutive weeks, then the dose was increased to 1000 µg on the fourth week. Patients who had their dose reduced could increase to the next highest dose if their platelet count was $< 50 \times 10^9/L$ for 3 consecutive weeks.
- Supportive care, defined as not including treatments that affected platelet production, aggregation, activation, granulocyte-macrophage-colony-stimulating factors or any other investigational agents was allowed throughout the study.
- Due to concerns regarding the potential for transient increases in blast cell counts and the risk for progression to or treatment for AML, the study was discontinued prematurely in February 2011, but remained on study for follow-up.
- Patients could receive any standard-of-care MDS treatments. After completion of the 58-week study period or early discontinuation of study drug, patients entered LTFU.

Outcomes

Outcomes and time points reported

- Overall survival
- Mortality during study
- Transformation to AML
- Number of all bleeding events (analysed as incidence of bleeding events in this review)
- Transfusion requirement
- Platelet response
- Serious adverse events
- Adverse events $\geq$ grade 3

Notes

- Conflict of interest disclosures Dr. Giagounidis has served on advisory boards and as a speaker for Amgen and GlaxoSmithKline. Dr. Mufti has served as a consultant for and received research funding from Celgene. Dr. Fenaux has received honoraria and research funding from Amgen, Celgene, Janssen Roche, GlaxoSmithKline, and Novartis. Dr. Sekeres has served on advisory boards for Amgen and Celgene. Dr. Szer has been on advisory boards and received honoraria from Amgen, Celgene, Novartis and Alexion. Dr. Platzbecker has served as a consultant for Amgen, GlaxoSmithKline, Celgene, and Novartis. Dr. Kuendgen has received honoraria from Celgene. Dr. Gaidano has served on advisory boards for Amgen, Celgene, Roche, Onyx, GlaxoSmithKline, and Bristol Myers Squibb, and as a speaker for Amgen, Roche, and GlaxoSmithKline. Dr. Wiktor-Jedrzejczak has served as a consultant for Janssen-Cilag, Amgen, Novartis, Pfizer and Bayer; on advisory boards for Bristol Myers Squibb; and as a speaker for Celgene, Genzyme, Novartis, Genopharm, and Bristol Myers Squibb. Drs. Hu and Yang are employees of and stockholders in Amgen. Dr. Woodard is a former employee of and stockholder of Amgen. Dr. Kantarjian has received research grants from Amgen.
- The trial was registered with ClinicalTrials.gov (NCT00614523)

Risk of bias

Giagounidis 2014 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was facilitated throughout the interactive voice response system (IVRS) [...]".
Allocation concealment (selection bias)	Low risk	<u>Quote:</u> "[...] patients [...] were randomised [...]". <u>Comment:</u> The method of concealment was not reported, but we assume it was adequate.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<u>Quote:</u> "This phase 2, multicenter, randomised, double blind study [...]". <u>Comment:</u> Unlikely that the blinding was broken
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<u>Quote:</u> "This phase 2, multicenter, randomised, double blind study [...]". <u>Comment:</u> Unlikely that the blinding was broken
Incomplete outcome data (attrition bias) All outcomes	Low risk	<ul style="list-style-type: none"> Although there was a high rate of withdrawal due to premature discontinuation of the trial, all included patients were analysed as previously announced
Selective reporting (reporting bias)	Low risk	A study protocol is available (ClinicalTrials.gov: NCT00614523) and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way. No indication of selective reporting
Other bias	High risk	<ul style="list-style-type: none"> This trial was discontinued earlier due to concerns regarding the potential for transient increases in blast cell counts and the risk for progression to or treatment for AML The study was funded by <i>Amgen Inc.</i> Medical writing assistance, supported financially by <i>Amgen Inc.</i>, was provided by Susanna Mac of <i>Amgen Inc.</i>

Greenberg 2013

Methods	<u>Randomisation</u> <ul style="list-style-type: none"> A phase II, multicentre, randomised, double-blind, placebo-controlled study with 2 arms: 1. arm: 750 µg romiplostim plus decitabine versus 2. arm: placebo plus decitabine <u>Allocation ratio</u> <ul style="list-style-type: none"> 1:1 <u>Recruitment period</u> <ul style="list-style-type: none"> No information provided <u>Median follow-up time</u> <ul style="list-style-type: none"> No information provided
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> ≥18 years of age Both gender MDS diagnosed by bone marrow biopsy based on the World Health Organization (WHO) classification

Greenberg 2013 (Continued)

- IPSS low, intermediate-1 or intermediate-2 risk category MDS
- Decitabine treatment for at least four cycles
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
- Adequate liver and kidney function

Exclusion criteria

- Previous received > 3 cycles of decitabine or any hypomethylation agent within 30 days prior to screening
- Prior history of leukaemia, aplastic anaemia or history of bone marrow transplant
- Prior malignancy (other than *in situ* cervical cancer, controlled prostate cancer or basal cell skin cancer) unless disease-free for ≥ 3 years before randomisation
- Active or uncontrolled infection, uncontrolled cardiovascular disease, history of arterial thrombosis within 1 year of screening or venous thrombosis requiring anticoagulation therapy
- Receive of interleukin-11 or any experimental drug within 4 weeks of screening or any other thrombopoietic growth factor

Patients randomised (n = 29)

- Placebo: n = 14
- Romiplostim 750 μ g: n = 15

Mean age, years

- Placebo: 72 (range 52 to 84)
- Romiplostim 750 μ g: 68 (range 55 to 81)
- Total: 68 (range 52 to 84)

Sex, male participants, %

- Placebo: 79
- Romiplostim 750 μ g: 53
- Total: 66

Race, (placebo, romiplostim 750 μ g, total), %

- Caucasian: 64, 73, 69
- African Americans: 7, 7, 7
- Hispanic: 14, 20, 17
- Asian: 14, 0, 7

MDS diagnosis (placebo, romiplostim 750 μ g, total), %

- Refractory anaemia (RA): 7, 0, 3
- Refractory anaemia with ring sideroblasts (RARS): 0, 13, 7
- Refractory cytopenia with multilineage dysplasia (RCMD): 14, 20, 17
- Refractory cytopenia with multilineage dysplasia & ring sideroblasts (RCMD-RS): 0, 0, 0
- MDS with isolated del (5q): 0, 7, 3
- Refractory with excess blasts (RAEB) -1: 36, 40, 38
- Refractory with excess blasts (RAEB) -2: 29, 7, 17
- Unclassifiable myelodysplastic syndrome (MDS-U): 14, 13, 14

IPSS score (placebo, romiplostim 750 μ g, total), %

- Low: 7, 13, 10
- Intermediate-1: 21, 53, 38
- Intermediate-2: 71, 27, 48
- High: 0, 7, 4

Greenberg 2013 (Continued)

Cytogenetic abnormalities, (placebo, romiplostim 750 µg, total), %

- Normal: 29, 47, 38
- +8: 14, 0, 7
- +6: 0, 7, 3
- -Y: 7, 0, 3
- -5q: 0, 33, 17
- -7q: 14, 27, 21
- Abnl 20q: 0, 7, 3
- Complex: 21, 7, 14
- Other: 29, 7, 17

Bleeding in the past year, %

- Placebo: 29
- Romiplostim 750µg: 33
- Total: 31

History of any transfusions, (placebo, romiplostim 750 µg, total), %

- All: 71, 67, 69
- Packed RBCs: 71, 60, 66
- Platelets: 36, 20, 28

Baseline platelet counts, (placebo, romiplostim 750 µg, total), %

- $< 50 \times 10^9/L$: 50, 53, 52
- $\geq 50 \times 10^9/L$: 50, 47, 48

Participating centres

- Recruitment from 60 centres in the USA

Interventions
Arm 1

- Romiplostim: 750 µg subcutaneously once weekly beginning on the first day of decitabine administration
- Decitabine: according to the approved label (15 mg/m² intravenous over 3 h repeated every 8 h for 3 days every 6 weeks) or a 5-day dosing regimen (20 mg/m² intravenous over 1 h for 5 days every 4 weeks)

Arm 2

- Placebo: 750 µg subcutaneously once weekly beginning on the first day of decitabine administration
- Decitabine: according to the approved label (15 mg/m² intravenous over 3 h repeated every 8 h for 3 days every 6 weeks) or a 5-day dosing regimen (20 mg/m² intravenous over 1 h for 5 days every 4 weeks)

Concomitant medications for supportive care were allowed throughout the study except for medications affecting platelet production, rescue medication, including platelet transfusions, could be given to patients at immediate risk of bleeding

Romiplostim was to be withheld if a patient had a platelet count $> 450 \times 10^9/L$ and resumed once the platelet count fell to $< 200 \times 10^9/L$.

Outcomes
Outcomes and time points reported

- Clinically significant thrombocytopenic events (CSTE) (analysed as incidence of thrombocytopenia in this review)
- Transfusion requirement

Greenberg 2013 (Continued)

- Incidence of major bleedings
- Adverse events
- Transformation to AML

Notes

Study start date: April 2008

Study completed: October 2009

Potential conflict of interest available at www.informahealthcare.com/lal

The trial was registered with ClinicalTrials.gov (NCT00321711)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<u>Quote:</u> "Patients were [...] randomly assigned 1:1 to placebo and romiplostim with an interactive voice response system."
Allocation concealment (selection bias)	Low risk	<u>Quote:</u> "Patients were [...] randomly assigned 1:1 [...]" <u>Quote:</u> "Placebo and romiplostim were providing in identical glass vials."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<u>Quote:</u> "A phase II, multicenter, randomised, double-blind, placebo-controlled study with 2 arms" <u>Comment:</u> Unlikely that the blinding was broken
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<u>Quote:</u> "A phase II, multicenter, randomised, double-blind, placebo-controlled study with 2 arms" <u>Comment:</u> Unlikely that the blinding was broken
Incomplete outcome data (attrition bias) All outcomes	Low risk	<ul style="list-style-type: none"> • No hint of incomplete outcome data
Selective reporting (reporting bias)	Low risk	A study protocol is available (ClinicalTrials.gov: NCT00321711) and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way. No indication for selective reporting
Other bias	High risk	<ul style="list-style-type: none"> • Small sample sizes • <u>Quote:</u> "This study was funded by <i>Amgen, Inc.</i>, which designed the study, collected and helped analyse the data, and provided medical writing support. Publication decisions were made by the authors in conjunction with <i>Amgen, Inc.</i>" • <u>Quote:</u> "[...]. The placebo and romiplostim groups were imbalanced with respect to the severity of their MDS (71% of patients in the placebo group were in the International Prognostic Scoring System intermediate-2 category or above, compared with only 33% in the romiplostim group). As increases in platelet counts in patients receiving romiplostim do not appear to become evident until the third week of treatment, assessment of the percentage of patients who experienced a clinically serious thrombocytopenic events (CSTE) from day 15 of cycle 1 through the end of the study may have underestimated the benefit of romiplostim treatment. Further in this study, romiplostim doses were not adjusted individually to bring platelet counts into a target range. Therefore, the potential benefit of this treatment may not have been fully realized."

Kantarjian 2010

Methods	<p><u>Randomisation</u></p> <ul style="list-style-type: none"> A phase II, multicentre, randomised, double-blind, placebo-controlled study with 3 arms: 1. arm: 500 µg romiplostim plus azacitidine versus 2. arm: 750 µg romiplostim plus azacitidine versus 3. arm: placebo plus azacitidine <p><u>Allocation ratio</u></p> <ul style="list-style-type: none"> 1:1:1 <p><u>Recruitment period</u></p> <ul style="list-style-type: none"> No information provided <p><u>Median follow-up time</u></p> <ul style="list-style-type: none"> No information provided
Participants	<p><u>Inclusion criteria</u></p> <ul style="list-style-type: none"> ≥18 years of age Both genders MDS diagnosed by bone marrow biopsy based on the World Health Organization (WHO) classification IPSS low, intermediate-1 or intermediate-2 risk category MDS Azacitidine treatment for at least four cycles Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 Adequate liver function Serum creatinine ≤ 2 mg/dL <p><u>Exclusion criteria</u></p> <ul style="list-style-type: none"> Previous received >3 cycles of azacitidine or any hypomethylation agent within 30 days Prior history of leukaemia, aplastic anaemia or history of bone marrow transplant Prior malignancy unless treated with curative intent and without disease evidence for ≥3 years Active infection, uncontrolled cardiovascular disease, recent myocardial infarction or arterial thrombosis, history of venous thrombosis or current use of anticoagulation therapy Receiving of interleukin-11 or any experimental drug or device within 4 weeks of screening or previously receiving another thrombopoietic growth factor <p><u>Patients randomised (n = 40)</u></p> <ul style="list-style-type: none"> Romiplostim 500 µg: n = 13 Romiplostim 750 µg: n = 14 Placebo: n = 13 <p><u>Mean age, years</u></p> <ul style="list-style-type: none"> Romiplostim 500 µg: 72 (range 56 to 86) Romiplostim 750 µg: 72 (range 61 to 81) Placebo: 64 (range 58 to 86) Total: 71 (range 56 to 86) <p><u>Sex, female participants, n (%)</u></p> <ul style="list-style-type: none"> Romiplostim 500 µg: 3 (23) Romiplostim 750 µg: 7 (50) Placebo: 6 (46) Total: 16 (40)

Kantarjian 2010 (Continued)

ECOG PS (romiplostim 500 µg, romiplostim 750 µg, placebo, total), n (%)

- 0: 6 (46), 5 (36), 9 (69), 20 (50)
- 1: 7 (54), 9 (64), 4 (31), 20 (50)

MDS diagnosis (romiplostim 500 µg, romiplostim 750 µg, placebo, total), n (%)

- Refractory anaemia (RA): 3 (23), 0 (0), 2 (15), 5 (13)
- Refractory anaemia with ring sideroblasts (RARS): 1 (8), 0 (0), 2 (15), 3 (8)
- Refractory cytopenia with multilineage dysplasia (RCMD): 2 (15), 8 (57), 4 (31), 14 (35)
- Refractory cytopenia with multilineage dysplasia & ring sideroblasts (RCMD-RS): 0 (0), 0 (0), 1 (8), 1 (3)
- MDS with isolated del (5q): 0 (0), 2 (14), 0 (0), 2 (5)
- Refractory with excess blasts (RAEB) -1: 5 (39), 2 (14), 3 (23), 10 (25)
- Refractory with excess blasts (RAEB) -2: 1 (8), 1 (7), 0 (0), 2 (5)
- Unclassifiable myelodysplastic syndrome (MDS-U): 1 (8), 0 (0), 1 (8), 2 (5)

IPSS score (romiplostim 500 µg, romiplostim 750 µg, placebo, total), n (%)

- Low: 1 (8), 1 (7), 1 (8), 3 (8)
- Intermediate-1: 9 (69), 9 (64), 5 (38), 23 (58)
- Intermediate-2: 3 (23), 4 (29), 7 (54), 14 (35)

Median duration of MDS, wk (interquartile range)

- Romiplostim 500 µg: 35 (range 7, 109)
- Romiplostim 750 µg: 47 (range 5, 86)
- Placebo: 41 (range 24, 144)
- Total: 43 (range 7, 124)

Bleeding events in previous year, n (%)

- Romiplostim 500 µg: 4 (31)
- Romiplostim 750 µg: 5 (36)
- Placebo: 4 (31)
- Total: 13 (33)

History of transfusion, n (%)

- Romiplostim 500 µg: 9 (69)
- Romiplostim 750 µg: 11 (79)
- Placebo: 10 (77)
- Total: 30 (75)

Median baseline platelets, $<50 \times 10^9/L$ (range)

- Romiplostim 500 µg: 40 (7 to 296)
- Romiplostim 750 µg: 41 (5 to 160)
- Placebo: 25 (8 to 433)
- Total: 40 (5 to 433)

Baseline platelet counts, ($<50 \times 10^9/L$), n (%)

- Romiplostim 500 µg: 8 (62)
- Romiplostim 750 µg: 8 (57)
- Placebo: 8 (62)
- Total: 24 (60)

Participating centres

Kantarjian 2010 (Continued)

- Not reported

Interventions	<p><u>Arm 1</u></p> <ul style="list-style-type: none">• Romiplostim: 500 µg by weekly subcutaneous injections beginning on the first day of azacitidine administration• Azacitidine: 75 mg/m² subcutaneous daily for the first seven days of each 28-day cycle <p><u>Arm 2</u></p> <ul style="list-style-type: none">• Romiplostim: 750 µg by weekly subcutaneous injections beginning on the first day of azacitidine administration• Azacitidine: 75 mg/m² subcutaneous daily for the first seven days of each 28-day cycle <p><u>Arm 3</u></p> <ul style="list-style-type: none">• Placebo: by weekly subcutaneous injections beginning on the first day of azacitidine administration• Azacitidine: 75 mg/m² subcutaneous daily for the first seven days of each 28-day cycle <p>Study drug was withheld if platelet counts exceeded 450 x 10⁹/L and resumed at the next scheduled dosing day after platelet counts had decreased < 200 x 10⁹/L. Azacitidine was delayed in 1-week increments for adverse events. If platelet or neutrophil counts had not recovered by day 42 of a cycle a 50% lower dose was administered starting on day 42. When azacitidine was delayed, treatment with romiplostim or placebo was continued.</p> <p>Concomitant treatments deemed necessary to provide adequate supportive care, including growth factors, were allowed at the investigator’s discretion, except for myelosuppressive chemotherapy, histone deacetylase inhibitors, immunomodulating agents or other medications known or suspected of affecting platelet production. Rescue medication was administered only when patients were considered at immediate risk. Platelet transfusions were administered according to standard practice at each Institution with the American Society of Clinical Oncology guidelines provided to investigators as suggested criteria.</p>
Outcomes	<p><u>Outcomes and time points reported</u></p> <ul style="list-style-type: none">• Clinically significant thrombocytopenic events (CSTE) (analysed as incidence of thrombocytopenia in this review)• Transfusion requirement• Incidence of major bleedings• Adverse events• Transformation to AML
Notes	The trial was registered with ClinicalTrials.gov (NCT00321711)
<i>Risk of bias</i>	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	<p>Low risk</p> <p>No information provided</p> <p><u>Comment:</u> Probably done, since part B of this study described random sequences by using an interactive voice response system for randomisation</p>
Allocation concealment (selection bias)	<p>Low risk</p> <p><u>Quote:</u> "Eligible patients were [...] randomised 1:1:1 [...]".</p> <p><u>Comment:</u> The method of concealment was not reported, but we assume it was adequate, because part B of this study described allocation concealment by providing identical glass vials for placebo and romiplostim</p>

Kantarjian 2010 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	<u>Quote:</u> "A phase II, multicenter, randomised, double-blind, placebo-controlled study with 3 arm" <u>Comment:</u> Unlikely that the blinding was broken
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<u>Quote:</u> "A phase II, multicenter, randomised, double-blind, placebo-controlled study with 3 arm" <u>Comment:</u> Unlikely that the blinding was broken
Incomplete outcome data (attrition bias) All outcomes	Low risk	No hint of incomplete outcome data
Selective reporting (reporting bias)	Low risk	A study protocol is available (ClinicalTrials.gov: NCT00321711) and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way. No indication for selective reporting
Other bias	High risk	<ul style="list-style-type: none"> <u>Quote:</u> "This study has several limitations. First, the study had a relatively small sample size with only 13 to 14 patients per arm." Patients were stratified by baseline platelet counts in an effort to balance groups for CSTE risk, but the small sample size led to some imbalances in baseline characteristics. Notably a higher proportion of patients had intermediate-2 risk in the placebo group. This study was funded by <i>Amgen, Inc.</i>, which designed the study, collected and helped analyse the data, and provided medical writing support. Publication decisions were made by the authors in conjunction with <i>Amgen, Inc.</i>

Platzbecker 2015

Methods	<u>Randomisation</u> <ul style="list-style-type: none"> A phase I/II, randomised, placebo-controlled, double-blind study with two arms: 1. arm: eltrombopag versus 2. arm: placebo <u>Allocation ratio</u> <ul style="list-style-type: none"> 2:1 <u>Recruitment period</u> <ul style="list-style-type: none"> May 2009 - May 2013 <u>Median follow-up time</u> <ul style="list-style-type: none"> No information provided
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> 18 years and older Both gender Diagnosis of advanced MDS, sAML/MDS or de novo AML with $\geq 10\%$ and $\leq 50\%$ blasts in bone marrow Dependence on platelet transfusion or platelet counts < 30 Gi/L 4 weeks prior to randomisation Relapsed, refractory or ineligible to receive azacitidine, decitabine, intensive chemotherapy or autologous/allogeneic stem cell transplantation Priory therapy with demethylating agents (azacitidine or decitabine), lenalidomide or IL-11 (oprelvekin) must have been completed at least 4 weeks before day 1; antithymocyte/antilymphocyte

Platzbecker 2015 (Continued)

globulin, intensive chemotherapy or autologous/allogenic stem cell transplantation must have been completed at least 2 months before day 1

- Participants must have platelet count and platelet transfusion data available over a period of 4 weeks prior to randomisation
- Participants with advanced MDS, sAML/MDS or de novo AML must have stable disease indicated by a doubling time of peripheral blast counts > 7 days during screening
- During the 4 weeks prior to randomisation, participants must have a baseline bone marrow examination including cytomorphology to confirm bone marrow blasts between 10% to 50% and cytogenetics
- Supportive/palliative therapies such as cytokines (except for IL-11; oprelvekin), valproic acid, all-trans retinoic acid or mild chemotherapy are allowed if part of the local SOC, provided those therapies have been at a stable dose for 4 weeks. If the participant chosen to discontinue these therapies prior to study entry, they must be completed 4 weeks prior to enrolment into this study, unless the therapy is discontinued due to lack of efficacy. Erythropoiesis-stimulating agents (ESAs) in anaemic participants or granulocyte colony-stimulating factor (G-CSF) in participants with severe neutropenia and recurrent infections are allowed during the study as per accepted standards. Participants who entered the study on ESAs or G-CSF should continue at the same dose schedule until the optimal dose of study medication has been established
- Eastern Cooperative Oncology Group (ECOG) status 0-3
- Participant is able to understand and comply with protocol requirements and instructions and has signed and dated informed consent
- Prothrombin time (PT/INR) and activated partial thromboplastin time (aPTT) must be within 80% to 120% of the normal range at baseline
- Adequate baseline organ function (total bilirubin $\leq 1.5 \times$ ULN, ALT and AST $\leq 3 \times$ ULN, creatinine $\leq 2 \times$ ULN, albumin must not be below the lower limit of normal (LLN) by more than 20%)
- Participant is practicing an acceptable method of contraception, female participants (or female partners of male participants) must either be of non-childbearing potential (hysterectomy, bilateral oophorectomy, bilateral tubal ligation or post-menopausal > 1 year), or of childbearing potential and use 1 of the following highly effective methods of contraception (i.e. Pearl Index < 1.0%) from 2 weeks prior to administration of study medication, throughout the study, and 28 days after completion or premature discontinuation from the study: complete abstinence of intercourse, intrauterine device (IUD), two forms of barrier contraception (diaphragm plus spermicide and for males condom plus spermicide), sterile male partner and only partner of the female or systemic contraceptives

Exclusion criteria

- Participants with a diagnosis of acute promyelocytic leukaemia
- History of treatment of cancer (other than MDS, sAML/MDS or de novo AML) with systemic chemotherapy and/or radiotherapy within the last 2 years
- History of treatment with romiplostim or other TPO-R agonists
- Pre-existing cardiovascular disease (including congestive heart failure, New York Heart Association [NYHA] grade III/IV), arrhythmia known to increase the risk of thromboembolic events or participants with a QTc > 450 msec (QTc > 480 msec for participants with Bundle Branch Block)
- Bone marrow fibrosis that leads to an inability to aspirate marrow for assessment
- Spleen size > 14 cm
- Leukocytosis $\geq 25,000/\mu\text{L}$ prior to day 1 of study medication
- Female participants who are nursing or pregnant (positive serum or urine β -human chorionic gonadotropin [β -hCG] pregnancy test) at screening or pre-dose on day 1
- Current alcohol or drug abuse
- Treatment with an investigating drug within 30 days or 5 half-lives preceding the first dose of study medication
- Active and uncontrolled infections (e.g. sepsis), infections with Hepatitis B, C or HIV
- Participants with liver cirrhosis

Patients randomised (advanced MDS, sAML/MDS or de novo AML) (n = 98)

- Eltrombopag: n = 34
- Placebo: n = 64

Platzbecker 2015 (Continued)

Diagnosis with advanced MDS (n = 32)

- Eltrombopag: n = 18
- Placebo: n = 14

Mean age, years

- Eltrombopag: 73 (range 29 to 88)
- Placebo: 71 (range 40 to 91)

Sex, (female: male participants)

- Eltrombopag: 30 : 34
- Placebo: 9 : 25

Disease at baseline, WHO criteria, n (%), MDS; AML

- Eltrombopag: 15 (23); 48 (75)
- Placebo: 11 (32); 22 (65)

Median platelets (range), Gi/L

- Eltrombopag: 17.4 (2.71)
- Placebo: 12.3 (2.38)

Participating centres

- 37 centres in ten countries in Europe, East Asia and the Americas

Interventions	<div>Arm 1</div> <ul style="list-style-type: none">Eltrombopag: 50 mg daily initial dose, adjusted every 2 weeks based on platelet response up to a maximum of 300 mg once daily (150 mg for East Asian patients) for 6 months as an oral tablet <div>Arm 2</div> <ul style="list-style-type: none">Placebo
Outcomes	<div>Outcomes and time points reported</div> <ul style="list-style-type: none">Overall survivalTransfusion requirementIncidence of minor bleedingsIncidence of major bleedingsProgression-free survivalAdverse eventsPlatelet response
Notes	The trial was registered with ClinicalTrials.gov (NCT00903422)
Risk of bias	
Bias	Authors' judgementSupport for judgement
Random sequence generation (selection bias)	Low risk <div>Quote: "Patients were randomly assigned via a telephone-based interactive voice-response system (GlaxoSmithKline Registration and Medication Ordering System) with a permuted-block randomisation schedule (block size of three), [...]"</div>
Allocation concealment (selection bias)	Low risk <div>Quote: "[...] patients were randomised 2:1 [...]"</div>

Platzbecker 2015 (Continued)

		<u>Comment:</u> The method of concealment was not reported, but we assume it was adequate.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<u>Quote:</u> "A phase I/II, randomised, placebo-controlled, double-blind study with two arms" <u>Comment:</u> Unlikely that the blinding was broken
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<u>Quote:</u> "A phase I/II, randomised, placebo-controlled, double-blind study with two arms" <u>Comment:</u> Unlikely that the blinding was broken
Incomplete outcome data (attrition bias) All outcomes	Low risk	No hint of incomplete outcome data
Selective reporting (reporting bias)	High risk	<ul style="list-style-type: none"> • A study protocol is available (ClinicalTrials.gov: NCT00903422) • The trial included both MDS and AML patients. MDS patients were only reported in a abstract publication as a subgroup analysis and no information regarding the total population was provided
Other bias	Low risk	<u>Acknowledgement:</u> "The study was sponsored by <i>GlaxoSmithKline</i> ; eltrombopag is an asset of <i>Novartis AG</i> as of March 2, 2015. All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors. Editorial support (assembling tables and figures, collating author comments, copyediting, fact checking, and referencing) and graphic services were provided by AOI Communications, L.P. and were funded by <i>Novartis</i> ."

Wang 2012

Methods	<u>Randomisation</u> <ul style="list-style-type: none"> • A phase II, multicentre, randomised, double-blind, placebo-controlled study with three arms: 1. arm: 500 µg romiplostim versus 2. arm: 750 µg romiplostim versus 3. arm: placebo <u>Allocation ratio</u> <ul style="list-style-type: none"> • 1:1:1 <u>Recruitment period</u> <ul style="list-style-type: none"> • No information provided <u>Median follow-up time</u> <ul style="list-style-type: none"> • No information provided
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> • Diagnosis of MDS on the basis of the World Health Organization 2001 classification of bone marrow biopsy findings • Low, intermediate-1 or intermediate-2 risk category MDS using the International Prognostic Scoring System • Eastern Cooperative oncology Group (ECOG) performance status of 0-2 • Adequate liver and kidney function • Agreement to receive ≥ 4 cycles of lenalidomide capsules 10 mg by mouth daily

Wang 2012 (Continued)

Exclusion criteria

- Previous exposure to > 3 cycles of lenalidomide or exposure to lenalidomide within the last 30 days
- History of leukaemia, aplastic anaemia, stem cell transplantation or prior malignancy (other than in situ cervical cancer or basal cell cancer of the skin) unless treated with curative intent and without disease evidence for ≥ 3 years before randomisation
- Active or uncontrolled infection, uncontrolled cardiovascular disease, history of arterial or venous thrombosis within the past year
- Administration of interleukin-11 or any experimental drug or device within 4 weeks of screening or receipt of another thrombopoietic growth factor

Patients recruited (n = 39)

- Romiplostim 500 μg : n = 14
- Romiplostim 750 μg : n = 13
- Placebo: n = 12

Median age, years

- Romiplostim 500 μg : 75 years (range 49 to 90)
- Romiplostim 750 μg : 65 years (range 49 to 83)
- Placebo: 79 years (range 39 to 87)
- Total: 74 years (range 39 to 90)

Sex, male, n (%)

- Romiplostim 500 μg : 8 (57)
- Romiplostim 750 μg : 8 (62)
- Placebo: 8 (67)
- Total: 24 (62)

Subtypes of MDS, based on World Health Organization classification system,
(romiplostim 500 μg , romiplostim 750 μg , placebo, total) n (%)

- Refractory anaemia (RA): 0 (0), 0 (0), 1 (8), 1 (3)
- Refractory anaemia with ring sideroblasts (RARS): 2 (14), 2 (15), 2 (17), 6 (15)
- Refractory anaemia with multilineage dysplasia (RCMD): 4 (29), 4 (31), 4 (33), 12 (31)
- Refractory anaemia with multilineage dysplasia with ring sideroblasts (RCMD-RS): 0 (0), 1 (8), 0 (0), 1 (3)
- MDS- del (5q): 3 (21), 2 (15), 1 (8), 6 (15)
- Refractory anaemia with excess blasts (RAEB-1): 3 (21), 3 (23), 2 (17), 8 (21)
- Unclassified myelodysplastic syndrome (MDS-U): 1 (7), 1 (8), 1 (8), 3 (8)
- Unknown: 1 (7), 0 (0), 1 (8), 2 (5)

International Prognostic Scoring System (romiplostim 500 μg , romiplostim 750 μg , placebo, total) n (%)

- 0: 4 (29), 6 (46), 4 (33), 14 (36)
- 0.5: 6 (43), 4 (31), 3 (25), 13 (33)
- 1.0: 2 (14), 3 (23), 3 (25), 8 (21)
- 1.5: 1 (7), 0 (0), 1 (8), 2 (5)
- Unknown: 1 (7), 0 (0), 1 (8), 1 (8)

Baseline platelet counts (romiplostim 500 μg , romiplostim 750 μg , placebo, total) n (%)

- $<50 \times 10^9/\text{L}$: 5 (36), 5 (39), 5 (42), 15 (39)
- $\geq 50 \times 10^9/\text{L}$: 8 (57), 8 (62), 6 (50), 22 (56)
- Unknown: 8 (57), 8 (62), 6 (50), 2 (5)

Participating centres

Wang 2012 (Continued)

- Recruitment in 24 centres throughout the USA

Interventions	<p><u>Arm 1</u></p> <ul style="list-style-type: none"> Romiplostim: 500 µg subcutaneously each week for 16 weeks Lenalidomide: 10 mg capsule orally each day for four 28-day cycles for a planned total dose of 1120 mg <p><u>Arm 2</u></p> <ul style="list-style-type: none"> Romiplostim: 750 µg subcutaneously each week for 16 weeks Lenalidomide: 10 mg capsule orally each day for four 28-day cycles for a planned total dose of 1120 mg <p><u>Arm 3</u></p> <ul style="list-style-type: none"> Placebo: 500 µg or 750 µg subcutaneously each week for 16 weeks Lenalidomide: 10 mg capsule orally each day for four 28-day cycles for a planned total dose of 1120 mg <p>For all arms concomitant medications for supportive care were allowed throughout the study except: any medication known or suspected to affect platelet production, immunomodulatory agents, histone deacetylase inhibitors, cyclosporine, mycophenolate, any myelosuppressive chemotherapy other than lenalidomide and any other investigational product. For patients at immediate risk, rescue medication was given to increase platelet counts.</p>
Outcomes	<p><u>Outcomes and time- points reported</u></p> <ul style="list-style-type: none"> Transformation to AML Transfusion requirement Adverse events Incidence of minor bleeding Incidence of major bleeding Clinically significant thrombocytopenic events (CSTE) (analysed as incidence of thrombocytopenia in this review)
Notes	<p>Study start date: March 2007</p> <p>Study completed: March 2009</p> <p>The trial was registered with ClinicalTrials.gov (NCT00418665)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<u>Quote:</u> "Patients were assigned identification numbers from an interactive voice response system (IVRS) and randomly assigned [...]"
Allocation concealment (selection bias)	Low risk	<u>Quote:</u> "Patients were randomly assigned" <u>Comment:</u> The method of concealment was not reported, but we assume it was adequate.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<u>Quote:</u> "[...] and randomly assigned [...]" <u>Quote:</u> "During the double-blind portion of the study, investigational product was packaged in two identical vials for each scheduled dose for each patient."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<u>Quote:</u> "During the double-blind portion of the study, investigational product was packaged in two identical vials for each scheduled dose for each patient." <u>Comment:</u> Low risk that blinding has been broken

Wang 2012 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No hint of incomplete outcome data
Selective reporting (reporting bias)	Low risk	A study protocol is available (ClinicalTrials.gov:NCT00418665) and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way. No indication of selective reporting
Other bias	High risk	<ul style="list-style-type: none"> Quote: "Inferences drawn from the study are limited by the small sample size, enrolment of patients with variable degrees of baseline thrombocytopenia and imbalances in MDS disease characteristics between treatment groups." Quote: "Two patients randomised to the placebo group each erroneously received one dose of romiplostim during the treatment period. These patients are included in the placebo group of the efficacy analysis set and in the romiplostim group of the safety analysis set." Quote: "Acknowledgements: This study was sponsored by Amgen Inc., which provided funding, designed the study, collected and helped analyse the data and furnished medical writing support. Publication decisions were made by the authors in conjunction with Amgen Inc. Mary Royer, a paid consultant of Amgen Inc., and Susan Mac, an employee of Amgen Inc., assisted with the preparation of the manuscript. Competing interests: ESW served on an advisory board for Amgen Inc. in 2011 and received a consulting fee; RML has served as a consultant and on a speakers bureau for Amgen Inc. and has received honoraria and research funding from Amgen Inc.; RAL has received research support from Amgen; SG, DL and CM declare, that they have no competing interests. BS has served as a speaker and consultant for Celgene. KH and AY are employees and stockholders of Amgen Inc."

Abbreviations: AEs - adverse events; AML- acute myeloid leukaemia; ASH- American Society of Hematology; BM- bone marrow; CSBE- clinically significant bleeding events; CSTE- clinically significant thrombocytopenic events; DMC- Data Monitoring Committee; ECOG- Eastern Cooperative Oncology Group; IPSS- International Prognostic Scoring System; IVRS- interactive voice response system; LTFU- long-term follow-up; MDS- myelodysplastic syndromes; OS- overall survival; PBO- placebo; PFS- progression-free survival; TPO-R- thrombopoietin receptor; WHO- World Health Organization

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Fenaux 2011	Not a randomised trial
Mavroudi 2011	Review
Mittelman 2016	No data of MDS subgroup reported
Perez Ruixo 2013	Not a randomised trial
Rice 2006	Review
Sekeres 2011	Not a randomised trial

MDS - myelodysplastic syndrome

Characteristics of ongoing studies [ordered by study ID]

NCT01440374

Trial name or title	A three-part study of eltrombopag in thrombocytopenic patients with myelodysplastic syndromes or acute myeloid leukaemia (part 1: open-label, part 2: randomised, double-blind, part 3: extension)
Methods	<p><u>Randomisation</u></p> <ul style="list-style-type: none"> A phase II, multi-centre, randomised, double-blind, placebo-controlled study with two arms: 1. arm: 100 mg eltrombopag daily to a maximum of 300 mg versus 2. arm: 100 mg placebo daily to a maximum dose of 300 mg
Participants	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> 18 years and older Both gender Diagnosis of MDS or AML (bone marrow blasts $\leq$ 50%) with thrombocytopenia due to the bone marrow insufficiency from the disease or prior treatment Grade 4 thrombocytopenia (platelet counts $<$ 25 Gi/L) due to bone marrow insufficiency or platelet count $\geq$ 25 Gi/L due to platelet transfusion One of the following criteria during the 4-week screening period: platelet transfusion, symptomatic bleeding or platelet count $<$ 10 Gi/L Platelet count, bleeding and platelet transfusion data available over a period of 4 weeks prior to randomisation Prior systemic treatment for malignancy, with the exception of hydroxyurea, must have been discontinued prior to entry into the study: at least 4 weeks before day 1 of the following: chemotherapy, demethylating agents (azacitidine or decitabine), lenalidomide, thalidomide, clofarabine and IL-11 (oprelvekin); at least 8 weeks before day 1 for antithymocyte/antilymphocyte globulin Participants with a prior SCT must have relapsed after SCT Participants must have stable disease and must be expected to complete a 12-week treatment period Eastern Cooperative Oncology Group (ECOG) status 0-2 Participants must be able to understand and comply with protocol requirement and instructions and has signed and dated and informed consent form Adequate baseline organ function Participants must be willing to practice acceptable methods of birth-control during the study, women of childbearing potential must have a negative serum pregnancy test within 7 days prior to the first dose of study treatment In France, a participant will be eligible for inclusion in this study only if either affiliated to, or a beneficiary of, a social security category <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Participants with MDS and an International Prognostic Scoring System of low or intermediate-1 risk, acute promyelocytic or megakaryocytic leukaemia or AML secondary to a myeloproliferative neoplasm History of treatment with romiplostim or other thrombopoietin agonists Participants with a QTc $>$ 480 msec (QTc $>$ 510 msec for participants with Bundle Branch Block) at baseline Participants with a palpable spleen must have a splenic ultrasound to confirm spleen length is $\leq$ 16 cm, participants with a palpable spleen $>$ 16 cm are not eligible Leukocytosis $\geq$ 25.000/μL on day 1 of treatment with study medication Participants with known thrombophilic risk factors (exception: participants for whom the potential benefits of participating in the study outweighs the potential risks of thromboembolic events, as determined by the investigator) Female women who are nursing or pregnant (positive serum or urine β-human chorionic gonadotropin [β-hCG] pregnancy test) at screening or pre-dose on day 1 Current alcohol or drug abuse

NCT01440374 (Continued)

- Treatment with an investigating drug within 30 days or 5 half-lives preceding the first dose of study medication
- Active and uncontrolled infections (e.g. sepsis), infections with Hepatitis B, C or HIV
- Participants with liver cirrhosis
- Participants receiving or planned to receive any prohibited medication
- Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drug chemically related to eltrombopag
- In France, participants who have participated in any study using an investigational drug during the previous 30 days

Patients recruited

- Estimated enrolment: n = 150
- This study is currently recruiting participants

Participating centres

- Worldwide

Interventions	<p>Arm 1</p> <ul style="list-style-type: none"> • Eltrombopag: 100 mg daily (50 mg for participants of East Asian heritage), intra-participant dose escalation to a maximum dose of 300 mg (150 mg for participants of East Asian heritage) <p>Arm 2</p> <ul style="list-style-type: none"> • Placebo: 100 mg daily (50 mg for participants of East Asian heritage), intra-participant dose escalation to a maximum dose of 300 mg (150 mg for participants of East Asian heritage)
Outcomes	<p><u>Outcomes and time points from the registered protocol of the study that are considered in the review will report</u></p> <ul style="list-style-type: none"> • Incidence of thrombocytopenia • Platelet responses • Transfusion requirement • Tumour control outcomes such as time to progression (e.g. progression-free survival, event-free survival or disease-free survival) • Adverse events • Health-related quality of life • Incidence of minor bleedings • Incidence of major bleedings
Starting date	September 2011
Contact information	<p>Informations provided by GlaxoSmithKline</p> <p>Sponsors, collaborators and investigators by GlaxoSmithKline</p> <p>US GSK Clinical Call Center 877-379-3718</p> <p>GSKClinicalSupportHD@gsk.com</p>
Notes	<p>Estimated primary completion date: March 2013</p> <p>Completed: March 2015</p> <p>No final results published, no results on number of MDS patients provided</p>

Oliva 2017

Trial name or title	Eltrombopag for the treatment of thrombocytopenia due to low- and intermediate risk myelodysplastic syndromes
Methods	<p><u>Randomisation</u></p> <ul style="list-style-type: none"> A phase II, multicentre, prospective, randomised, placebo-controlled, single-blind study with two arms: 1. arm: Eltrombopag versus 2. arm: placebo <p><u>Allocation ratios</u></p> <ul style="list-style-type: none"> 2:1
Participants	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Adult participants (18 years of age or older) with low or intermediate-1 IPSS risk MDS and stable disease Participants must have a platelet count taken within the 4 weeks prior to randomisation that is < 30 Gi/L Participants must be ineligible or relapsed or refractory to receive other treatment options (such as azacitidine or lenalidomide) and must be ineligible to receive intensive chemotherapy or autologous/allogeneic stem cell transplantation Participants must have platelet count and platelet transfusion data available over a period of 8 weeks prior to randomisation During the 2 months prior to randomisation, participants must have a baseline bone marrow examination which includes cytomorphology and cytogenetics Histopathology should be performed Erythropoiesis-stimulating agents (ESAs) in anaemic participants or granulocyte colony stimulating factor (G-CSF) in participants with severe neutropenia and recurrent infections are allowed during the study as per accepted standards ECOG (Eastern Cooperative Oncology Group) performance status 0-3 Participant is able to understand and comply with protocol requirements and instructions Participant has signed and dated informed consent Adequate baseline organ function <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> MDS with intermediate-2 or high IPSS risk History of treatment for cancer other than MDS with systemic chemotherapy and/or radiotherapy within the last 2 years History of treatment with romiplostim or other thrombopoietin receptor agonists Pre-existing cardiovascular disease Active and uncontrolled infections Participants infected with hepatitis B, C or human immunodeficiency virus (HIV). <p><u>Patients recruited</u></p> <ul style="list-style-type: none"> Estimated enrolment: n = 174 This study is currently recruiting participants <p><u>Participating centres</u></p> <ul style="list-style-type: none"> Worldwide
Interventions	<p>Arm 1</p> <ul style="list-style-type: none"> Eltrombopag 50 mg once daily has been selected as the starting dose for this study. Thereafter, dependent on platelet response the dose of study medication can be increased by 50 mg every 2 weeks, up to a maximum dose of 300 mg once daily (150 mg in participants of East Asian ethnicity).

Oliva 2017 (Continued)

Arm 2

- Placebo

Outcomes	<p><u>Outcomes and time-points from the study that are considered in the review reported</u></p> <ul style="list-style-type: none"> • Overall survival • Transformation to AML • Transfusion requirement • Incidence of major bleedings • Progression-free survival • Adverse events • Health-related quality of life
Starting date	June.2011
Contact information	Esther Natalie Oliva, +39 3297978204, qolone@gmail.com
Notes	<p>Sponsor: Associazione Qol-one</p> <p>Estimated primary completion date: June 2011</p> <p>Estimated study completion date: June 2019</p> <p>Interim results for the first 90 patients have been reported in March 2017 but not been included in this analysis as the study is still ongoing</p>

AML - acute myeloid leukaemia; IPSS - International Prognostic Scoring System; MDS - myelodysplastic syndromes; SCT - stem cell transplantation

DATA AND ANALYSES

Comparison 1. Thrombopoietin mimetics versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality during study - all	6	746	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.73, 1.27]
2 Mortality during study - all (sensitivity analysis, FE model)	6	746	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.74, 1.23]
3 Mortality during study - different types of thrombopoietin mimetics	6	746	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.73, 1.27]
3.1 Romiplostim	4	358	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.33, 1.55]
3.2 Eltrombopag	2	388	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.73, 1.46]
4 Mortality during study - different types of additional agents	6	746	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.73, 1.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Thrombopoietin mimetic monotherapy	2	282	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.51, 1.30]
4.2 Plus hypomethylating agent	3	425	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.23, 2.19]
4.3 Plus immunomodulatory agent	1	39	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Mortality during study - different types of MDS risk groups	6	746	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.73, 1.27]
5.1 Low risk & intermediate-1 risk	4	358	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.33, 1.55]
5.2 Intermediate-2 risk and high risk	1	32	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.25, 1.69]
5.3 Mixed risk group	1	356	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.81, 1.52]
6 Mortality during study - full-text versus abstract publication	6	746	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.73, 1.27]
6.1 full-text publication	5	390	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.48, 1.20]
6.2 abstract publication Mixed risk group	1	356	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.81, 1.52]
7 Transformation to AML - all	5	372	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.59, 1.77]
8 Transformation to AML - all (sensitivity analysis, FE model)	5	372	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.59, 1.86]
9 Transformation to AML - different types of thrombopoietin mimetics	5	372	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.59, 1.77]
9.1 Romiplostim	4	358	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.55, 2.14]
9.2 Eltrombopag	1	14	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.37, 2.33]
10 Transformation to AML - different types of additional agents	5	372	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.59, 1.77]
10.1 Thrombopoietin mimetic monotherapy	2	264	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.58, 1.84]
10.2 Plus hypomethylating agent	2	69	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.17, 5.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3 Plus immunomodulatory agent	1	39	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Transformation to AML - different types of MDS risk groups	5	372	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.59, 1.77]
11.1 Low risk & intermediate-1 risk	4	358	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.55, 2.14]
11.2 Intermediate-2 risk and high risk	1	14	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.37, 2.33]
12 Incidence of bleeding events - all	5	390	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.98]
13 Incidence of bleeding events - all (sensitivity analysis, FE model)	5	390	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.84, 1.03]
14 Incidence of bleeding events - >= grade 3 versus all bleeding events	5	390	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.98]
14.1 All bleeding events	4	358	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.99]
14.2 >= grade 3 bleeding events	1	32	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.10, 2.69]
15 Incidence of bleeding events - different types of thrombopoietin mimetics	5	390	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.98]
15.1 Romiplostim	4	358	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.99]
15.2 Eltrombopag	1	32	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.10, 2.69]
16 Incidence of bleeding events - different types of additional agents	5	390	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.98]
16.1 Thrombopoietin mimetics monotherapy	2	282	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.98]
16.2 Plus hypomethylating agent	2	69	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.54, 1.53]
16.3 Plus immunomodulatory agent	1	39	Risk Ratio (M-H, Random, 95% CI)	3.56 [0.50, 25.36]
17 Incidence of bleeding events - different MDS risk groups	5	390	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.98]
17.1 Low risk & intermediate-1 risk	4	358	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.2 Intermediate-2 risk and high risk	1	32	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.10, 2.69]
18 Transfusion requirement - all	4	358	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.66, 1.05]
19 Transfusion requirement - all (sensitivity analysis, FE model)	4	358	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.67, 1.06]
20 Transfusion requirement - different types of additional agents	4	358	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.66, 1.05]
20.1 Thrombopoietin mimetics monotherapy	1	250	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.68, 1.18]
20.2 Plus hypomethylating agent	2	69	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.43, 1.05]
20.3 Plus immunomodulatory agent	1	39	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.33, 2.39]
21 All adverse events - all	5	390	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.96, 1.07]
22 All adverse events - all (sensitivity analysis, FE model)	5	390	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.94, 1.06]
23 All adverse events - different types of thrombopoietin mimetics	5	390	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.96, 1.07]
23.1 Romiplostim	4	358	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.96, 1.07]
23.2 Eltrombopag	1	32	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.85, 1.22]
24 All adverse events - different types of additional agents	5	390	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.96, 1.07]
24.1 Thrombopoietin mimetics monotherapy	2	282	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.96, 1.10]
24.2 Plus hypomethylating agent	2	69	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.92, 1.09]
24.3 Plus immunomodulatory agent	1	39	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.41, 1.26]
25 All adverse events - different MDS risk groups	5	390	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.96, 1.07]
25.1 Low risk & intermediate-1 risk	4	358	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.96, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.2 Intermediate-2 risk and high risk	1	32	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.85, 1.22]
26 Adverse events >= grade 3 - all	4	138	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.74, 1.31]
27 Adverse events >= grade 3 - all (sensitivity analysis, FE model)	4	138	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.72, 1.29]
28 Adverse events >= grade 3 - different types of thrombopoietin mimetics	4	138	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.74, 1.31]
28.1 Romiplostim	3	106	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.63, 1.25]
28.2 Eltrombopag	1	32	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.74, 2.16]
29 Adverse events >= grade 3 - different types of additional agents	4	138	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.74, 1.31]
29.1 Thrombopoietin mimetics monotherapy	1	32	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.74, 2.16]
29.2 Plus hypomethylating agent	2	69	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.27, 1.82]
29.3 Plus immunomodulatory agent	1	37	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.60, 1.73]
30 Adverse events >= grade 3 - different MDS risk groups	4	138	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.74, 1.31]
30.1 Low risk & intermediate-1 risk	3	106	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.63, 1.25]
30.2 Intermediate-2 risk and high risk	1	32	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.74, 2.16]
31 Serious adverse events - all	4	356	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.54, 1.46]
32 Serious adverse events - all (sensitivity analysis, FE model)	4	356	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.85, 1.45]
33 Serious adverse events - different types of additional agents	4	356	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.54, 1.46]
33.1 Thrombopoietin mimetics monotherapy	1	250	Risk Ratio (M-H, Random, 95% CI)	1.51 [1.01, 2.27]
33.2 Plus hypomethylating agent	2	69	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.57, 1.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
33.3 Plus immunomodulatory agent	1	37	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.24, 0.98]

Analysis 1.1. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 1 Mortality during study - all.

Analysis 1.2. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 2 Mortality during study - all (sensitivity analysis, FE model).

Analysis 1.3. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 3 Mortality during study - different types of thrombopoietin mimetics.

Analysis 1.4. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 4 Mortality during study - different types of additional agents.

Analysis 1.5. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 5 Mortality during study - different types of MDS risk groups.

Analysis 1.6. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 6 Mortality during study - full-text versus abstract publication.

Analysis 1.7. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 7 Transformation to AML - all.

Analysis 1.8. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 8 Transformation to AML - all (sensitivity analysis, FE model). **Analysis 1.9. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 9 Transformation to AML - different types of thrombopoietin mimetics.**

Analysis 1.10. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 10 Transformation to AML - different types of additional agents.

Analysis 1.11. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 11 Transformation to AML - different types of MDS risk groups.

Analysis 1.12. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 12 Incidence of bleeding events - all.

Analysis 1.13. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 13 Incidence of bleeding events - all (sensitivity analysis, FE model).

Analysis 1.14. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 14 Incidence of bleeding events - >= grade 3 versus all bleeding events.

Analysis 1.15. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 15 Incidence of bleeding events - different types of thrombopoietin mimetics.

Analysis 1.16. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 16 Incidence of bleeding events - different types of additional agents.

Analysis 1.17. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 17 Incidence of bleeding events - different MDS risk groups.

Analysis 1.18. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 18 Transfusion requirement - all.

Analysis 1.19. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 19 Transfusion requirement - all (sensitivity analysis, FE model).

Analysis 1.20. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 20 Transfusion requirement - different types of additional agents.

Analysis 1.21. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 21 All adverse events - all.

Analysis 1.22. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 22 All adverse events - all (sensitivity analysis, FE model).

Analysis 1.23. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 23 All adverse events - different types of thrombopoietin mimetics.

Analysis 1.24. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 24 All adverse events - different types of additional agents.

Analysis 1.25. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 25 All adverse events - different MDS risk groups.

Analysis 1.26. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 26 Adverse events $\geq$ grade 3 - all.

Analysis 1.27. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 27 Adverse events $\geq$ grade 3 - all (sensitivity analysis, FE model).

Analysis 1.28. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 28 Adverse events $\geq$ grade 3 - different types of thrombopoietin mimetics.

Analysis 1.29. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 29 Adverse events $\geq$ grade 3 - different types of additional agents.

Analysis 1.30. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 30 Adverse events $\geq$ grade 3 - different MDS risk groups.

Analysis 1.31. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 31 Serious adverse events - all.

Analysis 1.32. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 32 Serious adverse events - all (sensitivity analysis, FE model).

Analysis 1.33. Comparison 1 Thrombopoietin mimetics versus placebo, Outcome 33 Serious adverse events - different types of additional agents.

ADDITIONAL TABLES

Table 1. Adverse events

	Giagounidis 2014	Greenberg 2013	Kantarjian 2010	Platzbecker 2015	Wang 2012
Number of patients	Placebo = 83 TPO mim. = 167 (PBO / TPO)	Placebo = 14 TPO mim. = 15 (PBO / TPO)	Placebo = 13 TPO mim. = 27 (PBO / TPO)	Placebo = 14 TPO mim. = 18 (PBO / TPO)	Placebo = 9 TPO mim. = 28 (PBO / TPO)
Any AE	76 / 157 ²⁾	14 / 15	13 / 27	13 / 17	8 / 13
Grade 1 AE	n. r.	0 / 1	n. r.	n. r.	n. r.
Grade 2 AE	n. r.	3 / 4	n. r.	n. r.	n. r.
Grade 3 AE	n. r.	7 / 7	n. r.	n. r.	5 / 13
≥Grade 3 AE	n. r.	1 / 2	2 / 1	8 / 13 ⁹⁾	6 / 19
Grade 4 AE	n. r.	2 / 2	n. r.	n. r.	1 / 6
Grade 5 AE	n. r.	2 / 1	n. r.	n. r.	n. r.
Constipation	n. r.	n. r.	5 / 14	2 / 5	n. r.
Fatigue	n. r.	n. r.	5 / 7	3 / 3	1 / 13
Dizziness	n. r.	n. r.	1 / 6	n. r.	n. r.

Table 1. Adverse events (Continued)

Headache	n. r.	n. r.	n. r.	2 / 2	n. r.
Pyrexia	n. r.	n. r.	n. r.	6 / 5	n. r.
Hypotension	n. r.	n. r.	1 / 7	n. r.	n. r.
Dyspnoea	n. r.	n. r.	6 / 6	n. r.	n. r.
Cough	n. r.	n. r.	n. r.	n. r.	n. r.
Peripheral oedema	n. r.	n. r.	4 / 6	3 / 4	n. r.
Contusion	n. r.	n. r.	3 / 7	n. r.	n. r.
Moderate thrombocytopenia	n. r.	n. r.	4 / 2	n. r.	3 / 10
Diarrhoea	n. r.	n. r.	1 / 10	1 / 6	5 / 10
Rash	n. r.	n. r.	2 / 6	n. r.	2 / 10
Rash & hypersensitivity	n. r.	n. r.	0 / 1	n. r.	n. r.
Nausea	n. r.	n. r.	7 / 11	1 / 3	0 / 9
Vomiting	n. r.	n. r.	n. r.	n. r.	n. r.
Decreased appetite	n. r.	n. r.	n. r.	3 / 3	n. r.
Asthenia	n. r.	n. r.	n. r.	n. r.	n. r.
Anorexia	n. r.	n. r.	0 / 6	n. r.	n. r.
Pain in extremity	n. r.	n. r.	1 / 7	n. r.	n. r.
IP-related adverse event	n. r.	3 / 5	4 / 14 ⁶⁾	6 / 10	2 / 13
Serious AE	22 / 67 ¹⁾	8 / 8	10 / 16	n. r.	6 / 9 ¹²⁾
Serious thrombocytopenia	n. r.	n. r.	n. r.	n. r.	0 / 4
Anaemia	n. r.	n. r.	3 / 5	2 / 4	0 / 3
Back pain	n. r.	n. r.	n. r.	n. r.	0 / 2
Bleeding events	80 / 148	6 / 4	7 / 15	3 / 2	1 / 8
≥ Grade 3 bleeding events	n. r.	n. r.	2 / 1	3 / 2	n. r.
Pulmonary haemorrhage	n. r.	n. r.	1 / 0	n. r.	n. r.
Haematoma	n. r.	n. r.	1 / 0	1 / 4	n. r.
Epistaxis	n. r.	n. r.	0 / 1	4 / 4	n. r.
Neutropenia	n. r.	n. r.	4 / 5	n. r.	n. r.

Table 1. Adverse events (Continued)

Febrile neutropenia	n. r.	n. r.	6 / 3	4 / 1	0 / 2
Myelofibrosis	3)	n. r.	1 / 0	n. r.	n. r.
Erythema nodosum	n. r.	n. r.	1 / 0	n. r.	n. r.
Hypokalemia	n. r.	n. r.	n. r.	n. r.	n. r.
Hyperkalemia	n. r.	n. r.	n. r.	n. r.	0 / 2
IP-related SAE	n. r.	0 / 1	2 / 2 ⁷⁾	n. r.	1 / 1
Cerebrovascular accident	n. r.	1 / 0	n. r.	n. r.	1 / 0
Endocarditis	n. r.	n. r.	1 / 0	n. r.	n. r.
Worsening thrombocytopenia	n. r.	n. r.	n. r.	n. r.	0 / 1
Pulmonary artery thrombosis	n. r.	0 / 1 ⁴⁾	n. r.	n. r.	n. r.
Infection	n. r.	n. r.	n. r.	3 / 1	n. r.
Pneumonia	n. r.	n. r.	n. r.	2 / 2	n. r.
Fungal pneumonia	n. r.	n. r.	1 / 0	n. r.	n. r.
Neutropenic sepsis	n. r.	1 / 0	n. r.	n. r.	n. r.
Sepsis	n. r.	0 / 1	n. r.	2 / 2	n. r.
Deaths	5 / 8	2 / 1 ⁵⁾	2 / 0 ⁸⁾	6 / 5	0 / 1 ¹⁰⁾
AE leading to withdrawal or IP discontinuation	4 / 20	4 / 2	3 / 3	4 / 5	3 / 3 ¹¹⁾

Legend: **AE** adverse event; **IP** investigational product; **n. r.** not reported

¹⁾Serious AE related to romiplostim: 12 patients (increased myeloblast count, colon cancer, deep vein thrombosis, extramedullary haemopoiesis, leukocytosis, myelofibrosis, pneumonia, pyrexia, splenic infarction, transient ischaemic attack, type 2 diabetes mellitus)

²⁾Adverse event in both study arms: Epistaxis, hematoma, petechiae

³⁾Two romiplostim-treated patients had myelofibrosis. One patient had disease progression and was reported to have grade 3 bone marrow fibrosis on day 35 of treatment. This event was reported being related to romiplostim. The second patient had a history of myelofibrosis and progressed to grade 2 bone marrow fibrosis on day 71 and grade 3 bone marrow fibrosis on day 99 of treatment. None of these event were considered related to romiplostim treatment.

⁴⁾One patient (7%) in the romiplostim group; pulmonary artery thrombosis was reported as treatment-related serious adverse event

⁵⁾Three deaths occurred during treatment period. None was considered related to treatment, although neutropenic sepsis was considered related to decitabine. No deaths occurred during extension period. One death was reported in the romiplostim group who died from cholecystitis ≥ 30 days after last dose of romiplostim

⁶⁾All treatment-related adverse events were grade 1 or 2, except for grade 3 arthralgia in one patient in the romiplostim 500 μ g group and one patient with grade 3 rash in the 750 μ g group.

⁷⁾Three patients had treatment-related serious adverse events, two in the placebo group (myelofibrosis and erythema nodosum) and one patient with grade 3 rash in the romiplostim 750 μ g group.

⁸⁾One patient died from fungal pneumonia and one from endocarditis.

⁹⁾The most common $\geq$ grade 3 AE in the eltrombopag vs PBO groups were: febrile neutropenia (6% / 29%), anaemia (11% / 14%), pneumonia (11% / 14%) and sepsis (11% / 14%).

10) One patient in the 750µg romiplostim group died during the extension period from intestinal obstruction, which was not considered related to romiplostim.

11) Adverse events leading to study withdrawal were pancytopenia, asthenia, and cerebrovascular accident in the placebo group; pancytopenia and rash in the romiplostim 500µg group; and thrombocytopenia in the 750µg group. Only cerebrovascular accident in the placebo group was considered related to IP.

12) Only two serious AE were considered related to treatment: Cerebrovascular accident in one patient in the placebo group and worsening thrombocytopenia in one patient in the romiplostim 500µg group.

APPENDICES

Appendix 1. CENTRAL search strategy

ID	Search
#1	MeSH descriptor Myelodysplastic Syndromes explode all trees
#2	(myeloplasti* or myelodysplasti* or dysmyelopoietic* or myelodysplas*)
#3	myelodysplasi*
#4	mds
#5	MeSH descriptor Preleukemia explode all trees
#6	(preleukam* or preleukaem*)
#7	MeSH descriptor Anemia, Refractory explode all trees
#8	(refrakta* NEAR/3 anem*) or (refrakta* NEAR/3 anaem*) or (refract* NEAR/3 anem*) or (refract* NEAR/3 anaem*)
#9	(refractor* NEAR/3 cytopen*) or (refractor* NEAR/3 zytopen*) or (refrakt* NEAR/3 cytopen*) or (refrakt* NEAR/3 zytopen*)
#10	raeb*
#11	rars*
#12	MeSH descriptor Anemia, Refractory, with Excess of Blasts explode all trees
#13	(smo*ldering* or smoldering*)
#14	raem*
#15	MeSH descriptor Anemia, Sideroblastic explode all trees
#16	(sideroblasti* NEAR/3 (anem* or anaem*))
#17	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18	MeSH descriptor Thrombopoiesis explode all trees
#19	thrombopoie*

(Continued)

#20	thrombocytopoie*
#21	megakaryocytopoies*
#22	megakaryocyte*
#23	MeSH descriptor Megakaryocytes explode all trees
#24	MeSH descriptor Receptors, Thrombopoietin explode all trees
#25	eltrombopag*
#26	(romiplostin* or romiplostim*)
#27	(amg531 or amg 531 or amg-531)
#28	(sb497115 or sb 497115 or sb-497115)
#29	(fab59 or fab 59 or fab-59)
#30	(AKR501 or AKR 501 or AKR-501)
#31	(YM477 or YM 477 or YM-477)
#32	Peg-TPOmp*
#33	Promacta*
#34	TPO*
#35	(thrombopoie* and agent*)
#36	(#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35)
#37	(#17 AND #36)
#38	#37 in Trials

Appendix 2. MEDLINE search strategy

#	Searches
1	exp MYELODYSPLASTIC SYNDROMES/
2	(myeloplasti\$ or myelodysplasti\$ or dysmyelopoietic\$ or mielodispl?sic\$).tw,kf,ot.
3	myelodysplasi\$.tw,kf,ot.

(Continued)

4	mds.tw,kf,ot.
5	PRELEUKEMIA/
6	preleuka?m\$.tw,kf,ot.
7	exp ANEMIA, REFRACTORY/
8	((refrakta?r\$ or refrakt\$) adj3 (anem\$ or anaem\$)).tw,kf,ot.
9	((refractor\$ or refrakt\$) adj3 (cytopen\$ or zytopen\$)).tw,kf,ot.
10	raeb\$.tw,kf,ot.
11	rars\$.tw,kf,ot.
12	"ANEMIA, REFRACTORY, WITH EXCESS OF BLASTS"/
13	((smo?ldering\$ or smoldering\$) adj3 leuka?m\$).tw,kf,ot.
14	raem\$.tw,kf,ot.
15	exp Anemia, Sideroblastic/
16	(sideroblasti\$ adj3 (anem\$ or anaem\$)).tw,kf,ot.
17	or/1-16
18	THROMBOPOIESIS/
19	thrombopoie\$.tw,kf,ot.
20	thrombocytopoie\$.tw,kf,ot.
21	megakaryocytopoies\$.tw,kf,ot.
22	megakaryocyte\$.tw,kf,ot.
23	MEGAKARYOCYTES/
24	THROMBOPOIETIN RECEPTOR/
25	eltrombopag\$.tw,kf,ot,nm.
26	(romiplastin\$ or romiplostim\$).tw,kf,ot,nm.
27	(amg531 or amg 531 or amg-531).tw,kf,ot,nm.
28	(sb497115 or sb 497115 or sb-497115).tw,kf,ot,nm.
29	(fab59 or fab 59 or fab-59).tw,kf,ot,nm.
30	(AKR501 or AKR 501 or AKR-501).tw,kf,ot,nm.
31	(YM477 or YM 477 or YM-477).tw,kf,ot.

(Continued)

32	Peg-TPOMP\$.tw,kf,ot.
33	Promacta\$.tw,kf,ot.
34	TPO.tw,kf,ot.
35	(thrombopoie\$ and agent\$).tw,kf,ot.
36	or/18-35
37	17 and 36
38	randomized controlled trial.pt.
39	controlled clinical trial.pt.
40	randomized.ab.
41	placebo.ab.
42	drug therapy.fs.
43	randomly.ab.
44	trial.ab.
45	groups.ab.
46	or/38-45
47	humans.sh.
48	46 and 47
49	37 and 48

CONTRIBUTIONS OF AUTHORS

Helga Dodillet: drafting of the review, data extraction, writing of the review.

Nicole Skoetz: provided methodological expertise, proof read and commented on the first and final draft.

Ina Monsef: developed the search strategies and ran the database searches, provided reference databases.

Karl-Anton Kreuzer: provided clinical expertise, proof read and commented on the final draft.

All authors have read and accepted the final version of the review.

DECLARATIONS OF INTEREST

Helga Dodillet: none known

Nicole Skoetz: none known

Ina Monsef: none known

Karl-Anton Kreuzer: none known

SOURCES OF SUPPORT

Internal sources

- Support, Germany.

Department 1 of Internal Medicine, University Hospital of Cologne.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- In accordance with Methodological Expectations of Cochrane Intervention Reviews (MECIR), we additionally searched the following clinical trial registers:
 - ISRCTN;
 - EU clinical trials register: <https://www.clinicaltrialsregister.eu/ctr-search/search>;
 - Clinicaltrials.gov: <https://clinicaltrials.gov/>.
- We did not identify any trials evaluating one thrombopoietin (TPO) mimetic versus another, moreover we did not identify trials involving patients with myelodysplastic syndrome (MDS) who were not thrombocytopenic. All the identified trials randomised thrombocytopenic patients, therefore all trials were analysed in one meta-analysis.
- We added one primary outcome that was not pre-defined in the protocol to our analysis: "Mortality during study" was established as all trials published valid data in comparison to lacking information content regarding the primary outcome of overall survival (OS).
- Further secondary outcomes were not reported or reported in a different way as pronounced in the protocol:
 - as thrombocytopenia represents a common symptom for MDS patients and may also occur as a drug-induced side effect, we judged this outcome as meaningless and therefore did not analyse incidence of thrombocytopenia;
 - because no trial subdivided bleeding events as minor or major bleeding events, these autonomous outcomes were grouped together as incidence of bleeding events.
- We added one secondary outcome that was not pre-defined in the protocol to our analysis: Adverse events $\geq$ grade 3.
- As we did not conduct any meta-analyses with at least 10 trials, we were unable to explore the potential publication bias by generating a funnel plot.
- Because of assumed clinical heterogeneity within the included trials (different concomitant medication), we used a random-effects model for meta-analyses. The fixed-effect model was used for the sensitivity analyses.
- We added a 'Summary of findings' table on absolute risks. We summarised the evidence of mortality during study, transformation to acute myeloid leukaemia (AML), incidence of bleeding events, transfusion requirement, health-related quality of life, all adverse events, and serious adverse events.

NOTES

We used a protocol template from the Cochrane Haematological Malignancies Group (CHMG) for creating the protocol of this systematic review.

INDEX TERMS

Medical Subject Headings (MeSH)

Azacitidine [analogs & derivatives] [therapeutic use]; Benzoates [*therapeutic use]; Blood Transfusion [statistics & numerical data]; Decitabine; Hemorrhage [chemically induced]; Hydrazines [*therapeutic use]; Lenalidomide; Leukemia, Myeloid, Acute [etiology]; Myelodysplastic Syndromes [*complications] [mortality]; Pyrazoles [*therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic; Receptors, Fc [*therapeutic use]; Recombinant Fusion Proteins [*therapeutic use]; Thalidomide [analogs & derivatives] [therapeutic use]; Thrombocytopenia [*drug therapy] [etiology]; Thrombopoietin [*therapeutic use]

MeSH check words

Adult; Female; Humans; Male