

4-23-2019

Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update.

Julia Bohlius
University of Bern

Kari Bohlke
American Society of Clinical Oncology

Roberto Castelli
University of Milan

Benjamin Djulbegovic
City of Hope, Duarte

Follow this and additional works at: <https://jdc.jefferson.edu/medoncfp>

Maryam B Lustberg
Ohio State University

[Let us know how access to this document benefits you](#)

See next page for additional authors

Recommended Citation

Bohlius, Julia; Bohlke, Kari; Castelli, Roberto; Djulbegovic, Benjamin; Lustberg, Maryam B; Martino, Massimo; Mountzios, Giannis; Peswani, Namrata; Porter, Laura; Tanaka, Tiffany N.; Trifirò, Gianluca; Yang, Hushan; and Lazo-Langner, Alejandro, "Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update." (2019). *Department of Medical Oncology Faculty Papers*. Paper 97.
<https://jdc.jefferson.edu/medoncfp/97>

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's [Center for Teaching and Learning \(CTL\)](#). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Department of Medical Oncology Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: JeffersonDigitalCommons@jefferson.edu.

Authors

Julia Bohlius, Kari Bohlke, Roberto Castelli, Benjamin Djulbegovic, Maryam B Lustberg, Massimo Martino, Giannis Mountzios, Namrata Peswani, Laura Porter, Tiffany N. Tanaka, Gianluca Trifirò, Hushan Yang, and Alejandro Lazo-Langner

Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update

Julia Bohlius,^{1,*} Kari Bohlke,² Roberto Castelli,³ Benjamin Djulbegovic,⁴ Maryam B. Lustberg,⁵ Massimo Martino,⁶ Giannis Mountzios,⁷ Namrata Peswani,⁸ Laura Porter,⁹ Tiffany N. Tanaka,¹⁰ Gianluca Trifirò,¹¹ Hushan Yang,¹² and Alejandro Lazo-Langner^{13,*}

¹University of Bern, Bern, Switzerland; ²American Society of Clinical Oncology, Alexandria, VA; ³University of Milan, Milan, Italy; ⁴City of Hope, Duarte, CA; ⁵Ohio State University, Columbus, OH; ⁶Azienda Ospedaliera Bianchi Melacrinò Morelli, Reggio Calabria, Italy; ⁷Henry Dunant Hospital Center, Athens, Greece; ⁸Advocate Medical Group, Orland Park, IL; ⁹Independent Patient Advocate, Washington, DC; ¹⁰UC San Diego Moores Cancer Center, La Jolla, CA; ¹¹University of Messina, Messina, Italy; ¹²Thomas Jefferson University, Philadelphia, PA; and ¹³Western University, London, ON, Canada

Purpose: To update the American Society of Clinical Oncology (ASCO)/American Society of Hematology (ASH) recommendations for use of erythropoiesis-stimulating agents (ESAs) in patients with cancer.

Methods: PubMed and the Cochrane Library were searched for randomized controlled trials (RCTs) and meta-analyses of RCTs in patients with cancer published from January 31, 2010, through May 14, 2018. For biosimilar ESAs, the literature search was expanded to include meta-analyses and RCTs in patients with cancer or chronic kidney disease and cohort studies in patients with cancer due to limited RCT evidence in the cancer setting. ASCO and ASH convened an Expert Panel to review the evidence and revise previous recommendations as needed.

Results: The primary literature review included 15 meta-analyses of RCTs and two RCTs. A growing body of evidence suggests that adding iron to treatment with an ESA may improve hematopoietic response and reduce the likelihood of RBC transfusion. The biosimilar literature review suggested that biosimilars of epoetin alfa have similar efficacy and safety to reference products, although evidence in cancer remains limited.

Recommendations: ESAs (including biosimilars) may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose hemoglobin has declined to < 10 g/dL. RBC transfusion is also an option. With the exception of selected patients with myelodysplastic syndromes, ESAs should not be offered to most patients with nonchemotherapy-associated anemia. During ESA treatment, hemoglobin may be increased to the lowest concentration needed to avoid transfusions. Iron replacement may be used to improve hemoglobin response and reduce RBC transfusions for patients receiving ESA with or without iron deficiency. Additional information is available at www.asco.org/supportive-care-guidelines and www.hematology.org/guidelines.

Introduction

Use of erythropoiesis-stimulating agents (ESAs) to manage anemia raises hemoglobin (Hgb) levels and reduces the need for RBC transfusions, but increases the risk of thromboembolic events.^{1,2} Studies have also reported decreased survival, increased mortality during active study phase, and/or an increased risk of cancer progression or recurrence with the use of ESAs in patients with cancer.³⁻⁶ The risks of ESAs prompted multiple regulatory actions by the US Food and Drug Administration (FDA) between 2004 and 2009, and in 2010, the FDA approved a Risk Evaluation

Submitted 21 December 2018; accepted 28 January 2019. DOI 10.1182/bloodadvances.2018030387.

*J.B. and A.L.-L. were Expert Panel co-chairs.

The full-text version of this article contains a data supplement.

This guideline was developed through a collaboration between the American Society of Hematology and the American Society of Clinical Oncology and has been published jointly by invitation and consent in both *Blood Advances* and the *Journal of Clinical*

Oncology. Copyright © 2019 American Society of Hematology and American Society of Clinical Oncology. All rights reserved. No part of this document may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without written permission by the American Society of Hematology or the American Society of Clinical Oncology.

The bottom line

Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update

Guideline question

When and how should erythropoiesis-stimulating agents (ESAs) be used to manage anemia in adults with cancer?

Target population

Adults with cancer and anemia.

Target audience

Oncologists, hematologists, oncology nurses, oncology pharmacists, and other health care professionals who care for patients with cancer, and patients with cancer.

Methods

An Expert Panel was convened to update clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

Clinical question 1

To reduce the need for RBC transfusions, should ESAs be offered to patients who have chemotherapy-associated anemia?

Recommendation 1.1. Depending on clinical circumstances, ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose hemoglobin (Hgb) has declined to < 10 g/dL. RBC transfusion is also an option, depending on the severity of the anemia or clinical circumstances (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.2. ESAs should not be offered to patients with chemotherapy-associated anemia whose cancer treatment is curative in intent (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Clinical question 2

To reduce the need for RBC transfusions, should ESAs be offered to anemic patients with cancer who are not receiving concurrent myelosuppressive chemotherapy?

Recommendation 2.1. ESAs should not be offered to most patients with nonchemotherapy-associated anemia (Type: informal consensus; Evidence quality: low; Strength of recommendation: strong).

Recommendation 2.2. ESAs may be offered to patients with lower risk myelodysplastic syndromes and a serum erythropoietin level ≤ 500 IU/L (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Clinical question 3

What special considerations apply to adult patients with nonmyeloid hematologic malignancies who are receiving concurrent myelosuppressive chemotherapy?

Recommendation 3. In patients with myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia, clinicians should observe the hematologic response to cancer treatment before considering an ESA. Particular caution should be exercised in the use of ESAs concomitant with treatment strategies and diseases where risk of thromboembolic complications is increased (see Recommendations 4 and 6). In all cases, blood transfusion is a treatment option that should be considered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Clinical question 4

What examinations and diagnostic tests should be performed before making a decision about using an ESA to identify patients who are likely to benefit from an ESA?

Recommendation 4. Before offering an ESA, clinicians should conduct an appropriate history, physical examination, and diagnostic tests to identify alternative causes of anemia aside from chemotherapy or an underlying hematopoietic malignancy. Such causes should be appropriately addressed before considering the use of ESAs. Suggested baseline investigations are listed in Table 1 (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: strong).

Clinical question 5

Among adult patients who receive an ESA for chemotherapy-associated anemia, do darbepoetin, epoetin beta and alfa originator, and currently available biosimilars of epoetin alfa differ with respect to safety or efficacy?

Recommendation 5. The Expert Panel considers epoetin beta and alfa, darbepoetin, and biosimilar epoetin alfa to be equivalent with respect to effectiveness and safety (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

The bottom line (continued)

Clinical question 6

Do ESAs increase the risk of thromboembolism?

Recommendation 6. ESAs increase the risk of thromboembolism, and clinicians should carefully weigh the risks of thromboembolism and use caution and clinical judgment when considering use of these agents (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Clinical question 7

Among adult patients who will receive an ESA for chemotherapy-associated anemia, what are recommendations for ESA dosing and dose modifications?

Recommendation 7. It is recommended that starting and modifying doses of ESAs follow FDA guidelines (see Table 2 for specific dosing information; Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Clinical question 8

Among adult patients who will receive an ESA for chemotherapy-associated anemia, what is the recommended target HgB level?

Recommendation 8. HgB may be increased to the lowest concentration needed to avoid or reduce the need for RBC transfusions, which may vary by patient and condition (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Clinical question 9

Among adult patients with chemotherapy-associated anemia who do not respond to ESA therapy (< 1 to 2 g/dL increase in HgB or no decrease in transfusion requirements), does continuation of ESA therapy beyond 6 to 8 weeks provide a benefit?

Recommendation 9. ESAs should be discontinued in patients who do not respond within 6 to 8 weeks. Patients who do not respond to ESA treatment should be reevaluated for underlying tumor progression, iron deficiency, or other etiologies for anemia (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: strong).

Clinical question 10

Among adult patients with chemotherapy-associated anemia, does iron supplementation concurrent with an ESA reduce transfusion requirements?

Recommendation 10. Iron replacement may be used to improve HgB response and reduce RBC transfusions for patients receiving ESA with or without iron deficiency. Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels is recommended (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: weak).

Additional resources

More information, including a Data Supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. Patient information is available at www.cancer.net. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline update.

ASCO and ASH believe that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

and Mitigation Strategy for ESA use in patients with cancer. In 2017, the FDA determined that the Risk Evaluation and Mitigation Strategy was no longer necessary: prescribers demonstrated acceptable knowledge of the risks of ESAs and the need to counsel patients about the risks, and utilization data suggested an increase in appropriate prescribing practices.⁷ The risks of ESAs remain, however, highlighting the ongoing importance of appropriate use. ESAs are indicated in patients with cancer who are receiving myelosuppressive chemotherapy with noncurative intent and anemia that cannot be adequately managed with transfusional support.

The American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) first published a joint evidence-based clinical practice guideline for the use of ESAs in adults with cancer and anemia in 2002,⁸ with updates in 2007⁹ and

2010.¹⁰ Since the 2010 update, additional information has emerged about the safety and efficacy of ESAs in patients with metastatic breast cancer and about the role of iron in conjunction with ESAs. Treatment options have also expanded with the 2018 FDA approval of a biosimilar of epoetin alfa, warranting a guideline update.¹¹

Guideline questions

This clinical practice guideline addresses 10 clinical questions: (1) To reduce the need for RBC transfusions, should ESAs be offered to patients who have chemotherapy-associated anemia? (2) To reduce the need for RBC transfusions, should ESAs be offered to anemic patients with cancer who are not receiving concurrent myelosuppressive chemotherapy? (3) What special considerations apply to adult patients with nonmyeloid hematologic malignancies

who are receiving concurrent myelosuppressive chemotherapy? (4) What examinations and diagnostic tests should be performed before making a decision about using an ESA to identify patients who are likely to benefit from an ESA? (5) Among adult patients who receive an ESA for chemotherapy-associated anemia, do darbepoetin, epoetin beta and alfa originator, and currently available biosimilars of epoetin alfa differ with respect to safety or efficacy? (6) Do ESAs increase the risk of thromboembolism? (7) Among adult patients who will receive an ESA for chemotherapy-associated anemia, what are recommendations for ESA dosing and dose modifications? (8) Among adult patients who will receive an ESA for chemotherapy-associated anemia, what is the recommended target HgB level? (9) Among adult patients with chemotherapy-associated anemia who do not respond to ESA therapy (< 1 to 2 g/dL increase in HgB or no decrease in transfusion requirements), does continuation of ESA therapy beyond 6 to 8 weeks provide a benefit? (10) Among adult patients with chemotherapy-associated anemia, does iron supplementation concurrent with an ESA reduce transfusion requirements?

Methods

Guideline update process

This systematic review-based guideline was developed by a multidisciplinary Expert Panel (Appendix Table A1), which included a patient representative and an ASCO guidelines staff member with health research methodology expertise. The Expert Panel met via webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of guideline, which was then circulated for external review and submitted to the *Journal of Clinical Oncology (JCO)* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee prior to publication. The guideline was also reviewed and approved by the ASH Guideline Oversight Subcommittee, the ASH Committee on Quality, and ASH Officers. All funding for the administration of the project was provided by ASCO.

The recommendations were developed using a systematic review of the literature from January 31, 2010, through May 14, 2018, and clinical experience. For all questions except the question on biosimilars, PubMed and the Cochrane Library were searched for randomized controlled trials (RCTs) and meta-analyses of RCTs. Publications were included if they assessed the efficacy and safety of ESAs in patients with cancer and included at least 50 patients per arm. For the question on biosimilars, PubMed and the Cochrane Library were searched for RCTs and meta-analyses of RCTs in patients with cancer or chronic kidney disease (CKD), or cohort studies in patients with cancer. For all questions, primary outcomes of interest were mortality, frequency of RBC transfusion, thromboembolic risk, and progression-free survival. In the case of biosimilars,

HgB response and immunogenicity were additional outcomes of interest. Secondary outcomes included quality of life, fatigue, and overall survival. Search terms are provided in the Data Supplement.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, or narrative reviews; (3) published in a non-English language; or (4) an RCT that was analyzed in an included meta-analysis.

The updated search was guided by the “signals”¹² approach that is designed to identify only new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on targeted routine literature searching and the expertise of Expert Panel members to help identify potential signals. Before publication, a review of the guideline’s feasibility for implementation was also conducted. Ratings for the type and strength of the recommendation and the quality of evidence are provided with each recommendation. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline update.

The Expert Panel and guidelines staff will work with co-chairs to keep abreast of the need for any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO and ASH will determine the need to update. This is the most recent information as of the publication date.

Guideline disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (ASCO) and the American Society of Hematology (ASH) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “must not,” “should,” and “should not” indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO and ASH provide this information on an “as is” basis and makes no warranty, express or implied, regarding the information. ASCO and ASH specifically disclaim any warranties of merchantability or fitness for a particular use or purpose. ASCO and ASH assume no

responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and conflicts of interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at <http://www.asco.org/rwc>), with additional policies mutually agreed upon with ASH. All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

Results

The primary literature review included 15 meta-analyses of RCTs^{1,2,13-25} and two RCTs.^{6,26} Three meta-analyses^{15,20,22} addressed the addition of iron to an ESA. The remaining 12 meta-analyses^{1,2,13,14,16-19,21,23-25} addressed ESA versus control (placebo or best standard therapy). The quality of the meta-analyses varied based on AMSTAR2 criteria, such as assessment and discussion of bias and heterogeneity. The two RCTs consisted of a large phase III RCT in metastatic breast cancer⁶ and a smaller trial in myelodysplastic syndrome (MDS).²⁶ Evidence tables and quality assessments for included meta-analyses and RCTs are provided in the Data Supplement.

For biosimilars, both of the included meta-analyses^{27,28} and one²⁹ of the two RCTs^{29,30} involved patients with CKD. The only RCT in patients with cancer³⁰ had a high likelihood of bias based on inadequate sample size, lack of an intent-to-treat analysis, and industry funding and authorship. The quality of the four included cohort studies of biosimilars³¹⁻³⁴ in patients with cancer was not formally assessed.

Recommendations

Clinical question 1

To reduce the need for RBC transfusions, should ESAs be offered to patients who have chemotherapy-associated anemia?

Recommendation 1.1

Depending on clinical circumstances, ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose HgB has declined to < 10 g/dL. RBC transfusion is also an option, depending on the severity of the anemia or clinical circumstances (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.2

ESAs should not be offered to patients with chemotherapy-associated anemia whose cancer treatment is curative in intent

(Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review update and analysis. In the 2010 guideline, use of ESAs in relation to intent of treatment (curative versus palliative) was addressed in a Special Note. In this update, the Expert Panel chose to address treatment intent in a recommendation.

The results of the updated systematic review confirmed that ESAs reduce the risk for RBC transfusion^{1,2,6,18,19,21,24} and increase the risk of thromboembolism.^{1,2,6,16,19,25} ESAs were associated with an increased risk of on-study mortality in some^{1,2} but not all^{18,24} meta-analyses. The two meta-analyses that reported nonsignificant associations with on-study mortality focused on specific subgroups of patients defined by cancer type²⁴ or HgB level¹⁸ and included relatively small sample sizes. Seven meta-analyses^{1,2,13,17,19,21,24} and an RCT⁶ reported on overall survival, with only one publication¹³ reporting a statistically significant association with ESA use. Aapro et al¹³ reported an increased risk of death in ESA users (odds ratio, 1.20; 95% confidence interval [CI], 1.03 to 1.40) based on nine RCTs in patients with breast cancer. Meta-analyses consistently reported statistically significant reductions in fatigue with ESA use,^{1,2,14,23} but the effect sizes were small and unlikely to be clinically important.³⁵

Little information about treatment intent is available from published studies, but one RCT⁶ in the updated literature review restricted to patients with metastatic breast cancer and one meta-analysis¹ developed a decision model that incorporated intent of treatment. The 2013 Agency for Healthcare Research and Quality meta-analyses by Grant et al¹ developed decision models for patients treated with curative or noncurative intent. The models suggest that ESAs increase quality-adjusted life-years but decrease life-years in both the curative and noncurative setting. The 2016 noninferiority trial by Leyland-Jones et al⁶ compared epoetin alfa to best supportive care in 2,098 patients with metastatic breast cancer. The primary outcome of interest—progression-free survival based on investigator-determined progressive disease—did not meet noninferiority criteria (hazard ratio [HR] 1.09; 95% CI, 0.99 to 1.20; prespecified noninferiority margin was 1.15). In their conclusion, the investigators state, "In light of these study results, RBC transfusion should be the preferred approach for the management of anemia during first- or second-line chemotherapy for metastatic breast cancer. If EPO is to be used in the more advanced settings of metastatic breast cancer, this should be done with caution and based on careful risk-benefit assessment."⁶ (p1205)

Subgroup analyses of ESA efficacy and safety by baseline HgB were provided by four meta-analyses^{1,2,14,21} and one RCT.⁶ In the 2013 Agency for Healthcare Research and Quality meta-analysis by Grant et al,¹ patients who initiated ESA use at a lower HgB level (≤ 10 g/dL) had a greater reduction in likelihood of RBC transfusion than patients who initiated ESA use at a higher baseline HgB level (relative risk, 0.46; 95% CI, 0.41 to 0.49, for patients with lower HgB at ESA initiation, compared with relative risk, 0.71; 95% CI, 0.65 to 0.79, for patients with higher HgB at ESA initiation; $P < .01$ for interaction). The effects of ESA use on on-study mortality and overall survival did not differ significantly by baseline HgB level. In the 2012 Cochrane review by Tonia et al,² three levels of baseline HgB were analyzed: ≤ 10 g/dL, 10 to 12 g/dL, and > 12 g/dL. Patients with a baseline HgB level of 10 to 12 g/dL had the greatest reduction in risk of RBC transfusion with ESA use. In the

remaining two meta-analyses, baseline HgB did not significantly modify the association between ESA use and fatigue¹⁴ or overall survival.²¹ In the 2016 RCT by Leyland-Jones et al,⁶ the HRs for progression-free survival were similar in patients with lower and higher baseline HgB levels (HR, 1.11; 95% CI, 0.92 to 1.33, for patients with baseline HgB < 10 g/dL; HR, 1.08; 95% CI, 0.96 to 1.21, for patients with baseline HgB ≥ 10 g/dL); a test for interaction was not reported, but 95% CIs are widely overlapping.

Clinical interpretation. As of the date of this publication, the FDA-approved labels state that ESAs are indicated for the treatment of anemia due to concomitant, myelosuppressive chemotherapy that is expected to continue for at least 2 additional months after ESA initiation. The labels state that ESAs are not indicated for use in patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion. A boxed warning includes several additional cautionary notes for use in cancer, including a statement that ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.

Unfortunately, it cannot be determined from the available evidence whether any particular group of potential ESA recipients has a greater or lesser risk of harm than other patients with chemotherapy-induced anemia. The mechanisms of harm are also unclear. The FDA-approved label's distinction between patients being treated with curative versus palliative intent may assist clinicians as they compare and discuss with patients the risk-to-benefit ratios of an ESA versus RBC transfusions. The decision to limit the indication for ESAs to patients undergoing chemotherapy for palliation (treatment intent) is not based on direct comparative analyses of data from clinical trials of ESA treatment based on the intent of any particular regimen used. Rather, it is based on the known risks, such as increased risk for thromboembolic events and short-term mortality and decreased overall survival. These increased risks have been observed across different patient groups.^{6,36} With currently available evidence, it is not possible to determine a patient group that could safely use ESAs.

Note also that determining the goal of treatment requires clinical judgment. Examples of diseases for which the treatment goal should generally be considered curative include (among others) testicular cancer, first-line therapy of Hodgkin disease, and early-stage solid tumors treated with adjuvant chemotherapy (eg, breast, colon, early lung). The Expert Panel acknowledges the FDA's assessment that the reported benefits of ESAs may be outweighed by risks considered unacceptable in patients who might otherwise expect cure or moderate to long survival from their chemotherapy. Clinicians are urged to exercise caution in considering ESA use in patients with malignancy being treated with curative intent. The Expert Panel stresses the importance of including a detailed discussion between health care providers and their patients about the potential harms and benefits of ESA therapy.

FDA-approved labeling for each ESA also states, "Initiate...in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/dL." The Expert Panel accepts that, although evidence is lacking to establish an optimal HgB threshold for starting ESA therapy, it is clinically prudent to wait until HgB

concentration decreases to less than 10 g/dL. However, the Expert Panel acknowledges that rare clinical circumstances (such as severe pulmonary or cardiovascular comorbidities) may warrant careful consideration of ESA use when HgB levels are ≥ 10 g/dL.

In rare circumstances, patients with cancer and renal insufficiency may have concurrent indications for the use of ESAs. Clinicians should also consider guidelines on ESA use for CKD-related anemia under these circumstances.

Clinical question 2

To reduce the need for RBC transfusions, should ESAs be offered to anemic patients with cancer who are not receiving concurrent myelosuppressive chemotherapy?

Recommendation 2.1

ESAs should not be offered to most patients with nonchemotherapy-associated anemia (Type: informal consensus; Evidence quality: low; Strength of recommendation: strong).

Recommendation 2.2

ESAs may be offered to patients with lower-risk MDSs and a serum erythropoietin level ≤ 500 IU/L (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review update and analysis. The recommendation against ESA use in patients who are not receiving concomitant myelosuppressive chemotherapy (with the exception noted in Recommendation 2.2) has been reworded, but the intent is the same as in 2010. Recommendation 2.2 has been revised to specify serum erythropoietin levels at which an ESA may be appropriate in MDS.

Two meta-analyses in the updated literature review presented subgroup results by cancer treatment.^{2,14} Neither provided evidence that would support a change to the Recommendation 2.1. In a 2014 meta-analysis of ESAs and fatigue,¹⁴ a benefit of ESAs was numerically greatest among patients treated with chemotherapy, although the test for interaction by type of cancer treatment was not statistically significant ($P = .22$). In a 2012 meta-analysis,² type of cancer treatment did not qualify for inclusion in multivariate models of ESA safety and efficacy.

In patients with MDS, one RCT evaluated the addition of epoetin beta to lenalidomide in 131 patients with RBC transfusion-dependent, low, or intermediate-1 risk (according to the International Prognostic Scoring System), ESA refractory, nondel(5q) MDS.²⁶ The combination of lenalidomide and epoetin beta increased the frequency of erythroid response relative to lenalidomide alone (39% v 23%; $P = .04$), but did not significantly affect duration of erythroid response (15 v 18 months; $P = .64$) or likelihood of transfusion independence (24% v 14%; $P = .13$). In subgroup analyses, patients with lower baseline serum erythropoietin levels had higher rates of erythroid response.

Clinical interpretation. There is no evidence that the relative effects of ESAs to reduce the risk for RBC transfusions differ in patients with and without myelosuppressive chemotherapy. However, according to current licensing, ESAs are only indicated in patients who are anemic from concurrent myelosuppressive chemotherapy and not in patients with cancer who are not receiving concurrent myelosuppressive chemotherapy.

In patients with MDS, some studies suggest that patients with elevated baseline erythropoietin levels (> 500 IU/L) are unlikely to respond to ESA therapy.³⁷ Furthermore, a recent study has suggested that an even lower baseline erythropoietin level (< 200 IU/L) is associated with a better Hgb response.³⁸ ESAs should be avoided in patients with MDS with elevated baseline erythropoietin levels (> 500 IU/L). Lower pretreatment RBC transfusion dependence (< 2 units per month) has also been associated with a higher likelihood of ESA response in patients with MDS.³⁹ Among the potential benefits of ESA therapy in patients with MDS is avoidance of secondary hemochromatosis, particularly for lower risk patients who may have years of survival.

Clinical question 3

What special considerations apply to adult patients with non-myeloid hematologic malignancies who are receiving concurrent myelosuppressive chemotherapy?

Recommendation 3

In patients with myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia, clinicians should observe the hematologic response to cancer treatment before considering an ESA. Particular caution should be exercised in the use of ESAs concomitant with treatment strategies and diseases where risk of thromboembolic complications is increased (see Recommendations 4 and 6). In all cases, blood transfusion is a treatment option that should be considered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review update and analysis. The 2012 Cochrane review by Tonia et al² conducted subgroup analyses by cancer type and provided results for mortality, RBC transfusion, thromboembolism, and fatigue. Interactions by cancer type were nonsignificant except for RBC transfusions: the reduction in risk of RBC transfusion with ESA use was greatest among patients with solid tumors. Other meta-analyses also evaluated subgroups of patients with hematologic malignancies, but only in relation to a single outcome: overall survival (nonsignificantly associated with ESA use based on a single study of 60 patients with lymphoma),²¹ thromboembolism (increased risk with ESA use),¹⁶ or fatigue (decreased risk with ESA use).¹⁴

Clinical interpretation. The FDA label now limits the indication for ESA use to patients receiving chemotherapy for noncurative intent. In patients with nonmyeloid hematologic malignancies, who are being treated with palliative intent and in whom a short survival can be reasonably expected, use of ESAs can be considered if anemia does not improve with treatment of the underlying malignancy and cannot be supported with transfusions due to logistical or personal factors or preferences. However, given the recent advances in the treatment of these diseases that have resulted in significant improvements in survival, very careful consideration should be given to the categorization of the treatment intent. Evaluation of individual cases must be based on the intent of treatment and the life expectancy for each patient. Because these malignancies recur in most patients but multiple treatments are currently available for this situation, determining the treatment intent and the expected survival requires clinical judgment of an individual patient's circumstances. Additionally, the risks of other complications, in particular, thromboembolic events, must be taken into account as many agents can increase the risk of this complication (eg,

Table 1. Suggested baseline investigations for anemia in patients with cancer receiving chemotherapy

Suggested investigation
Thorough drug exposure history
Review of a peripheral blood smear*
Analyses, where indicated, for iron, total iron-binding capacity, transferrin saturation, ferritin, folate, vitamin B ₁₂ , or hemoglobinopathy screening
Assessment of reticulocyte count, occult blood loss, and renal insufficiency
Baseline erythropoietin level
Testing of serum thyroid-stimulating hormone level, where indicated
Investigations may also include direct antiglobulin testing (eg, Coombs test) for patients with chronic lymphocytic leukemia, non-Hodgkin lymphoma, or a history of autoimmune disease

Suggestions are based on the consensus of the Expert Panel. This is not intended to be a comprehensive list of investigations.

*And in some cases, a bone marrow examination.

immunomodulatory drugs in multiple myeloma). Finally, it should be noted that there is little to no information regarding the risks and benefits of the concurrent use of ESAs and newer agents, such as monoclonal antibodies and targeted and cellular therapies, and therefore, no recommendations can be issued in this regard.

Clinical question 4

What examinations and diagnostic tests should be performed before making a decision about using an ESA to identify patients who are likely to benefit from an ESA?

Recommendation 4

Before offering an ESA, clinicians should conduct an appropriate history, physical examination, and diagnostic tests to identify alternative causes of anemia aside from chemotherapy or an underlying hematopoietic malignancy. Such causes should be appropriately addressed before considering the use of ESAs. Suggested baseline investigations are listed in Table 1 (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review update and analysis. No new eligible publications were identified by the updated literature review.

Clinical interpretation. Given the risks associated with the use of ESAs, it is of the utmost importance to assess the need for and the risks of their use. Therefore, changes to the previous recommendations include clarification of the investigations suggested in the work-up of anemia prior to considering the use of ESAs since addressing reversible causes of anemia is the preferred initial approach. Additionally, given the increased risk of thromboembolism, evaluating thrombotic risk is very important. This is addressed in Clinical Question 6.

Clinical question 5

Among adult patients who receive an ESA for chemotherapy-associated anemia, do darbepoetin, epoetin beta and alfa originator, and currently available biosimilars of epoetin alfa differ with respect to safety or efficacy?

Recommendation 5

The Expert Panel considers epoetin beta and alfa, darbepoetin, and biosimilar epoetin alfa to be equivalent with respect to effectiveness and safety (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review update and analysis. Three meta-analyses conducted subgroup analyses by type of ESA (epoetin versus darbepoetin).^{1,2,16} The two agents showed similar safety and efficacy. One exception to this was reported in the 2012 Cochrane review by Tonia et al.² Epoetin was associated with a larger improvement in fatigue than darbepoetin, but these results may have been confounded by three darbepoetin trials without anticancer treatment.

The systematic review of biosimilar ESAs included two meta-analyses^{27,28} and one RCT²⁹ in patients with CKD, and one RCT³⁰ and three cohort studies³¹⁻³³ in patients with cancer. In a 2017 meta-analysis of RCTs in CKD, Amato et al²⁷ reported that efficacy and safety outcomes did not differ significantly between patients treated with epoetin alfa originator or biosimilar but described the quality of evidence as low to very low. A 2017 Cochrane review by Hahn et al²⁸ focused on short-acting ESAs in predialysis patients. The review identified one trial of HX575 (a biosimilar of epoetin alfa), but results were not available; the trial was stopped early when two patients receiving HX575 developed antibodies to epoetin and pure red cell aplasia. HX575 was also evaluated in a 2017 RCT by Weir et al.²⁹ The trial enrolled adults with end-stage renal disease who were on dialysis and had been receiving stable doses of epoetin alfa. Patients were randomly assigned to continue epoetin alfa or to receive HX575. The two agents were similarly effective at maintaining stable HgB levels. Binding anti-erythropoietin antibodies developed in six patients (2.8%) in the HX575 arm and one patient (0.5%) in the epoetin alfa arm, but no patients developed neutralizing anti-erythropoietin antibodies.

The single RCT in patients with cancer was small: 60 patients assigned to HX575 and 34 assigned to epoetin alfa were included in the analysis.³⁰ All patients had solid tumors and chemotherapy-associated anemia. HX575 appeared to be effective with respect to HgB response, but the possibility of bias in this study limits firm conclusions. A large retrospective population-based cohort study in Italy evaluated more than 13,000 new ESA users, 8161 with CKD and 5,309 with cancer.³³ A biosimilar epoetin alfa had been used by 154 (1.9%) of the patients with CKD and 453 (8.5%) of the patients with cancer. Biosimilar and originator epoetin alfa had similar safety and efficacy in both CKD and cancer with one exception: among patients with cancer, biosimilar epoetin alfa was associated with lower overall mortality than the originator (HR, 0.82; 95% CI, 0.70 to 0.97), but this finding is not conclusive because residual confounding could not be excluded since more patients in the originator group died of cancer activity. A retrospective study of patients with MDS and refractory anemia evaluated 46 patients treated with biosimilar epoetin alfa and 46 patients with originator epoetin alfa. Median time to reach an HgB level > 12 g/dL was 10.5 weeks (range, 3 to 16 weeks) among patients treated with the biosimilar and 12 weeks (range, 4 to 18 weeks) among patients treated with the originator product.³¹ Finally, a retrospective study of 419 patients with cancer compared biosimilar epoetin alfa with darbepoetin alfa.³² Mean HgB increase was similar in the two groups. Blood transfusions were received by 8% of patients treated with biosimilar epoetin alfa and 14% of

patients treated with darbepoetin alfa ($P = .04$). These results were confirmed in another Italian retrospective cohort study, which did not find a difference in HgB response among new users of either biosimilars or reference product of epoetin alfa or other ESAs in either CKD or patients with cancer during the first 3 months of treatment.³⁴

Clinical interpretation. Based on limited evidence, it seems that compared with the originator, biosimilars of epoetin alfa are safe and effective. However, the evidence is of moderate to low quality, and this is derived from studies in patients with cancer and CKD. Biosimilars have been available in Europe for over 10 years, and no major concerns have arisen. In the United States, these agents are more recent. Users should review pertinent approvals and indications as per their local regulatory authorities. Ultimately, the choice of a particular agent will depend on cost, availability, convenience, and personal considerations or preference.^{40,41}

Clinical question 6

Do ESAs increase the risk of thromboembolism?

Recommendation 6

ESAs increase the risk of thromboembolism, and clinicians should carefully weigh the risks of thromboembolism and use caution and clinical judgment when considering use of these agents (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Literature review update and analysis. The publications in the updated review consistently report an increased risk of thromboembolism in ESA-treated patients.^{1,2,6,16,19,25} This increased thromboembolic risk with ESA use was observed across categories of baseline HgB,² type of cancer,^{2,16,25} and type of ESA.^{1,2,16}

Clinical interpretation. Meta-analyses and individual RCTs consistently report a 50%^{1,2} to 75%^{16,25} increased risk of thromboembolism and vascular arterial events among patients receiving ESA therapy. The Expert Panel continues to urge caution in the use of ESAs for patients judged to be at increased risk for venous thromboembolism. Several risk scores for predicting venous thromboembolism have been developed; these are discussed in more detail in the ASCO guideline on venous thromboembolism.⁴² Special attention should be given to patients with multiple myeloma who are being treated with thalidomide or lenalidomide and doxorubicin or corticosteroids since they are at particularly increased thrombotic risk.⁴³ There are no data from RCTs investigating concomitant use of anticoagulants or aspirin to lessen this risk.

Clinical question 7

Among adult patients who will receive an ESA for chemotherapy-associated anemia, what are recommendations for ESA dosing and dose modifications?

Recommendation 7

It is recommended that starting and modifying doses of ESAs follow FDA guidelines (see Table 2 for specific dosing information; Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review update and analysis. This recommendation remains unchanged. No publications in the updated literature review supported nonstandard dosing. Duration of treatment was analyzed in

Table 2. ESA adult dosing

Dose and modifications	Epoetin alfa*		Darbepoetin alfa	
	Initial dose†	150 U/kg SC TIW‡	40,000 U SC weekly§	2.25 µg/kg SC weekly‡
Dose increases	Increase dose to 300 U/kg SC TIW if HgB increases by < 1 g/dL and remains below 10 g/dL after 4 weeks of therapy	Increase dose to 60,000 U SC weekly if HgB increases by < 1 g/dL and remains below 10 g/dL after 4 weeks of therapy	Increase dose to 4.5 µg/kg weekly if HgB increases by < 1 g/dL and remains below 10 g/dL after 6 weeks of therapy	N/A
Dose reductions	Decrease dose by 25% when HgB reaches a level needed to avoid transfusion or HgB increases > 1 g/dL in 2 weeks		Decrease dose by 40% when HgB reaches a level needed to avoid transfusion or HgB increases > 1 g/dL in 2 weeks	
Dose withholding	If HgB exceeds a level needed to avoid transfusion, restart dose at 25% below previous dose when HgB approaches a level where transfusion may be required		If HgB exceeds a level needed to avoid transfusion, restart dose at 40% below previous dose when HgB approaches a level where transfusion may be required	
Discontinue	Following completion of chemotherapy course or if no response after 8 weeks of therapy (measured by HgB levels or continuing need for transfusions)		Following completion of chemotherapy course or if no response after 8 weeks of therapy (measured by HgB levels or continuing need for transfusions)	

Food and Drug Administration product labels were accessed on June 8, 2018, for epoetin (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103234s5363s5366lbl.pdf) and for darbepoetin (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103951s5374lbl.pdf).

ESA, erythropoiesis-stimulating agent; HgB, hemoglobin; N/A, not applicable; Q3W, every 3 weeks; SC, subcutaneously; TIW, three times per week.

*Including epoetin alfa-epbx.

†Initiate only if HgB is < 10 g/dL and there is a minimum of two additional months of planned chemotherapy. Use and dosing differ in patients with myelodysplastic syndromes.

‡Weight-based dose.

§Fixed dose.

||Patients who do not respond to ESA treatment should be re-evaluated for underlying tumor progression, iron deficiency, or other etiologies for anemia.

the 2012 Cochrane review and did not significantly modify the association between ESA use and on-study mortality, overall survival, likelihood of RBC transfusion, risk of thromboembolism, or fatigue.²

Clinical interpretation. No new evidence suggests that outcomes of ESA therapy would be improved by use of an initial dose or dose modification regimen other than those in the FDA-approved labels. Note that some aspects of the labels' dose increase recommendations have changed (Table 2).

Clinical question 8

Among adult patients who will receive an ESA for chemotherapy-associated anemia, what is the recommended target HgB level?

Recommendation 8

HgB may be increased to the lowest concentration needed to avoid or reduce the need for RBC transfusions, which may vary by patient and condition (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review update and analysis. No new eligible publications were identified by the updated literature review.

Clinical interpretation. An optimal target HgB concentration cannot be definitively determined from the available literature. Modification to reduce the ESA dose is appropriate when HgB reaches a level sufficient to avoid transfusion or the increase exceeds 1 g/dL in any 2-week period to avoid excessive ESA exposure, considering the risks of ESAs. Specific dose-reduction recommendations are provided in Table 2.

Clinical question 9

Among adult patients with chemotherapy-associated anemia who do not respond to ESA therapy (< 1 to 2 g/dL increase in HgB or no decrease in transfusion requirements), does continuation of ESA therapy beyond 6 to 8 weeks provide a benefit?

Recommendation 9

ESAs should be discontinued in patients who do not respond within 6 to 8 weeks. Patients who do not respond to ESA treatment should be reevaluated for underlying tumor progression, iron deficiency, or other etiologies for anemia (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review update and analysis. No publications in the updated literature review addressed ESA continuation in nonresponders.

Clinical interpretation. Given the known harms of ESAs, the exposure to ESAs should be minimized. In patients who have received appropriate ESA dosing (see Recommendation 7) and who do not respond, ESAs should be stopped and not continued.

Clinical question 10

Among adult patients with chemotherapy-associated anemia, does iron supplementation concurrent with an ESA reduce transfusion requirements?

Recommendation 10

Iron replacement may be used to improve HgB response and reduce RBC transfusions for patients receiving ESA with or without iron deficiency. Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels is recommended (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: weak).

Literature review update and analysis. The use of supplemental iron with an ESA was evaluated in three meta-analyses.^{15,20,22} Compared with an ESA alone, a 2016 Cochrane review by Mhaskar et al²⁰ reported that the combination of an ESA and iron increased the likelihood of hematopoietic response (RR, 1.17; 95% CI, 1.09 to 1.26) and reduced the likelihood of RBC transfusion (RR, 0.74; 95% CI, 0.60 to 0.92) without significantly

affecting risk of thromboembolism (RR, 0.95; 95% CI, 0.54 to 1.65) or quality of life (standardized mean difference, 0.01; 95% CI, -0.10 to 0.12). Intravenous (IV) iron provided a greater benefit than oral iron with respect to mean change in HgB level (IV iron mean difference, 0.84; 95% CI, 0.21 to 1.46; $P = .009$; oral iron mean difference, 0.07; 95% CI, -0.19 to 0.34; $P = .59$; $P = .03$ for interaction). Route of iron administration did not significantly modify the association with hematopoietic response ($P = .16$). Findings in the two earlier meta-analyses^{15,22} were generally similar.

Clinical interpretation. This recommendation changed from previous versions based on new information published after the last guideline. The Expert Panel believes that the use of iron supplementation in all patients receiving ESAs should be considered, independent of the iron status. This is based on evidence that iron supplementation reduces the risk for RBC transfusion. Additionally, in patients with evidence of iron deficiency, the cause of the deficiency should be investigated and corrected.

Oral and IV iron formulations are both acceptable options for iron supplementation. Choice of agents depends on patient and doctor preferences, formulation availability, cost, and comorbidities. IV iron preparations have the advantage of being able to deliver larger amounts of elemental iron in a single application and may also be more adequate in patients with poor oral intake or absorption problems. They have the disadvantages of being associated with more serious systemic reactions and higher costs. There is some limited evidence that IV iron is superior to oral iron based on improvement in HgB level. However, the results were not consistent across all other hematologic outcomes, and the quality of adverse outcomes reporting was poor.^{15,20,22} Safety has been better studied in a systematic review and meta-analysis in patients with CKD, which showed no difference in mortality or serious adverse events in patients receiving intravenous iron, although there were more episodes of hypotension with IV iron.⁴⁴

Discussion

Although the use of ESAs reduces the need for transfusions in anemic patients with cancer receiving chemotherapy, it is associated with increased complications, including higher mortality and increased risk of thromboembolic and cardiovascular events. For these reasons, the use of ESAs in cancer is now generally limited to patients who are receiving chemotherapy with palliative intent and who are expected to have short survival. The decision about using ESAs must be made in this context and with a thorough discussion regarding each patient's preferences, priorities, values, and spiritual needs.

Patient-clinician communication

Patient counseling regarding the risks and benefits of ESA therapy is essential to ensure that patients are making informed decisions. The Expert Panel encourages health care providers to have an open dialogue with their patients to help them make informed decisions by considering the scientific evidence and weighing their individual risks with potential harms and benefits of ESA therapy.

In addition to providing a medication guide, health care providers should discuss the following with patients considering ESA therapy:

- When used, the goal of ESA therapy for patients with chemotherapy-induced anemia is to reduce RBC transfusion requirements.

- The FDA has indicated that ESAs should not be given to patients who are being treated for cancer when the goal is to cure the patients of cancer.
- ESAs have been found to shorten overall survival and/or speed tumor growth in some patients with cancer.
- ESAs have risks of adverse events, such as thromboembolism (ie, blood clots), so individual risk factors need to be considered.
- ESAs are not recommended for patients with cancer who are not receiving chemotherapy, except in the case of patients with lower risk MDS.

For general recommendations and strategies to optimize patient-clinician communication, see "Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline."⁴⁵

Health disparities

Although ASCO and ASH clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.⁴⁶⁻⁴⁹ Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

Multiple chronic conditions

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to consider the complexity and uncertainty created by the presence of MCC and highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with

Table 3. Estimated prices of ESAs and supplemental iron

Agent	HCPCS code dosage	Medicare payment limit (US\$)	Initial dose	Regimen	Price
ESAs					
Darbepoetin alfa (non-ESRD)	1 µg	3.779	2.25 µg/kg SC	Weekly (SC)	\$1,785.58 per 3-week cycle*
			500 µg SC	Every 3 weeks (SC)	\$1,889.50 per 3-week cycle
Epoetin alfa (non-ESRD)	1,000 U	13.333	150 U/kg	3 times weekly (SC)	\$1,259.97 per 3-week cycle*
			40,000 U	Weekly (SC)	\$1,599.96 per 3-week cycle
Iron supplements					
Iron dextran	50 mg	13.669	Variable	IV	\$273.38 per 1,000 mg
Ferric gluconate	12.5 mg	2.179	Variable	IV	\$174.32 per 1,000 mg
Iron sucrose	1 mg	0.234	Variable	IV	\$234.00 per 1,000 mg
Ferrous sulfate	N/A	N/A	Variable	Oral	Available over the counter. Prices at a sample of online retailers ranged from \$0.01-\$0.11 per 325-mg tablet

Drug prices were estimated from a third-party payer perspective, based on reimbursement rates from the Centers for Medicare and Medicaid Services that are widely accepted by providers, computed at the manufacturer's average sales price. Other treatment-related direct and indirect costs were not considered, such as diagnostic laboratory tests. Actual treatment costs and reimbursement will vary considerably across regions, payers, institutions, and practices, as well as over time, and readers should consult current local cost information specific to their practice setting. Costs were based on Medicare Part B payment allowance limits effective July 1, 2018 (with no administration fees or other adjustments; Medicare Part B Drug Average Sales Price: <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2018ASPFiles.html>).

ESAs, erythropoiesis-stimulating agents; ESRD, end-stage renal disease; HCPCS, Healthcare Common Procedure Coding System; IV, intravenously; N/A, not applicable; SC, subcutaneously.

*Based on an adult weighing 70 kg.

MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

Cost implications

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.^{50,51} Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.^{52,53}

Discussion of cost can be an important part of shared decision making.⁵⁴ Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.⁵⁴

Table 3 shows estimated prices for the available treatment options addressed in this guideline. Of note, medication prices may vary markedly, depending on negotiated discounts and rebates.

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.⁵⁴

Open comment

The draft recommendations were released to the public for open comment from August 15, 2018, through August 29, 2018.

Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation with two written comments received. Both respondents either agreed or agreed with slight modifications to the recommendations. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated prior to ASCO Clinical Practice Guidelines Committee review and approval.

Guideline implementation

ASCO and ASH guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners, survivors of cancer, and caregivers, as well as the need to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guidelines Implementation Network. ASCO and ASH guidelines are posted on each organization's Web site, and this guideline is jointly published in *JCO* and *Blood Advances*.

Limitation of the research and future research

There is clear evidence regarding the ability of ESAs to increase HgB and avoid transfusions. There is also very consistent evidence of harm associated with their use across a spectrum of conditions. Since in recent years the number of new trials is somewhat limited yet consistent with previous findings, we believe that rather than focusing on the occurrence of adverse effects, the most pressing

need for additional research is studies that further clarify the mechanisms of harm and, particularly, the groups of patients or circumstances of clinical use that are least associated with these risks. This information is paramount to the ability of clinicians to extend the benefit of these drugs while reducing the risks.

Editor's note

This American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/supportive-care-guidelines and is available as a supplement to the *Blood Advances* version of the article. Additional evidence-based clinical practice guidelines are also available at www.hematology.org/guidelines.

Acknowledgment

The Expert Panel wishes to thank Bryan Schneider, Charles Shapiro, the ASCO Clinical Practice Guidelines Committee, the ASH Guideline Oversight Subcommittee, the ASH Committee on Quality, and ASH Officers for their thoughtful reviews of this guideline.

Authorship

Contribution: J.B., B.D., M.M., L.P., G.T., and A.L.-L. conceived and designed the study; J.B., M.M., G.M., N.P., L.P., T.N.T., G.T.,

H.Y., and A.L.-L. collected and assembled data; J.B., K.B., R.C., B.D., M.B.L., M.M., G.M., L.P., T.N.T., G.T., H.Y., and A.L.-L. analyzed and interpreted data; and all authors wrote the manuscript, approved the final manuscript, and are accountable for all aspects of the work.

Conflict-of-interest disclosure: B.D. received research funding from GlaxoSmithKline (to the author's institution [Inst]). M.B.L. served in a consulting or advisory role for Tempus, Pled-Pharma, and Hologic/Cynosure. M.M. served in a consulting or advisory role for Italfarmaco, Kyowa Hakko Kirin, Teva, Sandoz-Novartis, Amgen, and Takeda; and received travel, accommodations, or expense compensation from Takeda, Janssen-Cilag, Celgene, and Sanofi. G.M. received honoraria from Roche, Boehringer Ingelheim, AstraZeneca, Merck Sharp & Dohme, and AstraZeneca Greece; was on the speakers' bureau for AstraZeneca; and received travel, accommodations, or expense compensation from AstraZeneca and Ipsen. G.T. served in a consulting or advisory role for Bayer, Novartis, Servier, Sandoz-Novartis, Ipsen, Sanofi, Grünenthal Group, Otsuka, and Biogen; and received research funding from Amgen (Inst), Daiichi Sankyo (Inst), IBSA (Inst), and AstraZeneca (Inst). A.L.-L. received research funding from Alexion Pharmaceuticals (Inst), Bayer (Inst), Daiichi Sankyo (Inst), Pfizer (Inst), and Bristol-Myers Squibb (Inst). The remaining authors declare no competing financial interests.

Correspondence: American Society of Hematology, 2021 L St NW, Suite 900, Washington, DC 20036; e-mail: guidelines@hematology.org.

Appendix

Table A1. Expert Panel membership: Management of cancer-associated anemia with erythropoiesis-stimulating agents: American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update

Name	Affiliation/institution	Role/areas of expertise
Julia Bohlius	Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland	Systematic review and meta-analyses; evidence-based medicine and guideline development
Alejandro Lazo-Langner	Western University, London, ON, Canada	Hematology; epidemiology
Roberto Castelli	Department of Biomedical and Clinical Sciences Luigi Sacco, Luigi Sacco Hospital Milan, University of Milan, Milan, Italy	Hematology
Benjamin Djulbegovic	City of Hope, Departments of Supportive Medicine and Hematology, Duarte, CA	Hematology, supportive care
Maryam B. Lustberg	Ohio State University, Columbus, OH	Medical oncology, breast cancer, treatment-related toxicity, survivorship
Massimo Martino	Azienda Ospedaliera Bianchi Melacchino Morelli, Hematology and Stem Cell Transplant Unit, Reggio Calabria, Italy	Hematology
Giannis Mountzios	251 General Air Force Hospital and 2nd Medical Oncology Department, Henry Dunant Hospital Center, Athens, Greece	Tumor biology, genitourinary cancer, lung cancer, biologic therapy, clinical trials/biostatistics/epidemiology; medical oncology
Namrata Peswani	Advocate Medical Group, Orland Park, IL	Hematology/oncology, palliative care, ASCO Practice Guidelines Implementation Network
Laura Porter	Washington, DC	Independent patient advocate
Tiffany N. Tanaka	UC San Diego Moores Cancer Center, La Jolla, CA	Hematology, myelodysplastic syndrome, supportive care
Gianluca Trifirò	Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy	Clinical pharmacology, pharmacovigilance, and pharmacoepidemiology
Hushan Yang	Division of Population Science, Department of Medical Oncology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA	Cancer biomarkers, statistical models for cancer risk and prognosis assessment
Kari Bohlke	American Society of Clinical Oncology, Alexandria, VA	Staff/health research methodologist

References

1. Grant MD, Piper M, Bohlius J, et al. AHRQ Comparative Effectiveness Reviews: Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment: Comparative Effectiveness Update. Comparative Effectiveness Review No. 113 (AHRQ Publication No. 13-EHC077-EF). Rockville, MD: Agency for Healthcare Research and Quality; 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
2. Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database Syst Rev*. 2012;12:CD003407.
3. 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*. 2005;23:5960-5972.
4. Thomas G, Ali S, Hoebbers FJ, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. *Gynecol Oncol*. 2008;108:317-325.
5. Untch M, von Minckwitz G, Konecny GE, et al. PREPARE trial: A randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel, and CMF versus a standard-dosed epirubicin-cyclophosphamide followed by paclitaxel with or without darbepoetin alfa in primary breast cancer—outcome on prognosis. *Ann Oncol*. 2011;22:1999-2006.
6. Leyland-Jones B, Bondarenko I, Nemsadze G, et al. A randomized, open-label, multicenter, phase III study of epoetin alfa versus best standard of care in anemic patients with metastatic breast cancer receiving standard chemotherapy. *J Clin Oncol*. 2016;34:1197-1207.
7. US Food and Drug Administration. Information on erythropoiesis-stimulating agents (ESA) epoetin alfa (marketed as Procrit, Epogen), darbepoetin alfa (marketed as Aranesp). <https://www.fda.gov/Drugs/DrugSafety/ucm109375.htm>.
8. 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*. 2002;20:4083-4107.
9. Rizzo JD, Somerfield MR, Hagerty KL, et al. 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*. 2008;26:132-149.
10. Rizzo JD, Brouwers M, Hurley P, et al. American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *J Clin Oncol*. 2010;28:4996-5010.
11. US Food and Drug Administration. FDA approves Retacrit as a biosimilar to Epogen/Procrit. <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm607723.htm>.
12. Shojania KG, Sampson M, Ansari MT, et al. How quickly do systematic reviews go out of date? A survival analysis. *Ann Intern Med*. 2007;147:224-233.
13. Aapro M, Moebus V, Nitz U, et al. Safety and efficacy outcomes with erythropoiesis-stimulating agents in patients with breast cancer: A meta-analysis. *Ann Oncol*. 2015;26:688-695.
14. Bohlius J, Tonia T, Nuesch E, et al. Effects of erythropoiesis-stimulating agents on fatigue- and anaemia-related symptoms in cancer patients: Systematic review and meta-analyses of published and unpublished data. *Br J Cancer*. 2014;111:33-45.
15. Gafter-Gvili A, Rozen-Zvi B, Vidal L, et al. Intravenous iron supplementation for the treatment of chemotherapy-induced anaemia—systematic review and meta-analysis of randomised controlled trials. *Acta Oncol*. 2013;52:18-29.
16. Gao S, Ma JJ, Lu C. Venous thromboembolism risk and erythropoiesis-stimulating agents for the treatment of cancer-associated anemia: A meta-analysis. *Tumour Biol*. 2014;35:603-613.
17. Hedenus M, Osterborg A, Tomita D, et al. Effects of erythropoiesis-stimulating agents on survival and other outcomes in patients with lymphoproliferative malignancies: A study-level meta-analysis. *Leuk Lymphoma*. 2012;53:2151-2158.
18. Li X, Yan Z, Kong D, et al. Erythropoiesis-stimulating agents in the management of cancer patients with anemia: A meta-analysis. *Chin J Cancer Res*. 2014;26:268-276.
19. Marchetti C, De Felice F, Palaia I, et al. Erythropoiesis-stimulating agents in gynecological malignancies: A study-level meta-analysis. *Crit Rev Oncol Hematol*. 2016;99:123-128.
20. Mhaskar R, Wao H, Miladinovic B, et al. The role of iron in the management of chemotherapy-induced anemia in cancer patients receiving erythropoiesis-stimulating agents. *Cochrane Database Syst Rev*. 2016;2:CD009624.
21. Ohashi Y, Uemura Y, Fujisaka Y, et al. Meta-analysis of epoetin beta and darbepoetin alfa treatment for chemotherapy-induced anemia and mortality: Individual patient data from Japanese randomized, placebo-controlled trials. *Cancer Sci*. 2013;104:481-485.
22. Petrelli F, Borgonovo K, Cabiddu M, et al. Addition of iron to erythropoiesis-stimulating agents in cancer patients: A meta-analysis of randomized trials. *J Cancer Res Clin Oncol*. 2012;138:179-187.
23. Tomlinson D, Robinson PD, Oberoi S, et al. Pharmacologic interventions for fatigue in cancer and transplantation: A meta-analysis. *Curr Oncol*. 2018;25:e152-e167.
24. Vansteenkiste J, Glaspy J, Henry D, et al. Benefits and risks of using erythropoiesis-stimulating agents (ESAs) in lung cancer patients: Study-level and patient-level meta-analyses. *Lung Cancer*. 2012;76:478-485.
25. Zhan P, Wang Q, Qian Q, et al. Risk of venous thromboembolism with the erythropoiesis-stimulating agents (ESAs) for the treatment of cancer-associated anemia: A meta-analysis of randomized control trials. *Linchuang Zhongliuxue Zazhi*. 2012;1:19.
26. Toma A, Kosmider O, Chevret S, et al. Lenalidomide with or without erythropoietin in transfusion-dependent erythropoiesis-stimulating agent-refractory lower-risk MDS without 5q deletion. *Leukemia*. 2016;30:897-905.

27. Amato L, Addis A, Saulle R, et al. Comparative efficacy and safety in ESA biosimilars vs. originators in adults with chronic kidney disease: A systematic review and meta-analysis. *J Nephrol.* 2018;31:321-332.
28. Hahn D, Esezobor CI, Elserafy N, et al. Short-acting erythropoiesis-stimulating agents for anaemia in predialysis patients. *Cochrane Database Syst Rev.* 2017;1:CD011690.
29. Weir MR, Pergola PE, Agarwal R, et al. A comparison of the safety and efficacy of HX575 (epoetin alfa proposed biosimilar) with epoetin alfa in patients with end-stage renal disease. *Am J Nephrol.* 2017;46:364-370.
30. Weigang-Köhler K, Vetter A, Thyroff-Friesinger U. HX575, recombinant human epoetin alfa, for the treatment of chemotherapy-associated symptomatic anaemia in patients with solid tumours. *Onkologie.* 2009;32:168-174.
31. Giordano G, Mondello P, Tambaro R, et al. Biosimilar epoetin α is as effective as originator epoetin- α plus liposomal iron (Sideral®), vitamin B12 and folates in patients with refractory anemia: A retrospective real-life approach. *Mol Clin Oncol.* 2015;3:781-784.
32. Rodriguez Garzotto A, Cortijo Casacajares S, Pernaut C, et al. Erythropoiesis-stimulating agents for the treatment of chemotherapy-induced anemia: Comparisons from real-world clinical experience. *J Blood Med.* 2014;5:43-48.
33. Trotta F, Belleudi V, Fusco D, et al. Comparative effectiveness and safety of erythropoiesis-stimulating agents (biosimilars vs originators) in clinical practice: A population-based cohort study in Italy. *BMJ Open.* 2017;7:e011637.
34. Ingrasciotta Y, Giorgianni F, Marciano I, et al. Comparative effectiveness of biosimilar, reference product and other erythropoiesis-stimulating agents (ESAs) still covered by patent in chronic kidney disease and cancer patients: An Italian population-based study. *PLoS One.* 2016;11:e0155805.
35. Cella D, Eton DT, Lai JS, et al. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manage.* 2002;24:547-561.
36. Bohlius J, Schmidlin K, Brillant C, et al. Erythropoietin or darbepoetin for patients with cancer—meta-analysis based on individual patient data. *Cochrane Database Syst Rev.* 2009;(3):CD007303.
37. Hellström-Lindberg E, Gulbrandsen N, Lindberg G, et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: Significant effects on quality of life. *Br J Haematol.* 2003;120:1037-1046.
38. Fenaux P, Santini V, Spiriti MAA, et al. A phase 3 randomized, placebo-controlled study assessing the efficacy and safety of epoetin- α in anemic patients with low-risk MDS. *Leukemia.* 2018;32:2648-2658.
39. Hellström-Lindberg E, Ahlgren T, Beguin Y, et al. Treatment of anemia in myelodysplastic syndromes with granulocyte colony-stimulating factor plus erythropoietin: Results from a randomized phase II study and long-term follow-up of 71 patients. *Blood.* 1998;92:68-75.
40. Aapro M, Krendyukov A, Schiestl M, et al. Epoetin biosimilars in the treatment of chemotherapy-induced anemia: 10 years' experience gained [published correction appears in *BioDrugs.* 2018;32:137-138]. *BioDrugs.* 2018;32:129-135.
41. Goldsmith D, Dellanna F, Schiestl M, et al. Epoetin biosimilars in the treatment of renal anemia: What have we learned from a decade of European experience? *Clin Drug Investig.* 2018;38:481-490.
42. Lyman GH, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2013;31:2189-2204.
43. Bennett CL, Angelotta C, Yarnold PR, et al. Thalidomide- and lenalidomide-associated thromboembolism among patients with cancer. *JAMA.* 2006;296:2558-2560.
44. Shepshelovich D, Rozen-Zvi B, Avni T, et al. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: An updated systematic review and meta-analysis. *Am J Kidney Dis.* 2016;68:677-690.
45. Gilligan T, Coyle N, Frankel RM, et al. Patient-clinician communication: American Society of Clinical Oncology consensus guideline. *J Clin Oncol.* 2017;35:3618-3632.
46. US Cancer Statistics Working Group. United States cancer statistics: 1999–2012 incidence and mortality web-based report. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2015. <https://gis.cdc.gov/Cancer/USCS/DataViz.html>.
47. Howlader N, Noone AM, Krapcho M, et al. SEER cancer statistics review, 1975-2013. http://seer.cancer.gov/csr/1975_2013/.
48. Mead H, Cartwright-Smith L, Jones K, et al. Racial and Ethnic Disparities in US Health Care: A Chartbook. New York, NY: The Commonwealth Fund; 2008.
49. American Cancer Society. Cancer facts and figures for African Americans 2016-2018. <http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-047403.pdf>.
50. Schnipper LE, Davidson NE, Wollins DS, et al. Updating the American Society of Clinical Oncology value framework: Revisions and reflections in response to comments received. *J Clin Oncol.* 2016;34:2925-2934.
51. Schnipper LE, Davidson NE, Wollins DS, et al. American Society of Clinical Oncology statement: A conceptual framework to assess the value of cancer treatment options. *J Clin Oncol.* 2015;33:2563-2577.
52. Dusetzina SB, Winn AN, Abel GA, et al. Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. *J Clin Oncol.* 2014;32:306-311.
53. Streeter SB, Schwartzberg L, Husain N, et al. Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. *J Oncol Pract.* 2011;7(3 suppl):46s-51s.
54. Meropol NJ, Schrag D, Smith TJ, et al. American Society of Clinical Oncology guidance statement: The cost of cancer care. *J Clin Oncol.* 2009;27:3868-3874.