Progetto Ematologia Romagna

Vecchi e nuovi farmaci che migliorano l'eritropoiesi inefficace

Maria Domenica Cappellini
Fondazione Ca Granda Policlinico
Università di Milano

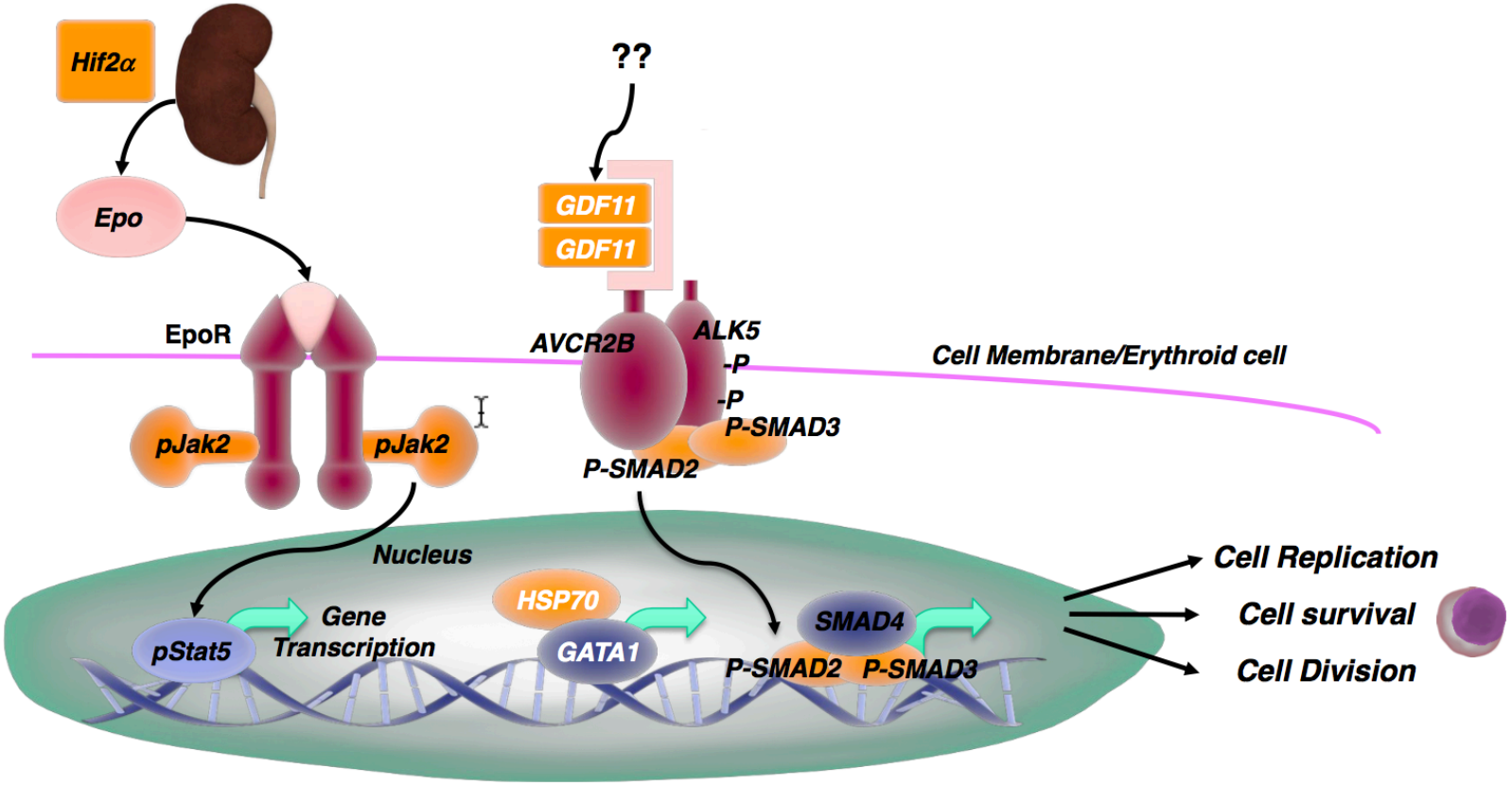
FAENZA 19 Ottobre 2019

Disclosures

Advisory board member for:

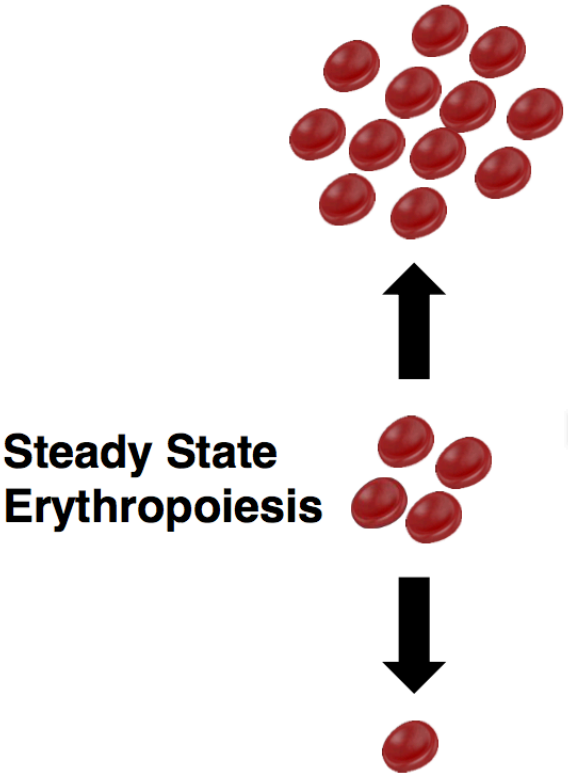
- Sanofi Genzyme
- Novartis
- Shire
- Celgene
- CRISP
- Ionis
- Protagonist

Steady state erythropoiesis



Camaschella C, N Engl J Med. 2015
Rivella S, Haematologica, 2015
Ganz T, Nemeth E, Nat Rev Immunol. 2015
Arlet JB et al, Curr Opin Hematol. 2016
Muckenthaler MU et al, Cell 2017

From steady state to aberrant erythropoiesis

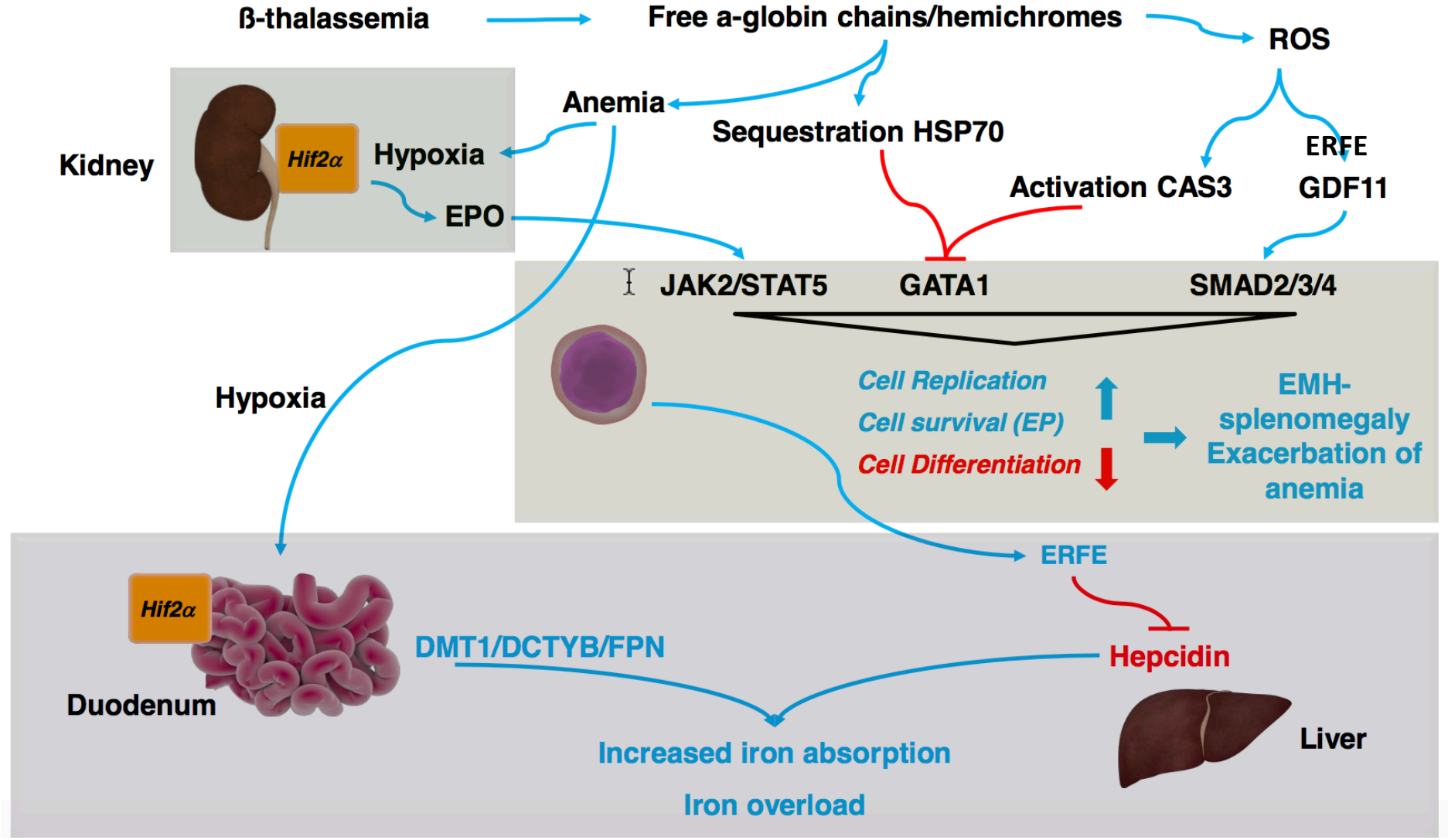


Steady State
Erythropoiesis

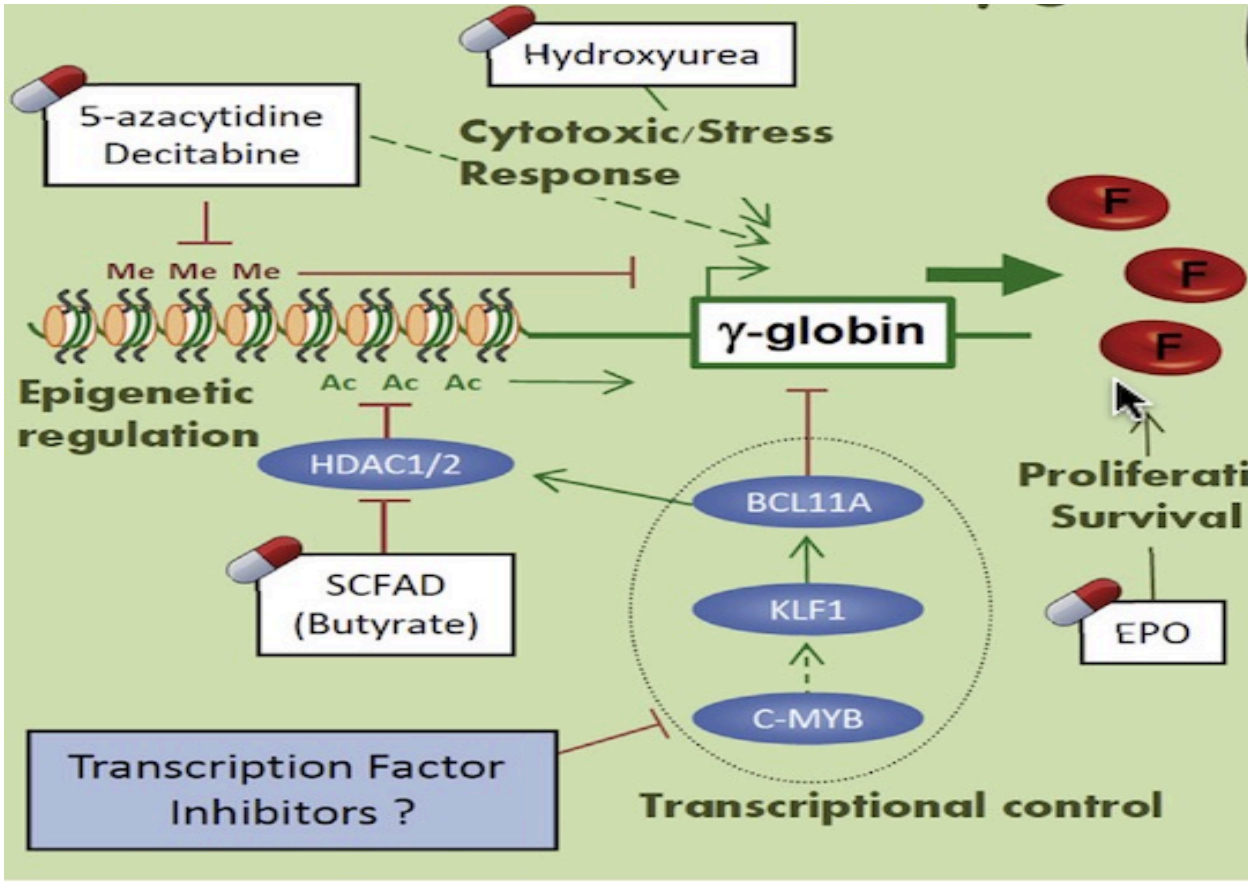
Erythrocytosis (increased EPO production, JAK2 mutations, ….)

Anemia (iron deficiency, aplastic anemia, ineffective erythropoiesis, inflammation, ….)

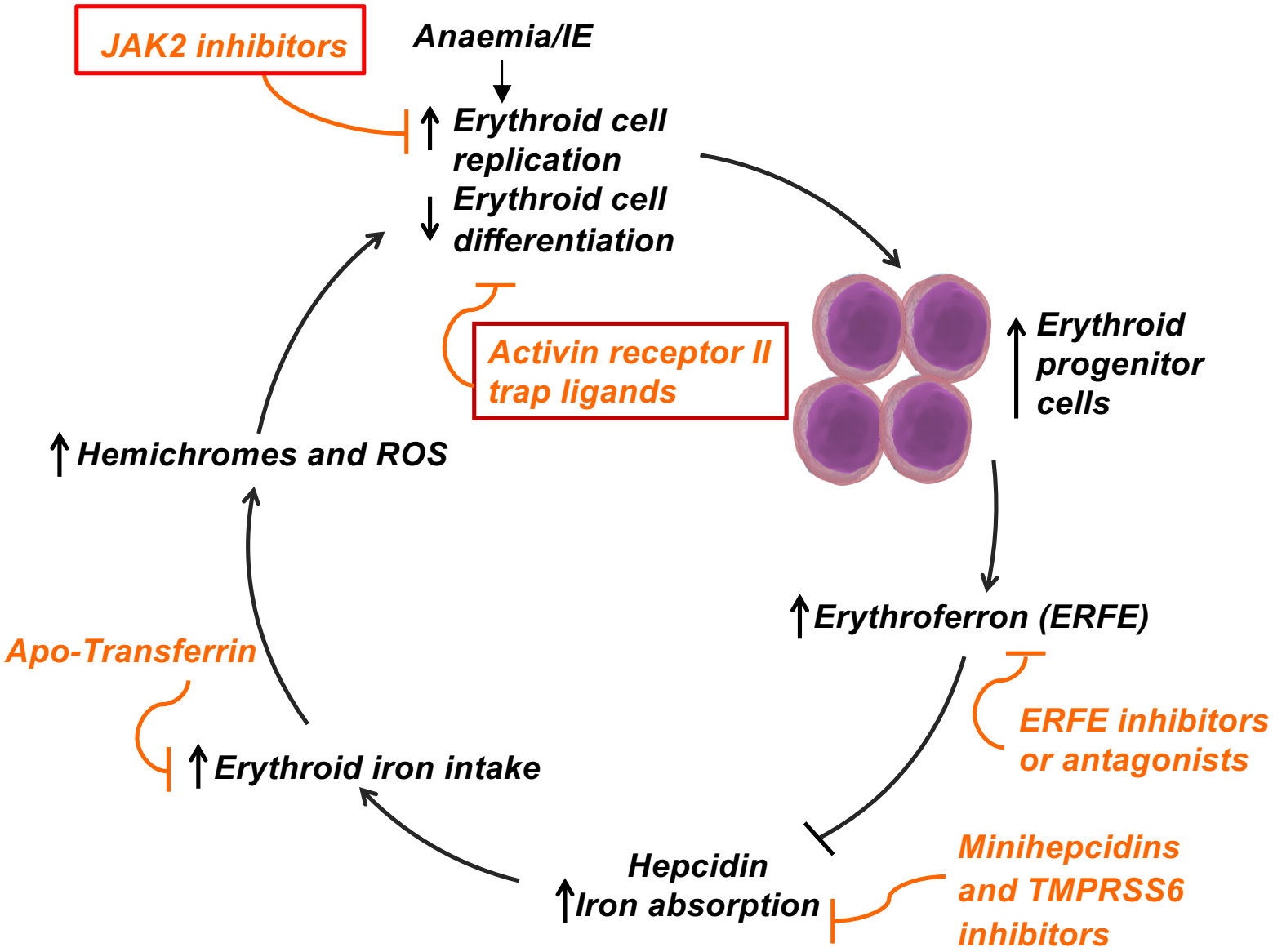
From steady state to ineffective erythropoiesis



Pharmaceutical induction of gamma-globins

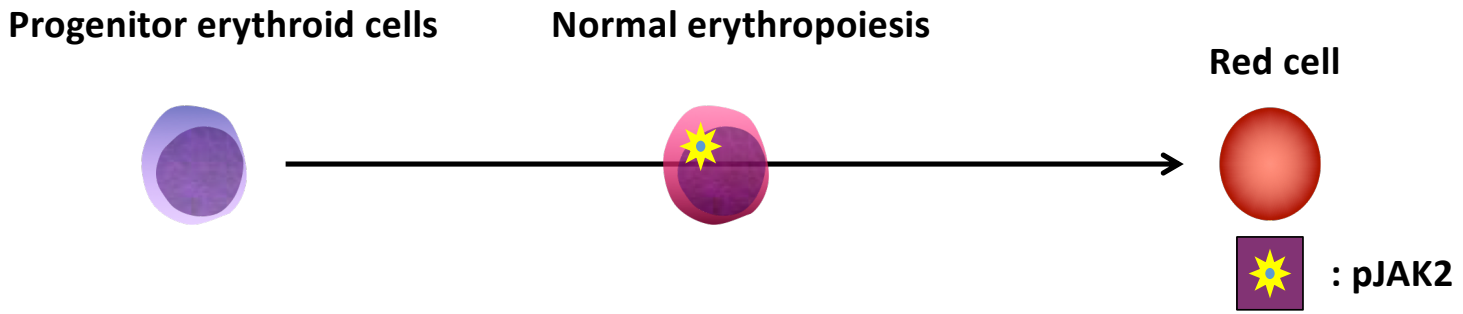


E. de Dreuzy Biomedical journal 39 (2016) 24e38

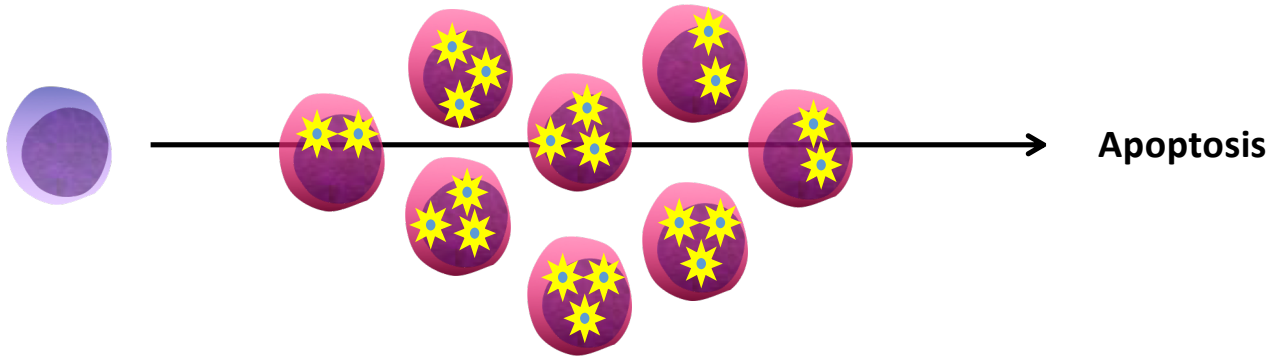

JAK2 inhibitors
Anaemia/IE
↑ Erythroid cell replication
↓ Erythroid cell differentiation
Activin receptor II trap ligands
↑ Erythroid progenitor cells
↑ Erythroferron (ERFE)
ERFE inhibitors or antagonists
Hepcidin
↑ Iron absorption
Minihepcidins and TMPRSS6 inhibitors
↑ Erythroid iron intake
Apo-Transferrin
↑ Hemichromes and ROS

Potential use of JAK2 or HIF2α inhibitors for the treatment of ß-thalassemia

JAK2: a gene that controls red cell production

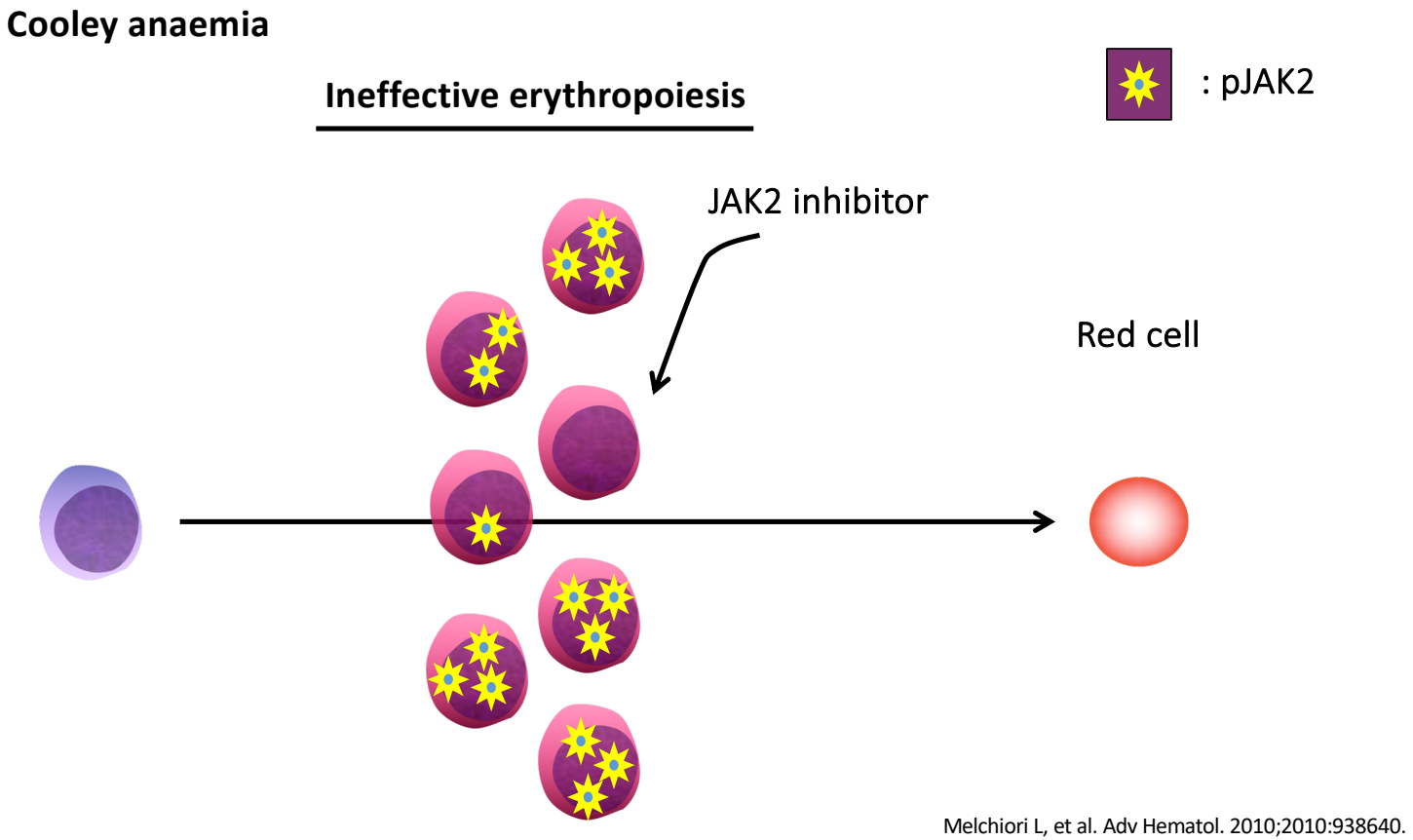


Ineffective erythropoiesis in ß-thalassemia:
chronic stress erythropoiesis + apoptosis limit RBC production



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

Potential effect of JAK2 inhibitors on ineffective erythropoiesis



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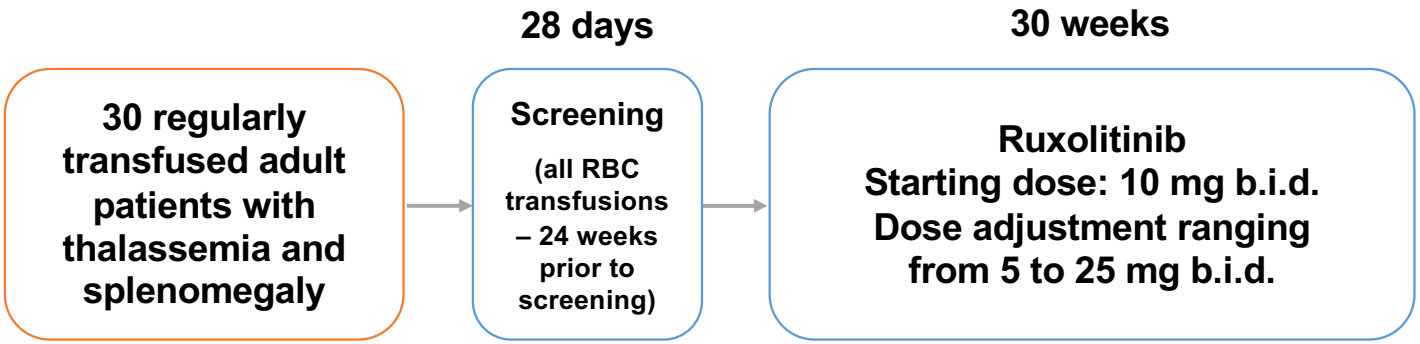
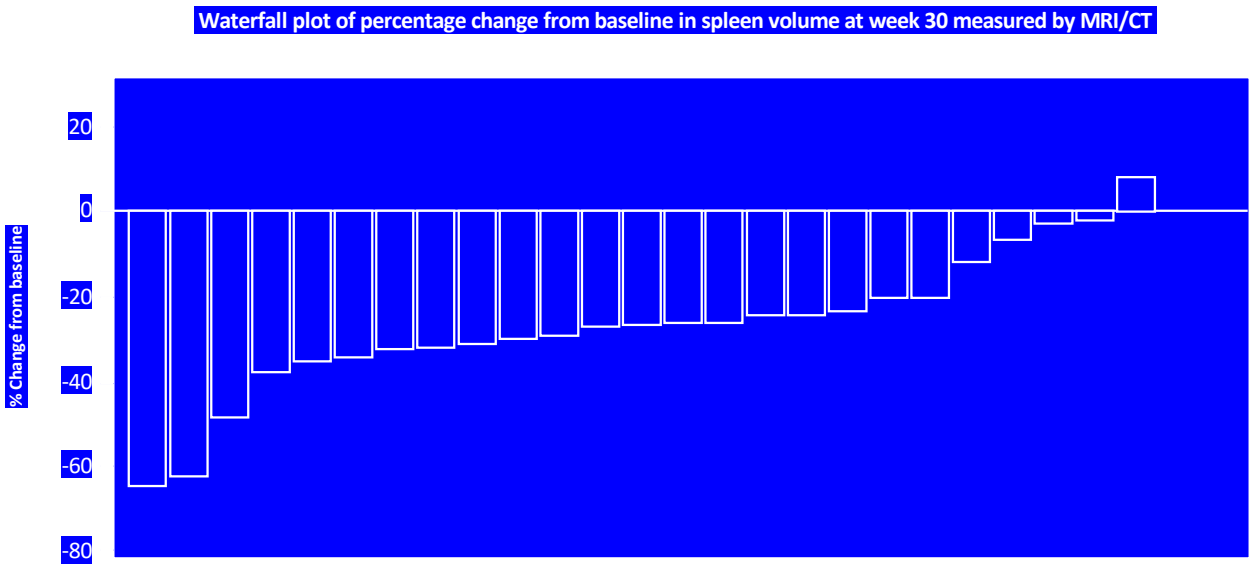


- Primary end-point
  - percent change in RBC transfusion requirement between weeks 6 and 30 compared with baseline
- Secondary end-points
  - change of spleen volume from baseline measured by MRI or CT
  - change of pre-transfusion Hb level from baseline at each post-baseline visit
  - pharmacokinetics
  - safety

Taher AT et al. Blood Nov 2, 2017 NCT02049450.

CT, computerized tomography; MRI, magnetic resonance imaging.

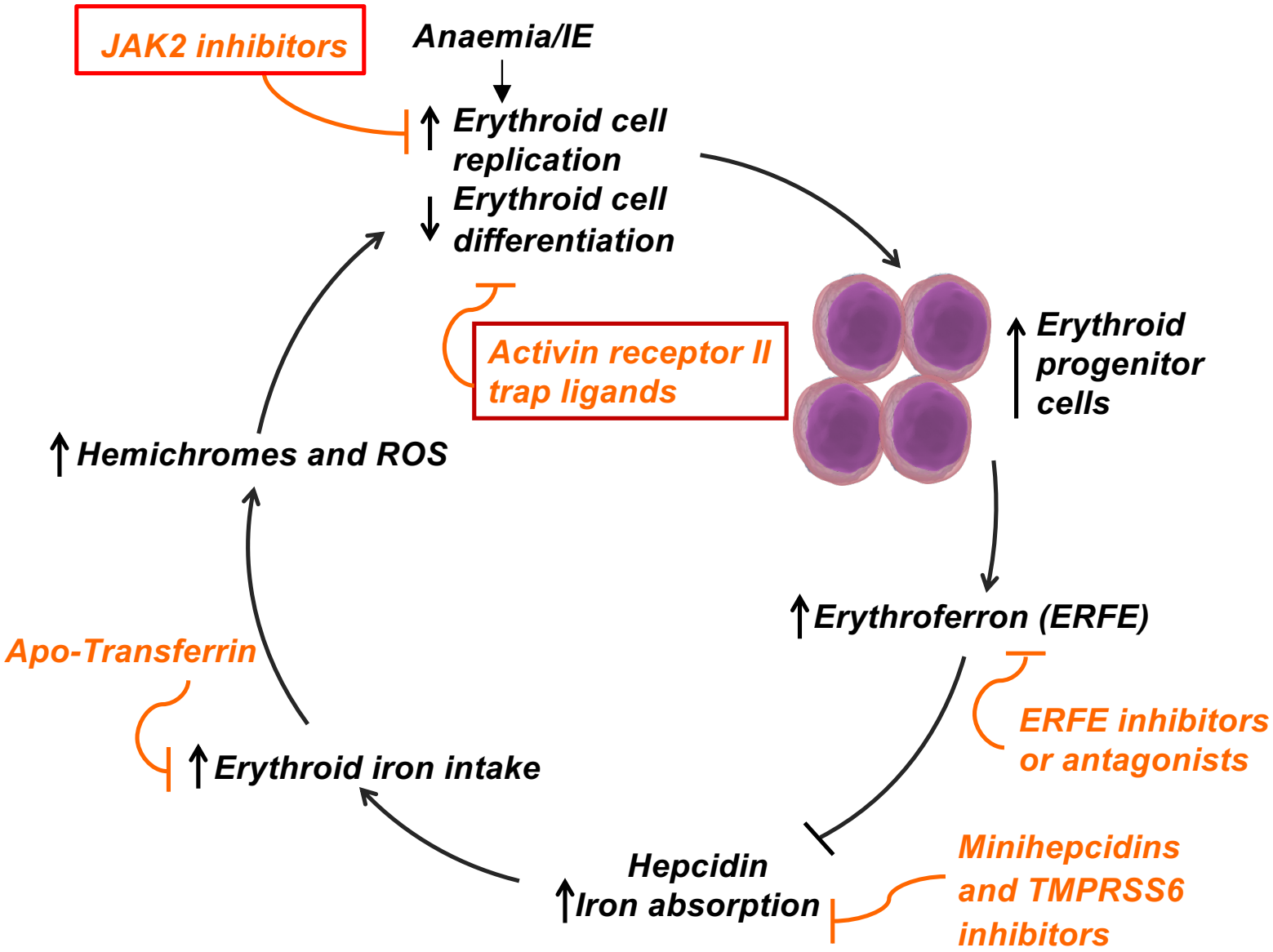
Percent Change From Baseline in Spleen Volume at Week 30



- The mean spleen volume reduction from baseline at week 12 (N = 26) and week 30 (N = 25) was −19.7% and −26.8%, respectively
  - At week 30, one patient* who had initially showed a decrease of 15% spleen volume at week 12 demonstrated an increase in spleen volume.

Ruxolitinib Conclusions

- In addition to a noticeable reduction in spleen volume over time with ruxolitinib treatment, a trend for improvement in transfused red cells and a slight improvement in pretransfusion hemoglobin was noted with ruxolitinib treatment.
- A majority of patients continued with the treatment beyond the core study.
- Ruxolitinib was well tolerated in the study population with modest incidences of grade 3 or 4 and serious AEs, with no new safety findings.
- Given the sustained decrease in spleen volume, ruxolitinib treatment may serve as an alternative option in patients with TDT who are potential candidates for splenectomy.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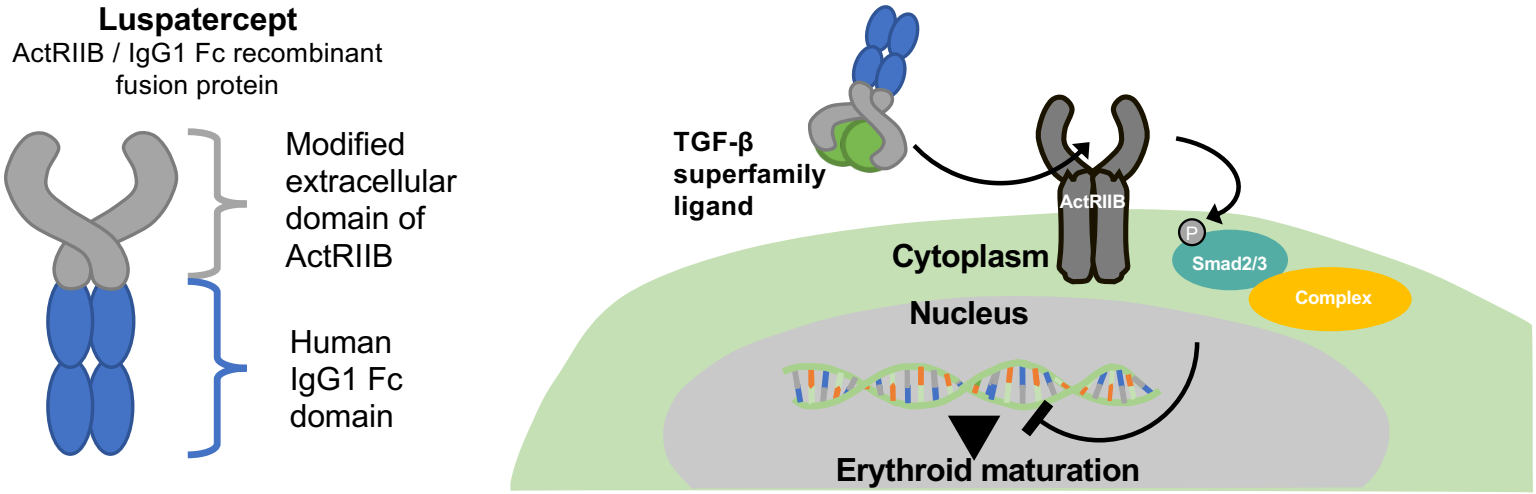
↑ Erythroid iron intake
Apo-Transferrin
↑ Hemichromes and ROS

Luspatercept

- Luspatercept is an investigational first-in-class erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis[1,2]

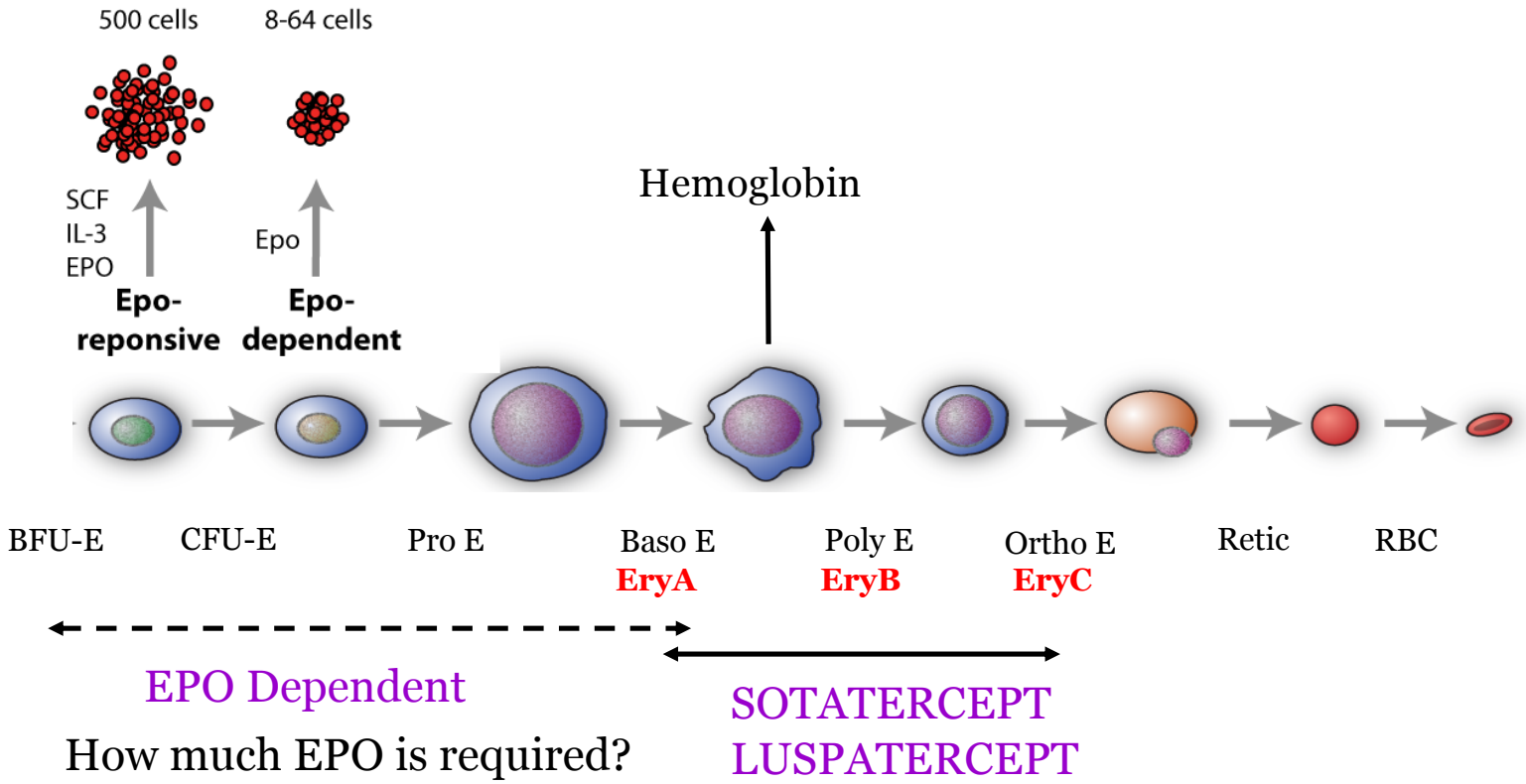


1. Attie KM, et al. Am J Hematol. 2014;89:766-770.
2. Suragani RN, et al. Nat Med. 2014;20:408-414.

ActRIIB, human activin receptor type IIB; IgG1 Fc, immunoglobulin G1 fragment crystallizable; TGF-β, transforming growth factor beta.

The BELIEVE Trial studied adult patients.

Where Does Sotatercept/Luspatercept Impact Erythropoiesis?



***Lancet Oncol* 2017; 18: 1338–47**

Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose- nding study with long-term extension study

Uwe Platzbecker, Ulrich Germing*, Katharina S Götze*, Philipp Kiewe*, Karin Mayer*, Jörg Chromik*, Markus Radsak*, Thomas Wol *, Xiaosha Zhang, Abderrahmane Laadem, Matthew L Sherman, Kenneth M Attie, Aristoteles Giagounidis**

BLOOD SPOTLIGHT| FEBRUARY 21, 2019

Luspatercept for the treatment of anemia in myelodysplastic syndromes and primary myelofibrosis

Pierre Fenaux

, Jean Jacques Kiladjian

, Uwe Platzbecker

Blood (2019) 133 (8): 790-794.

https://doi.org/10.1182/blood-2018-11-876888

MEDALIST Trial
Study Design – A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study

Patient Population

- MDS-RS (WHO): ≥ 15% RS or ≥ 5% with *SF3B1* mutation
- < 5% blasts in bone marrow
- No del(5q) MDS
- IPSS-R Very Low-, Low-, or Intermediate-risk
- Prior ESA response
  - Refractory, intolerant
  - ESA naive: EPO > 200 U/L
- Average RBC transfusion burden ≥ 2 units/8 weeks
- No prior treatment with disease-modifying agents (e.g. iMIDs, HMAs)

Randomize 2:1

[redacted] 1.0 mg/kg (s.c.) every 21 days
n = 153

Dose titrated up to a maximum of 1.75 mg/kg

Placebo (s.c.) every 21 days
n = 76

Disease & Response Assessment week 24 & every 6 months
Treatment discontinued for lack of clinical benefit or disease progression per IWG criteria; no crossover allowed

Subjects followed ≥ 3 years post final dose for AML progression, subsequent MDS treatment and overall survival

Data cutoff: May 8, 2018 Includes last subject randomized + 48 weeks.
EPO, erythropoietin; HMA, hypomethylating agent; iMID, immunomodulatory drug; IWG, International Working Group; s.c., subcutaneously; *SF3B1*, splicing factor 3b subunit 1; WHO, World Health Organization.

MEDALIST Trial
Study Endpoints

Primary endpoint:

- Red blood cell transfusion independence ≥ 8 weeks (weeks 1–24)

Key secondary endpoint:

- Red blood cell transfusion independence ≥ 12 weeks (weeks 1–24 and weeks 1–48)

Additional secondary endpoints:

- HI-E (IWG 2006 criteria[1]) for any consecutive 56-day period
  - Reduction in red blood cell transfusion burden ≥ 4 RBC units/8 weeks[a] or
  - Mean Hb increase of ≥ 1.5 g/dL/8 weeks[b]
- Duration of response
- Hb change from baseline

[a] In patients with baseline RBC transfusion burden ≥ 4 units/8 weeks. [b] In patients with baseline RBC transfusion burden < 4 units/8 weeks.
Hb, hemoglobin; HI-E, hematological improvement–erythroid.

1. Cheson BD, et al. Blood. 2006;108:419-425.

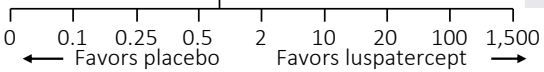
MEDALIST Trial
Primary Endpoint: Red Blood Cell Transfusion Independence ≥ 8 Weeks

RBC-TI ≥ 8 weeks	Luspatercept (n = 153)	Placebo (n = 76)
Weeks 1–24, n (%)	**58 (37.9)**	**10 (13.2)**
95% CI	30.2–46.1	6.5–22.9
P value[a]	< 0.0001	

[a] Cochran–Mantel–Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 units vs < 6 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate).
CI, confidence interval.

MEDALIST Trial
Primary Endpoint: Subgroup Analysis

	Luspatercept, n (%)	Placebo, n (%)	OR (95% CI)	*P* Value
Overall	58/153 (37.9)	10/76 (13.2)	5.06 (2.28–11.3)	< 0.0001
Average baseline RBC transfusion requirement				
≥ 6 units/8 weeks	6/66 (9.1)	1/33 (3.0)	3.20 (0.37–27.7)	0.2699
< 6 units/8 weeks	52/87 (59.8)	9/43 (20.9)	5.61 (2.40–13.1)	< 0.0001
4 to < 6 units/8 weeks	15/41 (36.6)	1/23 (4.3)	12.7 (1.55–104)	0.0046
< 4 units/8 weeks	37/46 (80.4)	8/20 (40.0)	6.17 (1.95–19.5)	0.0013
Baseline serum EPO (U/L)				
< 100	23/51 (45.1)	7/31 (22.6)	2.82 (1.03–7.71)	0.0413
100 to < 200	14/37 (37.8)	2/19 (10.5)	5.17 (1.04–25.9)	0.0338
200–500	17/43 (39.5)	1/15 (6.7)	9.15 (1.10–76.2)	0.0188
Age group				
≤ 64 years	17/29 (58.6)	3/16 (18.8)	6.14 (1.43–26.3)	0.0108
65–74 years	23/72 (31.9)	4/29 (13.8)	2.93 (0.91–9.41)	0.0635
≥ 75 years	18/52 (34.6)	3/31 (9.7)	4.94 (1.32–18.5)	0.0120
Gender				
Male	32/94 (34.0)	4/50 (8.0)	5.94 (1.96–18.0)	0.0006
Female	26/59 (44.1)	6/26 (23.1)	2.63 (0.92–7.48)	0.0673
Time since initial diagnosis at baseline				
≤ 2 years	14/40 (35.0)	3/19 (15.8)	2.87 (0.71–11.6)	0.1312
> 2–5 years	30/62 (48.4)	4/34 (11.8)	7.03 (2.21–22.3)	0.0004
> 5 years	14/51 (27.5)	3/23 (13.0)	2.52 (0.65–9.83)	0.1756
Baseline IPSS-R risk				
Very Low or Low	48/127 (37.8)	9/63 (14.3)	3.65 (1.65–8.05)	0.0009
Intermediate	10/25 (40.0)	1/13 (7.7)	8.00 (0.89–71.6)	0.0398
Baseline platelet count				
< 100 × 10^9/L	2/8 (25.0)	1/6 (16.7)	1.67 (0.11–24.3)	0.7171
100–400 × 10^9/L	42/128 (32.8)	8/61 (13.1)	3.24 (1.41–7.42)	0.0042
> 400 × 10^9/L	14/17 (82.4)	1/9 (11.1)	37.3 (3.31–422)	0.0006



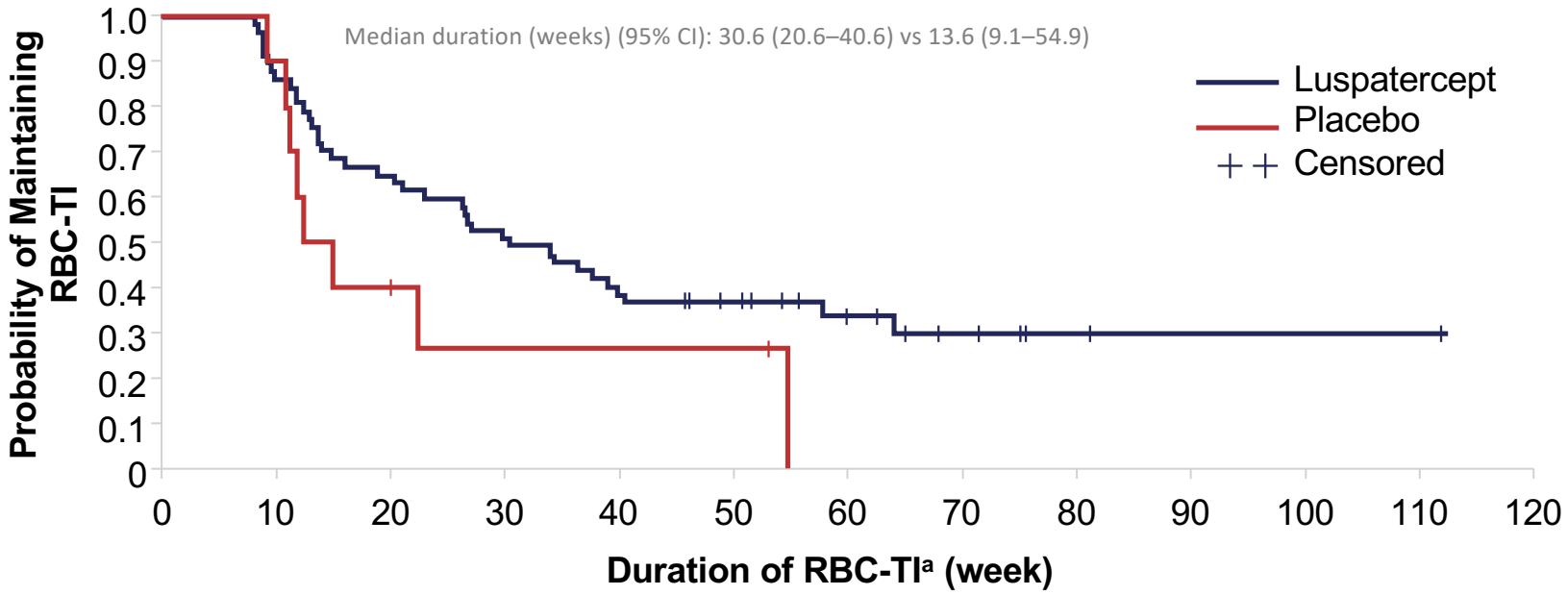
OR, odds ratio.

MEDALIST Trial
Key Secondary Endpoint: Red Blood Cell Transfusion Independence ≥ 12 Weeks

RBC-TI ≥ 12 Weeks	Luspatercept (n = 153)	Placebo (n = 76)
Weeks 1–24, n (%)	**43 (28.1)**	**6 (7.9)**
95% CI	21.14–35.93	2.95–16.40
P value[a]	0.0002	
Weeks 1–48, n (%)	**51 (33.3)**	**9 (11.8)**
95% CI	25.93–41.40	5.56–21.29
P value[a]	0.0003	

[a] Cochran–Mantel–Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 units vs < 6 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate).

MEDALIST Trial
Duration of RBC-TI Response in Primary Endpoint Responders

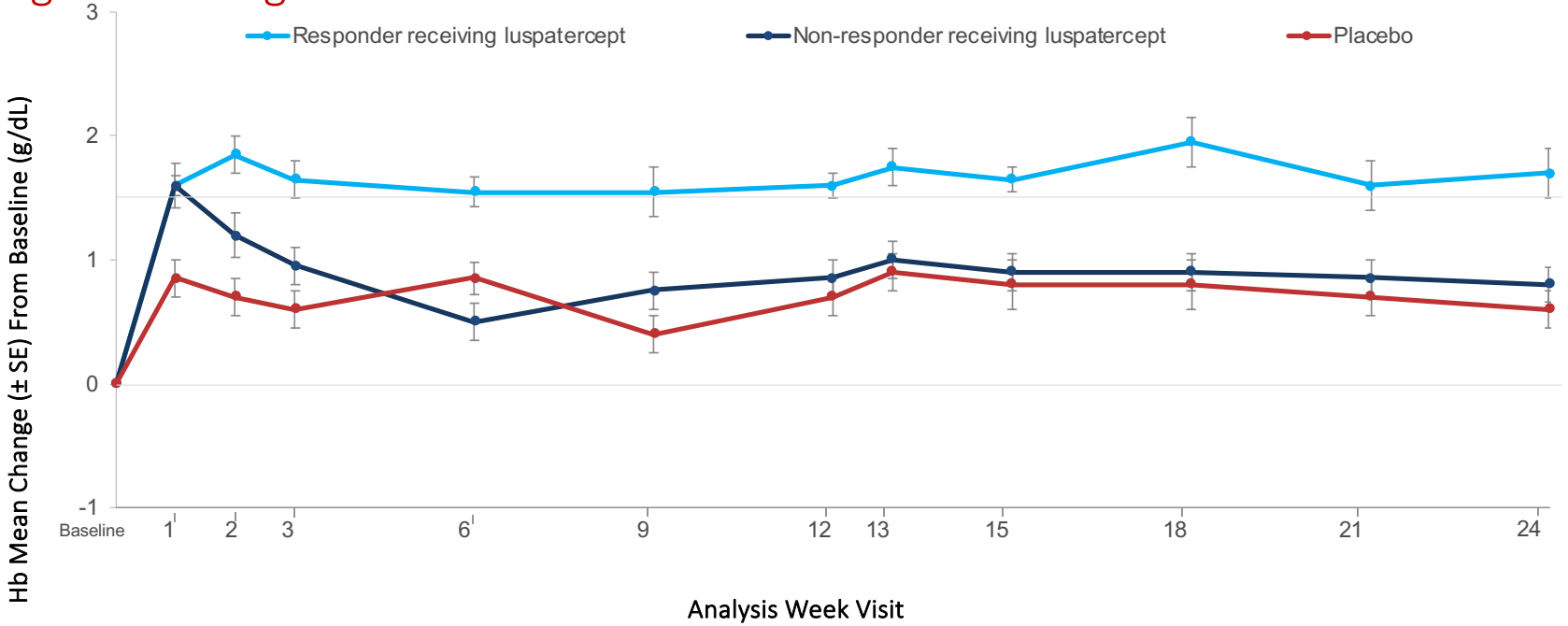


Number of patients													
Luspatercept	58	49	37	29	22	18	10	6	3	2	1	1	0
Placebo	10	9	3	2	2	2	0						

[a] During indicated treatment period. Patients who maintained RBC-TI at the time of analysis are censored.

MEDALIST Trial

Change in Hemoglobin Concentration



- Median peak hemoglobin increase in luspatercept responders: 2.55 g/dL (1–4.1 g/dL)

Number of patients												
Responder[a]	153	24	36	55	53	52	50	42	47	50	42	45
Non-responder		33	51	61	52	60	53	34	45	56	48	35
Placebo	76	32	36	41	47	44	52	29	44	47	44	32

[a] LS mean difference (95% CI) for luspatercept responders versus placebo: 1.08 (0.84, 1.31), $P < 0.0001$.

Only patients with RBC-TI ≥ 8 weeks during weeks 1–24 are included. Hb measurement was excluded within 14 days after a RBC transfusion unless within 3 days prior to another RBC transfusion. Mean and SE were not calculated if the number of patients was < 8 in the luspatercept non-responder group or < 4 in the placebo group. SE, standard error.

MEDALIST Trial
Author's Conclusions

- In lower-risk, RS-positive MDS, treatment with luspatercept resulted in a significantly higher percentage of patients who achieved RBC-TI, major RBC transfusion reduction, or hemoglobin increase, compared with placebo
- Erythroid responses were durable, with approximately 40% of patients achieving RBC-TI sustained at 12 months of treatment
- Luspatercept was generally well tolerated in this patient population
- Luspatercept is a potential new therapy for the treatment of patients with lower-risk, RS-positive MDS with RBC transfusion-dependent anemia

blood®

Plenary Paper

CLINICAL TRIALS AND OBSERVATIONS

Luspatercept improves hemoglobin levels and blood transfusion requirements in a study of patients with β-thalassemia

Antonio Piga,[1] Silverio Perrotta,[2] Maria Rita Gamberini,[3] Ersi Voskaridou,[4] Angela Melpignano,[5] Aldo Filosa,[6] Vincenzo Caruso,[7] Antonello Pietrangelo,[8] Filomena Longo,[1] Immacolata Tartaglione,[2] Caterina Borgna-Pignatti,[9] Xiaosha Zhang,[10] Abderrahmane Laadem,[11] Matthew L. Sherman,[10] and Kenneth M. Attie[10]

[1]Department of Clinical and Biological Sciences, Turin University, Turin, Italy; [2]Dipartimento della Donna, del Bambino e della Chirurgia Generale e Specialistica, Università degli Studi della Campania "Luigi Vanvitelli," Naples, Italy; [3]Thalassemia Unit, Arcispedale S. Anna, Ferrara, Italy; [4]Laiko General Hospital, Athens, Greece; [5]Ospedale "A. Perrino," Brindisi, Italy; [6]Rare Red Blood Cell Disease Unit, Cardarelli Hospital, Naples, Italy; [7]Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione Garibaldi, Catania, Italy; [8]Centro Emocromatosi e Malattie Eredometaboliche del Fegato, Medicina 2, Modena, Italy; [9]Section of Pediatrics, Department of Medical Sciences, University of Ferrara, Ferrara, Italy; [10]Acceleron Pharma, Cambridge, MA; and [11]Celgene Corporation, Summit, NJ

Red Cell Biology & its Disorders

ARTICLE

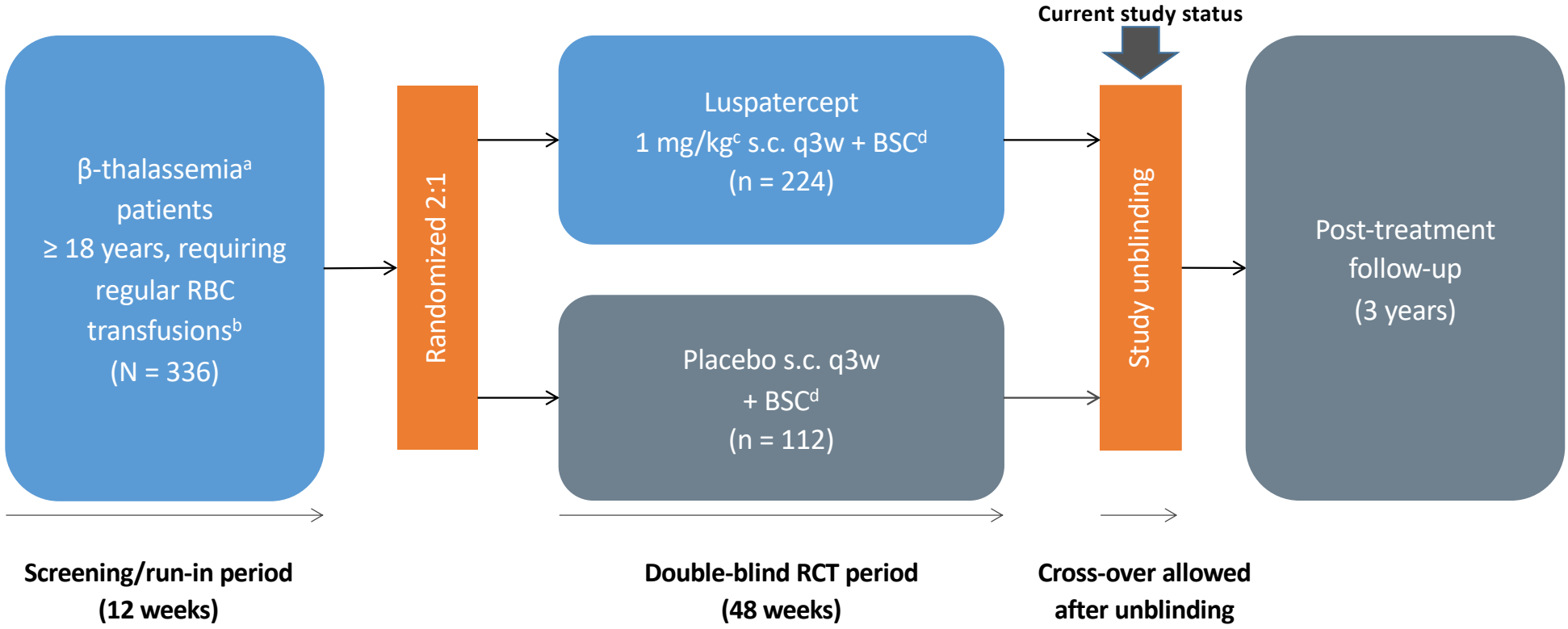
Ferrata Storti Foundation

Sotatercept, a novel transforming growth factor β ligand trap, improves anemia in β-thalassemia: a phase II, open-label, dose-finding study

Maria Domenica Cappellini,[1] John Porter,[2] Raffaella Origa,[3] Gian Luca Forni,[4] Ersi Voskaridou,[5] Frédéric Galactéros,[6] Ali T. Taher,[7] Jean-Benoît Arlet,[8,9,10] Jean-Antoine Ribeil,[11] Maciej Garbowski,[2] Giovanna Graziadei,[1] Chantal Brouzes,[11] Michaela Semeraro,[11] Abderrahmane Laadem,[12] Dimana Miteva,[13] Jun Zou,[12] Victoria Sung,[14] Tatiana Zinger,[13] Kenneth M. Attie[15] and Olivier Hermine[9,10,16]

Haematologica 2019
Volume 104(3):477-484

Believe Study:A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study



[a] β-thalassemia or hemoglobin E/β-thalassemia (β-thalassemia with mutation and/or multiplication of α globin was allowed); [b] Defined as: 6–20 RBC units in the 24 weeks prior to randomization with no ≥ 35-day transfusion-free during that period; [c] May be titrated up to 1.25 mg/kg; [d] RBC transfusions and iron chelation therapy to maintain each patient's baseline hemoglobin level.

LPFD, last patient first dose; q3w, every 3 weeks; RCT, randomized clinical trial; s.c., subcutaneously.

BELIEVE Trial studied in adult patients only.

Study endpoints

- Primary endpoint
  - Erythroid response from Week 13–24 compared to the 12-week interval prior to randomization
    - Erythroid response was defined as a ≥ 33% reduction from baseline in transfusion burden (units RBC/time) with a reduction of ≥ 2 units

- Pre-specified key secondary and additional endpoints included:
  - Reduction from baseline in RBC transfusion burden
    - ≥ 33% reduction from Week 37–48
    - ≥ 50% reduction from Week 13–24 and from Week 37–48
    - ≥ 33% reduction over any 12 and 24 weeks on study
  - Mean change from baseline in
    - Transfusion burden from Week 13–24
    - Serum ferritin, LIC, and myocardial iron

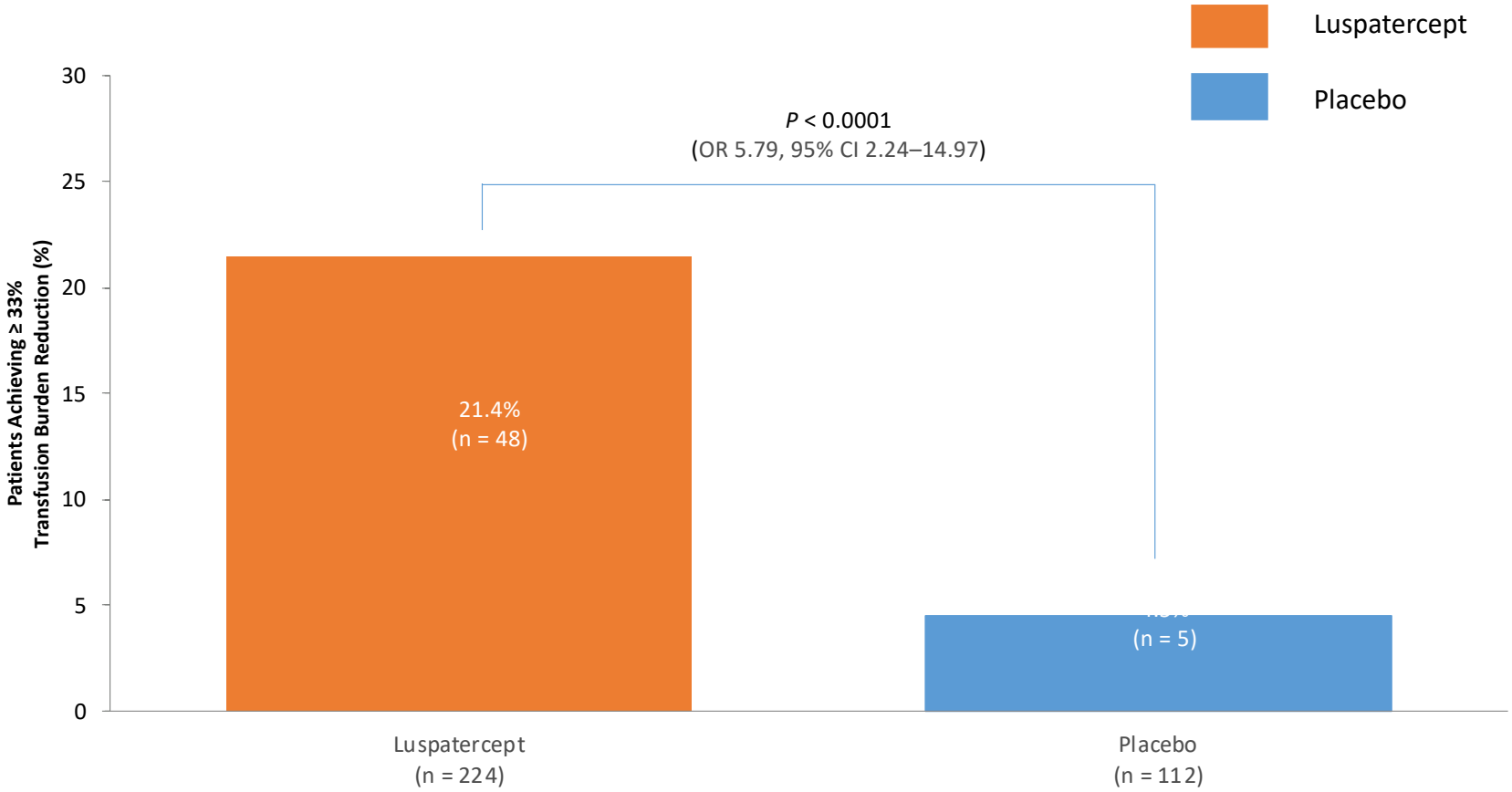
LIC, liver iron concentration.

BELIEVE Trial studied in adult patients only.

BELIEVE Trial

Primary endpoint MET: Rate of Erythroid Response

A significantly greater proportion of luspatercept-treated patients achieved a ≥ 33% reduction from baseline in transfusion burden during weeks 13 to 24

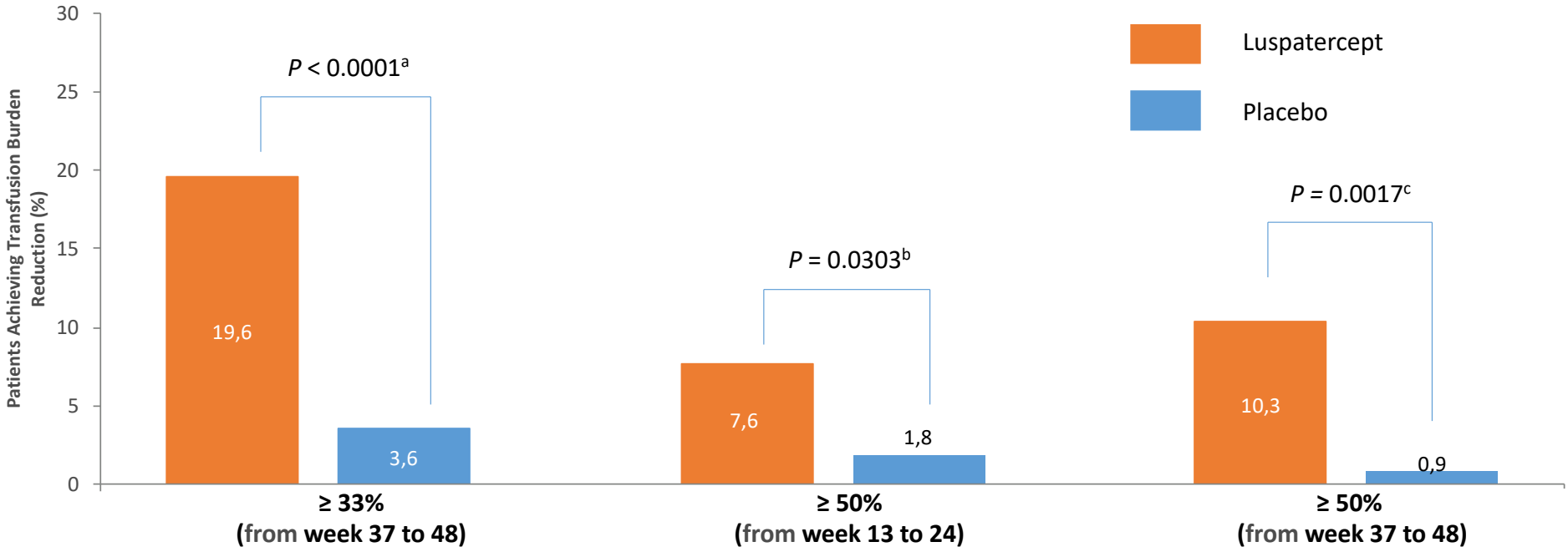


CI, confidence interval; OR, odds ratio.
The BELIEVE Trial studied adult patients.

BELIEVE Trial

All key secondary endpoints MET: Rates of Erythroid Response

A significantly greater proportion of luspatercept-treated patients achieved clinically meaningful reductions in transfusion burden of ≥ 33% and ≥ 50%



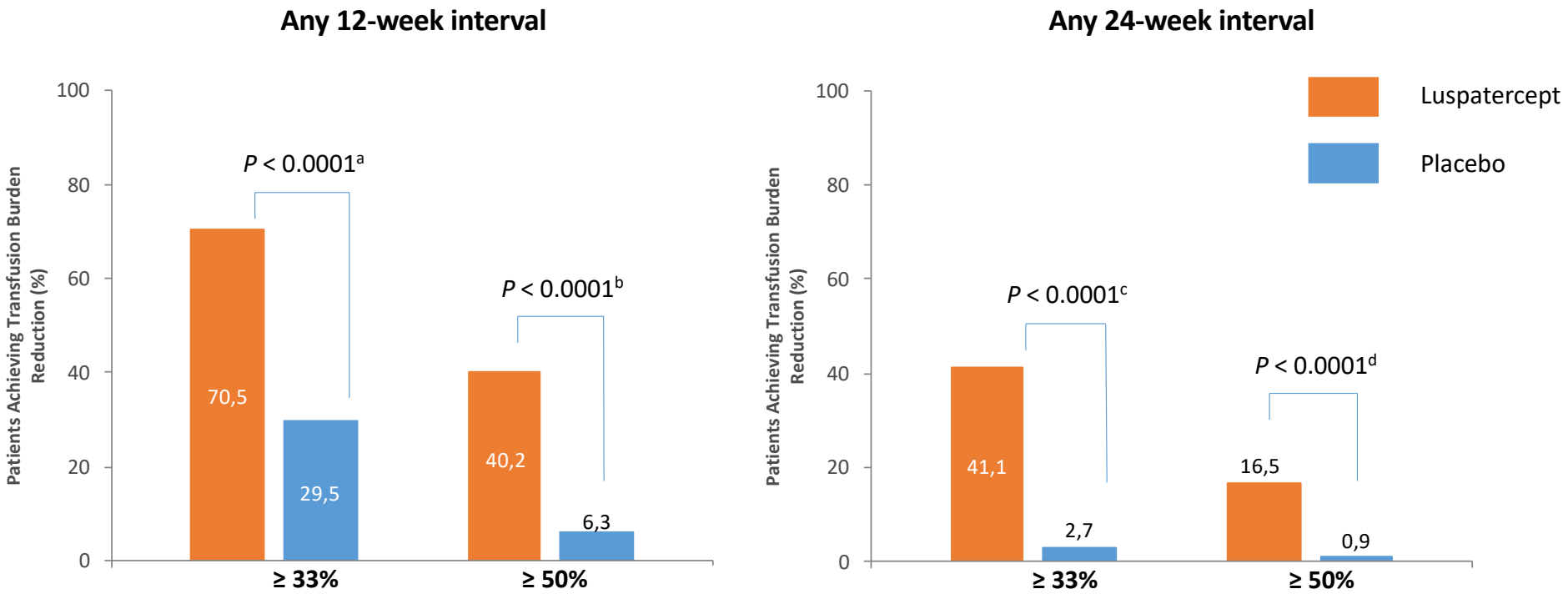
- The least squares mean change in transfusion burden from baseline to weeks 13–24 (luspatercept versus placebo) was −1.35 RBC units/12 weeks (95% CI −1.77 to −0.93; *P* < 0.0001)

[a] OR 6.44, 95% CI 2.27–18.26. [b] OR 4.55, 95% CI 1.03–20.11. [c] OR 11.92, 95% CI 1.65–86.29.
The BELIEVE Trial studied adult patients.

BELIEVE Trial

Reduction in transfusion burden during ANY 12- and 24-week interval

During any 12- or 24-week interval, a significantly greater proportion of luspatercept-treated patients achieved clinically meaningful reductions in transfusion burden of ≥ 33% and ≥ 50%



[a] OR 5.69, 95% CI 3.46–9.35. [b] OR 9.95, 95% CI 4.44–22.33. [c] OR 25.02, 95% CI 7.76–80.71. [d] OR 20.37, 95% CI 2.86–144.94.
The BELIEVE Trial studied adult patients.

BELIEVE Trial

Additional Endpoints: Iron Parameters

	Luspatercept (n = 224)	Placebo (n = 112)	LS Mean of Difference	95% CI	*P* Value
Mean change from baseline at week 48					
Serum ferritin, µg/L (SD)	−245 (780)	105 (521)	−340	−502, −177	< 0.0001
LIC, mg/g dry weight (SD)	0.10 (5.760)	0.08 (5.229)	0.11	−1.16, 1.38	0.8685
Myocardial iron by T2*, ms (SD)	−1.83 (15.084)	0.02 (6.843)	−2.39	−4.67, −0.12	0.0391

SD, standard deviation.

The BELIEVE Trial studied adult patients.

BELIEVE Trial

Safety Summary

Treatment-Emergent Adverse Events, n (%)	Luspatercept (n = 223[a])	Placebo (n = 109[a])
Patients with at least 1 TEAE (any grade)	214 (96.0)	101 (92.7)
Patients with at least 1 grade TEAE (grade ≥ 3)[c]	65 (29.1)	17 (15.6)
Patients with at least 1 serious TEAE[b]	34 (15.2)	6 (5.5)
Patients with at least 1 TEAE resulting in the following:		
Death[d]	0	1 (0.9)
Study drug discontinuation	12 (5.4)	1 (0.9)

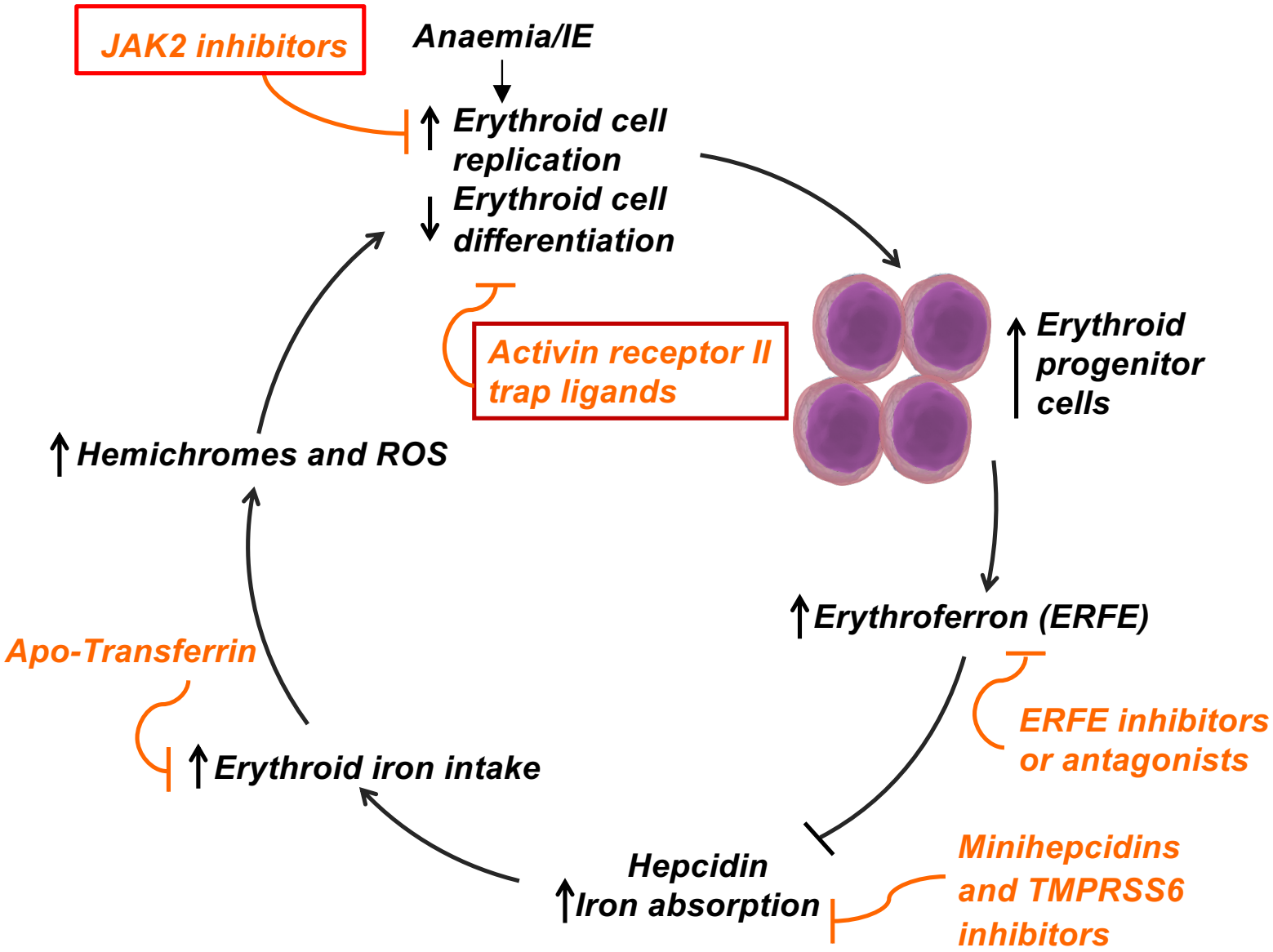
[a] Safety population. [b] Anemia was the only serious TEAE occurring in > 1% of patients in either arm (luspatercept, n = 3 [1.4%]; placebo, n = 0 [0%]).
[c] No one organ class or system was predominant. [d] TEAE of acute cholecystitis resulted in death in 1 of 109 (0.9%) placebo patients; no luspatercept-treated patients died due to TEAEs.
TEAE, treatment-emergent adverse event.
The BELIEVE Trial studied adult patients.

BELIEVE Trial

[redacted]: conclusions

- [redacted] showed a statistically significant improvement in the primary endpoint of ≥ 33% reduction in transfusion burden compared with placebo
- Statistical significance was also demonstrated with [redacted] versus placebo for all key secondary endpoints, including ≥ 33% and ≥ 50% reductions in transfusion burden
- Luspatercept showed a statistically significant and clinically meaningful reduction in transfusion burden compared with placebo during any 12 or 24 weeks in the study period
- Luspatercept was generally well tolerated in this patient population
- Luspatercept is a potential new treatment for adult patients with β-thalassemia who require regular RBC transfusions

The BELIEVE Trial studied adult patients.


JAK2 inhibitors
Anaemia/IE
↑ Erythroid cell replication
↓ Erythroid cell differentiation
Activin receptor II trap ligands
↑ Erythroid progenitor cells
↑ Erythroferron (ERFE)
ERFE inhibitors or antagonists
Hepcidin
↑ Iron absorption
Minihepcidins and TMPRSS6 inhibitors
↑ Erythroid iron intake
Apo-Transferrin
↑ Hemichromes and ROS

LJPC-401: Synthetic Human Hepcidin

- LJPC-401 is a proprietary formulation of synthetic human hepcidin, a **naturally occurring** regulator of iron absorption and distribution
- LJPC-401 has been shown to be effective at reducing serum iron levels in preclinical and Phase 1 human testing
- Scalable manufacturing process capable of producing a pure, properly folded, stable hepcidin formulation developed
- Orphan Drug Designation granted (EU)
- Agreement reached with European Medicines Agency (EMA) on pivotal study design

Take home messages

- A new era of novel therapeutics is unfolding in thalassemia care
- Several targets have been identified that can ameliorate the genetic defect, ineffective erythropoiesis, or iron dysregulation
- A number of these targets now have agents in pre-clinical and clinical development
- Clinical data from these agents as monotherapies or combinations with existing therapies are highly awaited