

Use of Epoetin and Darbepoetin in Patients With Cancer: 2007 American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update

J. Douglas Rizzo, Mark R. Somerfield, Karen L. Hagerty, Jerome Seidenfeld, Julia Bohlius, Charles L. Bennett, David F. Cella, Benjamin Djulbegovic, Matthew J. Goode, Ann A. Jakubowski, Mark U. Rarick, David H. Regan, and Alan E. Lichtin

A B S T R A C T

Purpose

To update the American Society of Clinical Oncology/American Society of Hematology (ASCO/ASH) recommendations for the use of epoetin. The guideline was expanded to address use of darbepoetin and thromboembolic risk associated with these agents.

Method

An Update Committee ("Committee") reviewed and analyzed data published since 2002 through July 2007. MEDLINE and the Cochrane Collaboration Library databases were searched.

Recommendations

For patients with chemotherapy-associated anemia, the Committee continues to recommend initiating an erythropoiesis-stimulating agent (ESA) as hemoglobin (Hb) approaches, or falls below, 10 g/dL, to increase Hb and decrease transfusions. ESA treatment continues to be recommended for patients with low-risk myelodysplasia for similar reasons. There is no evidence showing increased survival as a result of ESA treatment. Conclusive evidence is lacking that, absent clinical circumstances necessitating earlier treatment, initiating ESAs at Hb levels greater than 10 g/dL either spares more patients from transfusion or substantially improves their quality of life.

Starting doses and dose modifications based on response or lack thereof should follow the package insert. Continuing ESAs beyond 6 to 8 weeks in the absence of response, assuming appropriate dose increase has been attempted in nonresponders as per US Food and Drug Administration–approved labeling, does not seem to be beneficial, and ESA therapy should be discontinued. The Committee recommends monitoring iron stores and supplementing iron intake for ESA-treated patients. ESAs should be used cautiously with chemotherapy, or in clinical states, associated with elevated risk for thromboembolic complications. The Committee also cautions against ESA use for patients with cancer who are not receiving chemotherapy, since recent trials report increased thromboembolic risks and decreased survival under these circumstances.

J Clin Oncol 26. This guideline was developed through a collaboration between the American Society of Clinical Oncology and the American Society of Hematology and has been published jointly by invitation and consent in both the *Journal of Clinical Oncology* and *Blood*. Copyright © 2007 American Society of Clinical Oncology and American Society of Hematology. All rights reserved. No part of this document may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without written permission by the American Society of Clinical Oncology or the American Society of Hematology.

SPECIAL ANNOUNCEMENT

The US Food and Drug Administration (FDA) announced revisions to erythropoiesis-stimulating agent (ESA) product labels on November 8, 2007, when this guideline was in press. These revisions warn that data are not sufficient to exclude the possibility of shortened survival and tumor progression in cancer patients when ESAs are dosed to reach a

hemoglobin (Hb) level between 10 and 12 g/dL. Clinicians are advised to consider this warning, as discussed in sections IIIB and XI. For convenience, an additional table (Table 6A) has been added to the Appendix to reflect the new dosing recommendations of the FDA label. The guideline panel strongly supports additional research to more clearly define risks of ESA use in anemic cancer patients receiving chemotherapy, and factors that determine those risks.

Medical College of Wisconsin, Milwaukee, WI; American Society of Clinical Oncology, Alexandria, VA; Blue Cross and Blue Shield Association; Northwestern University, Chicago; Evanston Northwestern Healthcare, Evanston, IL; University Hospital of Cologne, Cologne, Germany; H. Lee Moffitt Cancer Center, Tampa, FL; Patient Representative, Mesa, AZ; Memorial Sloan-Kettering Cancer Center, New York, NY; NW Kaiser Permanente, US Oncology, Portland, OR; and Cleveland Clinic Foundation, Cleveland, OH.

Submitted September 24, 2007; accepted September 26, 2007; published online ahead of print at www.jco.org on October 22, 2007.

Approved by the ASCO Board of Directors on August 15, 2007. Approved by the Executive Committee of ASH on August 14, 2007.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: American Society of Clinical Oncology, 1900 Duke St, Suite 200, Alexandria, VA 22314; e-mail: guidelines@asco.org.

This guideline was developed through a collaboration between the American Society of Clinical Oncology and the American Society of Hematology and has been published jointly by invitation and consent in both the *Journal of Clinical Oncology* and *Blood*. Copyright © 2007 American Society of Clinical Oncology and American Society of Hematology. All rights reserved. No part of this document may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without written permission by the American Society of Clinical Oncology or the American Society of Hematology.

0732-183X/08/2601-1/\$20.00

DOI: 10.1200/JCO.2007.14.3396

INTRODUCTION

The American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) first published evidence-based clinical practice guidelines for the use of epoetin in 2002.¹ ASCO guidelines are updated at intervals by an Update Committee of the original Expert Panel. For the 2007 update, the ASCO/ASH Update Committee (Appendix 1) expanded the scope of the guideline to include recommendations to address the use of darbepoetin alfa, and to address thromboembolic risk associated with the use of epoetin and darbepoetin. See Table 1 for a summary of the guideline recommendations.

Of note, the term “epoetin” is used in this document to refer to both epoetin alfa and epoetin beta. (Epoetin beta is not commercially available in the United States.) Although there are no published comparative analyses of epoetin alfa and epoetin beta, the US FDA considers these agents to be members of the same pharmacologic class; biochemical differences between the agents do not translate into differences in their pharmacodynamic properties when they are used at the recommended doses.² This is reflected in the product labeling. Thus, the recommendations in this update regarding initiation, dosing, indications, benefits, and risks can be considered to apply to both epoetin alfa and epoetin beta.

UPDATE METHODOLOGY

For the 2007 update, the ASCO/ASH Update Committee completed a review and analysis of data published since 2002. The Update Committee’s literature review focused attention on available systematic reviews and meta-analyses of published clinical trials. Computerized literature searches of MEDLINE and the Cochrane Collaboration Library were performed. Searches of the English-language literature from 2002 to July 2007 were conducted to address each of the original guideline questions and two new questions concerning, respectively, the comparative effectiveness of epoetin and darbepoetin, and thrombosis risk of ESAs. Relevant practice guidelines from other oncology and national organizations were identified through a search of Medline and of the National Guideline Clearinghouse Web site. Details of the literature searches are provided in Appendix 2.

The Update Committee had a single face-to-face meeting to consider the evidence for each of the 2007 recommendations. Additional meetings were held via teleconference. The guideline was circulated in draft form to the Update Committee, ASCO’s Health Services Committee, ASH’s Committee on Practice, ASH’s Subcommittee on Quality of Care, and the ASCO Board of Directors and the ASH Executive Committee for review and approval.

SUMMARY OF LITERATURE REVIEW RESULTS

The literature search conducted for this update identified a range of relevant reports, including five comprehensive systematic reviews and meta-analyses of randomized controlled trials: the 2006 Cochrane Review³; the 2006 Agency for Healthcare Research and Quality–sponsored comparative effectiveness systematic review on epoetin and darbepoetin⁴; the systematic review of epoetin alfa, epoetin beta, and darbepoetin by Wilson et al, conducted to support the National Institute for Health and Clinical Excellence appraisal determination⁵; and the system-

atic reviews on, respectively, the role of erythropoietin in the management of patients with nonhematologic malignancies,⁶ and the treatment for anemia with erythropoietic agents in patients with nonmyeloid hematological malignancies,⁷ which were conducted to support Cancer Care Ontario (CCO) guidelines on these topics. These five systematic reviews serve as the primary evidence base for the guideline update. Tables 2 and 3 present the characteristics of the five systematic reviews; Table 4 summarizes data on the outcomes reported. Material presented at the May 2004 and May 2007 Oncology Drugs Advisory Committee meeting were also reviewed to identify additional data. Finally, additional studies reviewed, which included relevant meta-analyses, practice guidelines based on systematic reviews of the literature, and randomized clinical trials, are described in the literature update and discussion sections below, as appropriate.

It important to emphasize that guidelines and technology assessments cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations, and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same result.

Accordingly, ASCO and ASH consider adherence to this guideline assessment to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient’s individual circumstances. In addition, this guideline describes the use of procedures and therapies in clinical practice; it cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a condition for which improved staging and treatment is needed. In that guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions and settings for further research.

Differences Between the 2002 and 2007 guideline recommendations appear in italicized text.

2007 GUIDELINE RECOMMENDATIONS

I. GENERAL RECOMMENDATION

2007 Recommendation

As in any medical situation, it is essential to consider other correctable causes of anemia before initiating therapy with stimulants of erythropoiesis. Therefore, it is advisable to conduct an appropriate history and physical, and to consider relevant diagnostic testing aimed at identifying causes of anemia aside from chemotherapy or underlying hematopoietic malignancy. At a minimum, one should take a thorough drug exposure history, carefully review the peripheral blood smear (and in some cases, the bone marrow), consider iron, folate, and B₁₂ deficiency where indicated, and assess for occult blood loss *and renal insufficiency*. Coomb’s testing may be appropriate for patients with chronic lymphocytic leukemia, *non-Hodgkin’s lymphoma, and for those with a history of autoimmune disease*;

Table 1. Summary of Recommendations

Recommendation Category	Recommendation	
	2002	2007
1. General recommendation	As in any medical situation, it is essential to give consideration to other correctable causes of anemia before proceeding to therapy with stimulants of erythropoiesis. Therefore, it is advisable to conduct an appropriate history and physical and to consider relevant diagnostic testing aimed at identifying causes of anemia aside from chemotherapy or underlying hematopoietic malignancy. At a minimum, one should take a thorough drug exposure history, carefully review the peripheral blood smear (and in some cases, the bone marrow), consider iron, folate, and B ₁₂ deficiency where indicated, and assess for occult blood loss. Coomb's testing may be appropriate for patients with chronic lymphocytic leukemia; endogenous erythropoietin levels may predict response in patients with myelodysplasia.	As in any medical situation, it is essential to consider other correctable causes of anemia before initiating therapy with stimulants of erythropoiesis. Therefore, it is advisable to conduct an appropriate history and physical and to consider relevant diagnostic testing aimed at identifying causes of anemia aside from chemotherapy or underlying hematopoietic malignancy. At a minimum, one should take a thorough drug exposure history, carefully review the peripheral blood smear (and in some cases, the bone marrow), consider iron, folate, and B ₁₂ deficiency where indicated, and assess for occult blood loss and renal insufficiency . Coomb's testing may be appropriate for patients with chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and for those with a history of auto-immune disease ; endogenous erythropoietin levels may predict response in patients with myelodysplasia. Consideration should be given to minimize use of ESAs in patients with high risk of thromboembolic events, as further discussed in Recommendation 4.
2. Special commentary on the comparative effectiveness of epoetin and darbepoetin*		Based on a comprehensive systematic review comparing outcomes of epoetin and darbepoetin in patients with chemotherapy-induced anemia; and on identical cancer-related indications, warnings, and cautions in the relevant FDA-approved package inserts, the Update Committee considers these agents to be equivalent with respect to effectiveness and safety.
3. Chemotherapy-induced anemia		
Threshold for initiating ESA therapy, Hb concentration approaching or < 10 g/dL	The use of epoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a Hb concentration that has declined to a level of ≤ 10 g/dL. RBC transfusion is also a treatment option depending on the severity of anemia or clinical circumstances.	The use of epoetin or darbepoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a Hb concentration that is approaching, or has fallen below, 10 g/dL, to increase Hb and decrease transfusions . Red blood cell (RBC) transfusion is also an option depending upon the severity of the anemia or clinical circumstances.
Initiation threshold, > 10 g/dL but < 12 g/dL	For patients with declining Hb levels but less severe anemia (those with Hb concentration < 12 g/dL, but who never have fallen below 10 g/dL), the decision of whether to use epoetin immediately or to wait until Hb levels fall closer to 10 g/dL should be determined by clinical circumstances. RBC transfusion is also a therapeutic option when warranted by severe clinical conditions.	For patients with declining Hb levels but less severe anemia (those with Hb concentration < 12 g/dL, but who have never fallen near 10 g/dL), the decision of whether to use epoetin or darbepoetin immediately or to wait until the Hb levels fall closer to 10 g/dL should be determined by clinical circumstances (including but not limited to elderly individuals with limited cardiopulmonary reserve, those with underlying coronary artery disease or symptomatic angina, or substantially reduced exercise capacity, energy, or ability to carry out activities of daily living [ADLs]) . RBC transfusion is also an option when warranted by clinical conditions.
4. Thromboembolic risk*		Clinicians should carefully weigh the risks of thromboembolism in patients for whom epoetin or darbepoetin are prescribed. Randomized clinical trials and systematic reviews of available randomized clinical trials demonstrate an increased risk of thromboembolism in patients receiving epoetin or darbepoetin. Specific risk factors for thromboembolism have not been defined in these trials; therefore, clinicians should use caution and clinical judgment when considering use of these agents. Established, general risk factors for thromboembolic events include previous history of thromboses, surgery, and prolonged periods of immobilization or limited activity. Multiple myeloma patients who are being treated with thalidomide or lenalidomide and doxorubicin or corticosteroids are at increased risk. ¹⁸ There are no data regarding concomitant use of anticoagulants or aspirin to modulate this risk.

(continued on following page)

Table 1. Summary of Recommendations (continued)

Recommendation Category	Recommendation	
	2002	2007
5. Starting and escalating doses	The recommendations are based on evidence from trials in which epoetin was administered subcutaneously thrice weekly. The recommended starting dose is 150 U/kg thrice weekly for a minimum of 4 wk, with consideration given for dose escalation to 300 U/kg thrice weekly for an additional 4 to 8 wk in those who do not respond to the initial dose. Although supported by less strong evidence, an alternative weekly dosing regimen (40,000 U/wk), based on common clinical practice, can be considered. Dose escalation of weekly regimens should be under similar circumstances to thrice weekly regimens.	The FDA-approved starting dose of epoetin is 150 U/kg TIW or 40,000 U weekly subcutaneously. The FDA-approved starting dose of darbepoetin is 2.25 µg/kg weekly or 500 micrograms every 3 wk subcutaneously. Alternative starting doses or dosing schedules have shown no consistent difference in effectiveness on outcomes including transfusion and Hb response, although they may be considered to improve convenience. Dose escalation should follow FDA-approved labeling (Table 6); no convincing evidence exists to suggest differences in dose escalation schedules are associated with different effectiveness.
6. Discontinuing therapy for no response	Continuing epoetin treatment beyond 6 to 8 wk in the absence of response (eg, < 1-2 g/dL rise in Hb), assuming appropriate dose increase has been attempted in nonresponders, does not appear to be beneficial. Patients who do not respond should be investigated for underlying tumor progression or iron deficiency. As with other failed individual therapeutic trials, consideration should be given to discontinuing the medication.	Continuing epoetin or darbepoetin treatment beyond 6-8 wk in the absence of response (eg, < 1-2 g/dL rise in Hb or no diminution of transfusion requirements), assuming appropriate dose increase has been attempted in non-responders as per the FDA-approved label, does not appear to be beneficial and ESA therapy should be discontinued. Patients who do not respond should be investigated for underlying tumor progression, iron deficiency, or other etiologies for anemia.
7. Hb target	Hb levels can be raised to (or near) a concentration of 12 g/dL, at which time the dosage of epoetin should be titrated to maintain that level or restarted when the level falls to near 10 g/dL. Insufficient evidence to date supports the "normalization" of Hb levels to above 12 g/dL.	Hb can be raised to (or near) a concentration of 12 g/dL, at which time the dosage of epoetin or darbepoetin should be titrated to maintain that level. Dose and dose modification recommendations recorded in the package insert as of March 2007 and approved by the FDA can be found in Table 6 (and table 6A based on the November 8, 2007, FDA labeling announcement). Dose reductions are also recommended when Hb rise exceeds 1 g/dL in any 2 wk period or when the Hb exceeds 11 g d/L. Risk of venous thromboembolism should also be considered when determining dose reduction schedules.
8. Iron monitoring and supplementation	Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels and instituting iron repletion when indicated may be valuable in limiting the need for epoetin, maximizing symptomatic improvement for patients, and determining the reason for failure to respond adequately to epoetin. There is inadequate evidence to specify the optimal timing, periodicity, or testing regimen for such monitoring.	There is no change to the recommendation from the 2002 guideline.
9. Anemia in patients not receiving concurrent chemotherapy	There is evidence from one well-designed, placebo-controlled, randomized trial that supports the use of epoetin in patients with anemia associated with low-risk myelodysplasia, but there are no published high-quality studies to support its use in anemic myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients in the absence of chemotherapy. Treatment with epoetin for myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients experiencing chemotherapy-associated anemia should follow the recommendations outlined above.	There is evidence that supports the use of epoetin or darbepoetin in patients with anemia associated with low-risk myelodysplasia. There are no published high-quality studies to support its exclusive use in anemic myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients in the absence of concurrent chemotherapy. Analyses of primary data from Study 20010103 (as yet unpublished) submitted to the FDA in March of 2007, support a stronger recommendation against the use of ESAs to treat anemia associated with malignancy, or the anemia of cancer, among patients with either solid or non-myeloid hematological malignancies who are not receiving concurrent chemotherapy. This recommendation is consistent with the black-box warning that was added to the prescribing information for both epoetin alfa and darbepoetin in March of 2007, as follows: "Use of ESAs increased the risk of death when administered to a target Hb of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated in this population."

(continued on following page)

Table 1. Summary of Recommendations (continued)

Recommendation Category	Recommendation	
	2002	2007
10. Treatment of anemia in patients with non-myeloid hematological malignancies who are receiving concurrent chemotherapy	Physicians caring for patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia are advised to begin treatment with chemotherapy and/or corticosteroids and observe the hematologic outcomes achieved solely through tumor reduction before considering epoetin. If a rise in Hb is not observed after chemotherapy, epoetin should be used in accordance with the criteria outlined above for chemotherapy-associated anemia if clinically indicated. Blood transfusion is also a therapeutic option.	Physicians caring for patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia are advised to begin treatment with chemotherapy and/or corticosteroids and observe the hematologic outcomes achieved solely through tumor reduction before considering epoetin. If a rise in Hb is not observed following chemotherapy, treatment with epoetin or darbepoetin for myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients experiencing chemotherapy-associated anemia should follow the recommendations outlined above. Particular caution should be exercised in the use of epoetin or darbepoetin concomitant with chemotherapeutic agents and diseases where risk of thromboembolic complications is increased (refer to Recommendation IV). Blood transfusion is also a therapeutic option.

NOTE. Bold font indicates differences between the 2002 and 2007 guideline recommendations. Abbreviations: Hb, hemoglobin; FDA, US Food and Drug Administration. *This topic is new to the guideline.

endogenous erythropoietin levels may predict response in patients with myelodysplasia. *Consideration should be given to minimize use of ESAs in patients with high risk of thromboembolic events, as further discussed in Recommendation IV.*

II. SPECIAL COMMENTARY ON THE COMPARATIVE EFFECTIVENESS OF EPOETIN AND DARBEPOETIN (NOTE. THIS TOPIC IS NEW TO THE GUIDELINE.)

2007 Update Committee Statement

Based on a comprehensive systematic review comparing outcomes of epoetin and darbepoetin in patients with chemotherapy-

induced anemia; and on identical cancer-related indications, warnings, and cautions in the relevant US Food and Drug Administration-approved package inserts, the Update Committee considers these agents to be equivalent with respect to effectiveness and safety.

Literature Review and Analysis

Since the original ASCO/ASH guideline was published in 2002, a long-acting erythropoietic stimulant, darbepoetin alfa ("novel erythropoiesis-stimulating protein," or NESP) has been evaluated in randomized clinical trials and approved by the US

Table 2. Summary of Systematic Review Characteristics

Study	Time Period	Study Designs Included	ESA	Indication for ESA		
				CT-Induced Anemia	Anemia of Cancer	MDS
Seidenfeld et al 2006 ⁴	1985-2005	RCTs	EPO- α , EPO- β , and DAR	59 studies (n = 11,757)		
Bohlius et al 2006 ³ (Cochrane); Bohlius et al 2006 (JNCI) ³⁹	Studies from January 1, 1985 to December 31, 2001 for first Cochrane review; January 1, 2002 to April 13, 2005	RCTs	EPO- α , EPO- β , and DAR	57 studies (n = 9,353)*	NR	
Quirt et al 2005 ⁶	1966-2005	RCTs	EPO- α , EPO- β , and DAR	NR	NR	NR
Shehata et al 2007 ⁷	1985-2005	RCTs	EPO- α , EPO- β , and DAR- α	NR	NR	NR
Wilson et al 2007 ⁵	2000-2004 (EPO- α and EPO- β); 1996-2004 (DAR)	RCTs	EPO- α , EPO- β , and DAR (collapsed into one ESA category)	NR	4 studies (n = 386)	3 studies (n = 192)

Abbreviations: ESA, erythropoiesis-stimulating agent; CT, chemotherapy; MDS, myelodysplastic syndrome; RCT, randomized controlled trial; NR, not reported; EPO- α , epoetin alfa; EPO- β , Epoetin beta; DAR, darbepoetin; DAR- α , darbepoetin alfa; NR, not reported. *Represents total number of studies, not restricted to CT-induced anemia, although the majority of these studies were in this population.

Table 3. Summary of Patient Populations

Variable	No.										Bohlius et al ^{3,39}	Quirt et al ⁶	Shehata et al ⁷	Wilson et al ^{5†}
	Seidenfeld et al (AHRQ) ⁴ Subgroup													
	Transfusion			Thromboembolism			Survival							
	EPO v DAR	EPO v Control	DAR v Control	EPO v DAR	EPO v Control	DAR v Control	EPO v DAR	EPO v Control	DAR v Control					
Malignancy type														
Solid tumors, mixed types														
Trials	6	22	2	2	20	NR	NR	23	2	34	29		25	
Patients	2,158	2,924	552	670	4,108			4,526	563	5,330	2,927		3,827	
Hematologic														
Trials		6	2		5	NR	NR	6	2	9		15	7	
Patients		1,111	398		898			1,044	410	1,519		2,454	1,091	
Mixed solid and hematologic														
Trials						NR	NR	6		11	6		7	
Patients								1,348		2,221	1,366		1,190	
Mixed/unknown														
Trials		7		1	5	NR	NR							
Patients		1,175		1,209	1,086									
MDS														
Trials						NR	NR			2			3	
Patients										153			147	
NR														
Trials						NR	NR			1	2		1	
Patients										130	217		127	
Hb level, g/dL														
< 10														
Trials	2	15	3		10	NR	NR	14	3	22	NR	NR	NR	
Patients	199	2,803	636		2,172			2,830	659	3,936				
10-12														
Trials	4	12	1	3	7	NR	NR	7	1	14	NR	NR	NR	
Patients	1,959	1,781	314	1,879	1,394			1,398	314	2,141				
>12														
Trials		5			5	NR	NR	7		10	NR	NR	NR	
Patients		302			1,505			1,696		1,872				
Not categorized														
Trials		2			8	NR	NR	7		11	NR	NR	NR	
Patients		322			1,021			994		1,404				

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; MDS, myelodysplastic syndrome; EPO, epoetin; CT, chemotherapy; RT, radiotherapy; NR, not reported; Hb, hemoglobin.

[†]Based on description of study population.

[†]Reports on 43 of 46 studies. When all 46 studies were included and study tables were cross-referenced, numbers changed for four categories: solid tumors, mixed 26 studies (n = 4,076); hematologic malignancies, eight studies (n = 1,434); mixed eight studies (n = 1,422); MDS three studies (n = 192); one NR remained same. Total patient No. may not correspond to total reported in narrative.

Food and Drug Administration for the treatment of anemia associated with cancer chemotherapy (and other indications).

In 2006, the BlueCross and BlueShield Association's Technology Evaluation Center, under contract to the Agency for Healthcare Research and Quality (AHRQ), conducted a Comparative Effectiveness Review (CER) of epoetin (alfa or beta) or darbepoetin for managing anemia in patients receiving treatment for cancer.⁴ The AHRQ CER review compared available ESAs in terms of both efficacy and adverse effects, including survival, hypertension, thrombocytopenia and/or hemorrhage, thromboembolic events, seizures, and rashes or similar symptoms. The methods and results of the AHRQ CER are summarized in Tables 2 to 4.

The CER found no clinically significant differences between epoetin and darbepoetin with respect to hematologic response rates, transfusion rates, or thromboembolic events. The available evidence was found to be insufficient to permit conclusions comparing effects of either epoetin or darbepoetin

on quality-of-life (QOL) outcomes, tumor response or progression, or survival. Evidence was also insufficient for conclusions regarding differential adverse effects of epoetin and darbepoetin other than thromboembolic events. There was no statistically significant difference between epoetin and darbepoetin from a pooled analysis of three trials that directly compared thromboembolic events rates between these agents.

Based on their 2006 systematic review and meta-analysis of the literature, Ross et al⁸ similarly concluded that the available agents did not differ with respect to transfusion rates, thromboembolic events, or QOL. The authors considered a total of 40 studies, including 28 randomized controlled trials representing a total of 8,323 patients. Of these 28 trials, 10 trials (5,514 patients) directly compared epoetin and darbepoetin.

In summary, the Update Committee considers epoetin and darbepoetin, used at dosages recommended in current US Food and Drug Administration–approved package inserts, to be equivalent with respect to effectiveness and safety based on the

Epoetin and Darbepoetin Guideline Update

Table 4. Summary of Systematic Review Outcomes

Study	Thrombosis					Transfusion					No. of Trials	No. of Patients	
	Events: ESA Arms	Control Arms	Relative Risk	95% CI	No. of Trials	No. of Patients	Events: ESA Arms	Control Arms	Relative Risk	95% CI			
Seidenfeld et al ⁴													
EPO v DAR	58/948 (DAR)	66/931 (EPO)	0.86	0.61 to 1.21	3	189	252/1,169	198/989	1.10	0.93 to 1.29	6	2,158	
EPO v control	218/3,355	112/2,737	1.69	1.36 to 2.10	30	6,092	864/2,859	1,110/2,351	0.63	0.59 to 0.67	34	5,210	
DAR v control	7/155	5/159	1.44	0.47 to 4.43	1	314	165/566	196/384	0.61	0.52 to 0.72	4	950	
Bohlius et al ^{3,39}	229/3,728	118/3,041	1.67	1.35 to 2.06	35	6,769	1,118/3,637	1,385/2,873	0.64	0.60 to 0.68	42	6,510	
Quirt et al ⁶	DVT-2 studies report: Schwartzberg (2004): EPO, n = 1/155; DAR, n = 1/157; Rosenzweig (2004): EPO, n = 4/14; pulmonary embolism, 2 studies report: Schwartzberg (2004): EPO, n = 1/155; DAR, n = 0/157; Rosenzweig (2004): EPO, n = 2/14	Rosenzweig (2004): control n = NA for both DVT + PE	NR				385/1,750	588/1,419	0.52	0.46 to 0.60	30 trials (33 comparisons)	3,169	
Shehata et al ⁷	Thrombosis: EPO α or β frequency, range, 3%-7%, control frequency, range, 2%-6%; DAR α , not reported, 5 trials		NR						EPO α or β absolute risk reduction ranged from 15%–24%, 6 trials; DAR α absolute risk reduction ranged from 17%–30%, 2 trials				
Wilson et al ⁵	Study 1: vascular: BP, VT, PE, CVA 20/180; study 2: thrombic events 4/14; study 3: thrombic events 7/156	Study 1: vascular 9/171; study 2: NR; study 3: thrombic events 5/158	NR				834/2,637	988/1,976	0.63	0.58 to 67	35	4,613	

Study	Overall Survival				Tumor Response				No. of Trials	No. of Patients		
	Events: ESA Arms	Control Arms	Hazard Ratio	95% CI	No. of Trials	No. of Patients	Events: ESA Arms	Control Arms			Relative Risk	95% CI
Seidenfeld et al ⁴												
EPO v DAR	29/180	23/178	1.25	0.76 to 2.07	1	358						
EPO v control	1,008/3,825	830/3,093	1.11	1.00 to 1.22	35	6,918	216/344	211/344	1.00	0.92 to 1.10	5	688
DAR v control	181/583	183/390	0.96	0.78 to 1.17	4	973						
Bohlius et al ^{3,39}	NR	NR	1.08	0.99 to 1.18	42	8,167	413/1,509	324/1,324	1.12	1.01 to 1.23	13	2,833
Quirt et al ⁶	NR	NR	NR				NR	NR				
Shehata et al ⁷	Littlewood et al (2001) report EPO α = 60% for patients with solid tumors and hematologic malignancies, control = 40% (P = .13); Osterborg et al (2005) report EPO α = 65%, control = 63%, HR = 1.04 (0.80-1.36); DAR α HR = 0.95, P = .619, 4 trials											
Wilson et al ⁵	675/2,986 deaths	545/2,322	1.03	0.92 to 1.16	28	5,308	169/723	91/537	1.31	1.08 to 1.60	8	1,260

Abbreviations: EPO- α , epoetin α ; EPO- β , epoetin β ; DAR, darbepoetin; NA, not applicable; NR, not reported.

data presented above and the current (July 2007) US Food and Drug Administration–approved package inserts for these products. Epoetin and darbepoetin are identical with respect to: (a) indications for use in chemotherapy-induced anemia, (b) Hb

limits for adjusting doses or discontinuing treatment, (c) warnings and cautions to consider, and (d) increased rates of thromboembolic events in the experimental arms of separate trials on each product versus controls/placebo.

IIIa. CHEMOTHERAPY-INDUCED ANEMIA: THRESHOLD FOR INITIATING ESA THERAPY (Hb CONCENTRATION APPROACHING OR < 10 g/dL)

2007 Recommendation

The use of epoetin or darbepoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a Hb concentration *that is approaching, or has fallen below, 10 g/dL, to increase Hb and decrease transfusions*. RBC transfusion is also an option depending on the severity of the anemia or clinical circumstances.

Literature Update and Discussion

The 2002 guideline recommendation was based largely on an earlier AHRQ-sponsored systematic review and meta-analysis conducted by Seidenfeld et al,⁹ which found that the strongest evidence for the effects of epoetin therapy on transfusion and QOL outcomes was from clinical trials in patients with a baseline Hb of 10 g/dL or less. This previous review also found insufficient evidence to demonstrate that starting epoetin therapy at Hb levels greater than 10 g/dL resulted in fewer transfusions and improved QOL outcomes compared with trials that started epoetin therapy at mean Hb levels of 10 g/dL or lower.

Overview of relevant clinical trials. Evidence published^{10,11} or presented¹² since the 2002 guideline relevant to a Hb threshold for initiating epoetin or darbepoetin in asymptomatic patients undergoing chemotherapy was addressed in the 2006 AHRQ CER. The review identified three nonblinded randomized trials that compared the effects of immediate versus delayed treatment at a Hb threshold for initiating ESAs on transfusion rates, thromboembolic event rates, survival, and QOL outcomes.⁴ Patients in these trials were randomized to one of two treatment arms: “immediate” or “delayed” treatment with epoetin or darbepoetin after Hb fell to a prespecified threshold. If Hb did not fall below the prespecified threshold in the

“delayed” arm, no epoetin or darbepoetin was administered. The results of these three trials are summarized in Table 5.

In each of the three trials,¹⁰⁻¹² transfusion rates were higher in the delayed versus the immediate arms; however, the differences were not statistically significant in any of the trials. Straus et al reported a statistically significant increase in thromboembolic events in the immediate (11%) compared with the delayed treatment arm (3%). There were no differences in thromboembolic event rates between the two arms in the Rearden et al and Crawford et al trials. Finally, Straus et al reported statistically significant differences favoring the early therapy arm in mean scores on the physical and functional well-being subscales of the Functional Assessment of Cancer Therapy-General (FACT-G); in the total anemia scale (FACT-An) and the fatigue subscale of the FACT-An; and in a range of functional activity and productivity measures. The other two studies (Rearden et al and Crawford et al) did not report statistically significant differences between the immediate and delayed groups on QOL measures.

Lyman and Glaspy¹³ conducted a meta-analysis of five trials, including the three reviewed above, to evaluate clinical benefits associated with initiating ESA therapy in mild (Hb \geq 10 g/dL) versus moderate (Hb < 10 g/dL) anemia. Across these five trials, a comparison between early and late ESA treatment showed that the weighted summary relative risk of a transfusion with earlier ESA treatment was 0.55 (95% CI, 0.42 to 0.73; $P = .0001$). Based on their analyses, Lyman and Glaspy concluded that ESA treatment among mildly anemic patients is associated with a significant reduction in transfusion requirements as compared with treatment at a lower Hb threshold.

The validity of combining data from the five trials considered by Lyman and Glaspy is questionable, and thus make interpretation of their results difficult. Differences across the three trials of immediate versus delayed ESA treatment in mean Hb thresholds for treatment resulted in marked differences in the proportion of patients in the delayed arms of the trials who received ESA therapy.⁴ In the delayed

Table 5. Summary of Findings From Studies Evaluating Thresholds for Initiating Treatment From the AHRQ CER

Study	Randomly Assigned (No.)		Malignancy	Drug and Treatment Duration	Hb When EPO/DARB Initiated		Patients Given EPO/DARB (%)		Transfused (%)		Between Arm Differences in Δ (FACT measures) From Baseline	Thromboembolic Events (%)	
	I	D			I	D	I	D	I	D			
Straus 2006 ¹¹	135	134	Hematologic	Epoetin \leq 16 wk	11.1 \pm 0.7*	< 9	100	19.4	17.8	26.1	FACT-An 8.22 (2.62) unadjusted mean, 6.67 (2.25) estimated mean \ddagger ; FACT-fatigue 3.13 (1.16) unadjusted mean, 2.67 (0.94) estimated mean \ddagger	11.1	3 \dagger
Rearden 2004 ¹²	102	102	Mixed solid or hematologic	Darbepoetin 12 wk§	11.1 \pm 0.07¶	< 10	100	62.7	17.2	26.5	NS	2	1
Crawford 2007 ¹⁰	109	107	Non-small-cell lung cancer	Epoetin 16 wk (D group from first administration to end of study)	13.1 \pm 1.0*	\leq 10	100	46.0	12.3	20.0	NS	12	15

NOTE. Adapted from original work done by Seidenfeld et al.⁴

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; CER, comparative effectiveness review; I, erythropoietic stimulant therapy begun immediately after random assignment; D, erythropoietic stimulant therapy delayed until Hb falls to threshold; Hb, hemoglobin; DARB, darbepoetin; EPO, epoetin; FACT, Functional Assessment of Cancer Therapy; NS, no significant difference; NR, not reported.

*Mean \pm standard deviation.

\dagger Statistically significant differences.

\ddagger Estimated mean based on the treatment effect using a random coefficient linear growth curve model.

\S Transfusion data include 22 weeks follow-up as patients received chemotherapy throughout.

¶Mean \pm standard error.

||Included seven participants who received EPO despite having Hb > 10 g/dL.

arms of the Straus et al,¹¹ Rearden et al,¹² and Crawford et al¹⁰ trials, 80.6%, 37.3%, and 54% of patients, respectively, were not treated with an ESA at any time during the study. Additionally, clinicians responsible for making decisions regarding transfusion were not blinded to assigned treatment. This could have resulted in a bias in favor of the immediate treatment arms. The open-label design of these trials may also make measurement of QOL subject to response bias.¹⁴ Finally, neither of the other two trials in the meta-analysis randomized patients to immediate versus delayed therapy.

Clinical significance of QOL effects. In the Straus et al trial,¹¹ the absolute changes in QOL scores from baseline, though statistically significant, were small. The authors noted that all observed mean differences in QOL assessments exceeded the “clinically meaningful thresholds” that Cella and colleagues have published.¹⁵⁻¹⁷

The body of published research on ESA use and QOL is extensive, but questions remain. Based on an analysis of data from six trials that reported on the FACT-fatigue subscale, the AHRQ CER review authors⁴ concluded that some of the QOL improvements observed in these trials are reported to be clinically significant, with small effect sizes. Another systematic review of the literature⁵ considered the significance of changes in patients’ QOL using a vote-counting methodology. Wilson et al classified 20 QOL studies they identified through a literature search as showing a “positive,” “negative,” or “neutral” effect. The net result was a positive effect in favor of ESAs on health-related QOL, but Wilson et al characterized the clinical importance of these effects as “uncertain.”

Based on a 2004 meta-analysis of both published and unpublished studies, Jones et al concluded that epoetin significantly improved cancer patients’ QOL. Jones et al reported mean change from baseline score of 4.6 for the FACT-fatigue scale after adjustment for potential confounding factors. Among the limitations of this meta-analysis are the inclusion of large single arm or nonrandomized studies, and inclusion of studies where large amounts of missing QOL data are not addressed in the meta-analysis. The authors conducted secondary analyses excluding the uncontrolled studies and adjusting statistically for the placebo effect. They reported that the results in QOL improvement remained statistically significant. However, the actual score, and its clinical meaningfulness, were not reported for the secondary analyses.

The AHRQ CER,⁴ and the Cochrane 2006³ review concluded that data on the effects of ESAs on QOL outcomes should be interpreted with caution. Each review was limited to the use of published data, and neither performed meta-analyses of the QOL outcomes. Published studies, particularly older clinical trials, did not commonly report the data (standard deviations or other appropriate measures of variance) that are needed for meta-analysis. QOL is more difficult to measure in clinical trials than Hb or transfusion changes. For instance, in nine studies that reported 14 comparisons of ESA versus control using FACT-G, FACT-An, or the FACT-fatigue subscale, the proportion of enrolled patients omitted from QOL analyses ranged from 4% to 40%. When possible, future clinical trials should strive to limit missing QOL assessments, and should continue to report the data needed to calculate effect sizes and clinically meaningful QOL changes. (Interested readers are referred to Chapter 4 of the AHRQ CER for a more detailed discussion of methodological issues.)

IIIB. CHEMOTHERAPY-INDUCED ANEMIA: INITIATION THRESHOLD > 10 g/dL BUT < 12 g/dL

2007 Recommendation

For patients with declining Hb levels but less severe anemia (those with Hb concentration < 12 g/dL, but who have never fallen near 10 g/dL), the decision of whether to use epoetin or *darbepoetin* immediately or to wait until the Hb levels fall closer to 10 g/dL should be determined by clinical circumstances (*including but not limited to elderly individuals with limited cardiopulmonary reserve, those with underlying coronary artery disease or symptomatic angina, or substantially reduced exercise capacity, energy, or ability to carry out activities of daily living [ADLs]*). RBC transfusion is also an option when warranted by clinical conditions.

Literature Update and Discussion

There is no change to the recommendation from the 2002 guideline, except that substantially reduced exercise capacity, energy, or ability to carry out ADL’s has been added as a clinical circumstance. The use of ESAs in this context should continue to be guided by clinical circumstances and judgment. The Update Committee recognizes that there is a subset of patients for whom initiating ESAs at a higher Hb may be worth considering. These patients might include elderly individuals with limited cardiopulmonary reserve, or those with underlying coronary artery disease or symptomatic angina or those with impaired physical functioning due to decreased energy or exercise capacity. Based on available QOL studies, the best clinical opinion of the Update Committee is that a trial of ESAs may be warranted for such patients. Clinicians should very carefully weigh the risks and benefits of initiating ESAs in this range of anemia as outlined elsewhere in this guideline update (section IIIA and Table 5), and promptly discontinue ESAs in patients who do not achieve the desired benefit in the appropriate timeframe.

IV. THROMBOEMBOLIC RISK (NOTE. THIS TOPIC IS NEW TO THE GUIDELINE.)

2007 Recommendation

Clinicians should carefully weigh the risks of thromboembolism in patients for whom epoetin or darbepoetin is prescribed. Randomized clinical trials and systematic reviews of available randomized clinical trials demonstrate an increased risk of thromboembolism in patients receiving epoetin or darbepoetin. Specific risk factors for thromboembolism have not been defined in these trials; therefore, clinicians should use caution and clinical judgment when considering use of these agents. Established, general risk factors for thromboembolic events include previous history of thromboses, surgery, and prolonged periods of immobilization or limited activity. Multiple myeloma patients who are being treated with thalidomide or lenalidomide and doxorubicin or corticosteroids are at increased risk.¹⁸ There are no data regarding concomitant use of anticoagulants or aspirin to modulate this risk.

Literature Review and Analysis

Initial concern over increased thromboembolic event risk with ESAs was raised in 2003 when three clinical trials with epoetin were discontinued prematurely as a 25% rate of thromboembolic events was noted.² A review of phase III licensing trials in the United States and Europe in 2004 led to the addition of a warning to the package

inserts advising physicians of increased thromboembolic event risks with ESAs in the oncology setting. There is now strong and consistent evidence from meta-analyses of randomized clinical trial data, that therapy with epoetin and darbepoetin increases the risk of thromboembolic events. In the 2006 Cochrane Collaboration meta-analysis of 35 trials (representing 6,769 total patients) reported by Bohlius et al,³ epoetin or darbepoetin treatment was statistically significantly associated with increased risk for thromboembolic events, including deep vein thromboses, pulmonary emboli, strokes, myocardial infarctions, or transient ischemic attacks (relative risk [RR], 1.67; 95% CI, 1.35 to 2.06). Of note, the studies reporting thromboembolic events generally appear to have low quality for the assessment of these events. Only a few studies outlined a prespecified definition for thromboembolic events in the available publications.^{19,20} None of the studies reported whether thromboembolic events were detected with active screening and adjudicated by the means of an independent and blinded panel.

Based on this analysis, the number needed to harm (NNH) would be 74.63 (95% CI, 47.17 to 142.86) for a population with baseline risk of a thromboembolic event of 2%. This means that one thromboembolic event would occur for every 75 patients treated with epoetin or darbepoetin. The NNH would be 7.5 (95% CI, 3.1 to 15.6) for a population with a baseline risk of 20%. A subset analysis limited to trials on chemotherapy-induced anemia reported in the AHRQ CER provided very similar results.⁴ The AHRQ CER identified only one trial that reported the rates of thromboembolic events from a comparison of darbepoetin versus control. In a study of patients with lung cancer receiving chemotherapy (n = 320), Vansteenkiste and colleagues reported a thromboembolic event rate of 4.5% in the darbepoetin arm and an event rate of 3.1% in the control arm.²¹ The difference between the two arms was not statistically significant (RR, 1.44; 95% CI, 0.47 to 4.43). Additional data on thromboembolic event risk were presented to the ODAC panel at the 2007 meeting.²²

It has become increasingly recognized that the transfusion-sparing effects of ESAs are obtained at the cost of potentially increased risk of thromboembolic complications. The Update Committee urges caution in the use of these agents with patients judged to be at high risk for thromboembolic events. Established risk factors for thromboembolic events include previous history of thromboses, surgery, and prolonged periods of immobilization or limited activity. Additionally, multiple myeloma patients who are being treated with thalidomide or lenalidomide are at increased risk.¹⁸

V. STARTING AND ESCALATING DOSES

2007 Recommendation

The US Food and Drug Administration–approved starting dose of epoetin is 150 U/kg *three times per week* or 40,000 U *weekly subcutaneously*. The US Food and Drug Administration–approved starting dose of darbepoetin is 2.25 µg/kg *weekly* or 500 µg *every 3 weeks subcutaneously*. Alternative starting doses or dosing schedules have shown no consistent difference in effectiveness on outcomes including transfusion and Hb response, although they may be considered to improve convenience. Dose escalation should follow US Food and Drug Administration–approved labeling (Table 6); no convincing evidence exists to suggest that differences in dose escalation schedules are associated with different effectiveness.

Literature Update and Discussion

The US Food and Drug Administration–approved labeling for dose and dose escalations are in the package inserts for both products, and are reproduced in Table 6. There is no evidence published since the 2002 guideline that would support alternatives to US Food and Drug Administration–approved doses or dosing schedules. The AHRQ systematic review identified 18 trials that evaluated the effect of different dosing strategies on the safety and effectiveness of epoetin and darbepoetin.⁴ A range of strategies has been studied; interested readers are referred to the AHRQ CER for details of and citation information for each study. Three trials compared different weight-based doses of epoetin, and three compared different weight-based doses of darbepoetin; five compared different fixed doses of epoetin; one trial each compared weight-based versus fixed doses for epoetin and darbepoetin, respectively; two compared more versus less frequent dosing of epoetin; two compared front-loaded versus reduced or constant dosing of darbepoetin; and one compared titrated versus constant-dose regimens of epoetin.

The AHRQ review found remarkably few differences in safety and efficacy outcomes among the dosing strategies tested in the 18 trials, although nearly all these trials were small and underpowered to detect such differences. Reported benefits of doses that exceeded US Food and Drug Administration–approved labeling, either administered using weight-based dosing or fixed dosing, were limited in magnitude. There were statistically significant but modest differences in Hb response rates, but there were no statistically significant differences observed between trial arms in QOL or

Table 6. ESA Dosing (The doses contained on the FDA label as of March 2007 [shown below] have been revised. The November 8, 2007, FDA label is shown in Table 6A in the Appendix.)

Dose and Modifications	Epoetin Alfa		Darbepoetin Alfa	
Initial dose	150 U/kg SC TIW	40,000 U SC weekly	2.25 mcg/kg SC weekly	500 mcg SC Q3W
Dose increase	Increase dose to 300 U/kg TIW if no reduction in transfusion requirements or rise in Hb after 8 wk	Increase dose to 60,000 U SC weekly if no increase in Hb by ≥1 g/dL after 4 wk of therapy, in the absence of a RBC transfusion	Increase dose to 4.5 mcg/kg if there is <1 g/dL increase in Hb after 6 wk	—
Dose reductions	Decrease dose by 25% when Hb approaches 12 g/dL or Hb increases >1 g/dL in 2 wk		Decrease dose by 40% of previous dose when Hb exceeds 11 g/dL or Hb increases >1 g/dL in 2 wk	
Dose withholding	If Hb exceeds 12 g/dL, withhold dose until Hb <11 g/dL; restart dose at 25% below previous dose		If Hb exceeds 12 g/dL, withhold dose until Hb = 11 g/dL; restart dose at 40% below previous dose	

Abbreviations: ESA, erythropoiesis-stimulating agent; FDA, US Food and Drug Administration; SC, subcutaneous; TIW, three times per week; Q3W, every 3 weeks; Hb, hemoglobin; wk, week.

transfusion rates. Finally, some trials reported a greater incidence of thromboembolic events at the highest doses studied, but these differences also were not statistically significant. Given the infrequent and incomplete reporting of adverse events across the trials, it is not possible to reach conclusions concerning the relative safety of the alternate dosing strategies.

VI. DISCONTINUING THERAPY FOR NO RESPONSE

2007 Recommendation

Continuing epoetin or darbepoetin treatment beyond 6 to 8 weeks in the absence of response (eg, < 1-2 g/dL rise in Hb or no diminution of transfusion requirements), assuming appropriate dose increase has been attempted in nonresponders *as per the US Food and Drug Administration–approved label*, does not appear to be beneficial, and ESA therapy should be discontinued. Patients who do not respond should be investigated for underlying tumor progression, iron deficiency, or other etiologies for anemia.

Literature Update and Discussion

Some studies have investigated early indicators of response, with a view toward ending treatment sooner in nonresponders, while other trials have investigated predictors of response, such as baseline concentrations of endogenous erythropoietin.⁴ A substantial number of studies has evaluated the use of baseline endogenous erythropoietin levels to predict Hb response to ESAs. Though a few of these studies report statistically significant higher baseline erythropoietin levels in nonresponders compared to responders, most reported no significant differences, and the predictive power of such testing appears insufficient to be clinically useful, except in myelodysplastic syndrome (MDS).²³ In all other settings, there are insufficient data to support the use of endogenous erythropoietin testing either to justify initiation of ESAs or to predict response to ESAs.

VII. Hb TARGET

2007 Recommendation

Hb can be raised to (or near) a concentration of 12 g/dL, at which time the dosage of epoetin or darbepoetin should be titrated to maintain that level. *Dose and dose modification recommendations recorded in the package insert as of March 2007 and approved by the US Food and Drug Administration can be found in Table 6 (and Table 6A based on the November 8, 2007, FDA label announcement). Dose reductions are also recommended when Hb rise exceeds 1 g/dL in any 2 week period or when the Hb exceeds 11 g d/L. Risk of venous thromboembolism should also be considered when determining dose reduction schedules.*

Literature Update and Discussion

Since the 2002 guideline, there has been increasing attention to the safety of ESA treatment in patients with cancer. Two placebo-controlled phase III randomized clinical trials published in 2003 showed evidence of harmful effects of ESAs on survival and/or tumor outcomes. Leyland-Jones et al²⁴ conducted a trial of 939 patients receiving chemotherapy for metastatic breast cancer. Henke et al performed a randomized double-blinded trial in 351 patients with head and neck cancer undergoing radiotherapy.²⁵ Each trial reported higher mortality in the epoetin arm than in the placebo arm, and in the Henke et al study there was a significantly shorter locoregional progression-free survival and time to locore-

gional progression in ESA-treated patients. Another more recent trial²⁶ in patients with non-small-cell lung cancer (NSCLC) unsuitable for curative therapy was terminated early after an unplanned interim safety analysis showed a significant difference in median survival in favor of the placebo arm. (Refer to the section of the update, “Special Commentary on ESAs, Survival, and Tumor Response” for a detailed description and analysis of these and other trials.)

The Henke et al and Leyland-Jones et al trials, combined with more recent clinical studies—the majority of which were conducted in nonindicated patient populations and/or raised Hb to a target above 12 g/dL—showed harms associated with ESA use in cancer patients,²⁷ and prompted the US Food and Drug Administration to add a black-box warning to the prescribing information for epoetin and darbepoetin in March 2007. The black-box warning highlights the increased risk for death and for serious cardiovascular events when ESAs are administered to a target of more than 12 g/dL, and instructs that the “dose should be adjusted for each patient to maintain the lowest Hb level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL.”

In May 2007, the US Food and Drug Administration convened the ODAC to re-evaluate the safety and net clinical benefit of ESA use in patients with cancer. The ASCO/ASH guideline recommendations will be updated as needed in response to any changes made by the US Food and Drug Administration to the product labeling information based on information that the US Food and Drug Administration received after the May 2007 Oncologic Drugs Advisory Committee (ODAC) meeting.

VIII. IRON MONITORING AND SUPPLEMENTATION

2007 Recommendation

Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels and instituting iron repletion when indicated, may be valuable in limiting the need for epoetin or darbepoetin, maximizing symptomatic improvement for patients, and determining the reason for failure to respond adequately to ESA therapy. There is inadequate evidence to specify the timing, periodicity, or testing regimen for such monitoring. There is no change to the recommendation from the 2002 guideline.

Literature Update and Discussion

Since the publication of the 2002 guideline, three randomized controlled trials have examined the role of iron supplementation in conjunction with ESA administration. All three studies were open-label, multicenter trials, with two conducted in the United States^{28,29} and one in Sweden.³⁰

The earliest study, published in 2004,²⁸ randomized 157 patients with solid tumors or hematologic malignancies being treated with chemotherapy (patients with MDS were excluded) to one of four arms; (1) no iron (n = 36); (2) oral iron 325 mg twice daily (n = 43); (3) iron dextran 100 mg IV bolus at each visit to the calculated dose for iron replacement (n = 37); or (4) iron dextran total dose infusion (TDI) (n = 41). For patients in arms 3 and 4, the total dose of iron dextran was calculated with a formula to reach a desired Hb level of 14 g/dL. Patients were required to have a Hb level of ≤ 10.5 g/dL and a serum ferritin concentration of ≤ 450 pmol/L or ≤ 675 pmol/L with a transferrin saturation of ≤ 19%.

All patients received epoetin alfa 40,000 U subcutaneously weekly; dose escalation or reduction of epoetin was not permitted. Target enrollment was 188 patients, but the study was closed before this target was reached. Patients were followed for 6 weeks, with the exception of those in the IV bolus arm, who were followed until the end of their treatment course.

A total of 155 patients were included in the efficacy analyses. All treatment groups showed significant increases in Hb level from baseline to end point ($P < .0001$). For the no iron, oral iron, IV bolus, and TDI groups, respectively, the mean increases (in g/dL) were 0.9, 1.5, 2.5, and 2.4. For these same groups, the mean end point Hb levels were 10.5, 11.2, 12.2, and 11.9, respectively. There were statistically significant differences in mean end point Hb levels between the IV bolus group and the no-iron and oral iron groups ($P < .05$), and between the TDI group and the no-iron group ($P < .05$). Mean Hb increases for both IV iron groups were statistically significantly higher than the no-iron and oral iron arms ($P < .02$), but there was no difference between the no-iron and oral iron groups ($P = .21$).

Henry et al²⁹ randomized 187 patients with various nonmyeloid malignancies and planned chemotherapy to one of three arms: (1) sodium ferric gluconate complex (FG), 125 mg IV once weekly; (2) ferrous sulfate, 325 mg orally three times a day; or (3) no iron. Patients were required to have a baseline Hb of less than 11, and a serum ferritin level ≤ 100 ng/mL or transferrin saturation $\leq 15\%$. Patients received study treatment (iron: oral, IV, or none) for 8 weeks, with a 4-week follow-up period. Epoetin alfa was given for 12 weeks, at an initial dose of 40,000 U subcutaneously, and dose escalation or reduction was allowed.

Of the 187 patients in the safety population, 154 completed the study (82.4%). Twenty-five of these patients were excluded from the evaluable population, mainly as a result of early transfusions or discontinuations, leaving an evaluable population of 129 patients (69% of all randomized patients). In the evaluable population, there was a significantly larger increase in mean Hb from baseline to end point in FG patients (2.4 g/dL; 95% CI, 2.1 to 2.7) compared to patients on oral iron or no iron ($P = .0092$ and $P = .0044$, respectively). Mean Hb increase was 1.6 g/dL (95% CI, 1.1 to 2.1) in the oral iron arm, and 1.5 g/dL (95% CI, 1.1 to 1.9) in the no-iron arm. The difference in Hb increase between these two arms was not significant ($P = .7695$). The Hb response rates for patients in the FG, oral iron, and no-iron groups were 73%, 45%, and 41%, respectively, with statistically significant differences between the FG and oral iron or no-iron groups ($P = .0099$ and $P = .0029$, respectively), but not between the oral iron and no-iron groups ($P = .6687$).

Hedenus et al³⁰ randomized 67 patients with lymphoproliferative malignancies not receiving chemotherapy to IV iron sucrose or no iron supplement. Iron sucrose was given at a dose of 100 mg once weekly from weeks 0 to 6, and then at 100 mg every second week from weeks 8 to 14. All patients received weekly epoetin beta at 30,000 U subcutaneously once weekly for 16 weeks; dose escalation and reduction were allowed. Patients had to be transfusion-independent, have a Hb level of 9 to 11 g/dL, and have stainable iron in a bone marrow aspirate. Patients were excluded if they had a serum ferritin greater than 800 $\mu\text{g/L}$.

Sixty patients completed the study. Patients in both arms showed a significant ($P < .05$) increase in mean Hb during the trial.

In the intention-to-treat (ITT) population, the difference in mean Hb between the iron and no-iron arms at the end of treatment was 0.99 g/dL (95% CI, 1.61 to 0.37; $P = .0023$), and the mean change in Hb from baseline was 2.76 g/dL in the iron group versus 1.56 g/dL in the no-iron group ($P = .0002$). Eighty-seven percent of patients in the iron group achieved a Hb response, compared to 53% in the no-iron group ($P = .0014$).

Beginning at week 5 onwards there was a difference in mean weekly epoetin dose administered, with patients in the iron arm receiving less epoetin, but this difference was statistically significant only at week 13 ($P = .029$). By week 15, there was still an average difference of more than 10,000 U in favor of the iron group, but this difference was not statistically significant. The mean total cumulative patient dose of epoetin in the iron group was 511,400 U (per-protocol population) or 532,000 U (ITT population), and in the no-iron group it was 626,600 U (per-protocol population) or 629,000 U (ITT population). While there was a smaller epoetin dose, it was not significant ($P = .051$, per protocol population; $P = .059$, ITT population).

These studies suggest that IV iron given in conjunction with ESAs may enhance Hb response to ESAs; however, limitations of these studies should be considered when interpreting the results. In the largest study conducted,²⁹ a three-arm study of IV versus oral versus no iron, more than 30% of randomized patients were not included in the final efficacy analyses. In the ITT population ($n = 180$), Hb increased by a mean of 1.6 g/dL, 1.2 g/dL, and 1.1 g/dL in the FG, oral iron, and no-iron groups, respectively; the Hb response rates were 53%, 36%, and 36%, respectively. These results can be compared to the evaluable population, with a mean Hb increase of 2.4, 1.6, and 1.5 g/dL, and response rates of 73%, 45%, and 41%, respectively. The study was not powered to detect a difference in transfusion requirements, and no difference was seen. In the second-largest study ($n = 157$),²⁸ the trial was closed before target enrollment was met, and no statistical adjustment for multiple comparisons was made. Finally, despite the increased hematopoietic response to the combination of an ESA and iron, the one study³⁰ designed to test whether addition of iron would allow for a decreased dose of epoetin showed a statistically significant difference in epoetin dose at only one weekly time point during a 16-week study, despite a clear trend in favor of a decreased dose in the iron arm starting at week 5 of the study. Likewise, the mean total cumulative patient dose of epoetin was not statistically significantly different between the iron and no-iron arms.

The Auerbach and Henry studies both examined patients with solid tumors undergoing chemotherapy (19% of the patients in the Auerbach study were patients with hematologic malignancies), and both examined different routes of iron administration (IV or oral) versus none, in conjunction with ESA use. Results were consistent across these studies, with patients who received IV iron showing a significant increase in mean Hb concentrations compared to no-iron controls. Of interest, both studies also showed no difference between the no-iron or oral iron groups. These results suggest that, if iron is given to patients undergoing chemotherapy, the IV route may be more efficacious than the oral route in enhancing response to ESAs. The studies considered earlier herein each used a different iron preparation and examined different study populations, which complicates cross-study comparisons. There is

currently insufficient data to recommend one specific form of iron over another.

The incidence of adverse effects was somewhat different across the two studies, with seven patients (no more than 8% in any one arm) in the Auerbach study experiencing adverse events related to treatment. Henry et al reported that 15 FG patients (23.8%), 18 oral iron patients (29.5%), and 16 no-iron patients (25.4%) experienced serious adverse events; of these, two serious adverse events (angina and dehydration, one in the FG group, one in the oral iron group) were considered possibly related to study drug. Twelve drug-related adverse events were reported by eight patients in the FG group, and 38 drug-related adverse events were reported by 19 patients in the oral iron group. Drug-related adverse events led to study discontinuation in six patients (two in the FG group, four in the oral iron group).

IX. ANEMIA IN PATIENTS NOT RECEIVING CONCURRENT CHEMOTHERAPY

2007 Recommendation

There is evidence that supports the use of epoetin or *darbepoetin* in patients with anemia associated with low-risk myelodysplasia. There are no published high-quality studies to support its *exclusive* use in anemic myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients in the absence of concurrent chemotherapy. *Analyses of primary data from Study 20010103 (as yet unpublished) submitted to the US Food and Drug Administration in March 2007, support a stronger recommendation against the use of ESAs to treat anemia associated with malignancy, or the anemia of cancer, among patients with either solid or nonmyeloid hematological malignancies who are not receiving concurrent chemotherapy. This recommendation is consistent with the black-box warning that was added to the prescribing information for both epoetin alfa and darbepoetin in March 2007, as follows: "Use of ESAs increased the risk of death when administered to a target Hb of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated in this population."*

Literature Update and Discussion

The recommendation related to ESA therapy for anemia associated with low-risk myelodysplasia is unchanged from the original guideline. The recommendation is based on a randomized, double-blind, placebo-controlled trial of ESA therapy in patients with low-risk MDS, which was reviewed in the 2002 guideline; and on a second randomized open-label phase III clinical trial of erythropoietin and granulocyte colony-stimulating factor versus best supportive care reported in 2004.³¹ Additional data on the benefits of ESAs in this population have been published since the 2002 guideline; however, all but one of these studies were prospective observational studies, retrospective cohort studies, or single-institution reviews.

There is no evidence to support a recommendation for ESA treatment of anemia associated with malignancy, or the anemia of cancer, among patients not receiving chemotherapy. The updated recommendation has been expanded to address ESA use for anemia of cancer among patients with solid tumors; the prior recommendation was limited to patients with nonmyeloid hematological malignancies. Several clinical trials^{26,32-36} have been conducted since 1993 regarding anemia of cancer. These trials have had vary-

ing inclusion criteria and varying definitions of anemia of cancer (eg, time since last chemotherapy). Most are small and therefore underpowered to show statistical differences, and did not have survival as a primary or secondary outcome. The exception is Amgen study 20010103, the largest of these studies. A meta-analysis that would address size and heterogeneity and further inform this guideline has not been published in the peer-reviewed literature. Data submitted by Amgen in 2007 to the US Food and Drug Administration from Study 20010103, conducted in anemic patients with nonmyeloid malignancies who were not receiving concurrent chemotherapy or myelosuppressive radiation therapy, have raised safety concerns about the use of ESAs in this population.

Study 20010103 was a randomized phase III, double-blind, placebo-controlled trial of darbepoetin. The trial randomized 989 patients with active disease to darbepoetin or placebo. The most common cancers were NSCLC (18%), breast cancer (13%), and prostate cancer (11%). Most patients (82%) had either stage III or stage IV disease. The primary end point of the trial was the proportion of blood transfusions; secondary end points were first occurrence of a transfusion from week 5 to week 17 of the trial, change in Hb concentrations, and the safety end points of overall survival and adverse events. Based on analyses reported in the Clinical Study Report submitted by Amgen and on the US Food and Drug Administration's analysis of primary data submitted in March 2007, respectively, there was no evidence of a difference in transfusion risk (hazard ratio [HR], 0.85; 95% CI, 0.62 to 1.17) and overall survival was poorer in the darbepoetin versus control arm (HR 1.30, 95% CI, 1.07 to 1.57, $P = .008$). The US Food and Drug Administration analysis also revealed an increased incidence of arterial and venous thromboembolic events in patients treated with darbepoetin, 3.1% v 1.3%. The black-box warning added to the prescribing information for epoetin alfa and darbepoetin in March 2007 references this trial and specifies that "ESAs are not indicated for this population" of patients with active malignant disease receiving neither chemotherapy nor radiation therapy.

X. TREATMENT OF ANEMIA IN PATIENTS WITH NONMYELOID HEMATOLOGICAL MALIGNANCIES WHO ARE RECEIVING CONCURRENT CHEMOTHERAPY

2007 Recommendation

Physicians caring for patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia are advised to begin treatment with chemotherapy and/or corticosteroids and observe the hematologic outcomes achieved solely through tumor reduction before considering epoetin. If a rise in Hb is not observed following chemotherapy, treatment with epoetin or *darbepoetin for myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients experiencing chemotherapy-associated anemia should follow the recommendations outlined previously. Particular caution should be exercised in the use of epoetin or darbepoetin concomitant with chemotherapeutic agents and diseases where risk of thromboembolic complications is increased. (Refer to Recommendation IV.)* Blood transfusion is also a therapeutic option. This recommendation is essentially unchanged from the 2002 guideline. Slight modifications to the recommendation appear in italics.

Literature Update and Discussion

Since the publication of the 2002 guideline, three systematic reviews have considered data on ESA use in patients with nonmyeloid hematological malignancies who are receiving concurrent chemotherapy. The systematic review performed by CCO identified 13 trials of epoetin (12 unique trials) and two trials of darbepoetin (Tables 2 to 4 provide details of the review). The CCO review found no statistically significant differences in survival or mortality outcomes in the epoetin and darbepoetin trials. For transfusion outcomes in the epoetin trials reviewed, the absolute risk reduction for the proportion of patients transfused ranged from 15% to 24%; the NNT (number needed to treat; to prevent one transfusion) ranged from 4 to 6. For the darbepoetin trials reviewed, the absolute risk reduction for the proportion of patients transfused ranged from 17% to 30%; the NNT ranged from 3 to 6. Six of seven trials included in the CCO review reported positive effects on some measure of QOL. However, the CCO review authors could not reach definitive conclusions about the effect of ESAs on QOL in this population of patients with nonmyeloid hematological malignancies, due to inconsistent reporting and analysis. In particular, missing data occurred across the trials reviewed. Of note, the authors of the CCO review chose not to conduct pooled analyses of data across the trials. This was based on the small amount of data available from the published reports, variations in reporting, and the availability of the 2004 Cochrane Review that had included updated patient data from six trials of patients with hematological malignancies.

The AHRQ CER included subgroup analyses of, respectively, six trials of epoetin (1,044 total patients) and two trials of darbepoetin (410 total patients) in patients with nonmyeloid hematological malignancies receiving chemotherapy. Results indicated that patients treated with epoetin had a reduced risk of RBC transfusion (RR, 0.74; 95% CI, 0.66 to 0.84), as did patients treated with darbepoetin (RR, 0.66; 95% CI, 0.49 to 0.83). Meta-analyses of the survival data from these epoetin and darbepoetin trials showed no statistically significant difference between patients treated with epoetin or darbepoetin and controls. The pooled hazard ratio for the six epoetin trials was 1.02 (95% CI, 0.81 to 1.29) and for the two darbepoetin trials, the hazard ratio was 1.36 (95% CI, 0.98 to 1.89). Finally, results of a pooled analysis of data from five trials (898 total patients) showed that patients treated with epoetin had an increased risk of thromboembolic events (RR, 3.00; 95% CI, 1.10 to 8.12).

XI. SPECIAL COMMENTARY ON ESAs, SURVIVAL, AND TUMOR RESPONSE

Since publication of the 2002 guideline, a number of published studies on ESAs in cancer patients have raised safety concerns. Additional studies have completed accrual or were terminated prematurely and do not have complete data available. Much of the non-peer-reviewed data in the public domain comes from briefing documents made available in conjunction with US Food and Drug Administration ODAC meetings in 2004 and 2007.^{2,22} In this commentary, we discuss those studies, both published and unpublished, that showed a detrimental effect on survival or tumor response.

Brief Background on US Food and Drug Administration Regulatory Activity

In May 2004, the US Food and Drug Administration convened a meeting of its ODAC² to review the results of the BEST (EPO-INT-76) study,²⁴ the ENHANCE study,²⁵ and Study N93-004.² A number of recommendations were issued by members of ODAC after review of these studies, primarily concerning the design of future trials needed to answer the questions raised by previous studies with negative outcomes.

The US Food and Drug Administration reconvened ODAC in May 2007, after the release of results from subsequent trials that raised additional safety concerns. Before this meeting, in March 2007, the US Food and Drug Administration updated the Warning Sections and “Black Box” warning of the approved labels for both epoetin and darbepoetin, based on recently released study results. At its May 2007 meeting, ODAC members issued an additional series of recommendations. These recommendations included setting a baseline Hb level at which to initiate ESA therapy in asymptomatic patients, reassessing anemia at the start of each new chemotherapy regimen, restricting ESA use to certain tumor types, further restrictions to ESA indications on the US Food and Drug Administration-approved label, and the conduct of future clinical trials.²²

Review of Relevant Studies

Several randomized trials to date have demonstrated decreased survival times in cancer patients receiving ESAs (BEST, ENHANCE, 20010103, 20000161, EPO-CAN-20), and two randomized trials have demonstrated poorer locoregional control or progression-free survival in cancer patients receiving ESAs (ENHANCE, DAHANCA-10/SE 2002-9001). The BEST and ENHANCE studies were included in the meta-analysis by Bohlius et al.³ Three of these studies—BEST, ENHANCE, and EPO-CAN-20²⁴⁻²⁶—have been published in peer-reviewed journals. The remaining studies are not yet available as full reports, but data are publicly available in ODAC briefing documents posted on the US Food and Drug Administration Web site.

The BEST study²⁴ randomized 939 women with metastatic breast cancer receiving first-line chemotherapy to epoetin alfa versus placebo in a double-blind fashion. Epoetin alfa was initiated if the baseline Hb was less than or equal to 13 g/dL, or when Hb decreased below that point during the trial. Mean baseline Hb at trial entry was 12.5 g/dL in both study arms. The target Hb was 12 to 14 g/dL; epoetin alfa was given for 12 months. Concurrent radiotherapy and hormonal therapy were also allowed. The study's primary end point was one-year overall survival, and secondary end points included objective tumor response rates and time to disease progression. Following a recommendation from the data monitoring committee, the study was terminated early (but after enrollment was completed), due to higher mortality in the ESA-treated arm. At the time of study termination, the analysis of interim data showed that within 12 months of random assignment there were 138 (28%) deaths in the ESA group, versus 111 (23%) in the placebo group ($P = .02$). Final analysis of the one-year overall survival rate for the ITT population showed a lower one-year overall survival in the ESA-treated arm compared to the placebo arm (70% versus 76%, respectively; HR 1.37, $P = .01$). There were no significant

differences between study groups in objective response rates, time-to-progression, or duration of progression-free survival.

The ENHANCE study²⁵ was a randomized, multicenter, double-blind, placebo-controlled trial with a primary end point of locoregional progression-free survival (defined as time to locoregional tumor progression or death). Secondary end points included overall survival and time to locoregional tumor progression. The study population consisted of 351 patients with advanced head and neck cancer receiving definitive or postoperative radiotherapy (but without chemotherapy). Patients were randomized to epoetin beta or placebo throughout the duration of radiotherapy; the target Hb was 14.5 g/dL for women and 15 g/dL for men. Median baseline Hb at study entry was 11.8 g/dL for the placebo group and 11.7 g/dL for the epoetin beta group. Study results published in 2003 showed significantly shorter locoregional progression-free survival in ESA-treated patients (HR, 1.62; 95% CI, 1.22 to 2.14, $P = .0008$); a significantly shorter time to locoregional progression in ESA-treated patients (HR, 1.69; 95% CI, 1.16 to 2.47, $P = .007$); and a significantly shorter overall survival in ESA-treated patients (HR, 1.39; 95% CI, 1.05 to 1.84, $P = .02$).

EPO-CAN-20,²⁶ a randomized, multicenter, double-blind, placebo-controlled trial, was designed with QOL as the primary outcome. At study entry, patients were initially required to have a baseline Hb of less than 12 g/dL, with NSCLC unsuitable for curative therapy. Patients were stratified by the concurrent planned use or not of palliative radiotherapy. The protocol was later amended to allow non-platinum-based palliative chemotherapy, as the growing use of palliative chemotherapy was adversely influencing accrual. At the time of study publication, it was reported that 23% of patients had received prior systemic therapy (non-platinum-based) and no patients received additional systemic therapy. Mean Hb at baseline was 10.3 g/dL for both arms; target Hb was 12 to 14 g/dL. The proposed sample size was 300 patients, but reports of thrombotic events in other trials led to an unplanned safety analysis after 70 patients were randomized. The safety analysis, based on 66 patients, showed a significant difference in median survival in favor of the placebo arm (63 v 129 days; HR, 1.84; 95% CI, 1.01 to 3.35, $P = .04$), and the trial Steering Committee terminated the trial. At the time of the unplanned analysis, one patient in the ESA arm and two patients in the placebo arm had experienced thrombotic events; further follow-up on all 70 patients showed two additional events, one in each arm of the study.

The DAHANCA 10 trial by the Danish Head and Neck Cancer Group was a randomized, multicenter, open-label trial of darbeпоetin use in head and neck cancer patients receiving radiotherapy.³⁷ (Note. Published results of this study have been presented: Overgaard J, Hoff C, Sand Hansen H, et al: Randomized study of the importance of novel erythropoiesis stimulating protein [Aranesp] for the effect of radiotherapy in patients with primary squamous cell of the head and neck [HNSCC]: The Danish Head and Neck Cancer Group DAHANCA 10 rand. *Eur J Cancer Suppl* 5:7, 2007.) Baseline Hb was ≤ 14.5 .²² The trial was temporarily stopped in October of 2006 due to unexpected adverse events that seemed to be related to the presence of epoetin receptors as tested for in the study. According to the investigators, this trial suspension occurred almost simultaneously with a planned interim analysis. The decision was made to suspend accrual and await outcome of the planned analysis before making any final decisions regarding

trial disposition. The planned interim analysis was made publicly available online, with authorship attributed to Jens Overgaard, Principal Investigator of the DAHANCA 10 protocol, and dated December 1, 2006.³⁷ At the time of this analysis, the trial had randomized 522 patients of a planned 600; a total of 484 patients were included in the interim analysis. Only summary data were reported, which included significantly poorer outcomes in the darbeпоetin arm for the primary end point of locoregional failure. Overall survival showed a smaller and nonsignificant difference between the two study arms.

Study 20010103 has not been published in a peer-reviewed journal, but summary results were reported in the US Food and Drug Administration ODAC briefing document.²² Study 20000161 was published in 2003,³⁸ and an updated data set was provided to US Food and Drug Administration in April of 2007. Neither study had survival as a primary outcome. The primary end point for Study 20010103 was transfusion rates, and for Study 20000161, the primary end point was the proportion of patients achieving an increase in Hb of ≥ 2 g/dL. The following statistics are based on US Food and Drug Administration analysis of primary data submitted by the study sponsor before the May 2007 ODAC meeting. Study 20010103 enrolled 989 patients with nonmyeloid malignancies not receiving chemotherapy, with a baseline Hb of ≤ 11 g/dL. The target Hb was 12 to 13 g/dL. Overall survival was poorer in the ESA versus control arm (HR, 1.30; 95% CI, 1.07 to 1.57, $P = .008$), with no difference in rates of transfusion (HR, 0.85; 95% CI, 0.62 to 1.17). Study 20000161 enrolled 344 patients with lymphoproliferative malignancies receiving chemotherapy, with a baseline Hb of ≤ 11 g/dL. The target Hb was more than 15 g/dL (males) or ≥ 14 g/dL (females). Overall survival was poorer in the ESA versus control arm (HR, 1.37; 95% CI, 1.02 to 1.83, $P = .037$). Progression-free survival was no different between the two study arms (HR, 1.02; 95% CI, 0.80 to 1.30).

The Update Committee is also aware of additional studies²² whose results have not been submitted for publication in peer-reviewed journals. Some of these trials were closed early due to safety concerns, while others have completed accrual. Much of this evidence has been summarized by the US Food and Drug Administration in its two previous briefings to ODAC.^{2,22} The US Food and Drug Administration's analyses of these studies were based on data submitted to them by the drug sponsors.

Due to the designs of the trials discussed above, there is difficulty in interpreting their results and applying them to current clinical practice. All of the studies, with the exception of 20010103, had a target Hb greater than 12 g/dL, and all enrolled patients with a baseline mean or median Hb more than 10 g/dL (for studies specifically reporting this parameter), although EPO-CAN-20 utilized criteria closest to currently recommended ASCO/ASH guidelines, with a baseline Hb of 10.3 g/dL in each arm. The ENHANCE²⁵ and DAHANCA-10³⁷ studies examined head and neck cancer patients receiving only radiotherapy; Study 20010103² investigated ESA use in patients with active, nonmyeloid disease, receiving no therapy; and the EPO-CAN-20²⁶ study population consisted of patients with NSCLC not given concomitant systemic therapy.

It is, therefore, unknown whether these results apply to a population of chemotherapy-treated cancer patients receiving ESAs at doses titrated to achieve and maintain a Hb level of close to

12 g/dL. Adequately-powered, well-designed trials designed to detect differences in tumor response or survival are lacking in patients for whom ESAs are prescribed to decrease the need for transfusion secondary to myelosuppressive chemotherapy. While there is a body of literature supporting the safety and efficacy of ESAs in selected patients with MDS, randomized trials could further define which patients are most likely to benefit from ESA use.

RESEARCH PRIORITIES

The literature-based systematic reviews and meta-analyses conducted to date used published data from available randomized controlled trials on ESAs, often averaged across heterogeneous patient groups. A patient-level meta-analysis of completed trials on ESAs could estimate potential benefits and harms in more homogeneous patient subgroups, and thus support more individualized clinical decisions. Patient-level meta-analysis might also help generate useful hypotheses on factors contributing to transfusion and/or adverse event risks; or to faster tumor progression or shorter survival in some ESA-treated patients; or provide a better understanding of effectiveness of ESAs for anemia not related to chemotherapy (anemia of cancer) and thus help guide design of new clinical trials.

Other priorities for future research include the following:

- more consistent and comprehensive assessment and reporting of adverse events graded by severity, particularly from trials that compare alternative dosing strategies;
- increased effort, using both basic laboratory and clinical research, to understand the functional impact and clinical consequences of exposing tumors with erythropoietin receptors to exogenous ESAs;
- better evidence regarding the benefits of supplementing ESA therapy with iron, including ESA dose-sparing effect, appropriate dosing, and formulation of iron therapy;
- additional prospective trials regarding use of ESAs in MDS, to better define factors predictive of response, appropriate duration of treatment, and risks of treatment;
- better evidence on contribution of changes in Hb concentration to changes in QOL outcomes by: more comprehensive research on all causes of fatigue in cancer patients, and by testing prespecified hypotheses with a consensus set of core measures, comparing blinded

randomized controlled trial arms for absolute and relative change from baseline, with measures of variance; and

- collecting and reporting economic outcomes, particularly when comparing doses, treatment frequencies, and alternative dosing strategies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Charles L. Bennett, Amgen (C); Benjamin Djulbegovic, Amgen (C); Alan E. Lichtin, Amgen (Advisory Board Meeting) (U) **Stock Ownership:** None **Honoraria:** Julia Bohlius, Amgen; Charles L. Bennett, Amgen **Research Funding:** Charles L. Bennett, Amgen; David F. Cella, Amgen, Johnson and Johnson; Benjamin Djulbegovic, Johnson and Johnson; Alan E. Lichtin, Amgen **Expert Testimony:** None **Other Remuneration:** Julia Bohlius, Amgen

AUTHOR CONTRIBUTIONS

Conception and design: J. Douglas Rizzo, Mark R. Somerfield, Benjamin Djulbegovic, David H. Regan, Alan E. Lichtin

Administrative support: Mark R. Somerfield

Collection and assembly of data: J. Douglas Rizzo, Mark R. Somerfield, Karen L. Hagerty, Jerome Seidenfeld, Julia Bohlius, Charles L. Bennett, David H. Regan

Data analysis and interpretation: J. Douglas Rizzo, Mark R. Somerfield, Karen L. Hagerty, Jerome Seidenfeld, Julia Bohlius, Charles L. Bennett, Benjamin Djulbegovic, Ann A. Jakubowski, Mark U. Rarick, David H. Regan, Alan E. Lichtin

Manuscript writing: J. Douglas Rizzo, Mark R. Somerfield, Karen L. Hagerty, Jerome Seidenfeld, Julia Bohlius, Charles L. Bennett, David F. Cella, Ann A. Jakubowski, Alan E. Lichtin

Final approval of manuscript: J. Douglas Rizzo, Jerome Seidenfeld, Julia Bohlius, Charles L. Bennett, David F. Cella, Benjamin Djulbegovic, Matthew Goode, Ann A. Jakubowski, Mark U. Rarick, David H. Regan, Alan E. Lichtin

REFERENCES

1. Rizzo JD, Lichtin AE, Woolf SH, et al: Use of epoetin in patients with cancer: Evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *J Clin Oncol* 20:4083-4107, 2002
2. Food and Drug Administration. Oncologic Drugs Advisory Committee Briefing Document. Safety Concerns Associated with Aranesp (darbepoetin alfa) Amgen, Inc. and Procrit (epoetin alfa) Ortho Biotech, L.P., for the Treatment of Anemia Associated with Cancer Chemotherapy. 2004. http://www.fda.gov/ohrms/dockets/ac/04/briefing/4037b2_04.pdf
3. Bohlius J, Wilson J, Seidenfeld J, et al: Erythropoietin or darbepoetin for patients with cancer (review). *The Cochrane Library Issue 2*, 2007

4. Seidenfeld J, Piper M, Bohlius J, et al: Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment. Comparative Effectiveness Review No. 3. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-02-0026.) Agency for Healthcare Research and Quality, 2006. www.effectivehealthcare.ahrq.gov/reports/final.cfm
5. Wilson J, Yao GL, Raftery J, et al: A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment. *Health Technol Assess* 11:1-220, 2007
6. Quirt I, Bramwell V, Charette M, et al: The Role of Erythropoietin in the Management of Cancer Patients with Non-hematologic Malignancies Receiving Chemotherapy. *Cancer Care Ontario*, 2007. <http://www.cancercare.on.ca/pdf/pebc12-11.pdf>

7. Shehata N, Walker I, Meyer R, et al: Treatment for Anemia with Erythropoietic Agents in Patients with non-Myeloid Hematological Malignancies: A Clinical Practice Guideline. *Cancer Care Ontario*, 2007. <http://www.cancercare.on.ca/pdf/pebc6-12s.pdf>

8. Ross SD, Allen IE, Henry DH, et al: Clinical benefits and risks associated with epoetin and darbepoetin in patients with chemotherapy-induced anemia: A systematic review of the literature. *Clin Ther* 28:801-831, 2006

9. Seidenfeld J, Piper M, Flamm C, et al: Epoetin treatment of anemia associated with cancer therapy: A systematic review and meta-analysis of controlled clinical trials. *J Natl Cancer Inst* 93:1204-1214, 2001

10. Crawford J, Robert F, Perry MC, et al: A randomized trial comparing immediate versus delayed treatment of anemia with once-weekly epoetin alfa in patients with non-small cell lung cancer

scheduled to receive first-line chemotherapy. *J Thorac Oncol* 2:210-220, 2007

11. Straus DJ, Testa MA, Sarokhan BJ, et al: Quality-of-life and health benefits of early treatment of mild anemia: A randomized trial of epoetin alfa in patients receiving chemotherapy for hematologic malignancies. *Cancer* 107:1909-1917, 2006

12. Rearden TP, Charu V, Saidman B, et al: Results of a randomized study of every three-week dosing (Q3W) of darbepoetin alfa for chemotherapy-induced anemia (CIA). *J Clin Oncol* 22:745s, 2004 (suppl, abstr 8064)

13. Lyman GH, Glaspy J: Are there clinical benefits with early erythropoietic intervention for chemotherapy-induced anemia? A systematic review. *Cancer* 106:223-233, 2006

14. Browman GP: Standards of proof, standards of practice, and proof of standards: A tale of two trials. *J Clin Oncol* 23:2583-2585, 2005

15. Cella D, Herbst RS, Lynch TJ, et al: Clinically meaningful improvement in symptoms and quality of life for patients with non-small-cell lung cancer receiving gefitinib in a randomized controlled trial. *J Clin Oncol* 23:2946-2954, 2005

16. Cella D, Kallich J, McDermott A, et al: The longitudinal relationship of hemoglobin, fatigue and quality of life in anemic cancer patients: Results from five randomized clinical trials. *Ann Oncol* 15: 979-986, 2004

17. Mallinson T, Cella D, Cashy J, et al: Giving meaning to measure: Linking self-reported fatigue and function to performance of everyday activities. *J Pain Symptom Manage* 31:229-241, 2006

18. Bennett CL, Angelotta C, Yarnold PR, et al: Thalidomide- and lenalidomide-associated thromboembolism among patients with cancer. *JAMA* 296: 2558-2560, 2006

19. ten Bokkel Huinink WW, de Swart CA, van Toorn DW, et al: Controlled multicentre study of the influence of subcutaneous recombinant human erythropoietin on anaemia and transfusion dependency in patients with ovarian carcinoma treated with platinum-based chemotherapy. *Med Oncol* 15: 174-182, 1998

20. Thatcher N, De Campos ES, Bell DR, et al: Epoetin alpha prevents anaemia and reduces transfusion requirements in patients undergoing primarily

platinum-based chemotherapy for small cell lung cancer. *Br J Cancer* 80:396-402, 1999

21. Vansteenkiste J, Pirker R, Massuti B, et al: Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. *J Natl Cancer Inst* 94:1211-1220, 2002

22. Food and Drug Administration Oncologic Drugs Advisory Committee Briefing Document. Continuing Reassessment of the Risks of Erythropoiesis-Stimulating Agents (ESAs) Administered for the Treatment of Anemia associated with Cancer Chemotherapy. 2007. <http://www.fda.gov/ohms/dockets/ac/07/briefing/2007-4301b2-02-FDA.pdf>

23. A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes: Italian Cooperative Study Group for rHuEpo in Myelodysplastic Syndromes. *Br J Haematol* 103:1070-1074, 1998

24. Leyland-Jones B, Semiglazov V, Pawlicki M, et al: Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: A survival study. *J Clin Oncol* 23:5960-5972, 2005

25. Henke M, Laszig R, Rube C, et al: Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: Randomised, double-blind, placebo-controlled trial. *Lancet* 362: 1255-1260, 2003

26. Wright JR, Ung YC, Julian JA, et al: Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. *J Clin Oncol* 25:1027-1032, 2007

27. Khuri FR: Weighing the hazards of erythropoiesis stimulation in patients with cancer. *N Engl J Med* 356:2445-2448, 2007

28. Auerbach M, Ballard H, Trout JR, et al: Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: A multicenter, open-label, randomized trial. *J Clin Oncol* 22:1301-1307, 2004

29. Henry DH, Dahl NV, Auerbach M, et al: Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. *Oncologist* 12:231-242, 2007

30. Hedenus M, Birgegard G, Nasman P, et al: Addition of intravenous iron to epoetin beta in-

creases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: A randomized multicenter study. *Leukemia* 21:627-632, 2007

31. Casadevall N, Durieux P, Dubois S, et al: Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: A randomized, controlled trial. *Blood* 104:321-327, 2004

32. Abels RI, Larholt KM, Krantz KD, et al: Recombinant Human Erythropoietin (rHuEPO) for the Treatment of the Anemia of Cancer. *Oncologist* 1:140-150, 1996

33. Charu V, Belani CP, Gill AN, et al: Efficacy and safety of every-2-week darbepoetin alfa in patients with anemia of cancer: A controlled, randomized, open-label phase II trial. *Oncologist* 12:727-737, 2007

34. Gordon DH, Nichols G, Ben-Jacob A, et al: Treating anemia of cancer with darbepoetin alfa administered every 4 weeks: Final results from a phase 2, randomized, double-blind, placebo-controlled study in cancer patients not receiving chemotherapy and/or radiotherapy. *Blood* 108:328a, 2006 (abstr 1304)

35. Mystakidou K, Kalaidopoulou O, Katsouda E, et al: Evaluation of epoetin supplemented with oral iron in patients with solid malignancies and chronic anemia not receiving anticancer treatment. *Anticancer Res* 25:3495-3500, 2005

36. Smith RE Jr, Tchekmedyan NS, Chan D, et al: A dose- and schedule-finding study of darbepoetin alpha for the treatment of chronic anaemia of cancer. *Br J Cancer* 88:1851-1858, 2003

37. Danish Head and Neck Cancer Group (DAHANCA). Study of the importance of Novel Erythropoiesis Stimulating Protein (Aranesp) for the effect of radiotherapy in patients with primary squamous cell carcinoma of the head and neck. 2006.http://www.dahanca.dk/get_media_file.php?mediaid=125

38. Hedenus M, Adriansson M, San Miguel J, et al: Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: A randomized, double-blind, placebo-controlled study. *Br J Haematol* 122:394-403, 2003

39. Bohlius J, Wilson J, Seidenfeld J, et al: Recombinant human erythropoietins and cancer patients: Updated meta-analysis of 57 studies including 9353 patients. *J Natl Cancer Inst* 98:708-714, 2006

Acknowledgment

The Update Committee wishes to express its gratitude to Christopher Flowers, MD, Barbara McAneny, MD, Deborah Schrag, MD, the ASCO Health Services Committee, the ASH Committee on Practice, and the ASH Subcommittee on Quality of Care for their thoughtful reviews of earlier drafts. Also, special thanks to Kaitlin Einhaus, Sarah Temin, and Patricia Hurley for developing summary tables.

Appendix 1: 2007 ASCO/ASH Epoetin and Darbepoetin Update Panel

Update Panel Member Institution

Alan E. Lichtin, MD, Co-Chair Cleveland Clinic Foundation
 J. Douglas Rizzo, MD, Co-Chair Medical College of Wisconsin
 Charles L. Bennett, MD, PhD, Northwestern University
 Julia Bohlius, MD, University Hospital of Cologne
 David F. Cella, PhD, Evanston Northwestern Healthcare
 Benjamin Djulbegovic, MD, PhD, H. Lee Moffitt Cancer Center
 Matthew Goode, Patient Representative
 Ann A. Jakubowski, MD, PhD, Memorial Sloan-Kettering Cancer Center
 Mark U. Rarick, MD, NW Kaiser Permanent
 David H. Regan, MD, US Oncology

Jerome Seidenfeld, PhD, BlueCross and BlueShield Association

Appendix 2

For the 2007 update, pertinent information published was reviewed to address each of the original guideline questions and the new topics. As noted in the Introduction, five comprehensive systematic reviews and meta-analyses of randomized controlled trials served as the primary evidentiary basis for this update. Supplementary searches of the Medline database (National Library of Medicine, Bethesda, MD) were conducted to identify relevant information (2003 to 2007) from additional published randomized clinical trials, systematic reviews, meta-analyses, and practice guidelines for this update. A series of searches was conducted using the medical subject headings or text words “erythropoietin, recombinant,” “epoetin alfa,” “epoetin beta,” “darbepoetin alfa,” and “neoplasms,” and variants thereof. (Details of the searches can be obtained from guidelines@asco.org on request.) Search results were limited to human studies and English-language articles. Editorials, letters, and commentaries were excluded from consideration, as were systematic reviews and meta-analyses that were limited to single agents given the US Food and Drug Administration’s position that available ESAs are members of the same pharmacologic class. The Cochrane Library was searched for available systematic reviews and meta-analyses with the phrases, “erythropoietin,” “epoetin,” “darbepoetin,” “cancer,” and “malignancies.” Directed searches based on the bibliographies of primary articles were also performed. Finally, Update Committee members and ASCO staff contributed articles from their personal collections.

Appendix 3: Funding Disclosures

JDR, MRS, KLH, JS, MJG, AAJ, DHR, and MUR have no conflicts related to this guideline to declare. JB has received honoraria and other funding from AMGEN. CLB has received consultant compensation, honoraria and research funding from AMGEN. DFC has received research funding from AMGEN and Johnson and Johnson. BD has received consultant compensation from AMGEN and research funding from Johnson and Johnson. AEL has provided uncompensated consultation to AMGEN, and has received research funding from AMGEN.

Table 6A. ESA Dosing (This table includes new doses contained in the FDA-approved label as released on November 8, 2007.)

Dose and Modifications	Epoetin Alfa		Darbepoetin Alfa	
Initial dose	150 U/kg SC TIW	40,000 U SC weekly	2.25 mcg/kg SC weekly	500 mcg SC Q3W
Dose increase	Increase dose to 300 U/kg TIW if no reduction in transfusion requirements or rise in Hb after 8 wks	Increase dose to 60,000 U SC weekly if no increase in Hb by ≥ 1 g/dL after 4 wks of therapy, in the absence of a RBC transfusion	Increase dose to 4.5 mcg/kg if there is < 1 g/dL increase in Hb after 6 wks	
Dose reductions	Decrease dose by 25% when Hb reaches a level needed to avoid transfusion or Hb increases > 1 g/dL in 2 wks		Decrease dose by 40% of previous dose when Hb reaches a level needed to avoid transfusion or Hb increases > 1 g/dL in 2 wks	
Dose withholding	If Hb exceeds 12 g/dL, withhold dose until Hb approaches a level where transfusions may be required ; restart dose at 25% below previous dose		If Hb exceeds 12 g/dL, withhold dose until Hb approaches a level where transfusions may be required ; restart dose at 40% below previous dose	

NOTE. New label text is shown in bold type.
Abbreviations: ESA, erythropoiesis-stimulating agent; FDA, US Food and Drug Administration; SC, subcutaneous; TIW, three times per week; Q3W, every 3 weeks; Hb, hemoglobin; wk, week.

ERRATA

The February 20, 2007, correspondence by Howard, Inskip, and Travis, entitled "Suicide After Childhood Cancer" (J Clin Oncol 25:731, 2007) contained errors due to the inaccurate calculation of underlying expected rates from the data management company.

In the third paragraph, the overall standardized mortality ratio (SMR) was given as 11 (95% CI, 7.8 to 15.3), whereas it should have been 1.10 (95% CI, 0.77 to 1.53). SMRs for less than 1 year, 1 to 4 years, 5 to 9 years, and 10 or more years after initial diagnosis were given as 11.7, 5.9, 13.8 and 11.7 respectively, whereas it should have been 1.17, 0.59, 1.38, and 1.17 respectively. SMRs for patients diagnosed at 0 to 4 years of age, 5 to 9 years, 10 to 14 years, and 15 to 20 years were given as 3.26, 8.8, 12.9, and 12.1 respectively, whereas it should have been 0.32, 0.88, 1.28, and 1.20 respectively. The SMR for males was given as 10.9 (95% CI, 7.3 to 15.6), and for females as 11.8 (95% CI, 4.7 to 24.4), whereas it should have been 1.08 (95% CI, 0.73 to 1.56) and 1.18 (95% CI, 0.47 to 2.44) respectively. The SMR for patients diagnosed before 1985 was given as 11.9 (95% CI, 7.8 to 17.5), and for those in subsequent years as 9.2 (95% CI, 4.4 to 17.0), whereas it should have been 1.19 (95% CI, 0.78 to 1.75) and 0.92 (95% CI, 0.44 to 1.70) respectively. The SMR for patients initially treated with radiation was given as 9.8 (95% CI, 5.2 to 16.8), and for those who did not receive radiotherapy as 11.9 (95% CI, 7.5 to 17.8), whereas it should have been 0.98 (95% CI, 0.52 to 1.68) and 1.18 (95% CI, 0.75 to 1.78) respectively.

DOI: 10.1200/JCO.2008.16.4434



The January 1, 2008, special article by Rizzo et al entitled, "Use of Epoetin and Darbepoetin in Patients With Cancer: 2007 American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update" (J Clin Oncol 26:132-149) contained errors.

In section VIII, "Iron Monitoring and Supplementation", under Literature Update and Discussion, the second sentence of the fourth paragraph should have indicated that patients were required to have a serum ferritin level ≥ 100 ng/mL or transferrin saturation $\geq 15\%$.

The online version has been corrected in departure from the print.

DOI: 10.1200/JCO.2008.16.4475
