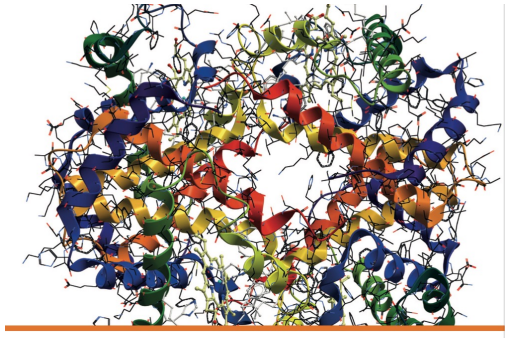
AGGIORNAMENTO SU DIAGNOSI E TERAPIA DELLE EMOGLOBINOPATIE

Milano, 15 Novembre 2024 | Starhotels E.C.H.O.



Con il patricinio di SITE SOCIETA' ITALIANA TALASSEMIE ED EMOGLOBINOPATIE

Terapie delle sindromi talassemiche

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SS Emoglobinopatie, disturbi ereditari del metabolismo e del sistema immunitario
Dipartimento Area Medica
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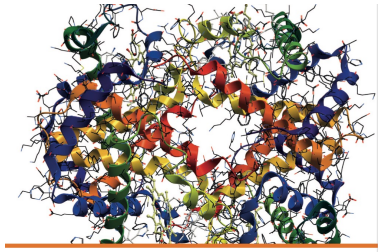
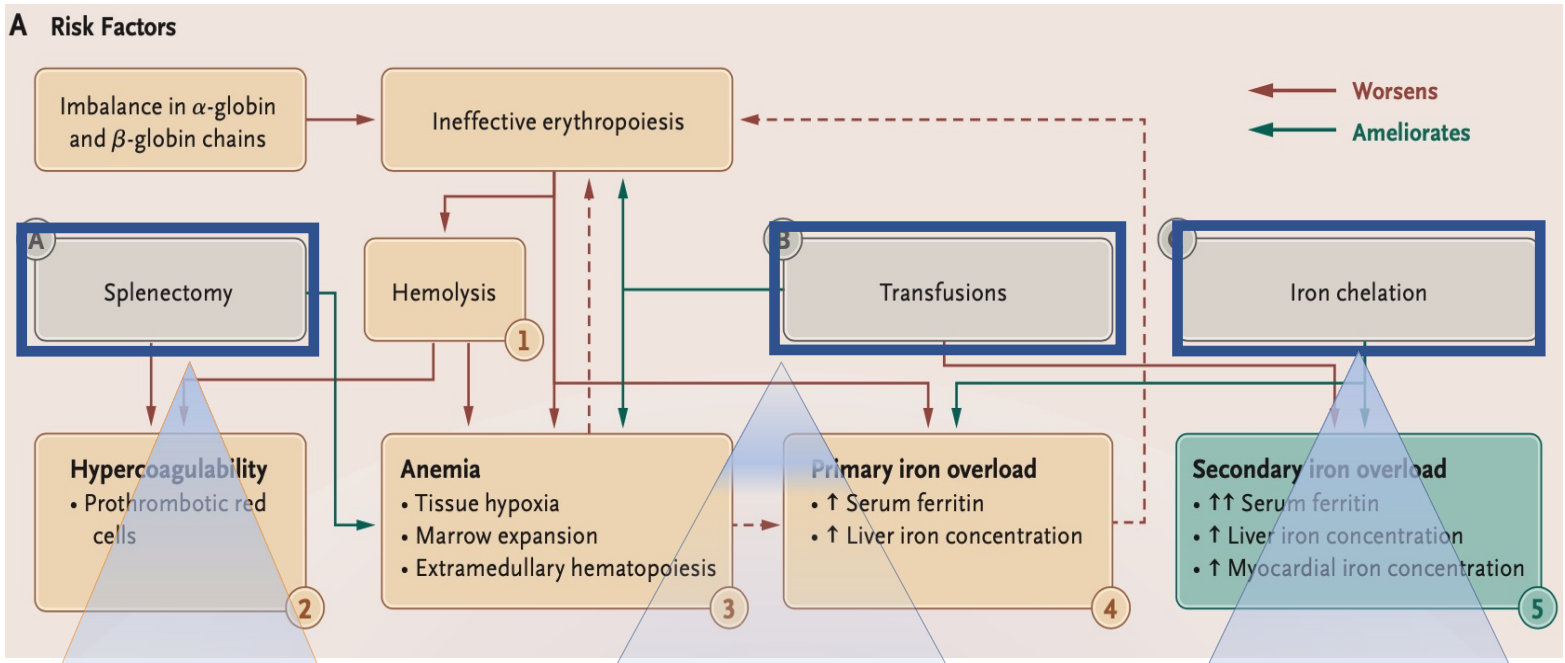
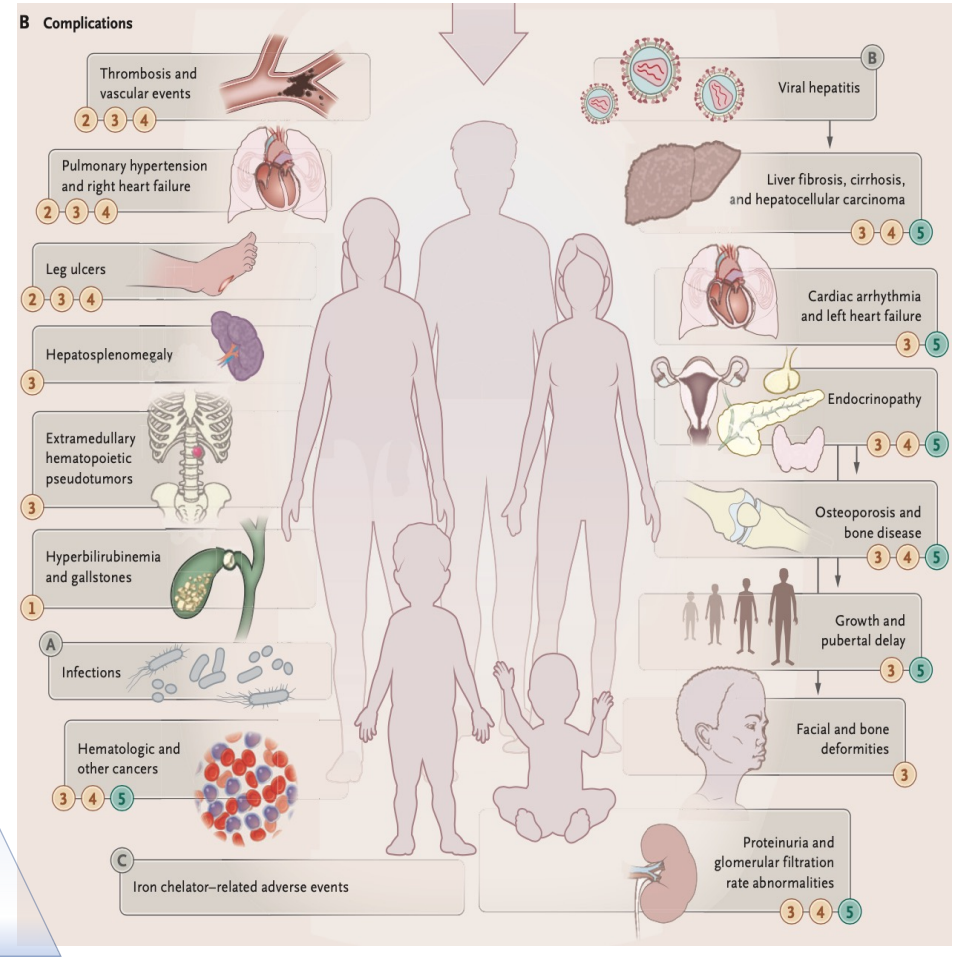
Terapie «cardine»







Selected cases

Lifesaving

Pretransfusion Hb levels

Blood availability and donors

Alloimmunization

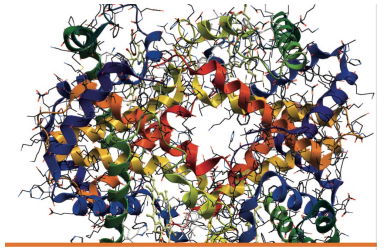
Complications related to blood transfusion

Time to initiate

Monitoring the overload

Drugs (options and schemes)

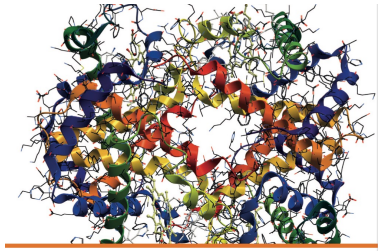
Blood transfusions: guidelines



Transfusion	Iron Chelation Therapy	Splenectomy
• TDT patients must receive regular blood transfusions for survival • Indications for transfusion NTDT: 1) **Occasional blood transfusions** : Surgery, Severe infections, Pregnancy 2) **Frequent blood transfusions:** (a) Children with growth failure and poor performance at school (b) Adults with diminished exercise tolerance, failure of secondary sexual development, declining hemoglobin level and with a huge enlargement of spleen (>3 cm/year) 3) **Preventive transfusions:** Patients at high risk of thrombotic disease, PHTN, extramedullary hematopoiesis leg ulcers.	• **Indication to initiate ICT:** TDT: SF levels ≥ 1000µg/L NTDT: SF ≥ 800 ng/mL and/or LIC ≥ 5 mg/g dry wt. liver • **Indications to intensify ICT:** TDT: SF ≥ 2500 ng/mL and/or LIC > 7 mg/g dry wt. liver and/or cardiac T2* < 20 msec. NTDT: LIC after 6 months of treatment > 7 mg/g dry wt. liver or SF >1500-2000 ng/mL and < 15% decrease from baseline. • **Indications to stop ICT:** TDT: SF < 300 ng/mL and/or LIC <3 mg/g dry wt. liver NTDT patients: SF < 300 ng/mL and/or LIC <3 mg/g dry wt. liver	• Main **indications for splenectomy** in both TDT and NTDT are: (a) **hypersplenism leading to cytopenias** and (b) **splenomegaly heralding imminent rupture** or accompanied by left upper quadrant pain or early satiety. • Also indicated in TDT patients with **increased blood requirement** preventing adequate control with iron chelation therapy • Also indicated in NTDT patients with **worsening anemia** leading to poor growth and development • Splenectomy, however, should be restricted to certain indications in view of the associated increased risk of venous thrombosis, pulmonary hypertension, and overwhelming post-splenectomy infections. • **Splenectomy is becoming obsolete in patients with TDT**

Taher AT, Lancet 2018; 391: 155–67

Blood transfusions: guidelines in TDT



LIFELONG REGULAR BLOOD TRANSFUSIONS

TARGET HB LEVELS: 9.5-10.5 G/DL

TIMETABLE: EVERY 2 TO 5 WEEKS

REGULAR GROWTH

NORMAL PHYSICAL and DAILY ACTIVITIES

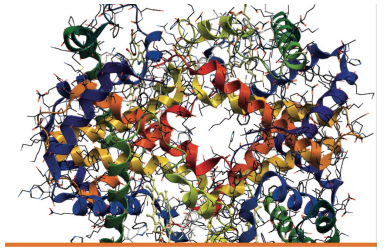
BONE MARROW SUPPRESSION

MINIMIZES TRANSFUSIONAL IRON ACCUMULATION

TIME TO TRANSFUSE ONE UNIT OF BLOOD: 60-90 MINUTES

Cappellini MD, Guidelines for Management on TDT, TIF 4th Edition, 2021

Blood transfusions: guidelines



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Taher AT, Lancet 2018; 391: 155–67

Safe blood transfusions

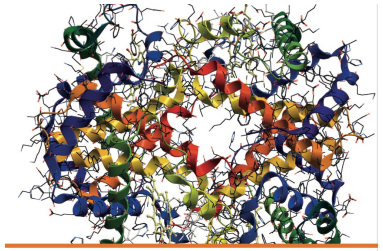


Table 1. Current international recommendations for safe blood transfusion of patients with transfusion-dependent β-thalassemia.

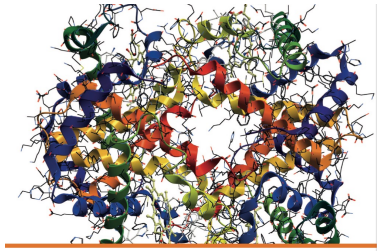
Thalassemia International Federation 2021 recommendations for transfusions

- Patients with confirmed β-thalassemia should receive RBC transfusions every 2–5 weeks to maintain a pre-transfusion level of hemoglobin in the range 9–10.5 g/dL (11–12 g/dL recommended for patients with cardiac complications)
- Ensure appropriately screened donor blood is available (voluntary, regular and non-remunerated donations preferred)
- Extended RBC antigen typing of patients to be carried out prior to first transfusion. Type for at least D, C,c, E, e, and K antigens
- Transfuse ABO, Rh-compatible blood at each transfusion, matched for ABO, C, c, E, e, and K antigens if possible
- A full cross-match and screening for new antibodies should be carried out before each transfusion (centers that meet regulatory requirements perform an electronic cross match)
- Leukoreduced packed RBCs should be used for transfusion; filtration before storage is highly recommended but blood bank pre-transfusion filtration is acceptable (bedside filtration is only acceptable if the other two filtration options are not available)
- Washed RBCs should be used for patients who have severe allergic reactions
- RBCs stored in CPD-A should be transfused within 1 week of collection; RBCs stored in additive solutions should be transfused within 2 weeks of collection
- Post-transfusion hemoglobin levels should be kept lower than 14–15 g/dL
- Records for each patient should be kept detailing annual transfusion requirement, red cell antibodies, and any transfusion reactions/allergic reactions

CPD-A, citrate-phosphate-dextrose-adenine; RBC, red blood cell [8].

Taher AT. EXPERT REVIEW OF HEMATOLOGY 2021, VOL. 14, NO. 10, 897–909

Alloimmunisation



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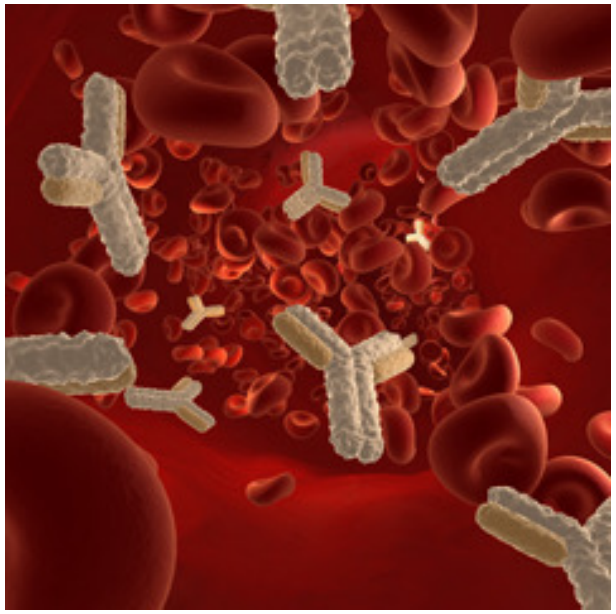
Risk factors

Age, female gender, splenectomy

Units received/frequency

Etnic correlation between donors and recipient

Higher alloAb in NTDT



Protective factors for alloantibodies

Increased antigen matching for Rh and kell

Use of leucoreduced RBC

Franchini M, Blood Transfus 2019; 17:4-15

Anemia e valori di Hb

Di fronte a pazienti con tratto talassemico o con talassemia (trasfusione/non trasfusione dip.)

La riduzione marcata dei livelli di Hb nonostante supporto trasfusionale puo' essere secondaria a differenti cause (gravidanza e parto, infezioni, perdite, positività per HP etc) e prevede accertamenti per verificare la causa della riduzione rispetto ai valori abituali

Es. ematomi intraddominali post partum, parvovirus, immunizzazione etc

I livelli ridotti di Hb rispetto all'abituale devono avere una causa che deve essere ricercata

Anemia e valori di Hb

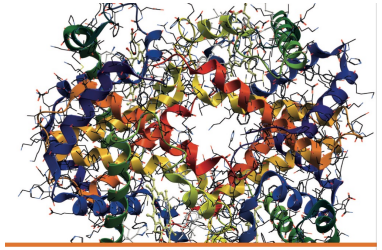
Di fronte a pazienti con tratto talassemico o con talassemia (trasfusione/non trasfusione dip.)

Terapia con ferro ev o per os solo in caso di carenza marziale verificata con tutti i parametri (emocromo, sideremia, transferrina, ferritina, saturazione transferrina) previe indagini per identificarne la causa.

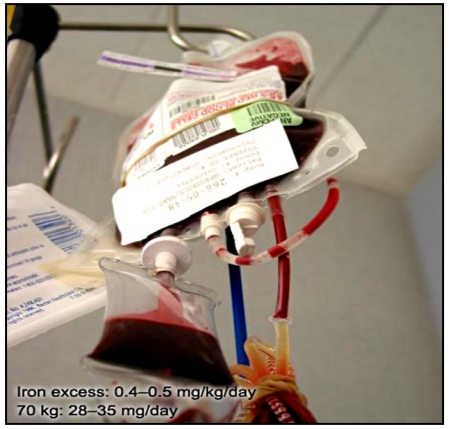
Es. perdita per stillicidio cronico da emorroidi sanguinanti e da metrorragie

Il paziente talassemico, che non ha condizione di sideropenia, non necessità di terapia marziale per correggere i valori di Hb

Blood transfusions and iron overload

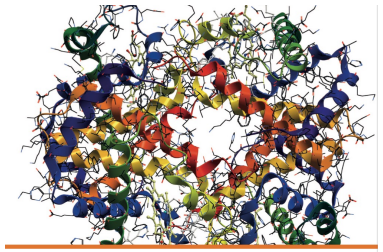


- A unit processed from 420 ml of donor blood contains approximately 200 mg of iron
- Iron intake (mg/kg/day) = [blood transfused (ml) x hematocrit (%) x 1.08]/weight/days
- Total body iron: 3–4 g
- Absence of mechanisms reducing the exceeding iron

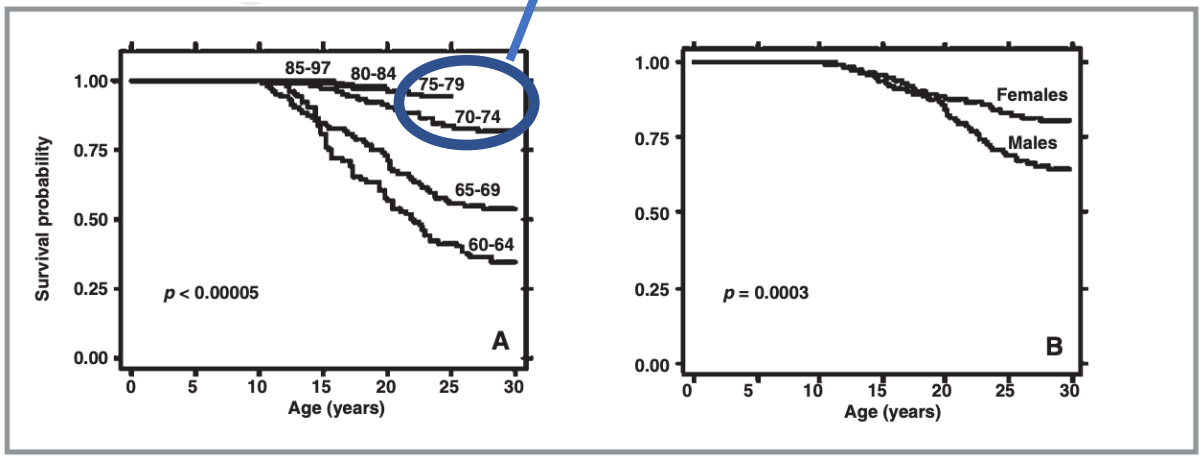


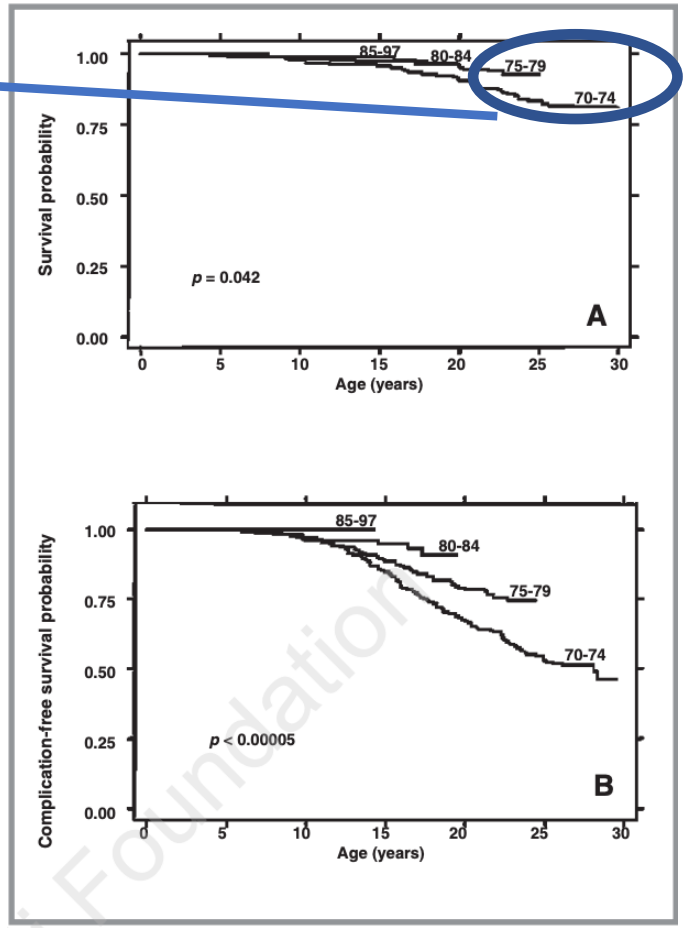
Cappellini MD, Farmakis D, Porter J, Taher A. Guidelines for the management of transfusion dependent thalassaemia (TDT). 4° Edition (version 2.0) 2021.
Porter JB. Br J Haematol. 2001;115:239

Chelation treatment: increased survival



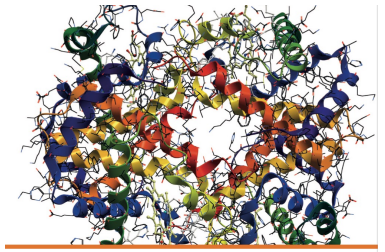
Chelation treatment





Borgna-Pignatti et al. Haematologica, 2004;89:1187-1193

Chelation treatment: what we look for?

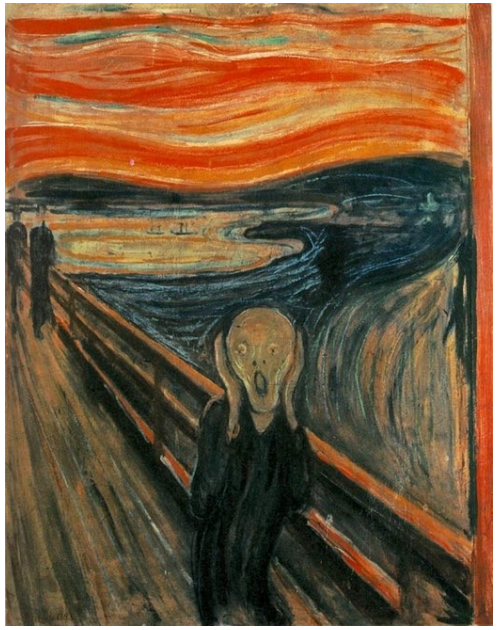


Choosing drug

Iron burden

Target of iron overload

Transfusional iron intake and history of the patients for chelation therapy



Dosage of chelators

Patient/family preferences

Adverse effect profiles

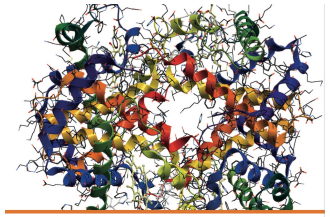
Adherence

Guidelines for chelation treatment in some group of patients

Tailored therapy

Ware HM et al. Pediatr Clin N Am 60 (2013) 1393–1406

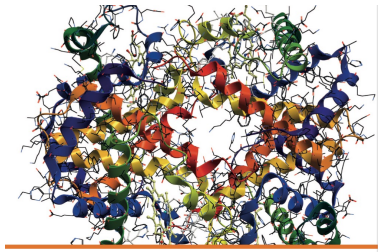
Chelation treatments available



Parameter	Deferoxamine	Deferiprone	Deferasirox
Administration	SC or IV 8-12 hours, 5-7 days/week	Oral 3 times daily	Oral Once daily
Half-life of iron free drug	20-30 min	3-4 hr	12-16 hr
Lipid solubility	Low	Intermediate	High
Route of iron excretion	Urinary and fecal	Urinary	Fecal
Recommended dose	30-60 mg/kg/day	75-100 mg/kg/day	7-28 mg/kg/die
TIF guidelines indication			
TDT	>2 years: first-line	2-6 years: no sufficient data >6 years: second-line*	2-6 years: first-line (US), second-line (EU) >6 years: first-line
NTDT	No sufficient data	No sufficient data	>10 years: first-line
Most relevant clinical data			
TDT	• Reduction in SF and LIC • Improvement in cardiac T2* • Improvement in cardiac dysfunction with continuous infusion	• Improvement of cardiac T2 in monotherapy or combination with deferoxamine (higher doses that commonly used in clinical practice)†[125,126] • Improvement in cardiac dysfunction in combination with deferoxamine*†[127] • Improvement in endocrine dysfunction in combination with deferoxamine or deferasirox[128,129]	• Reduction in SF and LIC up to five years and cardiac T2* up to three years of therapy even in severely loaded patients • Non-inferior to deferoxamine for improvement of cardiac T2* • Improvement in hepatic fibrosis and inflammation • Stabilization of heart function • Stabilization of endocrine function
NTDT	Data restricted to case series and small studies	Data restricted to case series and small studies	Significant reduction in SF and LIC up to two years of therapy
Main adverse events	Ocular, auditory, bone growth retardation, local reactions, allergy	Gastrointestinal, arthralgia, agranulocytosis/neutropenia	Gastrointestinal, increased creatinine, increased hepatic enzymes
Pregnancy	Contraindicated (but has been used in third trimester)	Contraindicated	Contraindicated

Modified from Taher AT, Lancet 2018; 391: 155–67

Unmet needs



ACCESSIBILITY

- Limited access to regular and safe blood transfusions
- Limited availability of iron chelators
- Lack of specialists and multidisplinary teams

COST

- Financial and economic burden to patient and the family
- Higher medication and medical costs

ADVERSE EVENTS

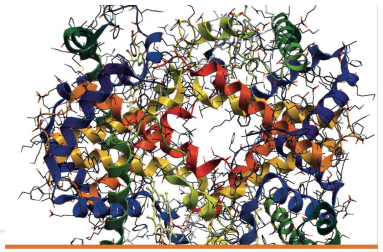
- Alloimmunization
- Transfusion-related reactions (allergic, hemolytic, etc)
- Infections

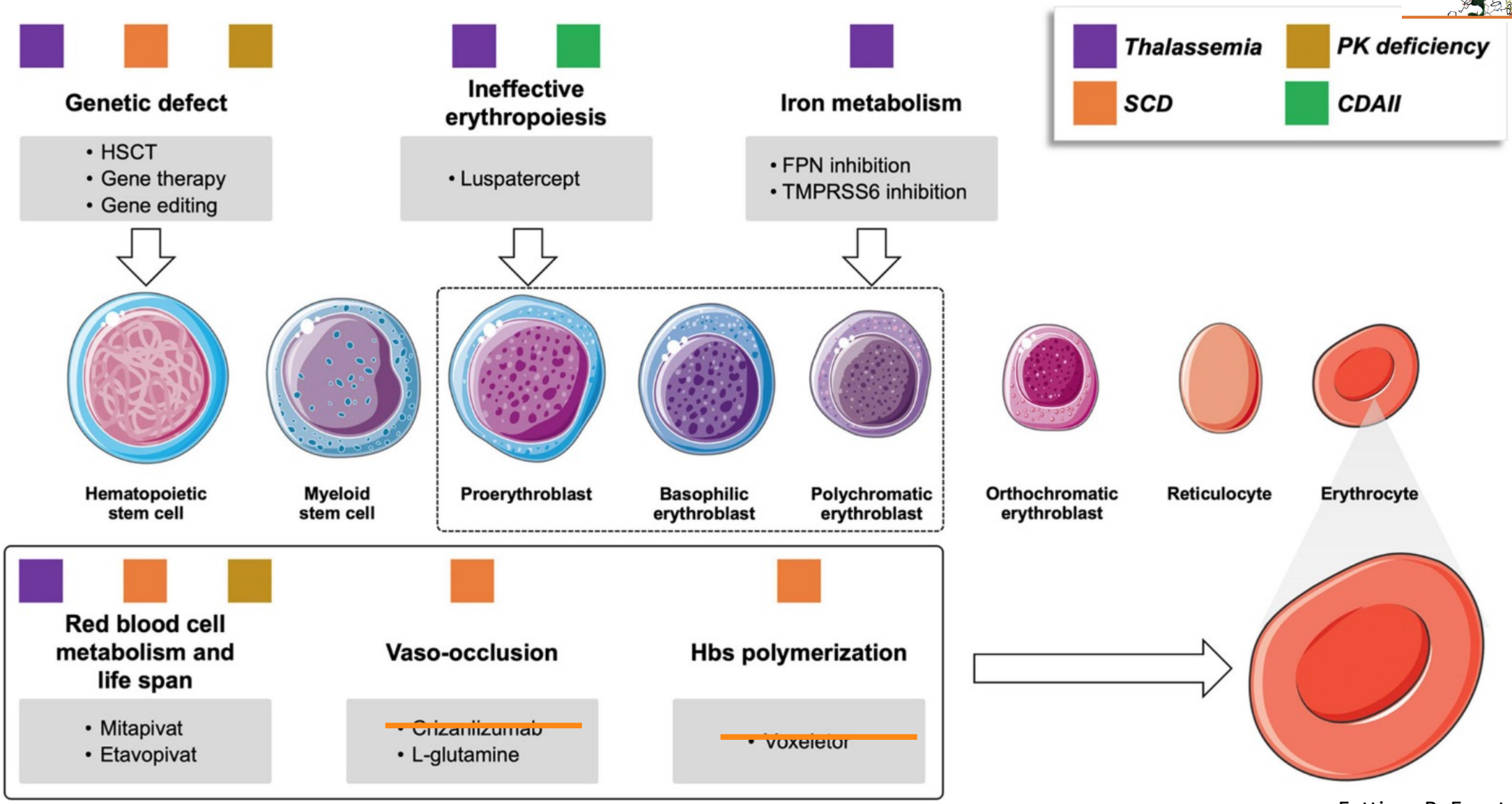
CONVENIENCE

- Lack of compliance and adherence to therapy
- Frequent monitoring and outpatient visits needed

From Njeim R.. et al., Transfusion clinique et biologique, 31 (2024): 48–55.

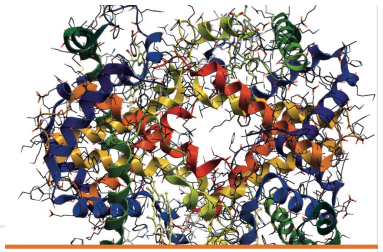
Novel treatments: future and not

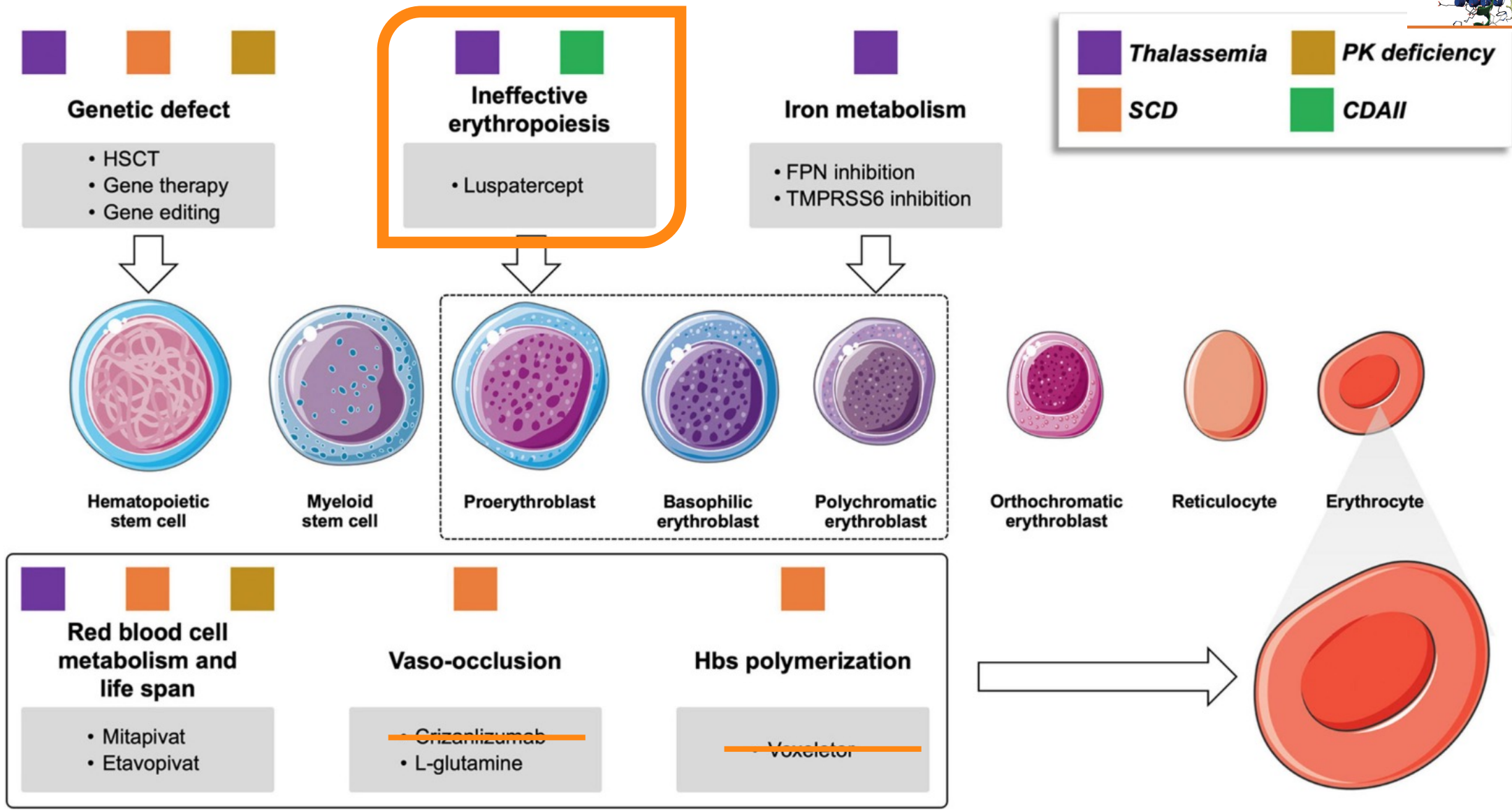




Fattizzo B, Front Med 2023

Novel treatments: future and not

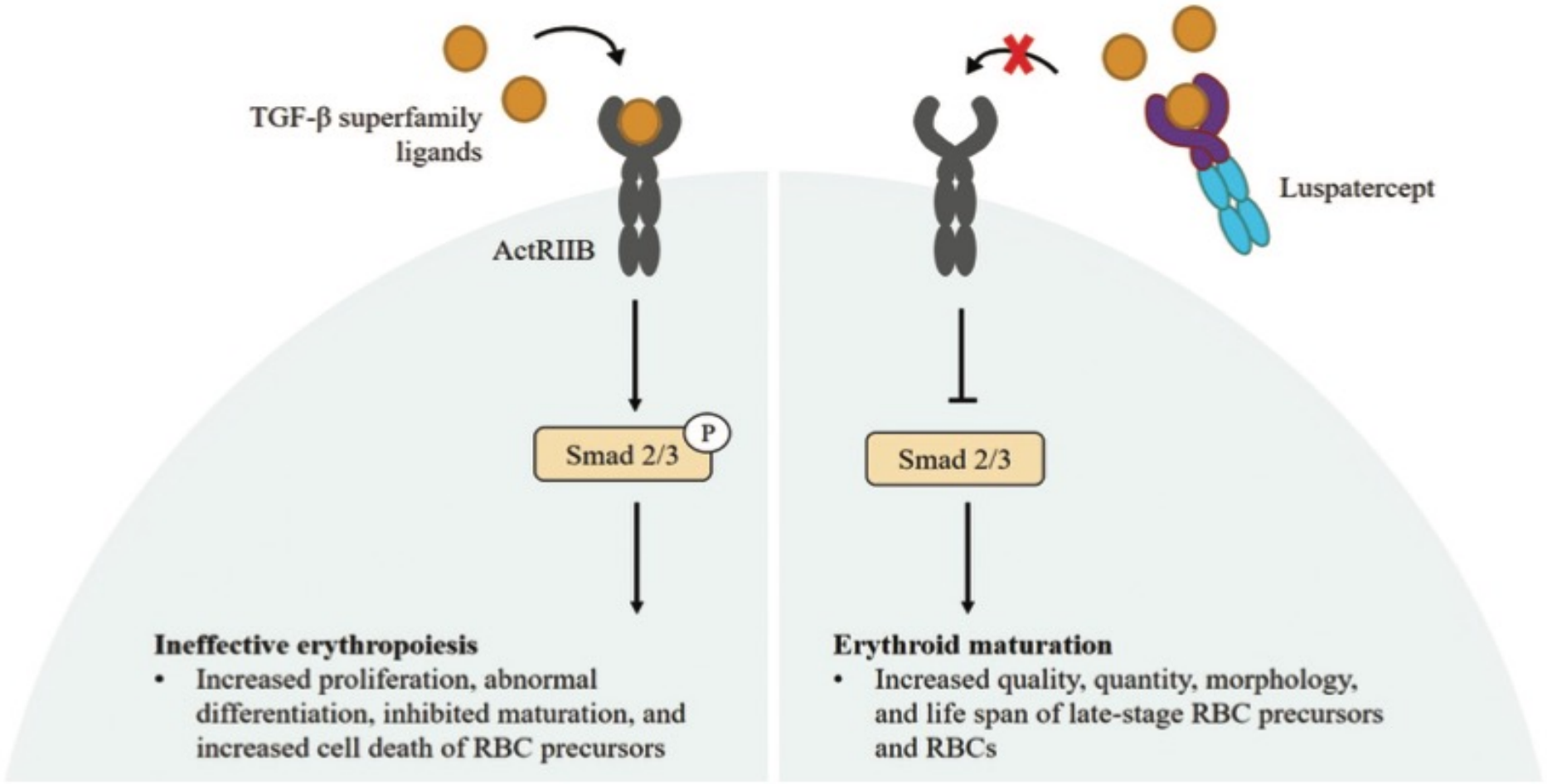




Fattizzo B, Front Med 2023

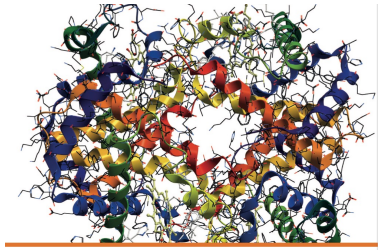
Luspatercept

Luspatercept competes with the extracellular domain of the activin receptor to act as a ligand trap for TGF-β, reducing Smad 2/3 signaling, improving erythrocyte maturation, and reducing ineffective erythropoiesis.



Taher AT et al, EXPERT REVIEW OF HEMATOLOGY 2021, VOL. 14, NO. 10, 897–909

Luspatercept: fase 3, BELIEVE STUDY



β-thalassemia[a] patients ≥ 18 years, requiring regular RBC transfusions (defined as: 6–20 RBC units in the 24 weeks prior to randomization with no ≥ 35-day transfusion-free period during that time) (N = 336)

Randomized 2:1

Luspatercept[b] 1 mg/kg s.c. every 21 days + BSC (n = 224)

May be titrated up to 1.25 mg/kg

Placebo[b] s.c. every 21 days + BSC (n = 112)

Current study status[c]

Study unblinding

Open-label (up to 5 years)

Post-treatment follow-up (3 years)

12-week period historical transfusions

12-week period screening / run-in transfusions

Double-blind period (48 weeks)

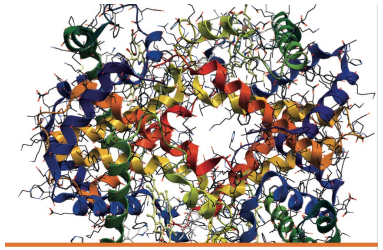
Crossover permitted

[a] β-thalassemia or hemoglobin E / β-thalassemia (β-thalassemia with mutation and / or multiplication of α-globin was allowed. [b] RBC transfusions and iron chelation therapy to maintain each patient's baseline hemoglobin level. [c] The trial is fully enrolled and patients continue to receive treatment or follow-up.

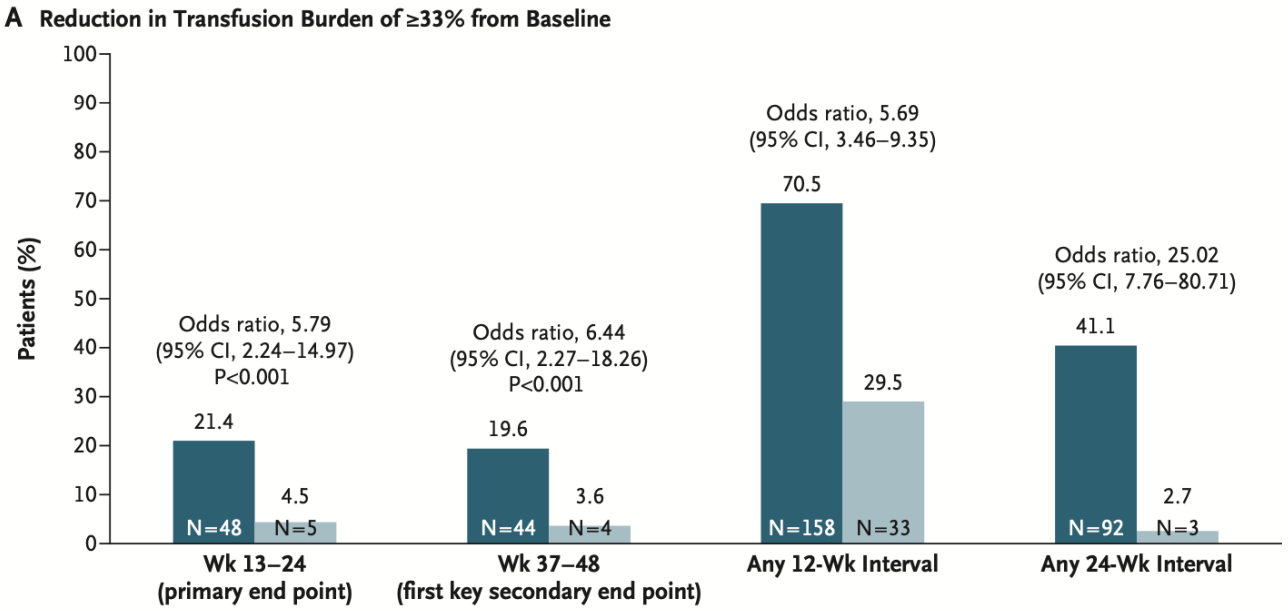
BSC, best supportive care; RBC, red blood cell; s.c., subcutaneously.

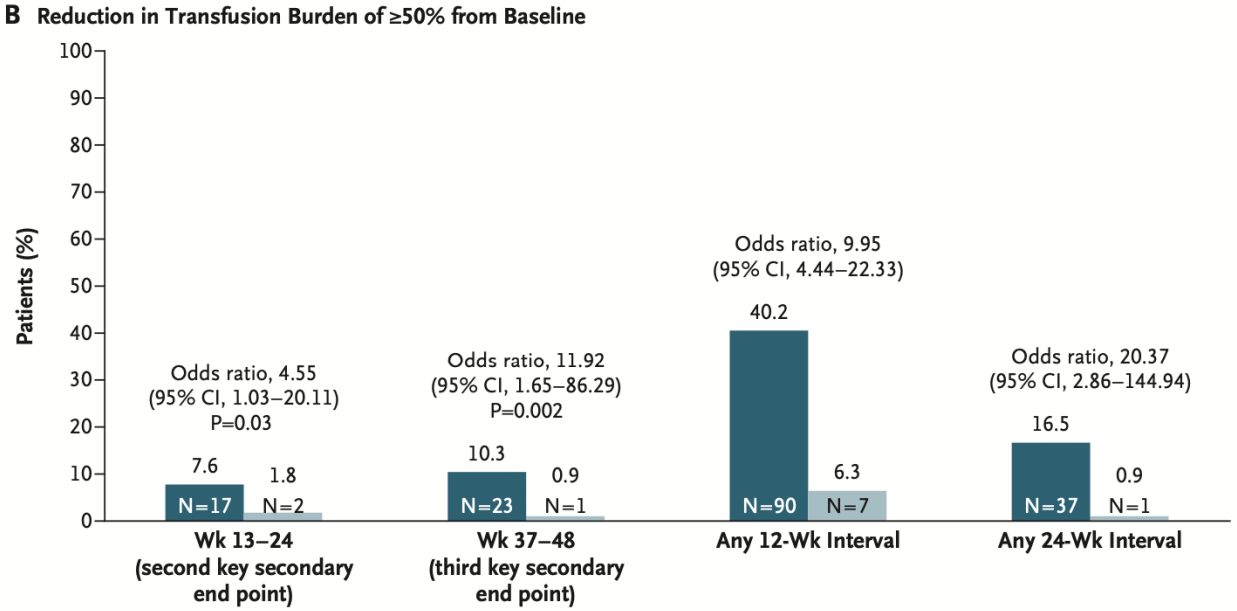
Cappellini MD. N Engl J Med. 2020 Mar 26;382(13):1219-1231.

Believe: results



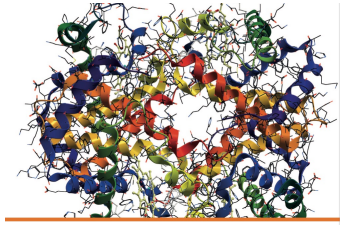
Luspatercept (N=224) Placebo (N=112)





Cappellini MD. N Engl J Med. 2020 Mar 26;382(13):1219-1231.

Luspatercept: adverse events

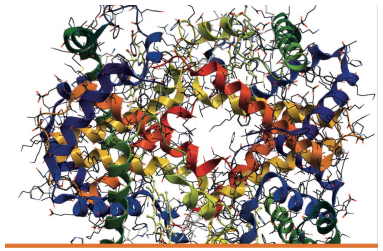


Adverse Event†	Luspatercept Group (N=223)		Placebo Group (N=109)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Patients with ≥1 adverse event	214 (96.0)	65 (29.1)	101 (92.7)	17 (15.6)
Back pain	61 (27.4)	3 (1.3)	32 (29.4)	1 (0.9)
Upper respiratory tract infection	59 (26.5)	2 (0.9)	36 (33.0)	0
Headache	58 (26.0)	1 (0.4)	26 (23.9)	1 (0.9)
Bone pain	44 (19.7)	3 (1.3)	9 (8.3)	0
Arthralgia	43 (19.3)	0	13 (11.9)	0
Pyrexia	36 (16.1)	0	23 (21.1)	0
Cough	32 (14.3)	1 (0.4)	12 (11.0)	0
Fatigue	30 (13.5)	0	14 (12.8)	0
Oropharyngeal pain	28 (12.6)	0	12 (11.0)	0
Diarrhea	27 (12.1)	1 (0.4)	11 (10.1)	0
Dizziness	25 (11.2)	0	5 (4.6)	0
Myalgia	22 (9.9)	0	11 (10.1)	0
Asthenia	22 (9.9)	0	11 (10.1)	0
Pain in extremity	21 (9.4)	0	9 (8.3)	0
Pharyngitis	20 (9.0)	1 (0.4)	13 (11.9)	0
Nausea	20 (9.0)	0	6 (5.5)	0
Influenza	19 (8.5)	0	6 (5.5)	0

Adverse Event†	Luspatercept Group (N=223)		Placebo Group (N=109)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Abdominal pain	18 (8.1)	0	7 (6.4)	0
Vomiting	18 (8.1)	1 (0.4)	8 (7.3)	0
Hypertension	18 (8.1)	4 (1.8)	3 (2.8)	0
Influenza-like illness	17 (7.6)	0	8 (7.3)	0
Hyperuricemia	16 (7.2)	6 (2.7)	0	0
Abdominal pain upper	15 (6.7)	0	7 (6.4)	0
Viral upper respiratory tract infection	14 (6.3)	1 (0.4)	2 (1.8)	0
Musculoskeletal pain	14 (6.3)	0	9 (8.3)	0
Pain	13 (5.8)	0	4 (3.7)	0
Gastroenteritis	12 (5.4)	2 (0.9)	8 (7.3)	0
Nasal congestion	12 (5.4)	0	5 (4.6)	0
Liver iron concentration increased	12 (5.4)	6 (2.7)	2 (1.8)	1 (0.9)
Neck pain	10 (4.5)	0	8 (7.3)	0
Osteoporosis	9 (4.0)	0	6 (5.5)	0
Musculoskeletal chest pain	5 (2.2)	0	7 (6.4)	0
Urinary tract infection	4 (1.8)	0	7 (6.4)	0
Fall	4 (1.8)	0	7 (6.4)	0

Cappellini MD. N Engl J Med. 2020 Mar 26;382(13):1219-1231.

Luspatercept approval



AGENZIA ITALIANA DEL FARMACO

DETERMINA 24 novembre 2021

Riclassificazione del medicinale per uso umano , ai sensi dell'articolo 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. DG/1401/2021). (21A07129)

(GU n.292 del 9-12-2021)

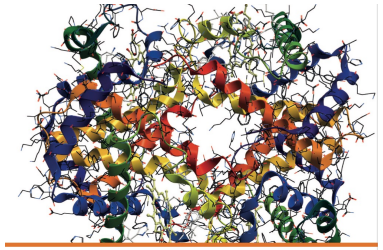
Art. 3

Classificazione ai fini della fornitura

La classificazione ai fini della fornitura del medicinale luspatercept e' la seguente:

per l'indicazione beta-talassemia: medicinale soggetto a prescrizione medica limitativa, da rinnovare volta per volta, vendibile al pubblico su prescrizione di centri di riferimento per le talassemie ed emoglobinopatie identificati nell'ambito del servizio sanitario regionale (RNRL);

Luspatercept in clinical practice



CRITERI DI PRESCRIZIONE/UTILIZZO secondo PT AIFA

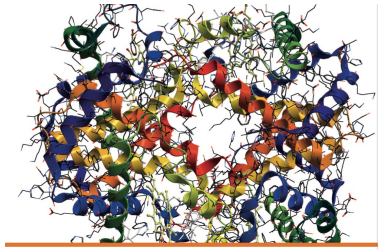
Luspatercept è attualmente approvato per soggetti con **età>18 anni**

Luspatercept è indicato in soggetti con β-Talassemia Trasfusione Dipendente **(TDT)**, senza distinzione di genotipo.

Trasfusione di 6-24 U di EC nelle 24 settimane precedenti l'inizio della terapia

Buone pratiche SITE «IDENTIFICAZIONE E GESTIONE DEL PAZIENTE CON INDICAZIONE AL TRATTAMENTO CON LUSPATERCEPT, Giugno 2024

Luspatercept in clinical practice



CRITERI DI PRESCRIZIONE/UTILIZZO secondo PT AIFA

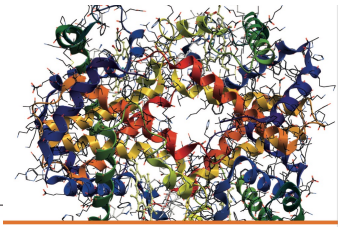
Assenza di danno d'organo maggiore (Diabete mellito non controllato, malattia cardiaca, insufficienza cardiaca classificata secondo (NYHA) ≥3 e/aritmia cardiaca non controllata, malattia epatica con livelli di ALT ≥ 3 volte il limite di riferimento, clearance della creatinina < 60 mL/min, proteinuria di grado maggiore al 3 secondo
NCI CTCAE versione 5.0.

Luspatercept è **controindicato in soggetti con storia di neoplasia onco-ematologica**.

Valutazione attenta della storia familiare e personale di trombosi

Buone pratiche SITE «IDENTIFICAZIONE E GESTIONE DEL PAZIENTE CON INDICAZIONE AL TRATTAMENTO CON LUSPATERCEPT, Giugno 2024

Luspatercept in clinical practice



Received: 29 June 2024 | Revised: 24 August 2024 | Accepted: 27 August 2024
DOI: 10.1002/ajh.27474

CORRESPONDENCE

Real-world efficacy and safety of luspatercept and predictive factors of response in patients with transfusion-dependent β-thalassemia

Received: 30 December 2023 | Revised: 4 March 2024 | Accepted: 16 March 2024
DOI: 10.1002/ccr3.8795

CASE REPORT

Luspatercept's use in a patient with transfusion-dependent beta-thalassemia and intrathoracic extramedullary hematopoiesis (EMH)

Mohammed Najdat Seijari[1] | Awni Alshurafa[2] | Mohamed A. Yassin[2]

Home > Annals of Hematology > Article

Acute liver injury after SARS-CoV-2 vaccination and luspatercept administration in a patient with β-thalassemia

LETTER TO THE EDITOR | Published: 03 January 2024
Volume 103, pages 1025–1026, (2024) Cite this article

Annals of Hematology

LETTER TO BLOOD | NOVEMBER 30, 2023

Splenic iron decreases without change in volume or liver parameters during luspatercept therapy

Clinical Trials & Observations

Christopher C. Denton, Sadanand Vodala, Saranya Veluswamy, Thomas C. Hofstra, Thomas D. Coates, John C. Wood

Check for updates

Blood (2023) 142 (22): 1932–1934.
https://doi.org/10.1182/blood.2023021839

Article history

Received: 26 January 2024 | Accepted: 9 April 2024
DOI: 10.1111/bjh.19480

LETTER TO THE EDITOR

Unplanned pregnancy in women with beta-thalassaemia treated with luspatercept

PharmacoEconomics - Open (2024) 8:471–480
https://doi.org/10.1007/s41669-024-00482-x

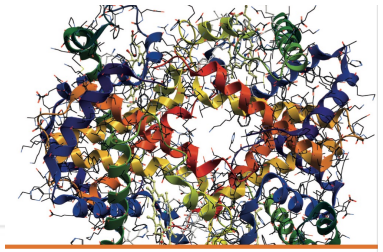
ORIGINAL RESEARCH ARTICLE

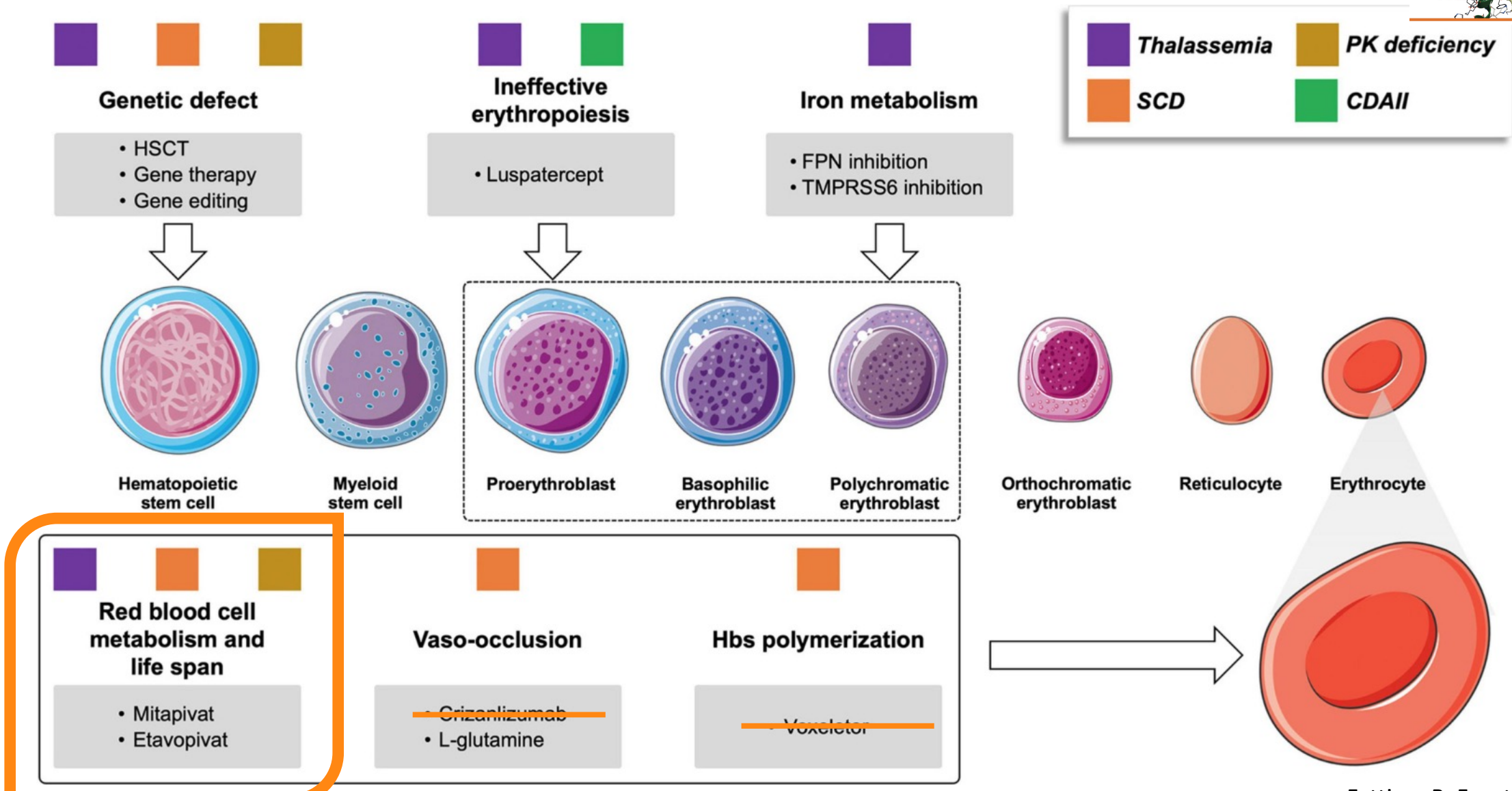
Can Cyprus Afford Luspatercept? A Budget Impact Analysis of the Reimbursement of Luspatercept for the Management of Thalassaemia in Cyprus

Olga Pitsillidou[1,2] · Panagiotis Petrou[2,3] · M. J. Postma[1,4]

Accepted: 3 March 2024 / Published online: 4 April 2024

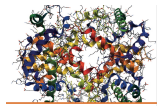
Novel treatments: future and not

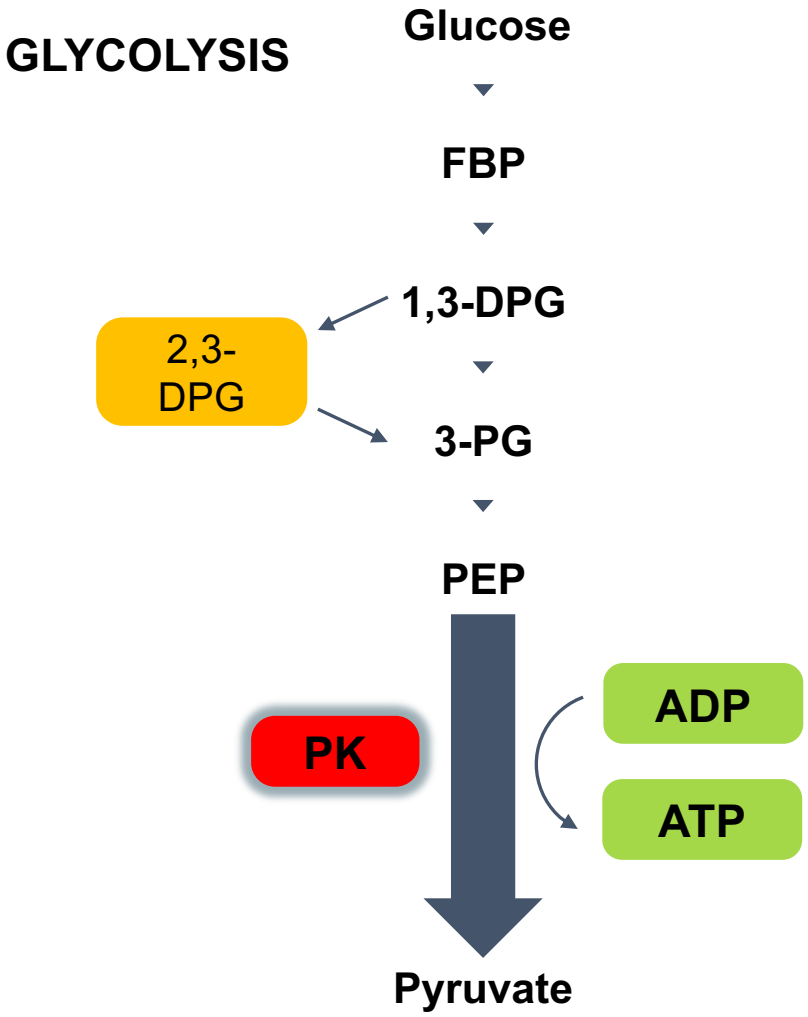


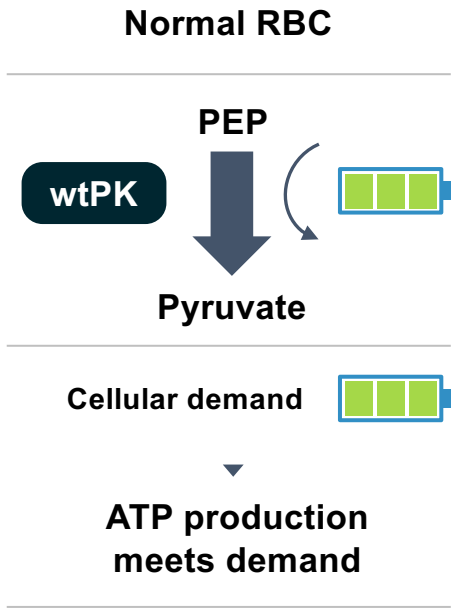


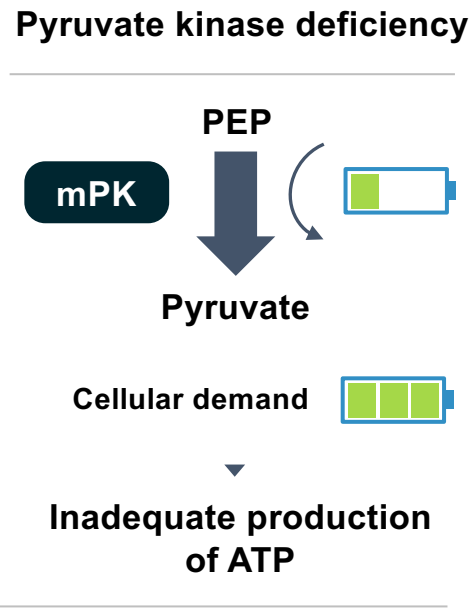
Fattizzo B, Front Med 2023

PK activation represents a unique mechanism of action with the potential to address a broad range of hemolytic anemias

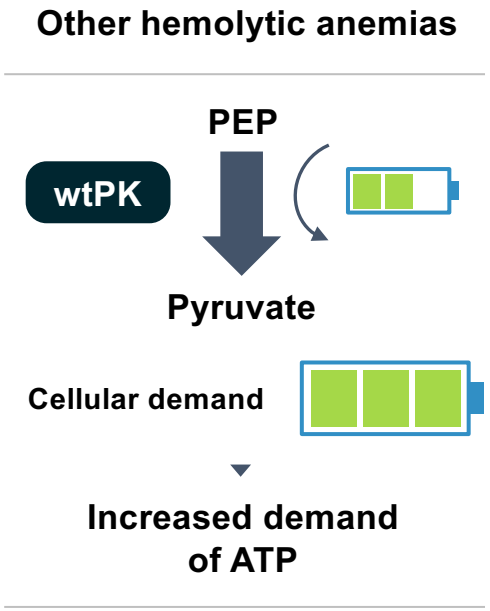








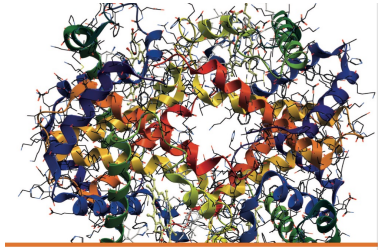
PK mutations decrease PK stability, ATP generation, and RBC membrane integrity and increase RBC destruction, leading to chronic hemolytic anemia



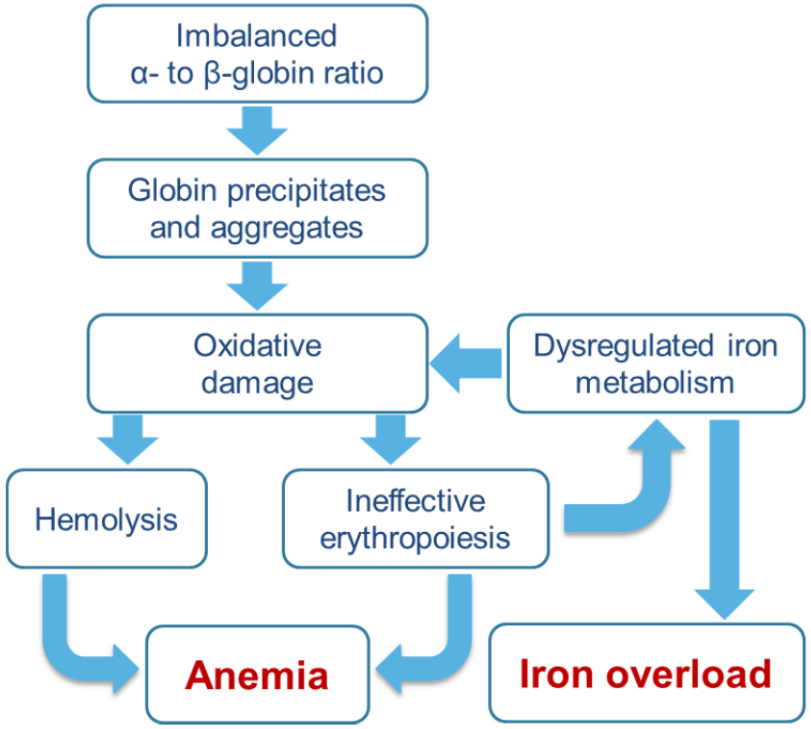
In many other hemolytic anemias, there is an increase in ATP demand and impaired ATP production, leading to damage and premature death of RBCs, hemolysis, and anemia

ADP = adenosine diphosphate; ATP = adenosine triphosphate; DPG = diphosphoglycerate; FBP = fructose bisphosphate; PEP = phosphoenolpyruvate; PG = phosphoglycerate; PK = pyruvate kinase; wt = wild-type.

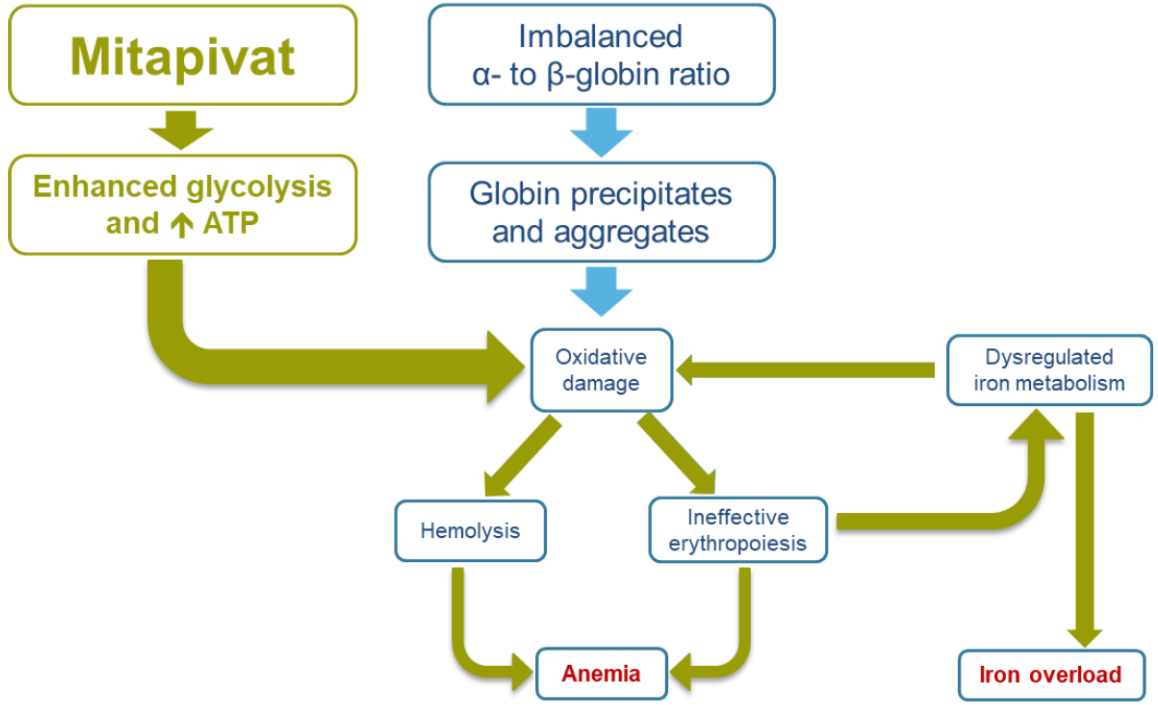
Mitapivat mechanisms in thalassemia



Pathophysiology

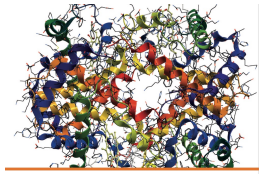


Mechanism of Action

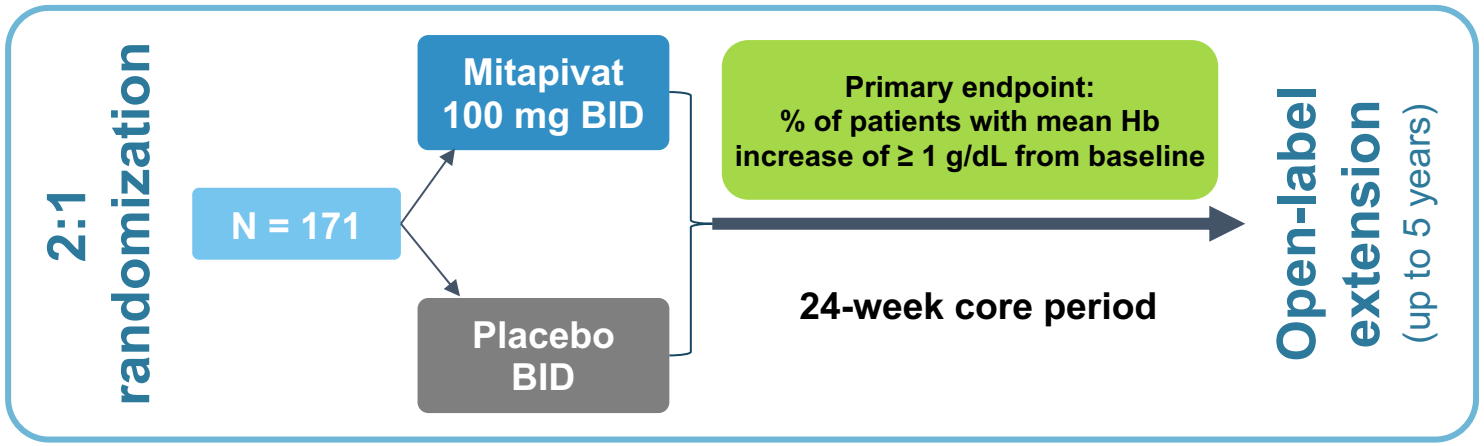


ATP, adenosina trifosfato.

Two Phase 3, global, randomized, controlled trials of mitapivat in adults with α- or β-thalassemia



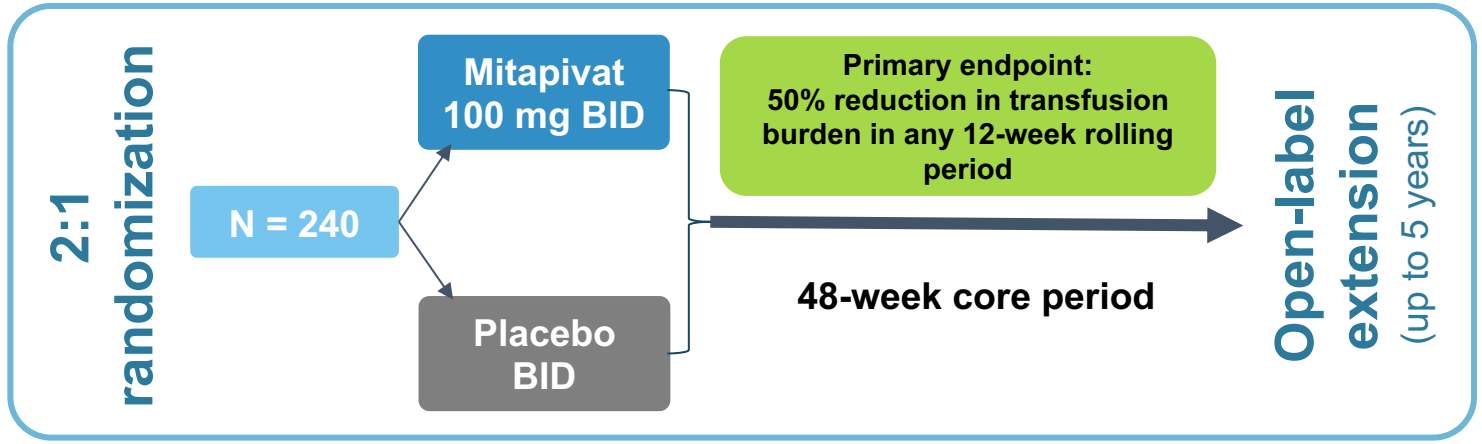
ENERGIZE



Key inclusion criteria

- ≥ 18 years
- β-thalassemia ± α-globin mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Non-transfusion-dependent (≤ 5 RBC units during the 24-week period before randomization and no RBC transfusions ≤ 8 weeks prior)
- Hb ≤ 10.0 g/dL

ENERGIZE-T

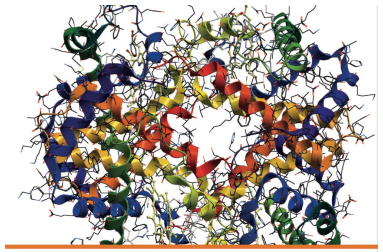


Key inclusion criteria

- ≥ 18 years
- β-thalassemia ± α-globin mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Transfusion-dependent (6–20 RBC units transfused and ≤ 6-week transfusion-free period during the 24-week period before randomization)

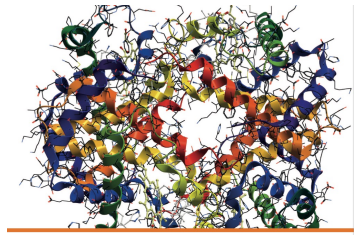
BID = twice daily; Hb = hemoglobin; HbE = hemoglobin E; HbH = hemoglobin H; RBC = red blood cell.
ClinicalTrials.gov: ENERGIZE (NCT04770753); ClinicalTrials.gov: ENERGIZE-T (NCT04770779).

Countries involved



UAE: United Arab Emirates.

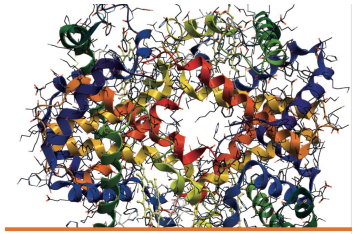
ENERGIZE: population



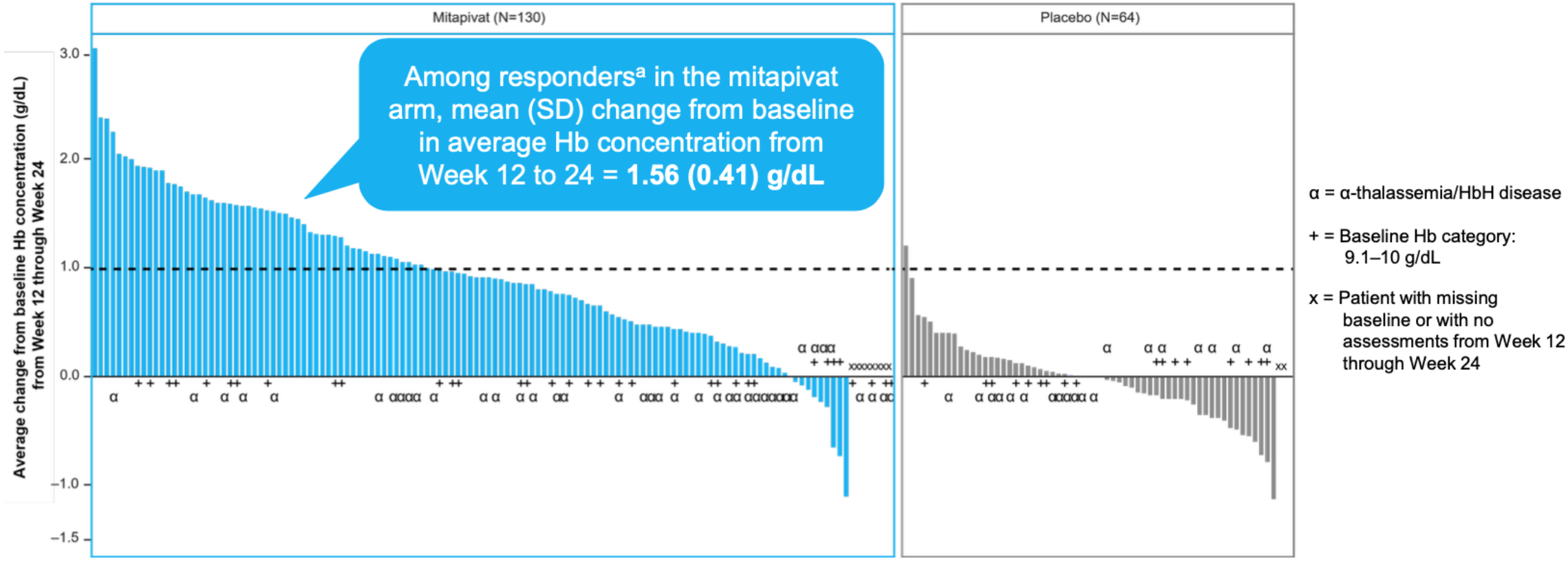
Demographics and disease characteristics	Mitapivat (N=130)	Placebo (N=64)
Age, mean (±SD), years	42.4 (13.0)	38.9 (13.0)
Female, n (%)	84 (64.6)	39 (60.9)
Thalassemia type, n (%) α-thalassemia/HbH disease β-thalassemia	 42 (32.3) 88 (67.7)	 20 (31.3) 44 (68.8)
Transfusion burden,[a] n (%) 0 1–2 3–5 >5	 114 (87.7) 10 (7.7) 6 (4.6) 0 (0.0)	 54 (84.4) 7 (10.9) 3 (4.7) 0 (0.0)
Prior splenectomy,[b] n (%)	47 (36.2)	25 (39.1)
Prior cholecystectomy,[b] n (%)	45 (34.6)	16 (25.0)
Received iron chelation in prior year,[c] n (%)	46 (35.4)	22 (34.4)
Hb, median (range), g/dL	8.4 (5.3–10.4)	8.4 (5.9–10.7)
Indirect bilirubin, median (range), µmol/L	23.4 (2.2–155.8)	22.6 (2.7–81.6)
LDH, median (range), U/L	264 (108–1208)	267 (110–1009)
Haptoglobin,[d] median (range), g/L	0.1 (0.1–1.7)	0.1 (0.1–2.8)
Reticulocyte percentage, median (range), %	4.6 (0.3–29.8)	4.4 (0.0–21.9)
Erythropoietin, median (range), IU/L	65.1 (8.3–1587.0)	64.1 (15.7–4710.0)

Analysis conducted on Full Analysis Set. aA Hb response was defined as an increase of ≥1.0 g/dL in average Hb concentration from Week 12 through Week 24, compared with baseline. Hb, hemoglobin; HbH, hemoglobin H

ENERGIZE: results

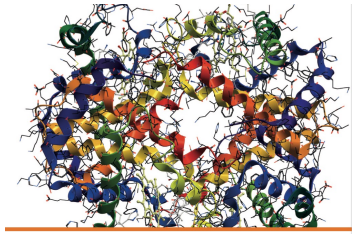


	Mitapivat N=130	Placebo N=64	2-sided p-value
Hb response,[a] n (%)	55 (42.3)	1 (1.6)	p<0.0001



Analysis conducted on Full Analysis Set. aA Hb response was defined as an increase of ≥1.0 g/dL in average Hb concentration from Week 12 through Week 24, compared with baseline. Hb, hemoglobin; HbH, hemoglobin H

ENERGIZE: conclusions

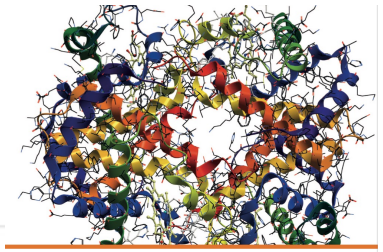


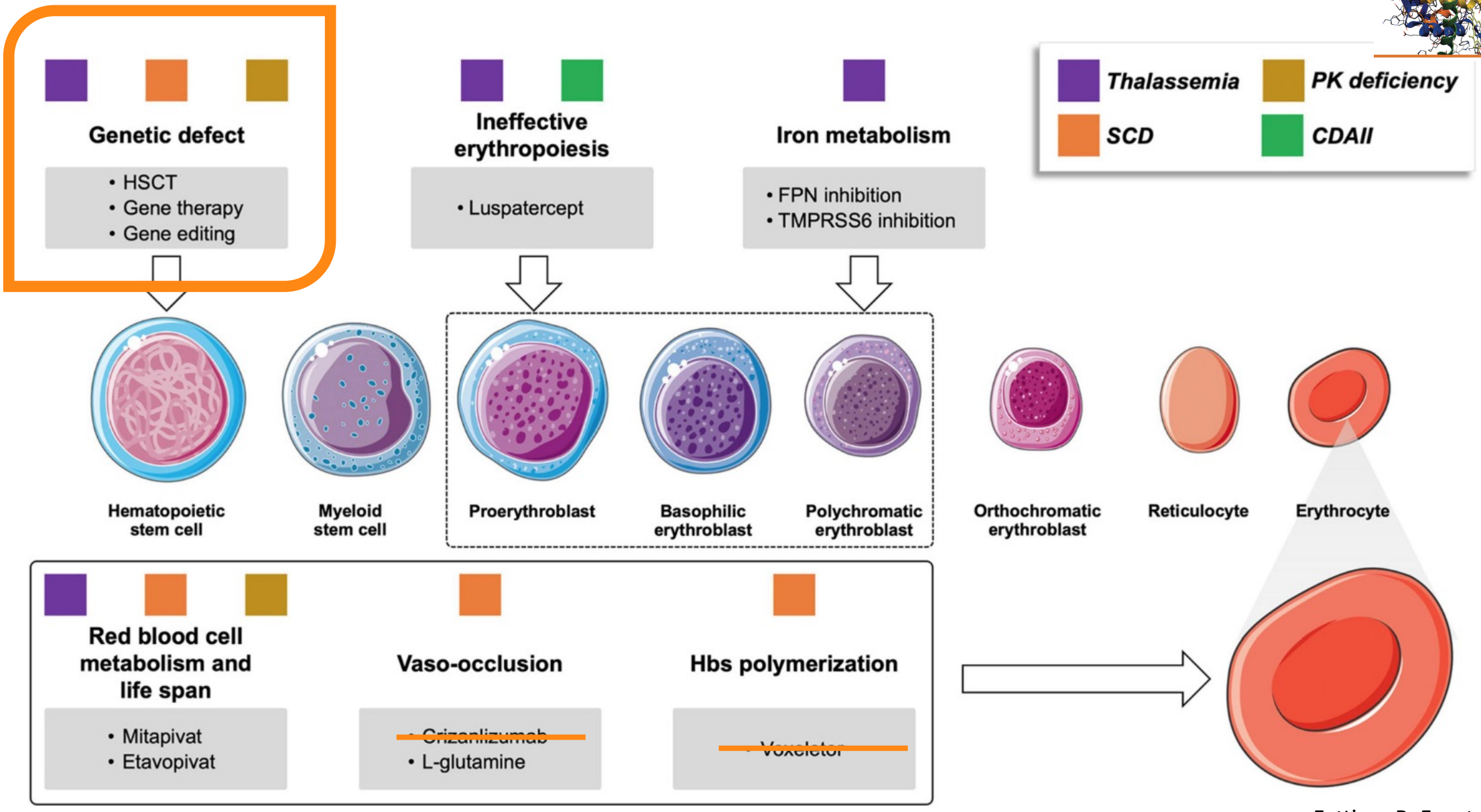
- This global study was the first to enroll patients with α-thalassemia in addition to β-thalassemia
- The primary and key secondary endpoints were met, with statistically significant improvements in Hb and fatigue with mitapivat vs placebo
  - All prespecified subgroup analyses favored mitapivat vs placebo
- Improvements in markers of hemolysis and erythropoietic activity were observed, consistent with the mechanism of mitapivat[1–3]
- Mitapivat was generally well tolerated in this study, with a low treatment discontinuation rate and a safety profile consistent with other studies[3–6]

Hb, hemoglobin; NTDT, non–transfusion-dependent thalassemia

1. Kung C et al. *Blood* 2017;130:1347–56; 2. Matte A et al. *J Clin Invest* 2021;131:e144206; 3. Kuo KHM et al. *Lancet* 2022;400:493–501;
4. Al-Samkari H et al. *NEJM* 2022;386:1432–42; 5. Glenthøj A et al. *Lancet Haematol* 2022;9:e724–32; 6. Idowu M et al. *Blood* 2023;142:271.

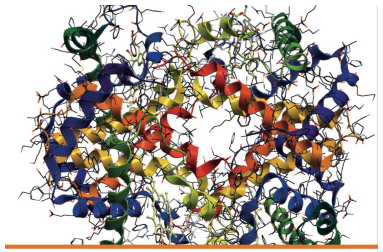
Novel treatments: future and not





Fattizzo B, Front Med 2023

Gene editing - CRISPR-Cas9



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

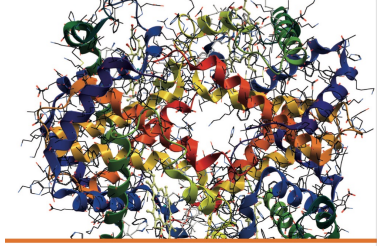
Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia

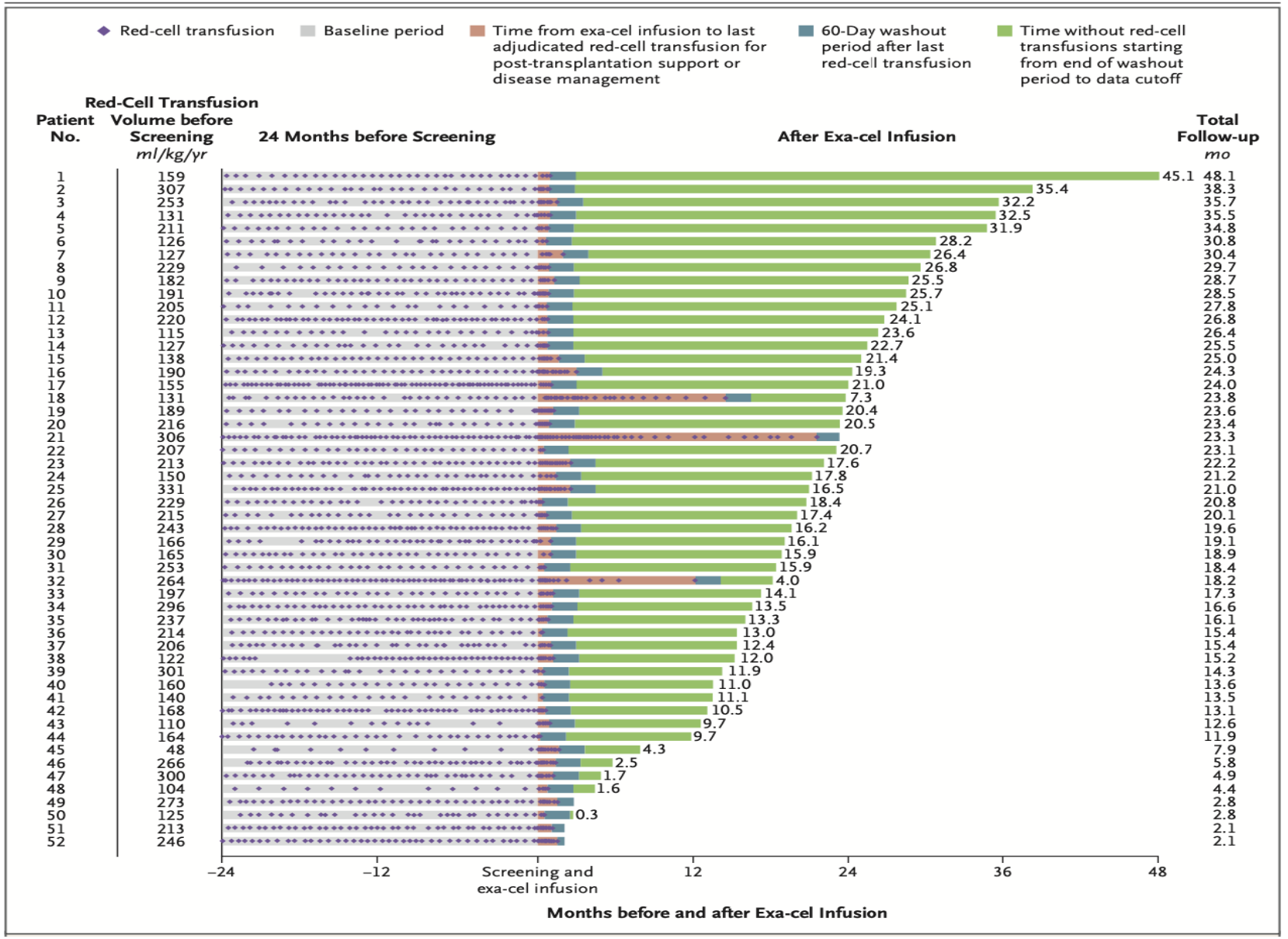
F. Locatelli, P. Lang, D. Wall, R. Meisel, S. Corbacioglu, A.M. Li, J. de la Fuente, A.J. Shah, B. Carpenter, J.L. Kwiatkowski, M. Mapara, R.I. Liem, M.D. Cappellini, M. Algeri, A. Kattamis, S. Sheth, S. Grupp, R. Handgretinger, P. Kohli, D. Shi, L. Ross, Y. Bobruff, C. Simard, L. Zhang, P.K. Morrow, W.E. Hobbs, and H. Frangoul, for the CLIMB THAL-111 Study Group*

Characteristic	Full Analysis Population (N=52)	Primary Efficacy Population (N=35)
Sex — no. (%)		
Male	27 (52)	18 (51)
Female	25 (48)	17 (49)
Age at screening		
Mean — yr	21.5±6.7	21.1±6.1
Distribution — no. (%)		
12 to <18 yr	18 (35)	11 (31)
≥18 to 35 yr	34 (65)	24 (69)
Race or ethnic group — no. (%)†		
White	18 (35)	15 (43)
Asian	22 (42)	13 (37)
Data not collected per local regulations	7 (13)	4 (11)
Other	2 (4)	0
Multiracial	3 (6)	3 (9)

Locatelli F. N Engl J Med 2024;390:1663-76. DOI: 10.1056/NEJMoa2309673

Gene editing - CRISPR-Cas9





Among the 35 evaluable patients, transfusion independence (weighted average hemoglobin level of ≥9 g per deciliter without red-cell transfusion for at least 12 consecutive months) occurred in all except Patients 18, 21, and 32.

Locatelli F. N Engl J Med 2024;390:1663-76. DOI: 10.1056/NEJMoa2309673

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