XIX Congresso della Società GITMO

RIUNIONE NAZIONALE GITMO

TORINO, CENTRO CONGRESSI LINGOTTO, 5 - 6 MAGGIO 2025

Storia della guarigione della talassemia. Dal trapianto allogenico alla terapia genica.

Emanuele Angelucci

UO Ematologia e Terapie Cellulari.

IRCCS Ospedale Policlinico San Martino.

Genova

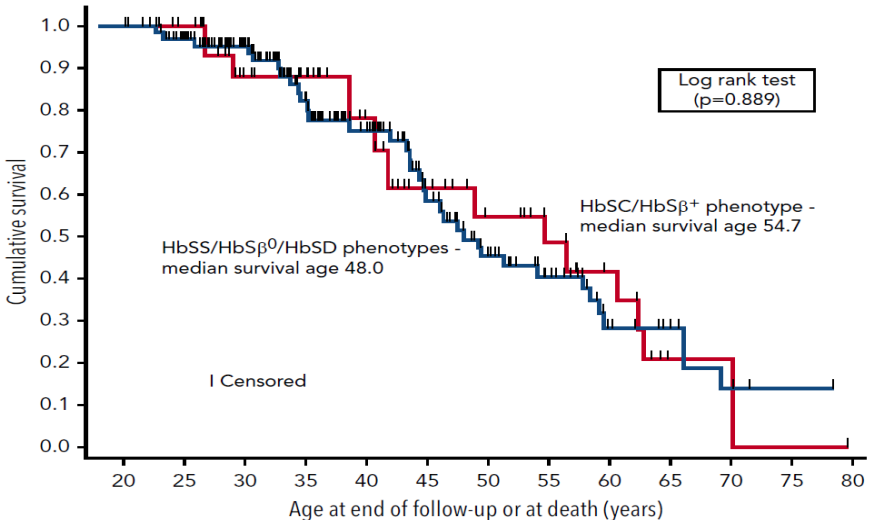
OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria

Disclosures of Emanuele Angelucci

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Vertex							DMC
BMS					X		DMC
Sanofi			X		X		
Menarini-Stemline			X		X		
Johson & Johnson			X				

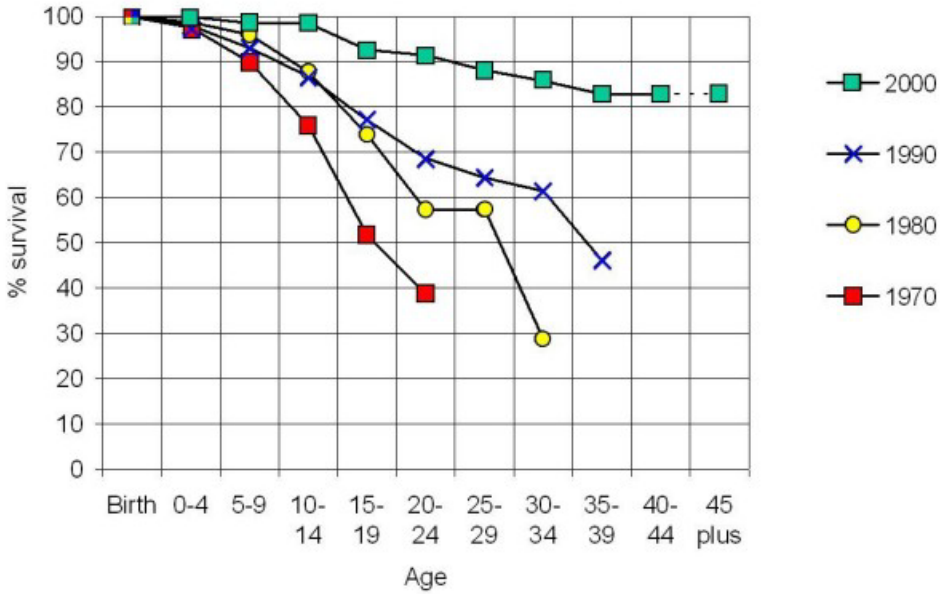
Significantly shortened median OS for patients with SCD and TDT despite optimal care

SCD



DeBaun et al. Blood. 2019 Feb 7;133(6):615-617.

TDT



Modell et al, Journal of Cardiovascular Magnetic Resonance 2008, 10:42

Relationship Between Pretransfusion Hemoglobin Level and Mortality in Adult Patients with Transfusion-Dependent β-Thalassemia

Context of research

- A pretransfusion Hb of 9-10 g/dL has been previously shown to adequately suppress the expanded erythropoiesis in β-thalassemia
- The impact of different pretransfusion Hb levels on thalassemia-related mortality is yet unclear

Patients and Methods

- 779 patients
- Multivariate Cox regression model with the outcome of thalassemia-related mortality as the dependent variable

$$h(t)$$

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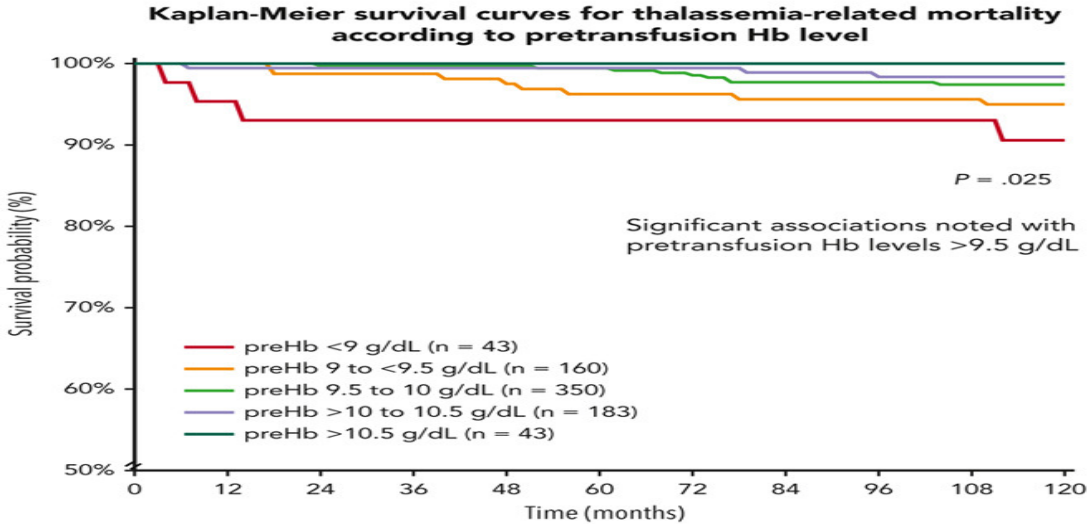
Main findings



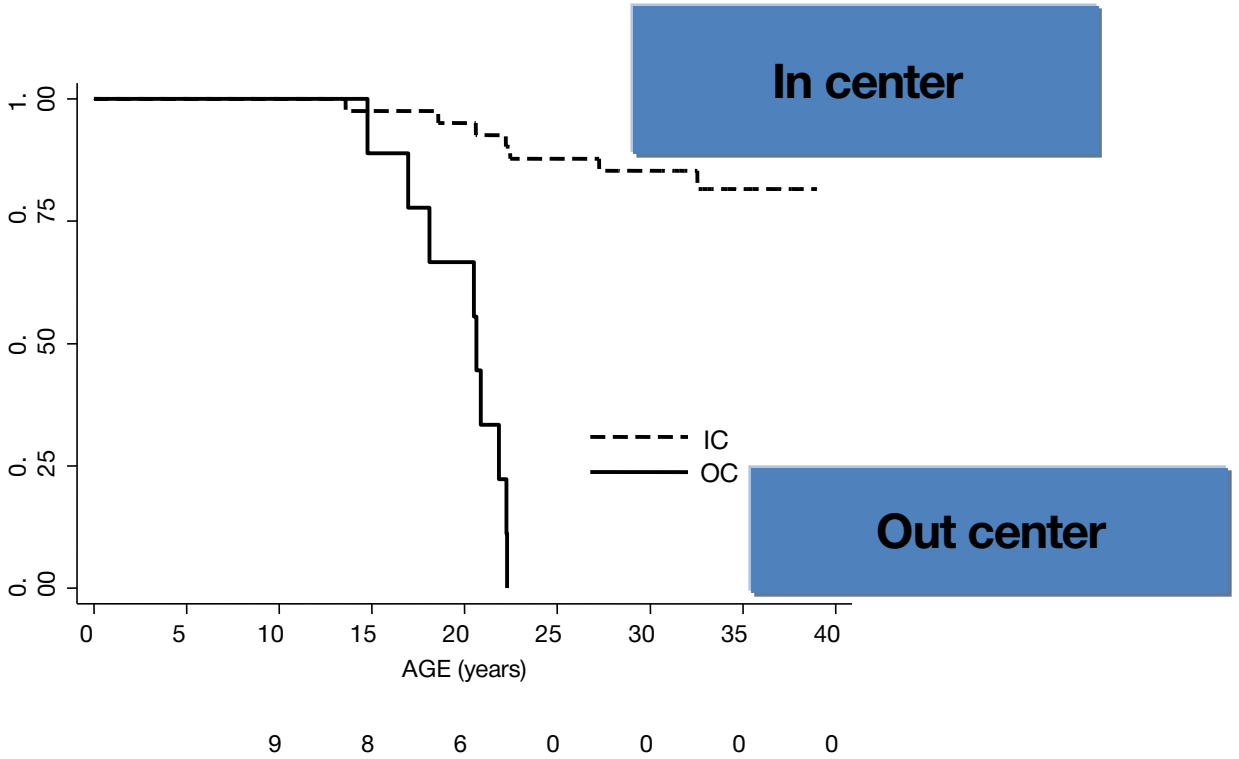
Conclusion: In adult patients with transfusion-dependent β-thalassemia, higher pretransfusion Hb levels (starting at 9.5 g/dL) were associated with lower thalassemia-related mortality.

*Musallam et al. DOI: 10.1182/**blood**.2023022460*

blood Visual Abstract

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

The influence of treatment in specialized centers on survival of patients with thalassemia major



Forni G et al. Am J Hematol. 2009 May;84(5):317-8.

HCT in TDT

Replacement of the entire hematopoietic system and not only of the diseased erythropoiesis[2]

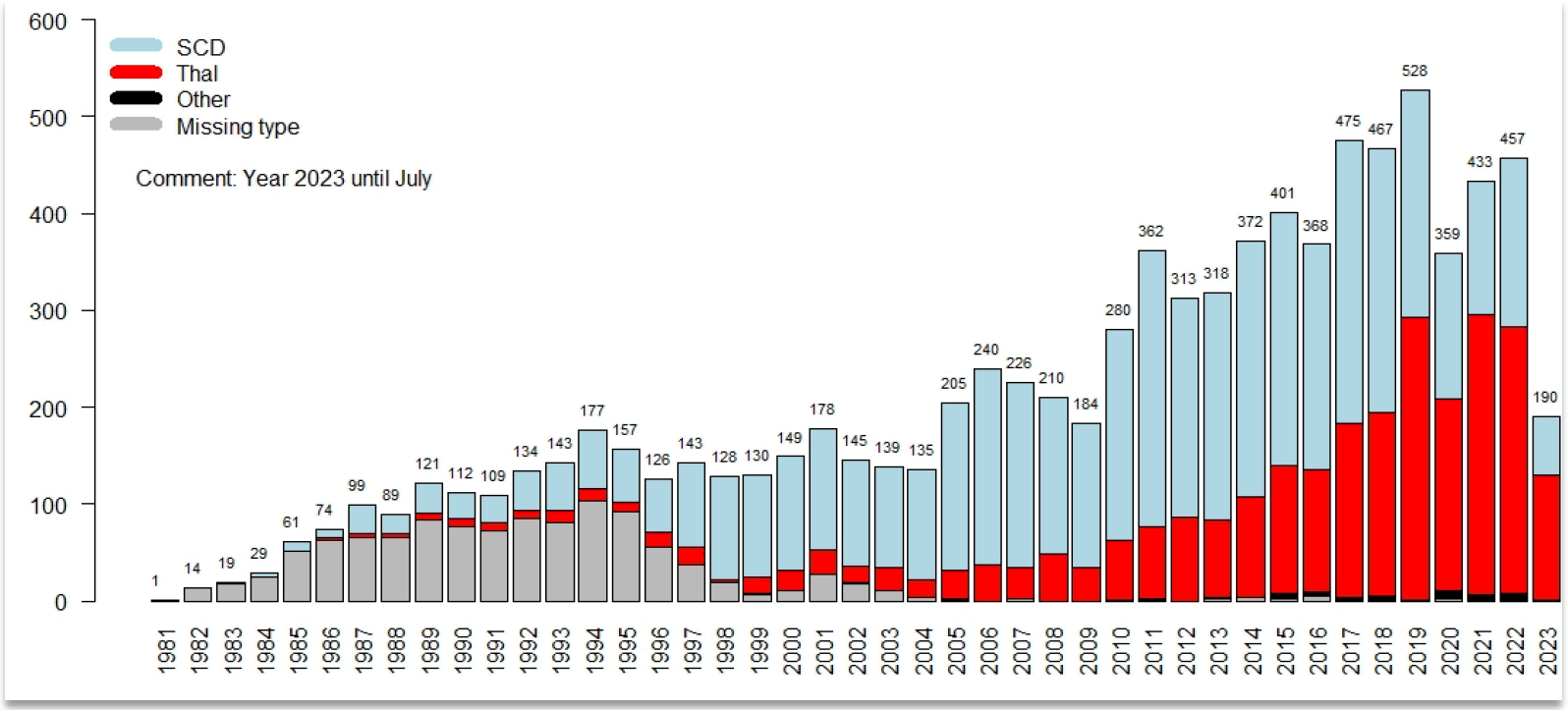
Myeloablation + immunosuppression needed[3]
Risk of GvHD.

HCT, hematopoietic cell transplantation.
1. Dong A, et al. Transl Res. 2013;161:293-306; 2. Speaker's own opinion; 3. Pasquini MC, et al. Biol Blood Marrow Transplant. 2016;22:1424-1430.

The first experiences: >40 years ago

02.12.1981	FHCRC Seattle	ED Thomas et al. The Lancet 1982: 31: 227-9
17.12.1981	Ospedale S. Salvatore Pesaro	Lucarelli G. et al. Exp Hematol 1984; 12: 676-81

HCT in hemoglobinopathies: 40 years of experience



HCT, hematopoietic cell transplantation; SCD, sickle cell disease.
Slide provided by Emanuele Angelucci from the EBMT Haemoglobinopathies Working Party data.

THE LANCET

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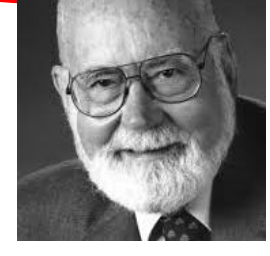
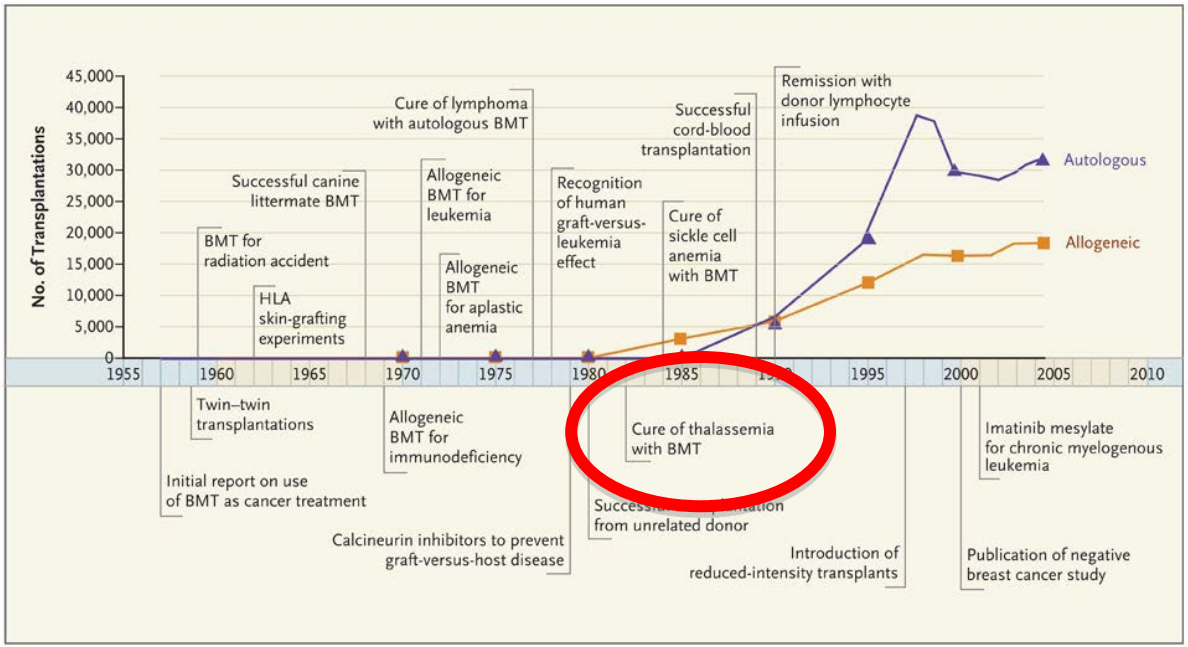


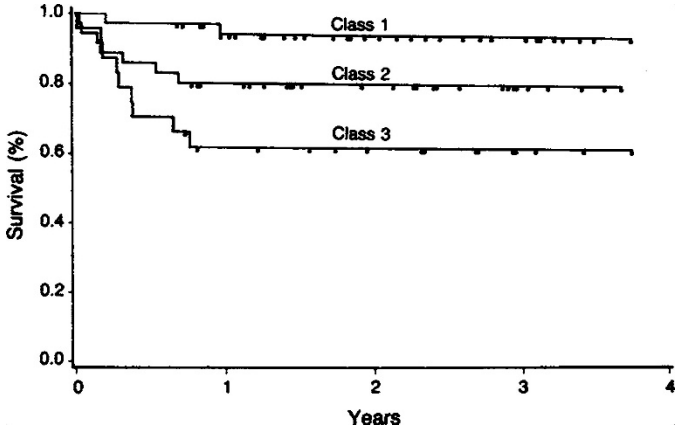
Timeline Showing Numbers of Bone Marrow Transplantations and Advances in the Field, 1957-2006

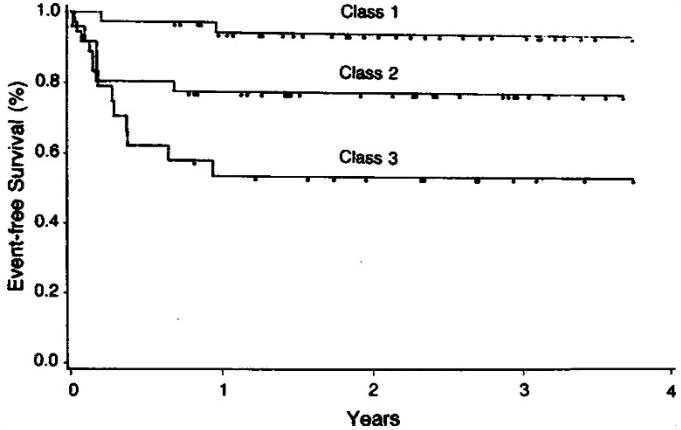


The NEW ENGLAND JOURNAL of MEDICINE

Appelbaum F. N Engl J Med 2007;357:1472-1475

Transplantation for Thalassemia. Pesaro results in the 80ties





Lucarelli G. et al. N Engl J Med 1990;322:417-421

Transplantation in thalassemia: Revisiting the Pesaro risk factors 25 years later

Predictive variables of outcome after hematopoetic cell transplantation in pediatric patients with thalassemia

Risk factor	Adverse	Favourable
Hepatomegaly (cm from costal arch)	>2cm	≤2cm
Liver fibrosis	Presence	Absence
Iron chelation therapy	Irregular	Regular
Risk class		
Class I patients have all three favourable risk factors		
Class II patients have one or two adverse risk factors		
Class III patients have all three adverse risk factors		

These data are still important after >40 years because they provide the proof of concept of how **prolonged exposure to iron toxicity can be the cause of the oxidative damage to human tissues**, which are consequently made more susceptible to damage after HCT toxicity

HCT, hematopoietic cell transplantation.

Adapted from: Angelucci E, et al. [published online ahead of print Mar 22, 2017] *Am J Hematol*. doi: 10.1002/ajh.24674.

EBMT
European Society
for Blood and Marrow Transplantation

Real world data

EBMT Hemoglobinopathy Working Party

2891 TDT Patients: Donor and Outcome

Donor	MSD	Match Related	MM Related	UD 10/10	UD<10/10
OS	91.8 %	88.3 %	85.3%	93.2%	81.4%
PFS	83 %	79.5 %	62.4%	85.7%	68 %
Rejection	8.8%	8.8%	22.9%	7.5%	13.4%
NRM	8.1%	11.6%	14.6%	6.7%	18.5%
Ac GVHD >2	6.6%	9,3%	3,1%	12,7%	14.2%
Cr GVHD	13.1%	15.9%	9.3%	15%	17.8%

There is a need to increase the pool of donors

Ac, acute; Cr, chronic; EBMT, European Group for Blood and Marrow Transplantation; GVHD, graft-versus-host disease; MM, mismatch; MSD, matched sibling donor; NRM, non-relapse mortality; OS, overall survival; PFS, progression-free survival; TDT, transfusion-dependent β-thalassemia; UD, unrelated donor.

EBMT 2020 Analysis: Data provided by speaker.

Allo-HSCT from HLA-identical sibling donor:

More favourable outcomes in younger vs older patients with thalassemia major

EBMT Hemoglobinopathy Registry

Retrospective, non-interventional study of 1493 thalassemia major patients who underwent allo-HSCT

Results by age group

Patients (n)	OS*		EFS†	
	Events	2-y OS	Events	2-y EFS
< 2 y (66)	3	95% (+/-3%)	4	93% (+/-3%)
2 to < 5 y (226)	13	94% (+/-2%)	32	86% (+/-3%)
5 to < 10 y (352)	33	90% (+/-2%)	52	83% (+/-2%)
10 to < 14 y (197)	8	96% (+/-2%)	24	86% (+/-3%)
14 to < 18 y (97)	14	82% (+/-4%)	20	74% (+/-5%)
≥ 18 y (82)	16	80% (+/-5%)	18	76% (+/-5%)
P-value (for trend)	<0.001		<0.001	

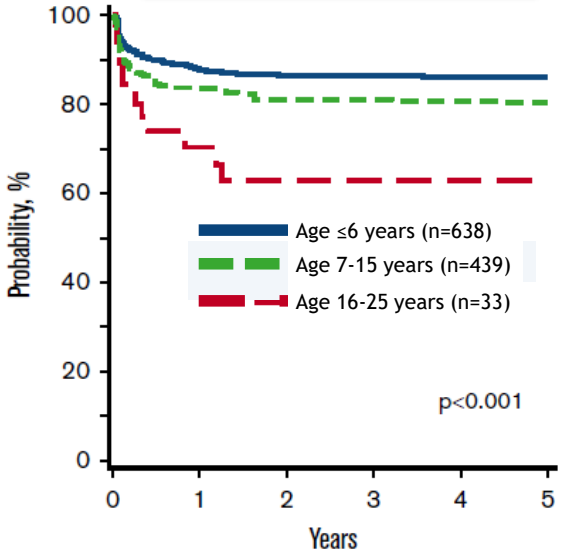
There is a significant unmet need for older adolescents and adults

Age data was missing for one patient. *OS was calculated from the date of first stem cell transplantation to death from any cause. †EFS was calculated as the time to death or thalassemia recurrence, whichever was first. allo-HSCT: allogeneic hemopoietic stem-cell transplantation; EBMT, European Group for Blood and Marrow Transplantation; EFS, event-free survival; HLA, human leukocyte antigen; HSCT, hemopoietic stem cell transplantation; OS, overall survival.

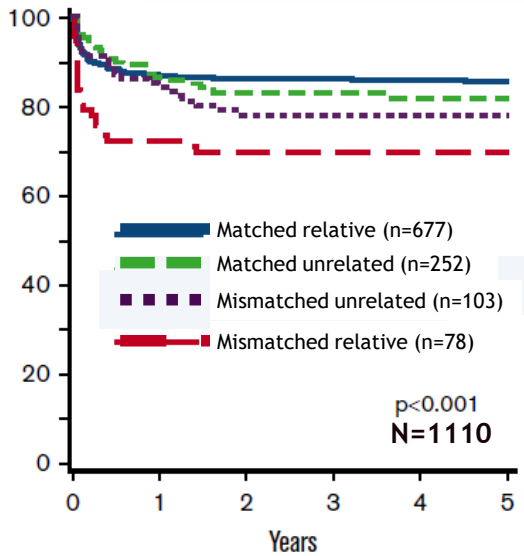
Adapted from: Baronciani D, et al. *Bone Marrow Transplant*. 2016;51:536-541.

Related and unrelated donor transplantation for B-thalassemia major: Results of an international survey (2000–2016). #1110 patients aged <25 years (US, India, China)

5-year probability of EFS by Age



5-year probability of EFS by Donor



- All patients received myeloablative-conditioning regimen
- Grade II-IV acute GVHD
  - Higher in patients aged 16–25 years (HR: 2.23; 95% CI: 1.30-3.84) compared with patients aged 7–15 years (HR: 1.10; 95% CI: 0.71-1.7) and ≤ 6 years (HR: 1.00)
  - Higher in patients who had transplantations prior to 2012
- **Grade II-IV acute and chronic GVHD was more common after transplantation from donors other than HLA-matched donors**

The primary outcome of the study was EFS.
Ninety-nine patients reported graft failure; 56 were primary graft failure and 43 were secondary graft failure
EFS, event-free survival; GVHD, graft versus host disease.

Adapted from: Li C. et al. *Blood Adv*. 2019;3:2562–2570.

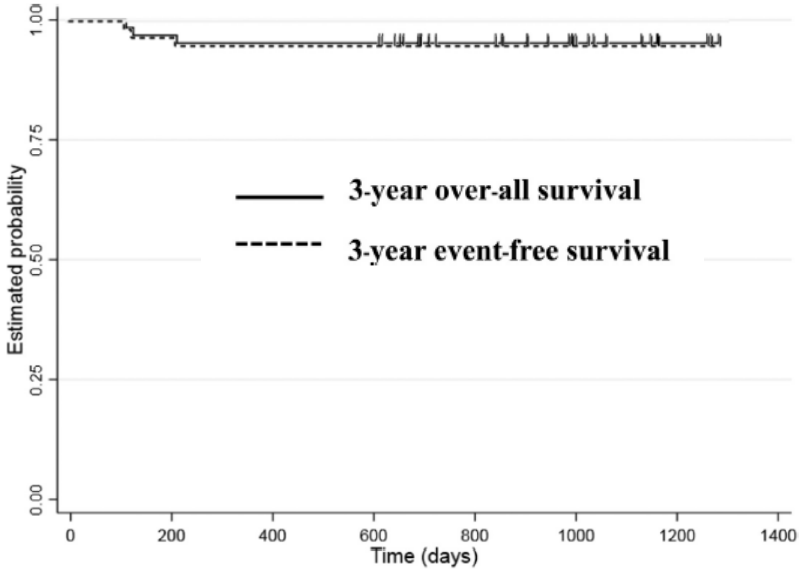
India and China results.

	Patients	Outcome (5 years outcome)	ref
India	264 (median age 6y)	TFS: **MSD 96%**, MFD 94%, MUD **84%** Age < 7 years = 95% Age > 7 years = 90%	Swaminathan VV. et al. Biol Blood Marrow Transplantation 2020
China	486 (median age 6 years; range 2-23)	OS 94.7%, TFS 93.3%, Rejection 2.8%, TRM 5.3% MSD: OS and TFS: 97.4%	Yelin He, et al . A J Hem. August 2020

Hematopoietic Stem Cell Transplantation for Severe Thalassemia Patients from Haploidentical Donors Using a Conditioning Regimen

Patients (n=83, median age 12 years, range 1-28)

CD34 dose: 10.4×10^6/kg (range 4-19)



Median follow-up:
15 mo (range 7–53)

3 years OS-TFS:
96% (CI 85.7-98.4)

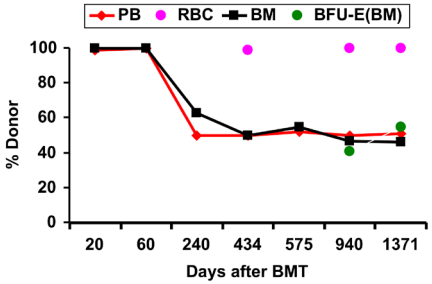
- Pharmacologic pretransplant immune suppression phase and two courses of dexamethasone and fludarabine, followed by pretransplant conditioning with fludarabine-IV busulfan
- Twenty-nine patients developed grade II acute GVHD that resolved with steroids
- Six patients had grade III acute GVHD that resolved with basiliximab and/or infliximab
- The GVHD prophylaxis consisted of cycolophosphamide 50 mg/kg/d on days SCT +3 and SCT +4, and on day SCT +5, tacrolimus or sirolimus was started, together with mycophenolate mofetil
- 15 mg/kg orally twice daily for 60 days
- **One patient had severe grade IV acute GVHD, following a second PBPC infusion**
- **Thirty-four patients developed limited chronic GVHD**
- **Three patients developed extensive chronic GVHD**

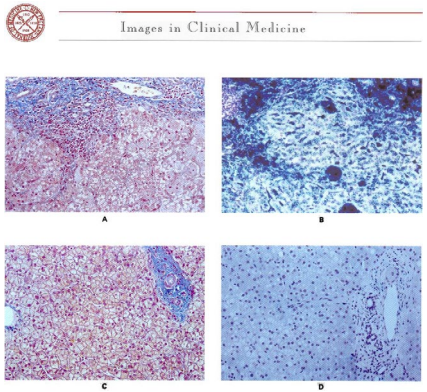
GVHD, graft versus host disease; mo, months; OS, overall survival; PBPC, Peripheral blood progenitor cells; SCT, stem-cell transplant; TFS, thalassemia-free survival.

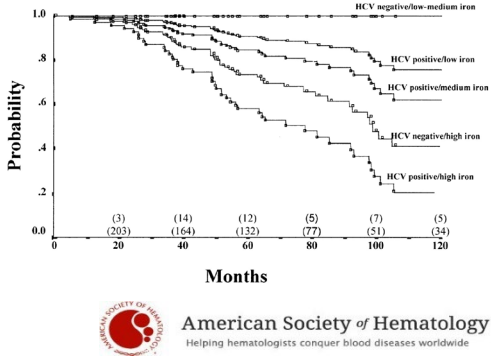
Adapted from: Anurathapan U, et al. *Biol Blood Marrow Transplant*. 2020;26:1106–1112.

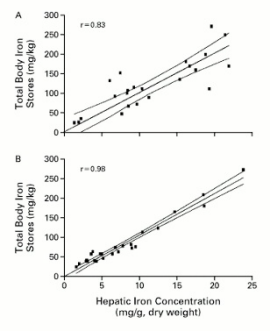
Achiements of Pesaro experience

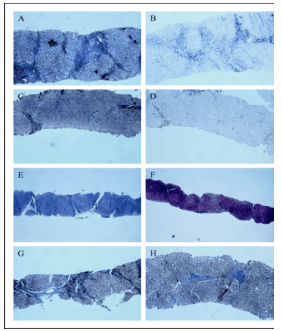
- Mixed chimerism
- Possibility of complete Iron removal by phlebotomy
- Link between liver iron and total iron
- Risk of cirrhosis by iron and viral infections
- Restitutio ad integrum of severe iron damage











HCT in TDT

HCT is CURE of the disease[1]
>90% success rate. Thousands of patients. Long follow up. Cost effective

Replacement of the entire hematopoietic system and not only of the diseased erythropoiesis[2]

Myeloablation + immunosuppression needed[3]

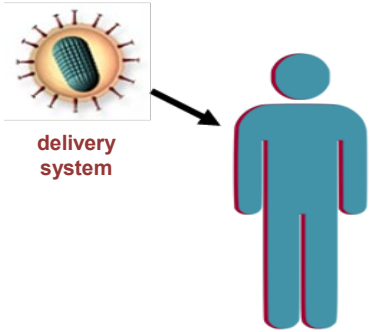
Limitation:
Patients missing HLA identical donor (for caucasian 40% probability to find a 8/8 HLA identical unrelated donor (*Sacchi N. Human Immunology 2021).* Adult patients. Risk of GvHD

HCT, hematopoietic cell transplantation.
1. Dong A, et al. Transl Res. 2013;161:293-306; 2. Speaker's own opinion; 3. Pasquini MC, et al. Biol Blood Marrow Transplant. 2016;22:1424-1430.

Gene therapy (addition): the use of genes as medicine

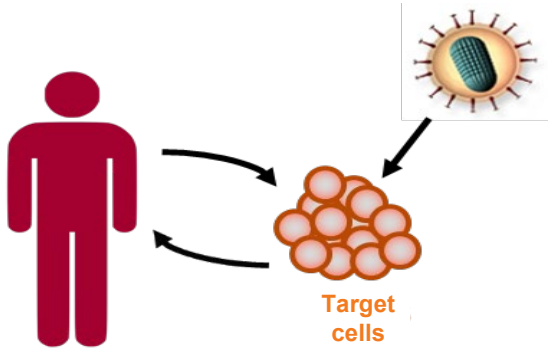
- It is based on the **transfer of a therapeutic or working gene** copy into somatic cells of an individual in order to repair a defective gene copy
  - **replace a faulty gene**, or to
  - **introduce a new gene** whose function is lacking
  - **changes in the DNA sequence**, customizing its genetic makeup
- to cure or to favorably modify the clinical course of a condition. **Clinical benefit**

Gene Therapy
Methods of Administration



in vivo

In vivo gene therapy: direct delivery of genes into the cells of a particular tissue in the body



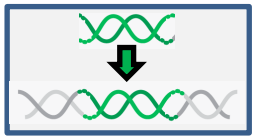
ex vivo

Ex vivo gene therapy:
transfer of genes to cells isolated from the body, followed by reintroduction of those modified cells back into the body

Conditioning required

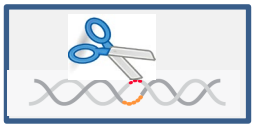
Potential Methods for Permanently Modifying HSCs for Long-Term Effect

- **Gene Addition (using viral vectors)**



  - Adding a copy of β–globin (for example, HbA^{T87Q})
  - Fetal globin (a β-like anti-sickling globin) activation via transcriptional regulation

- **Genome Editing (using engineered / programmable nucleases)**

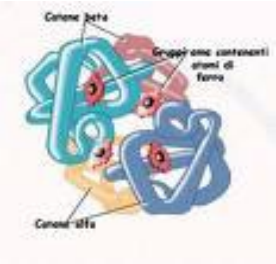


  - Gene correction: fixing the mutation itself (HbS)
  - Generating de novo mutations that result in Hereditary Persistence of Fetal Hemoglobin (HPFH)

Gregory. ASH Educational Lecture. Dec 2017.

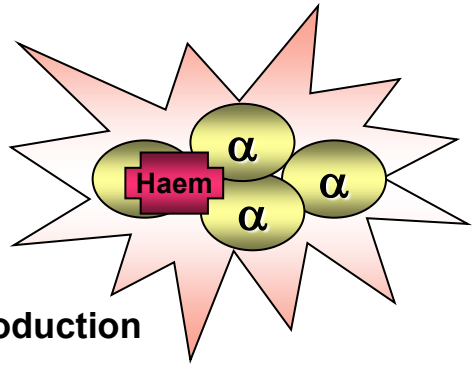
β-Thalassaemia

Adult haemoglobin



Mutations in the β-globin gene

Alpha/haem aggregates



Consequences of reduced β-globin chain production

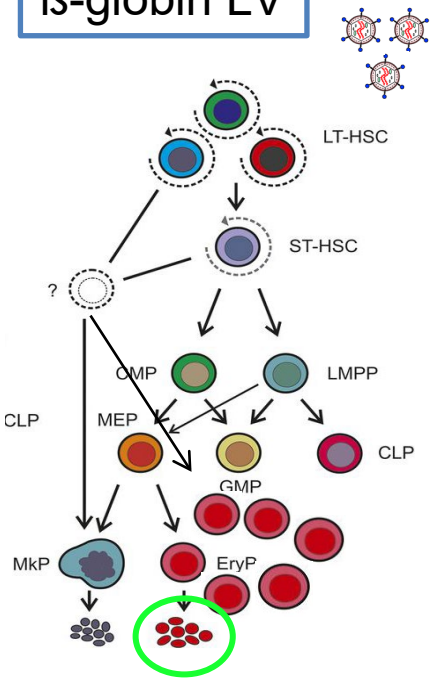
Ineffective erythropoiesis

- **Anaemia**
- **Iron overload**
- **Erythroid marrow Expansion of splenomegaly**

Melchiori L, et al. Adv Hematol. 2010;2010:938640. Epub 2010 May 19.

Rationale for gene therapy of BTHAL

ß-globin LV



ß-globin gene transfer in HSCs

↓

chains imbalance reduction

↓

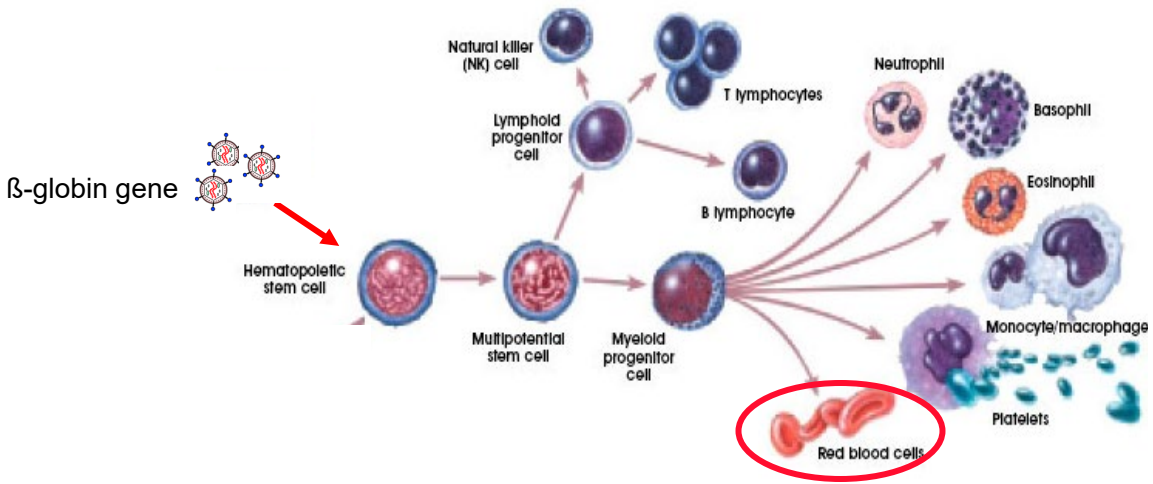
production of functional RBCs

Adequate production of β/γ-globin to reduce globin chains unbalance and obtain normal Hb/HbF"

- Transfusion independence
- Absence of ineffective erythropoiesis and ineffective erythropoiesis stigmata

Gene Therapy in Thalassemia: Rationale

The ß-globin gene transfer into HSCs reduces globin chains unbalance in erythroid cells



The story:

Initial clinical experiments (n = 2) by Cline and coworkers were clearly "scientifically premature":

Mercola KE, Cline MJ. Sounding boards. The potentials of inserting new genetic information. ***N Engl J Med. 1980;303:1297-1300.***

Mercola KE, Bar-Eli M, Stang HD, Slamon DJ, Cline MJ. Insertion of new genetic information into bone marrow cells of mice: comparison of two selectable genes. Ann N Y Acad Sci. ***1982;397:272-280****.*

Sun M. Cline loses two NIH grants. ***Science. 1981;214:1220****.*

Cline MJ. Perspectives for gene therapy: inserting new genetic information into mammalian cells by physical techniques and viral vectors. Pharmacol Ther. ***1985;29:69-92***

The story:
catastrophic complication of leukemia

- Gene therapy for primary immunodeficiency disorders was plagued by catastrophic complication of leukemia transformation *(Nat Rev Cancer. 2003;3:477-488).*
  - This complication has been researched and corrected, leading to generation of safer "targeted" vectors such as self-inactivating γ retroviral or lentiviral vectors (*Trends Mol Med. 2016;22:317-327; N Engl J Med. 2014;371:1407-1417)*

The story:

Preclinical and early clinical studies has demonstrated the safety and potential efficacy of this novel curative approach in. hemoglobinopathies.

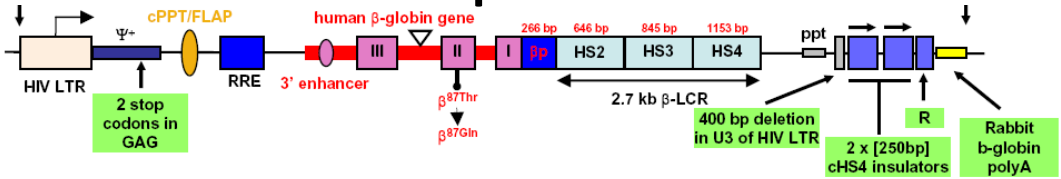
May C, Rivella S, Chadburn A, Sadelain M. Successful treatment of murine beta-thalassemia intermedia by transfer of the human beta-globin gene. ***Blood. 2002;99:1902-1908****.*

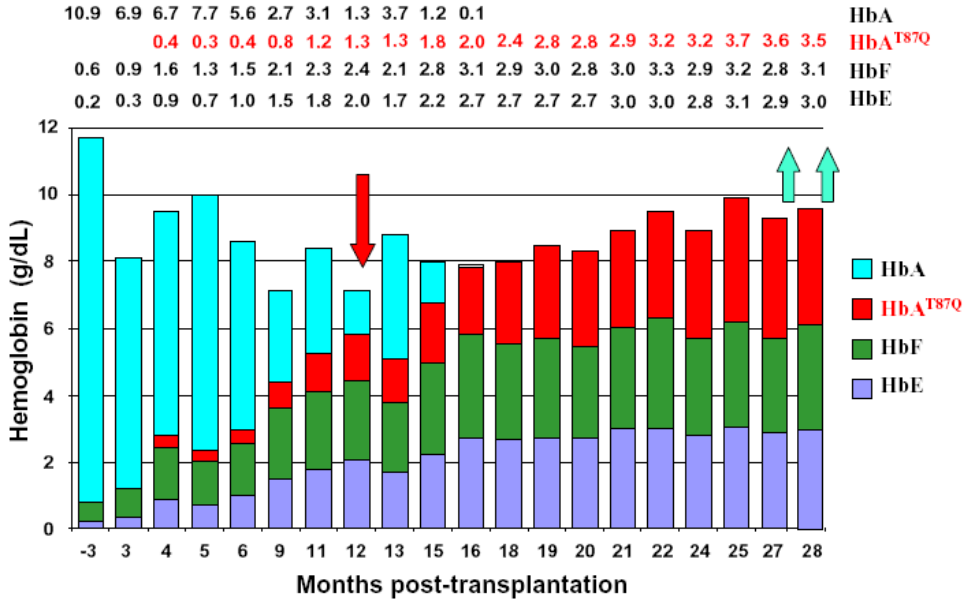
Yannaki E, Papayannopoulou T, Jonlin E, et al. Hematopoietic stem cell mobilization for gene therapy of adult patients with severe beta-thalassemia: results of clinical trials using G-CSF or plerixafor in splenectomized

and nonsplenectomized subjects. ***Mol Ther. 2012;20:230-238.***

Boulad F, Wang X, Qu J, et al. Safe mobilization of CD34+ cells in adults with beta-thalassemia and validation of effective globin gene transfer for clinical investigation. ***Blood. 2014;123:1483-1486****.*

Clinical Trial: Gene Transfer of the β^{87} lenti-vector into a β^{E}/β^{0} thalassemia patient promotes transfusion independence





Cavazzana-Calvo,Nature2010

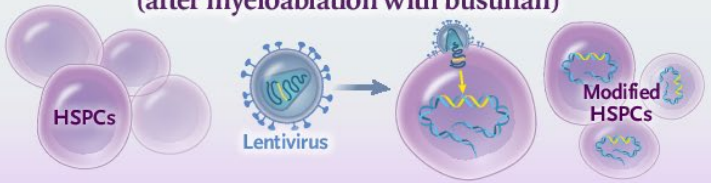
The NEW ENGLAND JOURNAL of MEDICINE

Betibeglogene Autotemcel Gene Therapy for Non–β^0/β^0 Genotype β-Thalassemia

OPEN-LABEL, PHASE 3 STUDY

23
Adult and pediatric patients with transfusion-dependent β-thalassemia and a non–β^0/β^0 genotype

Beti-cel gene therapy
(after myeloablation with busulfan)



Transfusion independence (median follow-up, 29.5 mo)	20 of 22 patients
Average hemoglobin level during transfusion independence	11.7 g/dl (range, 9.5–12.8)
Median gene therapy–derived adult hemoglobin level at 12 mo	8.7 g/dl (range, 5.2–10.6)

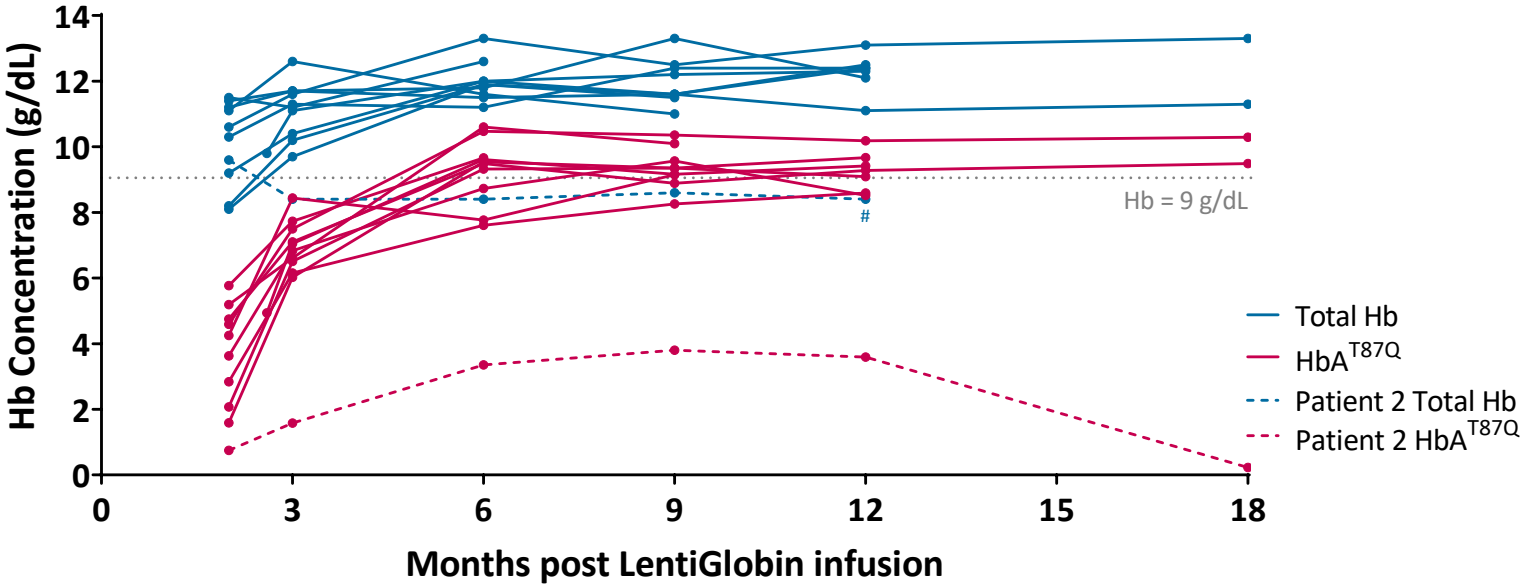
Beti-cel treatment resulted in transfusion independence in most patients.

F. Locatelli et al. 10.1056/NEJMoa2113206

HGB-207: Stable total Hb and gene therapy-derived HbA^{T87Q} in 10/11 patients with ≥ 6 months follow-up

Median Hb in patients free from transfusions at last study visit (g/dL)

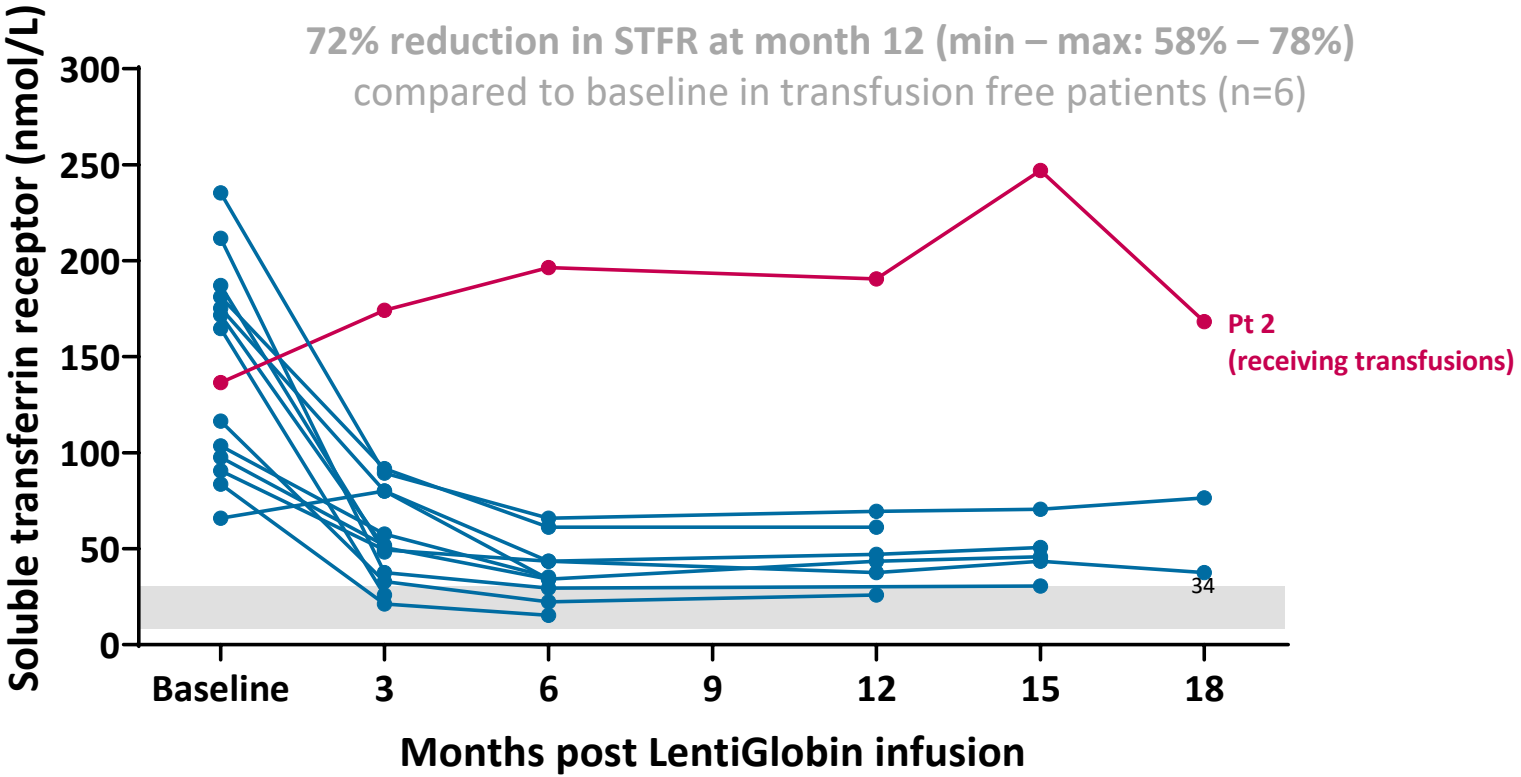
	M6 (n=10)	M9 (n=9)	M12 (n=7)	M18 (n=2)
Total Hb	**11.9**	**11.6**	**12.4**	**12.3**



#Last Hb before hemoglobin

HGB-207: Improvement in erythropoiesis post LentiGlobin

STFR normalizes in patients who stopped transfusions



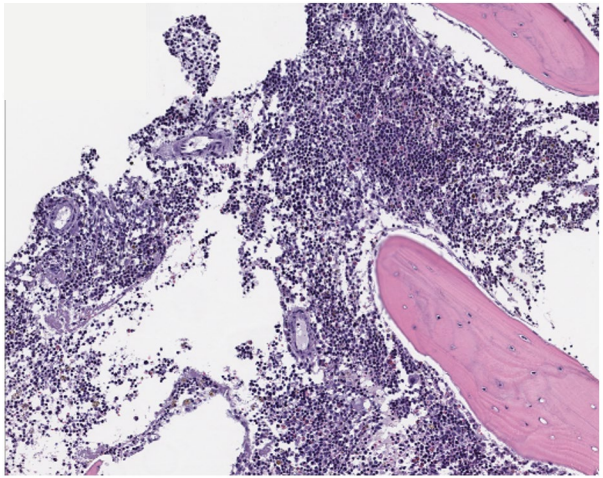
STFR, soluble transferrin receptor

Data as of June 16, 2019

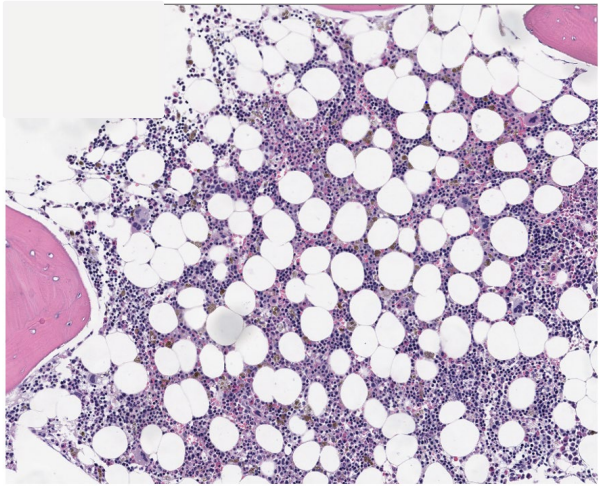
HGB-207: Improvement in erythropoiesis post LentiGlobin
Improvement in bone marrow histology and M:E ratio

Patient 1 (20 yr-old) bone marrow analysis

Screening

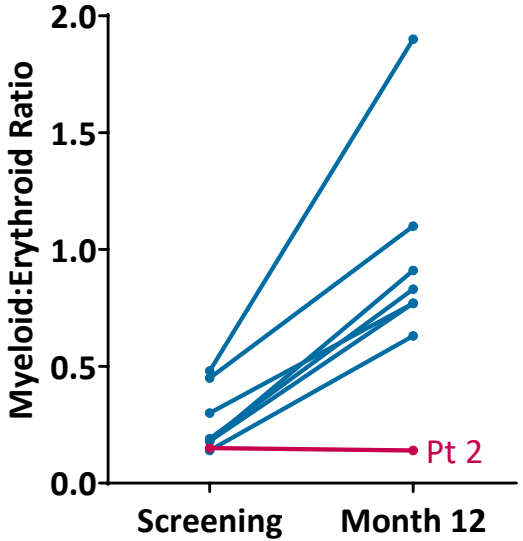


Month 12 post-LentiGlobin



Hb at Month 12: 13.1 g/dL

Myeloid:Erythroid ratio following LentiGlobin gene therapy (n=8)



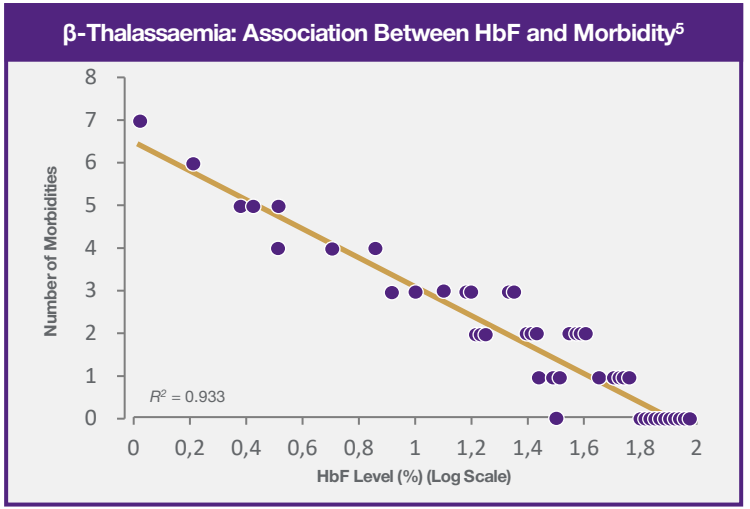
Normal M:E Ratio[1]: 3-4:1

1. Origa R. GeneReviews®. 2018.

A Naturally Occurring Genetic Variation Results in Persistence of HbF and Alleviates Symptoms[1-3]

Elevated HbF is associated with decreased disease severity

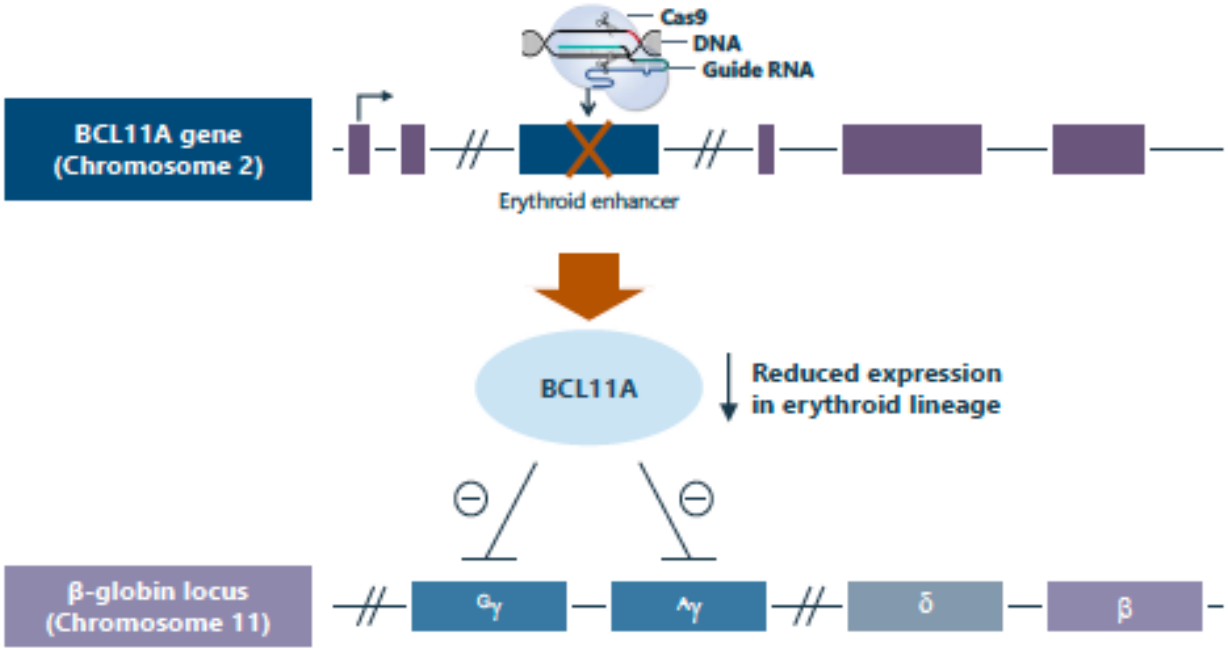
- A subset of patients with β-thalassaemia continue to express HbF into adulthood, a condition known as hereditary persistence of HbF (HPFH)[1-3]
- These patients experience reduced or no symptoms with no detrimental effects[1-3]
- The goal of this investigational approach is to reactivate HbF and recapitulate the HPFH phenotype[4]



HbF, foetal haemoglobin.

1. Murray N, et al. *Br J Haematol*. 1988;69(1):89-92. 2. Conley CL, et al. *Blood*. 1963;21:261-281. 3. Bank A. *Blood*. 2006;107(2):435-443. 4. Frangoul H, et al. *N Engl J Med*. 2021;384(3):252-260. 5. Musallam KM, et al. *Blood*. 2012;119(2):364-367.

Our approach disrupts the BCL11A erythroid enhancer

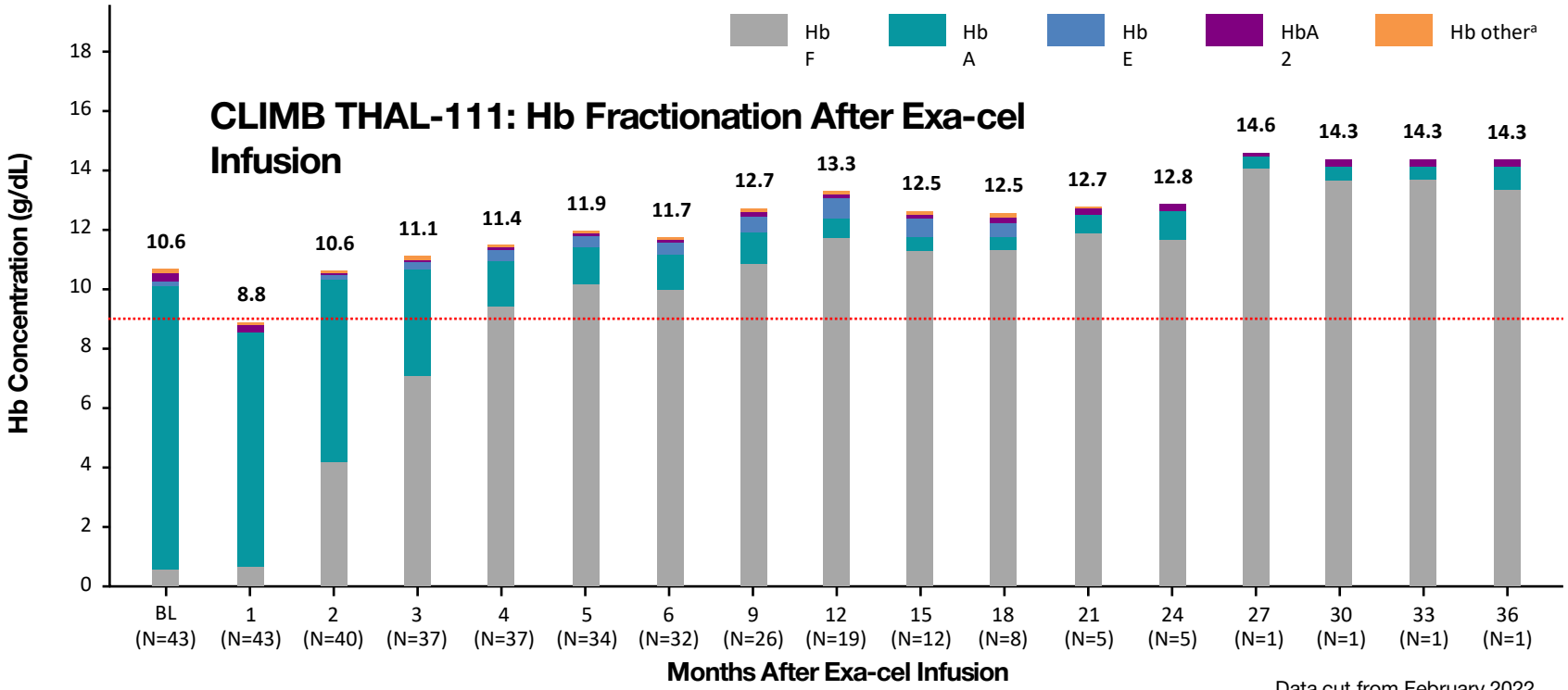


Disruption of the erythroid enhancer region of BCL11A leads to re-expression of γ-globin (HbF)

Gene editing - Overview

- Precise genome editing using CRISPR-Cas9 technology increases γ-globulin and HBF and will potentially lead to improved α-globin chain pairing with the goal of achieving transfusion independence in patients with TDT.
- Preclinical and toxicology studies have enabled the start of a phase I/II study in TDT and SCD patients (enrolling)
- Mobilization and conditioning similar to autologous HC transplantation followed by infusion of CRISPR-Cas9 edited cells

The information on this slide is about an investigational approach that is not approved by any Health Authority. Safety and efficacy have not been established.



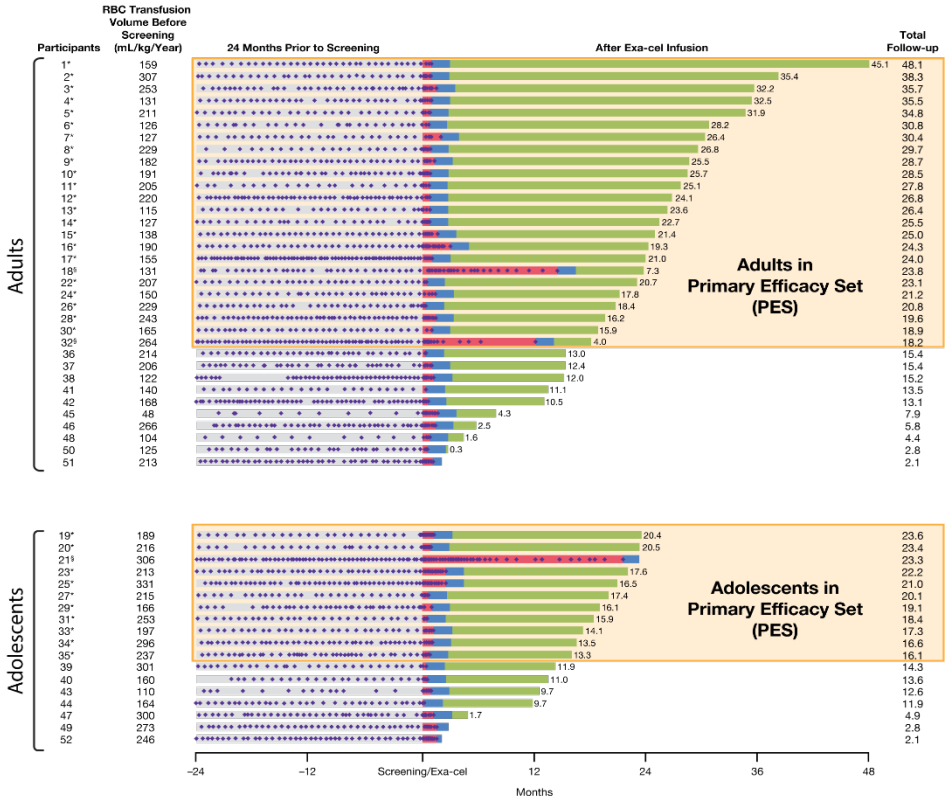
BL, baseline; exa-cel, exagamglogene autotemcel; Hb, haemoglobin; HbA, adult haemoglobin; HbA2, haemoglobin, alpha 2; HbE, haemoglobin E; HbF, foetal haemoglobin; TDT, transfusion-dependent β-thalassaemia.

Mean total Hb concentrations are shown directly above bars. [a]Hb adducts and other variants.

1. Locatelli F, et al. Oral presentation. Presented at the 27th Annual European Hematology Association; 12 June 2022

Data cut from February 2022.
Adapted from Locatelli F, et al. Presented at the 27th Annual European Hematology Association; 12 June 2022.

Clinically Meaningful Benefit and Consistent Efficacy Between Adults and Adolescents in TDT



F Locatelli Courtesy

*participants who achieved TI12; §participants who did not achieve TI12

exa-cel, exagamglogene autotemcel; **RBC,** red blood cell; **TDT,** transfusion dependent β-thalassemia; **TI12;** proportion of participants transfusion independent for ≥12 consecutive months while maintaining a weighted average hemoglobin ≥9 g/dL.

Hurdles to the Adoption of Gene Therapy as a Curative Option for Transfusion-Dependent Thalassemia

Isabelle Thuret, Annalisa Ruggeri ,*, Emanuele Angelucci, Christian Chabannon

Long term adverse events (insertional mutagenesis)

Pricing and additional costs

Production issues

COST – The wholesale acquisition cost (WAC) of a single dose of gene therapy range from $2.2 million to $2.8 million.
The Medical Letter May 13, 2024

Haemoglobinopathies epidemiology

- >330,000 new born with hemoglobinopathy every year
- 17% Thalassemia (> 23.000 new born/year)

Modell B et al. Global epidemiology of haemoglobin disorders and derived service indicators.
Bull World Health Organ 2008;86:480-7.

MEDICINES CAN CURE DISEASES BUT ONLY DOCTORS CAN CURE PATIENTS.

C. G. Jung.

XIX Congresso della Società GITMO

RIUNIONE NAZIONALE GITMO

TORINO, CENTRO CONGRESSI LINGOTTO, 5 - 6 MAGGIO 2025

Thank you for your kind attention