

To treat anemia in patients with non-myeloid malignancies receiving concomitant myelosuppressive chemotherapy

Which factors should you consider in determining whether Mike* is an appropriate candidate to initiate Aranesp® treatment?

Meet Mike



Would Mike's prior myelosuppressive chemotherapy make him an appropriate candidate for Aranesp® treatment?

- 68 years old; 2 children and 8 grandchildren
- Retired building and safety inspector
- Enjoys painting

Medical history

- History of smoking
- Controlled hypertension
- COPD

Initial cancer diagnosis

- Stage IV non-small cell lung cancer with adrenal metastasis and mild left pleural effusion

Prior adjuvant treatment and disposition

- Carboplatin + VEGF inhibitor
- Was iron replete and had shortness of breath
- Last 2 Hb levels with carboplatin + VEGF inhibitor
 - 10.9 g/dL
 - 9.8 g/dL
- Palliative radiation to relieve airway obstruction

Mike's current state and new palliative treatment plan

- New liver lesions signal disease progression
- About to begin new cycle of docetaxel

*Hypothetical patient.

COPD = chronic obstructive pulmonary disease; ESA = erythropoiesis-stimulating agent; Hb = hemoglobin; VEGF = vascular endothelial growth factor.

Indication

Aranesp® is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

Limitations of Use

Aranesp® has not been shown to improve quality of life, fatigue, or patient well-being.

Aranesp® is not indicated for use:

- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.
- As a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia.

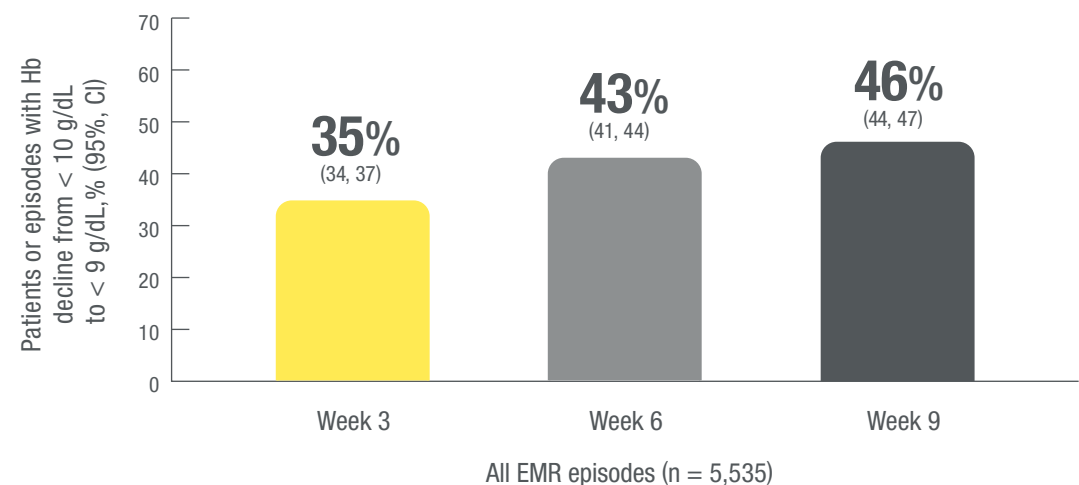
Please see Important Safety Information, including **Boxed WARNINGS** about **INCREASED RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE**, on last page.

injection
Aranesp®
darbepoetin alfa

Once Hb begins to fall, it can continue to decline in many patients with cancer receiving myelosuppressive chemotherapy¹

Based on a retrospective analysis of electronic medical records (EMRs), 35% of patients had a Hb decline from < 10 g/dL to < 9 g/dL at week 3 of chemotherapy¹

Proportion of episodes of Hb decline from < 10 g/dL to < 9 g/dL in cancer patients receiving chemotherapy¹



Data are from an aggregated US community oncology clinic electronic medical record (EMR) database of 10,523 patients (representing 10,942 chemotherapy episodes). Patients were at least 18 years of age with non-myeloid malignancies and baseline Hb \geq 10 g/dL and < 11 g/dL on or after the start of the chemotherapy episode. Patients were treated with a myelosuppressive chemotherapy doublet and could not have received an ESA within 9 weeks before the baseline Hb measurement or at any time during the 18-week study unless Hb was < 9 g/dL. Patients could be in any cycle of their chemotherapy regimen as long as they received at least 2 additional cycles at \leq 35-day intervals after baseline Hb measurement. Chemotherapy episodes were re-indexed when the Hb level was < 10 g/dL to estimate the proportions of episodes and patients that further declined to hemoglobin < 9 g/dL by 3, 6, and 9 weeks without ESA therapy. The total number of EMR episodes with Hb decline from < 10 g/dL to < 9 g/dL was 5,535.¹

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) list the following possible physiologic symptoms as indications for red blood cell transfusion:²

- Sustained tachycardia
- Chest pain
- Syncope
- Tachypnea
- Dyspnea on exertion
- Severe fatigue, preventing work and usual activity
- Lightheadedness

Important Safety Information

- Aranesp[®] is contraindicated in patients with:
 - Uncontrolled hypertension
 - Pure red cell aplasia (PRCA) that begins after treatment with Aranesp[®] or other erythropoietin protein drugs
 - Serious allergic reactions to Aranesp[®]

Dosing Information

- Initiate Aranesp[®] in patients on cancer chemotherapy:
 - Only when Hb < 10 g/dL
 - Only when 2 additional months of myelosuppressive noncurative chemotherapy are planned
 - Only with the lowest dose necessary to avoid RBC transfusions

Please click [here](#) to see the complete dosing guidelines.

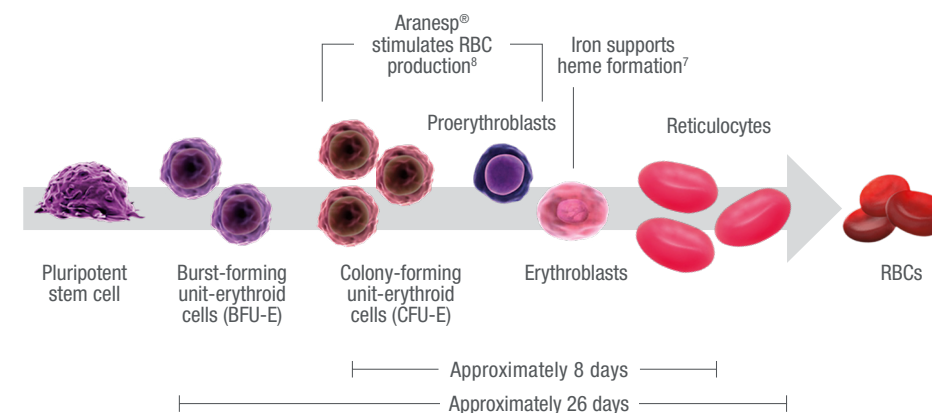
Please see additional Important Safety Information, including **Boxed WARNINGS**, on last page.

It takes time for hemoglobin to rise^{3,4}

New RBC production requires approximately 26 days³⁻⁷

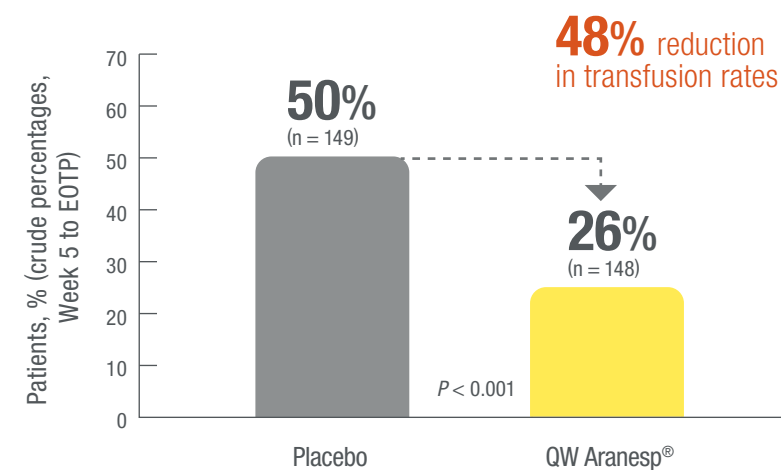
Increased hemoglobin levels are not generally observed until 2-6 weeks after starting treatment with Aranesp[®]⁸

- It takes approximately 26 days for a stem cell to develop into a mature RBC
- Erythropoietin is needed for RBC production
- Once stimulated by erythropoietin, it takes approximately 8 days for CFU-E cells to differentiate into a reticulocyte
- Reticulocytes mature into RBCs, and as the number of RBCs increases, hemoglobin (Hb) levels rise



Aranesp[®] reduced the need for RBC transfusion vs placebo^{8,9}

Patients requiring RBC transfusions^{8,9}



EOTP = end of trial period; QW = once weekly.

Data from a randomized, double-blind, placebo-controlled trial of 314 patients with Hb \leq 11 g/dL who had lung cancer and were receiving platinum-containing chemotherapy. Patients received once-weekly treatment with either Aranesp[®] (2.25 mcg/kg) or placebo, administered by subcutaneous injection, for up to 12 weeks. Per the pivotal trial protocol, doses were withheld if Hb exceeded 14 g/dL in women or 15 g/dL in men—the P-value is based on Kaplan-Meier (K-M) proportions.^{8,9}

Based on data from 7 randomized, double-blind, placebo-controlled studies⁸

- Thrombovascular adverse reactions occurred in 6.1% of 1,203 patients treated with Aranesp[®] and 4.1% of 909 patients receiving placebo—of which 1.2% (Aranesp[®]) and 0.6% (placebo) were arterial; 5% (Aranesp[®]) and 3.5% (placebo) were venous; and 1.7% (Aranesp[®]) and 1.9% (placebo) were cerebrovascular disorders
- Abdominal pain (13.2% vs 9.4%) and edema (12.8% vs 9.7%) were reported more frequently in patients receiving Aranesp[®] compared to patients receiving placebo in the same 7 studies



For patients you determine to be appropriate candidates for erythropoiesis-stimulating agent (ESA) therapy, start Aranesp[®] therapy when Hb < 10 g/dL and, upon initiation, there is a minimum of two additional months of planned chemotherapy.^{8,*}

*Prior to treatment, inform patients of the risks and benefits of Aranesp[®].

injection
Aranesp[®]
darbepoetin alfa

To treat anemia in patients with non-myeloid malignancies receiving concomitant myelosuppressive chemotherapy

Important Safety Information, including Boxed WARNINGS, for Aranesp® (darbepoetin alfa)

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE

Chronic Kidney Disease:

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.
- No trial has identified a hemoglobin target level, Aranesp® dose, or dosing strategy that does not increase these risks.
- Use the lowest Aranesp® dose sufficient to reduce the need for red blood cell (RBC) transfusions.

Cancer:

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.
- To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions.
- Use ESAs only for anemia from myelosuppressive chemotherapy.
- ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- Discontinue following the completion of a chemotherapy course.

Aranesp® is contraindicated in patients with:

- Uncontrolled hypertension
- Pure red cell aplasia (PRCA) that begins after treatment with Aranesp® or other erythropoietin protein drugs
- Serious allergic reactions to Aranesp®
- In controlled clinical trials of patients with cancer, Aranesp® and other ESAs increased the risks for death and serious adverse cardiovascular reactions. These adverse reactions included myocardial infarction and stroke.
- In controlled clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and the risk of deep venous thrombosis (DVT) in patients undergoing orthopedic procedures.
- Control hypertension prior to initiating and during treatment with Aranesp®.
- For lack or loss of hemoglobin response to Aranesp®, initiate a search for causative factors. If typical causes of lack or loss of hemoglobin response are excluded, evaluate for PRCA.
- Cases of PRCA and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin have been reported in patients treated with Aranesp®.
 - This has been reported predominantly in patients with CKD receiving ESAs by subcutaneous administration.
 - PRCA has also been reported in patients receiving ESAs for anemia related to hepatitis C treatment (an indication for which Aranesp® is not approved).
 - If severe anemia and low reticulocyte count develop during treatment with Aranesp®, withhold Aranesp® and evaluate patients for neutralizing antibodies to erythropoietin.
 - Permanently discontinue Aranesp® in patients who develop PRCA following treatment with Aranesp® or other erythropoietin protein drugs. Do not switch patients to other ESAs.
- Serious allergic reactions, including anaphylactic reactions, angioedema, bronchospasm, skin rash, and urticaria may occur with Aranesp®. Immediately and permanently discontinue Aranesp® if a serious allergic reaction occurs.
- Blistering and skin exfoliation reactions including Erythema multiforme and Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with ESAs (including Aranesp®) in the postmarketing setting. Discontinue Aranesp® therapy immediately if a severe cutaneous reaction, such as SJS/TEN, is suspected.
- Adverse reactions ($\geq 1\%$) in Aranesp® clinical studies in cancer patients receiving chemotherapy were abdominal pain, edema, and thrombovascular events.

*Please click for the full Prescribing Information, including **Boxed WARNINGS**, and the **Medication Guide**.*

References: 1. Pirker R, Pirolli M, Quigley J, et al. Hemoglobin decline in cancer patients receiving chemotherapy without an erythropoiesis-stimulating agent. *Support Care Cancer*. 2013;21:987-992. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors V.2.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed August 12, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. 3. Guyton AC, Hall JE. Red blood cells, anemia, and polycythemia. In: *Textbook of Medical Physiology*. 11th ed. Philadelphia, PA: WB Saunders; 2006:419-428. 4. Bunn H. Pathophysiology of the anemias. In: Isselbacher KJ, Wilson JD, Braunwald E, eds. *Harrison's Principles and Practice of Internal Medicine*. 13th ed. New York, NY: McGraw-Hill; 1994:1717-1721. 5. Dessypris EN. Erythropoiesis. In: Lee GR, Foerster J, Lukens J, Wintrobe MM, eds. *Wintröbe's Clinical Hematology*. Vol. 1. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1998:169-192. 6. Papayannopoulou T, D'Andrea AD, Abkowitz JL, Migliaccio AR. Biology of erythropoiesis, erythroid differentiation, and maturation. In: Hoffman R, Benz EJ Jr, Shattil SJ, et al, eds. *Hematology: Basic Principles and Practice*. 4th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005:267-294. 7. Hillman RS, Finch CA. General characteristics of the erythron. In: Hillman RS, Finch CA, eds. *Red Cell Manual Edition*. 7th ed. 1996. Philadelphia, PA: F.A. Davis Company; 1996:1-15. 8. Aranesp® (darbepoetin alfa) prescribing information, Amgen. 9. 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*. 2002;94:1211-1220.

The NCCN Guidelines® are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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