



Clinical and Pharmacoeconomic Implications of Iron Supplementation in Cancer Patients with Anemia

Supported by an educational grant from Watson

Disclosures

- Stacy S. Shord, PharmD, BCOP has received consulting fees from Watson Pharmaceuticals, Inc
- David M. Baribeault, RPh, BCOP has received consulting fees from Sanofi-Aventis and Watson Pharmaceuticals, Inc. and fees for non-CE services from Roche and Valeant Pharmaceuticals International

Learning Objectives

- Describe the clinical rationale for use of IV versus oral iron in conjunction with ESAs in cancer patients with anemia
- Devise a patient-individualized care plan for test dosing and therapeutic dosing of IV iron
- Project potential institutional cost savings following implementation of routine IV iron administration with ESAs



Why IV Iron in Cancer Patients with Anemia?

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Lecture Objectives

- Describe the current management of CIA
- Define states of absolute and functional iron deficiency
- Explain the relationship between functional iron deficiency and non-response to ESA therapy
- Characterize the clinical inertia and safety concerns pertaining to parenteral iron

Defining Anemia

- Standard definition for anemia is lacking
- Generally defined as a reduction in hemoglobin (Hb) or the total red blood cell count, which causes a decreased ability of the blood to carry oxygen to the tissues
- Normal Hb levels are 12 to 16 g/dL for women and 14 to 18 g/dL for men

Current Management of Anemia

- Clinical practice guidelines
 - Consider correctable causes of anemia before starting an ESA
 - Recommend starting an ESA to increase Hb and decrease transfusions as Hb approaches or falls below 10 g/dL
 - Recommend considering clinical circumstances when Hb <12 g/dL (but never <10 g/dL) when determining whether to use ESA immediately or to wait until Hb <10 g/dL

Assessing Iron Status

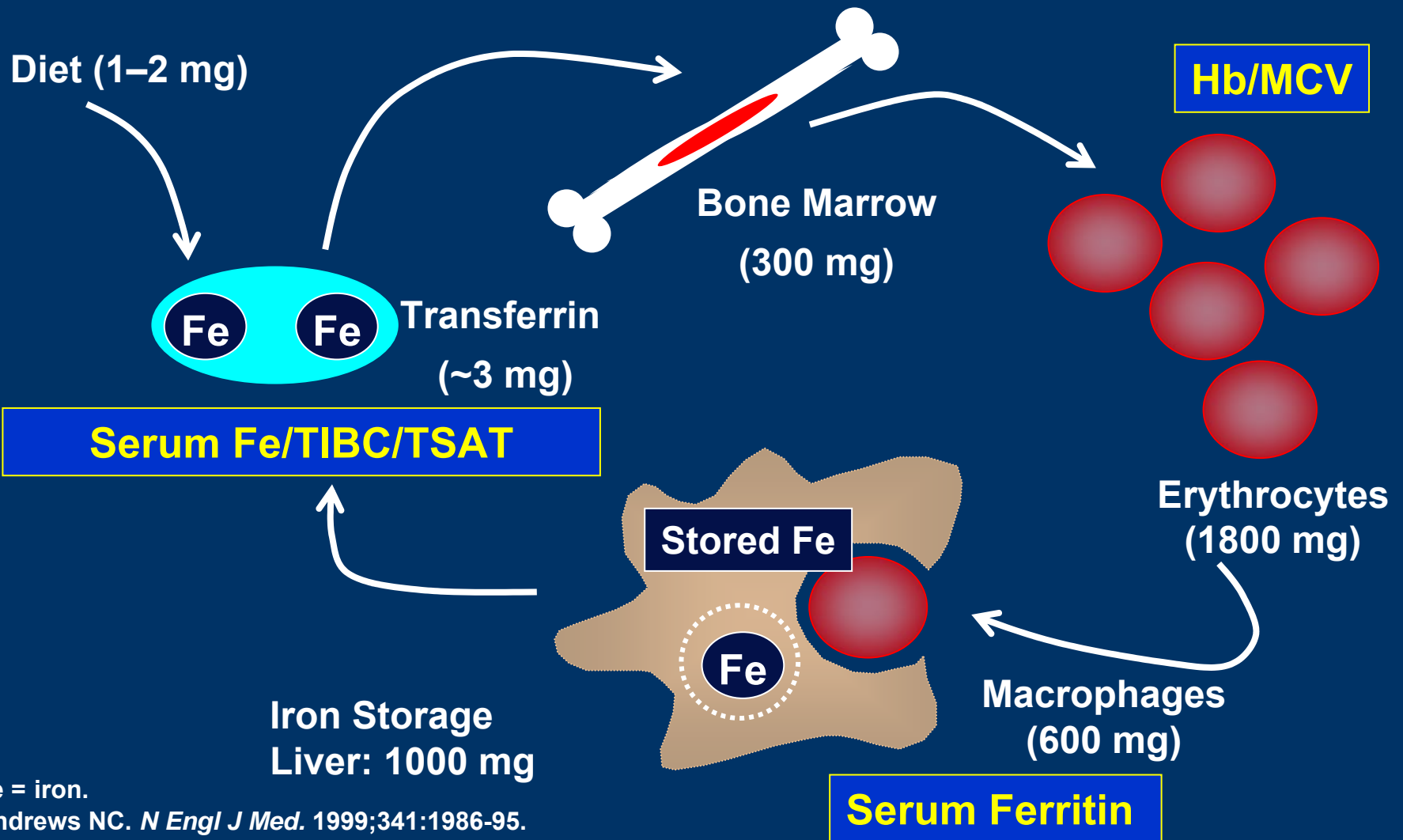
Laboratory Test	Measurement	Reference Range in Normal Adults
Serum iron	Iron available for hemoglobin synthesis	50–170 µg/dL men 30–160 µg/dL women
TIBC	Total iron binding capacity	250–435 µg/dL
TSAT	Iron available for hemoglobin synthesis; calculated value	20%–50% men 15%–50% women
Serum ferritin	Reflects total body iron stores	20–250 ng/mL men 10–120 ng/mL women

TIBC = total iron binding capacity; TSAT = transferrin saturation.
Lexi-Comp ONLINE™ Laboratory Users Guide.

Iron in the Clinical Practice Guidelines

- National Comprehensive Cancer Network
 - Additional evaluation, iron panel, including serum iron, TIBC, and serum ferritin
 - Treatment evaluation, ESA \pm iron supplementation as indicated by serum ferritin <100 ng/mL and TSAT $<20\%$
- American Society Clinical Oncology/American Society of Hematology
 - Baseline and periodic monitoring of iron, TIBC, TSAT, or serum ferritin levels and instituting iron repletion when indicated may be valuable in limiting the need for ESA, maximizing symptomatic improvement, and determining the reason for failure to respond adequately to ESA

Understanding Iron Status



Fe = iron.

Andrews NC. *N Engl J Med.* 1999;341:1986-95.

Defining Iron Deficiency

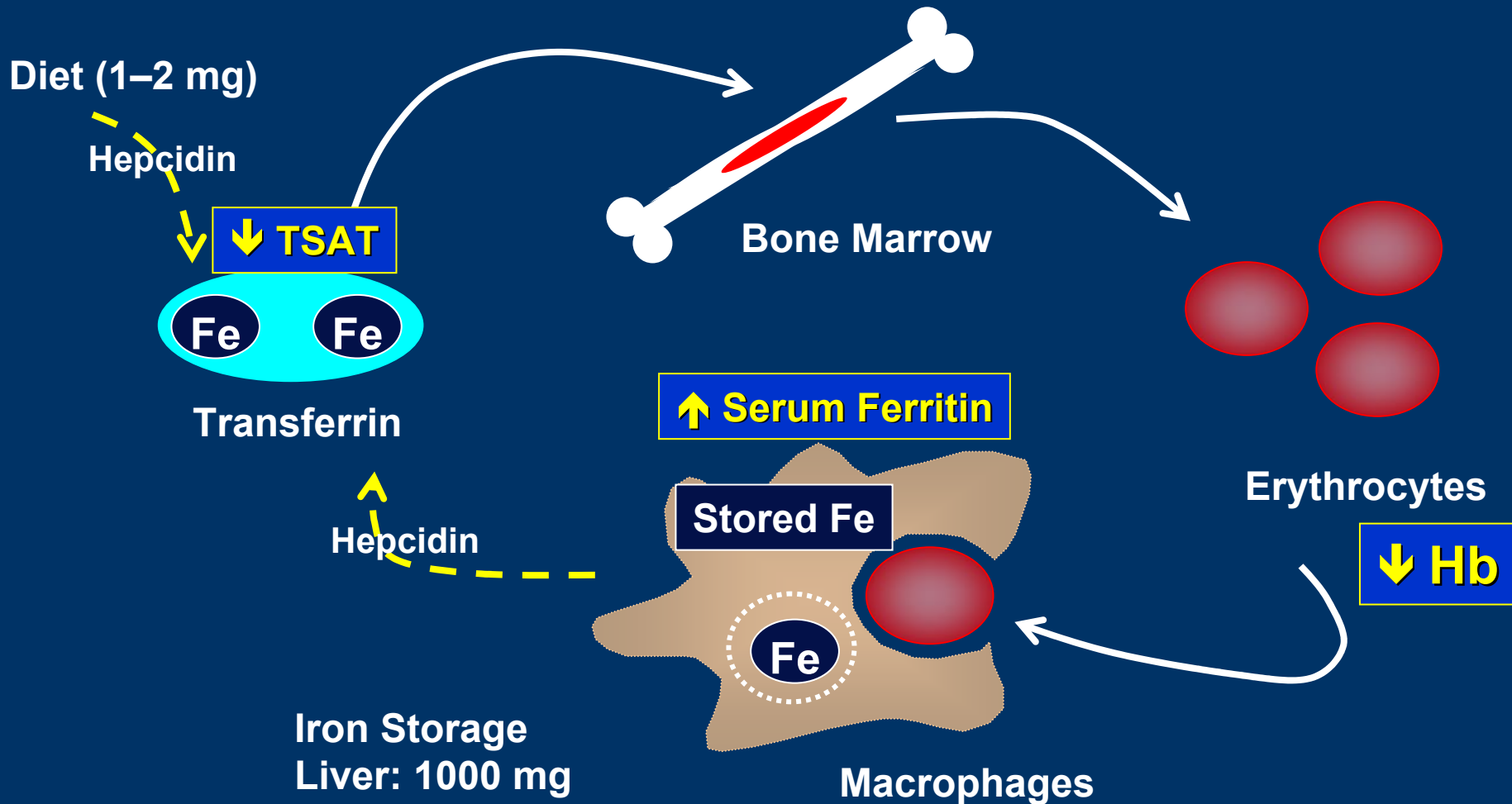
■ Absolute Iron Deficiency

- Includes states ranging from iron depletion to iron deficiency anemia
 - Iron depletion occurs when the amount of stored iron is reduced
 - Iron deficiency anemia occurs when amount of total body iron is reduced and clinical signs and symptoms are present

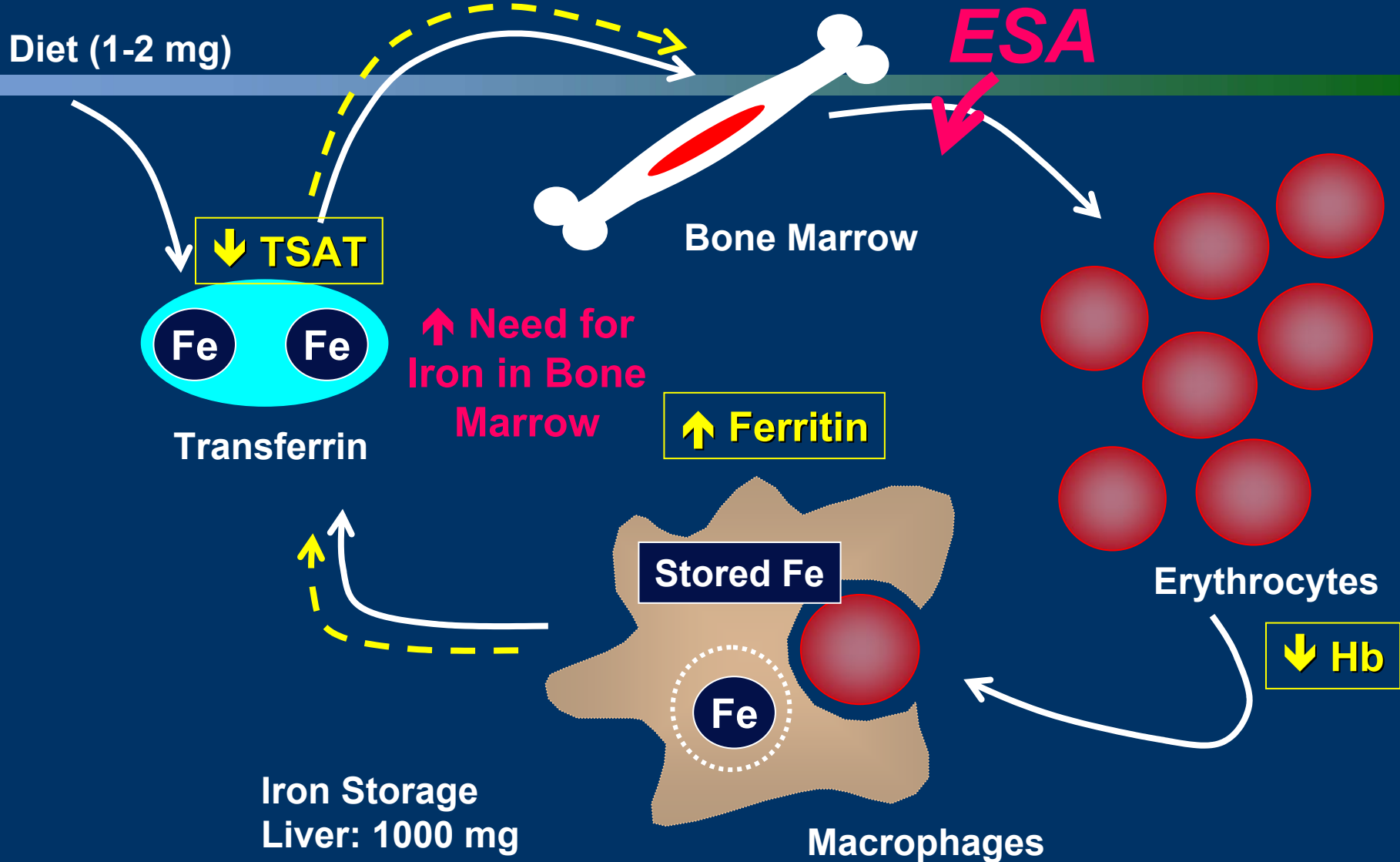
■ Functional Iron Deficiency

- Also known as iron restricted erythropoiesis or acquired iron insufficiency syndrome
 - State where the total iron content of the body is normal or even elevated, but the iron is `locked away` and unavailable for the production of red blood cells
 - Arbitrarily defined as TSAT <20% and serum ferritin \geq 100 ng/mL

Impact of Inflammation on Iron Parameters



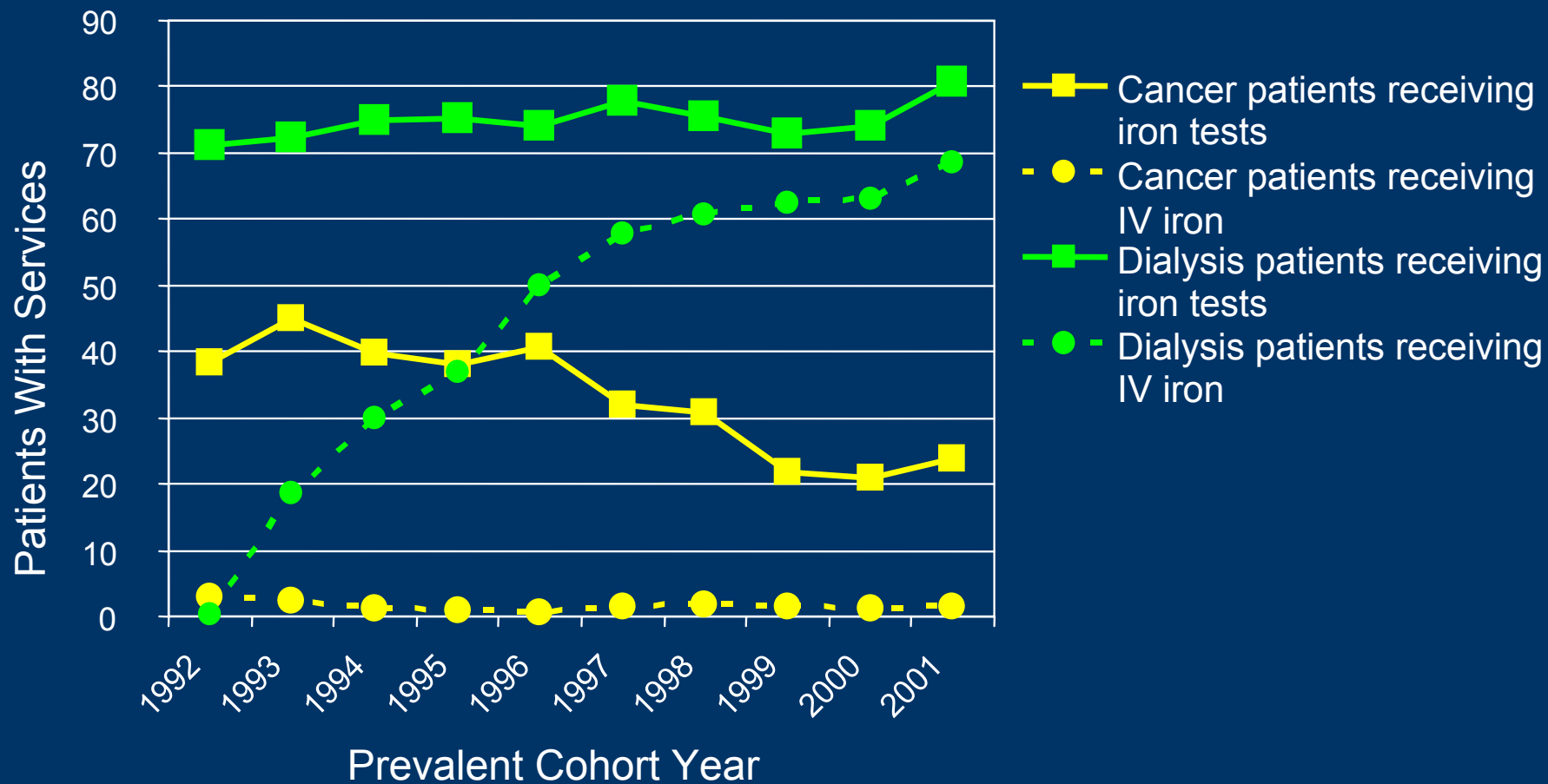
Iron-Restricted Erythropoiesis



Iron Deficiency in Anemic Cancer Patients

	TSAT		Total
	≥20%	<20%	
Ferritin ≥100 ng/mL	96 (37%)	120 (46%)	216 (83%)
Ferritin <100 ng/mL	10 (4%)	34 (13%)	44 (17%)
Total	106 (41%)	154 (59%)	260 (100%)

Trends in Iron Testing and Parenteral Iron Dosing in CIA – 1992 to 2001



Presented by Dr. Al Collins, Director of U.S. Renal Database System analyzing CMS billing records, at the annual American Society of Hematology meeting 2003.

Oral Iron Preparations

■ Pros

- Inexpensive
- Convenient

■ Cons

- 4 to 6 months to replace iron stores
- Reduced absorption in patients with cancer
 - Elevated expression of hepcidin in liver
 - Reduced absorption with iron deficiency
 - Absorption not affected by cancer
- Limited effect with ESA therapy
- Poor adherence, gastrointestinal adverse events

Weinstein DA, et al. *Blood*. 2002;100:3776-81; Nemeth E, et al. *Science*. 2004;306:2090-3; Andrews NC. *J Clin Invest*. 2004;113:1251-3; Haurani FL, et al. *Am J Med Sci*. 1965;249:537-47; Savonije JH, et al. *Cancer Invest*. 2006;24:562-6; Auerbach MC, et al. *J Clin Oncol*. 2004;22:1301-7; Henry DH, et al. *Oncologist*. 2007;12:231-42.

Selecting the Parenteral Iron Formulation

- Efficacy – similar outcomes observed in clinical trials, but no head-to-head comparisons
- Adverse events – most commonly reported with high molecular weight iron dextran
- Dose versatility – intravenous push or infusion
- Cost – iron dextran average wholesale price 2-fold less compared to iron sucrose or ferric gluconate
- Reimbursement – only iron dextran approved for iron deficiency anemia secondary to nonrenal diseases
- Time – replace total iron stores with 1 dose or multiple doses (days to weeks)

Parenteral Iron Preparations

Iron Preparation	Indication	Dose
DexFerrum[®] (high-molecular-weight iron dextran) <i>American Regent</i>	Documented iron deficiency in which oral administration is unsatisfactory or impossible	100 mg elemental iron IVP daily until total dose of elemental iron replaced;
INFeD[®] (low-molecular-weight iron dextran) <i>Watson-Pharma</i>		consider test dose (25 mg or 0.5 mL)

IVP = intravenous bolus.

DexFerrum (iron dextran injection, USP) [package insert]. Shirley, NY: American Regent, Inc.;

INFeD (iron dextran injection USP) [package insert]. Morristown, NJ: Watson Pharma, Inc.

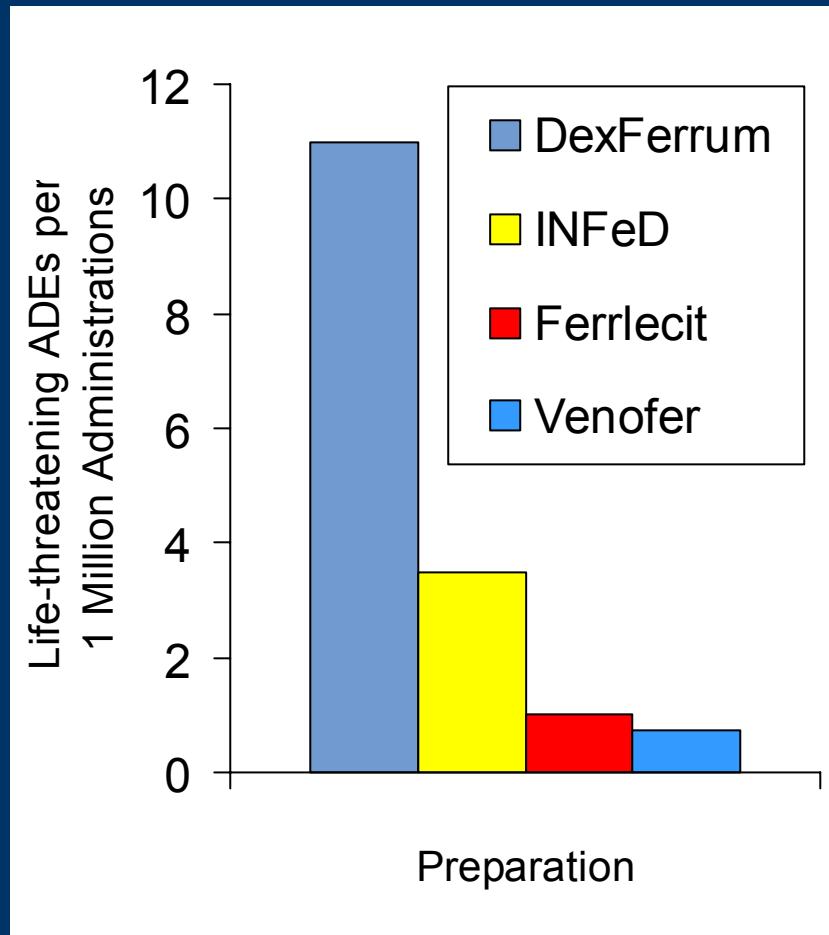
Parenteral Iron Preparations

Iron Preparation	Indication	Dose
Ferrlecit[®] (sodium ferric gluconate) <i>Watson-Pharma</i>	IDA in adults undergoing chronic HD with supplemental ESA therapy	125 mg elemental iron IVP or in 100 mL NS IVPB over 1 hour x 8 consecutive dialysis sessions
Venofer[®] (iron sucrose) <i>American Regent</i>	IDA in adults with CKD undergoing chronic HD or PD receiving ESA therapy or non-dialysis dependent patients with CKD receiving or not receiving ESA therapy	200 mg elemental iron IVP x 5 doses within 14 days

IDA = iron deficiency anemia; HD = hemodialysis; IVPB = intravenous infusion; CKD = chronic kidney disease; PD = peritoneal dialysis; NS = normal saline.

Ferrlecit (sodium ferric gluconate complex in sucrose injection) [package insert]. Morristown, NJ: Watson Pharma, Inc.; Venofer (iron sucrose injection, USP) [package insert]. Shirley, NY: American Regent, Inc.

Major Adverse Drug Events (ADEs) by Parenteral Iron Formulation – 1998 to 2003



- DexFerrum was associated with a 5.5-fold increase in ADEs versus INFeD
- DexFerrum was associated with a 3.4-fold increase in life-threatening ADEs versus INFeD

Dosing Regimens for Iron Dextran

- Multiple intravenous boluses
- Total dose infusion
 - Administer total dose of elemental iron needed to replace iron stores
 - Dilute iron dextran in 500 mL of 0.9% sodium chloride
 - Administer at 175 mL/hour (~3 hours)
 - Administer corticosteroid 30 minutes before and after dose (no antihistamines)
 - Consider test dose (0.5 mL or 25 mg)
- Multiple infusions
 - 250 mg IVPB in 100 mL 0.9% sodium chloride over 30 minutes

Why Is IV Iron Not More Actively Utilized in Oncology?

- No specific guidelines in oncology
- Lack of education and experience
- Not necessary before reimbursement and prescribing changes; safety concerns about ESA therapy
- Concerns and misconceptions about the safety of IV iron
- Not enough clinical studies...until now...

Summary

- Current practice guidelines advocate ESA therapy, but changes in reimbursement and prescribing of ESA therapy have occurred
- About 60% of anemic cancer patients have iron deficiency; most have functional iron deficiency
- Functional iron deficiency occurs when the body cannot use its iron stores needed for erythropoiesis
- Low-molecular weight iron dextran appears safe, inexpensive, and versatile compared with other parenteral iron formulations



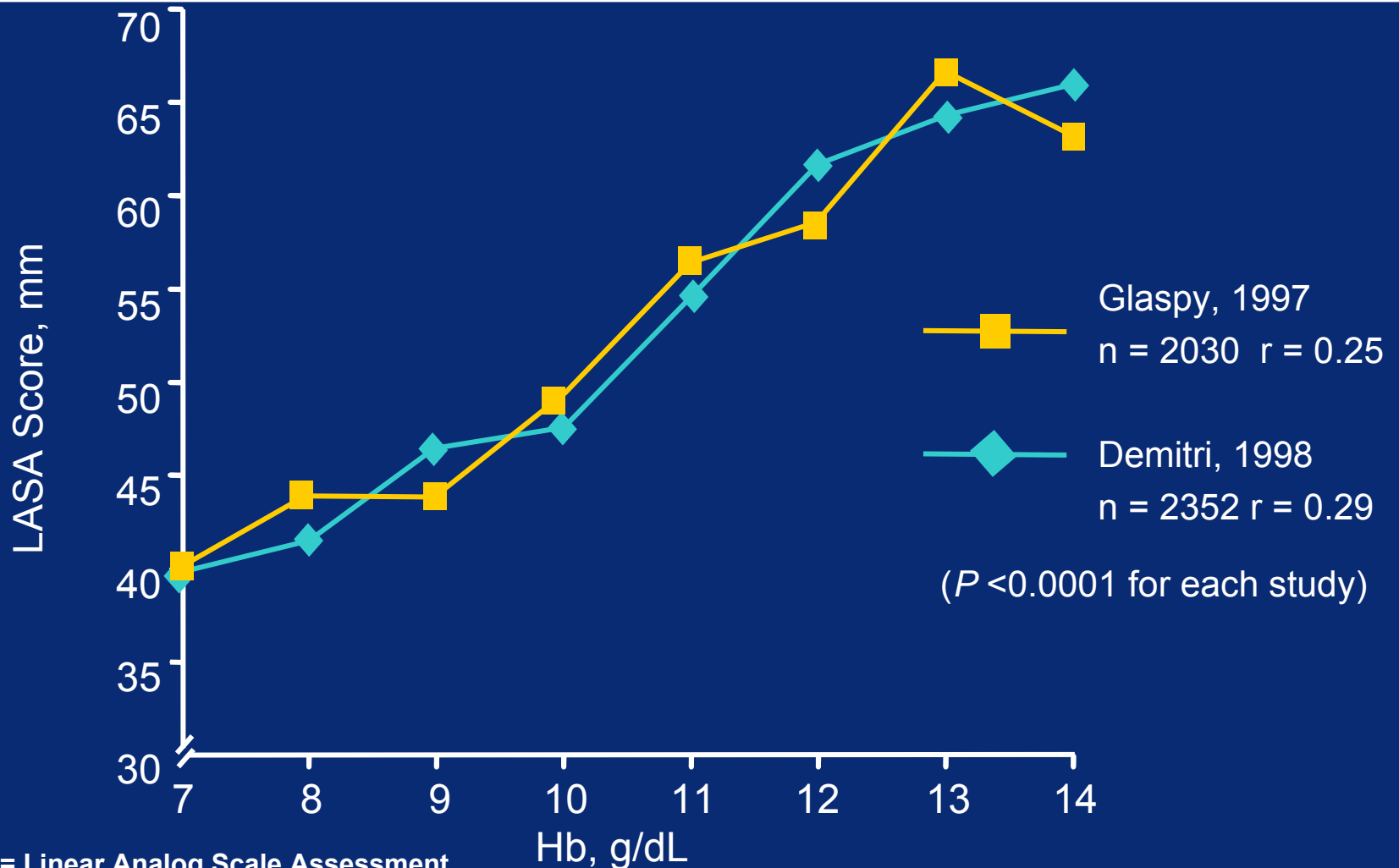
Clinical and Pharmacoeconomic Benefits of IV Iron

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Lecture Objectives

- **Compare and contrast the response rates to stimulated erythropoiesis based on baseline iron stores and iron repletion**
- **Evaluate the differences in ESA dosing required to accomplish Hb levels corresponding to improved QoL when using or when not using parenteral iron**

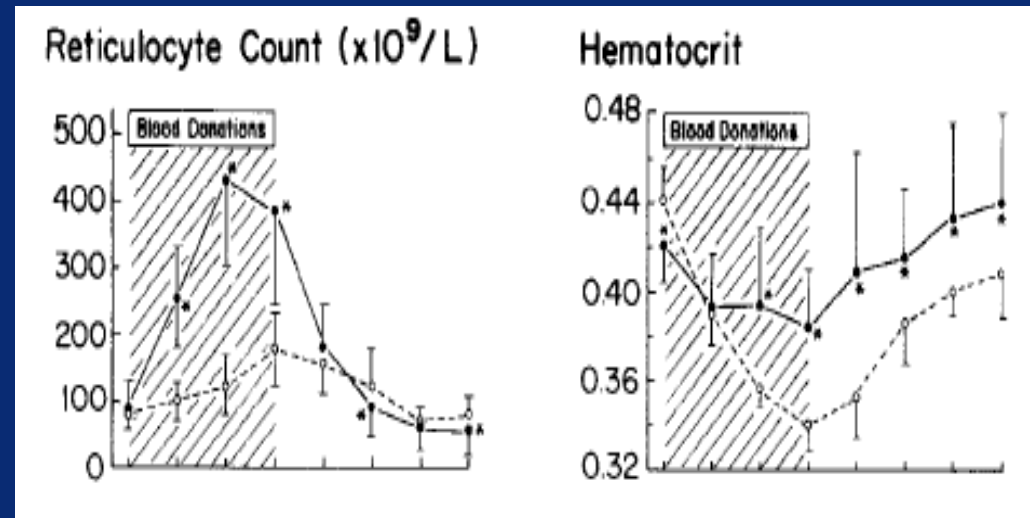
Correlation Between Hb Level and QOL in Cancer Patients



LASA = Linear Analog Scale Assessment.
Crawford J, et al. *Cancer*. 2002;95:888-95. Permission requested.

Stimulated Erythropoiesis: RBC Effects

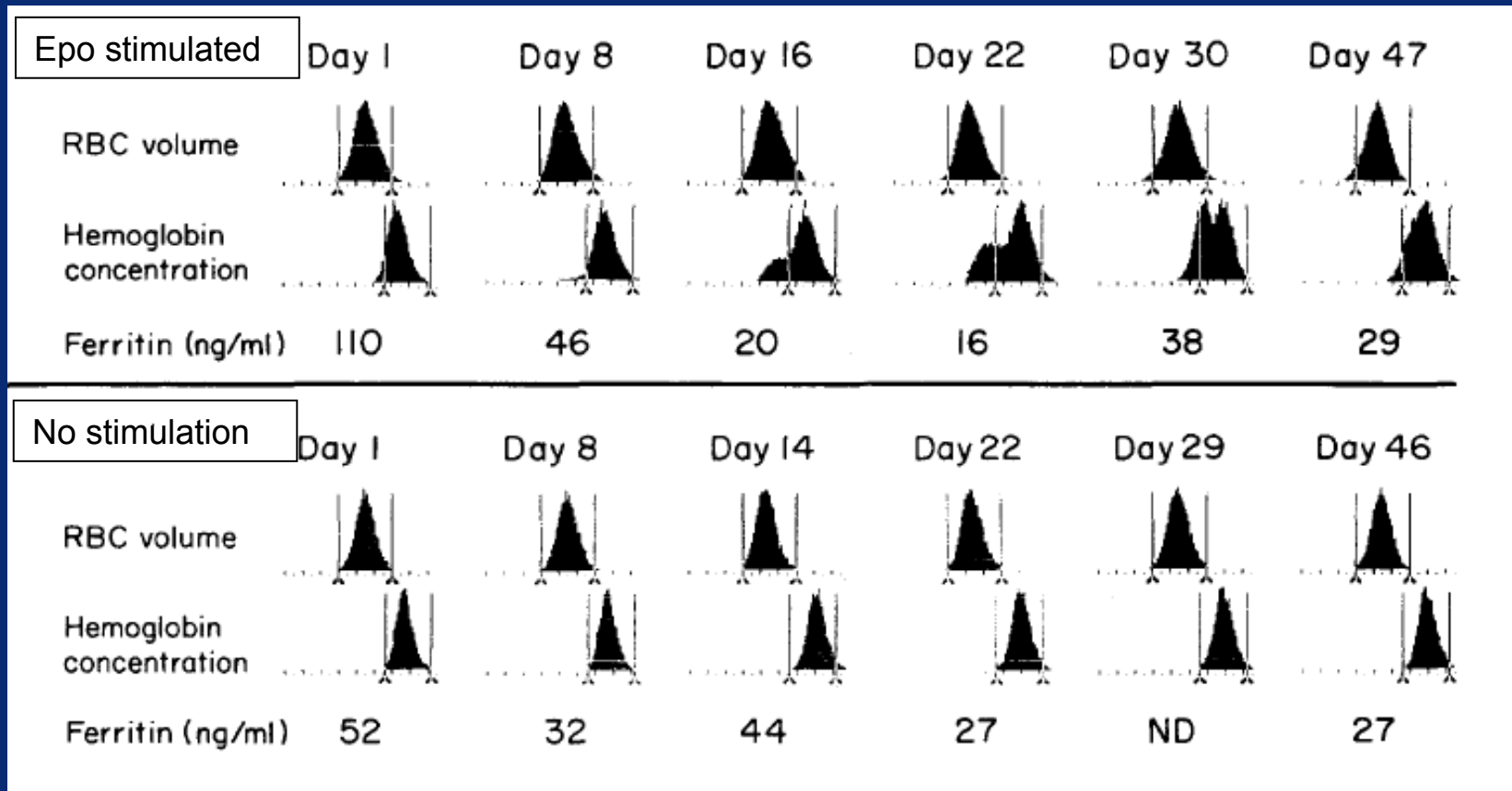
- Epo-stimulated blood donation vs nonstimulated
- All patients iron replete
- Oral iron supplementation
- Marked reticulocytosis
- Hemoglobin-deficient RBCs



Epo = erythropoietin; RBC = red blood cell.

This research was originally published *Blood*. Brugnara C, et al. *Blood*. 1993;81:956-64. © American Society of Hematology.

Stimulated Erythropoiesis: RBC Effects



Iron in Combination with ESAs

- **Significant experience with CKD population**
 - Financial incentives
- **Only 5 trials in the anemic oncology population**

Studies of IV Iron in Oncology

	No. of Patients	Study Period	Patient Population
Auerbach	157	6 weeks or until end bolus treatments	Nonmyeloid malignancy Chemotherapy
Henry	187	8 weeks	Nonmyeloid malignancy Starting cycle of chemotherapy
Hedenus	67	16 weeks	Lymphoproliferative malignancy No chemotherapy
Bastit	396	16 weeks	Nonmyeloid malignancy Chemotherapy
Pedrazzoli	149	12 weeks	Nonmyeloid malignancy Chemotherapy

IV = intravenous.

Auerbach M, et al. *J Clin Oncol*. 2004;22:1301-07; Henry DH, et al. *Oncologist*. 2007;12:231-42; Hedenus M, et al. *Leukemia*. 2007;21:627-32; Bastit L, et al. *J Clin Oncol*. 2008;26:1611-8; Pedrazzoli P, et al. *J Clin Oncol*. 2008;26:1619-25.

Studies of IV Iron in Oncology (cont.)

Inclusion Criteria

	TSAT/Serum Ferritin	Hb	ESA Dosing
Auerbach	Ferritin ≤ 200 ng/mL or ferritin ≤ 300 ng/mL plus TSAT $\leq 19\%$	≤ 10.5 g/dL	Epoetin alfa 40,000 U/week No dose adjustments
Henry	Ferritin ≥ 100 ng/mL or TSAT $> 15\%$; ferritin < 900 ng/mL and TSAT $< 35\%$	< 11 g/dL	Epoetin alfa 40,000 U/week Dose \uparrow allowed after 4 weeks
Hedenus	Ferritin < 800 ng/mL Stainable iron in bone marrow	9–11 g/dL	Epoetin beta 30,000 U/week Dose adjustments
Bastit	Ferritin > 10 ng/mL < 800 ng/mL TSAT $> 15\%$	< 11 g/dL	Darbepoetin alfa 500 μg Q3
Pedrazzoli	Ferritin > 100 ng/mL <i>and</i> TSAT $> 20\%$	< 11 g/dL	Darbepoetin alfa 150 μg /week

TSAT = transferrin saturation.

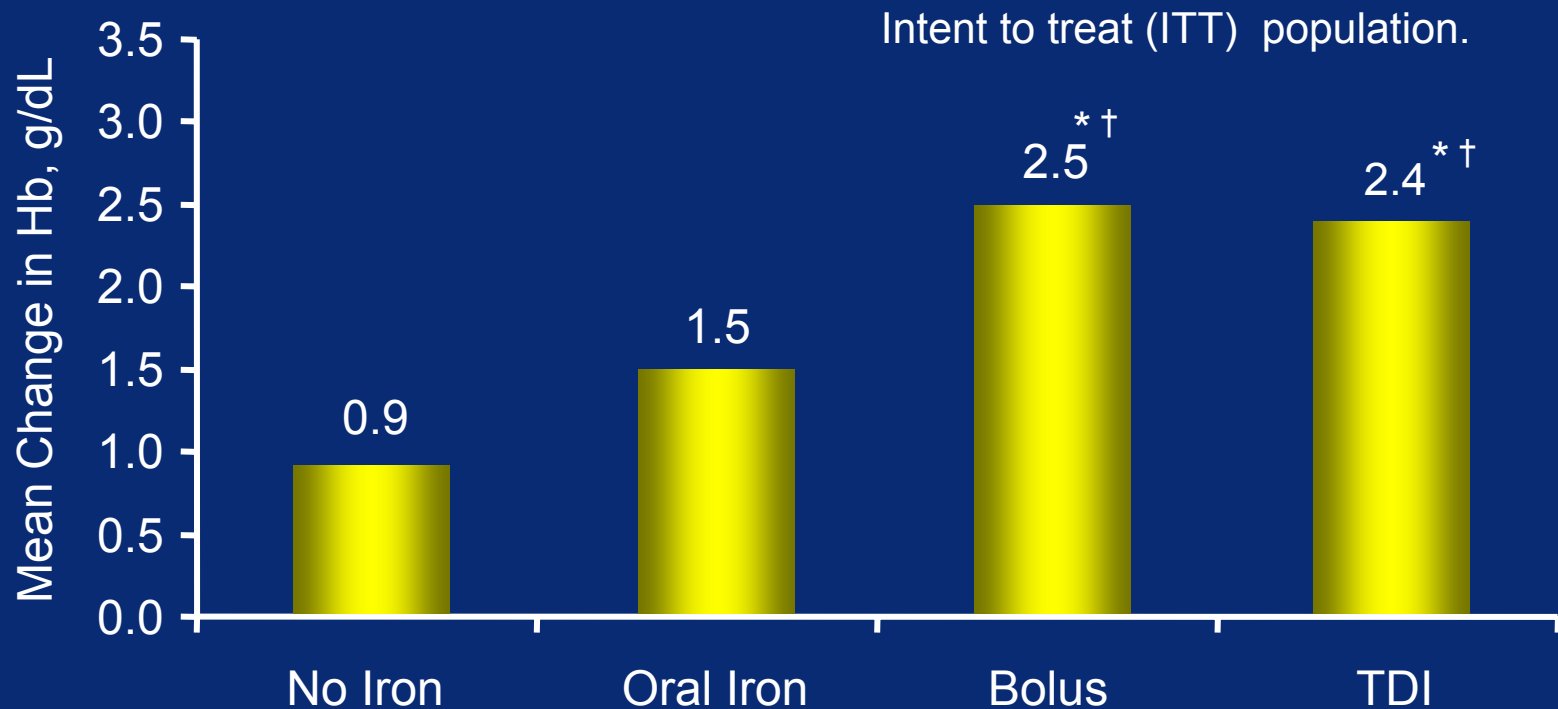
Auerbach M, et al. *J Clin Oncol*. 2004;22:1301-07; Henry DH, et al. *Oncologist*. 2007;12:231-42; Hedenus M, et al. *Leukemia*. 2007;21:627-32; Bastit L, et al. *J Clin Oncol*. 2008;26:1611-8; Pedrazzoli P, et al. *J Clin Oncol*. 2008;26:1619-25.

Studies of IV Iron in Oncology (cont.)

	Treatment Arms	IV Iron	Overall Iron Dose
Auerbach	IV iron vs oral iron vs no iron	Iron dextran	1000–3000 mg (actual)
Henry	IV iron vs oral iron vs no iron	Ferric gluconate	990.9 mg (actual)
Hedenus	IV iron vs no iron	Iron sucrose	1000 mg (protocol)
Bastit	IV iron vs oral iron vs no iron	Ferric gluconate or iron sucrose	1000 mg
Pedrazzoli	IV iron vs oral iron vs no iron	Ferric gluconate	1000 mg

Auerbach M, et al. *J Clin Oncol.* 2004;22:1301-07; Henry DH, et al. *Oncologist.* 2007;12:231-42; Hedenus M, et al. *Leukemia.* 2007;21:627-32; Bastit L, et al. *J Clin Oncol.* 2008;26:1611-8; Pedrazzoli P, et al. *J Clin Oncol.* 2008;26:1619-25.

Mean Change in Hb



Overall changes from baseline, $P < 0.0001$. Overall difference between groups, $P < 0.0001$.

*Differs from no iron group, $P < 0.05$.

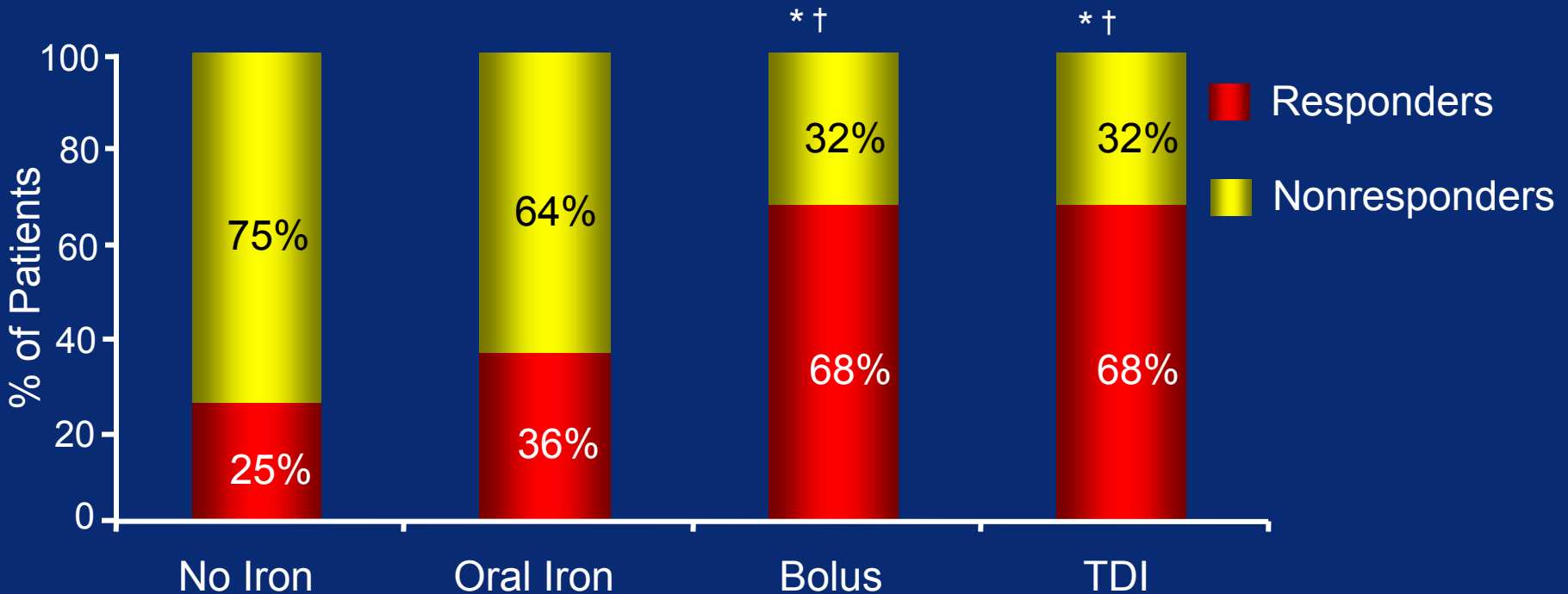
†Differs from oral iron group, $P < 0.05$.

TDI = total dose infusion.

Auerbach M, et al. *J Clin Oncol*. 2004;22:1301-07.

Erythropoietic Response

% of Patients With Peak Hb ≥ 12 g/dL
or Increase ≥ 2 g/dL

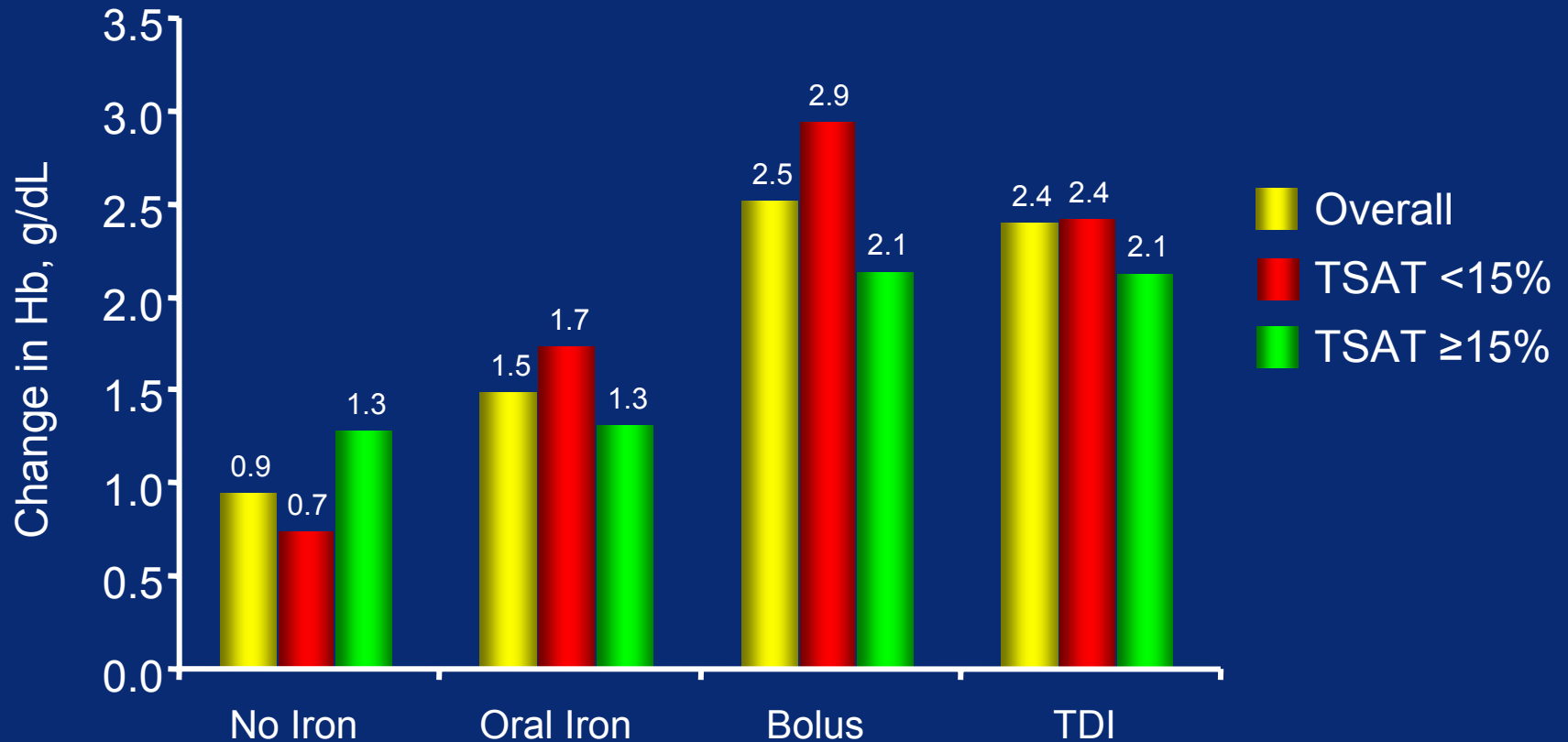


*Differs from no iron group, $P < 0.01$.

†Differs from oral iron group, $P < 0.01$.

ITT population.

Change in Hb: Stratified by TSAT

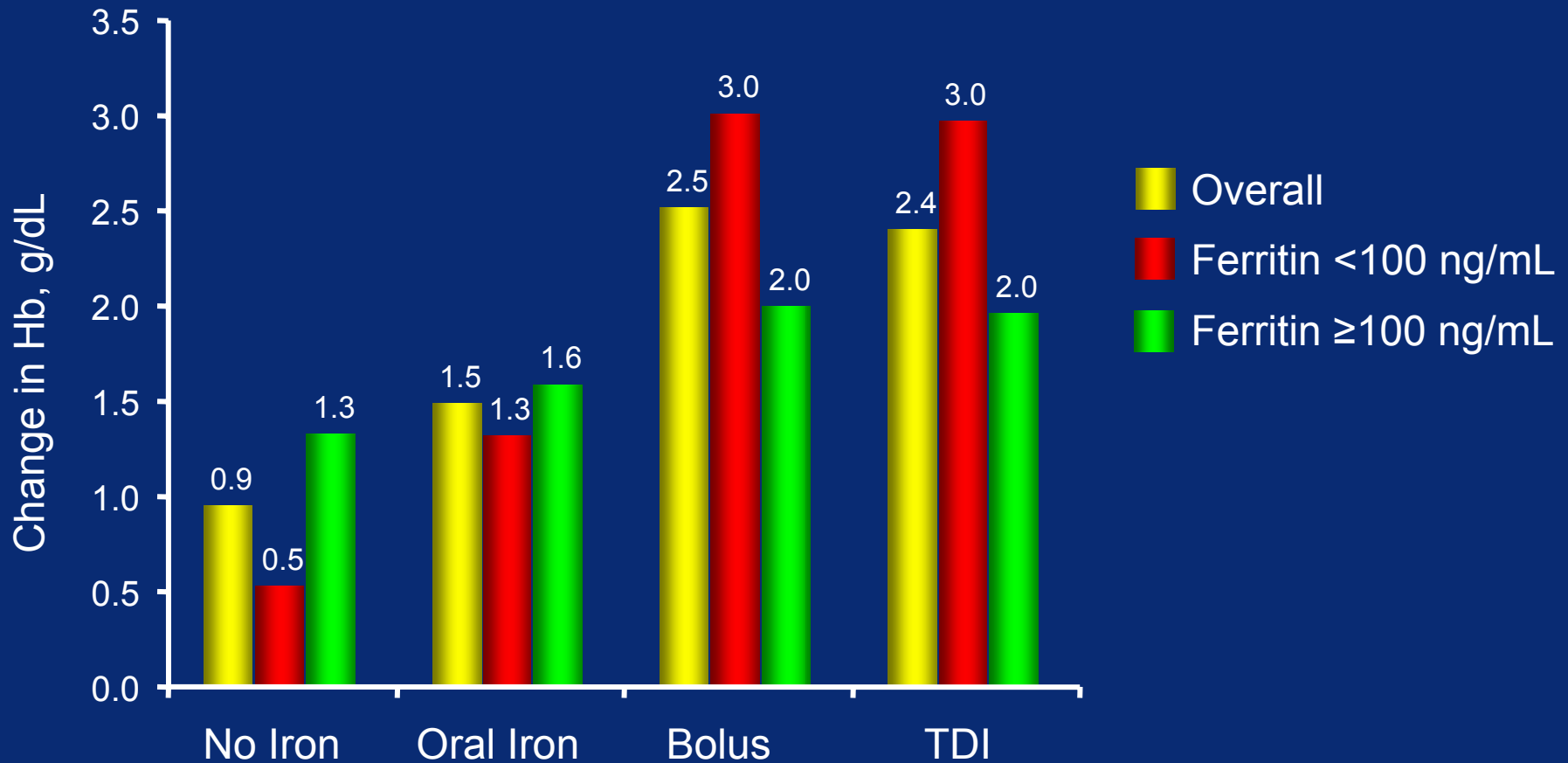


ITT population.

No significant differences in baseline Hb, $P = 0.73$.

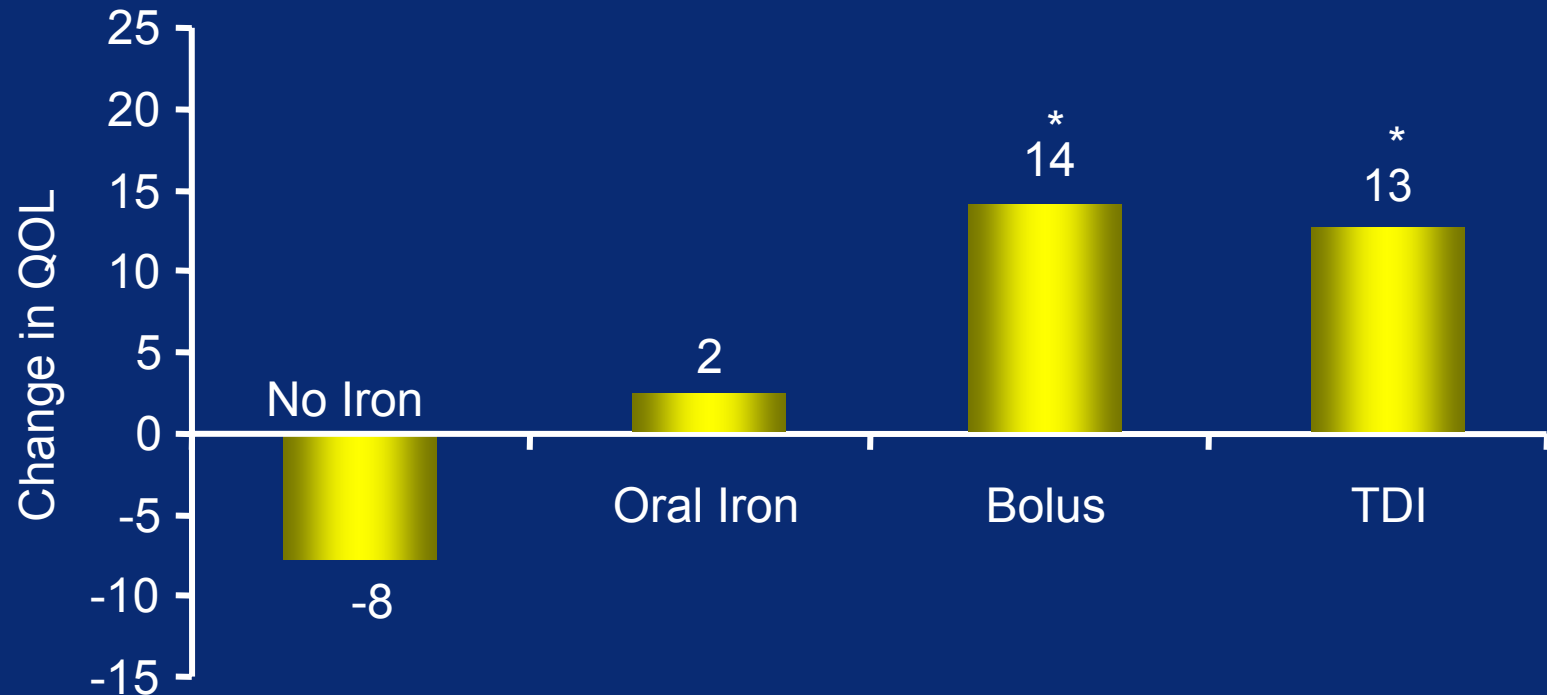
Auerbach M, et al. *J Clin Oncol*. 2004;22:1301-07.

Change in Hb: Stratified by Ferritin



ITT population.

Change in QOL



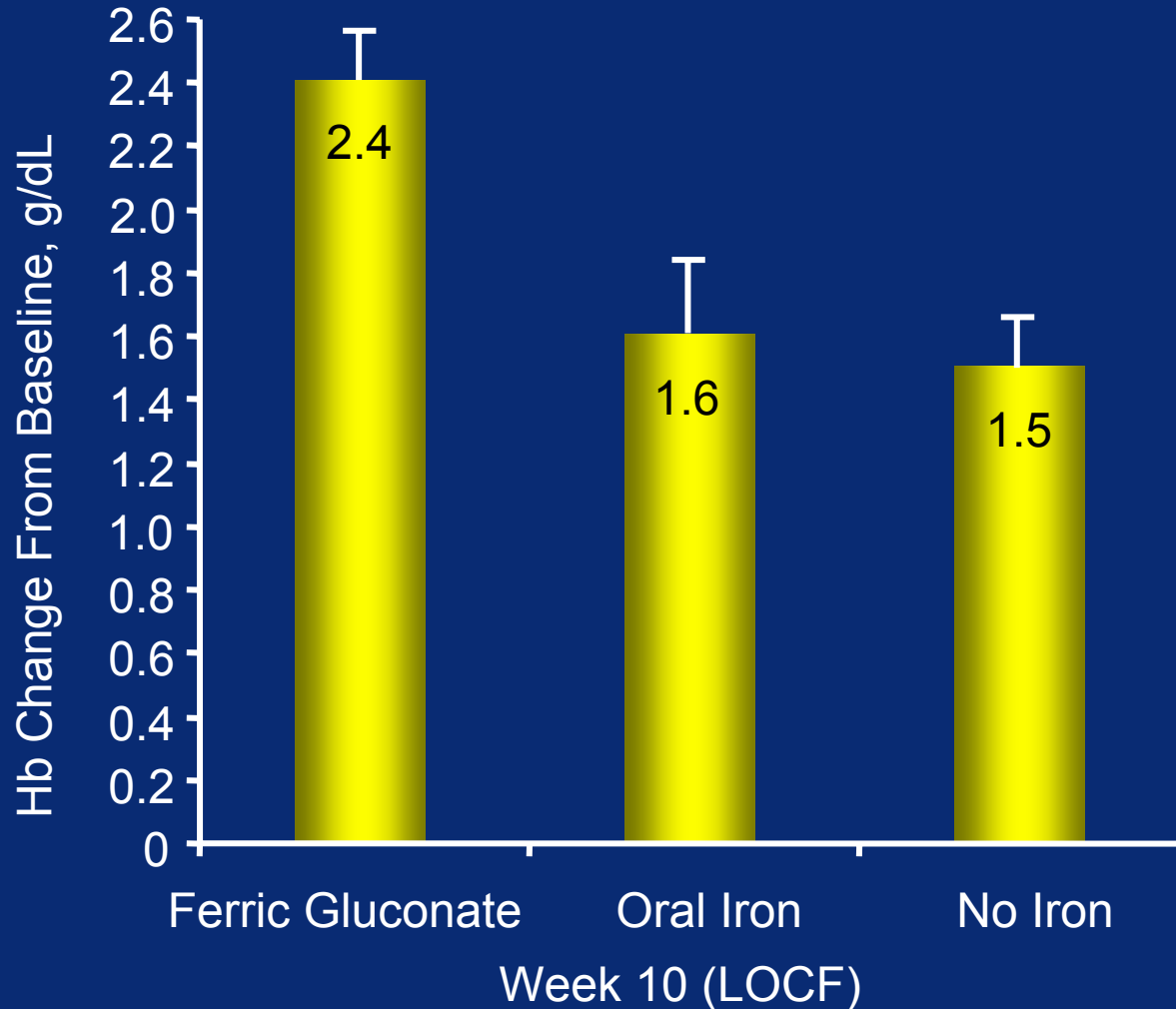
Overall, $P = 0.003$.

*Differs from no iron group, $P < 0.05$.

ITT population.

Auerbach M, et al. *J Clin Oncol*. 2004;22:1301-07. Adapted with permission from the American Society of Clinical Oncology.

Hb Change From Baseline (Evaluable Population)

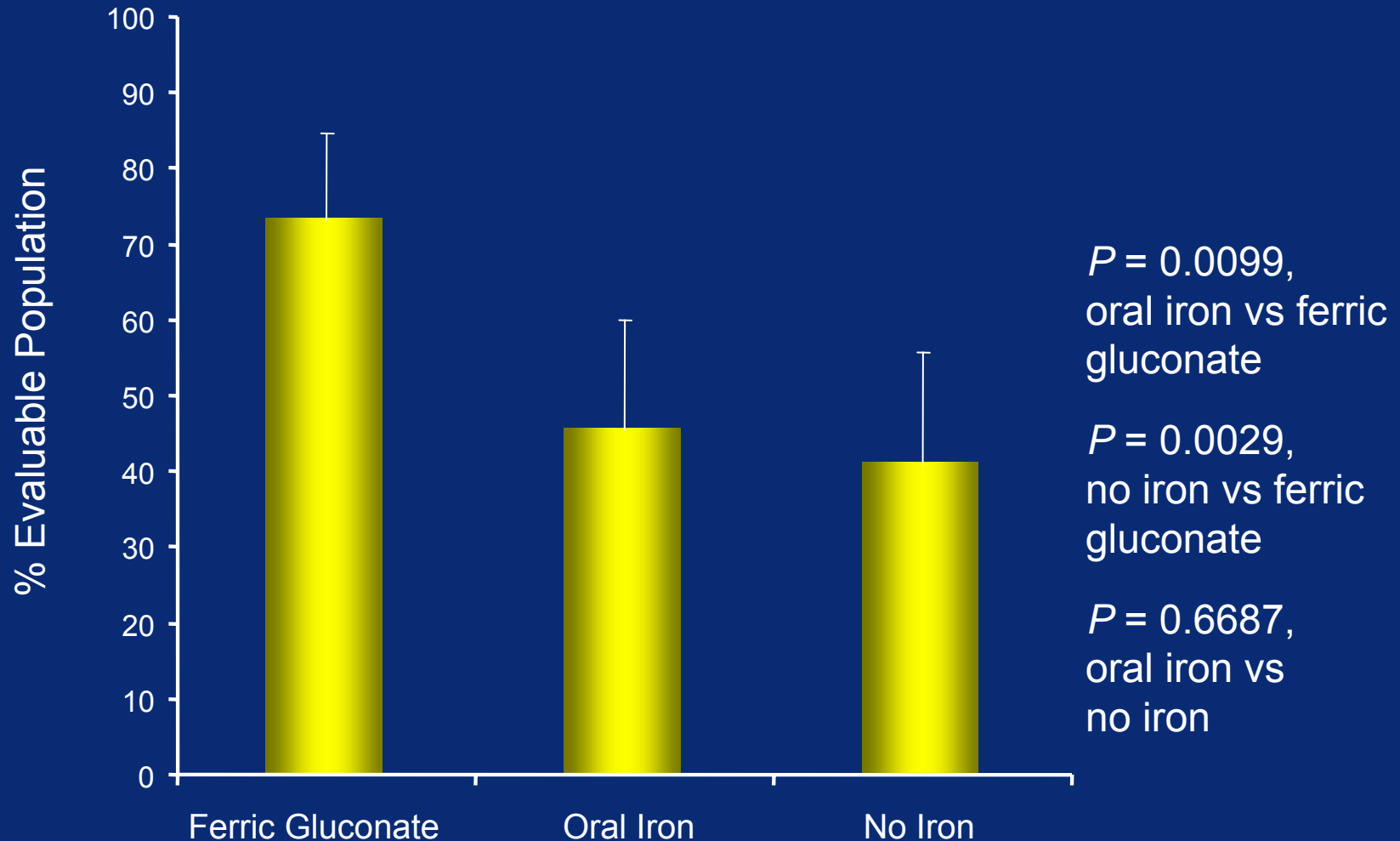


$P = 0.0092$,
oral iron vs ferric
gluconate

$P = 0.0044$,
no iron vs ferric
gluconate

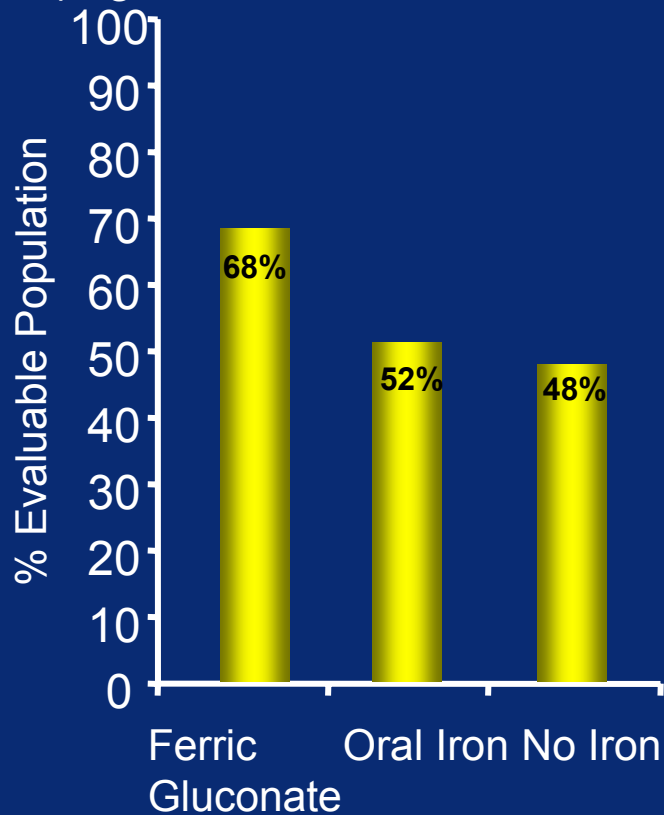
$P = 0.7695$, oral
iron vs no iron

Hb Responder Rate (Evaluable): Change From Baseline Hb ≥ 2 g/dL

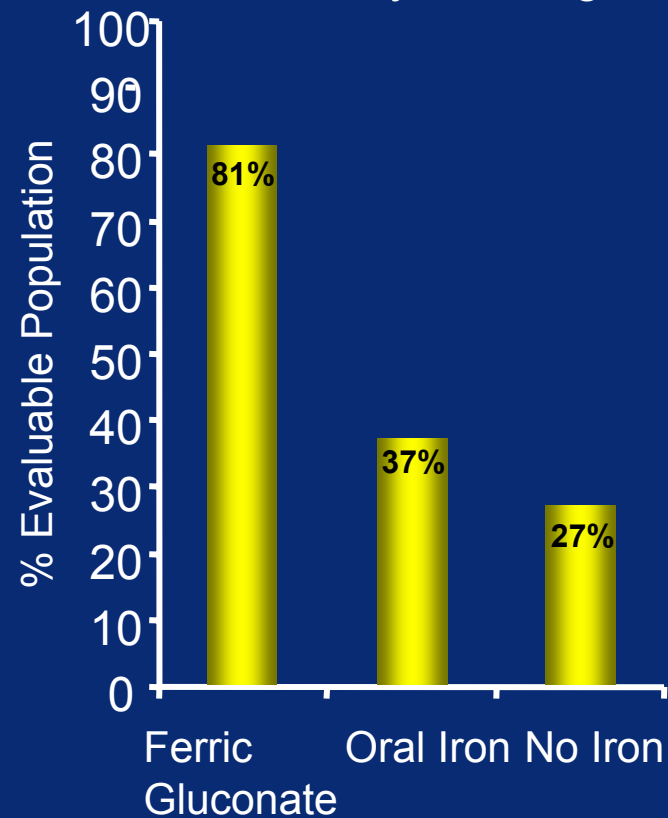


Hb Responder by Baseline TSAT (Evaluable Population)

CFB Hb ≥ 2 g/dL; baseline TSAT $\geq 20\%$
(regardless of serum ferritin level)



CFB Hb ≥ 2 g/dL; baseline TSAT $< 20\%$
(serum ferritin mostly > 100 ng/mL)

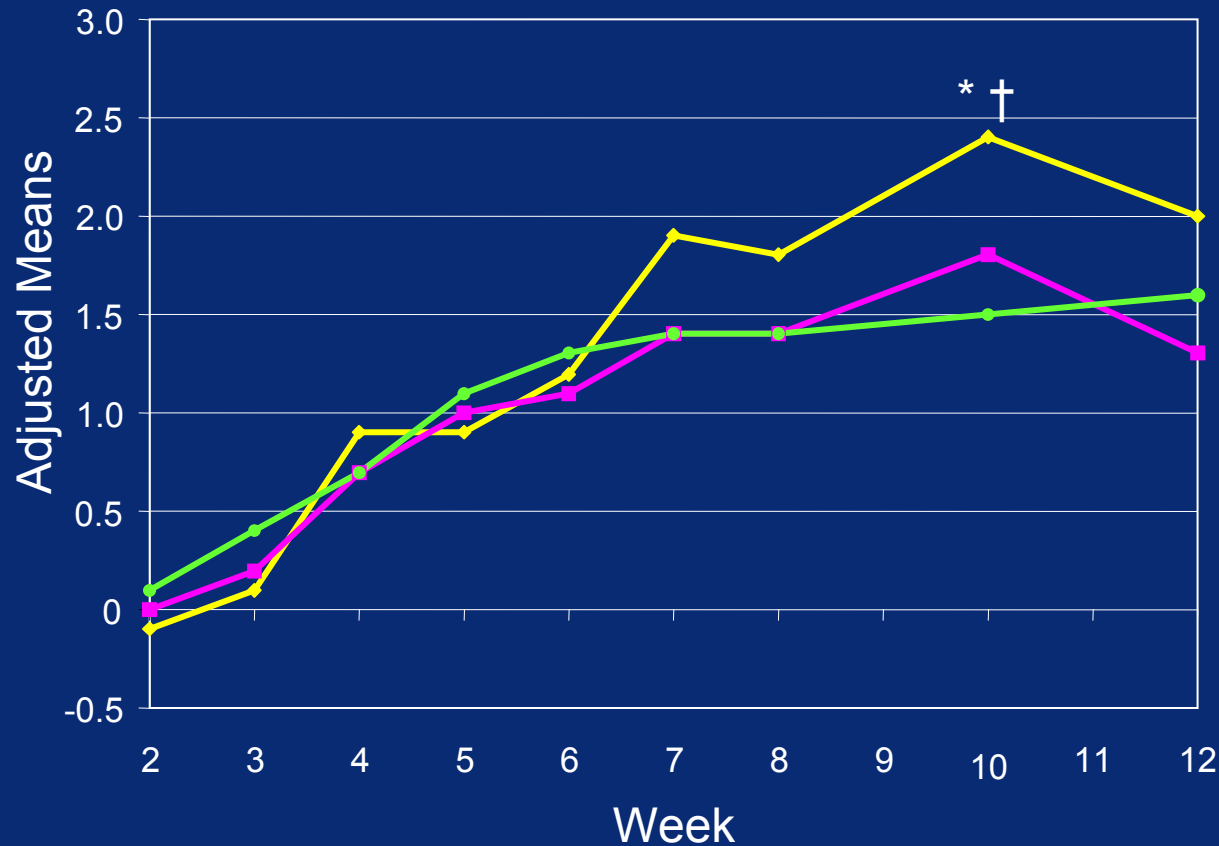


CFB = change from baseline.
Henry DH, et al. *Oncologist*. 2007;12:231-42.

$P = 0.0091$, oral iron vs ferric gluconate
 $P = 0.0027$, no iron vs ferric gluconate
 $P = 0.535$, oral iron vs no iron

Hb Response Profile Over Time (Evaluable Population)

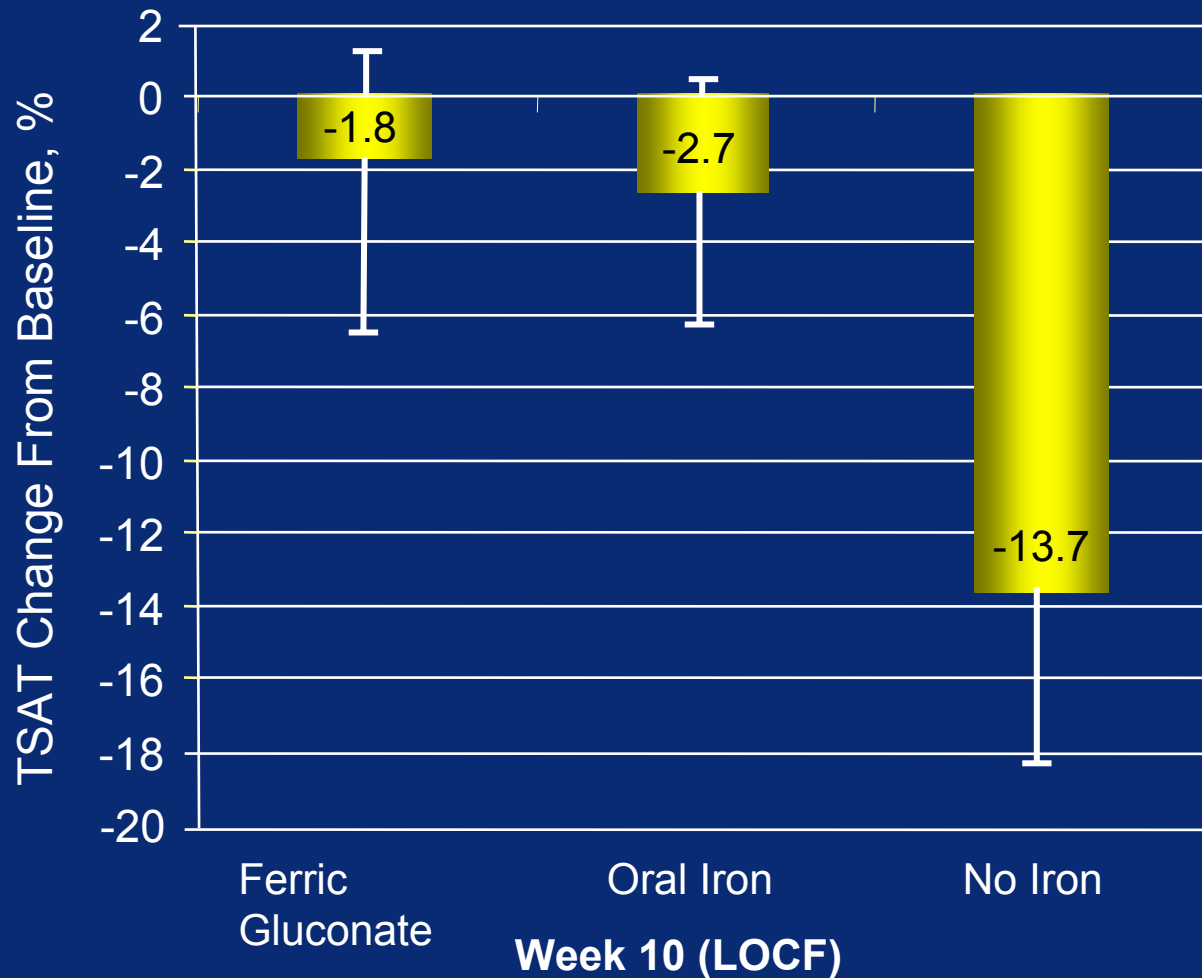
Hb Response Over Time



* $P = 0.0017$ vs
no iron
† $P = 0.0201$ vs
oral iron

—◆— Ferric Gluconate —■— Oral Iron —●— No Iron

TSAT Change From Baseline (Evaluable Population)

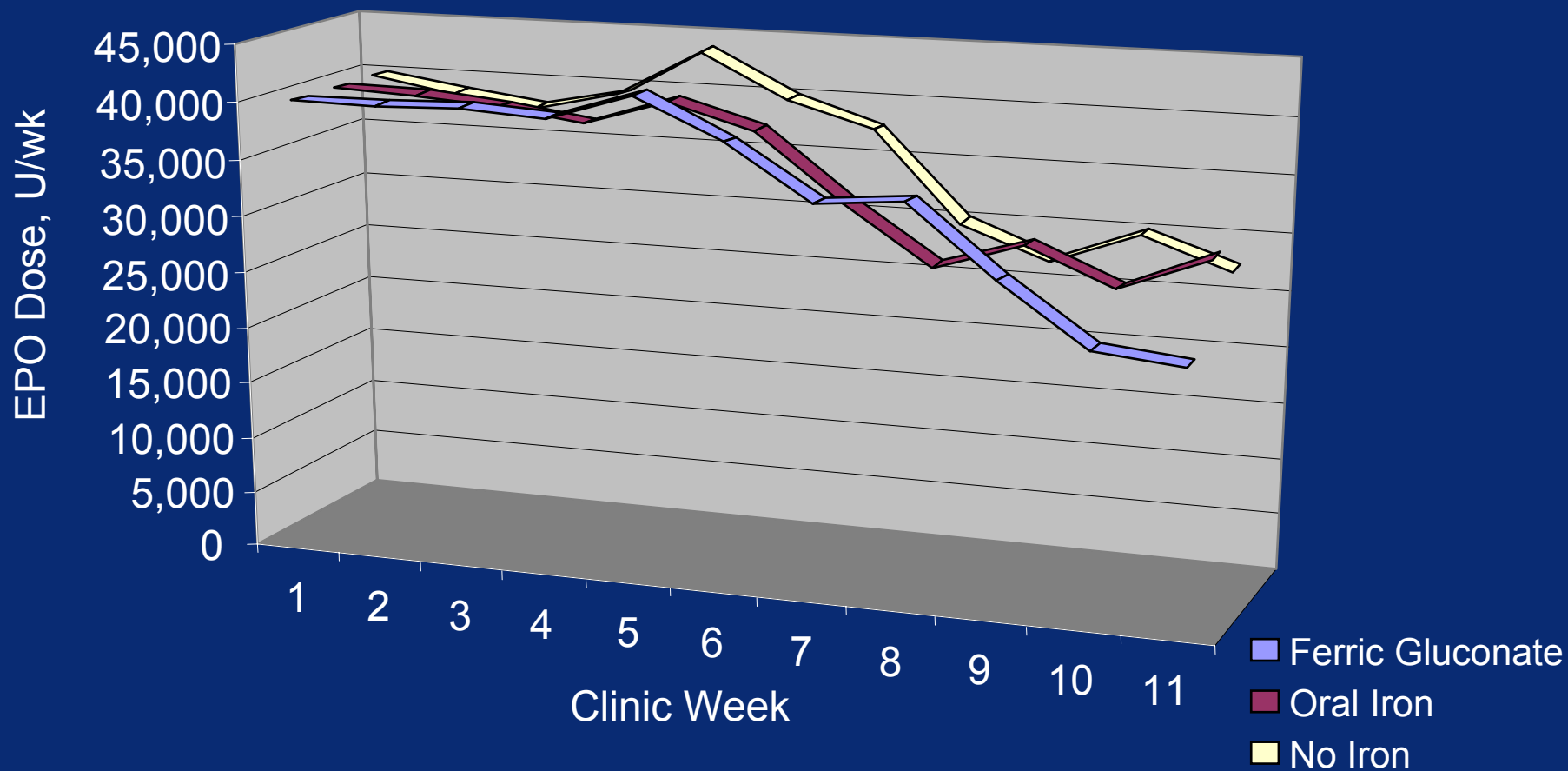


$P = 0.762$, oral iron vs ferric gluconate

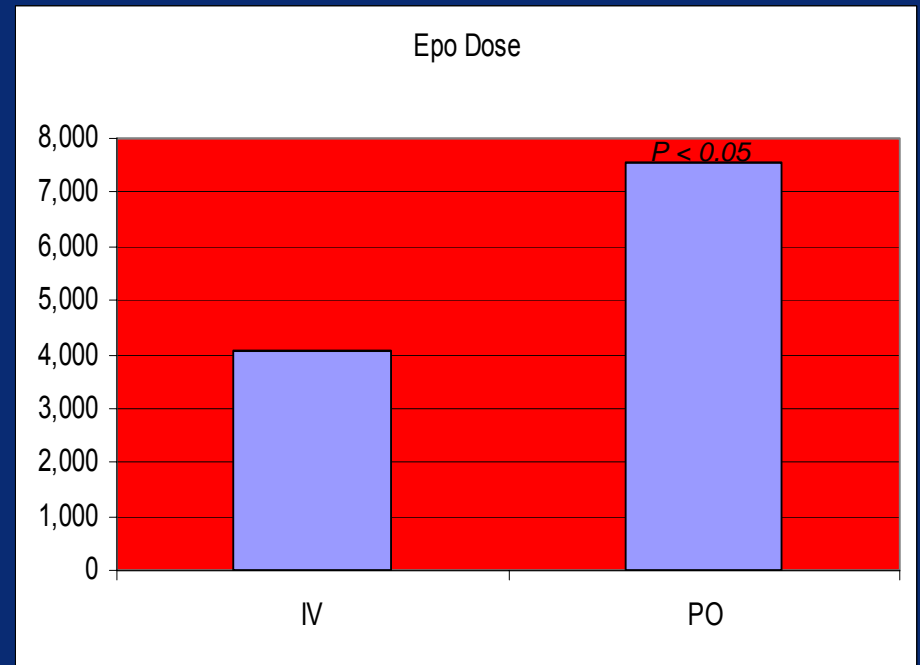
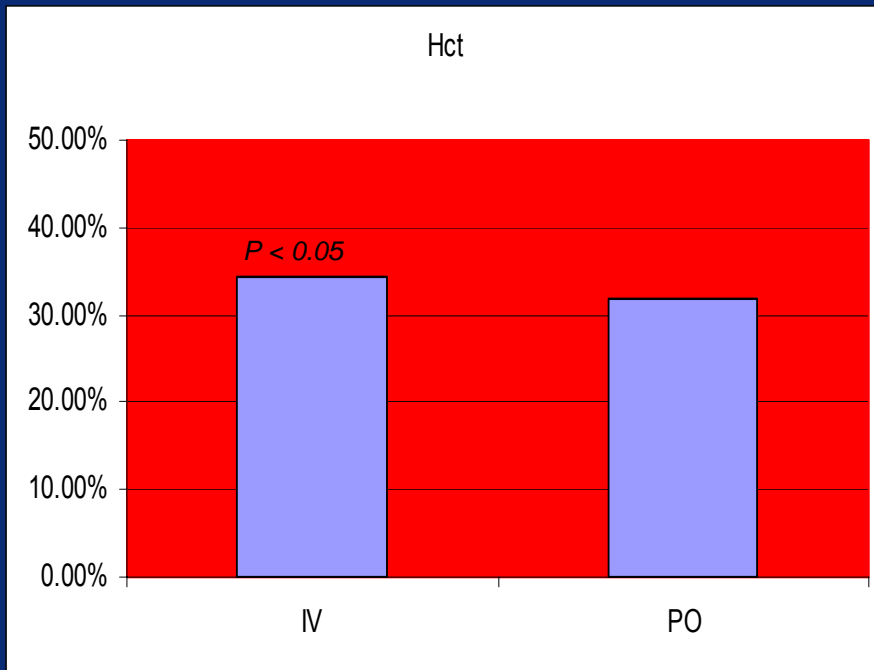
$P = 0.109$, no iron vs ferric gluconate

$P = 0.184$, oral iron vs no iron

Weekly EPO Dose (Evaluable Population)



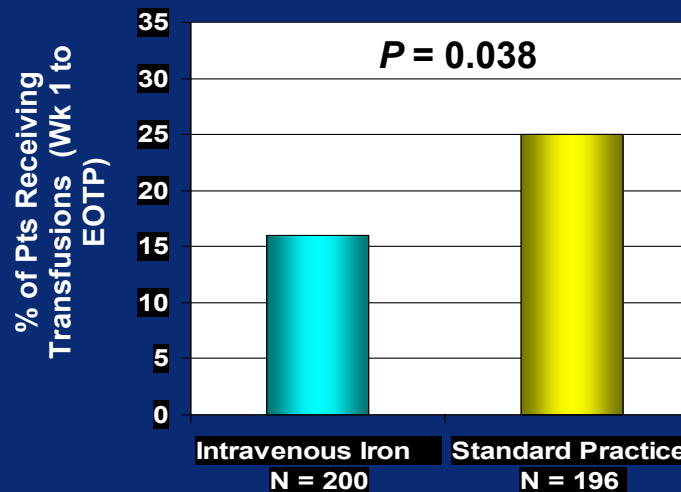
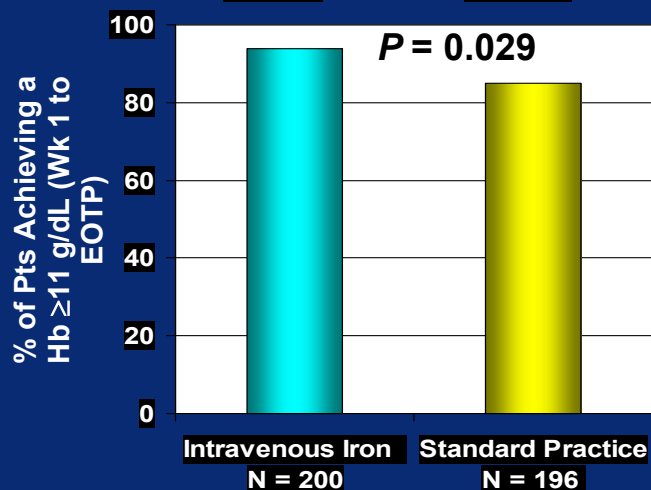
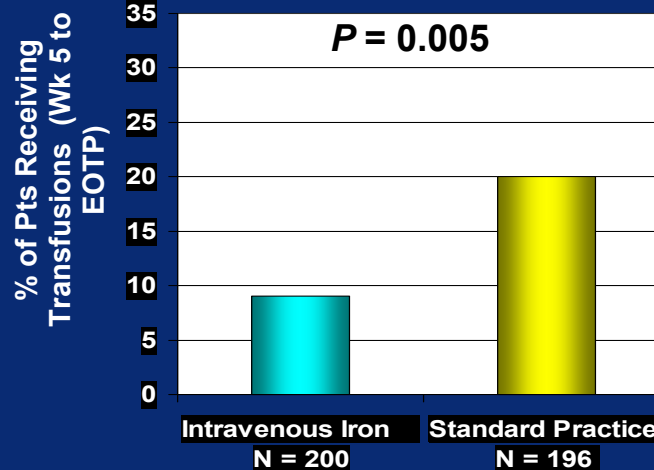
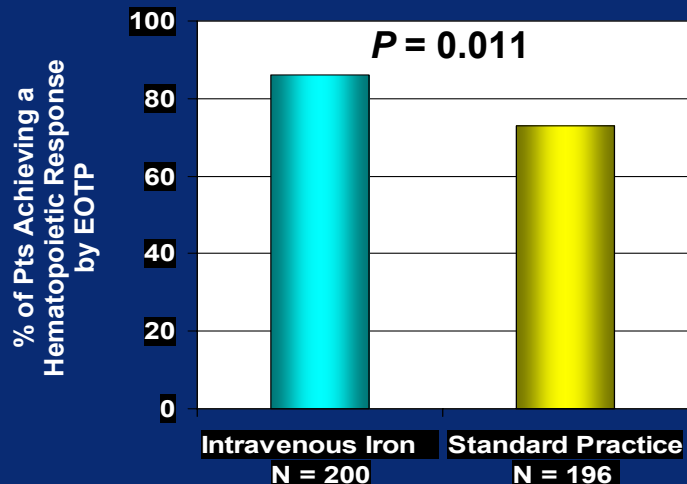
Iron in Hematopoiesis



Hct = hematocrit; PO = by mouth.
Fishbane S, et al. *Am J Kidney Dis.* 1995;26:41-6.

Iron Therapy and ESAs

Phase III RCT: IV iron* vs no iron in CIA managed with darbepoetin alfa Q3W



Hematopoietic response = achieved Hb ≥ 12 g/dL or \uparrow Hb ≥ 2 g/dL. *IV iron = sodium ferric gluconate in sucrose or iron sucrose injection; RCT = randomized, controlled trial; Bastit L, et al. *J Clin Oncol.* 2008;26:1611-18. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.

Iron Therapy and ESAs

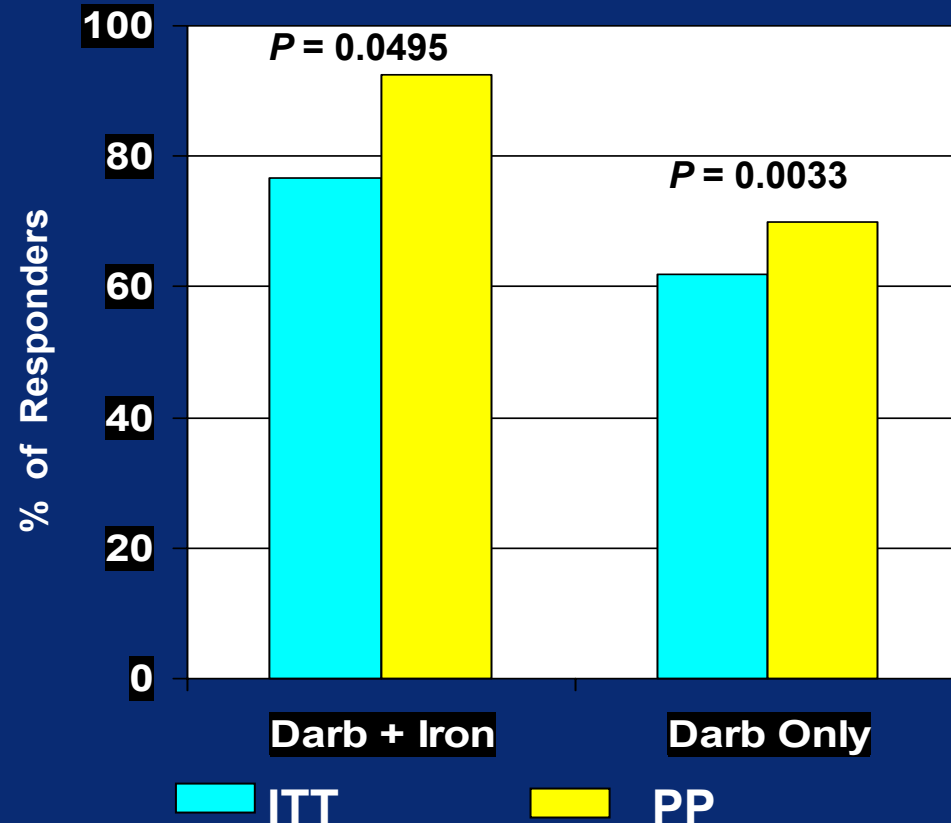
Primary end point = hematopoietic response*

- IV iron (ferric gluconate) vs no iron in CIA managed with darbepoetin alfa 150 mcg QW for 12 weeks
- N = 149, Hb \leq 11 g/dL (no functional or absolute iron deficiency)
- % of responders scientifically greater in iron + darbepoetin alfa group (ITT, PP)
- Significant \uparrow in Hb AUC in darbepoetin alfa + iron: ITT ($P = 0.025$) and PP ($P = 0.023$)
- Median time to target Hb was less for darbepoetin alfa + iron vs darbepoetin alfa alone (NS)

* Hematopoietic response = achieved Hb \geq 12 g/dL or \uparrow Hb \geq 2 g/dL.

ITT = intent to treat; PP = per protocol; AUC = area under the curve.

Pedrazzoli P, et al. *J Clin Oncol*. 2008;26:1619-25. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.



Conclusions

- Increasing hemoglobin levels correlates with an increased QoL in anemic cancer patients
- Stimulated erythropoiesis, irrespective of baseline iron status, requires concomitant administration of *parenteral* iron to be effective
- Use of parenteral iron in combination with ESAs could lead to dramatic reductions in ESA use, effecting equivalent results