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Luspatercept: la nuova realtà nel Trattamento della Beta-Talassemia

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Direttrice SC Microcitemie e Anemie Rare

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Transfusion requirement is used to distinguish two major clinical phenotypes of ß-thalassemia: NTDT and TDT[1,2]

Transfusions seldom required

Occasional transfusions required
(e.g. surgery, pregnancy, infection)

More frequent transfusions required
(e.g. poor growth and development, specific morbidities)

NTDT ► TDT conversion is not uncommon[3]

Lifelong regular transfusions required for survival

Transfusion requirement

NTDT		TDT
ß-thalassemia minor/trait $ß^+/ß$ or $ß^0/ß$	ß-thalassemia intermedia Mild/moderate HbE/ß-thalassemia $ß^+/ß^+$ or $ß^0/ß^+$	ß-thalassemia major Severe HbE/ß-thalassemia $ß^0/ß^0$
• Borderline asymptomatic anemia • RBC abnormalities (microcytosis, hypochromia)	• Delayed presentation (> 2 years) • Mild to moderate anemia	• Early presentation (≤ 2 years) • Severe anemia • Severe clinical symptoms

ß, wild-type allele with no mutation; $ß^0$, severe mutations and absent ß-globin production; $ß^+$, mild mutations and reduced ß-globin production; HbE, hemoglobin E; NTDT, non-transfusion-dependent ß-thalassemia; RBC, red blood cell; TDT, transfusion-dependent ß-thalassemia.

1. Taher AT, et al. Guidelines for the management of non-transfusion-dependent thalassaemia (NTDT). 3rd ed. Thalassaemia International Federation; 2023; 2. Musallam KM, et al. Haematologica 2013;98:833-844; 3. Musallam KM, et al. Am J Hematol 2024;99:490-493.

Phenoconversion

Am J Hematol. 2024 Mar;99(3):490-493. doi: 10.1002/ajh.27194. Epub 2024 Jan 2.

'Phenoconversion' in adult patients with β-thalassemia

Khaled M Musallam [1], Susanna Barella [2], Raffaella Origa [3], Giovanni Battista Ferrero [4], Roberto Lisi [5], Annamaria Pasanisi [6], Filomena Longo [7], Barbara Gianesin [8], Gian Luca Forni [8]; Webthal® project

Collaborators, Affiliations + expand

PMID: 38165006 DOI: 10.1002/ajh.27194

Free article

Phenoconversion rate 13.8 %

(46/286)

Abstract

Rate and risk factors for phenoconversion from non-transfusion-dependent β-thalassemia (NTDT) to transfusion-dependent β-thalassemia (TDT) during a 10-year follow up of adult patients in Italy.

Patients with TDT face several unmet needs

The burden of regular RBC transfusions and iron chelation therapy on patients, their families, and society is significant[1,2]

- Increased health care costs[1]
- Associated costs (transport, lost opportunities to work)[1]
- Lost work productivity[1]
- Time and inconvenience[2]
- Side effects, particularly iron overload[1]
- Complications and comorbidities[1]
- Premature immune system aging[1,3]
- Physical and mental HRQoL[1]

Contributing factors to the burden of TDT include fatigue, pain symptoms, and disease-management time[5]

Clinical complications in patients with TDT[4]

- Hypothyroidism
- Hypogonadism
- Osteoporosis
- Cardiac siderosis
- Left-sided heart failure
- Hepatic failure
- Viral hepatitis
- Diabetes mellitus

Iron overload from chronic transfusions is a major driver of morbidity in TDT [6,7]

Treatment options are needed to provide effective management of TDT and address these unmet needs

HRQoL, health-related quality of life; RBC, red blood cell; TDT, transfusion-dependent ß-thalassemia.

1. Forni GL, et al. Front Hematol 2023;2:1187681; 2. Aydinok Y, et al. Ther Adv Hematol 2024;15:1-16; 3. Carsetti R, et al. Blood 2022;140:1735–1738; 4. Musallam KM, et al. Haematologica 2013;98:833-844; 5. Paramore C, et al. Patient 2021;14:197-208; 6. Taher AT, Saliba AN. Hematology Am Soc Hematol Educ Program 2017;2017:265-271; 7. Taher AT, et al. Guidelines for the management of transfusion-dependent thalassaemia (TDT). 5th ed. Thalassaemia International Federation; 2025.

Quality of Life in Thalassemia Major

V P Choudhry [1] [2]

Improving outcomes and quality of life for patients with transfusion-dependent β-thalassemia: recommendations for best clinical practice and the use of novel treatment strategies

Ali T Taher [1], Rayan Bou-Fakhredin [1], Antonis Kattamis [2], Vip Viprakasit [3], Maria Domenica Cappellini [4]

Quality of Life and Burden of Disease in Italian Patients with Transfusion-Dependent Beta-Thalassemia

Fabio Tedone [1], Piero Lamendola [1], Stefania Lopatriello [1], Davide Cafiero [1], Danie Gian Luca Forni [3]

Quality of Life and Related Factors in β-Thalassemia Patients

...osh Etemad [1], Parisa Mohseni [1], Mohammad Aghighi [2], Ayad Bahadorimonfared [3], ...eh Hantooshzadeh [4], Niloufar Taherpour [5], Negar Piri [6], Sahar Sotoodeh Ghorbani [1], ...meh Malek [7], Fatemeh Kheiry [8], Azimeh Khodami [9], Tannaz Valadbeigi [10], Mahmoud Hajipour [1]

Quality of life in Sardinian patients with transfusion-dependent Thalassemia: a cross-sectional study

Francesca Floris [1], Federica Comitini [1], GiovanBattista Leoni [2], Paolo Moi [1], Maddalena Morittu [2], Valeria Orecchia [2], Maria Perra [2], Maria Paola Pilia [2], Antonietta Zappu [2], Maria Rosaria Casini [2], Raffaella Origa [3]

Long-Term Health-Related Quality of Life and Clinical Outcomes in Patients with β-Thalassemia after Splenectomy

Giovanni Caocci [1], Olga Mulas [1], Susanna Barella [2], Valeria Orecchia [2], Brunella Mola [1], Alessandro Costa [1], Fabio Efficace [3], Giorgio La Nasa [1]

Evidence-based guidelines provide monitoring and management recommendations for patients with TDT

Determining transfusion suitability[1]

Laboratory criteria for initiating transfusion therapy[1]:

- Hb level < 7 g/dL on two occasions > 2 weeks apart in asymptomatic patients[1]

Clinical criteria for initiating transfusion[1]:

- Significant symptoms of anemia
- Poor growth or failure to thrive
- Complications from excessive intramedullary hematopoiesis
- Clinically significant extramedullary hematopoiesis

3. PRACTICAL CONSIDERATIONS FOR TRANSFUSION THERAPY

3.1. Criteria for initiating transfusion therapy

The decision to initiate a long-term regular transfusion regimen should be driven by the current clinical phenotype of the patient, anticipated short- and longer-term outcomes, and in discussion with the patient and/or parents, as appropriate. The decision should primarily be based on evidence of failure to thrive as manifested by poor feeding, a drop in growth velocity and/or a failure to gain weight, the severity of the anaemia in repeated measurements and in the absence of intercurrent infections, the level of ineffective erythropoiesis and the development (ideally, prevention) of bony changes.

If available, knowledge of the patient's specific diagnosis, including molecular genetics, can help inform the decision to start regular transfusions but it should not be the primary indicator. Once a regular programme of transfusion is started, to ensure good outcomes, it is important that the pretransfusion haemoglobin target is maintained at an optimal threshold.

A transient drop in haemoglobin due to an intercurrent infection should not drive the initiation of a regular transfusion programme and repeat assessment of clinical parameters is important after a single top-up transfusion to ensure decision making is appropriate.

For deciding when to transfuse on a regular basis, the following should be included in the investigations:

- Confirmed diagnosis of thalassaemia
- Laboratory criteria:
  - Haemoglobin level <7 g/dL on two occasions >2 weeks apart in asymptomatic patients with a $\beta^0\,\beta^0$ or $\beta^0\,\beta^+$ any other genotype known to cause TDT (excluding all other contributory causes such as infections), AND/OR
- Clinical criteria irrespective of haemoglobin level:
  - Significant symptoms of anaemia
  - Poor growth or failure to thrive
  - Complications from excessive intramedullary haematopoiesis such as pathological fractures and facial changes
  - Clinically significant extramedullary haematopoiesis

Monitoring and managing iron overload [1]

4. MONITORING OF IRON OVERLOAD
- 4.1. Serum ferritin
- 4.2. Liver iron concentration
- 4.2.1. *Methods of measuring liver iron concentration*
- 4.3. Myocardial iron estimation: T2* and other tools
- 4.4. Cardiac function
- 4.5. Monitoring of other organ function and iron-mediated damage
- 4.6. 24-hour urinary iron estimation
- 4.7. Plasma non-transferrin-bound iron and labile plasma iron

Chelation therapy helps prevent toxicity from iron and maintain iron balance following transfusion[1]

While the decision to initiate transfusion may be driven by clinical symptoms, evidence suggests improved survival rates in patients whose pretransfusion Hb level is > 10.5 g/dL[1,2]

Hb, hemoglobin; TDT, transfusion dependent ß-thalassemia.

1. Taher AT, et al. Guidelines for the management of transfusion-dependent ß-thalassaemia (TDT). 5th ed. Thalassaemia International Federation; 2025; 2. Musallam KM, et al. Blood 2024;143:930-932.

Review > Expert Rev Hematol. 2024 Sep;17(9):631-642. doi: 10.1080/17474086.2024.2383420. Epub 2024 Jul 26.

Anemia and iron overload as prognostic markers of outcomes in β-thalassemia

Khaled M Musallam [1 2], Sujit Sheth [2], Maria Domenica Cappellini [3], Gian Luca Forni [4], Aurelio Maggio [5], Ali T Taher [6]

A hemoglobin level lower than 10 g/dL has been consistently associated with an increased risk of morbidity and mortality in non-transfusion-dependent β-thalassemia, while elevations by 1 g/dL seem to reduce those risks.

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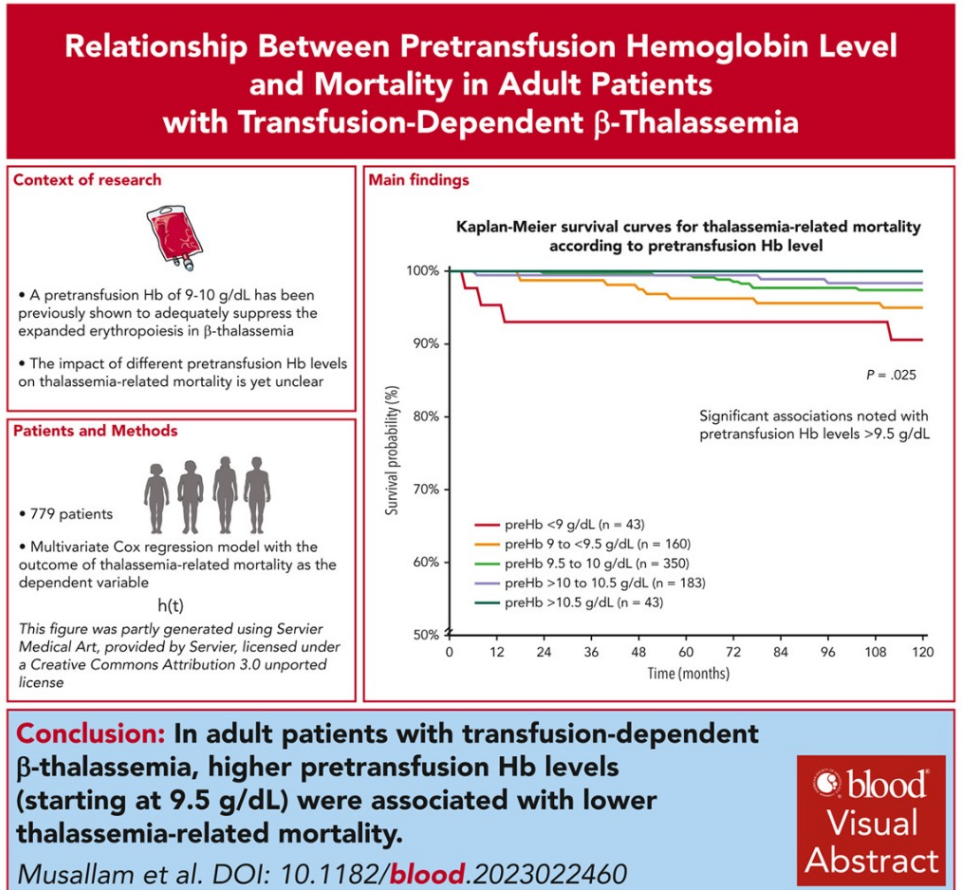
> Blood. 2024 Mar 7;143(10):930-932. doi: 10.1182/blood.2023022460.

Pretransfusion hemoglobin level and mortality in adults with transfusion-dependent β-thalassemia

Khaled M Musallam [1], Susanna Barella [2], Raffaella Origa [3], Giovanni Battista Ferrero [4], Roberto Lisi [5], Annamaria Pasanisi [6], Filomena Longo [7], Barbara Gianesin [8], Gian Luca Forni [8 9]



Advances in understanding of β-thalassemia have led to the development and recent approval of innovative therapies

In recent years, research has led to many advances in β-thalassemia treatment, including regulatory approval in several countries of gene therapy and disease-modifying therapy options

Note: Further information including exact dates for marketing authorization approvals (and withdrawal for beti-cel) can be found at www.ema.europa.eu and www.accessdata.fda.gov
Beti-cel, betibeglogene autotemcel; EMA, European Medicines Agency; exa-cel, exagamglogene autotemcel. NTDT, non-transfusion-dependent β-thalassemia; TDT, transfusion-dependent β-thalassemia.
Taher AT, et al. Guidelines for the management of transfusion-dependent β-thalassaemia (TDT). 5th ed. Thalassaemia International Federation; 2025.

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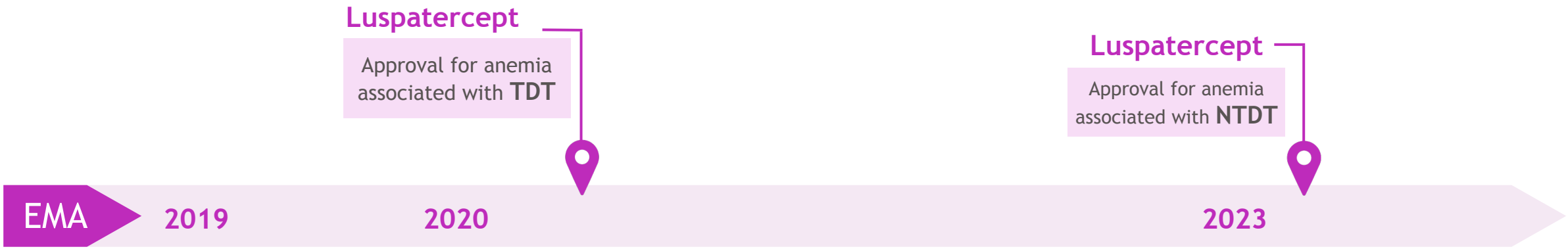

GU n.292/2021 , Determina AIFA 1401 (24.11.2021) Rimborsabilità Luspatercept per TDT
Approvato per NTDT ma ancora non rimborsabilità

Note: Further information including exact dates for marketing authorization approvals (and withdrawal for beti-cel) can be found at www.ema.europa.eu and www.accessdata.fda.gov
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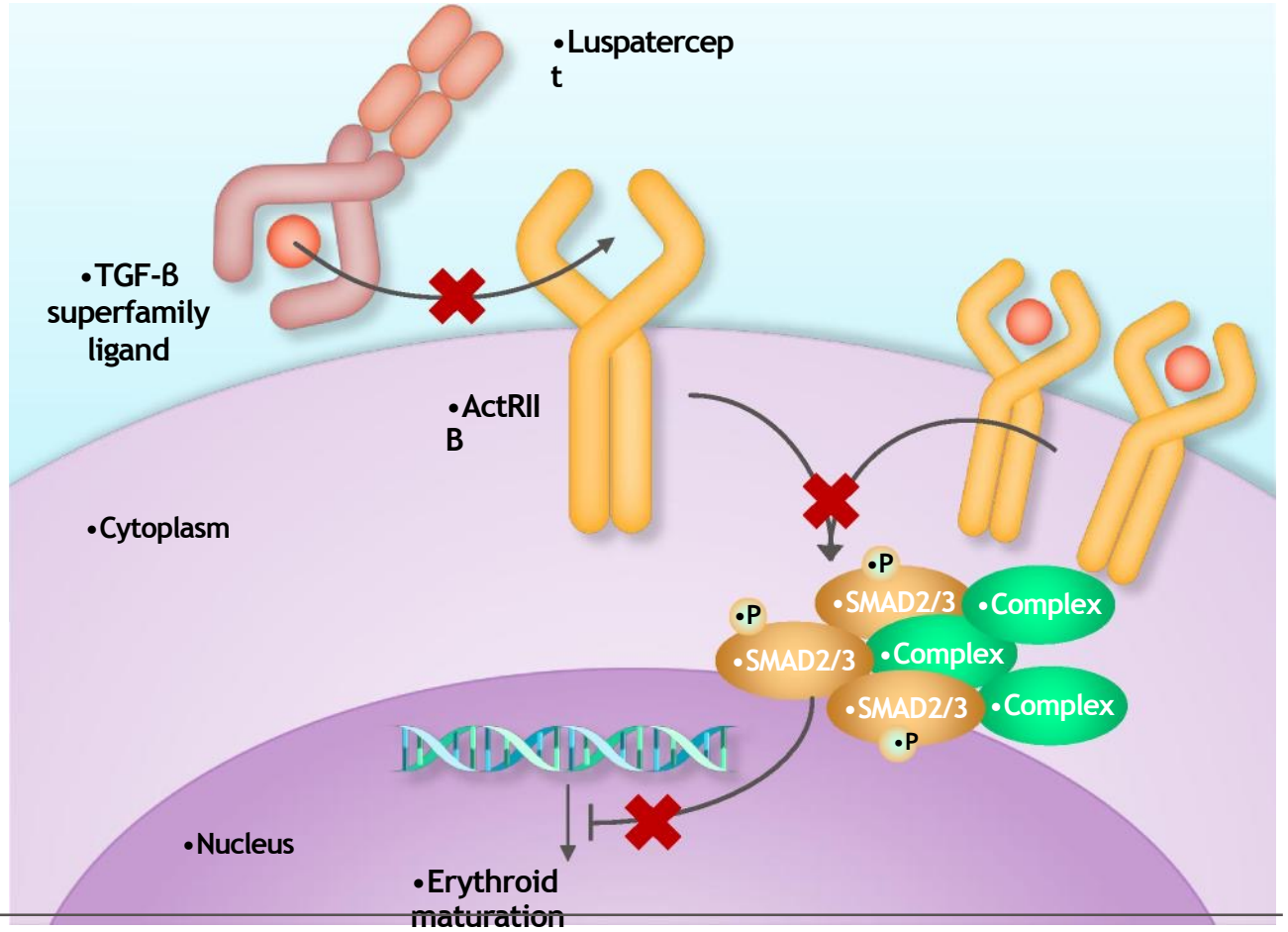
Luspatercept addresses ineffective erythropoiesis

Luspatercept is a first-in-class, recombinant protein that binds to select TGF-β superfamily ligands, inhibits aberrant SMAD2/3 signalings

- Luspatercept binds to select TGF-β superfamily ligands[1]

- This reduces signaling through ActRIIB, thereby inhibiting SMAD2/3 signaling[1]

- Inhibition of aberrant SMAD2/3 signaling restores/enhances erythroid maturation in late-stage erythropoiesis[2,3]



•ActRIIB, activin receptor type IIB; P, phosphorylated; SMAD2/3, mothers against decapentaplegic homolog 2/3; TGF-β, transforming growth factor beta. 1. Attie KM, et al. *Am J Hematol* 2014;89:766-770. 2. Suragani RNVS, et al. *Nat Med* 2014;20:408- 414 [research findings in a mouse model study]. 3. Suragani RNVS, et al. *Blood* 2014;123:3864-3872 [research findings in a mouse model study].

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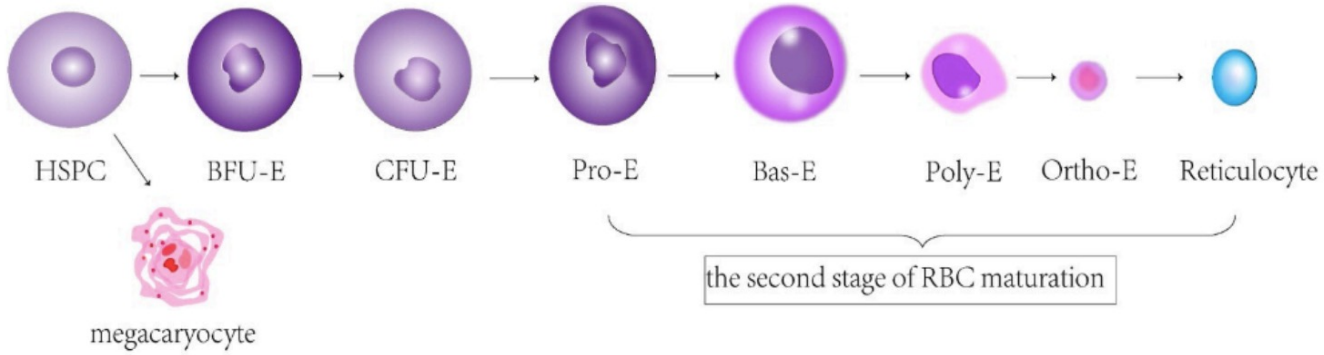

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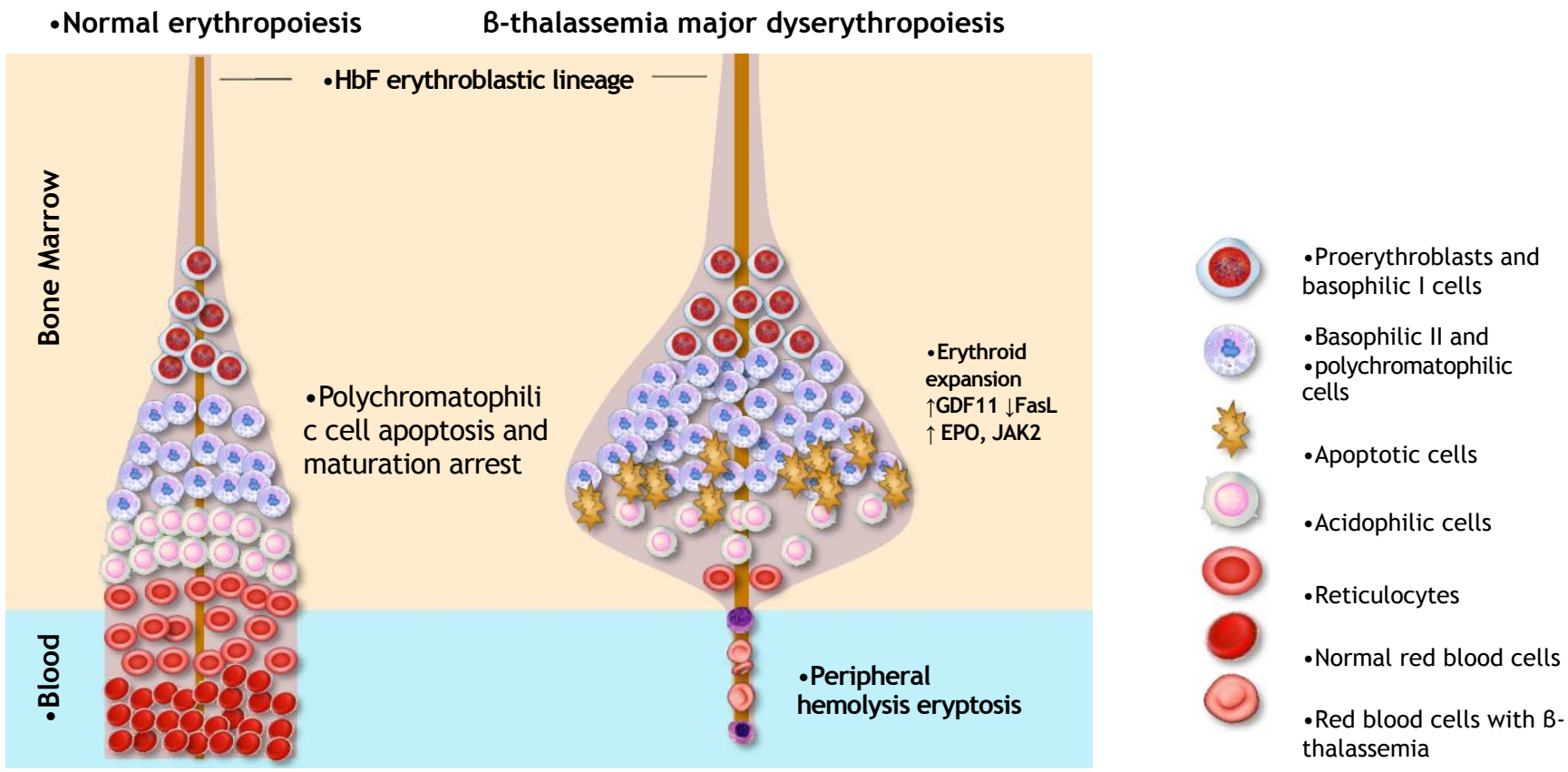
Ineffective erythropoiesis

Defects in erythropoiesis, as seen with β-thalassemia, may lead to accelerated differentiation and apoptosis of erythroid precursors, resulting in decreased RBC output



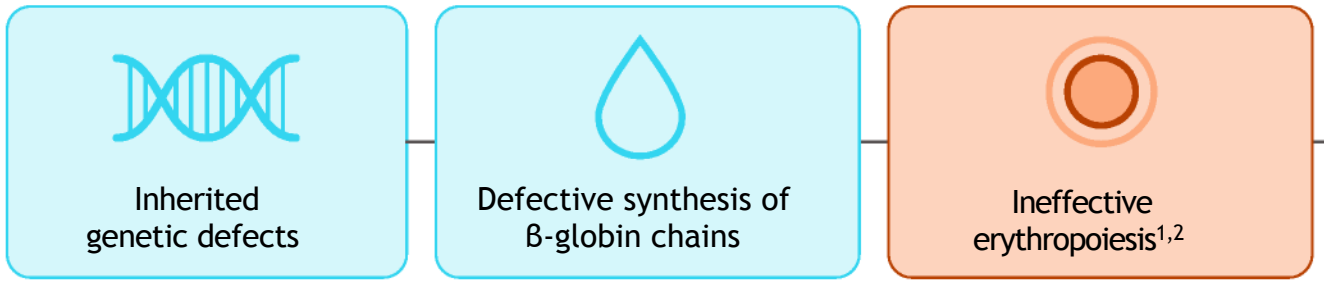
EPO, erythropoietin; FasL, Fas-ligand; GDF11, growth differentiation factor 11; HbF, fetal hemoglobin; JAK2, Janus kinase-2.

Arlet JB, et al. *Curr Opin Hematol* 2016;23:181–188.

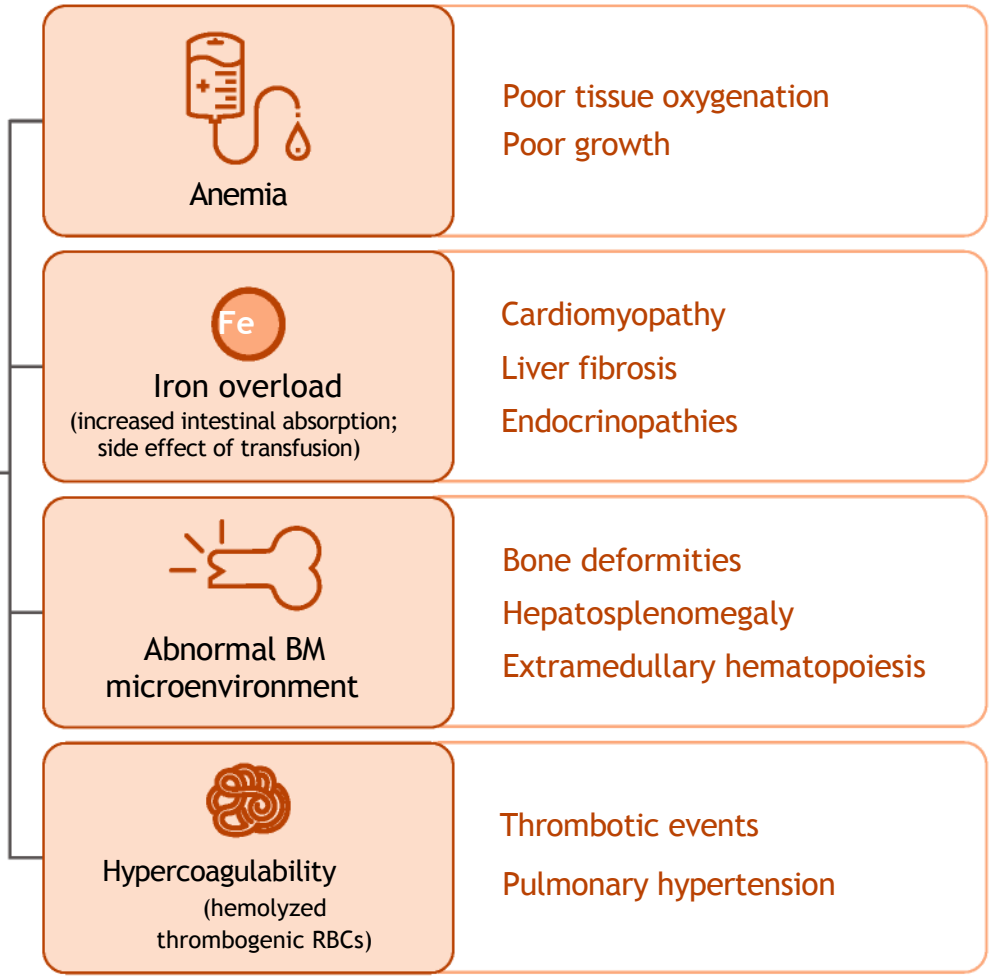
Ineffective erythropoiesis in β-thalassemia

- Anemia is a hallmark of β-thalassemia which, along with various clinical sequelae, can result from ineffective erythropoiesis[1]

Pathogenesis of β-thalassemia[1]



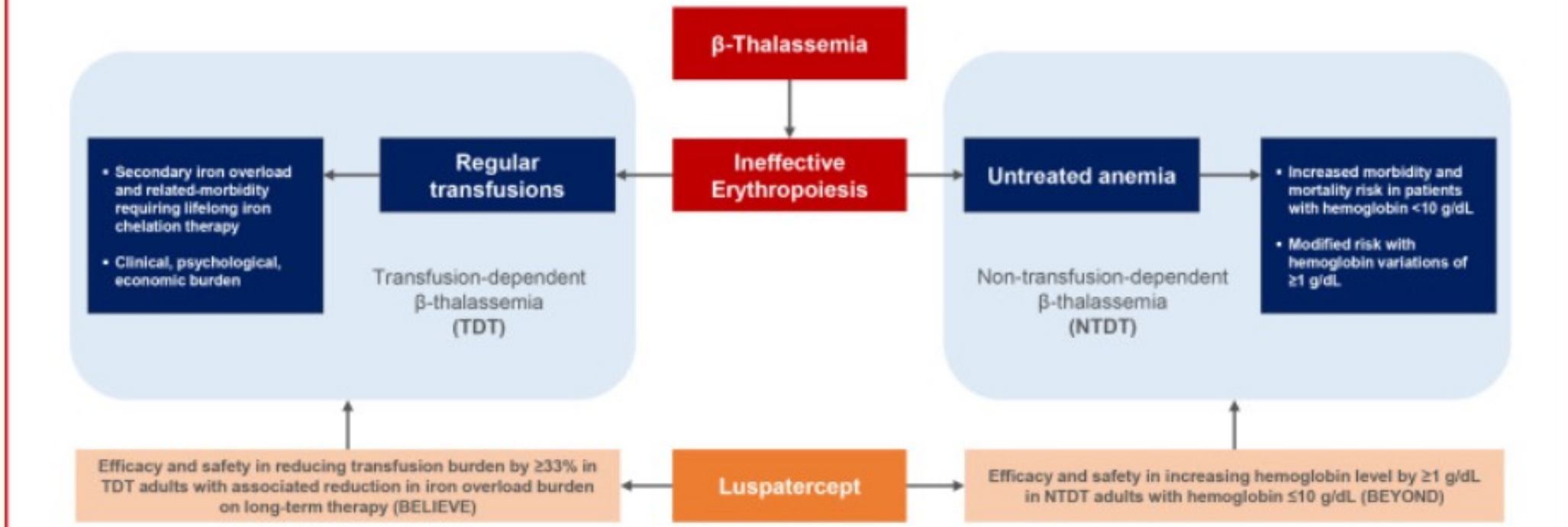
Symptoms of ineffective erythropoiesis[1,2]



BM, bone marrow; Fe, iron; RBC, red blood cell.

1. Cappellini MD, et al. *Blood Rev* 2018;32:300–311. 2. Musallam KM, et al. *Haematologica* 2013;98:833–844.

Luspatercept for β-thalassemia



Conclusions: 1) Luspatercept is an erythroid maturation agent with established benefit in reducing transfusion burden and improving anemia in transfusion-dependent and non-transfusion-dependent forms of β-thalassemia, respectively; 2) data from long-term follow up studies are awaited to demonstrate its impact on iron overload and other morbidity outcomes.

Musallam and Taher. DOI: 10.1182/hematology.2024000567

Luspatercept (Reblozyl®) è approvato in Italia dal 2021 per il trattamento dell'anemia trasfusione-dipendente nei pazienti adulti con sindromi mielodisplastiche (MDS) a rischio molto basso, basso o intermedio con sideroblasti ad anello e in quelli con beta-talassemia (TDT)

Luspatercept was first approved in the USA and Europe for the treatment of anemia in adult patients with TDT[1]

TIF guidelines for the management of TDT[1]

KEY POINTS AND RECOMMENDATIONS

1. Luspatercept is recommended in transfusion-dependent β-thalassaemia (TDT) adults (≥18 years) to achieve transfusion burden reduction (**Grade B, Class I**).
2. The following patient subgroups may be prioritised for luspatercept treatment (**Grade C, Class IIb**):
   - Patients receiving moderate transfusion regimens (≤4 packed red blood cell units/month).
   - Patients with non-β^0/β^0 genotype.
   - Splenectomised patients.
   - Patients unable to sustain transfusion regimen for target haemoglobin level.
   - Patients with progressive iron overload (nonadherence, poor tolerance/response to iron chelation therapy).
3. Luspatercept treatment dosing should follow local prescribing information; otherwise, the below guidance should be followed (**Grade B, Class I**):
   - Starting dose of 1 mg/kg subcutaneously every 3 weeks.
   - Dose increase to 1.25 mg/kg if patient has no reduction in transfusion burden after at least 2 consecutive doses (6 weeks) of 1 mg/kg

Guidelines recommend luspatercept treatment for adult patients with TDT to reduce transfusion burden, and provide expert consensus on patient subgroups who may be prioritized for treatment[1]

TDT, transfusion-dependent thalassemia; NTDT, non-transfusion-dependent ß-thalassemia; TIF, Thalassaemia International Federation.

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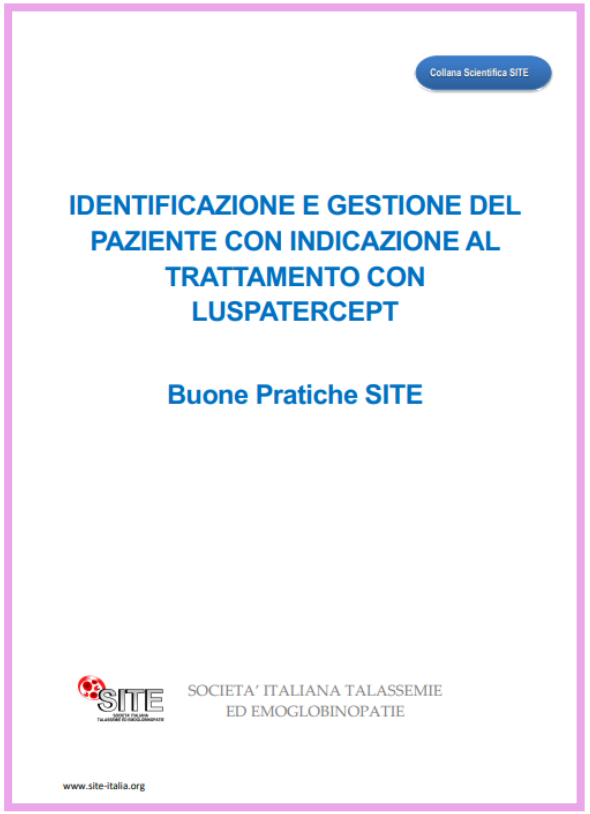

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An understanding of patients' needs and local healthcare system constraints can inform prioritization of patients for luspatercept

Expert opinion on the prioritization of patients with TDT who are eligible for luspatercept therapy[a]

Group 1	Group 2	Group 3
Moderate transfusion regimen (≤ 4 pRBC units/month)	**Heavy** transfusion regimen (>4 pRBC units/month)	Regular transfusions **only to manage specific morbidities** (i.e. prior NTD)
Non-β⁰/β⁰ genotype	**β⁰/β⁰ genotype**	**Specific morbidities** for which transfusions have shown **benefit**
Splenectomized	**Non-splenectomized**	**Good response on other concomitant agents** (e.g. hydroxycarbamide)
Unable to sustain transfusion regimen for target Hb level[b]	No challenges in **adherence to transfusion schedule**	
Progressive **iron overload** (ICT adherence/tolerance/ response issues)	**Low/controllable iron burden**	

[a] Treatment decisions must always take into consideration any applicable contraindications, warnings, and precautions per local prescribing information; [b] For example, due to shortage of blood or scheduling/travel challenges.
ICT, iron chelation therapy; pRBC, peripheral red blood cell; TDT, transfusion-dependent β-thalassemia.
Musallam KM, et al. Ther Adv Hematol 2023;14:1-5.

If luspatercept treatment is under consideration, it is important that HCP and patient align on a meaningful treatment goal[1-3]

Discuss impact of current approach on QoL

Identify patient preferences and concerns

Explain potential benefits and AE risks of luspatercept

Luspatercept decided as next step in treatment plan...

Consider and agree on goal of luspatercept treatment

Using a shared decision-making framework

Treatment goals should be individually tailored for patients with TDT, based on age, disease severity, genotype, comorbidities, patient preferences, and treatment access[2,4]

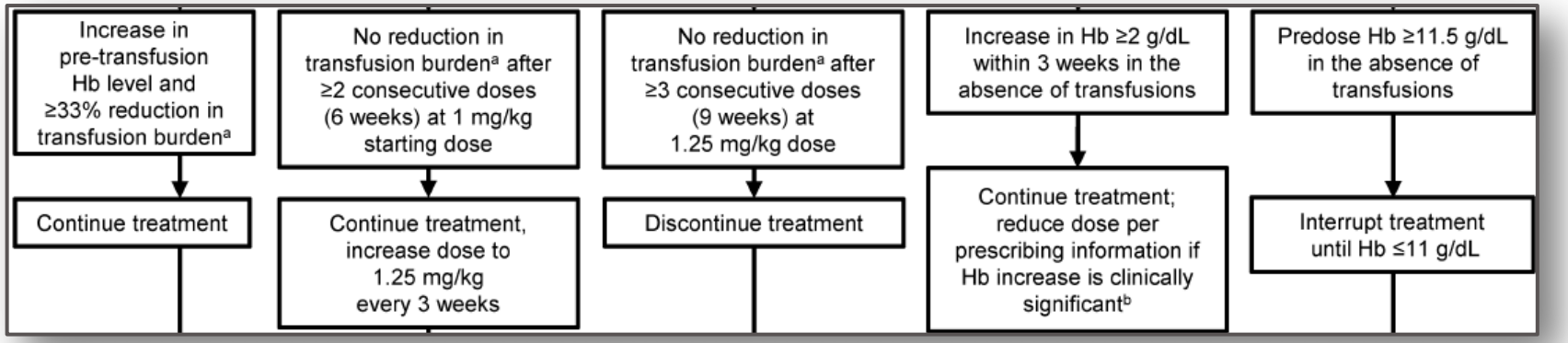
AE, adverse event; HCP, healthcare professional; QoL, quality of life.

1. Taher AT, et al. Guidelines for the management of transfusion-dependent thalassaemia (TDT). 5th ed. Thalassaemia International Federation; 2025; 2. Sheth S, et al. Br J Haematol 2023;201:824–831; 3. Renzi C, et al. Crit Rev Oncol Hematol 2016;99:134-40. 4. El-Beshlawy, et al. Blood Rev 2024;63:101138.

Practical management of patients receiving luspatercept in routine care is key to optimizing patient outcomes and experience[1]

Assess baseline status and agree treatment plan and goal	Include **baseline transfusion requirement** – Analyze ≥12-week period[a] prior to luspatercept initiation – Assess transfusion requirement (RBC units) and pretransfusion Hb level
Initiate luspatercept (1.0 mg/kg)	**Review Hb level** prior to each dose of luspatercept for dose evaluation
Assess safety and tolerability	**Refer to guidance in local prescribing information on managing AEs/EMH masses[2]**
Assess response	Manage within clinical framework (continue/dose adjust/interrupt/discontinue) to support patient's treatment goal

Evaluation of treatment response may be supported by a clinical framework that incorporates **flexibility for individualized treatment goals**



[a] Exclude periods of significant increases in packed RBC consumption, such as during infections and surgical intervention. AE, adverse event; EMH, extramedullary hemopoiesis; RBC, red blood cell.

1. Sheth S, et al. Br J Haematol 2023;201:824-831; 2. Reblozyl® (luspatercept) SmPC April 2025; Available at: https://www.ema.europa.eu/en/documents/product-information/reblozyl-epar-product-information_en.pdf.

Published expert opinion offers real-world insight into when and how to evaluate luspatercept treatment response in TDT[1,2]

Evaluation of treatment response at 6 months

Satisfactory response[2]	Good response[2]	Excellent response[2]
• Any decrease in transfusion requirement **within 6 months** of therapy at the **same or higher pretransfusion Hb level**	• Decrease of ≥ 33% in **transfusion** requirement **within 6 months** of therapy at **same or higher pretransfusion Hb** level	• Decrease of ≥ 50% in **transfusion** requirement **within 6 months** of therapy at **same or higher pretransfusion Hb** level
	• Increase of ≥ 1 g/dL in previously suboptimal **pretransfusion Hb** level on **same or lower transfusion regimen**	• Persistent increase of ≥ 2 g/dL in previously suboptimal **pretransfusion Hb** level on **same or lower transfusion regimen** • **Any decrease** of transfusion requirement or **increase in pretransfusion Hb level within 6 months** of therapy, with notable QoL improvement

Expert opinions suggest luspatercept treatment response should be evaluated at 6 months, based on average change in transfusion requirement over the 6-month treatment period[1,2]

BM, bone marrow; Hb, hemoglobin; QoL, quality of life; TDT, transfusion-dependent β-thalassemia.
1. Sheth S, et al. Br J Haematol 2023;201:824–831; 2 Musallam KM, et al. Ther Adv Hematol 2023;14:1–5.

Practical guidance is available to inform the management of AEs that may be of concern with luspatercept in patients with TDT[1]

	Insights from BELIEVE[1-3]	Recommendations for clinical practice[1]
Bone pain	• Incidence: 19.7% • Mostly low-grade, short duration • Managed with simple analgesics	• If Grade 3/4: **Interrupt treatment per SmPC**[4] • If Grade 1/2: Consider **dose adjustment** if patient can tolerate symptoms — Allows for some ongoing treatment effect so efficacy not completely lost, and facilitates a more reliable response assessment
Arthralgia	• Incidence: 19.3% • Mostly low grade • Caused luspatercept discontinuation in two patients	
Thromboembolic events	• Incidence: 3.6% (incl. two Grade ≥ 3) • In LTFU, incidence increased to 4.1% — All events were in splenectomized patients — All patients with an event had ≥ 1 other risk factor for thromboembolic disease[a]	• Discuss potential thrombotic risk with patient **prior to starting luspatercept** — Analyze potential **risk factors** — Ensure **informed decision is made with patient** • Consider **thromboprophylaxis** per clinical practice guidelines • **Monitor** closely for signs and symptoms

[a] Such as a history of thrombocytosis or venous thrombosis, iron overload at baseline, obesity, thrombocytosis, or diabetes.
AE, adverse event; LTFU, long-term follow-up.
1. Sheth S, et al. Br J Haematol 2023;201:824-831; 2. Cappellini M, et al. N Engl J Med 2020;382;1219-1231 (incl. suppl); 3. Cappellini M, et al. Lancet. 2025;E180-E189 (incl. suppl); 4. Reblozyl® (luspatercept) SmPC April 2025; Available at: https://www.ema.europa.eu/en/documents/product-information/reblozyl-epar-product-information_en.pdf.

Real-world studies provide practical insights and experience on how to optimize luspatercept treatment outcomes for patients with TDT

Real-world outcomes with luspatercept reflect findings from the BELIEVE study, including:

- ↑ Improvement in pretransfusion Hb level
- ↓ Reduction in RBC units transfused
- ↑ Increase in transfusion intervals
- ↑ Improvement in iron parameters
- ↑ Increase in quality of life

Insights from real-world studies include:

- **New potential predictors of response** to luspatercept e.g. baseline fetal Hb levels
- **Additional patient subgroups who may benefit** from luspatercept, including:
  - Those with **higher baseline TB** vs. BELIEVE study
  - Those with transfusion challenges due to **alloimmunization**
- **Potential for TI in patients who had converted from NTDT to TDT**

Studies of luspatercept in multiple real-world settings have shown similar outcomes to those in BELIEVE and have reiterated the importance of informed patient selection and treatment optimization

Insights from observational studies from Greece, Italy, USA, Turkey, and Malaysia.
NTDT, non-transfusion-dependent β-thalassemia; TB, transfusion burden; TDT, transfusion-dependent β-thalassemia; TI, transfusion independence.
Taher AT, et al. Guidelines for the management of transfusion-dependent thalassaemia (TDT). 5th ed. Thalassaemia International Federation; 2025.

Real World

CORRESPONDENCE OPEN ACCESS

Luspatercept for Transfusion-Dependent Beta-Thalassemia: Real-World Experience in a Large Cohort of Patients From Italy

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Keywords: extramedullary hematopoiesis | luspatercept | real-world setting | thromboembolism | transfusion-dependent thalassemia

To the Editor,

The randomized, placebo-controlled phase III BELIEVE study led to the approval of luspatercept to promote erythroid maturation in the United States and Europe [1]. Given the need for scientific evidence on its efficacy, tolerability, and safety in clinical practice, we evaluated the effects of luspatercept in 231 patients with transfusion-dependent thalassemia (TDT) (Figure S1) who received their first dose of the drug post-marketing at 27 Italian specialized centers under the patronage of the Società Italiana Talassemia ed Emoglobinopatie (Tables S1 and S2).

The median treatment duration was 272 days (Q1–Q3: 150–531, range: 21–1007). At the time of data collection, 106 patients (45.9%) had discontinued the drug after a median time of 172 days of treatment (Q1–Q3: 99–307, range: 21–671) (Figures S2 and S3, Table S3). In part, the high number of patients who prematurely discontinued may be associated with the fact that the lives of these patients revolve around transfusions and the transfusion cycle governs every aspect of their existence. Consequently, the loss of a normal transfusion schedule and/or transfusion independence can create anxiety and insecurity. A solid doctor-patient therapeutic alliance is essential to begin therapy under optimal conditions for success.

In our study, both the primary and secondary endpoints of the BELIEVE trial were achieved at comparable or significantly higher rates. During the treatment period, 44 patients (19%) had a transfusion-free interval of at least 8 weeks (median: 14.9 weeks, range: 8–115 weeks). Their characteristics are reported in Table S4. Notably, the analysis revealed a likelihood gradient: the probability of a greater response increased from β0 genotype to the association between heterozygosity for β-thalassemia and triplication or quadruplication of the α-globin genes.

In the 13–24-week follow-up, 69 (29.9%) and 38 (16.4%) experienced ≥ 33% and ≥ 50% reduction in transfusion requirements, respectively ($p = 0.05$ and $p = 0.006$ compared with the BELIEVE study) [1]. Across the 12-week follow-up periods, 178 (77%) and 91 (39.3%) patients had ≥ 33% and ≥ 50% decrease in blood transfusion rate. A pairwise *t*-test focusing on the initial six 12-week

231 pazienti provenienti da 27 Centri Italiani

15.5 % excellent response

43.9 % good response

22.0 % satisfactory response

18.2 % no efficacy

Real World

Dropout 45.9 % (lavorare su alleanza terapeutica)

Eventi trombo-embolici (8 pazienti)
2 stroke ischemici(attenzione a selezione pazienti)

7 pazienti con nuova EMH o peggioramento (attenta valutazione)

American Journal of Hematology

WILEY

AJH

COMMENTARY OPEN ACCESS

Luspatercept in Transfusion-Dependent β-Thalassemia: The Benefit Is Real, and So Are the Risks

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Luspatercept, an erythroid maturation agent promoting late-stage erythropoiesis, has been approved for the treatment of anemia in adult patients with transfusion-dependent β-thalassemia (TDT) since 2019. The marketing authorization was based on data from the phase 3 BELIEVE trial which showed that 21.4% of 224 patients had at least a 33% reduction in their transfusion requirement compared to 4.5% of 112 controls receiving placebo [1]. This was achieved in a fixed time window between weeks 13 and 24 compared with baseline. Patients also had to have at least 1 g/dL increase in pretransfusion hemoglobin level to allow for reduction of transfusion amount or delay of transfusion visit, both being permitted in the protocol. The trial also reported erythroid response (≥ 33% and ≥ 50% reduction) during several other fixed (weeks 13–24 or 37–48) and "rolling" (any 12 or 24 weeks) intervals throughout the trial. Long-term data from BELIEVE showed durability of response, with patients achieving ≥ 33% reduction during any 12-week interval having a median of 586 cumulative days in response [2, 3].

There were several challenges with interpreting BELIEVE's efficacy data and applying them to routine practice. First, the various definitions of erythroid response in the trial made it hard for patients and healthcare providers to realize what tangible benefits to expect from treatment in a real-life setting, and response definitions that guide dose escalation or treatment discontinuation in the prescribing information were too restrictive and short-termed. Second, subgroup analyses in BELIEVE showed response across all evaluated subgroups, making it difficult to ascertain which patients should be prioritized for treatment; a strategy that may be necessary in resource-limited settings considering the high cost of the drug. Thus, data from real-world studies were awaited to confirm luspatercept's efficacy and shed more light on these unanswered questions, but unfortunately, only few studies have been reported to date mostly stemming from single center case series, claims databases, or early access programs [4–11].

The study by Origa et al. [12] in this issue of the *American Journal of Hematology* comes in as the largest available real-world evidence on luspatercept's use in TDT, with 231 patients treated for a median of 272 days (longest 1007 days), and provides several clinically relevant learnings. When considering the various erythroid response definitions used in BELIEVE, the authors found similar or slightly better response rates, which are reassuring. Thus, irrespective of the response definition, it can now be established that what was observed in the trial translates back to the clinics.

An expert opinion was also published in 2023 [13], revisiting response considerations for patients receiving luspatercept and introducing modified response definitions categorized as excellent, good, and satisfactory based on what were believed to be more practical and clinically relevant criteria. Origa et al. [12] also evaluated response in their study based on these modified definitions (with minor adaptation). One key element of response in these definitions, which was not considered in BELIEVE, is considering patients who had an increase in pretransfusion hemoglobin level without necessarily having a reduction in transfusion requirement as responders. This may be the only benefit achievable in regions where average pretransfusion hemoglobin levels are already below guideline recommendations (e.g., some parts of the Middle East and Asia), and for whom the goal of

Real World

Patient 1: I. TDT

Sex: F
Age: 22 aa
At diagnosis: at DP

Genotype: $\beta^0$39/ $\beta^0$39
α genotype $\alpha\alpha/\alpha\alpha$
Promoter gene UGT1-A1 : (TA)7/ / (TA)7

SIGNS & SYMPTOMS/ DISEASE BURDEN

- Inizio terapia trasfusionale 4 mesi
- Splenomegalia
- Ittero
- Non sovraccarico marziale

TREATMENT

- Acido folico
- **Terapia chelante combinata**

Deferiprone 100 mg/Kg die +
Deferasirox 21 mg/kg per 3 volte/settimana

- Acido urso-dessossicolico

COMORBIDITIES/ OTHER CONSIDERATIONS

- Calcolosi biliare
- Gilbert Syndrome
- Proteinuria ortostatica benigna

Patient 1 : Aligning on a luspatercept treatment goal is critical in guiding patient expectations and engaging them in their treatment plan

46 unità/anno

Intervallo trasfusionale
2-3 settimane

Hb pre-
trasfusionale
8.5-9.4 gr/dl

19.12.2022

Luspatercept
1 mg/Kg

Non risposta

13.3.23

Luspatercept
1.25 mg/Kg

40 unità/anno

Intervallo trasfusionale
3 settimane

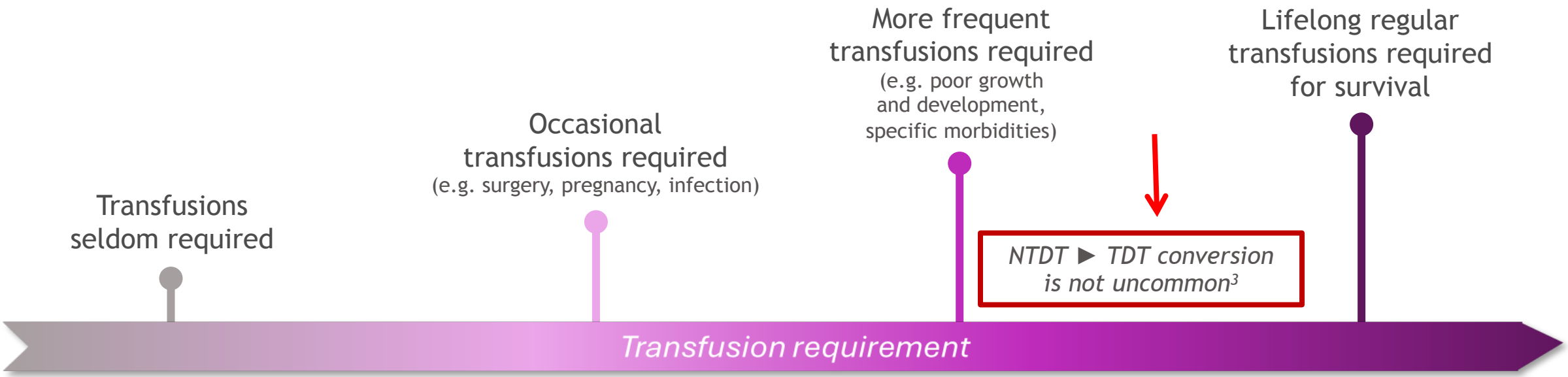
Hb pre-
trasfusionale
9.6/10.7 gr/dl

28.8.2025

Dose 48°

Terapia chelante invariata

Transfusion requirement is used to distinguish two major clinical phenotypes of ß-thalassemia: NTDT and TDT[1,2]



NTDT		TDT
ß-thalassemia minor/trait ß⁺/ß or ß⁰/ß	ß-thalassemia intermedia Mild/moderate HbE/ß-thalassemia ß⁺/ß⁺ or ß⁰/ß⁺	ß-thalassemia major Severe HbE/ß-thalassemia ß⁰/ß⁰
• Borderline asymptomatic anemia • RBC abnormalities (microcytosis, hypochromia)	• Delayed presentation (> 2 years) • Mild to moderate anemia	• Early presentation (≤ 2 years) • Severe anemia • Severe clinical symptoms

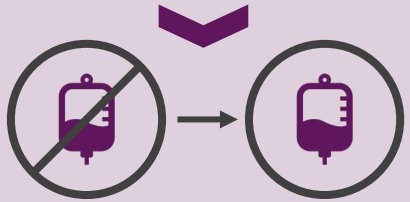
ß, wild-type allele with no mutation; ß⁰, severe mutations and absent ß-globin production; ß⁺, mild mutations and reduced ß-globin production; HbE, hemoglobin E; NTDT, non-transfusion-dependent ß-thalassemia; RBC, red blood cell; TDT, transfusion-dependent ß-thalassemia.

1. Taher AT, et al. Guidelines for the management of non-transfusion-dependent thalassaemia (NTDT). 3rd ed. Thalassaemia International Federation; 2023; 2. Musallam KM, et al. Haematologica 2013;98:833-844; 3. Musallam KM, et al. Am J Hematol 2024;99:490-493.

Patients with β^{+}/β^{+} or β^{0}/β^{+} genotypes may be diagnosed in adulthood and can transition from NTDT to TDT later in life[1,2]

- Patients with **β-thalassemia intermedia with mild genotypes** are sometimes **diagnosed late in adulthood**[2]
- These patients are **usually NTD, but may become TD** late in adulthood[2]
- Starting **regular transfusions can greatly impact QoL** for these patients[2]
- **Alloimmunization is more common** in patients who initiate transfusions in adulthood[2]
- **Treatments options for anemia** without transfusion in alloimmunized patients **are limited**[2]
- Older/frail patients with comorbidities are typically **excluded from RCTs**[2]

Retrospective cohort study of 305 adult patients with NTDT attending treatment centers across Italy[1]



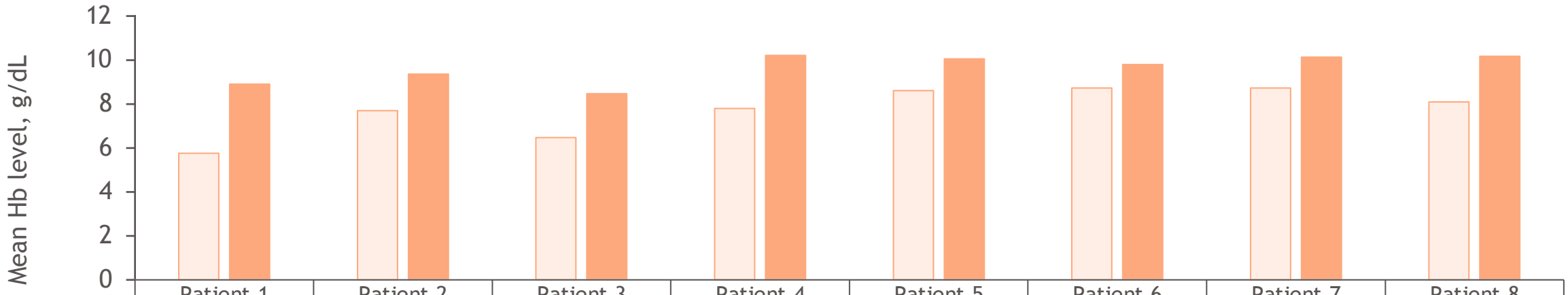
13.8%

of patients became TD during the 10-year observation period

NTDT, non-transfusion-dependent β-thalassemia; NTD, non-transfusion-dependent; QoL, quality of life; RCT, randomized clinical trial; TD, transfusion-dependent; TDT, transfusion-dependent β-thalassemia.
1. Musallam KM, et al. Am J Hematol. 2024;99:490-493; 2. Chatzidavid S, et al. Annual Sickle Cell & Thalassaemia Conference 2024; presentation 6448359.

Real-world data suggest that *neo*TD patients may experience anemia amelioration and transfusion independence with luspatercept

Mean Hb level pre- and post-luspatercept treatment



	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Pre-lusp	5,75	7,7	6,48	7,8	8,6	8,72	8,73	8,1
Post-lusp	8,91	9,36	8,47	10,21	10,06	9,8	10,14	10,18

RBC units/month								
Pre-lusp	0	1.3	2.5	2.3	1	2.5	2	1
Post-lusp	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

In *neo*TD patients, luspatercept treatment resulted in increased mean Hb levels with all patients achieving transfusion independence

Hb, hemoglobin; lusp, luspatercept; *neo*TDT, recent conversion from NTD to TD β-thalassemia; TI, transfusion independence.
Chatzidavid S, et al. ASCAT 2024. Oral presentation 6448369.

Patient 2: G. NTDT patient becomes *neo*TD later in life

Sex: M
Age: 64 y
At diagnosis: 4 y
Occupation: Engineer

β genotype: $\beta^0 39 / \beta^{6-A)}$
α genotype : αα/αα
Xmn +/–
Promoter gene UGT1-A1 : (TA)7 /(TA)/7

SIGNS & SYMPTOMS/ DISEASE BURDEN

Diagnosi effettuata per pallore e ittero

Pochissime, sporadiche trasfusioni nel corso della vita

Splenectomia + colecistectomia all' età di 36 anni

Hb media: 7.5-8.0 gr/dl)

Idrossiurea/acido folico

Deferioxamina 1 gr/ 2 volte/settimana

Rivaroxaban

Terapia cardiologica (bisoprololo fumarato, digossina, perindopril arginina, furosemide)

Terapia osteoporosi (colecarciferolo, calcio carbonato)

COMORBIDITIES

Ipertensione polmonare moderata
Eritropoiesi extra-midollare NO
Sovraccarico marziale NO
Fibrillazione atriale permanente
Osteoporosi
Gilbert Syndrome

Patient 2: Aligning on a luspatercept treatment goal is critical in guiding patient expectations and engaging them in their treatment plan

- Inizio terapia trasfusionale Febbraio 2023 (62 aa)
- 2-3 unità ogni 28 giorni (Hb pre-trasfusionale 8.0-8.5 gr/dl)
- 4 Dicembre 2024 : Hb 8.3 gr/dl : ultima trasfusione (2 unità)
  e inizio terapia Luspatercept (1 mg/Kg)
- Dopo 3 settimane Hb 9.8 gr/dl
- Dopo 28 giorni Hb 10.2 gr/dl
- Controlli e terapia ogni 3 settimane : Hb 9.9-10.6 gr/dl
- 3.9.2025 Dose 14° Hb 9.3 gr/dl . Possibile aumento dose in base a follow-up successivo

Patient 3: F. NTDT patient becomes *neo*TD much later in life

Sex: M
Age: 79 y
At diagnosis: 77 y
Occupation: retired

- Anamnesi: eterozigosi per β-talassemia con livelli di Hb 9.5/10 gr/dl
- Una trasfusione all' età di 75 aa in occasione di intervento chirurgico, seguita da terapia con ferro e.v.
- Consulenza ematologica per sospetta Sindrome mielodisplasica : splenomegalia (16 cm), lieve leucopenia (GB 4.000/mm3) e piastrinopenia (PP 118.000/mm3), moderata anemia (Hb 9.7 gr/dl)
- **Aspirato midollare e BOM: non criteri di emolinfopatia primitiva midollare o di citopenia di natura clonale**
- **NGS non eseguita**

Patient 3: NTDT patient becomes *neo*TD much later in life

Sex: M
Age: 79 y
At diagnosis: 77 y
Occupation: retired

- Ci viene inviato per sospetta NTDT
- Test Microcitemia : Hb 9.6 gr/dl MCV 77 fl, MCH 24.9 pg, HbA2: 4.0 % HbF : 13%
- **Ferritina 1.430 ng/L**

Patient 3: NTDT patient becomes *neo*TD much later in life

Sex: M
Age: 79 y
At diagnosis: 77 y
Occupation: retired

- Ci viene inviato per sospetta NTDT : β eterozigote + gene α triplicato ????
- Test Microcitemia : Hb 9.6 gr/dl MCV 77 fl, MCH 24.9 pg, HbA2: 4.0 % HbF : 13%
- **Ferritina 1.430 ng/L**
- Sequenze geni β: **$\beta^0$39 / β^+ -223 (T>C)promoter**
- **MLPA cluster α: negative per delezioni/duplicazioni**

Patient 3: NTDT patient becomes *neo*TD much later in life

Sex: M
Age: 79 y
At diagnosis: 77 y
Occupation: retired

Genotype: $\beta^0 39$ / β^+ -223 (T>C)promoter
MLPA cluster α: negative per delezioni/duplicazioni
α Genotype αα/αα

- Ci viene inviato per sospetta NTDT : β eterozigote + gene α triplicato ????
- Test Microci … % HbF : 13%
- **Ferritina 1.4**
- Sequenze geni β: **$\beta^0 39$ / β^+ -223 (T>C)promoter**
- **MLPA cluster α: negative per delezioni/duplicazioni**

Genotype–phenotype correlation and report of novel mutations in β-globin gene in thalassemia patients

Rachana Nagar [1], Sujata Sinha [2], Rajiva Raman [3]

Affiliations + expand

PMID: 25976460 DOI: 10.1016/j.bcmd.2015.03.005

Spectrum of mutations among various disease groups. The highlighted 3 mutations are novel to literature. OC = Obligate Carrier.

Mutations	TM (156 alleles)	TI (17 cases)	BTT (5 alleles)	OC (44 alleles)	Total
IVS1-5(G–C)	73	8	2	22	105 (52.7%)
CD16 (–C)	10	1	0	4	15 (7.5%)
CD30 (G–A)	9	4	0	3	15 (7.5%)
CD8/9(+G)	13	2	0	0	14 (7.0%)
HbE	7	6	0	1	14 (7.0%)
CD41/42(–TCTT)	9	1	0	2	12 (6.0%)
CD15 (G–A)	6	0	0	0	06 (3.0%)
IVS1-1(G–T)	4	0	1	0	05 (2.5%)
HbS	2	2	0	1	04 (2.0%)
619 bpΔ	2	0	1	0	03 (1.5%)
–88 (+T)	1	0	0	0	01 (0.5%)
Capsite +1 (A–C)	1	1	0	0	02 (0.1%)
CD5 (–CT)	1	1	0	0	02 (0.1%)
IVS1-1(G–A)	0	0	1	0	01 (0.5%)
CD2(–A)	0	0	0	1	01 (0.5%)
–42 (C–G)	0	1	0	0	01 (0.5%)
–223 (T–C)	1	0	0	0	01 (0.5%)
Total	139	27	5	34	206
Uncharacterized	17			8[a]	25 (10.4%)

[a] One of the family had both the parents with a triplicated alpha allele.

Patient 3: NTDT patient becomes *neo*TD much later in life

Sex: M
Age: 79 y
At diagnosis: 77 y
Occupation: retired

Genotype: $\beta^0$39 / β^+ -223 (T>C)promoter
MLPA cluster α: negative per delezioni/duplicazioni
α genotype αα/αα

- Ci viene
- Test Mic
- **Ferritin**
- Sequenze geni β: **$\beta^0$39 / β^+ -223 (T>C)promoter**
- **MLPA cluster α: negative per delezioni/duplicazioni**

20/06/22, 15:39 HbVar ID 3060

About HbVar | Summaries of mutation categories | Query form | Query history | FAQ | Contact us

HbVar: A database of Human Hemoglobin Variants and Thalassemias

Detail page display

beta nt -223 T>C **beta nt -223 T>C**

HbVar ID 3060
HGVS name HBB:c.-273T>C
Also Known As

Hematology and Clinical Presentation

	Clinical presentation	Laboratory findings	Comments
Heterozygote Hematological disorder(s) unlikely related to the variant	• severe Anemia • Other: Thalassemia major phenotype, on regular transfusion	• Hypochromia	Child with a TM phenotype since 6-months of age.

Mutation sequence analysis
DNA sequence changes are Experimental;
Protein sequence changes are Computed;
nt -223 T>C in beta

Occurrence

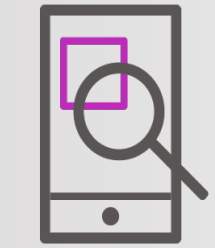
Ethnic background
Indian

Comments
The c.-273T>C mutation does not impose any effect on the function of HBB protein and should be considered as a benign variant

Patient 3: NTDT patient becomes *neo*TD much later in life

Sex: M
Age: 79 y
At diagnosis: 77 y
Occupation: retired

Genotype: $\beta^0 39$ / β^+ -223 (T>C)promoter
MLPA cluster α: negative per delezioni/duplicazioni
α Genotype αα/αα



- **Qualcosa non torna....**
- Dopo 6 mesi progressiva anemizzazione (Hb 7.5 gr/dl) fino a richiedere trasfusioni regolari (3 unità ogni 3 settimane)
- Lenta ma progressiva riduzione Leucociti e Piastrine
- Incrementa terapia chelante per rapido aumento Ferritina (2.930 ng/L)

Patient 3: NTDT patient becomes *neo*TD much later in life

Sex: M
Age: 79 y
At diagnosis: 77 y
Occupation: retired

Genotype: $\beta^0$39 / β^+ -223 (T>C)promoter
MLPA cluster α: negative per delezioni/duplicazioni
α Genotype αα/αα

- 17.5.2025 inizio terapia con **Luspatercept (1 mg/Kg)**
- Da allora Hb 9.8-10.7 gr/dl e 1 sola trasfusione per sintomatologia clinica (astenia)
- Contemporaneamente sollecitiamo altra consulenza ematologica per riduzione leucociti e piastrine

Patient 3: NTDT patient becomes *neo*TD much later in life

Sex: M
Age: 79 y
At diagnosis: 77 y
Occupation: retired

Genotype: $\beta^0 39$ / β^+ -223 (T>C)promoter
MLPA cluster α: negative per delezioni/duplicazioni
α Genotype αα/αα

- 17.5.2025 inizio terapia con L
- Da allora Hb 9.8-10.7 gr/dl e 1
- Contemporaneamente solleci iti e piastrine

Questo laboratorio aderisce alla rete GIMEMA LabNet e JAKNet

RICERCA DI MUTAZIONI IN NEXT GENERATION SEQUENCING (NGS)

NPL: **5-376** | Materiale esaminato: DNA da aspirato midollare | Struttura inviante:

Indicazione all'analisi: Neoplasia Mielodisplastica

L'indagine molecolare è stata eseguita mediante tecnologia di Next Generation Sequencing (NGS) su piattaforma Ion Torrent Gene Studio S5.

Il pannello dei geni Oncomine Myeloid Panel contiene: intera regione codificante dei *geni ASXL1 , BCOR, CALR,CEPBA, ETV6, EZH2, IKZF1,NF1, PHF6, PRPF8, RB1, RUNX1, SH2B3, TET2,TP53, ZRSR2* e regioni hotspot di *ABL1, BRAF, CBL, CSF3R, DNMT3A, GATA2, IDH1, IDH2, JAK2, KIT, KRAS, MPL, MYD88*, NPM1, *NRAS, PTPN11,SETBP1,SF3B1,SRSF2, U2AF1, WT1.*

RISULTATO

Sono state identificate le seguenti varianti:

Gene	Alterazione nucleotidica c.HGVS	Alterazione aminoacidica p.HGVS	Frequenza Allele Mutato (%)
SF3B1	c.2098A>G	p.Lys700Glu	32%

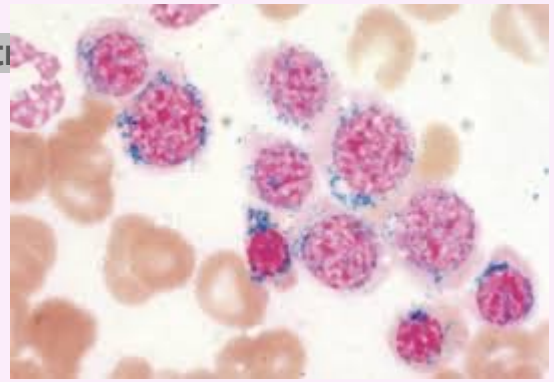
I risultati dell'analisi mutazionale devono essere integrati con i dati citogenetici, morfologici e immunofenotipici e interpretati nel contesto clinico del paziente

Patient 3: NTDT patient becomes *neo*TD much later in life

Sex: M
Age: 79 y
At diagnosis: 77 y
Occupation: retired

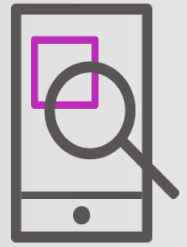
Genotype: $\beta^0 39$ / β^+ -223 (T>C)promoter
MLPA cluster α: negative per delezioni/duplicazioni
α Genotype αα/αα

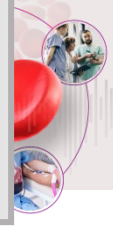
- 17.5.2025 inizio terapia con **Luspatercept (1 mg/Kg)**
- Da allora Hb 9.8-10.7 gr/dl e 1 sola trasfusione per sintomatologia clinica (astenia)
- Contemporaneamente sollecitiamo altra consulenza ematologica per riduzione leucociti e piastri
- NGS riscontro di mutazione gene SF3B1
- Rivalutazione aspirato midollare con colorazione MGG: riscontro di sideroblasti ad anello



Sex: M
Age: 79 y
At diagnosis: 77 y
Occupation: retired

Diagnosi : Mielodisplasia con sideroblasti ad anello





- Le sindromi mielodisplastiche con sideroblasti ad anello (MDS-SA) sono neoplasie mieloidi con caratteristiche morfologiche (presenza di sideroblasti ad anello) e biologiche (mutazione SF3B1) ben distinte.
- Sono associate a buona prognosi
- IPSS e IPSS-R le collocano tra le forme a basso rischio e in genere con outcome favorevole
- Gli studi clinici suggeriscono che i pazienti con la mutazione di SF3B1 sono più a rischio di manifestare un accumulo di ferro quando sottoposti a trasfusioni regolari.
- **La mutazione del gene SF3B1 nelle sindromi mielodisplastiche (MDS) è associata a una risposta positiva al Luspatercept, un farmaco innovativo. Questa terapia rappresenta rappresenta un'importante opzione per i pazienti con MDS e mutazione SF3B1, migliorando i risultati rispetto ai trattamenti convenzionali.**

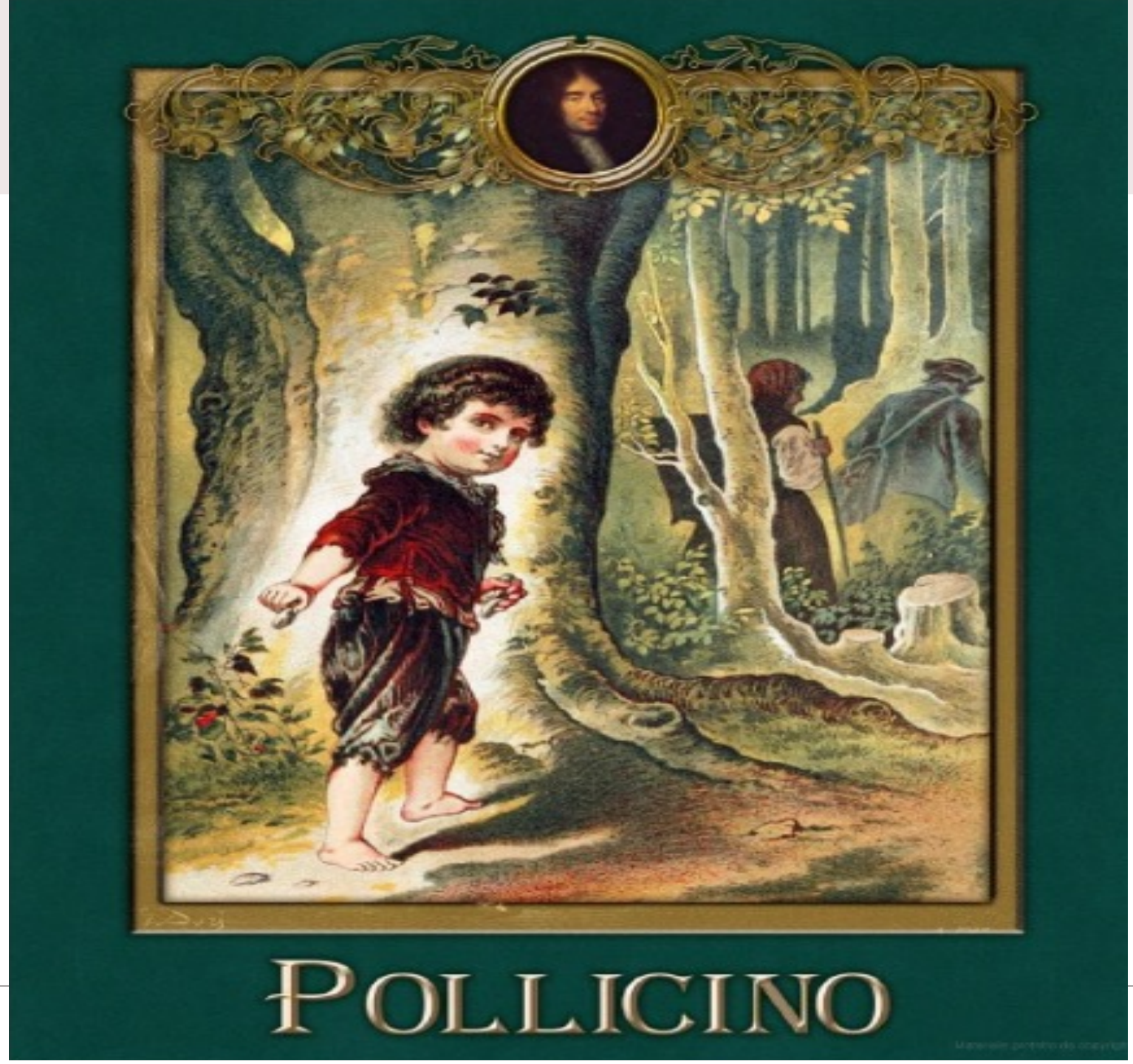
. Greenberg Pl et al. Blood 2012; Aber DA et al.Blood 2016

Patient 3: NTDT patient becomes *neo*TD much later in life

Sex: M
Age: 79 y
At diagnosis: 77 y
Occupation: retired

Diagnosi :
Mielodisplasia con sideroblasti ad anello

- 17.5.2025 inizio terapia con **Luspatercept (1 mg/Kg)**
- Da allora Hb 9.8-10.7 gr/dl e 1 sola trasfusione per sintomatologia clinica (astenia)
- 9.9.2025 Controllo dopo 3 settimane dalla trasfusione : **Hb 12.7 gr/dl -> rinviato Luspatercept**
- Leucociti nella norma
- Piastrinopenia in trattamento con Eltrombopag


POLLICINO