

# THALASSEMIA

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# Disclosures

- **Consultant**
  - Bluebird bio
  - Celgene Bristol Myers Squibb Acceleron
  - Agios
  - Chiesi
- **Steering**
  - CRISPR/ Vertex CTX001
- **Will discuss therapeutics not yet FDA approved**
  - results from clinical trials

# HEMOGLOBIN DISORDERS

## Qualitative Hemoglobinopathies

Globin gene mutations that result in structural abnormalities of the globin chain:

Hb S, Hb C, Hb E and other Hb variants

## Quantitative Hemoglobinopathies

(disorders of ineffective erythropoiesis)

Globin gene mutations that result in decreased production of globin chains:

Thalassemias (Alpha, Beta, Gamma, Delta)

# THE THALASSEMIA SYNDROMES

ALPHA: Decreased or Absent  $\alpha$  globin chains

BETA: Decreased or Absent  $\beta$  globin chains

DELTA: Decreased or Absent  $\delta$  globin chains

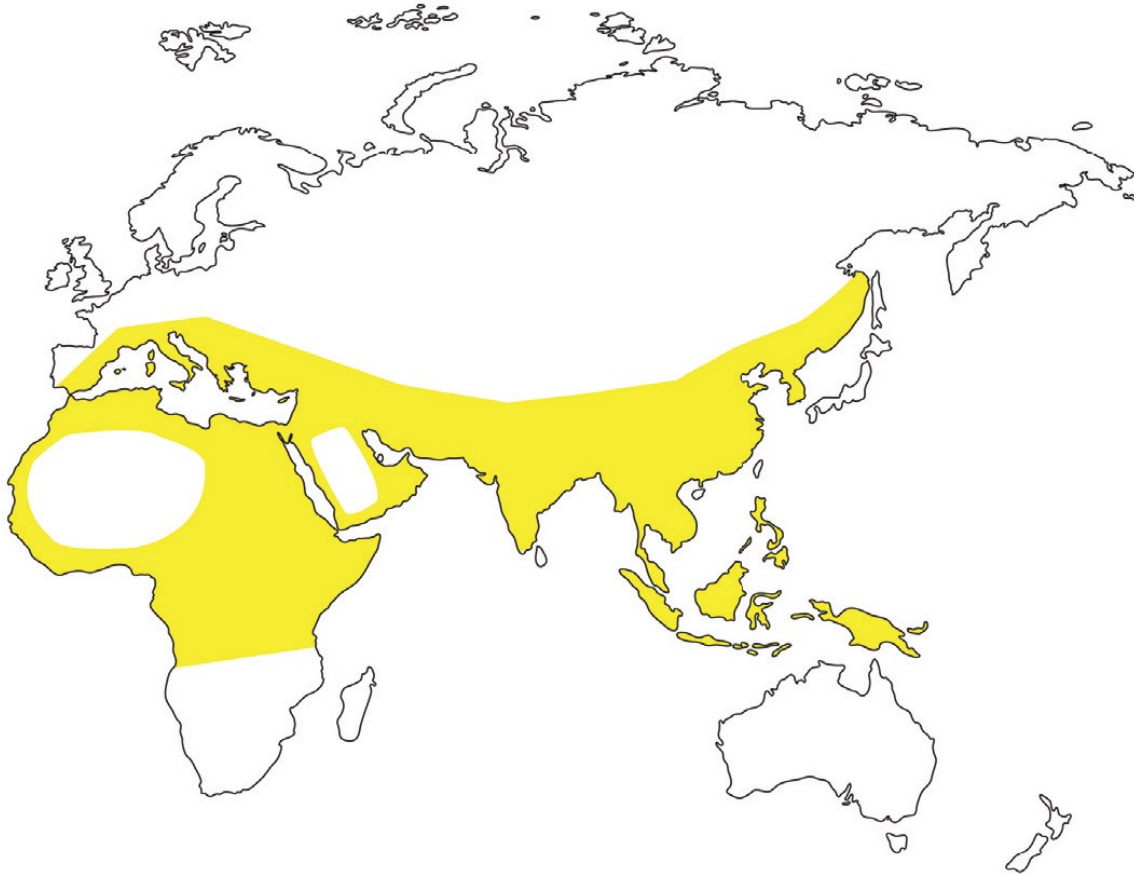
GAMMA: Decreased or Absent  $\gamma$  globin chains

## STRUCTURAL VARIANTS:

Hb Constant Spring ( $\alpha$ )      Hb E ( $\beta^{26\text{Glu-Lys}}$ )

Hb Hasharon ( $\alpha$ )      Hb Lepore ( $\delta\beta$  fusion)

# DISTRIBUTION



80-90 million carriers worldwide  
(~ 1.5% of population)<sup>[1]</sup>

60,000 affected individuals born  
annually<sup>[1]</sup>

Exact prevalence in US  
unknown; estimated to be ~  
2000 individuals<sup>[2]</sup>

Estimated prevalence in Italy: ~  
6000<sup>[3]</sup>

High prevalence in Asia—South  
and Southeast Asia, China<sup>[1]</sup>

Immigration patterns

# GENOTYPE-PHENOTYPE

Mild	Non Transfusion dependent	Transfusion dependent
Anemia ranging from very mild to low end of normal	Intermediate severity Moderate anemia	Severe anemia
<b><math>\alpha</math>-thalassemia trait/silent carrier</b>	<b><math>\alpha</math>-thalassemia intermedia-Hb H</b>	<b><math>\alpha</math>-thalassemia major/Hb Barts</b>
<b><math>\beta</math>-thalassemia minor/trait</b>	<b><math>\beta</math>-thalassemia intermedia</b>	<b><math>\beta</math>-thalassemia major</b>
	<b>Dominant <math>\beta</math>-thalassemia</b>	<b>Severe Hb E <math>\beta</math>-thalassemia</b>
	<b>Hb H Constant Spring</b>	<b>Severe Hb H Constant Spring</b>
	<b>Hemoglobin E <math>\beta</math>-thalassemia</b>	

**NOT SO BENIGN**

# $\beta$ THALASSEMIA

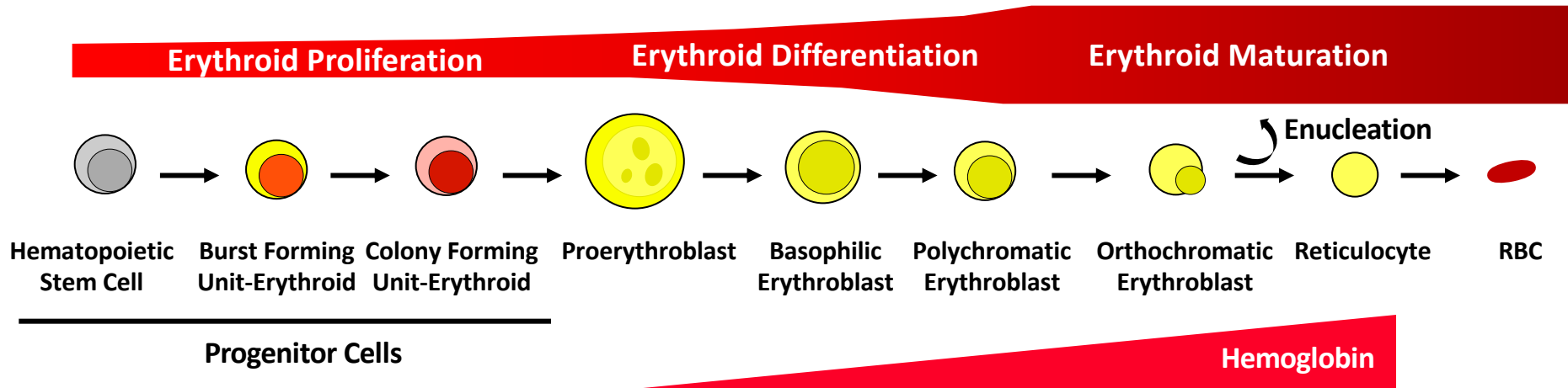
# MUTATIONS

- $\beta^0$  - nonsense, frameshift or splicing
- $\beta^+$  - promoter area CACCC or TATA box, polyadenylation signal, 5' or 3' UTR, or splicing defects
- Complex  $\delta\beta$  or  $\gamma\delta\beta$  thalassemsias - deletions of part of  $\beta$  globin gene cluster
- Deletion of LCR with intact  $\beta$  globin gene
- Silent - distal CACCC box, 5' unbalanced region, polyadenylation signal, some splicing defects

# NORMAL ERYTHROPOIESIS

Early-Stage Erythropoiesis

Late-Stage Erythropoiesis



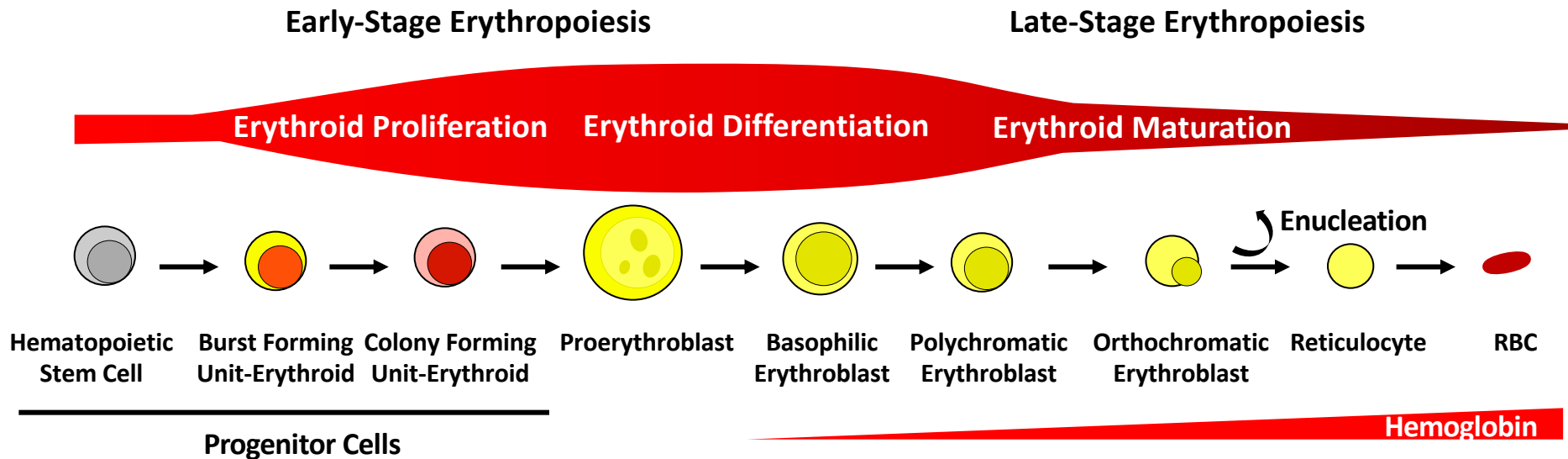
- Characterized by proliferation of progenitor cells
- Promoted by EPO

- Characterized by differentiation of erythroblasts, maturation of reticulocyte precursors into RBCs
- Regulated by TGF- $\beta$  ligands

# HEMOGLOBIN ABNORMALITY

- Imbalance between normal ratio of  $\alpha$  :  $\beta$  chain production
- Insufficient upregulation of complementary genes
- Precipitation of tetramers, formation of hemichromes
- Cell disruption - apoptosis
- Ineffective erythropoiesis

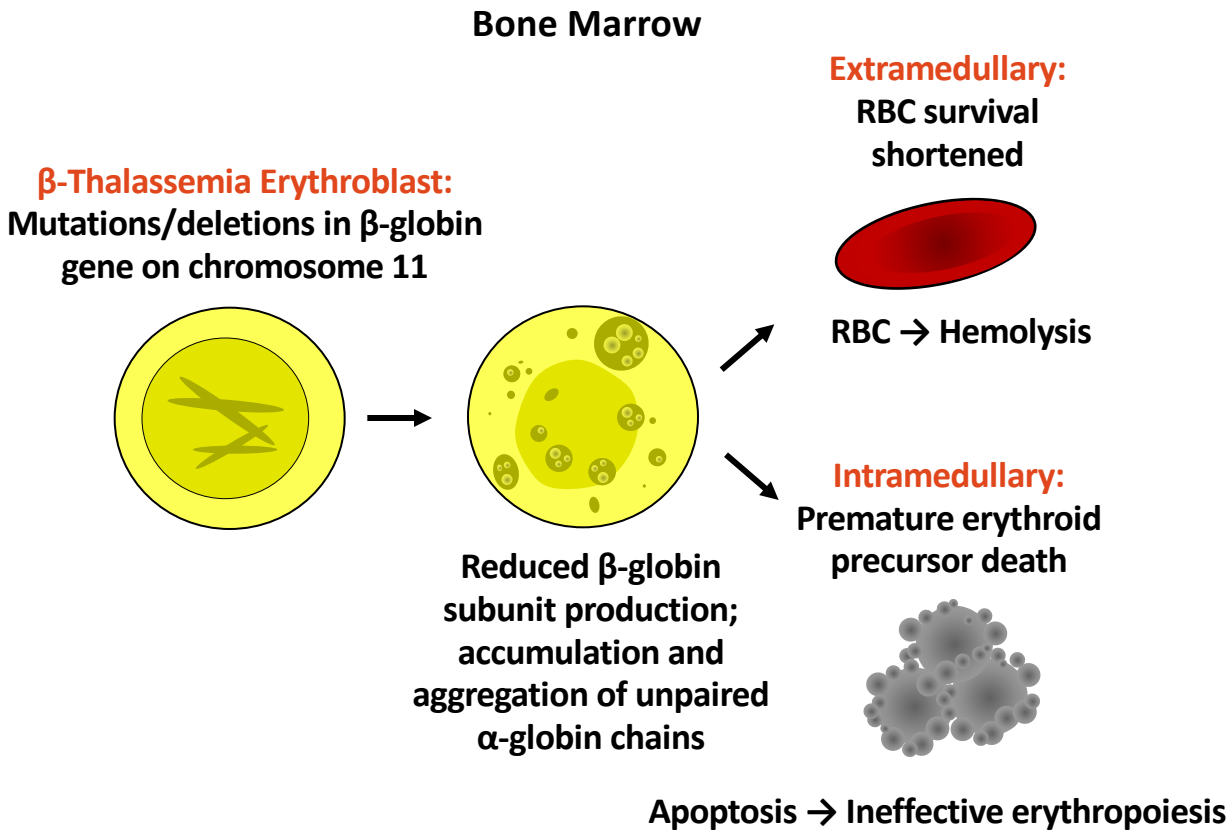
# INEFFECTIVE ERYTHROPOIESIS



- Characterized by expansion of early erythroid precursors

- Characterized by accelerated differentiation, maturation arrest in polychromatic erythroblast stage, and apoptosis
- Accumulation of TGF- $\beta$  ligands

# FEATURES OF INEFFECTIVE ERYTHROPOIESIS



- Impaired erythroid precursor maturation
- $\alpha$  and  $\beta$  chain imbalance
- Formation of toxic hemichromes from precipitation of unpaired  $\alpha$ -globin chains
- Apoptosis of erythroid precursors
- Reduced RBC survival
- Anemia
- Increased erythropoietic drive
- Extramedullary hematopoiesis
- Dysregulated iron metabolism

# CLINICAL PHENOTYPES IN BETA THALASSEMIA HETEROZYGOUS

Silent carrier <sup>1</sup>

Trait

Carrier with normal phenotype:

Normal CBC, retic, electrophoresis

Requires DNA testing for detection of mutations

Genotypes:  $\beta^+/\beta$

Minor <sup>1</sup>

Trait

Carrier of the classic trait

Slight anemia at worst with low MCV

Quantitative Electrophoresis:

Elevated A2, elevated F

Genotypes:  $\beta^+/\beta$  or  $\beta^0/\beta$

# CLINICAL PHENOTYPES IN BETA THALASSEMIA HOMOZYGOUS OR COMPOUND HETEROZYGOUS

Intermedia <sup>1</sup> Inherits two Thalassemia mutations  
Diagnosis usually at 2-5 years of age  
Moderate anemia; Hb >7-10 g/dL  
Elevated Ret, ct: 2-10%; NRBCs on smear  
Hepatosplenomegaly, Extramedullary Hematopoietic Masses  
Minimal or periodic transfusions  
Daily Folic Acid supplementation: 1 mg daily  
May benefit from splenectomy  
Genotypes:  $\beta^+/\beta^+$ ,  $\beta^+/\beta^0$ ,  $\beta^0/\beta^0$ ,  $\beta^E/\beta^+$ ,  $\beta^E/\beta^0$ ,  $\beta^+/\alpha\alpha\alpha\alpha$ ,  $\beta^0/\alpha\alpha\alpha\alpha$

Major <sup>1, 2</sup> Inherits two Thalassemia mutations  
Diagnosis in first year  
Severe anemia; Hb <7 g/dL  
Ret. Ct: 10-15%; many NRBCs on smear  
Lifelong transfusions  
Genotypes:  $\beta^0/\beta^0$ ,  $\beta^+/\beta^+$ ,  $\beta^E/\beta^0$ ,  $\beta^E/\beta^+$

1. Camaschella and Cappellini. *Haematologica*. 1995;80:58;
2. Weatherall et al. *Ciba Found Symp*. 1979;66:147.

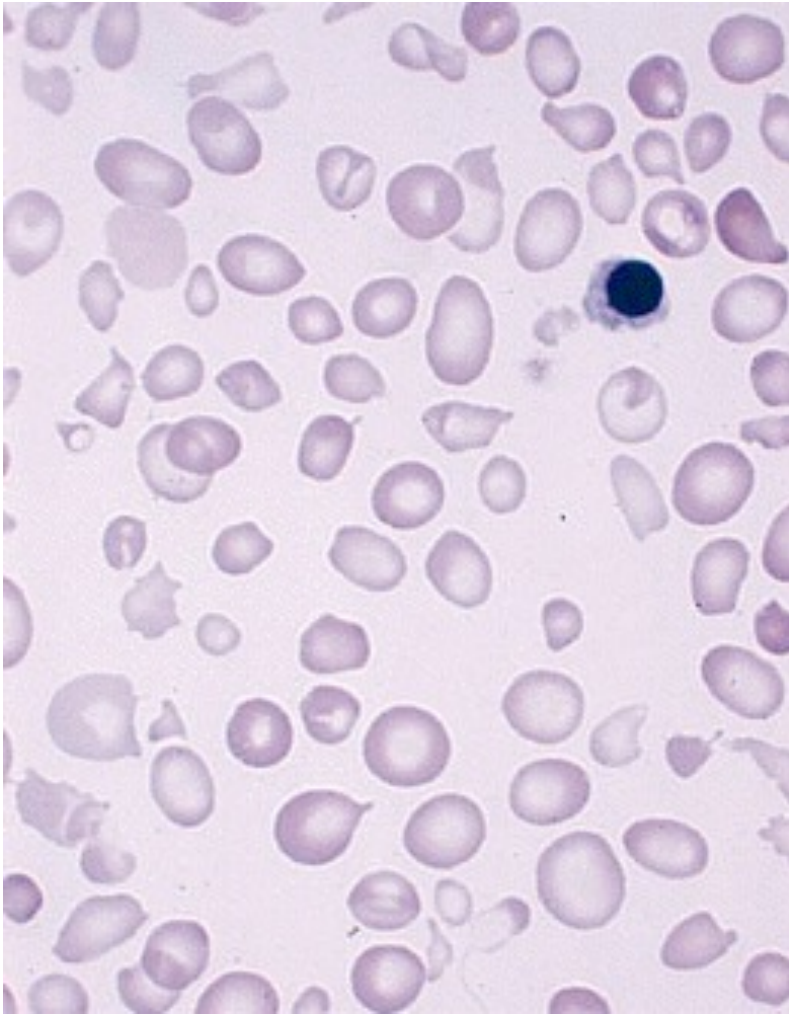
# SPECTRUM OF DISEASE

Syndrome	Genotype	Hematology	Disease Severity
Thalassemia major	$\beta^0/\beta^0$	<ul style="list-style-type: none"> <li>Complete absence of Hb A</li> <li>Severe anemia requiring transfusions from infancy</li> </ul>	<ul style="list-style-type: none"> <li><b>TD</b></li> <li>Lifelong supportive care required</li> </ul>
Thalassemia intermedia	$\beta^+/\beta^+$ or $\beta^0/\beta^+$	<ul style="list-style-type: none"> <li>Diminished production of Hb A</li> <li>Mild to moderate anemia</li> </ul>	<ul style="list-style-type: none"> <li><b>NTD</b></li> <li>May need occasional transfusions or may become <b>TD</b></li> <li>Significant variability in disease severity</li> </ul>
Thalassemia minor	$\beta^+/\beta$ or $\beta^0/\beta$	<ul style="list-style-type: none"> <li>Mild or no anemia</li> </ul>	<ul style="list-style-type: none"> <li><b>NTD</b></li> <li>May be asymptomatic</li> </ul>

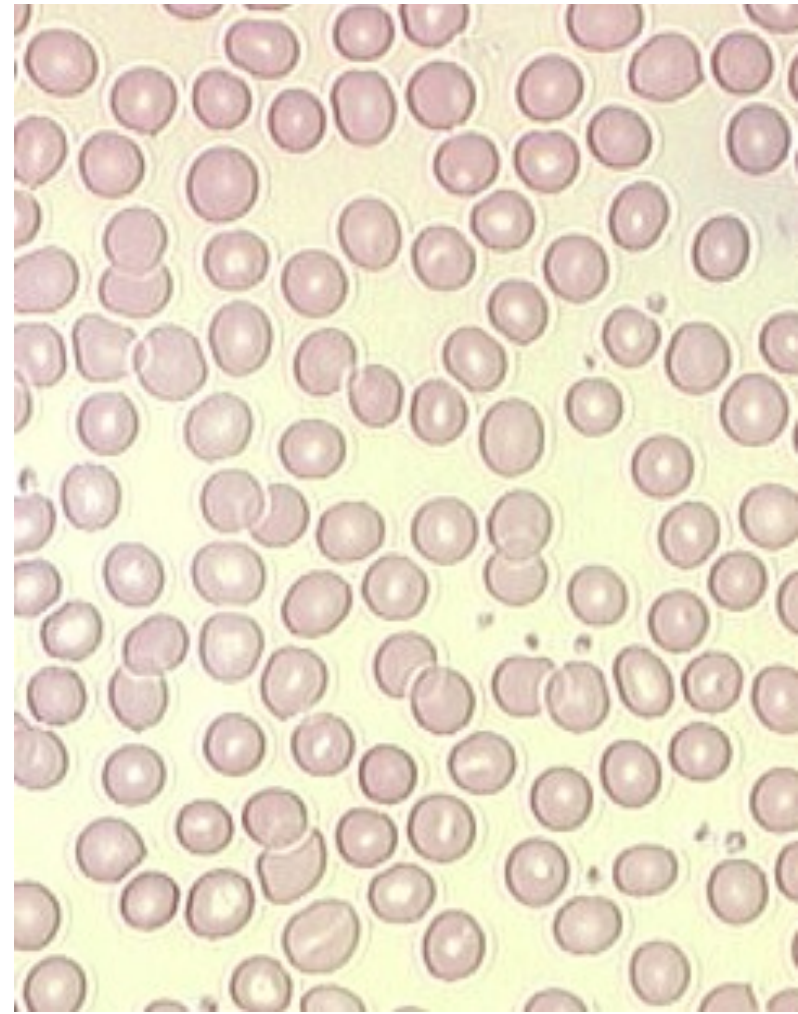
# DIAGNOSIS

- History - family history, ethnicity
- Clinical syndrome - anemia, hepatosplenomegaly, facies, skeletal abnormalities
- CBC - anemia with low MCV, low MCH, smear
- Hemoglobin electrophoresis
- Genetic testing

# THE BLOOD SMEAR

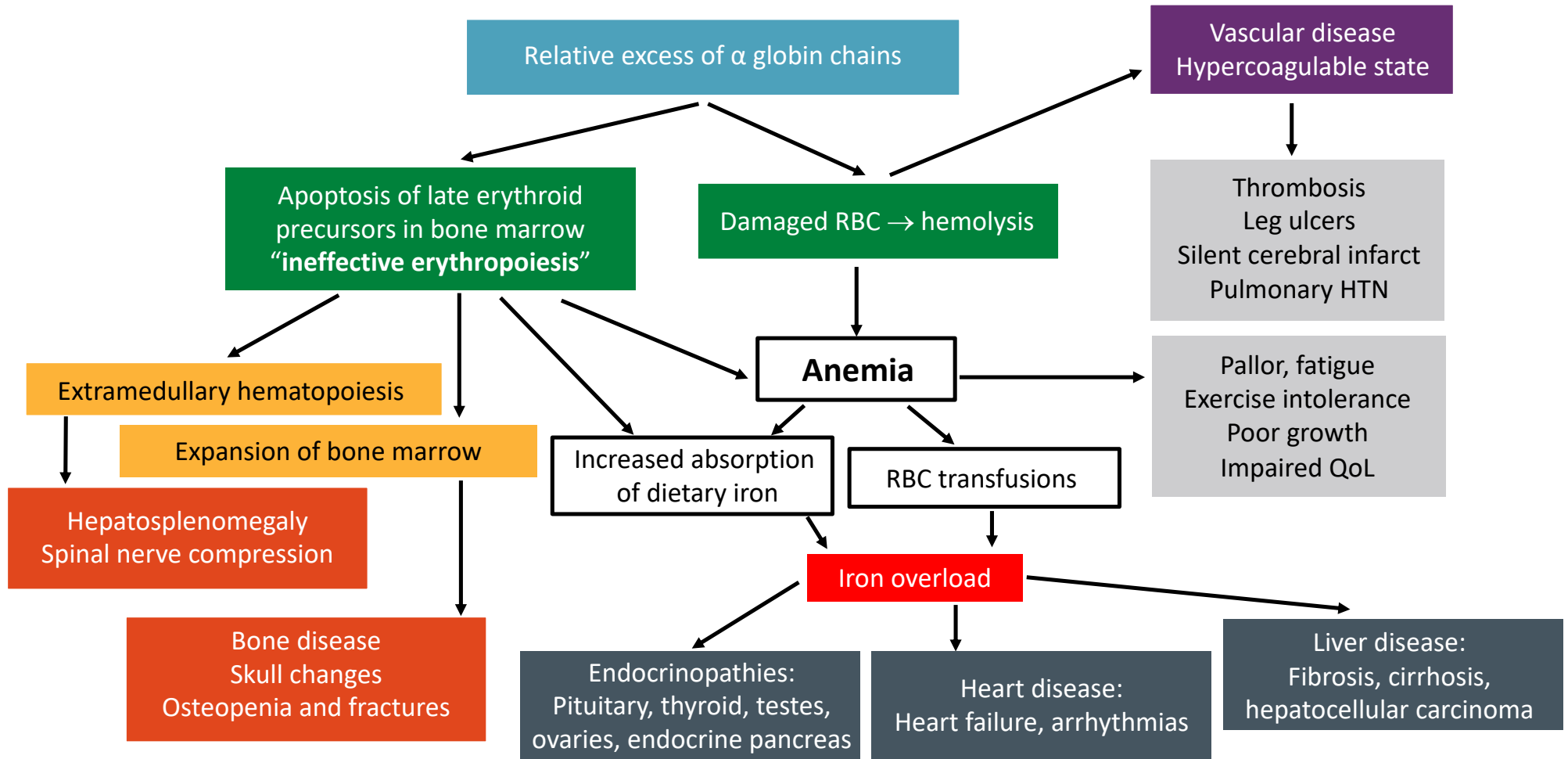


**Major**



**Minor**

# PATHOLOGY AND CLINICAL FEATURES



# CLINICAL MANIFESTATIONS

- **Anemia:** Impaired function, impaired growth, impaired QoL
- **Iron overload:** Increased GI absorption, transfused iron
- **Cardiac disease:** Anemia, iron deposition
- **Endocrinopathy:** Pituitary, thyroid, endocrine pancreas, gonads
- **Bone disease:** Erythroid hyperplasia, endocrinopathy
- **Gallbladder disease:** Increased red cell turnover
- **Extramedullary hematopoiesis:** Hepatosplenomegaly, spinal nodules
- **Vascular disease:** Leg ulcers, pulmonary hypertension, stroke

# COURSE - TDT

- Regular blood transfusions: Every 2-4 wks
- Splenectomy as needed
- Iron chelation therapy: Oral vs parenteral
- Monitoring for iron overload: MRI (annually)
- Monitoring for side effects of chelation (monthly)
- Monitoring for complications of disease and treatments (annually or more frequently if present)
- Hematopoietic stem cell transplantation

# COURSE - NTDT

- Supportive care: Bone health, vitamin D and folic acid supplementation, thromboprophylaxis
- Splenectomy: If severe anemia and splenomegaly
- Transfusions (periodic): Leg ulcers, splenomegaly, pregnancy, surgery
- Iron chelation
- Induction of Hb F: Hydroxyurea, 5'azacytidine, decitabine, butyrate
- Other: Luspatercept, ruxolitinib
- Stem cell transplantation, gene therapy

# MANAGEMENT ISSUES

- Transfusions, splenectomy
- Transfusion complications
- Complications of Iron overload
- Chelation - Side effects and monitoring
- Organ dysfunction
- Stem cell transplantation
- Newer therapies

# TRANSFUSION GOALS

- Correction of anemia Hgb > 10 gm/dl
- Suppression of (ineffective) erythropoiesis
- Prevention of bony changes, hepatosplenomegaly
- Inhibition of GI iron absorption
- Minimization of transfusional iron overload
  - Splenectomy
  - 15 mL/kg monthly approx. 0.3 – 0.6 mg/kg/day Fe
  - Short transfusion intervals q 2 wks

# TRANSFUSION COMPLICATIONS

- Complications related to transfusions
  - Alloimmunization
  - Infections
  - Iron overload
- Complications related to iron overload
  - Cardiac failure
  - Liver cirrhosis/fibrosis/cancer
  - Diabetes mellitus
  - Infertility
  - Arthritis

# SPLENECTOMY

- TDT
  - Hypersplenism with increasing transfusion requirement - >200 ml/kg/year PRBCs
- NTDT
  - Massive splenomegaly
  - Hypersplenism – extramedullary hematopoiesis
- Risks – infection, vascular disease
- Benefits – minimize transfusions and iron loading

# COMPLICATIONS

## Transfusion Dependent

Hypothyroidism  
Hypoparathyroidism

Cardiac siderosis  
Left-sided heart failure

Hepatic failure  
Viral hepatitis

Diabetes mellitus  
Hypogonadism

Osteoporosis

Transfusion reactions  
Alloimmunization

## Nontransfusion Dependent

Silent cerebral ischemia

PHT

Right-sided heart failure

Extramedullary  
hematopoietic pseudotumors

Hepatic fibrosis, cirrhosis, and cancer

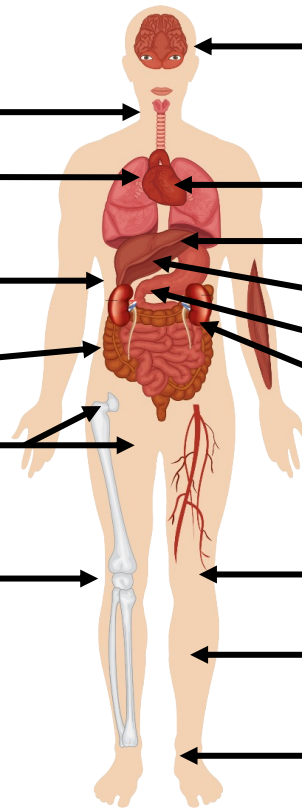
Gallstones

Splenomegaly

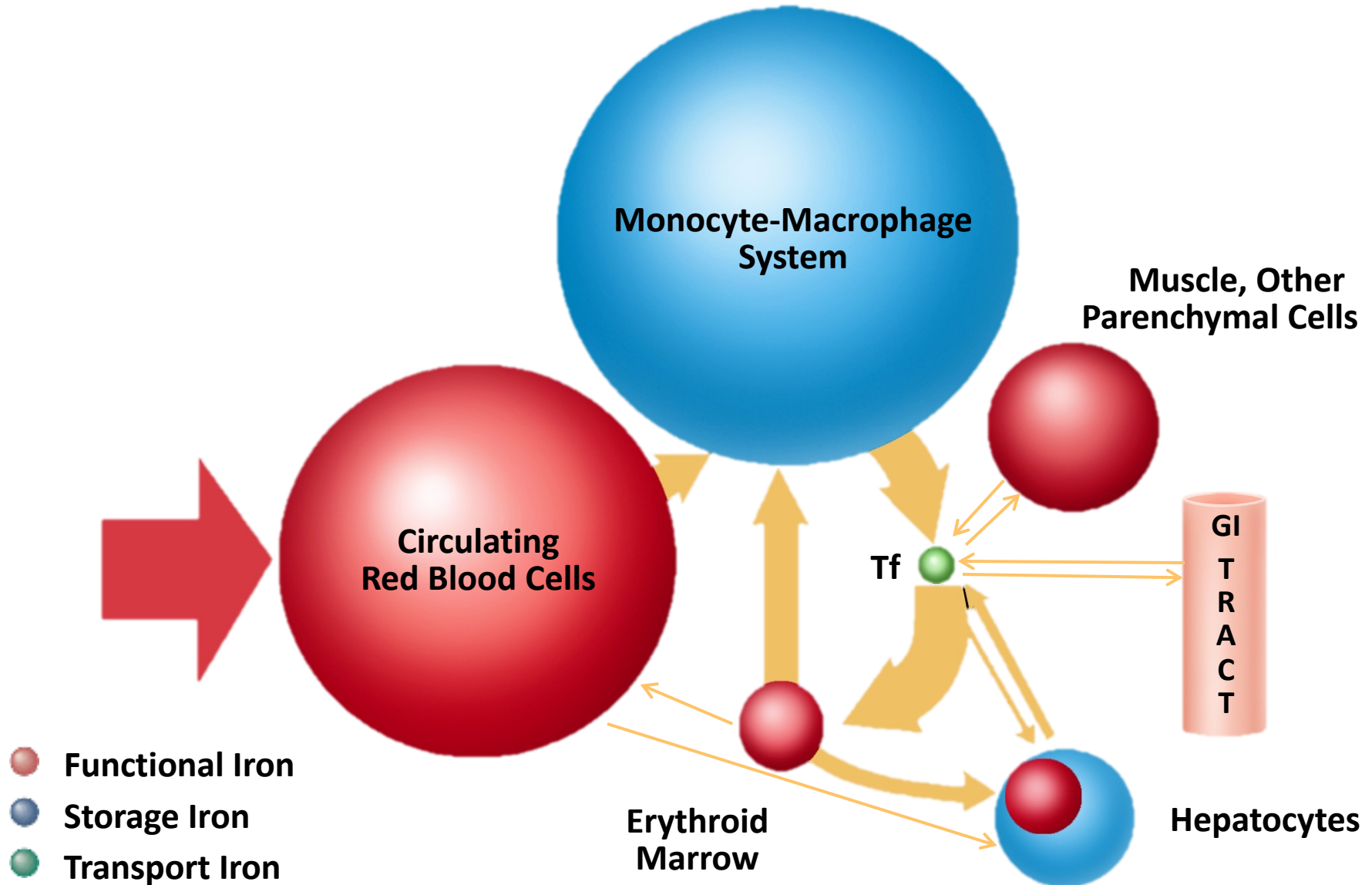
Osteoporosis

Venous thrombosis

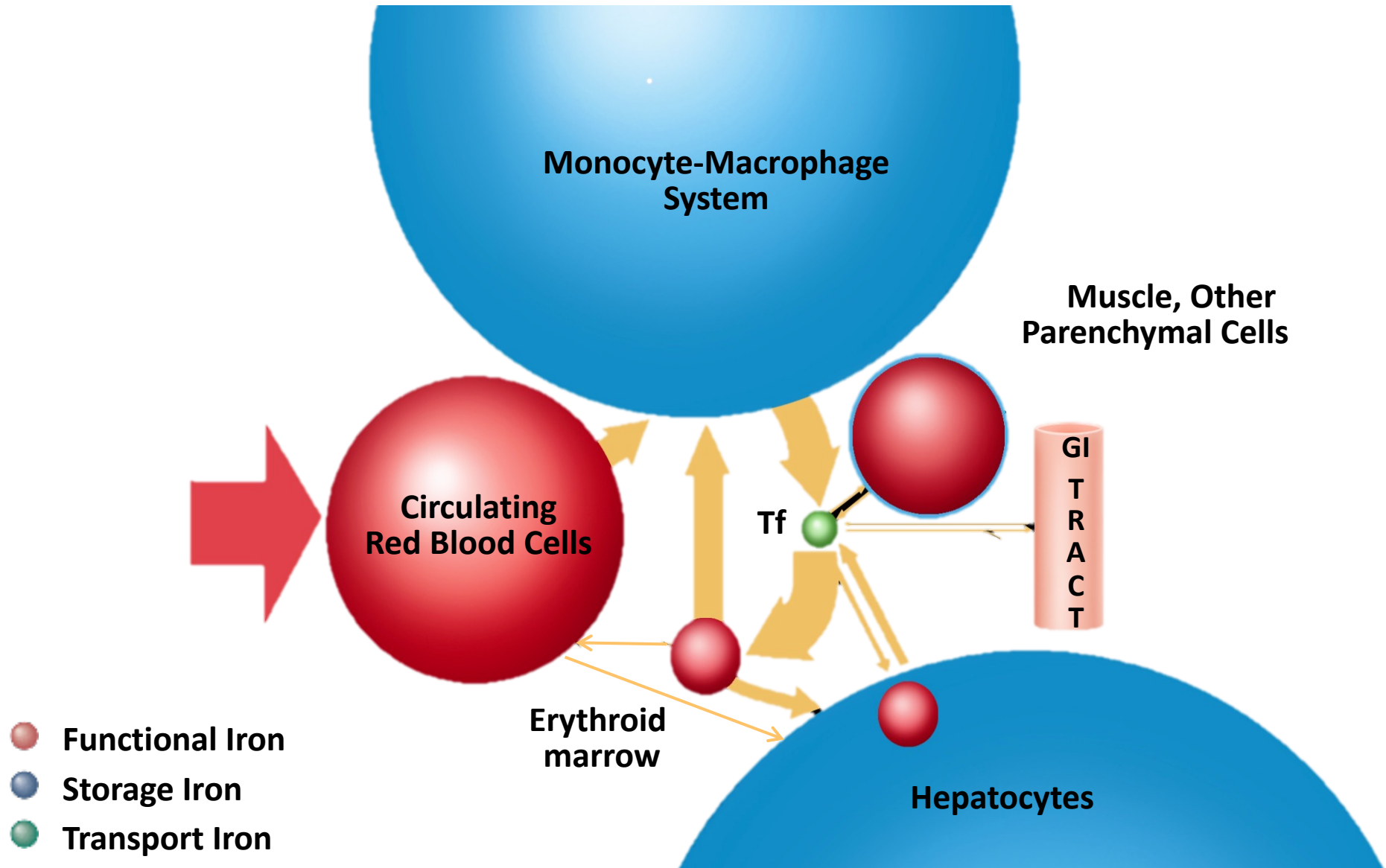
Leg ulcers



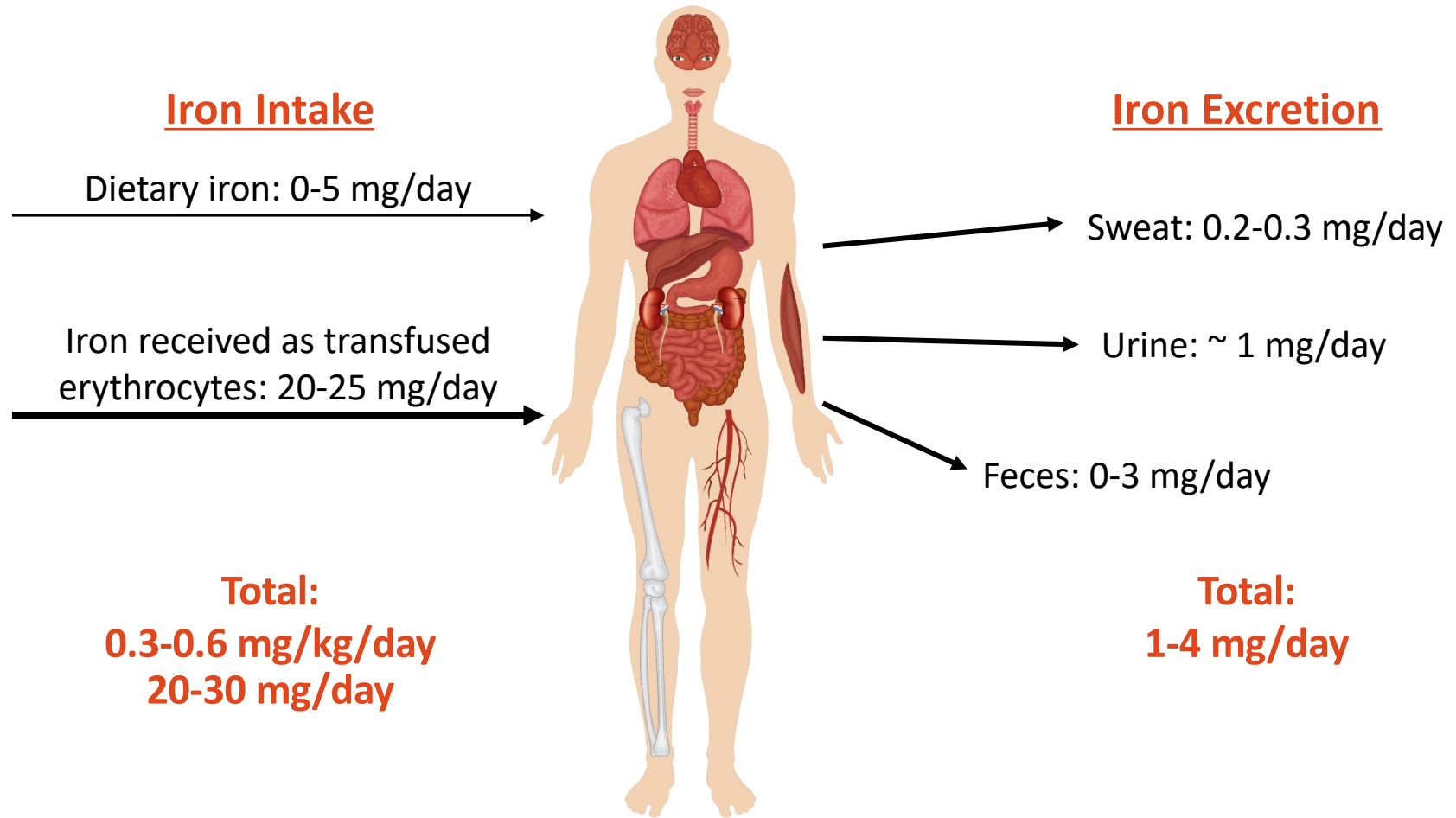
# TRANSFUSIONAL IRON OVERLOAD: 16 Units PRBC



# TRANSFUSIONAL IRON OVERLOAD: 100 Units PRBC



# IRON LOADING



**Toxicity = tissue iron x tissue sensitivity x time**

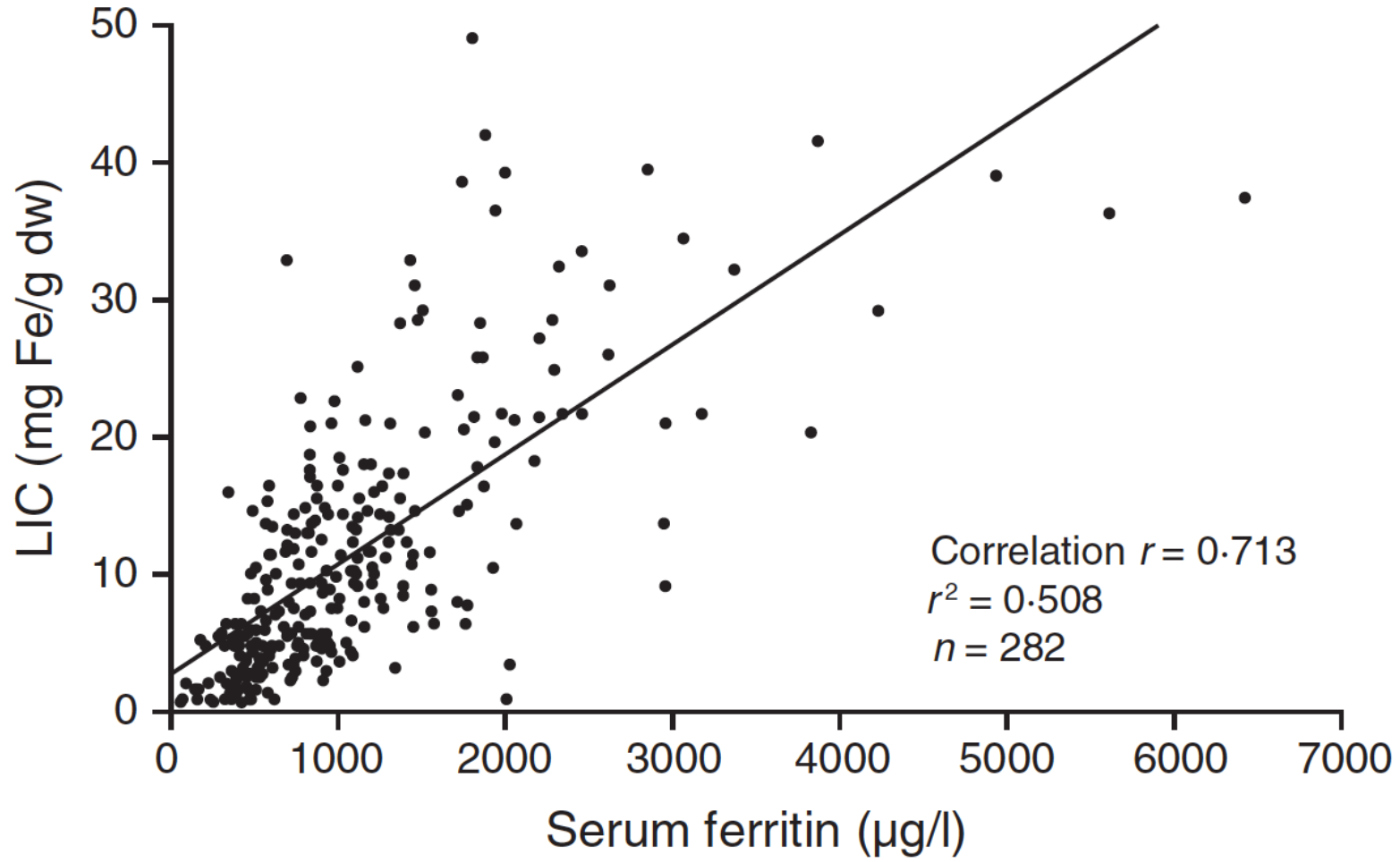
# RISK OF ORGAN DAMAGE

- Liver – all patients load the liver
  - Fibrosis, cirrhosis, risk of hepatocellular carcinoma
  - Hepatitis C independent risk factor
- Heart – patients with inappropriately low hepcidin
  - Contractile dysfunction - diastolic
  - Electrophysiologic dysfunction
- Endocrine – patients with inappropriately low hepcidin
  - Pituitary dysfunction
  - Diabetes
  - Gonadal dysfunction
  - Osteopenia

# MEASURING IRON BURDEN

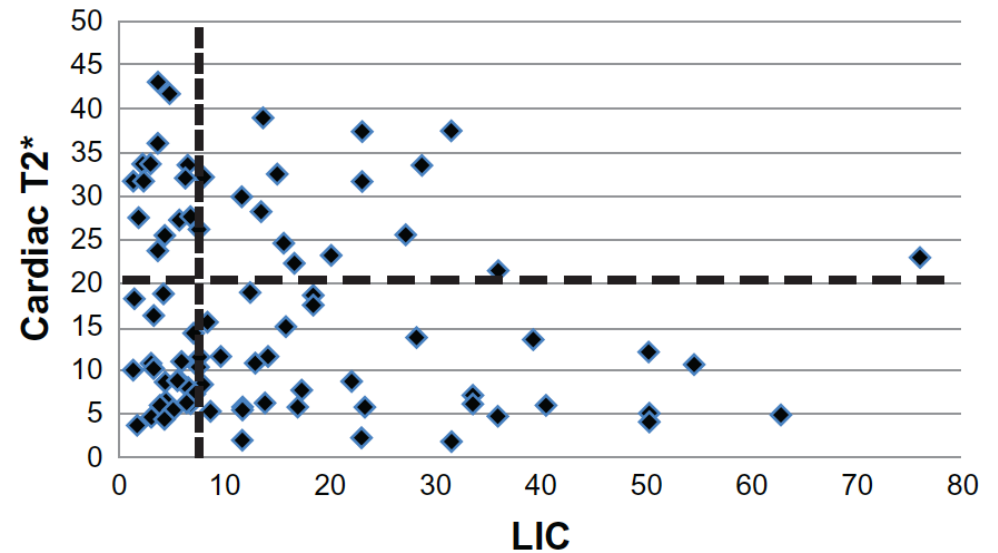
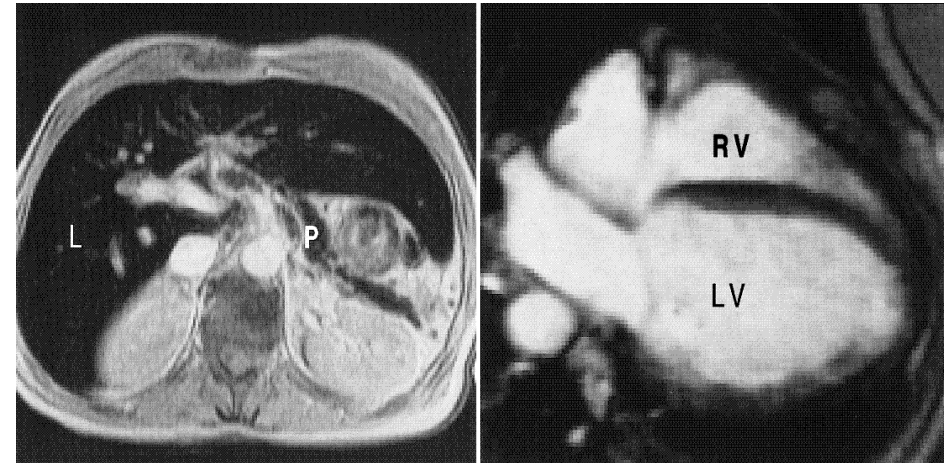
- Serum Ferritin
- Liver Biopsy LIC
- SQUID LIC
- MRI LIC R2/R2\*
- MRI Cardiac T2\*

# SERUM FERRITIN

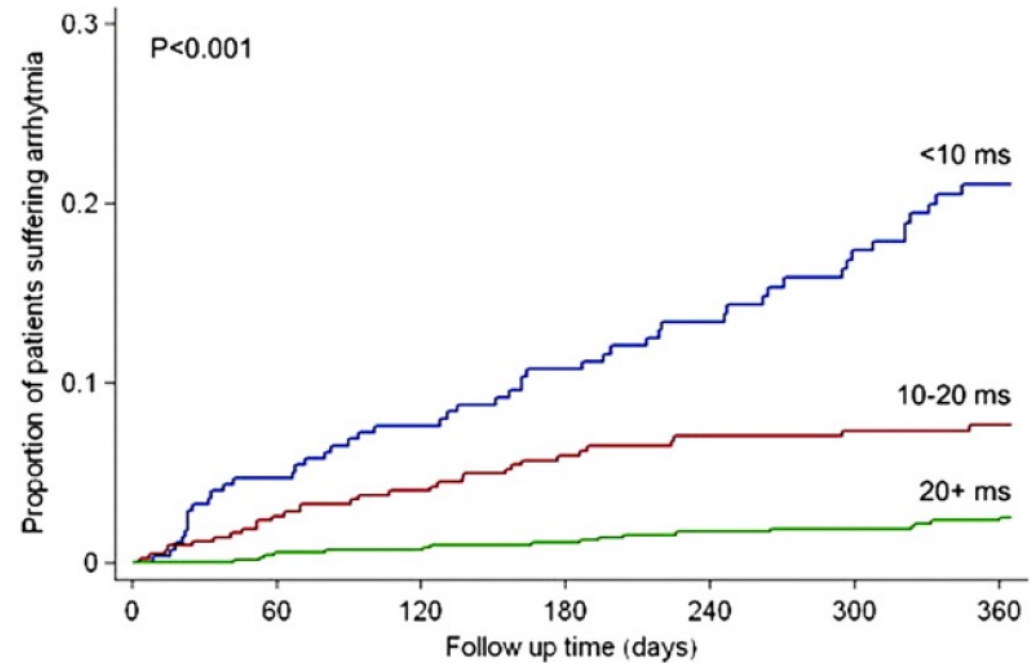
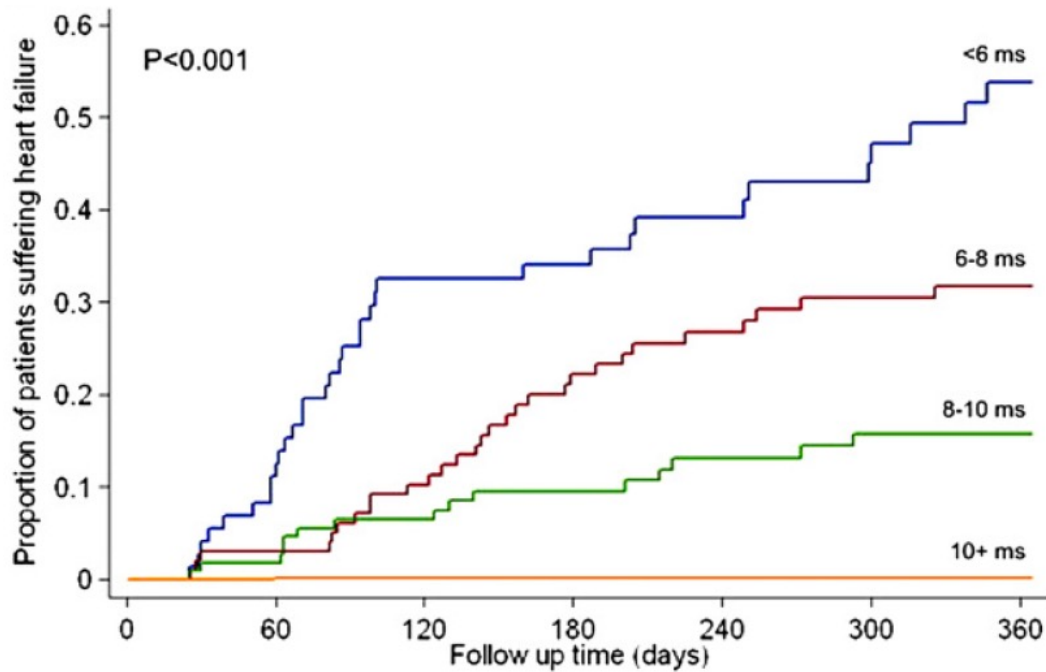


# MRI - IRON QUANTIFICATION

- Utility
  - Non-invasive
  - No irradiation
  - Easily accessed
- Caveats
  - Technique variability
  - Sensitivity
  - Not correlated between tissues



# CARDIAC T2\* - PROGNOSTIC VALUE (Thalassemia Major)



Kirk P et al. Circulation 2009.

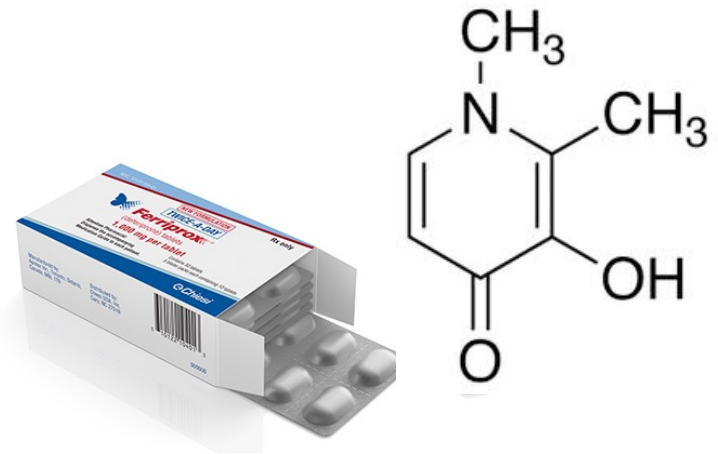
# CHELATION

- Which Chelator
  - Iron binding
  - Route of administration
  - Efficacy
  - Toxicity
- When to start
- Monitoring
- COMPLIANCE

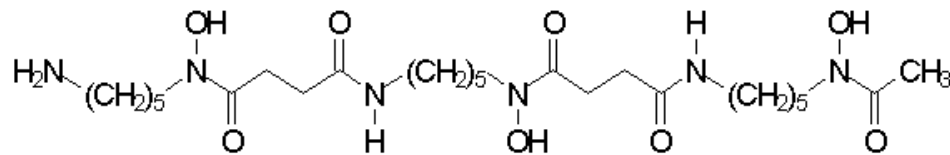
# DEFERASIROX (Exjade<sup>®</sup>, Jadenu<sup>®</sup>)



# DEFERIPRONE (Ferriprox<sup>®</sup>)



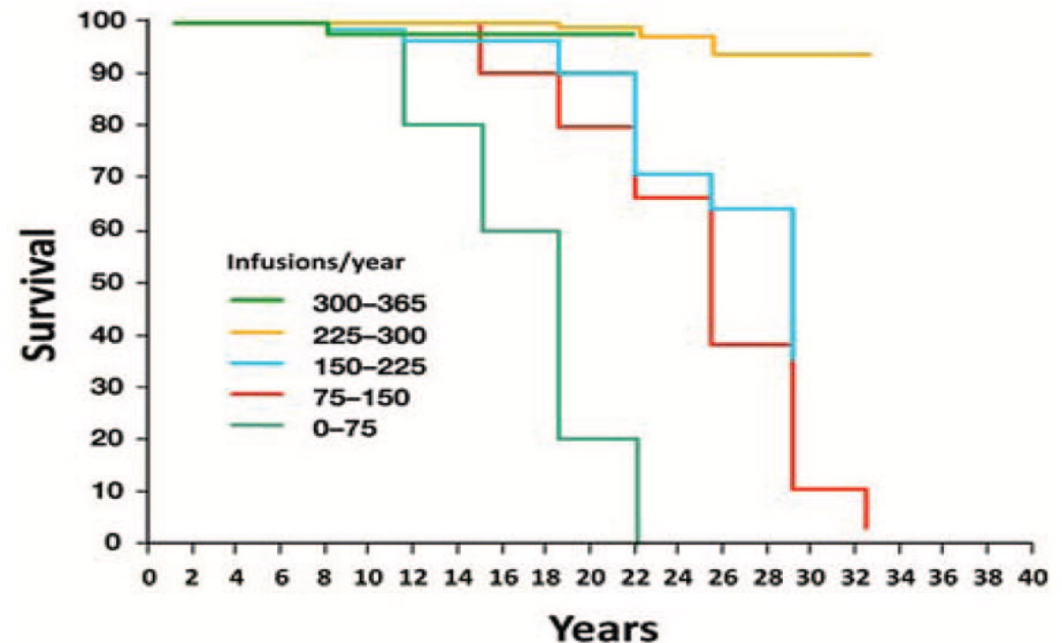
# DEFEROXAMINE (Desferal<sup>®</sup>)



# DEFEROXAMINE (Desferal<sup>®</sup>)

- Longest used approved effective iron chelator
- Challenges
  - Subcutaneous slow infusion 5 to 7 nights/week
  - Infusion-site reactions and pain
  - High degree of noncompliance
- Survival correlated with compliance in thalassemia

Wood JC et al. Blood 2008



# DEFERIPRONE (Ferriprox<sup>®</sup>)

- FDA approved November 2011
  - Second line and combination use
  - Less effective than deferoxamine in reducing LIC
  - More effective in removing cardiac iron
- Side effects
  - Nausea, vomiting, abdominal pain
  - Arthralgia
  - Neurologic syndrome
  - Reports of increased risk of liver fibrosis
  - Neutropenia/Agranulocytosis
    - Weekly neutrophil count recommended

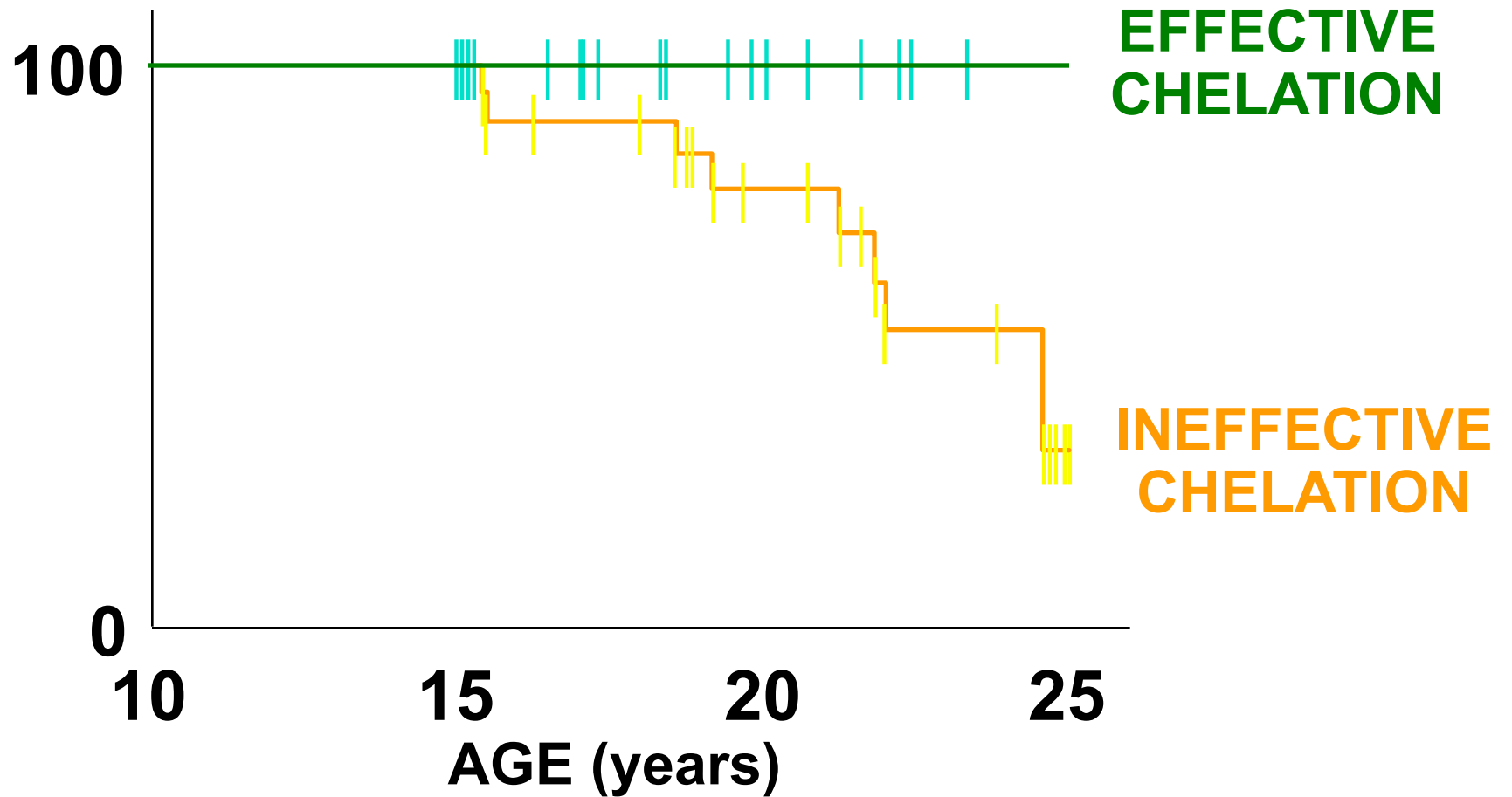
# DEFERASIROX (Exjade<sup>®</sup>, Jadenu<sup>®</sup>)

- FDA approved November 2005, 2015
  - Orally effective
  - Once a day only
  - Wide therapeutic index, dose range
- Side effects
  - Nausea, vomiting, abdominal pain
  - Liver and kidney toxicity
  - Rare reports of Neutropenia/Agranulocytosis
- Good long term safety and efficacy data
- Can be used in Combination therapy
- Demonstrated efficacy in cardiac iron removal

# MONITORING IRON OVERLOAD

Level of Iron Overload	Iron Overload Measurements	Frequency of MRI Testing
Target	<ul style="list-style-type: none"> <li>• LIC 2-5 mg/g DW</li> <li>• Ferritin &lt;1,000 ng/mL</li> <li>• T2*&gt;20 msecs</li> </ul>	<ul style="list-style-type: none"> <li>• Check LIC when chelation is first initiated and every year thereafter</li> <li>• Check cardiac T2* at age 10 and every 2 years thereafter</li> </ul>
Moderately Elevated	<ul style="list-style-type: none"> <li>• LIC 5-10 mg/g DW</li> <li>• Ferritin 1,000 to 2,500 ng/mL</li> <li>• T2*&gt;20 msecs</li> </ul>	<ul style="list-style-type: none"> <li>• Check LIC when chelation is first initiated and every year thereafter</li> <li>• Check cardiac T2* at age 10 and every 1-2 years thereafter based on LIC trends</li> </ul>
Seriously elevated	<ul style="list-style-type: none"> <li>• LIC &gt;10 mg/g DW</li> <li>• Ferritin &gt;2,500 ng/mL</li> <li>• T2*&lt;20 msecs</li> </ul>	<ul style="list-style-type: none"> <li>• Check LIC when chelation is first initiated and every 6 months thereafter, if on intensive chelation</li> <li>• Check cardiac T2* at age 10 and every year thereafter based on LIC trends</li> </ul>
Mild cardiac iron overload with normal cardiac function	<ul style="list-style-type: none"> <li>• T2* 10-20 msecs</li> </ul>	<ul style="list-style-type: none"> <li>• Check LIC and cardiac T2* when chelation is first initiated and every 6-12 months thereafter while on intensive chelation.</li> <li>• Monitor cardiac function (MRI/ECHO) every 6 months</li> </ul>
Severe cardiac iron overload with or without cardiac dysfunction	<ul style="list-style-type: none"> <li>• T2* &lt;10 msecs</li> </ul>	<ul style="list-style-type: none"> <li>• Check LIC and Cardiac T2*when chelation is first initiated and every 6 months thereafter on intensive chelation.</li> <li>• Monitor cardiac function (MRI/ECHO) every 6 months with cardiac specialist</li> </ul>

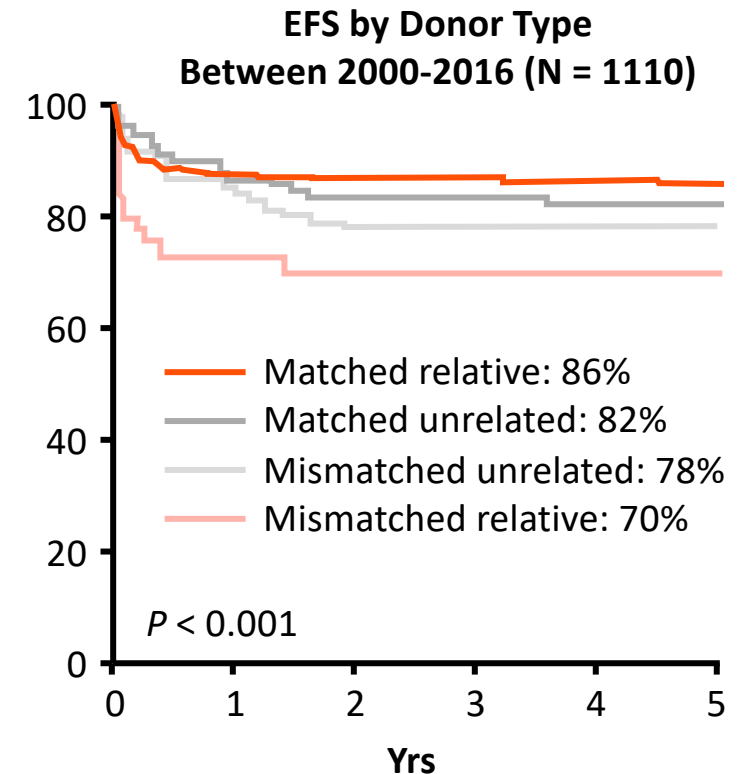
# SURVIVAL IN THALASSEMIA MAJOR WITH EFFECTIVE OR INEFFECTIVE CHELATION



Brittenham et al, New Engl J Med 1994;331:567-573

# STEM CELL TRANSPLANTATION

- Only currently available curative option
- Pretransplant organ function and iron status important; younger patients do better
- Excellent outcomes with matched sibling donors (including umbilical cord blood): 85% to 95% TFS
  - Matched unrelated donors: 68% to 80% TFS
- Nonmyeloablative regimens in clinical trials
- Alternative donor sources in clinical trials
  - Unrelated PBSC, UCB
  - Haploidentical donors

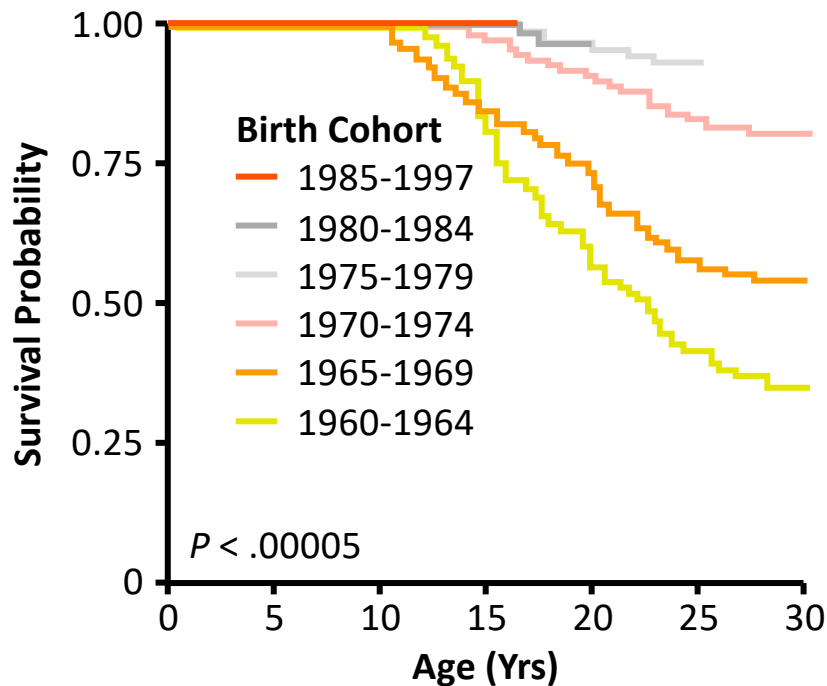


# QUALITY OF LIFE

- Issues related to:
  - Symptoms – fatigue
  - Physical appearance (NTDT)
  - Frequent visits to the hospital
  - Need for chelation compliance
  - Pain - Bone disease, extramedullary hematopoiesis (NTDT)
  - Endocrine – growth, development, fertility
  - Financial issues
- Psychosocial issues
  - Chronic illness
  - Reduced life expectancy with complications

# SURVIVAL

**$\beta$ -Thalassemia Major Survival by Birth Cohort\***



- Without treatment
  - $\beta^0/\beta^0$ : Die in first 2-5 yrs
  - Non-  $\beta^0/\beta^0$ : Variable clinical spectrum with complications
- $\beta^0/\beta^0$  and non- $\beta^0/\beta^0$  with treatment
  - Improving survival
  - Significant morbidity but with decreasing incidence
  - Deaths related to complications

\*Kaplan-Meier analysis included 977 patients who survived beyond first decade of life.

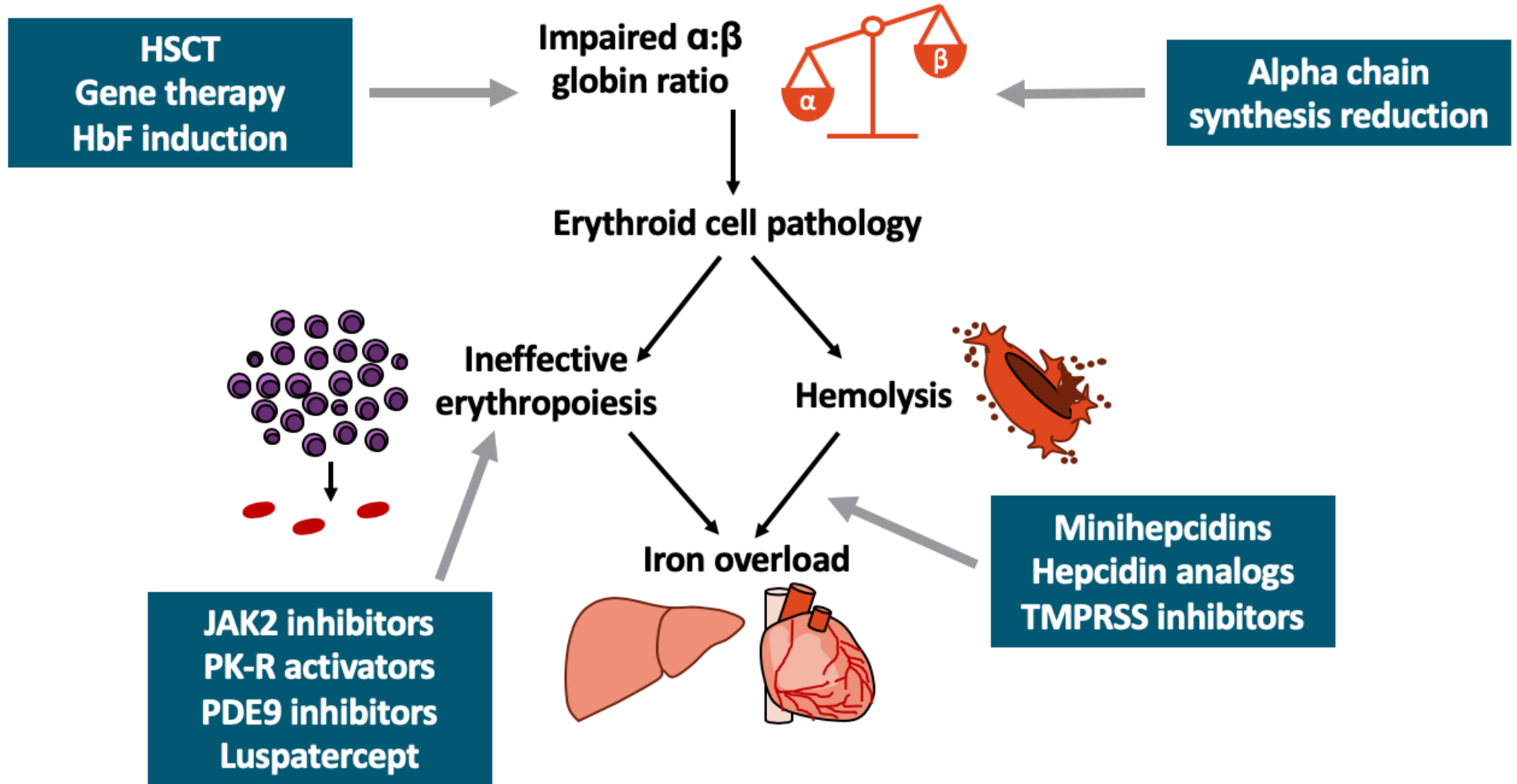
# IMPROVED CARE

- Improved safety of blood supply
- Reduced incidence of alloimmunization
- Oral iron chelation
- Improved monitoring of iron overload to enable individualized tailoring of treatment regimen
- Improved treatment for hepatitis
- Improved outcomes for stem cell transplantation

# UNMET NEEDS

- Curative options for those without matched sibling donors
- Means of ameliorating ineffective erythropoiesis
  - This could reduce/eliminate transfusion requirement
  - In turn, reducing iron loading
    - » From gut absorption
    - » From transfusions
- Prevent iron overload and its complications
- Reduce bone disease
- Improve quality of life

# NOVEL THERAPIES



# NOVEL THERAPIES

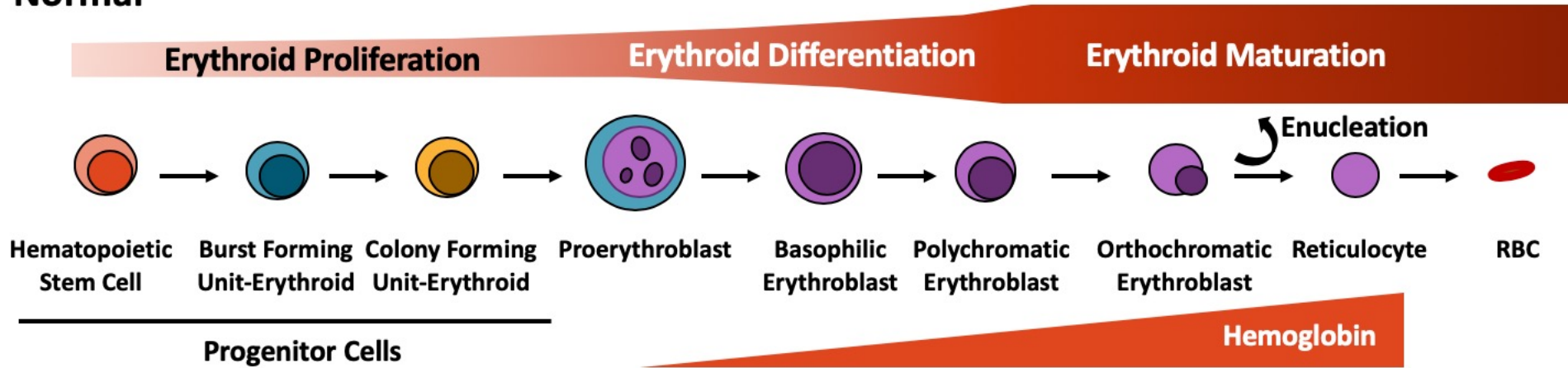
- Targeted therapies
  - Activin traps
  - Ruxolitinib
  - Hepcidin manipulation
  - Mitapivat
- Gene therapy
  - Gene insertion
  - Gene editing

# LUSPATERCEPT

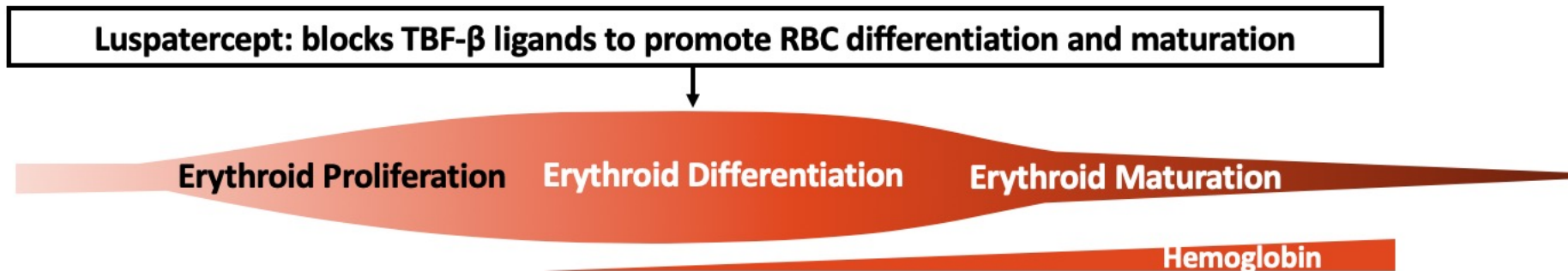
- Recombinant fusion protein containing a modified extracellular domain of ActRIIB<sup>[1]</sup>
- Binds to GDF11 and other TGF- $\beta$  superfamily ligands, inhibits Smad2/3 signaling, and promotes RBC differentiation/maturation<sup>[1]</sup>
- Early data
  - Animal studies<sup>[1]</sup>
  - Phase I study of healthy human volunteers<sup>[2]</sup>
  - Phase II clinical trial in patients with  $\beta$ -thalassemia showed improved Hb levels (NTDT) and RBC transfusion burden (TDT) with luspatercept<sup>[3]</sup>

# LUSPATERCEPT

## Normal

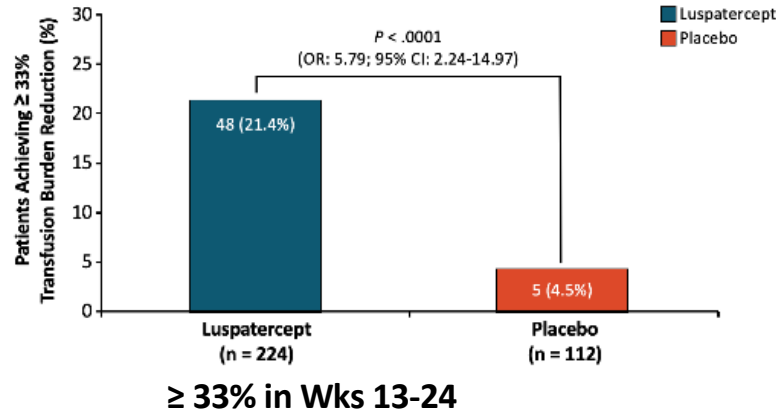


## Ineffective in $\beta$ -Thalassemia

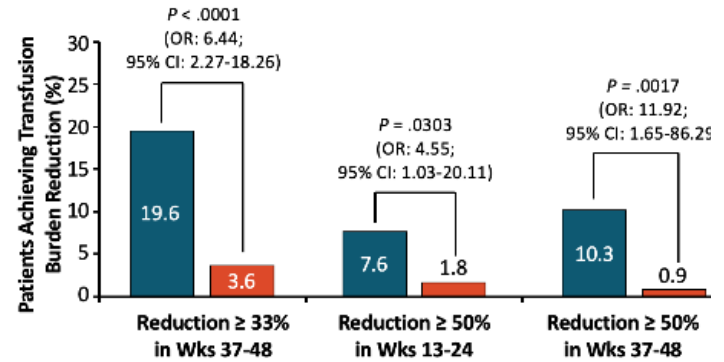


# BELIEVE: ENDPOINTS

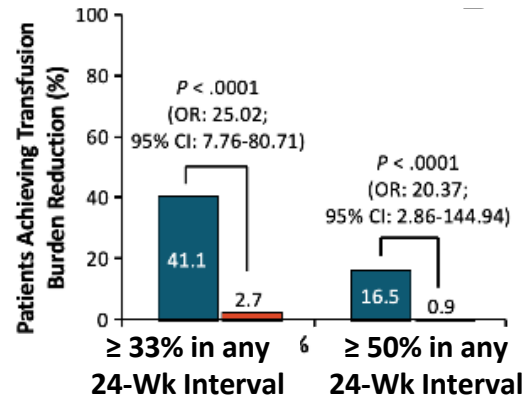
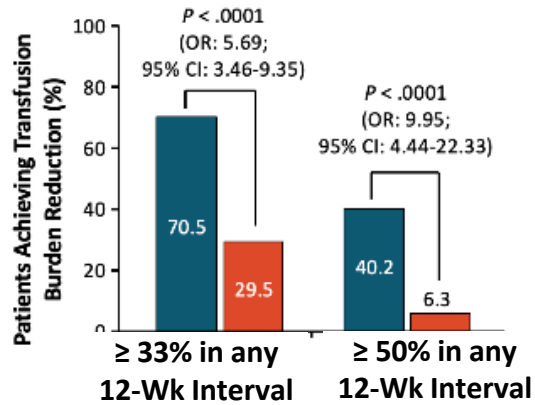
## Primary Endpoint



## Secondary Endpoints



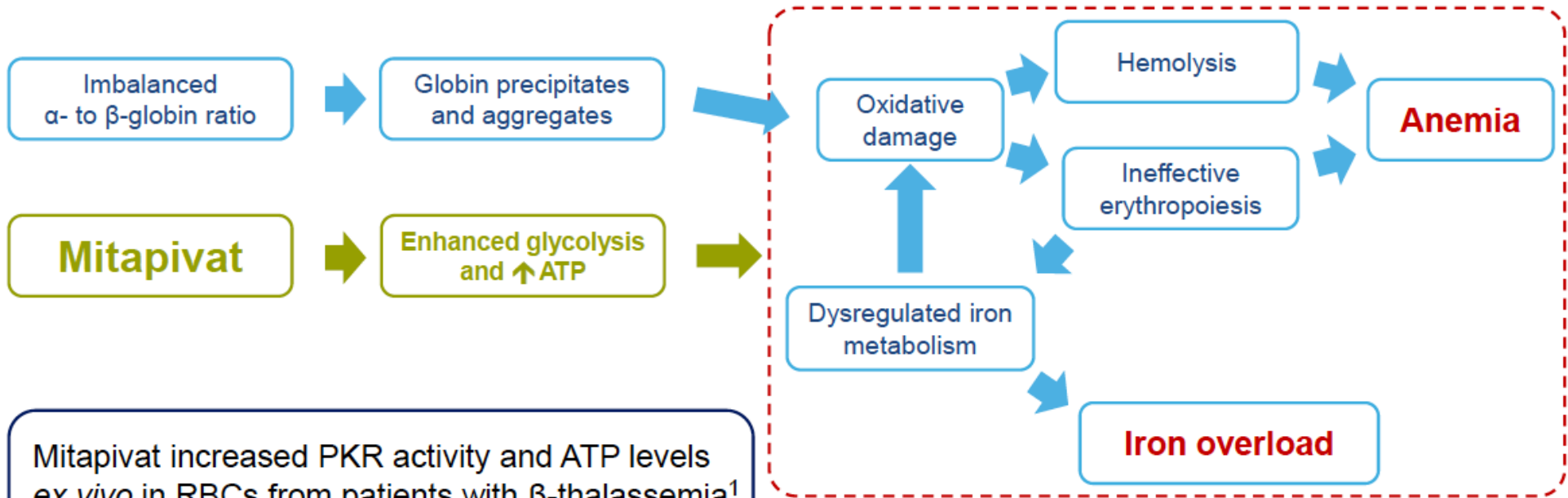
## Additional Endpoints



# BELIEVE: CONCLUSIONS

- BELIEVE met its primary endpoint, demonstrating statistically significant improvement, with a  $\geq 33\%$  reduction in RBC transfusion burden with luspatercept vs placebo
- Key secondary endpoints showed statistically significant improvement with luspatercept vs PBO, including  $\geq 33\%$  and  $\geq 50\%$  RBC transfusion burden reduction
- Luspatercept demonstrated a statistically significant, clinically meaningful reduction in RBC transfusion burden vs placebo during any 12-wk or 24-wk interval of the study period
- Luspatercept was generally well tolerated

# Mitapivat – Mechanism in thalassemia



Mitapivat increased PKR activity and ATP levels *ex vivo* in RBCs from patients with  $\beta$ -thalassemia<sup>1</sup>  
Mitapivat ameliorated ineffective erythropoiesis, iron overload, and anemia in the Hbb<sup>th3/+</sup> mouse model of  $\beta$ -thalassemia<sup>2</sup>

# Results

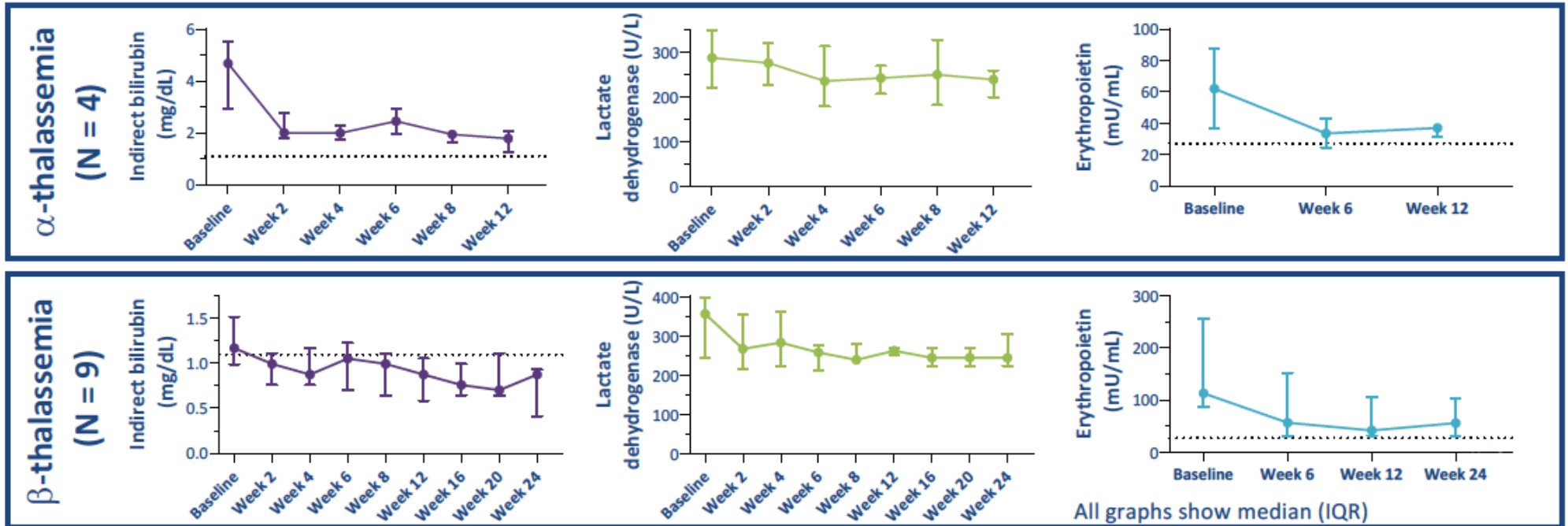
- Primary endpoint was met in 92.3% of patients

Endpoint	Genotype	n/N	%	90% CI
Hb responders during Weeks 4–12 (completed 12 weeks)	All	12/13	92.3	68.4, 99.6
	$\alpha$	4/4	100	47.3, 100
	$\beta$	8/9	88.9	57.1, 99.4
Hb responders during Weeks 12–24 (completed 24 weeks)	$\beta^a$	8/9	88.9	57.1, 99.4
Sustained responders: primary response and $\geq 2$ Hb responses during Weeks 12–24	$\beta^a$	7/8	87.5	52.9, 99.4

Patient population	N	Weeks	Mean (SD) change from baseline Hb, g/dL
All patients	13	4–12	1.34 (0.7)
$\alpha$ -thalassemia	4	4–12	1.17 (0.4)
$\beta$ -thalassemia	9	4–24	1.43 (0.8)

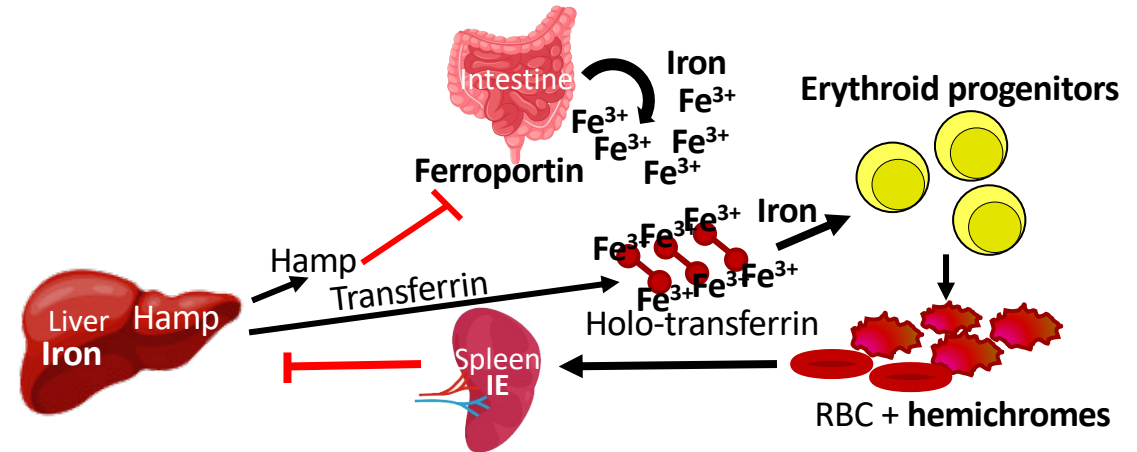
- Median (range) time to Hb increase of  $\geq 1$  g/dL among responders was 3.1 (1.4–7.1) weeks

# Results – Increased Hb, decreased hemolysis



# TARGETING THE HEPCIDIN PATHWAY

- In thalassemia, IE results in low levels of hepcidin leading to increased iron absorption, iron redistribution to organs
- Hepcidin mimetics function to:
  - Improve IE
  - Reduce iron absorption
  - Reduce iron to organs
- Trials of hepcidin mimetics
  - Trial of LJPC-401 did not meet endpoint
  - TRANSCEND trial of PTG-300 for TD or TDT and chronic anemia ongoing

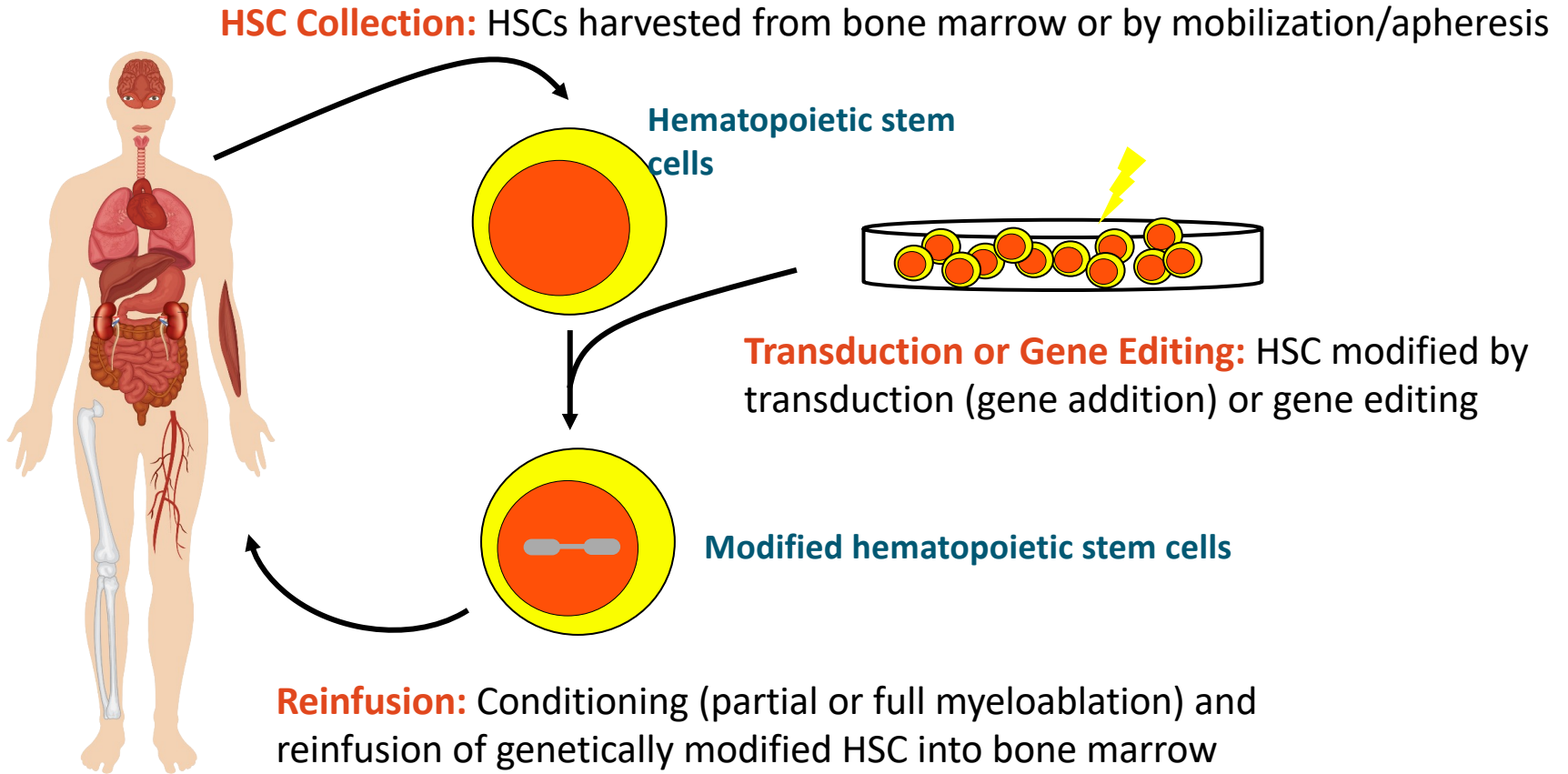


- TMPRSS6 is another potential target to decrease iron overload, improve RBC survival by increasing hepcidin levels
  - Inhibition of TMPRSS6 ameliorated iron overload and IE in a mouse model of  $\beta$ -thalassemia

# GENE THERAPY APPROACHES

- Globin gene addition
  - Functional  $\beta$ -globin gene
  - Functional  $\gamma$ -globin gene
- Gene editing
  - Reverse fetal hemoglobin repression
    - » BCL11A
  - Correct the  $\beta$ -globin mutation

# GENE THERAPY

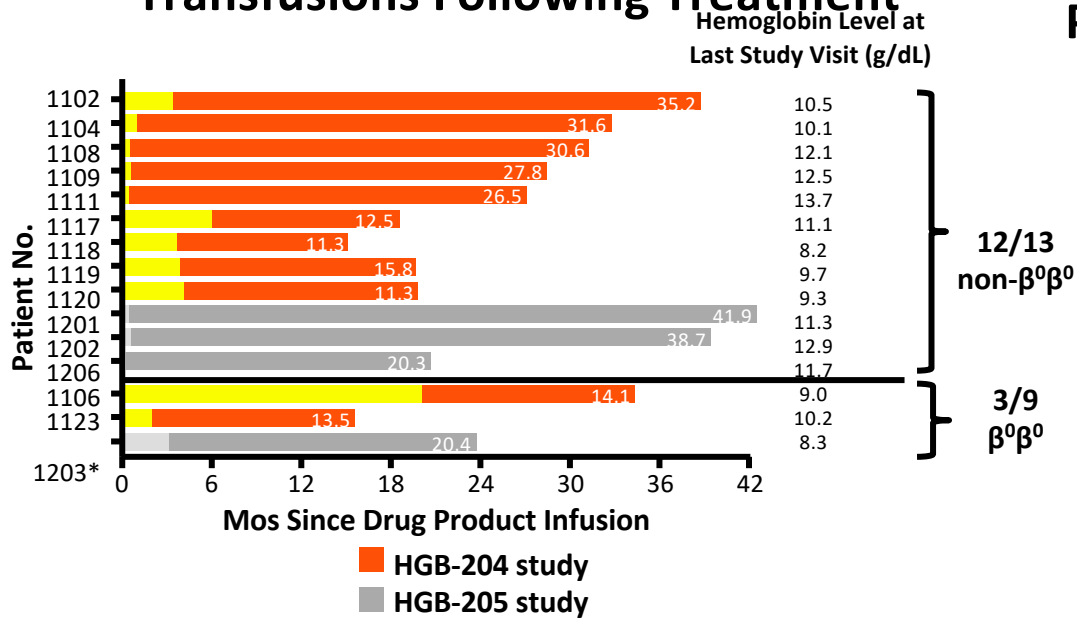


# GENE THERAPY – CURRENT TRIALS

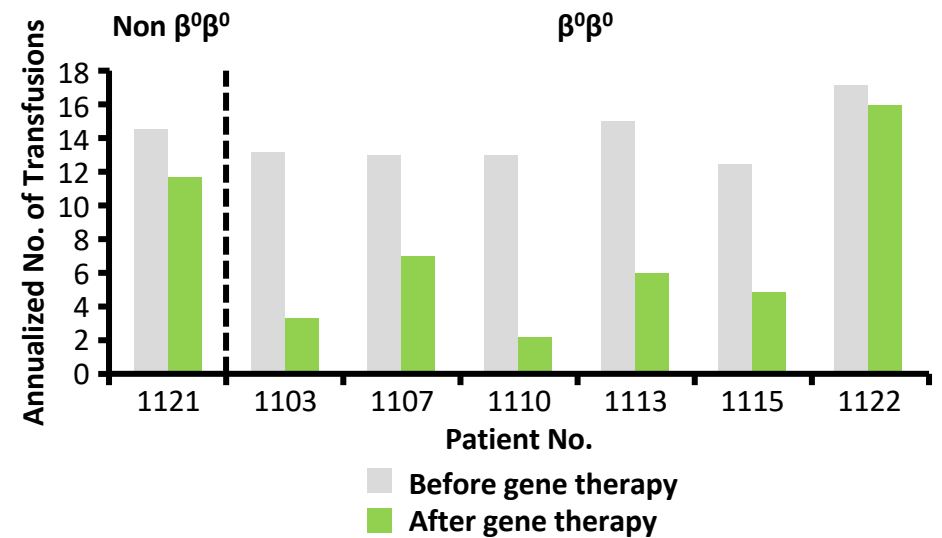
- Gene addition
  - LentiGlobin BB305
    - » Northstar trials
      - Early studies: HGB-204 and HGB-205<sup>[1]</sup>
      - More recent phase III studies: HGB-207 and HGB-212<sup>[2,3]</sup>
    - GLOBE lentiviral vector
      - » Phase I/II trial<sup>[4]</sup>
- Gene editing
  - Phase I/II Thales study of ST-400<sup>[5]</sup>
  - Phase I/II study of CRISPR/CAS9 gene-editing therapy CTX001<sup>[6]</sup>

# HGB-204/205: Early Studies of LentiGlobin BB305

## 15 of 22 Patients Discontinued Transfusions Following Treatment

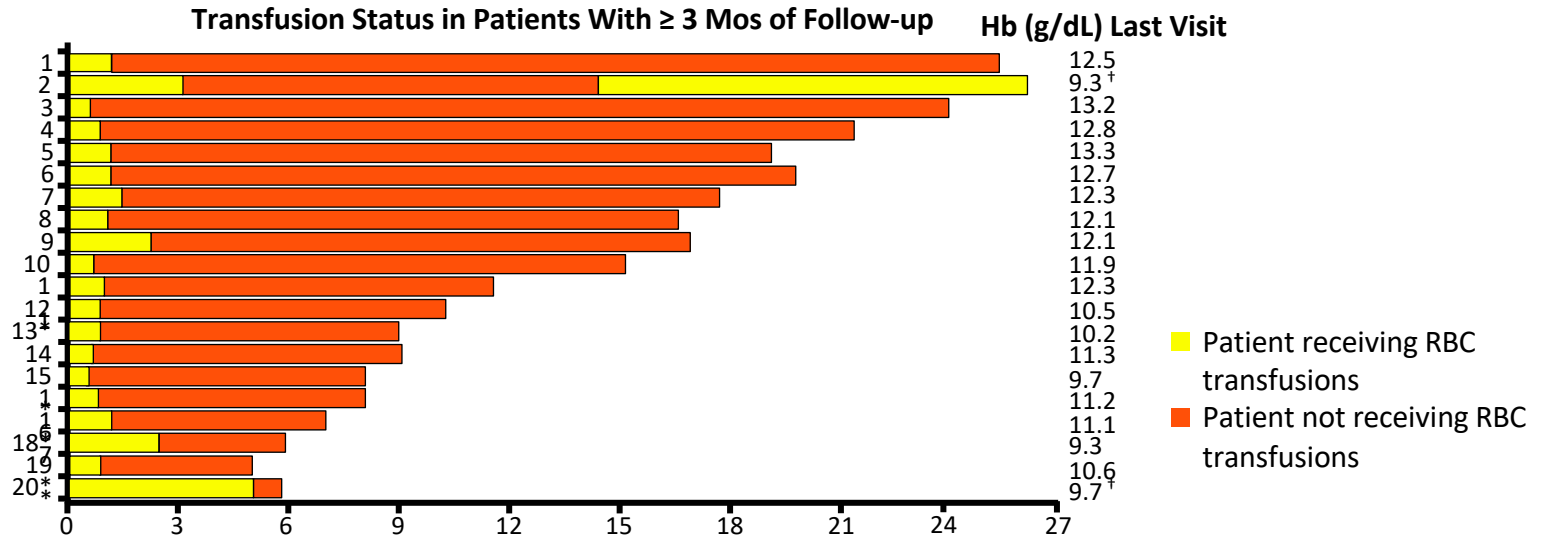


## Reduced Transfusion Requirements in Patients Not Achieving Transfusion Independence

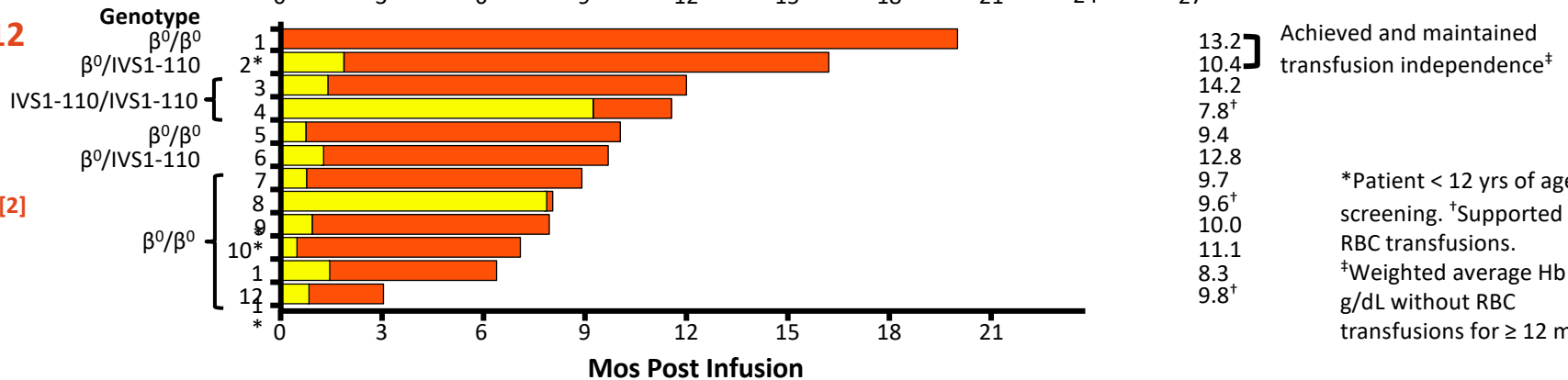


# HGB-207/212: Phase III Trials of LentiGlobin BB305

**HGB-207: 18/20  
non- $\beta^0/\beta^0$  Patients  
Achieved  
Transfusion  
Independence<sup>[1]</sup>**



**HGB-212: 11/12  
 $\beta^0/\beta^0$  Patients  
Achieved  
Transfusion  
Independence<sup>[2]</sup>**

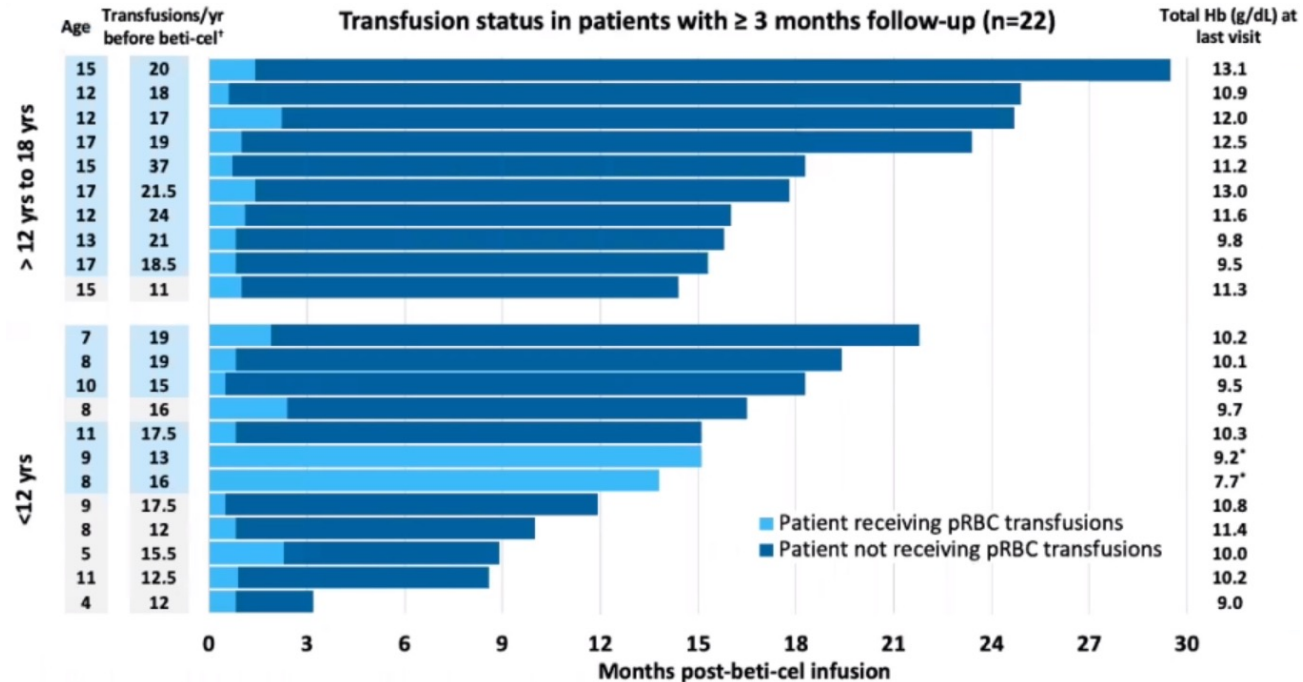


1. Thompson. ASH 2019. Abstr 3543. 2. Lal. ASH 2019. Abstr 815.

# Gene Therapy in Pediatric Patients (Subgroup Analysis of 2 Phase 3 Studies)

- **Safety (N = 24)**
  - AEs considered related or possibly related to the drug product
    - » Day of infusion: tachycardia and abdominal (one each, both grade 1)
    - » Post-infusion: 1 non-serious grade 3 event of thrombocytopenia
  - Veno-occlusive liver disease occurred in 3 patients (2 serious grade 4 and 1 grade 2); all events resolved with defibrotide
  - No vector-derived replication competent lentivirus

- **Efficacy (N = 15)**
  - 87% of evaluable pediatric patients achieved TI
  - Ineffective erythropoiesis improved after beti-cel gene therapy



**100% of patients between 12 and 18 years achieved TI**

# GENE THERAPY: SAFETY

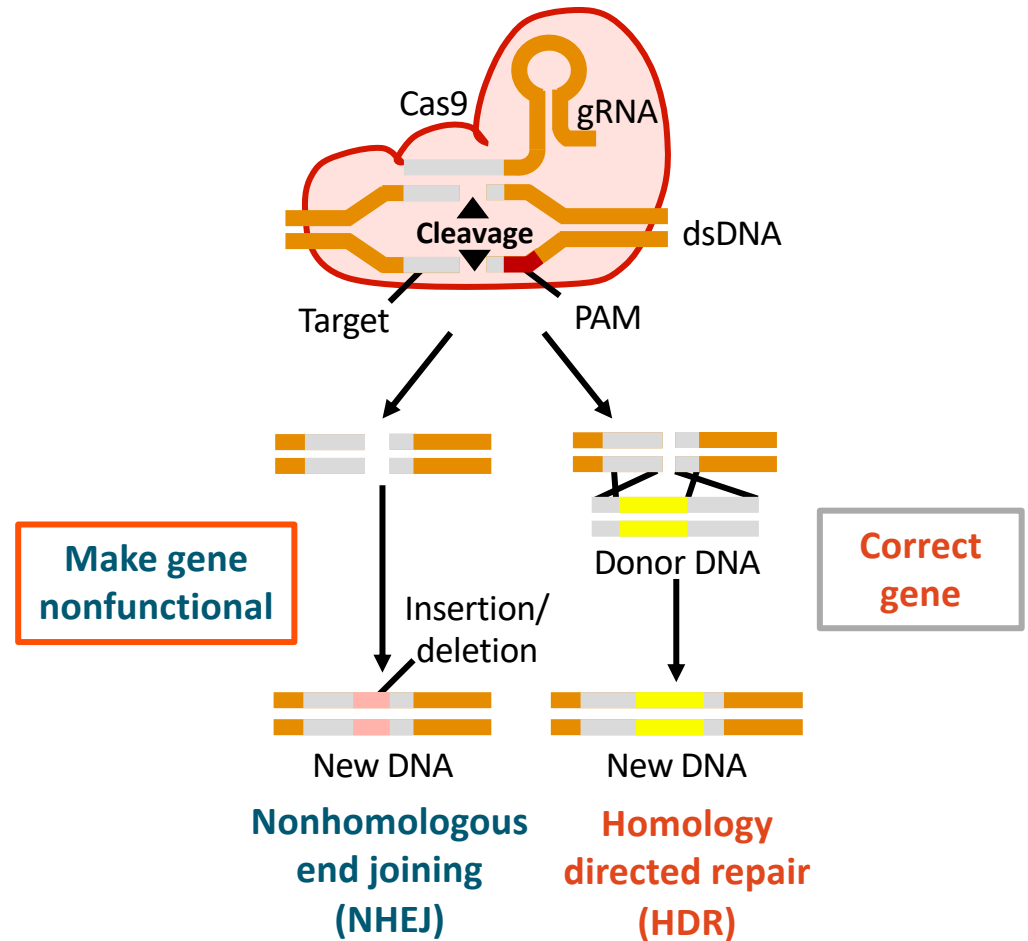
- No deaths to date
- Most toxicities associated with myeloablative conditioning including stomatitis, febrile neutropenia, thrombocytopenia, bleeding, elevated LFTs, hypotension, sepsis, transfusion reactions, lower respiratory infection
- Venooclusive disease seen in initial cohort (all treated successfully)
  - Now all subjects prophylaxed, reduced incidence in subsequent trials

# FACTORS AFFECTING SUCCESS GENE ADDITION

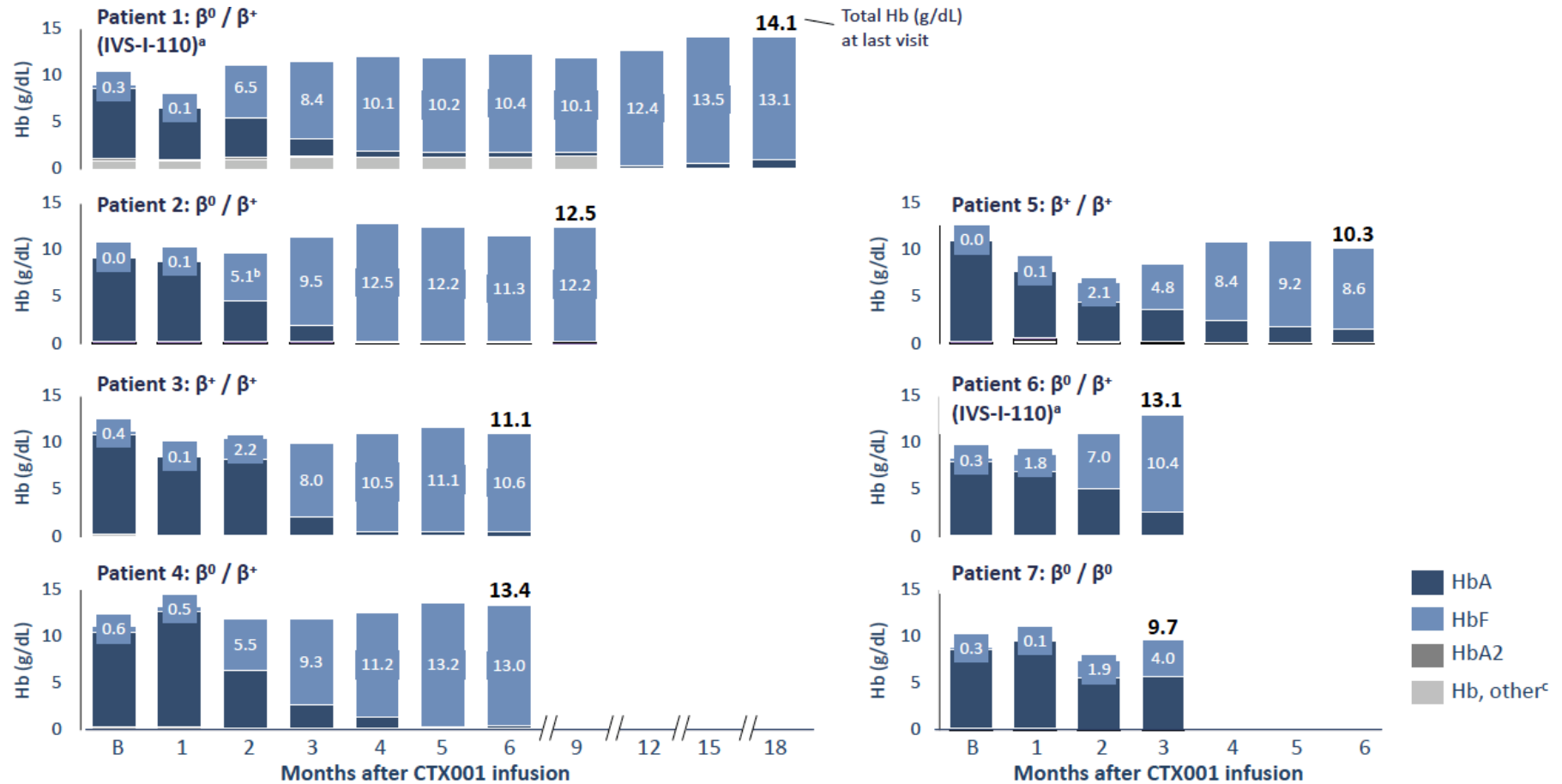
- Transduction efficiency
  - But does increasing VCN increase risk of insertional mutagenesis?
- Transgene expression levels
  - Improved  $\beta$ -globin expression per copy
- Genotype:  $\beta^+$  vs  $\beta^0$
- Quality of HSC
  - Mobilized vs bone marrow harvest
  - Pediatric vs adult
- Bone marrow microenvironment
  - Hypertransfusion
  - Myeloablation

# GENE EDITING

- Targets
  - Disruption of BCL11A using zinc finger nuclease or CRISPR/Cas9
  - Editing  $\beta$ -globin locus using CRISPR/CAS9
- Delivery of edited gene
  - HSC mobilization and myeloablation
  - Nonviral delivery
    - » Reduce risk of insertional mutagenesis
    - » Risk of off-target editing
- Phase I clinical trials underway



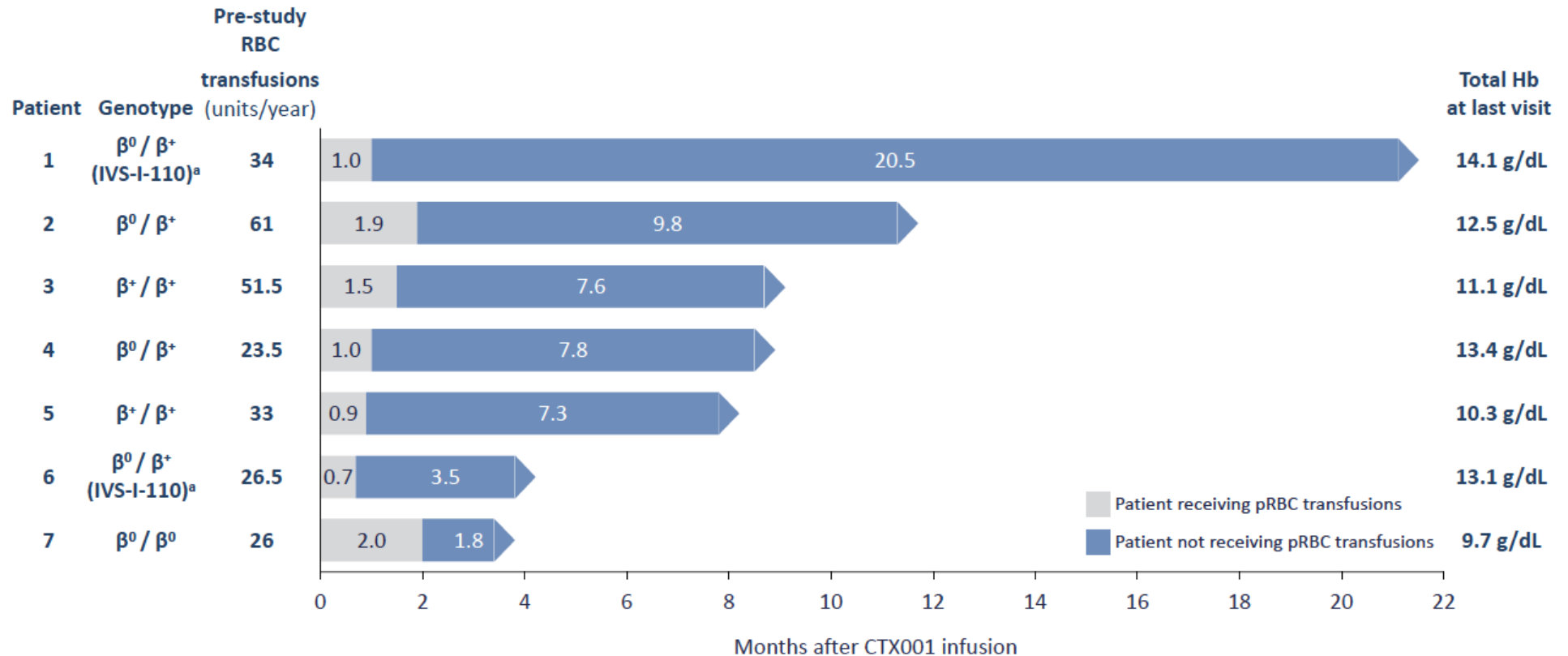
# Results: TDT



B: Baseline, Hb: hemoglobin; HbA: adult hemoglobin; HbF: fetal hemoglobin; TDT: transfusion-dependent  $\beta$ -thalassaemia. \*Total Hb from local laboratory and Hb fraction from central laboratory.

<sup>a</sup>IVS-I-110 phenotype is severe and similar to  $\beta^0 / \beta^0$  Hb adducts and other variants

# Results: TDT – transfusion free



<sup>a</sup>IVS-I-110 phenotype is severe and similar to  $\beta^0 / \beta^0$ .

Hb: hemoglobin; pRBC: packed red blood cell; RBC: red blood cell; TDT: transfusion-dependent  $\beta$ -thalassaemia.

# GENE THERAPY: CONCLUSIONS

- $\beta$ -globin gene addition trials have achieved transfusion independence in patients with  $\beta$ -thalassemia, especially with less severe genotypes
  - AEs typical of myeloablative conditioning observed; well tolerated in pediatric and adult patients
  - Long-term data lacking (especially with high VCN)
  - Some patients have poor response
- Gene editing targeting *BCL11A* to raise fetal hemoglobin levels in early clinical trials
- Expensive treatment; availability to patients needs to be addressed

# OVERALL SUMMARY

- $\beta$ -thalassemia is a chronic condition with significant morbidity and impact on QoL
- Monitoring and treating iron overload has significantly improved
- HSCT outcomes are better
- Targeted therapies have great potential to alter natural history of the disease and improve QoL for patients
- Gene therapy is on the horizon

