A virtual discussion on the clinical landscape in lower-risk MDS

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Introduction

Myelodysplastic syndromes are
a group of cancers in which immature blood cells
in the bone marrow do not mature or become healthy blood cells.
For this highly educational meeting on the clinical landscape
in lower-risk MDS, BMS invited some national and international experts
for a virtual discussion. This report is a summary of this meeting.

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Transfusion in MDS: a heavy burden?

Dr. Langemeijer, Hematologist (Radboud UMC, Nijmegen, The Netherlands)

The topic of this first presentation was the effect of **erythrocyte transfusions (RBCT)** in patients with myelodysplastic syndrome (MDS) on prognosis and quality of life.
Dr Langemeijer started her presentation by explaining that RBCT is the most frequently used therapy in lower-risk MDS patients.

Important independent prognostic factors in MDS patients

Dr Langemeijer explained that approx. 90% of MDS patients suffer from **anaemia**. From several clinical studies, we know that severe anaemia – a haemoglobin level of < 8 g/dL (females) or < 9 g/dL (males) and a high score in the IPSS-R (Revised International Prognostic Scoring System) scoring system – not only leads to a reduced quality of life but can also lead to cardiac complications and is associated with a worse survival prognosis.
Patients report that RBCT provides symptomatic relief, but it is challenging to show that in the retrospective studies.

Dr. Langemeijer

Before the development of the IPSS-R system, Malcovati et al. described an adjusted prognostic classification (WPSS: WHO Prognostic Scoring System) in which not anaemia but **transfusion dependency** was an important independent prognostic factor. The effect on survival was related to the severity of transfusion requirement and was more noticeable in low-risk patients.

Transfusion intensity is also an important independent prognostic factor: the more transfusions a patient needs, the worse the survival prognosis is.

Several studies show that patients on transfusions do worse than patients who are not transfusion dependent. This is related to 1) the severity of MDS, 2) comorbidities and 3) the side effects of transfusion.

Severity of MDS

Patients with a high or very high-risk score on the IPSS-R scale were much more likely to be RBCT dependent (Ryden et al., Leukemia, 2019). Malcovati et al. (JCO, 2005) also showed that even in the better cytogenetic risk groups, patients with transfusion dependency had a worse prognosis.

In all these retrospective studies, many patients with **higher-risk** IPSS-R MDS were included in which transfusion dependency is often related to e.g., chemotherapy. Dr. De Swart (Radboud University Medical Center) used data from the European MDS (EU MDS) registry to study the effect of transfusions on lower-risk MDS patients. This study showed that patients who don't receive transfusions do better than patients who do (figure 1). Patients with a low transfusion burden have a better survival prognosis than patients with a high transfusion burden, even in **lower-risk** MDS patients.

Comorbidities and transfusion dependency

A study by Goldberg et al., JCO, 2010 indicated that cardiac events, diabetes, dyspnoea and infectious complications occur more often in patients with transfusion dependency.

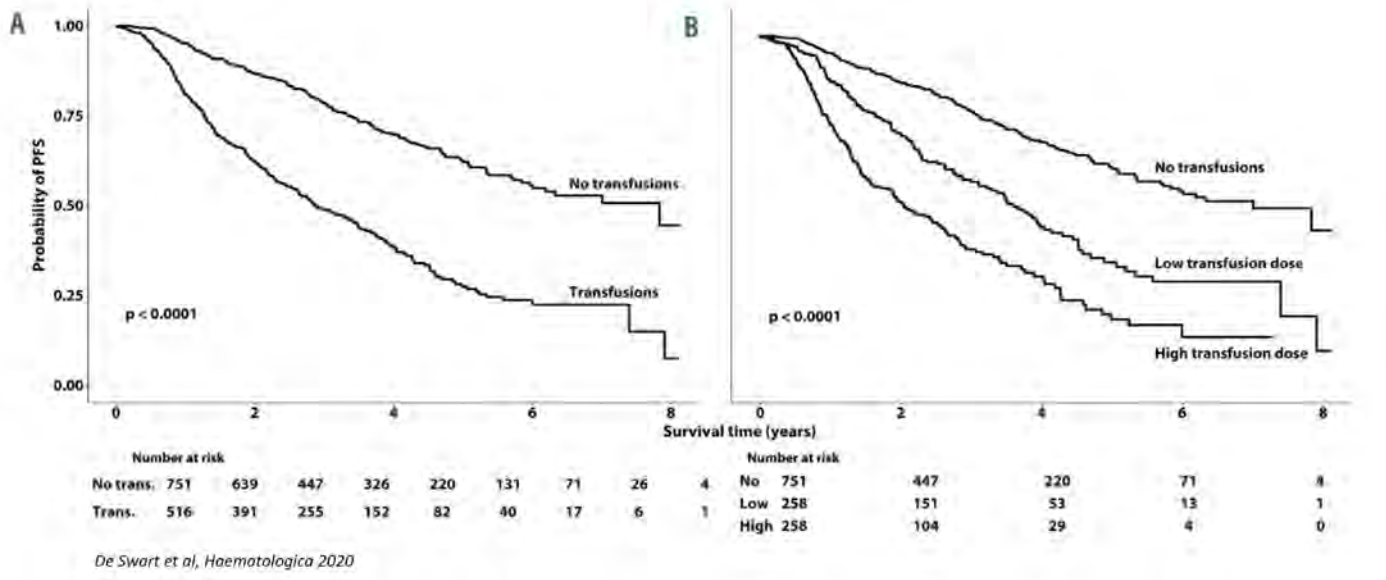


Figure 1 · Transfusions and progression-free survival

Side effects of transfusions

Dr. Langemeijer discussed some side effects of transfusions and their impact on prognosis.

Iron overload in MDS is caused by RBCT and/or ineffective erythropoiesis. It can have negative effects on the bone marrow and on several glands and organs. Although the value of **iron chelation therapy** (ICT) is still unproven in lower-risk MDS patients, different retrospective studies and meta-analyses show that prognosis and overall survival seem to be better in MDS patients who receive ICT. Dr Langemeijer showed various examples of these studies, including a retrospective study within the EUMDS registry from Dr Hoeks et al. where they tried to match the ICT patients with the non-ICT patients and corrected for variables concerning comorbidities etc. (figure 2). (Hoeks et al, Haematologica, 2020)

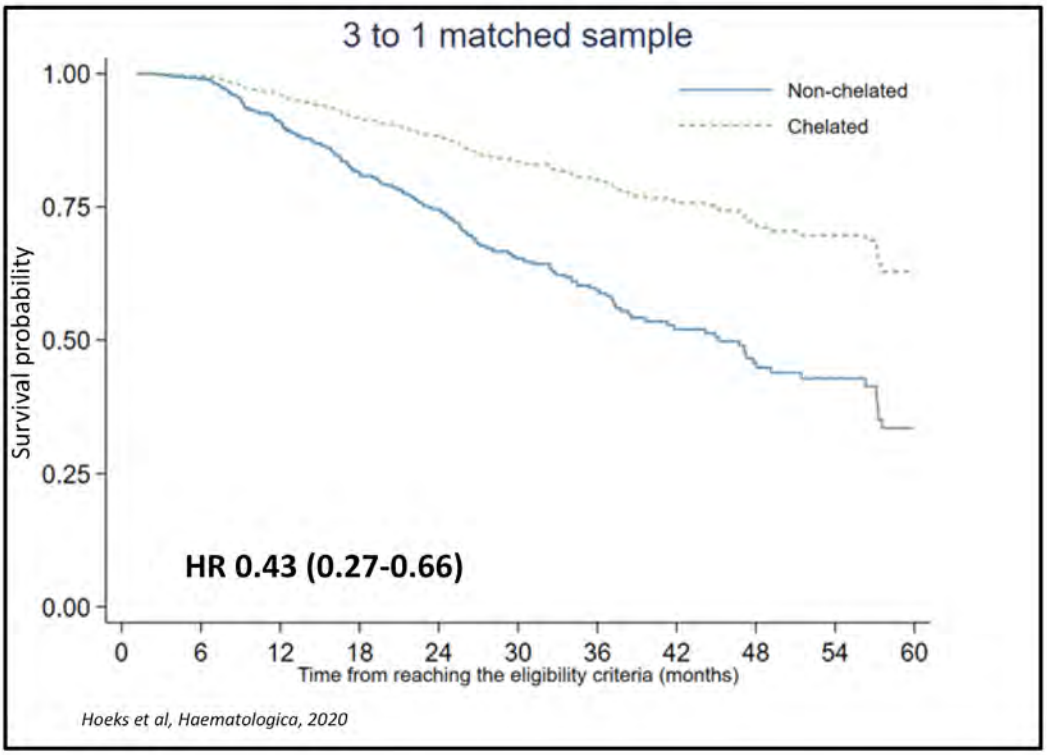


Figure 2 · Effect of iron chelation – Adjusted survival curve

Dr. Langemeijer emphasised that the problem with these retrospective studies is that doctors tend to prescribe ICT to patients in a better condition, having a predicted more prolonged overall survival. This means there may be a lot of bias.

The real prove that ICT is better must come from a randomised controlled trial. There is one published called the TELESTO trial (Angelucci, Ann Inter Med, 2020). This study showed a **difference in event-free survival** (EFS) (patients with ICT are more likely to have

a higher EFS) but **not in overall survival**. At the end of her presentation, Dr. Langemeijer added that according to the study coordinators of this trial, one explanation for this could be that patients in the non-chelated arm might have received ICT after the trial.

Dr. Langemeijer concluded that the effect of ICT on the survival of heavily transfused MDS patients is still a matter of debate. However, many studies point in the direction that ICT has an effect.

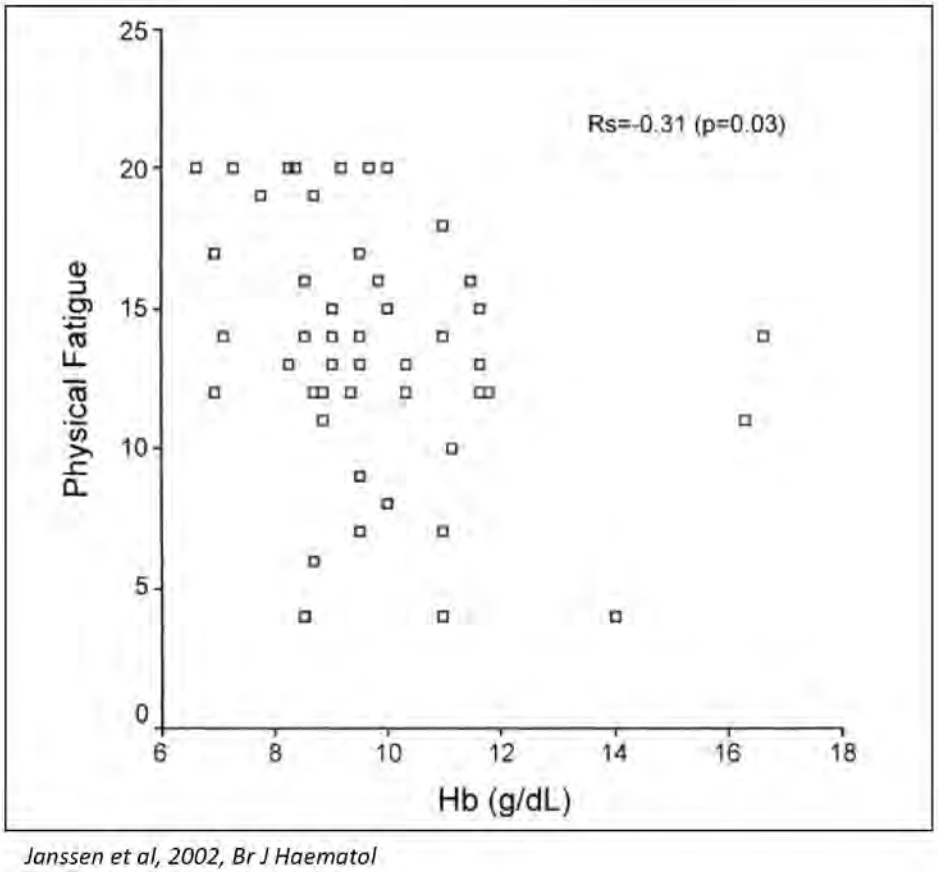
Another substantial potential side effect of RBCT is **alloimmunisation**. But the clinical relevance and the clinical impact of prophylactic red cell antigen matching to reduce the incidence of red cell alloimmunisation for the matched antigens is not yet clear.

Quality of life

The EUMDS registry also provides information about the quality of life in lower-risk MDS patients. Among other factors, patients with **anaemia** and patients with a **transfusion need** have a decreased quality of life (Stauder et al., Leukemia, 2018). Other research groups have also proved this.

Perfect transfusion trigger still unknown

There is a correlation between Hb level and



Janssen et al, 2002, Br J Haematol

Figure 3 · The perfect transfusion trigger is...

physical fatigue, but we can also see that patients with the same Hb level have very different fatigue scores (figure 3).

This makes it very difficult to determine for individual patients when they need a transfusion and how much better the transfusion would make them feel.

Liberal versus restrictive transfusion protocol

Dr. Langemeijer showed the results of a phase 2 trial (Nilsson-Ehle et al., Eur J Haematol, 2011) and discussed whether we are too restrictive regarding transfusions. This was examined in a randomised, blinded (pilot) study (REDDS, Stanworth et al., BJH, 2020) with two treatment arms, one with a liberal and one with a restrictive transfusion protocol. The patients with the liberal protocol did have higher Hb levels. There also seemed to be a trend towards a better quality of life in the patient group with the liberal protocol. But the range of scores was high for both groups, and there was considerable overlap as well.

Topics for future studies

An interesting subject for future studies, according to Dr. Langemeijer, would be the determination of the most crucial factor in our transfusion policy: survival curves, Hb level, side effects, quality of life (patient view) and quality of life (objective).

Ongoing study

Dr. Langemeijer discussed the ongoing REDDS2 study that examines the **transfusion frequency** in different trial arms (figure 4). This study looks at the feasibility of a weekly transfusion schedule and several outcome measurements, e.g. quality of life

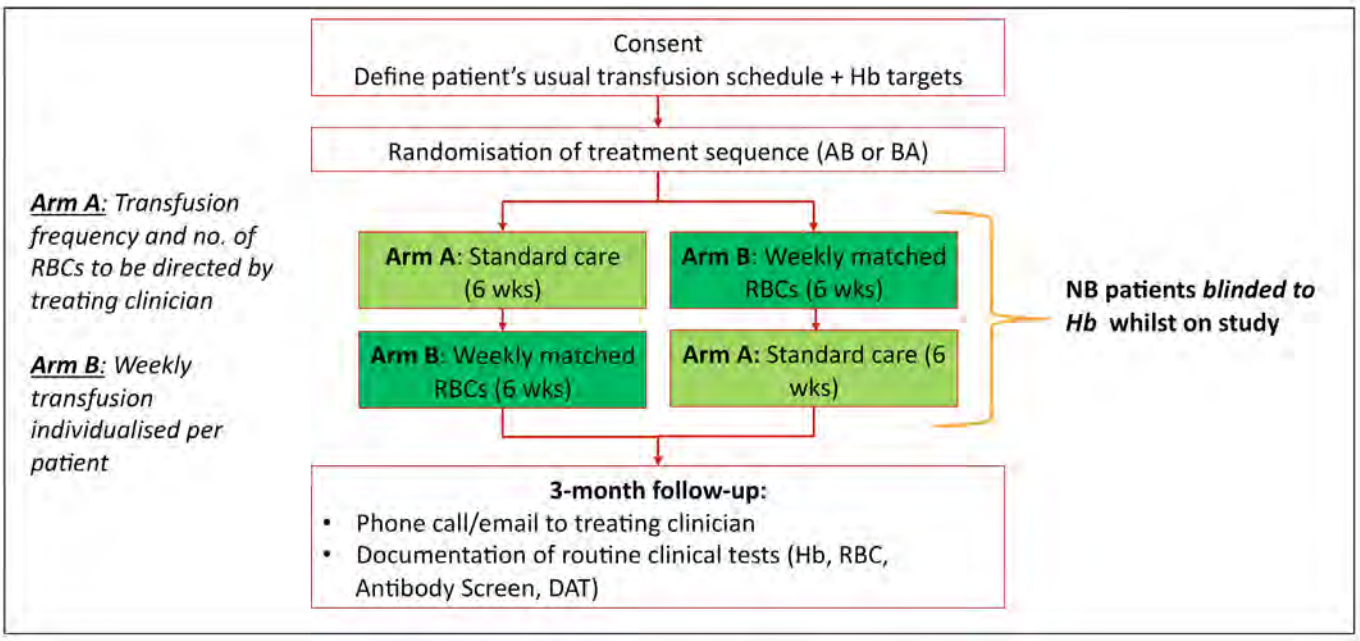


Figure 4 · The REDDS2 study

Dr. Langemeijer concluded her presentation by giving some take-home messages:

· Transfusions are associated with a worse prognosis and reduced quality of life in patients with MDS.

· There is no standard transfusion trigger.

· Factors to be considered are the haemoglobin level, comorbidities, symptoms, and symptom improvement after transfusion and patient preference.

· Tools to measure the effect of transfusions are limited.

· Value of ICT is still unproven but several data show that prognosis and overall survival seem to be better in MDS patients who receive ICT.

There were a few questions from the audience and the moderators. One of the questions was: In patients with renal failure who receive ESA, the haemoglobin level is always kept below 7.2 mmol/L because of a higher mortality rate. Does this also account for MDS patients on ESA therapy? Dr. Langemeijer answered that the same target level (7.2 or 7.4 nmol/L) is used in MDS, but there is no indication that a higher Hb level goes with a higher risk of mortality. The effect of ESA in MDS patients is temporary, so there may be some difference with patients with renal failure in that respect.

Ineffective erythropoiesis: understanding the biology, optimizing clinical practice

Prof. Dr. Aristoteles Giagounidis, Head Of Department, Clinic For Hematology, Oncology And Palliative Care (Marien Hospital, Düsseldorf, Germany)

Dr. Selleslag introduced the next speaker as an excellent physician, researcher, speaker, and entertainer, and characterised him with this simple phrase "**Professor Giagounidis is MDS**, and MDS is Professor Giagounidis". Naturally, after such an introduction, the audience was on the edge of their seats to hear his insights on this next topic.

Pathophysiology of MDS

Prof. Dr. Giagounidis started by reiterating the "traditional" understanding of the pathophysiology of MDS – there are genetic abnormalities, leading to altered stem cells, which then produce the MDS clone, transforming into AML later on. As it turns out, this is only part of the story.

Prof. Dr. Aristoteles Giagounidis

In recent years, we have found that there are damage or pathogen-associated molecular patterns (DAMPs or PAMPs) that lead to inflammation in the bone marrow, with one cell type playing an essential role in MDS, **the myeloid derived suppressor cell** (MDSC). This CD33 positive cell secretes inhibitory and inflammatory cytokines, but also so-called alarmins. These alarmins contribute to the MDSC's self-renewal and bind to the toll-like receptor (TLR), which ultimately leads to the formation of an inflammasome. Inflammasomes cause death of stem cells by pyroptosis, thus reducing the stem cell population and allowing the malignant clone to expand.

(Sallman et al., Clinical Lymphoma, Myeloma & Leukemia 2017; Cluzeau et al. Haematologica 2017; Chen et al. JEM 2013)

Prof. Dr. Giagounidis briefly discussed **the different genetic mutations** present in MDS, which can affect genes involved in DNA methylation, RNA splicing, chromatin

modification and others. Interestingly, certain specific mutations are very clear prognostic factors in low-risk MDS, with, for instance, SF3B1 conferring a better prognosis and TP53 and RUNX1 a worse one (Bejar et al., ASH 2016). Going further into the process of erythropoiesis, he explained that EPO exerts its role mainly in the early stage and much less in later stages. (figure 5A) Several transcription factors also play an essential role, such as the stimulatory GATA 1 and GATA 2, and the inhibitory TGF-β, thus ensuring a tight regulation of the process (figure 5B).

Several studies have been done on the use of erythropoietin in MDS, and Prof. Dr. Giagounidis highlighted the one by Fenaux et al., (EHA 2016). In this study, the use of erythropoietin alfa resulted in "any response over 24 weeks in about 46% of patients and haematological improvement in about 32% of patients (vs 4,4% in the placebo group for both endpoints)." In this study, it also became clear that patients with an endogenous EPO level of 200U/l or higher did not have a response to erythropoietin alfa at all.

Ineffective erythropoiesis

Getting back to the pathophysiology of MDS, he described that in this illness and others such as β thalassemia, **the main issue is ineffective erythropoiesis**, resulting in anaemia. Specifically, what happens in MDS (which is different from thalassemia), is a clonal expansion of mutated erythroid progenitors, leading to the production of dysplastic cells, with increased apoptosis and failure of late-stage maturation. Early-stage proliferation is high, but the cells do not make it to functional, mature erythrocytes, leading to anaemia and transfusion dependency.

Luspatercept and the MEDALIST trial

Luspatercept is **a novel recombinant fusion protein** that binds to select TGF-β superfamily ligands, inhibits aberrant Smad2/3 signalling and enhances late-stage erythropoiesis. It effectuates the same result in both MDS and β thalassemia.

Prof. Dr. Giagounidis discussed the MEDALIST trial, of which the design is shown in figure 6.

Endpoints of the trial

Primary endpoint of the trial was the red blood cell transfusion independence for 8 weeks or more (weeks 1–24). A secondary endpoint was the red blood cell transfusion independence for 12 weeks or more (weeks 1–24 and weeks 1–48). Other endpoints included a hematologic improvement – erythroid (IWG 2006 Criteria) for any consecutive 56-day period, a reduction in red blood cell transfusion burden ≥ 4 RBC units/8 weeks (for patients with a baseline transfusion need of ≥4 units/8 weeks), or mean

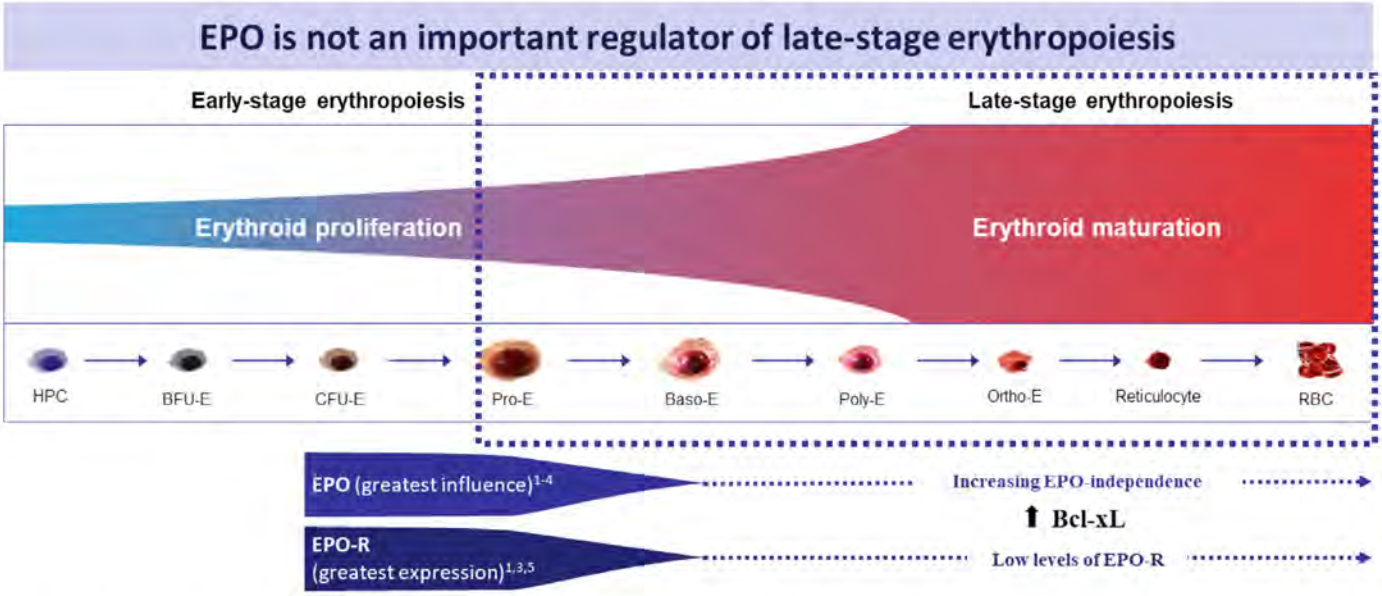


Figure adapted from Ponka P, et al. *Erythropoiesis, Hemoglobin Synthesis, and Erythroid Mitochondrial Iron Homeostasis.* In: The Handbook of Porphyrin Science; 2014:41–84; Zivot A, et al. *Mol Med* 2018;24:11

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Figure 5A

Erythropoiesis is a complex, tightly regulated process involving proliferation and maturation

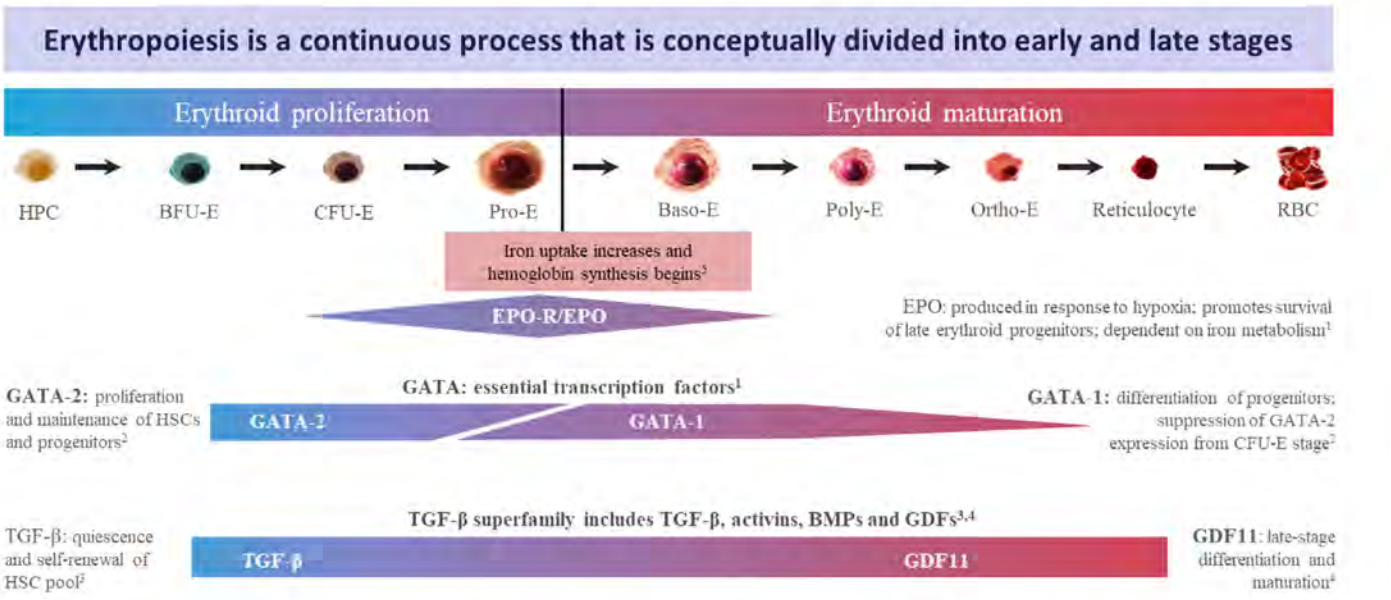

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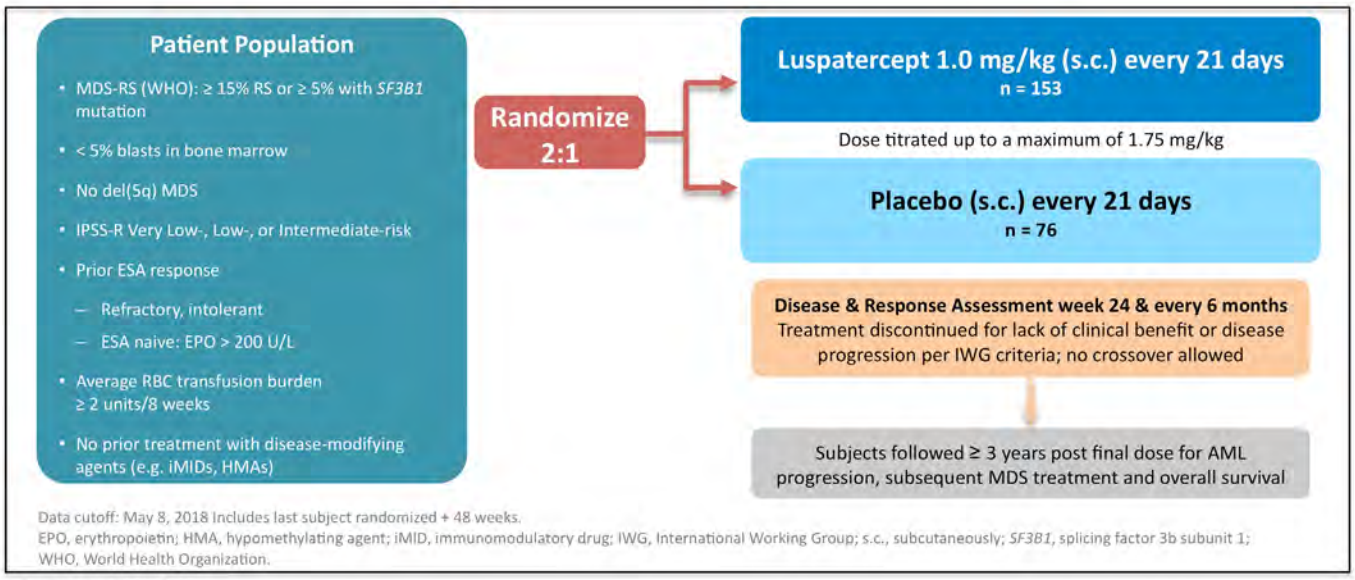
Figure 5B



Fenaux et al, ASH 2018

Figure 6 · MEDALIST Trial – Study Design

Hb increase of ≥ 1.5 g/dL/8 weeks (for patients with baseline transfusion need of <4 units/8 weeks). Also, the duration of response and the Hb change from baseline were measured.

Results

Baseline patient characteristics included around 95% of patients with RCMD-RS (Refractory cytopenia with multilineage dysplasia and ringed sideroblasts), refractory cytopenia with multilineage dysplasia with RS, a bit over 40% with a high transfusion need, a low median Hb of 7.6 g/dL, and presence of an SF3B1 mutation in around 90% of participants.

The primary endpoint, transfusion independence for 8 weeks or more in the first 24 weeks of treatment, was reached by 38% of patients in the luspatercept group versus 13% in the placebo group. A subgroup analysis from the primary endpoint revealed that luspatercept treatment was particularly beneficial in patients with a low transfusion need of less than 6 units/8 weeks and those with a high platelet count. Importantly, this last group also includes the patients with a phenotype of refractory anaemia with RS (RARS) and thrombocytosis, who were also allowed in the trial.

An additional analysis that looked at the proportion of patients who achieved transfusion independence for 8 weeks or more at any time during the treatment period, showed that almost 48% of patients in the luspatercept group achieved this, versus 16% in the placebo group, and the cumulative duration of this transfusion independency was 80 weeks vs 21 weeks for placebo.

The secondary endpoint of transfusion independence for 12 or more weeks in the first 24 weeks was achieved in 28% vs 8% of

patients. For week 1-48, these numbers went up to 33% and 12%, respectively. Not surprisingly, patients in the luspatercept group remained on treatment longer than those receiving placebo, namely a median of 49 vs 24 weeks.

The hematologic improvement – erythroid (HI-E) percentage was 53% at 24 weeks, and 59% at 48 in the luspatercept group, versus 12% and 17% in the placebo group.

Looking at safety results, we see that the proportion of patients discontinuing treatment because of adverse events is similar in both groups, namely around 8%. Some of the specific adverse events that occurred more frequently in the luspatercept group than in the placebo group were fatigue, diarrhoea, nausea and dizziness, but Prof. Dr. Giagounidis explained that in his experience, these were rarely severe enough to warrant discontinuation of treatment. (figure 7)

Subsequent analyses demonstrated that patients who achieved a dose escalation of luspatercept achieved higher rates of transfusion independence and HI-E. Interestingly, adverse events tended to occur mainly at the initial dose level and did not increase (and in some cases decreased) with up-titration of the dose.

Further data

Additional analysis of the trial led to further insights. Even in patients with a high transfusion burden, there was still a proportion of patients with good response. Also, patients experienced benefit from luspatercept whether or not they had received prior ESAs.

Prof. Dr. Giagounidis showed an interesting

	Luspatercept (n = 153)	Placebo (n = 76)
Patients with ≥ 1 TEAE, n (%)	**150 (98.0)**	**70 (92.1)**
Patients with ≥ 1 serious TEAE	48 (31.4)	23 (30.3)
Patients with ≥ 1 Grade 3 or 4 TEAE	65 (42.5)	34 (44.7)
Patients with TEAEs leading to death[a]	5 (3.3)	4 (5.3)
Patients with ≥ 1 TEAE causing discontinuation, n (%)	**13 (8.5)**	**6 (7.9)**

- TEAEs were balanced between the arms[b]
- Progression to AML occurred in 4 patients (3/153 [2.0%] in the luspatercept arm; 1/76 [1.3%] in the placebo arm)

[a] In luspatercept arm: sepsis (n = 2), multiple organ dysfunction syndrome, renal failure, and hemorrhagic shock; in placebo arm: sepsis, urosepsis, general physical health deterioration, and respiratory failure. [b] The most common grade 3 or 4 TEAEs reported in luspatercept-treated patients were anemia (6.5% of patients), fall (4.6%), and fatigue (4.6%).
TEAE, treatment-emergent adverse event.

Fenaux et al, ASH 2018

Figure 7 · MEDALIST Trial – Safety Summary

swimmer plot, demonstrating that some patients can have **multiple prolonged episodes of transfusion independence**, even if they require an occasional transfusion. Other genetic mutations than SF3B1 were shown not to affect the response to luspatercept. (Platzbecker et al., ASCO 2018 and 2019, Lancet Oncology 2017)

A slightly puzzling result was the level of fatigue, which was not better in the luspatercept group. This could be explained by the fact that the medication by itself can cause some fatigue, as well as the impact of transfusion on fatigue, which is actually quite good in the short term, and of course, patients in the placebo group received a lot more transfusions.

Conclusion

· In lower-risk, RS-positive MDS, treatment with luspatercept resulted in a significantly higher percentage of patients who achieved RBC transfusion independence, major RBC transfusion reduction, or haemoglobin increase, compared with placebo.

· Responses were durable, with about 40% of patients who achieved transfusion independence maintaining this at 12 months of treatment, and the treatment was generally well tolerated.

· Hence, luspatercept is a potential new therapy for treating patients with lower-risk, RS-positive MDS with RBC transfusion-dependent anaemia.

Following the presentation, there was a question from Prof. Dr. Beckers. She asked whether MDS could be treated by targeting inflammation, as we know this plays a vital role in the pathophysiology. Prof. Dr. Giagounidis replied that there are several efforts underway to study potential approaches. On the other hand, we already know that simply suppressing inflammation, e.g. by giving steroids, does not work, so it will have to be a multi-pronged approach, targeting several mechanisms at once.

Which patients are candidates for treatment with luspatercept?

Dr. Selleslag, Hematologist (AZ Sint-Jan, Bruges, Belgium)

Dr. Selleslag started his presentation with some background information about luspatercept.

The European Commission authorised luspatercept (Reblozyl) in June 2020. The drug is used to treat adult patients with transfusion-dependent anaemia due to very low-, low- or intermediate-risk myelodysplastic syndrome (MDS) with ring sideroblasts (RS) who had **an unsatisfactory response** to or are ineligible to erythropoietin-based therapy (ESA).

Dr. Selleslag explained the definition of an unsatisfactory response to ESA according to the inclusion criteria of the MEDALIST trial, namely a documented non-response or loss of response after at least 8 weeks of treatment at a dose of 40.000 IU/week of a recombinant human erythropoietin, or 500µg of darbepoetin alfa every 3 weeks for 4 doses (Fenaux et al., NEJM, 2020).

Dr. Selleslag

In Belgium, EPREX is the only ESA for MDS reimbursed with a maximum dose of 80.000 IU/wk. Treatment in Belgium must stop if the maximum dose fails (= **Hb reduction** of 1,5 g/dL compared to the best value achieved or **increasing transfusion needs**).

This means there is a discrepancy between the stopping rules for ESA in Belgium (lack or loss of response at 80.000 IU/wk, with no mention of the duration of treatment) versus the inclusion criteria used in the MEDALIST trial (lack of response at 40.000 IU/week, with a duration of treatment of 8 weeks minimum). Hence, the Belgian authorities will need to reconcile this when defining the reimbursement criteria for luspatercept, which could be problematic.

Insights that may help us to decide (or not) for luspatercept

Dr. Selleslag used the outcomes of a study by Park et al. JCO, 2017, to illustrate that there is **no evidence for a positive or negative effect**

of luspatercept on survival in ESA refractory MDS patients. We must also consider what type of clinical benefit we can expect from luspatercept and the duration of that benefit. The updated result of the MEDALIST trial (Fenaux et al., ASH, 2019) showed that patients with a **low transfusion dependency have a better response to luspatercept** than patients with a high transfusion dependency. But clinical benefit is more than transfusion independency (it also includes reduction of transfusion need and **hematologic improvement-erythroid** (HI-E)). Looking at the clinical benefit according to **baseline transfusion requirements**, we see that the effects of luspatercept are much better, also in the group of patients with a higher baseline transfusion burden (figure 8)

Clinical Benefit and Duration	Luspatercept	Placebo
Clinical benefit[a] – all patients, n/N (%)	**98/153 (64.1)**	**20/76 (26.3)**
Baseline transfusion burden ≥ 6 U/8 weeks	37/66 (56.1)	9/33 (27.3)
Baseline transfusion burden ≥ 4 to < 6 U/8 weeks	22/41 (53.7)	3/23 (13.0)
Baseline transfusion burden < 4 U/8 weeks	39/46 (84.8)	8/20 (40.0)
Duration of clinical benefit[b] – all patients, median (range), weeks	**92.3 (8–172)**	**26.8 (8–103)**
Baseline transfusion burden ≥ 6 U/8 weeks	66.0 (8–148)	23.9 (8–103)
Baseline transfusion burden ≥ 4 to < 6 U/8 weeks	96.1 (13–150)	45.7 (45–51)
Baseline transfusion burden < 4 U/8 weeks	91.7 (21–172)	26.8 (18–76)

ASH 2019, Fenaux et al, Data cutoff: July 1, 2019.

Figure 8 · MEDALIST Trial – Achievement and duration of clinical benefit

Dr. Selleslag then presented two cases of his own MDS patients who might be candidates for treatment with luspatercept.

Case 1

The first case was a 63-year-old woman with a medical history of osteoporosis. She presented in 2006 with a Hb level of 11.4 g/dL and 38% ring sideroblasts (RS). She had a normal karyotype. In 2017 she was tested with next-generation sequencing (NGS) and turned out to have an SF3B1 mutation. In 2010 her Hb dropped below 10 g/dL for the first time. She started on **darbepoetin** (500 µg/3 w), achieving a Hb > 9 g/dL without transfusions. In January 2019, she had to switch to EPREX (40.000 IU/wk.) because of reimbursement issues. Eight months later, she had her first transfusion, and very soon, her transfusion burden was 2 IU of packed RBC (RBCp)/4wks. In September 2020, her initially low ferritin level started to rise, and she was started on Exjade. From February until December 2020, she was included in the double-blind trial of **roxadustat** vs placebo, but she didn't respond, and the transfusion burden remained unchanged. In January 2021, she was included in the double-blind IMerge study (**imetelstat** vs placebo). At the start of this study, the status of her disease was 41% RS, with no transformation and fibrosis (grade 2). She still was low-risk on the IPSS-R scale, and her median survival was calculated at 5.3 years. Her transfusion burden now is 4U RBCp/8wks, and her ferritin level is rising (1940 µg/l) because she can't take Exjade adequately (diarrhoea).

Dr. Selleslag discussed with Dr. Langemeijer and Prof. Dr. Giagounidis whether this patient would be a good candidate for a first trial of **luspatercept** if imetelstat does not work or if she could be a candidate for an **allogeneic stem cell transplantation** (alloSCT)? We know she has an HLA identical sister, and she is not adequately iron chelated. Her expected 5-year survival without transplantation is 50 %. She has no comorbidities, which means she has a low risk of treatment-related mortality (TRM) should she receive alloSCT (14% at 2 years).

Dr. Langemeijer explained that she would consider alloSCT because of the **fibrosis in the bone marrow** and **the inadequate iron chelation**. However, Dr. Selleslag discussed that, based on the MEDALIST trial, treatment with luspatercept could decrease ferritin, so there would be a chance of bringing the patient in a better condition with luspatercept before the alloSCT. Prof. Dr. Giagounidis agreed with Dr. Langemeijer that fibrosis is not a very good prognostic sign. The panel agreed that poor iron chelation in a heavy transfusion dependent low-risk MDS patient is an argument to do an alloSCT, especially when there is an HLA identical sibling.

Case 2

Dr. Selleslag presented a second case of a 76-years-old female patient with no relevant medical history. She presented with fatigue in June 2019 and a Hb level of 10 g/dL. She had MDS-RS with multilineage dysplasia (MLD), a normal karyotype and an SF3B1 mutation. Her IPSS score was Int-1, and her IPSS-R was very low, with a median survival of 8 years. Her ferritin and EPO levels were relatively low, so she started with EPREX. She didn't need iron chelation because there was no transfusion need. In August 2020, however, her Hb dropped below 10 g/dL for the first time, so EPREX was increased from 40.000 to 80.000 IU/wk. Despite that, her Hb level is still dropping, and in December 2020, she was below 8.5 g/dL and started with RBCp transfusions (2U). Dr. Selleslag thinks she will become ESA refractory. All panel members agreed with Dr. Selleslag that this patient would be a good candidate for luspatercept because her transfusion burden will probably be low (less 4 U/8wks). The probability of clinical benefit (= reduction of transfusions) will be 85 % for a median duration of 91 wks. (based on the luspatercept data in patients with a low transfusion burden), which is quite significant.

Ongoing trials in low risk MDS in the Benelux

Prof. Dr. Beckers, Hematologist (Uz Leuven, Belgium)

To conclude the symposium, Prof. Dr. Beckers provided an overview of ongoing clinical trials in low-risk MDS in the Benelux. There are no less than three phase-3 trials and one observational study ongoing!

The first trial she discussed is the **COMMANDS trial** (NCT03682536), open in both Belgium and the Netherlands, which will further elucidate the role of luspatercept in MDS patients. COMMANDS is a phase 3 trial in patients with very low-, low- or intermediate-risk MDS, no prior ESA treatment and requiring 2-6 RBC units/8 weeks. Patients are stratified according to baseline transfusion need, endogenous EPO levels, and RS or non-RS, then randomised in an open-label fashion to receive luspatercept or epoetin alfa. The primary endpoint is transfusion independence for 12 weeks or longer in the first 24 weeks. A long-term follow-up is foreseen until 5 years after the first dose or 3 years after the last dose, whichever comes later.


Prof. Dr. Beckers

Prof. Dr. Beckers then reviewed the **IMERGE trial** (NCT02598661), also recruiting in both the Netherlands and Belgium. IMERGE is also a phase 3 trial, with a 2:1 randomisation to imetelstat or placebo. Imetelstat is a first-in-class telomerase inhibitor.

The main inclusion criteria are: low- to intermediate-risk MDS, with transfusion dependency despite prior treatment with ESAs (or ineligible for ESAs), a neutrophil count >1.5 x 10^9/L, and thrombocytes >75 x 10^9/L. These last two can be somewhat problematic in this population. Stratification will be according to transfusion need and low- or intermediate-risk MDS, and the primary endpoint is 8 weeks transfusion independence.

The last of the phase 3 studies highlighted is only open in Belgium. It concerns a

placebo-controlled trial with **roxadustat** (NCT03263091), which includes patients with very low-, low-, or intermediate-risk MDS, who have a transfusion need of 1-4 units in the 8 weeks before randomisation, and who cannot have received ESAs within the last 8 weeks. Roxadustat increases endogenous EPO levels, which at the time of screening must be below 400 U/l. Here as well, the primary endpoint is 8-week transfusion independence.

The last trial Prof. Dr. Beckers discussed was the multicenter observational Belgian study assessing the impact of newly started treatment on the Quality of Life (QoL) in patients suffering from MDS (NCT04053933) or Be-QUALMS. This trial is open to all patients starting a new treatment for MDS, whether newly diagnosed or with an established diagnosis, regardless of IPPS, with QoL assessments at inclusion and regularly after that.

Discover your peer's opinion on the potential of Reblozyl® for your MDS patients in Belgium

Discover the video-interviews of **Professor Doctor Marielle Beckers** (UZ Leuven) and **Doctor Dominik Selleslag** (AZ St Jan-Brugge) about:

- The unmet medical needs for lower risk MDS patients
- Their perception of the efficacy, safety and quality of life data of Reblozyl®
- Their hopes for the future

Reblozyl® Belgium
25 mg [1.566,68 €]
75 mg [4.698,98€]

ESSENTIAL INFORMATION ▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions. **NAME OF THE MEDICINAL PRODUCT** Reblozyl 25 mg powder for solution for injection Reblozyl 75 mg powder for solution for injection **QUALITATIVE AND QUANTITATIVE COMPOSITION** Reblozyl 25 mg powder for solution for injection Each vial contains 25 mg of luspatercept. After reconstitution, each mL of solution contains 50 mg luspatercept. Reblozyl 75 mg powder for solution for injection Each vial contains 75 mg of luspatercept. After reconstitution, each mL of solution contains 50 mg luspatercept. Luspatercept is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. For the full list of excipients, see section 6.1. **PHARMACEUTICAL FORM** Powder for solution for injection (powder for injection). White to off-white lyophilised powder. **CLINICAL PARTICULARS Therapeutic indications** Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy (see section 5.1). Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia associated with betathalassaemia (see section 5.1).**Posology and method of administration** Reblozyl treatment should be initiated by a physician experienced in treatment of haematological diseases. Posology Prior to each Reblozyl administration, the haemoglobin (Hb) level of patients should be assessed. In case of a red blood cell (RBC) transfusion occurring prior to dosing, the pretransfusion Hb level must be considered for dosing purposes. *Myelodysplastic syndromes* The recommended starting dose of Reblozyl is 1.0 mg/kg administered once every 3 weeks. In patients who are not RBC transfusion-free after at least 2 consecutive doses at the 1.0 mg/kg starting dose, the dose should be increased to 1.33 mg/kg. If patients are not RBC transfusion-free after at least 2 consecutive doses at the 1.33 mg/kg dose level, the dose should be increased to 1.75 mg/kg. The dose increase should not occur more frequently than every 6 weeks (2 administrations) and should not exceed the maximum dose of 1.75 mg/kg every 3 weeks. The dose should not be increased immediately after a dose delay. For patients with a pre-dose Hb level of > 9 g/dL and who have not yet achieved transfusion independence, a dose increase may be required at the physician's discretion; the risk of Hb increasing above the target threshold with concomitant transfusion cannot be excluded. If a patient loses response (i.e., transfusion independence), the dose should be increased by one dose level. *β-thalassaemia* The recommended starting dose of Reblozyl is 1.0 mg/kg administered once every 3 weeks. In patients who do not achieve a response, defined as a reduction in RBC transfusion burden of at least a third after ≥ 2 consecutive doses (6 weeks), at the 1.0 mg/kg starting dose, the dose should be increased to 1.25 mg/kg. The dose should not be increased beyond the maximum dose of 1.25 mg/kg every 3 weeks. If a patient loses response (if the RBC transfusion burden increases again after an initial response) the dose should be increased by one dose level. *MDS and β-thalassaemia Dose reduction and dose delay* In case of Hb increase > 2 g/dL within 3 weeks of luspatercept treatment in absence of transfusion, the Reblozyl dose should be reduced by one dose level. If the Hb is ≥ 11.5 g/dL in the absence of transfusion for at least 3 weeks, the dose should be delayed until the Hb is ≤ 11.0 g/dL. If there is also a concomitant rapid increase in Hb (> 2 g/dL within 3 weeks in absence of transfusion), a dose reduction to one step down (minimum 0.8 mg/kg) should be considered after the dose delay. Dose should not be reduced below 0.8 mg/kg. Dose reductions during treatment with luspatercept are provided below. **Table 1: Dose reductions for MDS Current dose Dose reduction** 1.75 mg/kg 1.33 mg/kg - 1.33 mg/kg 1 mg/kg - 1 mg/kg 0.8 mg/kg **Table 2: Dose reductions for β-thalassaemia Current dose Dose reduction** 1.25 mg/kg 1 mg/kg - 1 mg/kg 0.8 mg/kg If patients experience persistent treatment-related Grade 3 or higher adverse reactions (see section 4.8), the treatment should be delayed until toxicity has improved or returned to baseline. After a dose delay, patients should be re-started at their previous dose or at reduced dose as per dose reduction guidance. *Missed doses* In case of a missed or delayed scheduled treatment administration, the patient should be administered Reblozyl as soon as possible and dosing continued as prescribed with at least 3 weeks between doses. *Patients experiencing a loss of response* If patients experience a loss of response to Reblozyl, causative factors (e.g. a bleeding event) should be assessed. If typical causes for a loss of haematological response are excluded, dose increase should be considered as described above for the respective indication being treated. *Discontinuation* Reblozyl should be discontinued if patients do not experience a reduction in transfusion burden after 9 weeks of treatment (3 doses) at the maximum dose level if no alternative explanations for response failure are found (e.g. bleeding, surgery, other concomitant illnesses) or if unacceptable toxicity occurs at any time. Special populations *Elderly* No starting dose adjustment is required for Reblozyl (see section 5.2). *Hepatic impairment* No starting dose adjustment is required for patients with total bilirubin (BIL) > upper limit of normal (ULN) and/or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) < 3 x ULN (see section 5.2). No specific dose recommendation can be made for patients with ALT or AST ≥ 3 x ULN or liver injury CTCAE Grade ≥ 3 due to lack of data (see section 5.2). *Renal impairment* No starting dose adjustment is required for patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] < 90 and ≥ 30 mL/min/1.73 m²). No specific dose recommendation can be made for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²) due to lack of clinical data (see section 5.2). Patients with renal impairment at baseline should be closely monitored for renal function as per standard of care. *Paediatric population* There is no relevant use of Reblozyl in the paediatric population for the indication of myelodysplastic syndromes, or in paediatric patients less than 6 months of age in β-thalassaemia. For non-clinical data, see section 5.3. The safety and efficacy of Reblozyl in the paediatric patients aged from 6 months to less than 18 years have not yet been established in β-thalassaemia. For nonclinical data, see section 5.3. Method of administration For subcutaneous use. After reconstitution, Reblozyl solution should be injected subcutaneously into the upper arm, thigh or abdomen. The exact total dosing volume of the reconstituted solution required for the patient should be calculated and slowly withdrawn from the singledose vial(s) into a syringe. The recommended maximum volume of medicinal product per injection site is 1.2 mL. If more than 1.2 mL is required, the total volume should be divided into separate similar volume injections and administered across separate sites. If multiple injections are required, a new syringe and needle must be used for each subcutaneous injection. No more than one dose from a vial should be administered. If the Reblozyl solution has been refrigerated after reconstitution, it should be removed from the refrigerator 15-30 minutes prior to injection to allow it to reach room temperature. This will allow for a more comfortable injection. For instructions on reconstitution of the medicinal product before administration, see section 6.6. **Contraindications** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Pregnancy (see section 4.6). **Undesirable effects** Summary of the safety profile *Myelodysplastic syndromes* The most frequently reported adverse drug reactions in patients receiving Reblozyl (at least 15% of patients) were fatigue, diarrhoea, asthenia, nausea, dizziness, back pain and headache. The most commonly reported Grade 3 or higher adverse drug reactions (at least 2% of patients) included syncope/presyncope, fatigue, hypertension and asthenia. The most commonly reported serious adverse drug reactions (at least 2% of patients) were urinary tract infection, back pain and syncope. Asthenia, fatigue, dizziness and headache occurred more frequently during the first 3 months of treatment. Treatment discontinuation due to an adverse reaction occurred in 2.0% of patients treated with luspatercept. The adverse reactions leading to treatment discontinuation in the luspatercept treatment arm were fatigue and headache.*β-thalassaemia* The most frequently reported adverse drug reactions in patients receiving Reblozyl (at least 15% of patients) were headache, bone pain and arthralgia. The most commonly reported Grade 3 or higher adverse drug reaction was hyperuricaemia. The most serious adverse reactions reported included thromboembolic events of deep vein thrombosis, ischaemic stroke portal vein thrombosis and pulmonary embolism (see section 4.4). Bone pain, asthenia, fatigue, dizziness and headache occurred more frequently during the first 3 months of treatment. Treatment discontinuation due to an adverse reaction occurred in 2.6% of patients treated with luspatercept. The adverse reactions leading to treatment discontinuation in the luspatercept treatment arm were arthralgia, back pain, bone pain and headache. Tabulated list of adverse reactions The highest frequency for each adverse reaction that was observed and reported in the two pivotal studies in MDS and βthalassaemia is shown in Table 3 below. The adverse reactions are listed below by body system organ class and preferred term. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000). **Table 3. Adverse drug reactions (ADRs) in patients treated with Reblozyl for MDS and b-thalassaemia System organ class Preferred term Frequency (all grades) for MDS Frequency (all grades) for b-thalassaemia Infections and infestations** Very common Common bronchitis Very common Common urinary tract infection Common Very common upper respiratory tract infection Common Common influenza **Immune system disorders** Common Common hypersensitivity* **Metabolism and nutrition disorders** Common Common hyperuricaemia **Nervous system disorders** Very common Very common dizziness Very common Very common headache Common Common syncope/presyncope **Ear and labyrinth disorders** Common Common vertigo/vertigo positional **Vascular disorders** Common Common hypertension⁻ Common Common thromboembolic events§ **Respiratory, thoracic and mediastinal disorders** Very common Common dyspnoea **Gastrointestinal disorders** Very common Very common diarrhoea Very common Common nausea **Musculoskeletal and connective tissue disorders** Very common Very common back pain Common Very common arthralgia Common Very common bone pain **General disorders and administration site conditions** Very common Very common fatigue Very common Common asthenia Common Common injection site reactions‡ * Hypersensitivity includes eyelid oedema, drug hypersensitivity, swelling face, periorbital oedema, face oedema, angioedema, lip swelling, drug eruption.⁻ Hypertension reaction includes essential hypertension, hypertension and hypertensive crisis.‡ Injection site reactions include injection site erythema, injection site pruritus, injection site swelling and injection site rash.§ Thromboembolic events include deep vein thrombosis, portal vein thrombosis, ischaemic stroke and pulmonary embolism. Description of selected adverse reactions *Bone pain* Bone pain was reported in 19.7% of β-thalassaemia patients treated with luspatercept (placebo 8.3%) and in 2.6% of MDS patients treated with luspatercept (placebo 3.9%). In β-thalassaemia patients treated with luspatercept, bone pain was most common in the first 3 months (16.6%) compared to months 4-6 (3.7%). Most events (41/44 events) were Grade 1-2, with 3 events Grade 3. One of the 44 events was serious, and 1 event led to treatment discontinuation. *Arthralgia* Arthralgia was reported in 19.3% of β-thalassaemia patients treated with luspatercept (placebo 11.9%) and in 5.2% of MDS patients treated with luspatercept (placebo 11.8%). In the β-thalassaemia patients treated with luspatercept, arthralgia led to treatment discontinuation in 2 patients (0.9%). *Hypertension* Patients treated with luspatercept had an average increase in systolic and diastolic blood pressure of 5 mmHg from baseline not observed in patients receiving placebo. Hypertension was reported in 8.5% of MDS patients treated with luspatercept (placebo 9.2%) and in 8.1% of β-thalassaemia patients treated with luspatercept (placebo 2.8%). See section 4.4. In MDS patients, Grade 3 events were reported for 5 patients (3.3%) treated with luspatercept and in 3 patients (3.9%) receiving placebo. No patient discontinued due to hypertension. In β-thalassaemia patients, Grade 3 events were reported in 4 patients (1.8%) treated with luspatercept (0.0% placebo). No patient discontinued due to hypertension. See section 4.4. *Hypersensitivity* Hypersensitivity-type reactions (including eyelid oedema, drug hypersensitivity, swelling face, periorbital oedema, face oedema, angioedema, lip swelling, drug eruption) were reported in 4.6% of MDS (2.6% placebo) and 4.5% of β-thalassaemia patients treated with luspatercept (1.8% placebo). In clinical studies, all events were Grade 1/2. In β-thalassaemia patients treated with luspatercept, hypersensitivity led to treatment discontinuation in 1 patient (0.4%). *Injection site reactions* Injection site reactions (including injection site erythema, injection site pruritus, injection site swelling and injection site rash) were reported in 3.9% of MDS (placebo 0.0%) and in 2.2% of β-thalassaemia patients receiving luspatercept (placebo 1.8%). In clinical studies, all events were Grade 1 and none led to discontinuation. *Thromboembolic events* Thromboembolic events (including deep vein thrombosis, portal vein thrombosis, ischaemic stroke and pulmonary embolism) occurred in 3.6% of β-thalassaemia patients receiving luspatercept (placebo 0.9%). All events were reported in patients who had undergone splenectomy and had at least one other risk factor. No difference in TEEs was observed between luspatercept and placebo arms in MDS patients. See section 4.4.*Immunogenicity* In clinical studies in MDS, an analysis of 260 MDS patients who were treated with luspatercept and who were evaluable for the presence of anti-luspatercept antibodies showed that 23 (8.8%) MDS patients tested positive for treatmentemergent anti-luspatercept antibodies, including 9 (3.5%) MDS patients who had neutralising antibodies against luspatercept. In clinical studies in β-thalassaemia, an analysis of 284 β-thalassaemia patients who were treated with luspatercept and who were evaluable for the presence of anti-luspatercept antibodies showed that 4 (1.4%) β-thalassaemia patients tested positive for treatmentemergent anti-luspatercept antibodies, including 2 (0.7%) β-thalassaemia patients who had neutralising antibodies against luspatercept. Luspatercept serum concentration tended to decrease in the presence of neutralising antibodies. There were no severe systemic hypersensitivity reactions reported for patients with anti-luspatercept antibodies. There was no association between hypersensitivity type reactions or injection site reactions and presence of anti-luspatercept antibodies. Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V. **MARKETING AUTHORISATION HOLDER** Bristol Myers Squibb Pharma EEIG Plaza 254 Blanchardstown Corporate Park 2 Dublin 15, D15 T867 Ireland **MARKETING AUTHORISATION NUMBER(S)** EU/1/20/1452/001 EU/1/20/1452/002 **CLASSIFICATION** Medicinal product subject to medical prescription. **DATE OF REVISION OF THE TEXT** 04/02/2021 Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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Bristol Myers Squibb™

Reblozyl®
(luspatercept)