

VIIENNA

Optimal Hemoglobin Management

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Signs and Symptoms of Anemia

CNS

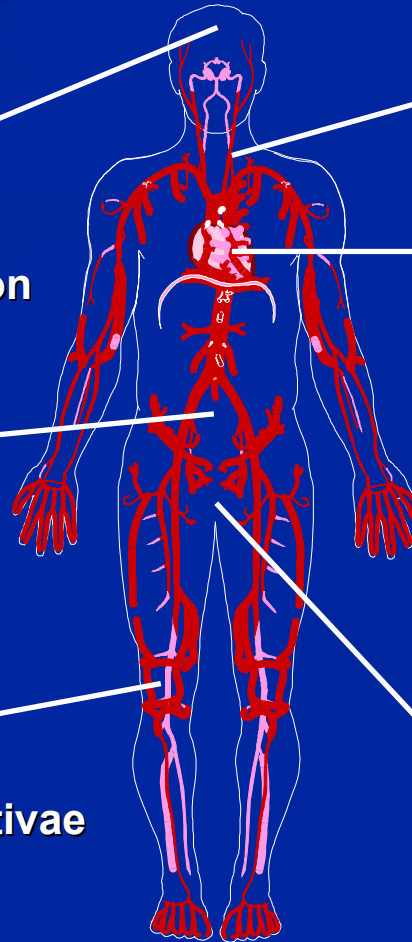
- Debilitating fatigue
- Dizziness, vertigo
- Depression
- Impaired cognitive function

Gastrointestinal system

- Anorexia
- Nausea

Vascular system

- Low skin temperature
- Pallor of skin, mucous membranes, and conjunctivae



Immune system

- Impaired T-cell and macrophage function

Cardiorespiratory system

- Exertional dyspnea
- Tachycardia, palpitations
- Cardiac enlargement, hypertrophy
- Increased pulse pressure, systolic ejection murmur
- Risk of life-threatening cardiac failure

Genital tract

- Menstrual problems
- Loss of libido

Co-Factors Influencing the Clinical Symptoms of Anemia

■ Patient/Malignancy

- Advanced age
- Comorbidity
- Uncontrolled underlying malignancy
- Organ impairment by the tumor
- Hemolysis

■ Therapy

- Overall treatment toxicity
- Cardiotoxicity
- Pulmonary toxicity
- Infection
- Bleeding

WHO Criteria for Assessment of Therapy-Induced Toxicity: Anemia

Severity of anemia	Hb range
Grade 0	≥ 11.0 g/dL
Grade 1	9.5-10.9 g/dL
Grade 2	8.0-9.4 g/dL
Grade 3	6.5-7.9 g/dL
Grade 4	< 6.5 g/dL

NCI Criteria for Assessment of Therapy-Induced Toxicity: Anemia

Severity of anemia	Hb range
Grade 0	WNL*
Grade 1 (mild)	10.0 g/dL to WNL*
Grade 2 (moderate)	8.0-10.0 g/dL
Grade 3 (serious/severe)	6.5-7.9 g/dL
Grade 4 (life threatening)	<6.5 g/dL

NCI = National Cancer Institute.

*WNL = within normal limits (Hb: 12.0-16.0 g/dL for women and 14.0-18.0 g/dL for men).

Transfusion in the Treatment of Anemia

- Cancer-related anemia has **historically** been treated with blood transfusion
- **Well-known risks** of transfusion include infectious disease transmission, allergic reactions, noncardiogenic pulmonary edema, alloimmunization, and hypervolemia
- Due to **limited supply and potential risk**, the use of blood transfusion is restricted to patients with severe anemia

Cancer and Treatment-Related Anemia

■ Before 1980

- Empiric RBC transfusion
- Hemoglobin (Hb) ≤ 10 g/dL

■ 1990s

- Approval of epoetin alfa
- Early data: benefits of anemia correction (quality of life [QOL])

■ 1980s

- Infection risks/shortages
- Transfusion guidelines
- Moderate/severe anemia
- Hb ≤ 8 g/dL

■ 2000s

- Meta-analysis of transfusions
- Refinement of QOL tools, and cancer-related fatigue construct
- Evaluating outcome
- New agents

Need for evidence-based guidelines

Use of Epoetin Alfa in Patients with Cancer: Evidence-Based Guidelines

ASH/ASCO Guidelines

- Epoetin alfa recommended for patients with CT-associated anemia and a Hb level ≤ 10 g/dL
- For patients with declining Hb levels but less severe anemia (Hb: 10–12 g/dL), epoetin alfa treatment should be determined by clinical circumstances

Use of Epoetin Alfa in Patients with Cancer: Evidence-Based Guidelines

National Comprehensive Cancer Network (NCCN) Guidelines

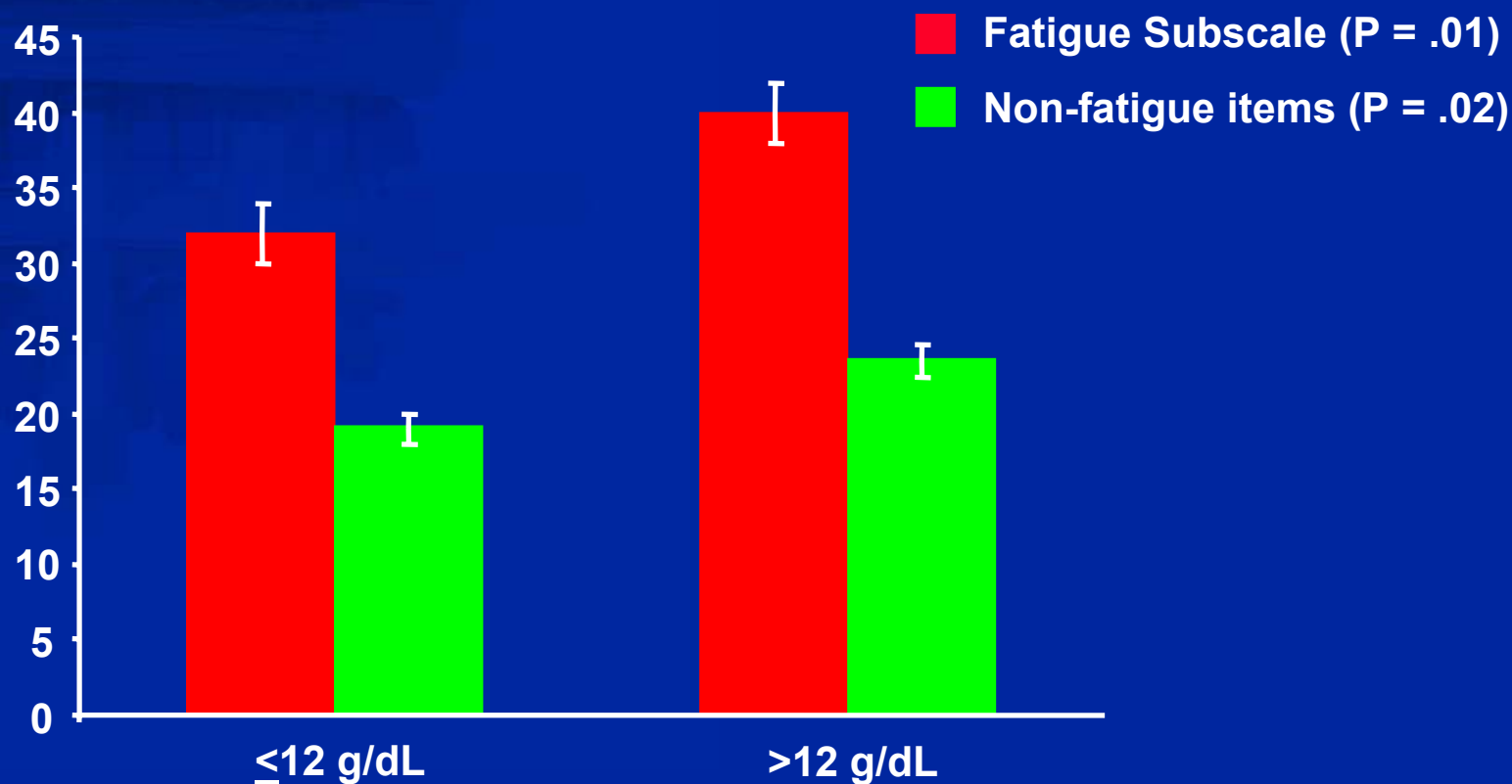
- Epoetin alfa recommended for patients with CT-associated anemia and a Hb level ≤ 10 g/dL
- For patients with Hb between 10 and 11 g/dL, epoetin alfa therapy should be considered.

Correlation of Anemia with QOL in Cancer Patients

- Pts with Hb >12 g/dL
 - ↓ fatigue ($P = 0.01$)
 - ↓ non-fatigue anemia symptoms (dizziness, H/A, SOB, CP, etc) ($P = 0.02$)
 - ↑ physical well-being ($P = 0.003$)
 - ↑ ability to participate in ADLs ($P = .001$)
 - ↑ general QOL ($P = 0.003$)
- Hb \leq 12 g/dL associated with
 - ↓ capacity to work ($P = 0.05$)
 - ↓ enjoyment of leisure activities
- Instruments: FACT-G Total; FACT- An Fatigue subscale; FACT- An

Relationship of Anemia to Fatigue

Mean Fatigue Subscale* and Nonfatigue Item* Scores by Hb Level



*Components of the Functional Assessment of Cancer Therapy-Anemia (FACT-An) instrument

Incremental Analysis

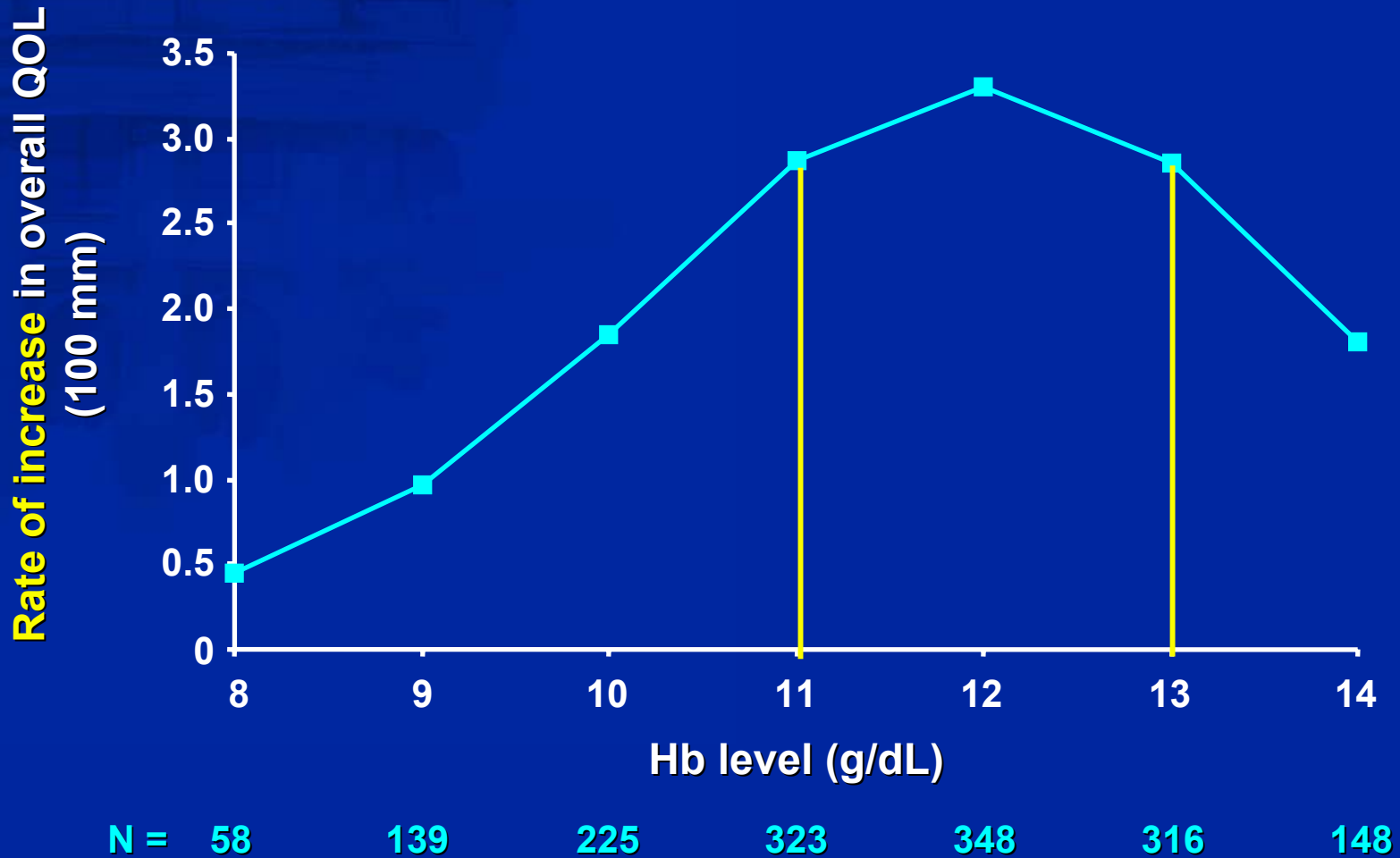
Multivariate regression analysis of data from multiple trials of epoetin alfa 3 times weekly (tiw) (N=4382)

- Examination of relationship between incremental change in hemoglobin (Hb) and change in patient-reported quality of life (QOL)

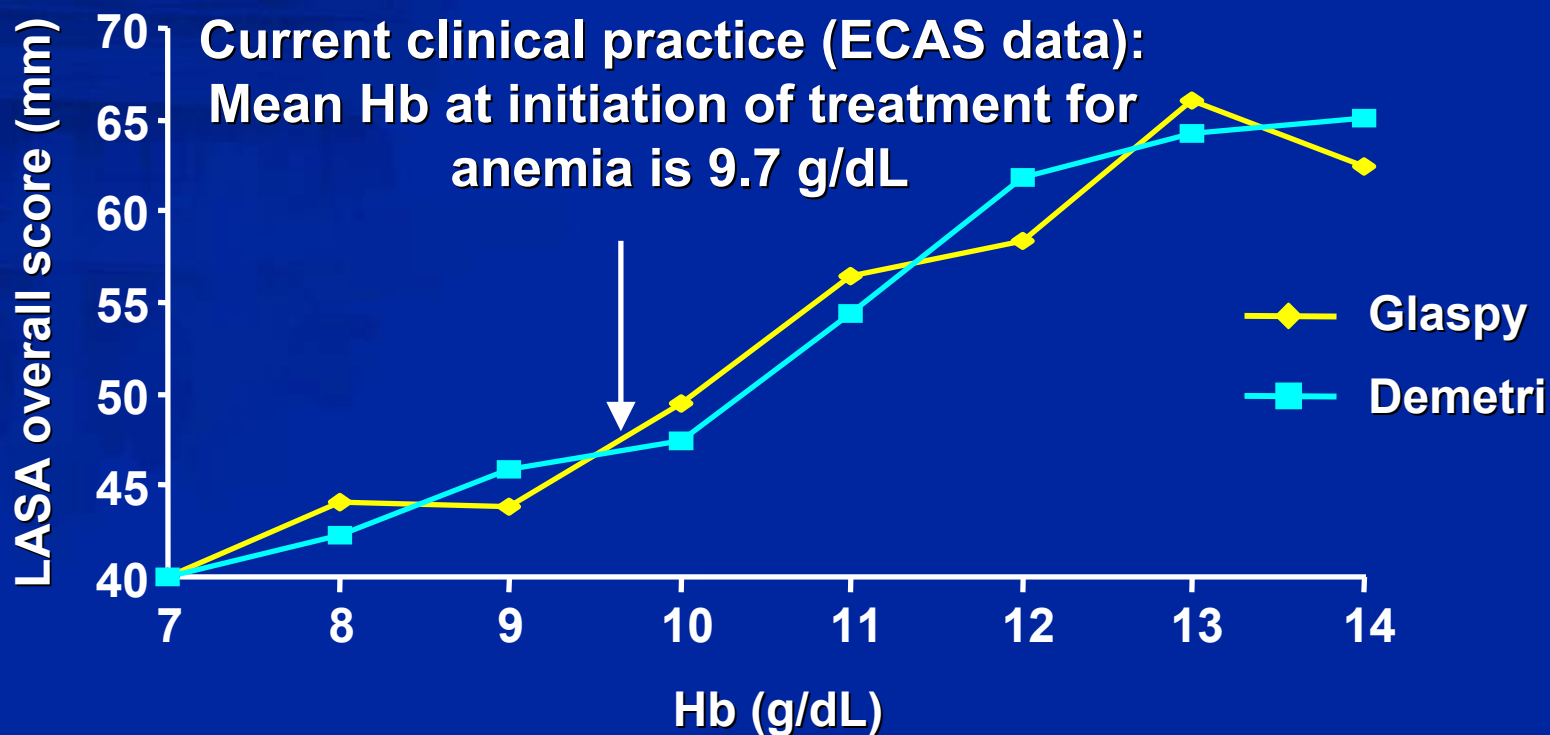
QOL instruments

- Linear Analog Scale Assessment (LASA, also known as Cancer Linear Analog Scale or CLAS): energy level, ability to do daily activities, and overall QOL
- Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale

Greatest QOL Improvement Peaks at Hb 12 g/dL (Increments Between 11 and 13 g/dL)



Does Increasing Hb Improve QOL?

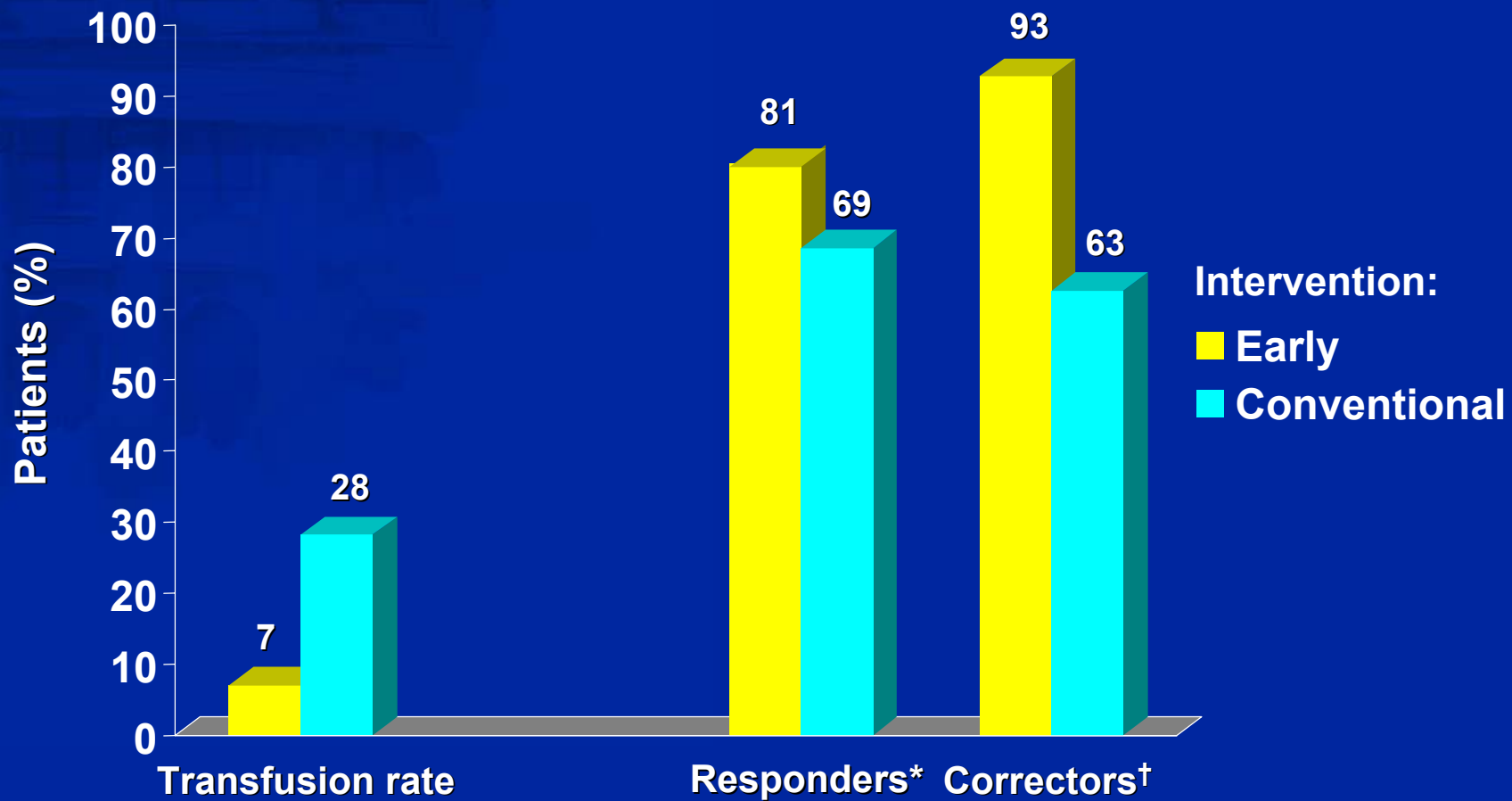


Glaspy (n)	181	551	818	680	472	345	221	114
Demetri (n)	118	497	812	931	515	286	278	125

Treatment of Mild-to-Moderate Anemia: Retrospective Analysis of a Randomized, Placebo-Controlled Trial

- Patients prospectively stratified by Hb level
 - early intervention (n=42)
 - treat at Hb >10.5 g/dL to ≤ 12 g/dL after a 1.5-g/dL Hb decrease per cycle since starting CT
 - conventional care (n=209)
 - treat at Hb ≤ 10.5 g/dL
- Transfusion use; Hb and QOL change from baseline

Treatment of Mild-to-Moderate Anemia: Hematologic Outcomes?



*Response: Hb increase of ≥ 2 g/dL without transfusion
†Correction: Attaining Hb ≥ 12 g/dL without transfusion

Littlewood (*J Clin Oncol* 2001)
Littlewood (ASH 2002)

Treatment of Mild-to-Moderate Anemia: What are the Clinical Benefits?

- Compared to treatment when Hb was <10.5 g/dL, earlier initiation of epoetin alfa therapy (Hb >10.5 but \leq 12 g/dL) resulted in:
 - higher Hb levels
 - greater response rates
 - lower transfusion rates
- Increased cost effectiveness: fewer patients in the higher vs the lower Hb stratum required doubling of their starting dosage (15% vs 25%, respectively)

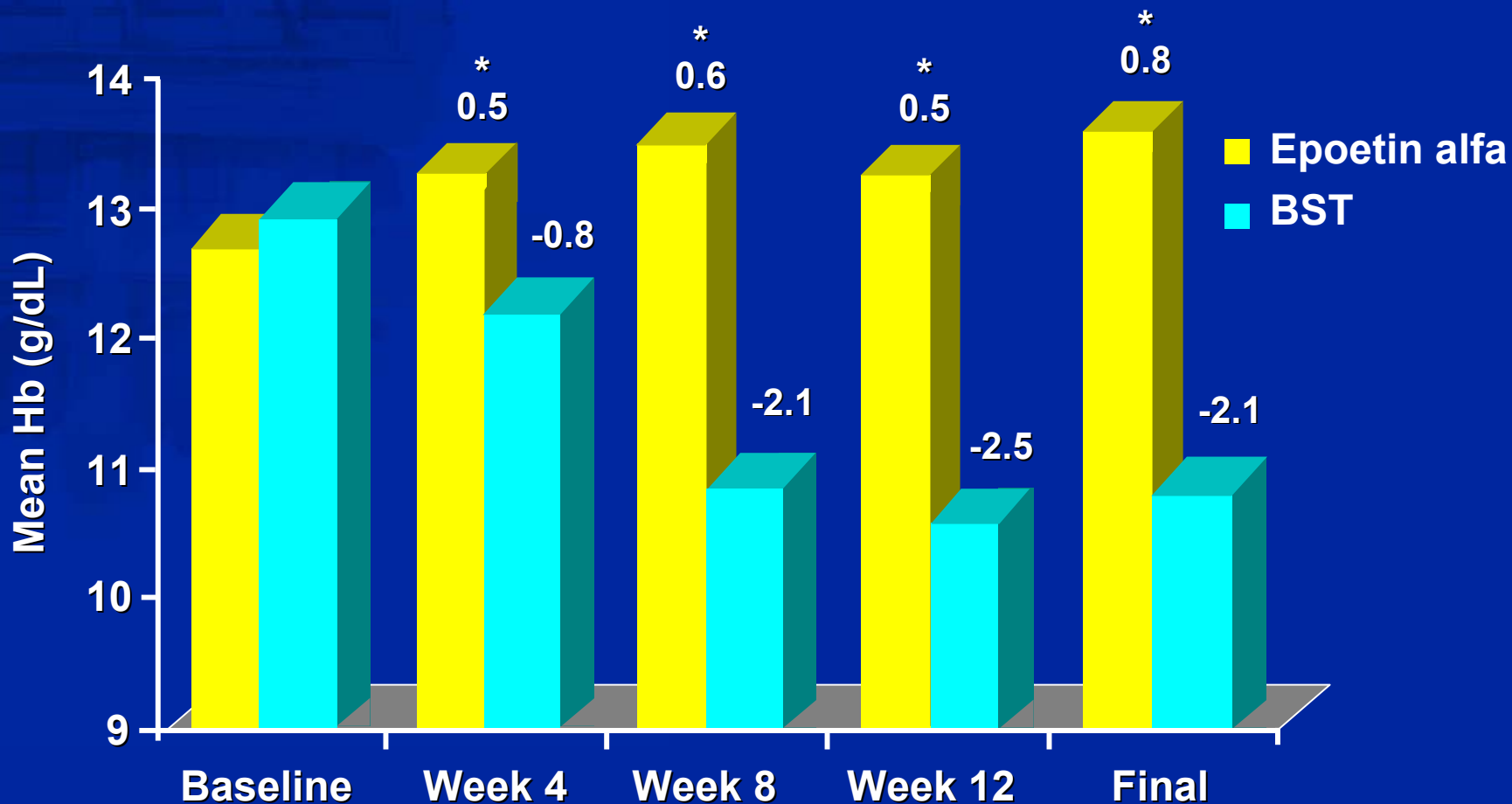
Other Benefits of Prompt Anemia Correction: Prevention of Cognitive Impairment

Effect of Epoetin Alfa on Cognitive Function and QOL

Study Design

- 94 Stage I-III breast cancer patients receiving anthracycline-based adjuvant/neoadjuvant CT
- Randomization: epoetin alfa 40,000 IU sc qw or placebo while receiving CT over 3 months
- Evaluated
 - cognitive function (EXIT 25)
 - asthenia (FACT-An)
 - QOL (LASA)

Epoetin Alfa QW Prevented Development of Anemia During Adjuvant CT



* $p < .001$, between-group differences and difference compared with baseline

Results: Changes in Cognitive Function and QOL

- A significant ($P=.02$) linear association found between Hb level and cognitive function score (EXIT 25)
- Patients who received epoetin alfa had greater improvements in QOL (LASA)
- Data suggest a relationship between decline in Hb and decline in cognitive function during adjuvant CT

Conclusions: What Is the Future of Optimal Hb Management?

- Anemia is a significant challenge in cancer treatment as length of survival increases
- Maintaining Hb levels ~12 g/dL optimizes QOL
- Earlier and/or more aggressive management of anemia may be appropriate as cancer treatment continues to evolve
- Treatment with epoetin alfa may prevent chemotherapy-induced declines in cognitive function