FDA BRIEFING DOCUMENT

March 13, 2008
Oncologic Drugs Advisory Committee

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List of Abbreviations

95% CI	95% confidence interval
AIDS	Acquired Immunodeficiency Syndrome
CBC	Complete blood count
CEA	Carcinoembryonic Antigen
CLL	Chronic Lymphocytic Leukemia
CMF	Cyclophosphamide, methotrexate, 5- fluorouracil
CSR	Clinical Study Report
CT	Computerized tomography
DFS	Disease-free Survival
DLBCL	Diffuse large B cell lymphoma
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EFS	Event free survival
EOTP	End of treatment period
ESA	Erythropoietin Stimulating Agent
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
FNA	Fine needle aspiration
GVHD	Graft versus host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDR	High dose rate brachytherapy
HR	Hazard ratio
HRQOL	Health-related quality-of-life
ITT	Intent to Treat
IVP	Intravenous pyelogram
KM	Kaplan-Meier
LDR	Low dose rate brachytherapy
LRC	Loco-regional Control
MRI	Magnetic resonance imaging
NSCLC	Non-small cell lung cancer
ODAC	Oncologic Drug Advisory Committee
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression free Survival
QOL	Quality-of-life
RBC	Red Blood Cell
RFS	Relapse free survival
RR	Response Rate
RT	Radiation Therapy
SCLC	Small cell lung cancer
tiW	Three times a week
TRALI	Transfusion related acute lung injury
TVE	Thrombo-Vascular Event

Executive Summary

Erythropoiesis-stimulating agents (ESAs) were first approved for the treatment of patients with chronic renal failure, in which anemia results primarily from decreased erythropoietin production by diseased kidneys. When used in this setting, ESAs may be considered a form of hormone-replacement therapy that is highly successful in reducing the red blood cell (RBC) transfusion requirements in the majority of patients with chronic renal failure.

In contrast to patients with renal failure, the etiology of anemia in patients with cancer is multifactorial and not primarily the result of low endogenous erythropoietin levels. The clinical benefit of ESAs in cancer patients that formed the basis for FDA approval was reduction in the proportion of patients who require RBC transfusions; these patients are not exposed to the risks of transfusions. Based on data provided to FDA, there is no evidence that ESAs improve quality of life or cancer outcomes. In controlled clinical studies supporting approval for the treatment of anemia in patients with cancer receiving myelosuppressive chemotherapy, the reduction in the proportion of patients receiving any transfusions has varied. Across several studies, approximately 50% of anemic patients receiving chemotherapy required transfusions as compared to approximately 20-25% of patients who received ESAs concurrently with chemotherapy. Thus, many more patients are exposed to the risks of ESAs than those who receive benefits in terms of avoidance of the risks of transfusions.

Since the first approval of an ESA for treatment of chemotherapy-associated anemia in 1993, the infectious risks of blood transfusions have decreased. In contrast, there are now eight controlled clinical studies which provide evidence of or suggest increased risks of mortality and/or tumor promotion in patients who receive ESAs and have head and neck cancer, breast cancer, non-small cell lung cancer, cervical cancer, and anemic cancer patients receiving no active anti-cancer therapy. These studies are notable in that they are either substantially larger or represent a different underlying histology than in studies used to establish safety of ESAs.

At this time, there is insufficient safety data to characterize the effects or rule out an risk of mortality or impaired tumor outcomes (shorter time to progression or lower loco-regional tumor control rates) in any primary cancer other than SCLC, when ESAs are used according to doses recommended in the labels. When ESAs are administered off-label (e.g., dosed to achieve and maintain hemoglobin levels substantially above that needed to avoid RBC transfusions, in anemia due to causes other than cancer chemotherapy), the risks are clearly unacceptable in light of the benefits. There is sufficient evidence to characterize the safety of ESA use in only one setting: for the treatment of anemia in patients with small cell lung cancer (SCLC) undergoing cisplatin-based chemotherapy. In two randomized (1:1), multicenter studies limited to patients with SCLC, Studies N93-004, 980297, and 2001-0145 enrolling 224, 314, and 596 patients respectively; there was no evidence of worsened survival or poorer tumor outcome among those who also received an ESA. However, results in trials with SCLC, an aggressive neuroendocrine tumor, may not be generalizable to more common epidermal malignancies. In contrast, there is also sufficient evidence to document an increased risk of tumor promotion and/or increased mortality in patients with head and

neck cancer receiving radiotherapy (ENHANCE and DAHANCA) and demonstration of increased mortality patients with cancer not receiving chemotherapy (EPO-CAN-20 and 2001-0103). In other cancers, including breast cancer, non-small cell lung cancer, lymphoid malignancies, and cervical cancer, the risks of decreased survival and/or decreased time to progression due to ESAs use is suggested by some but not all studies; no studies have been performed which clearly exclude clinically important risks in these cancer types.

Whereas at the time of approval, safety concerns were theoretical, there is now mounting evidence of documented effects on survival, tumor progression, and thrombotic events which require a re-assessment of the net benefits of this class of drugs. With the results of two additional clinical studies with evidence of harmful effects (a total of eight studies as of this date), FDA requests the Committee's advice with regards to appropriate actions to be taken at this time. These actions may include any of the following:

- Remove the indication for use to treat anemia due to cancer chemotherapy
- Restrict the indication to use only in patients who will not be cured by treatment intervention (e.g., metastatic disease) and contraindicate use in patients surgically resected for cure (e.g., as an adjunct to adjuvant therapy).
- Restrict use to specific cancer subtypes where safety has been adequately assessed (small cell lung cancer)
- Contraindicate use in clinical settings where harmful effects have been demonstrated, e.g., breast and head & neck cancers.
- Risk-management strategies to optimally communicate safety information to both health care providers and to patients. Such changes may include informed consent by patients, voluntary restriction of promotional activities, and limited distribution programs.

Regulatory background

Erythropoiesis-stimulating agents (ESAs) are approved for use in the treatment of anemia in patients with non-myeloid malignancies whose anemia is due to the effect of concomitantly administered chemotherapy. The approvals for ESAs were based on their ability to reduce the proportion of patients receiving red blood cell (RBC) transfusions. Two ESAs are approved in the oncology indication in the United States: Epoetin alfa and darbepoetin alfa. Epoetin alfa (Procrit®, Ortho Biotech, Bridgewater, NJ and Epogen®, Amgen Inc, Thousand Oaks, CA) and darbepoetin alfa (Aranesp®, Amgen Inc, Thousand Oaks, CA) were approved for the oncology indication in the United States (US) in 1993 and 2002, respectively (Figure 1). Epoetin alfa (Eprex®, Janssen Pharmaceutica, Belgium) and epoetin beta (NeoRecormon®, Roche, Switzerland) are marketed in Europe for use in oncology. FDA considers safety information derived from any ESA as relevant for characterization of risks for the entire class. ESAs have not been shown in adequately designed (double-blind, randomized, placebo-controlled) trials to improve the quality of life of cancer patients receiving chemotherapy. ESAs are supportive care products for cancer patients receiving chemotherapy and do not treat the underlying malignancies.

Additional indications for ESAs include the treatment of anemia associated with chronic renal failure, treatment of anemia associated with zidovudine therapy in patients with AIDS (epoetin alfa only), and pre-surgical administration to reduce perioperative

transfusion requirements (epoetin alfa only) (Figure 1). In the chronic renal failure indication, ESAs have demonstrated increased risk for cardiovascular event when used to target higher hemoglobins in the CHOIR and Normal Hematocrit studies, which has been the subject of a CardioRenal Advisory Committee in September 2007.[1 2 3] In the peri-operative setting, the SPINE study in patients undergoing major elective spinal surgery has demonstrated increased risk of deep venous thrombosis in patients receiving ESAs.[4]

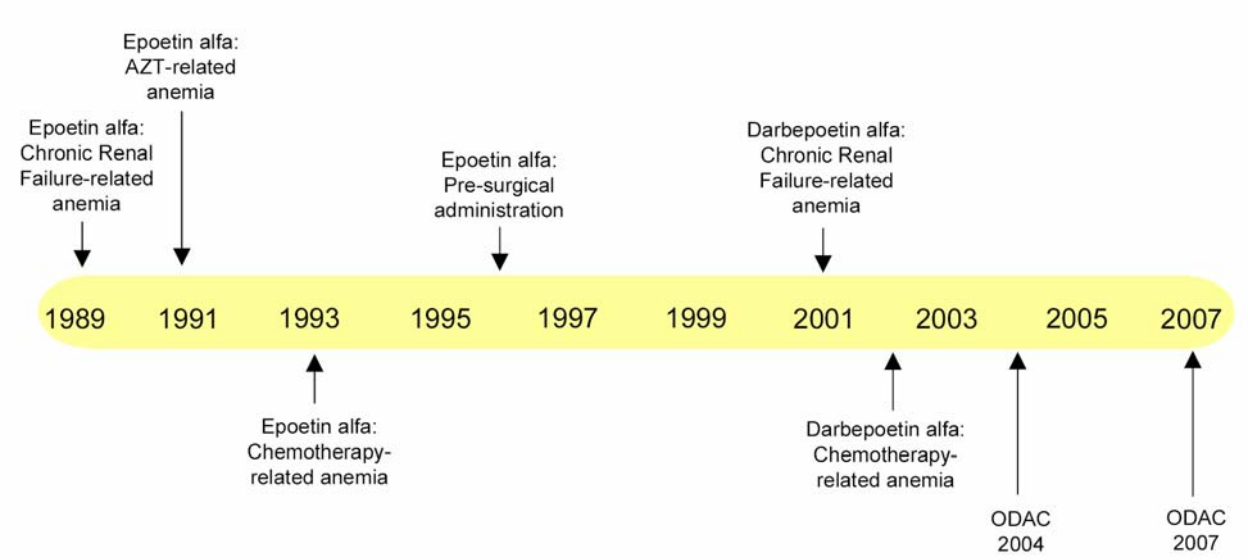


Figure 1: Approval history of epoetin alfa and darbepoetin alfa and dates ODAC meetings

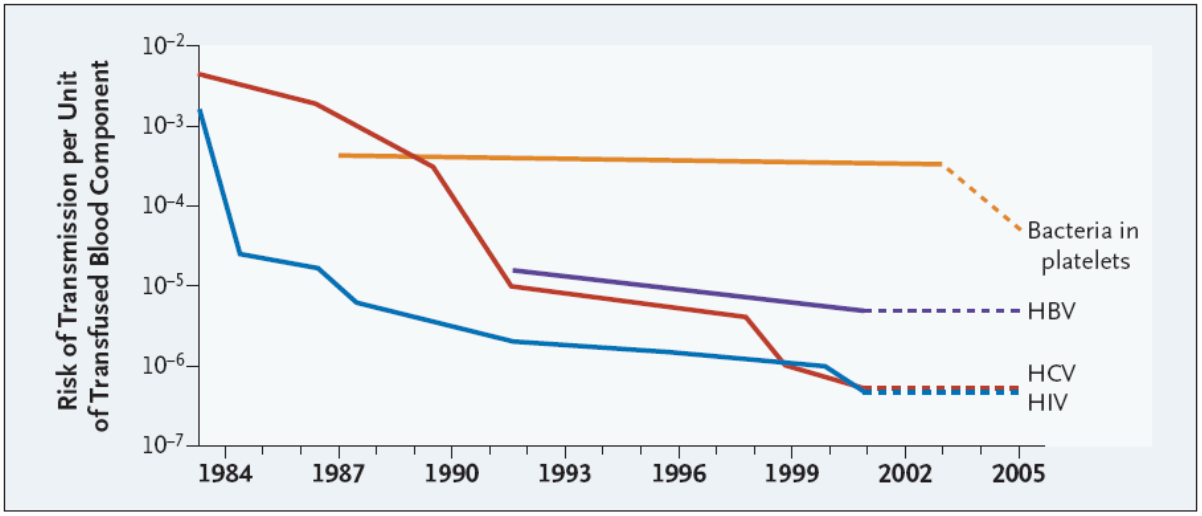
Benefits of ESAs in Trials Supporting Approval for Patients with Cancer

US marketing approval for ESAs was based on demonstration of clinically important, statistically significant reductions in the proportion of patients receiving RBC transfusions (Table 1). The approval of epoetin alfa in 1993 was supported by pooled data from six randomized, double-blind, placebo-controlled trials enrolling 131 anemic patients with various solid tumors or lymphoid cancers, receiving either cisplatin-based (45%) or non-cisplatin-based (55%) combination chemotherapy.[5] The approval of darbepoetin alfa in 2002 was based on a single, randomized, double-blind, placebo-controlled trial (Study 980297) enrolling 314 anemic patients with non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) undergoing initial treatment with a cisplatin-based chemotherapy regimen. In these approval studies, an approximately 20-30% absolute risk reduction was observed in the risk of receiving a RBC transfusion. Therefore, at best, 1 in 3 anemic patients receiving chemotherapy need to be treated with ESA and be exposed to their concomitant risks to avoid an RBC transfusion.

	Proportion of patients receiving red blood cell transfusions	
	Epoetin alfa N=51	Placebo N=58
% transfused*	22%	43%
	Darbepoetin alfa N=148	Placebo N=149
% transfused†	21%	51%

Table 1: Reduction in the proportion of cancer patients on chemotherapy receiving red blood cell transfusions in trials supporting licensure of ESAs
* as evaluated from Week 5 to 12 in pooled data from six randomized trials
† as evaluated from Week 5 to end of treatment in Study 980297

Use of ESAs to decrease the need for RBC transfusions in patients results in avoidance of exposure to transfusions with its attendant risks of serious and fatal viral infections, transfusion-related acute lung injury, and blood group incompatibility. However, due to better donor selection and improved screening, since the 1993 US approval of the first ESA for treatment of anemia due to cancer chemotherapy, the risks of transfusion-transmissable infections for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus have decreased (Figure 2).[6] Figure 3 illustrates the current risks of RBC transfusion.[7 8 9 10 11 12 13]



Risks of Transfusion-Transmitted HIV, HBV, HCV, and Bacterial Infection in the United States, 1984–2005.

Figure 2: Decreasing transfusion-related infectious risk of Hepatitis B virus (HBV), Hepatitis C virus (HCV), human immunodeficiency virus (HIV) in red blood cell transfusion.
Also shown is decrease in bacterial contamination of platelets. Dashed lines represent estimates. Reprinted with permission from New England Journal of Medicine.[6]

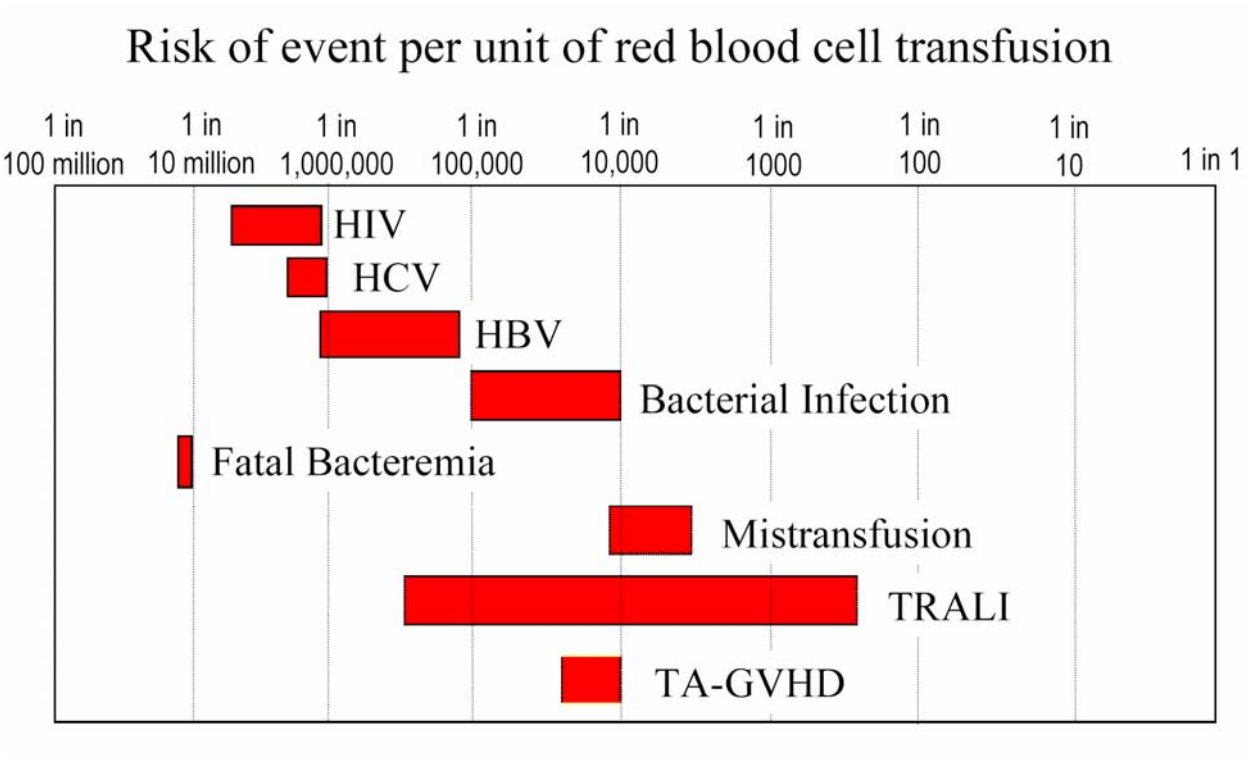


Figure 3: Current red blood cell transfusion risks (per red blood cell unit).
The horizontal bars represent the range of risks available from current literature. HBV denotes Hepatitis B virus; HCV, Hepatitis C virus; HIV, human immunodeficiency virus; TRALI, transfusion related acute lung injury; and TA-GVHD, transfusion associated graft versus host disease

Summary of ESA trials demonstrating decreased survival and/or decreased duration of locoregional tumor control in patients with cancer

Since the 1993 approval of epoetin alfa in the cancer indication, the risks of ESAs continue to evolve. The risks of ESAs were the subject of two separate ODACs, in May 2004 and May 2007. The trials that led to FDA seeking advice from both ODAC 2004 and 2007 are further described in Appendix 1. The ODACs in 2004 and in 2007 advised FDA on design of future clinical trials that could potentially further define the risks of ESAs in patients with cancer, and additional labeling restrictions.

The trials summarized in this document provide evidence linking ESAs to shorter survival, decreased locoregional tumor control, and shorter time-to-disease progression. At the May 2004 ODAC, two studies (BEST and ENHANCE) investigating the effects of ESAs on survival and tumor outcomes in patients with cancer demonstrated adverse outcomes in ESA-treated patients. As of the May 2007 ODAC, four additional studies (DAHANCA, 2000-0161, EPO-CAN-20, 2001-0103) investigating ESAs in oncology patients demonstrated shorter survival, shorter time to progression, or lower rate of loco-regional tumor control. Since May 2007, two additional studies (PREPARE and GOG-191) investigating ESAs in oncology patients receiving chemotherapy have shown decreased survival and/or decreased duration of locoregional tumor control. Therefore, a total of eight oncology studies with ESAs show decreased survival or decreased tumor control. These studies are summarized below in Table 2. In these eight studies, ESA

dosing was targeted to achieve and maintain hemoglobin values in excess of current recommendations, and in four of the eight studies (2001-0103, DAHANCA, ENHANCE, EPO-CAN-20), ESAs were administered to patients not receiving chemotherapy.

Study / Tumor / (n)	Hemoglobin Target	Achieved Hemoglobin (Median Q1,Q3)[1]	Primary Endpoint	Adverse Outcome for ESA-containing Arm
Chemotherapy				
BEST Study Metastatic breast cancer (n=939)	12-14 g/dL	12.9 g/dL 12.2, 13.3 g/dL	12-month overall survival	Decreased 12-month survival
2000-0161 Study Lymphoid malignancy (n=344)	13-15 g/dL (M) 13-14 g/dL (F)	11.0 g/dL 9.8, 12.1 g/dL	Proportion of patients achieving a hemoglobin response	Decreased overall survival
PREPARE Neoadjuvant breast cancer (n=733)	12.5-13 g/dL	13.2 g/dL 12.4, 13.9 g/dL	Relapse-free and overall survival	Decreased 3 year relapse-free Decreased overall survival
GOG 0191 Cervical Cancer (n=114)	12-14 g/dL	12.7 g/dL 12.1, 13.3 g/dL	Progression-free survival	Decreased 3 yr. progression-free survival Decreased overall survival Increased local and distant events
Radiotherapy Alone				
ENHANCE Head and neck cancer (n=351)	≥15 g/dL (M) ≥14 g/dL (F)	14.04 g/dL 13.0, 14.9 g/dL	Locoregional progression-free survival	Decreased 5-year locoregional progression-free survival Decreased overall survival
DAHANCA Head and neck cancer (n=522)	14-15.5 g/dL	Not available	Locoregional disease control	Decreased locoregional disease control
No Chemotherapy or Radiotherapy				
EPO-CAN-20 Non-small cell lung cancer (n=70)	12-14 g/dL	Not available	Quality of life	Decreased overall survival
2001-0103 Non-myeloid malignancy (n=989)	12-13 g/dL	10.6 g/dL 9.4, 11.8 g/dL	RBC transfusions	Decreased overall survival

Table 2: Randomized, Controlled ESA Trials with Decreased Survival and/or Decreased Locoregional Control

[1] Achieved Hemoglobin data was supplied by the Sponsors; confirmation of data by FDA is pending.

Events occurring after May 2007 ODAC

Labeling changes:
Revised labeling based on May 2007 ODAC advice

- May 31, 2007: FDA letter issued requesting revised labeling addressing ODAC recommendations
- September 7, 2007: FDA letter requested revised labeling updating Warnings within 30 days
- September 19 (Aranesp) and 21 (Procrit), 2007: revised labeling submitted
- November 8, 2007: labeling approved and issued with Dear Healthcare Provider letter. Boxed warning modified to:
    - List cancer primary tumors with adverse outcomes (advanced breast, head and neck, lymphoid, and non-small cell lung malignancies)
    - Note that risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target hemoglobin of < 12 g/dL.
    - Add warning for use only for treatment of anemia due to concomitant myelosuppressive chemotherapy.
    - Recommend discontinuation following completion of chemotherapy course.

Warnings updated to include adverse results from EPO-CAN-20 and 2000-0161 studies; studies also summarized in tabular format.

Medication Guide in place of patient package insert

- October 8, 2007: Applicant's proposed MedGuide
- Approval pending as of Feb. 13, 2008

Updated Warnings with PREPARE and GOG-191 study results

- November 30, 2007: Interim study report and datasets submitted
- December 7, 2007: Copy of manuscript for GOG-191 study
- December 7, 2007: Submission of updated labeling with inclusion of PREPARE and GOG-191 results in Warnings section of product labeling
- December 17, 2007: submission of GOG-191 datasets
- Approval pending as of February 13, 2008

Conversion to Physician Labeling Rules (PLR) format and re-submission of completed studies to support current labeling and address ODAC recommendations for re-analysis of completed ESA studies, both those used to support labeling changes and additional studies.

- December 20, 2007: supplement contains clinical study reports and datasets from completed studies

Results of Study 2001-0145 (Randomized clinical trial in SCLC)

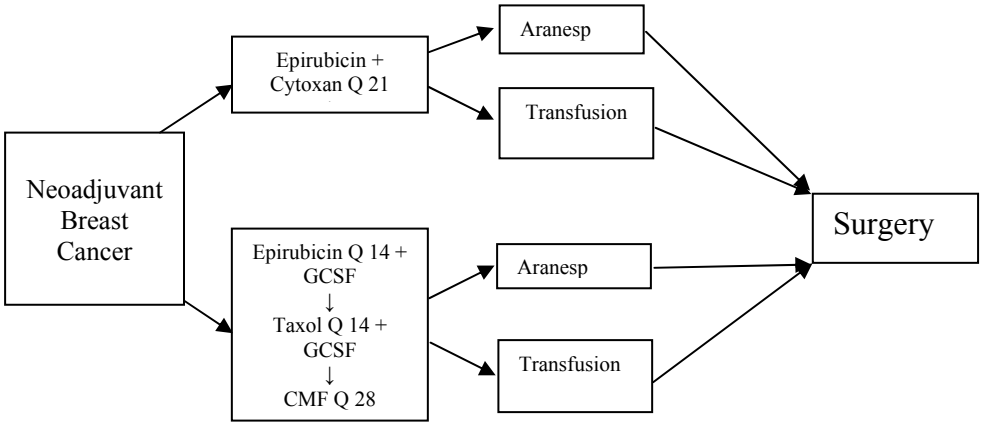
- April 2007: "Flash report" and interim datasets
- October 29, 2007: Interim clinical study report and updated interim datasets
- December 20, 2007: Interim report (Central Review) and updated interim datasets
- December 20, 2007: submission of labeling supplement requesting inclusion of 2001-0145 results in labeling

Submission of additional study data
Please see Table 5 and Table 6 for more information.

Additional studies with trends of increased tumor progression and poorer survival submitted to FDA after 2007 ODAC

Since ODAC 2007, two new studies [Neoadjuvant breast cancer (PREPARE) and cervical cancer (GOG-191)] have been presented to the FDA showed shorter survival and/or poorer locoregional tumor control. These two additional studies are discussed below.

Summary of the PREPARE study



The PREPARE study enrolled 733 patients receiving neoadjuvant breast cancer treatment in which darbepoetin alfa was administered to prevent anemia. This study was an open-label, randomized, 2 x 2 multifactorial design study intended to compare the efficacy of a preoperative, sequential chemotherapy regimen using epirubicin, and cyclophosphamide followed by paclitaxel in standard dosage and dosing intervals versus a dose-intensified, interval-shortened sequential chemotherapy regimen using epirubicin, paclitaxel, and cyclophosphamide, methotrexate, 5-fluorouracil (CMF) in patients with breast cancer. Darbepoetin alfa was given over the duration of chemotherapy. Eligibility criteria included a primary tumor that was ≥ 2 cm in size.

Co-primary endpoints

- Relapse-free survival in dose-intense vs. standard chemotherapy arms
- Overall survival in dose-intense vs. standard chemotherapy arm.

Secondary endpoints

- Comparisons of the 2 chemotherapy arms with respect to remission rate, QOL, number of blood transfusions, hemoglobin level, incidence of intramammary recurrences, lymph node status, pathologic CR rates.
- Comparisons of RFS and OS between Aranesp- and placebo-treated patients.

Outline of tumor assessments at baseline, during chemotherapy, and after surgery

- Systemic metastases at baseline were excluded by chest x-ray, upper abdominal ultrasound, a bone scan, chemistries, liver function tests, complete blood count (CBC), Carcinoembryonic Antigen (CEA), and CA 15-3. Mammogram and ultrasound of the involved breast were also performed at baseline. Baseline MRI of the involved breast was optional.
- During chemotherapy, physical exam was performed before each cycle. Clinical documentation of tumor sizes performed every six weeks by palpation and every 12 weeks by mammogram and breast ultrasound. If progression was suspected, mammogram, breast ultrasound, and if available, MRI of the breast were performed. After every second cycle, CEA and CA 15-3 were performed.
- At the end of chemotherapy, prior to surgery, clinical tumor size was measured. Repeat mammogram and breast ultrasound were performed. Repeat MRI of the breast was optional, but obligatory if it was performed at baseline. CEA, CA 15-3, chemistries, LFTs, and CBC were performed. If there was suspicion of metastases or progression, chest x-ray, abdomen ultrasound, and bone scan were performed.
- Follow-up care was specified as every 3 months physical exams, CBC, CEA, CA 15-3. Mammograms were performed every six months if breast conservation therapy was performed, otherwise it was performed annually. Chest x-ray, bone scan, abdominal ultrasound were performed annually. Chemistries and LFTs were not mandated as part of follow-up care.

The PREPARE study had already been initiated prior to FDA review of the protocol. Upon protocol review, FDA noted that a significant limitation of the neoadjuvant approach was that the evaluation of the effect of ESAs on tumor promotion would be limited to the 12 week duration of chemotherapy. Tumor removal subsequent to chemotherapy and ESA administration could preclude further assessment of ESAs on tumor promotion.

An interim analysis was performed after a median follow-up of approximately 3 years at which time the survival rate was lower (86% vs. 90%, HR 1.42, 95% CI: 0.93, 2.18) and RFS rate was lower (72% vs. 78%, HR 1.33, 95% CI: 0.99, 1.79) in the darbepoetin alfa-treated arm compared to the control arm.

RFS and OS for the PREPARE study are illustrated in Figure 4 and Figure 5.

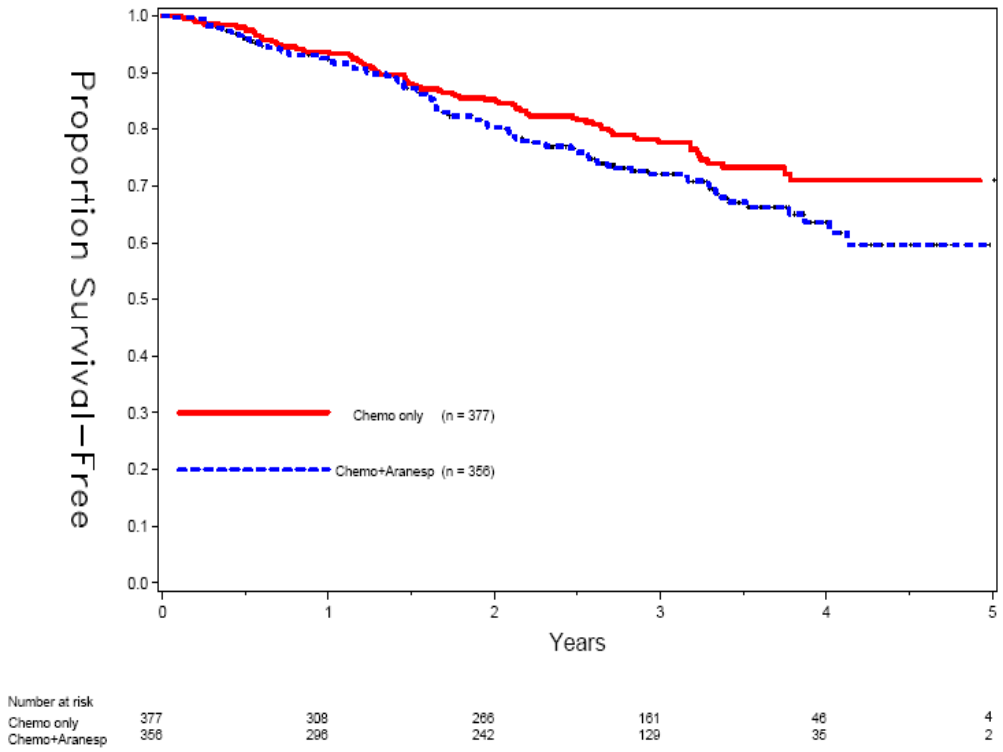


Figure 4: Kaplan-Meier plot for RFS, PREPARE study

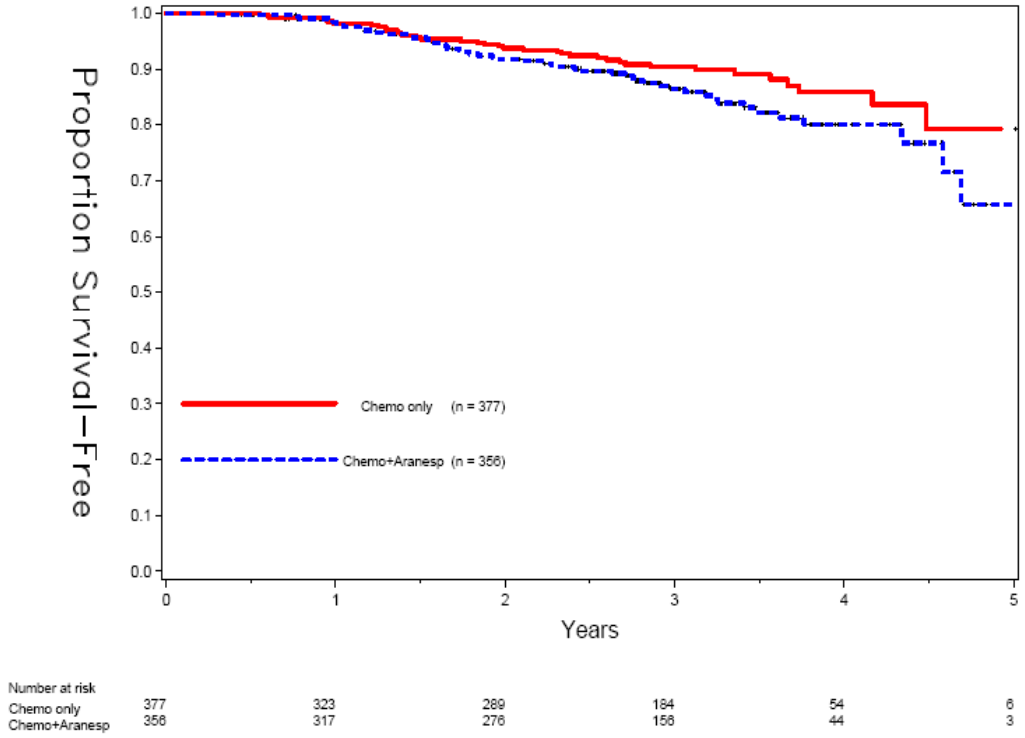
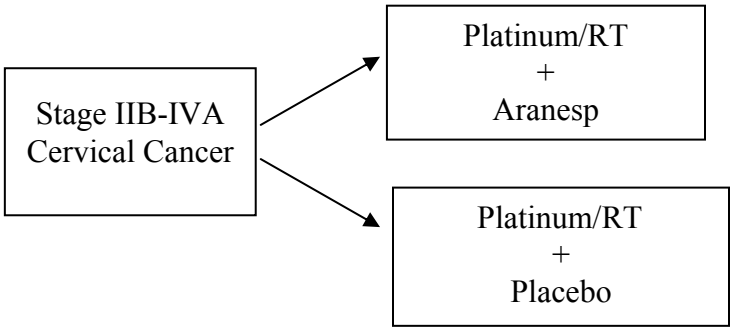


Figure 5: Kaplan-Meier plot for OS, PREPARE study

Summary of the GOG-191 study



The GOG-191 study was a randomized controlled study that enrolled 114 of a planned 460 cervical cancer patients receiving concurrent cisplatin and radiotherapy in which epoetin alfa was administered to prevent anemia. The treatment scheme was as follows:

Radiation Therapy:

- 45.0 Gy/1.8 Gy per fraction/25 fractions/five weeks pelvic RT.
- 40.0 Gy intracavitary brachytherapy in one to two implants by low dose rate brachytherapy (LDR) or 30.0 Gy intracavitary brachytherapy in 5 fractions by high dose rate brachytherapy (HDR).
- 5.40 - 9.00 Gy/1.8 Gy/3-5 fractions/3-5 days parametrial boost to involved parametria.
- Overall treatment time not to exceed eight weeks.

Chemotherapy:

- Cisplatin 40 mg/m^2 on days 1, 8, 15, 22, 29 and once during parametrial boost (6 cycles).

Epoetin alfa

- 40,000 units/week for seven weeks, starting on day 1. Dose was increased to 60,000 units/week if hemoglobin could not be maintained >12 g/dL

The primary endpoint of the study was PFS. Secondary endpoints were OS and local control. Local Control was defined as successful if any relapse or disease progression was contained within the pelvic field, and defined as failure if there was any tumor occurrence outside the pelvic field. Stratification variables were stage of disease (International Federation of Gynecology and Obstetrics (FIGO) stage IIB vs III vs IVA), brachytherapy method (LDR vs HDR), and surgical staging of PA nodes (Yes vs No).

Baseline hemoglobin <14 g/dL was required for eligibility. The target hemoglobin was 12 – 14 g/dL. Blood transfusion was given in the supportive care arm if the hemoglobin was <10 g/dL. Blood transfusion was given in the ESA arm if hemoglobin < 12 g/dL.

Initial FIGO staging of patients included a chest x-ray, and a CT or ultrasound or MRI of the abdomen. If no para-aortic lymphadenectomy had been performed, the para-aortic lymph node region had to be negative for metastasis by lymphangiogram, CT, or MRI. Patients found to have para-aortic lymphadenopathy on CT scan underwent fine needle aspiration (FNA). If disease was documented in the para-aortic nodes, the patient was

not eligible for study treatment. If the FNA of para-aortic lymph nodes was negative, patients could undergo extra-peritoneal para-aortic lymphadenectomy or laparoscopic para-aortic lymphadenectomy and only if the nodes are proven uninvolved would the patient be eligible. Additional non-invasive procedures, such as Intravenous Pyelogram (IVP), cystoscopy, proctoscopy, barium enema or lymphangiogram could be performed at the discretion of the investigator. Pelvic node dissection was not required. To monitor for recurrence, physical examinations were performed every three months x 2 years, then every six months x 3 years, and then annually. CT/MRI of the pelvis and abdomen was performed every year per the individual investigator's discretion in patients five years after treatment or at the time of recurrence as detected by physical exam.

This study was terminated prematurely by Ortho Biotech due to an increase in TVEs in Epoetin alfa-treated patients compared to control (19% vs. 9%). Both local recurrence (21% vs. 20%) and distant recurrence (12% vs. 7%) were more frequent in Epoetin alfa-treated patients compared to control. PFS at 3 years was lower in the Epoetin alfa-treated group compared to control (59% vs. 62%, HR 1.06, 95% CI: 0.58, 1.90; p=0.856 by log rank). OS at 3 years was lower in the Epoetin alfa-treated group compared to control (61% vs. 71%, HR 1.28, 95% CI: 0.68, 2.42; p=0.437 by log rank).

Given the addition of two new clinical trials to the existing evidence from six clinical trials for decreased survival and/or decrease duration locoregional to control, FDA is seeking advice from ODAC regarding further regulatory action and improved risk management.

Current state of safety and efficacy data for ESAs based on randomized, controlled clinical trials

As of February 13, 2008, data from randomized trials in patients with cancer in which effects of ESAs may be isolated have been submitted to and reviewed by FDA. A summary of the findings are provided in Table 3 and Table 4 below according to primary cancer studied and level of evidence supporting safety in the primary cancer.

Table 3: ESA oncology trials in primary cancers with no evidence of adverse effects on tumor growth or survival; primary study data reviewed by FDA

Primary Cancer Type	Study	Effects on survival or tumor promotion (ESA vs Control)
Small cell lung cancer	N93-004	ORR: 73% vs 67% (ESA vs. Control) OS: HR 1.17 (95% CI 0.89, 1.55)
	980297 (SCLC subset)*	OS: HR 0.68 (95% CI 0.41, 1.11, p=0.12)
	2001-0145	OS: HR 0.94 (95% CI 0.78, 1.12)

* denotes Study 980297, which enrolled patients with NSCLC or SCLC; randomization was stratified by primary tumor type

Table 4: Primary Cancer types with evidence of adverse effects on tumor growth or survival or for which safety has not been established		
Primary Cancer Type	Study	Effects on survival or tumor promotion (ESA vs Control)
Non-small cell lung cancer	980297 (NSCLC subset)*	OS: HR 0.86 (95% CI 0.62, 1.18, p=0.35)
	EPO-CAN-20†	OS: HR 1.84 (95% CI: 1.01, 3.35, p=0.04)
Breast cancer	BEST† (metastatic)	12 mo OS: 70% vs. 76% (p=0.0117)
	BRAVE (metastatic)	OS: HR 1.09 (95% CI 0.88, 1.35, p=0.415) PFS: HR 1.09 (95% CI 0.90, 1.31, 0.393)
	PREPARE (neoadjuvant)	OS: HR 1.42 (95% CI: 0.93, 2.17) RFS: HR 1.33 (95% CI: 0.99, 1.79)
Head and Neck cancer	ENHANCE	Locoregional PFS: HR 1.62 (95% CI 1.22, 2.14, p=0.0008) OS: HR 1.39 (95% CI 1.05, 1.84, p=0.02)
	DAHANCA†	Locoregional disease control: RR 1.44 (95% CI 1.06, 1.96, p=0.02) OS: RR 1.28 (95% CI 0.98, 1.68 ; p=0.08)
Lymphoid malignancies	2000-0161	OS: HR 1.37 (95% CI 1.02, 1.83; p=0.037)
Cervical Cancer	GOG-191†	OS HR 1.28 (95% CI 0.68, 2.42) PFS HR 1.06 (95% CI 0.58, 1.91) Local and distant events 33% vs 27%
Miscellaneous cancers – no active treatment	2001-0103	OS: HR 1.30 (95% CI 1.07, 1.57; p=0.008)
GI cancers, including colon cancer	none	
Myelodysplastic syndrome	none	

* denotes Study 980297, which enrolled patients with NSCLC or SCLC; randomization stratified by tumor type
† denotes studies prematurely terminated by Data Monitoring Committees or Data Safety Monitoring Boards

Current Status of Studies Identified by Applicant as Addressing Safety

Johnson & Johnson (Table 5) and Amgen (Table 6) provided timelines for submission of patient-level data and summary (clinical study) reports to FDA for all studies which Johnson & Johnson and Amgen have identified as adequate in design to provide information on safety of ESA use. Given the timing of these submissions, these studies will not be discussed at the March 13, 2008 ODAC meeting but may be considered for presentation at subsequent meetings, after FDA has had adequate time for review of the information. It should be noted that some of the trials listed below have not been conducted under US IND and FDA has not received clinical protocolS. Such studies are noted in the tables below.

Table 5: Randomized Trials of Epoetin alfa (Procrit or Eprex)				
Study	**Tumor Type (# enrolled)**	**Date Enrollment terminated**	**CSR Submission**	**Dataset Submission**
EPO-GBR-7	Head/Neck (n=301)	4/02	1/29/08 (received)	2/4/08 (received)
RTOG 9903	Head/Neck (n=148)	11/03	1/29/08 (received)	2/4/08 (received)
EPO-GER-22	NSCLC (n=389)	12/05	2/4/08 (projected)	3/4/08 (projected)
EPO-CAN-20	NSCLC (n=70)	11/03	2/4/08 (projected)	2/4/08 (projected)
EPO-CAN-17	Adjuvant & metastatic breast (n=354)	5/03	2/4/08 (received)	2/4/08 (received)
EPO-GER-8 AGO/NOGGO "Blohmer"	Cervical (n=264)	3/01	2/4/08 (received)	2/4/08 (received)
GOG 191	Cervical (n=114)	9/03	2/4/08 (received)	12/20/07 (received)
EPO-ANE-3010	Metastatic Breast N=236 (1000 planned)	Ongoing	2011 (projected)	2011 (projected)
EPO-CAN-15	SCLC (n=106)	9/03	2/4/08 (projected)	2/4/08 (projected)
N93-004	SCLC (n=224)	7/01	10/02	10/02 (received)
Moebus	Adjuvant breast (n=593)	4/03	2/4/08 (received)	2/4/08 (received)
HD-15	Hodgkin's Disease (n=1379)	12/06	unclear	2012 or beyond (projected)
EPO-INT-45*	Ovarian (n=182)	5/03	2/4/08 (projected; Summary report only)	2/4/08 (projected)
EPO-INT-47*	Adjuvant and metastatic breast (n=223)	7/02	2/4/08 (projected; Summary report only)	2/4/08 (projected)
EPO-INT-49*	NSCLC (n=424)	5/03	2/4/08 (projected)	2/4/08 (projected)

Table 5: Dates of estimated primary data submission to FDA for Johnson & Johnson studies.

Studies marked with * have been identified by Johnson & Johnson as relevant in design to assess risks of ESAs but protocol documents have not been submitted to the FDA.

Table 6: Randomized Trials of Darbepoetin alfa (Aranesp)				
Study	**Tumor Type # enrolled**	**Date Enrollment Terminated**	**CSR Submission**	**Dataset Submission**
2001-0145	SCLC (n=596)	7/06	Interim 10/29/07 & 12/20/07 Final projected 2009	Interims 10/29/07 & 12/20/07 Final projected 2009
PREPARE	Neoadjuvant breast (n=733)	3/05	Interim 12/3/07 (received) Final projected Q42008	Interim 12/3/07(received) Final Q42008 (projected)
ARA-03	Adjuvant breast (1090/1234 planned)	Ongoing	5/2011 (projected)	5/2011 (projected)
DAHANCA	Head/neck (n=522)	10/06	10/07 (interim)	Final – no projected date
GELA	DLBCL (458/600 planned)	Ongoing	3/2010 (projected)	3/2010 (projected)
2001-0103	Heterogeneous (n=989)	5/06	Flash 2/27/07 (received) Final 5/9/07 (received)	5/9/07 (received)
2000-0161	Heterogenous Lymphoid (n=344)	11/01	4/29/05 (received)	4/29/05 (received) Updated 4/07 (received)
2003-0232	Heterogeneous (n=391)	10/04	8/18/06 (received)	3/2/07 (received)
980297	SCLC + NSCLC (n=314)	7/00	9/01 (received)	9/01 (received) 4/05 (update received) 3/07 (update received)
980291	Heterogeneous (n=420)	Schedule 1 (Q3W): 04/01 Schedule 2 (Q4W): 09/01	Schedule 1 (Q3W): 9/01(received) 4/05 (update) Schedule 2 (Q4W): 4/05 (received)	Schedule 1 (Q3W): 9/01 (received) 4/05 (update received) Schedule 2 (Q4W): 4/05 (received)
2003-0204	Heterogeneous (n=220)	08/05	Week of 2/11/08 (projected)	4/07 (received)
DE-2004-0001*	CLL (96/400 planned)	Ongoing	2/18/08 (projected)	Final – no projected date

Table 6: Dates of estimated primary data submission to FDA for Amgen studies.
Study DE-2004-0001 marked with * has been identified by Amgen as relevant in design to assess risks of ESAs but protocol documents have not been submitted to the FDA.

Issues regarding Meta-analyses of ESA clinical trials

In both the 2004 and 2007 ODACs, meta-analyses were presented in an attempt to analyze the "totality" of the data for ESAs in the oncology indication. FDA is of the opinion that meta-analyses are not appropriate to detect safety signals for ESAs. Meta-analyses can obscure safety signals from individual studies. The results of meta-analyses depend on the studies included; earlier meta-analyses have suggested statistical significance on OS favoring ESAs, while later meta-analyses have suggested statistical significance on the OS favoring control. Cumulative meta-analyses and retrospective meta-analyses have issues on appropriate allocation of alpha. Meta-analyses also include heterogeneous trials that have variable quality, variable lengths of follow up, variable target hemoglobins, and heterogeneous tumor types.

Achieved versus Targeted Hemoglobin

Current labeling for ESAs recommends use of the lowest dose of ESAs possible to avoid transfusions and to not exceed a hemoglobin ≥12 g/dL. All eight of the trials shown in Table 2 used ESAs in dosages and schedules to target hemoglobins ≥12 g/dL. Data on the achieved hemoglobin level is available for six of the eight studies shown in Table 2 (BEST, ENHANCE, 2000-0161, PREPARE, GOG-191, 2001-0103).

In Table 2, both the targeted and achieved hemoglobin data are summarized. In this table, the lower value for the target hemoglobin range refers to the hemoglobin level below which ESA dosing was initiated, while the higher value in the target hemoglobin range refers to the level at which ESA dosing was withheld. For example, if a trial had a hemoglobin target 12-14 g/dL, ESA dosing was initiated when hemoglobin values were ≤12 g/dL, and ESA dosing would continue until hemoglobin values were ≥14 g/dL. This is contrasted with the median hemoglobin level achieved by study participants and the inter-quartile range (25% and 75% percentile). Based on the summary data provided by Amgen and J&J, the target hemoglobin level is generally higher than the hemoglobin level that the study population actually achieved in clinical trials. In four of the studies (BEST, PREPARE, GOG-191, and ENHANCE), the median hemoglobin level that was achieved was ≥12 g/dL. However, in two of the studies (2000-0161 and 2001-0103), the hemoglobin level achieved in the majority of patients was ≤12 g/dL. The adverse findings in these two studies raise the possibility that ESA use increases risks of tumor progression and mortality in oncology patients at the currently labeled doses.

At this time, there are no randomized, double-blind trials that have ruled out a clinically important effect on survival or on tumor outcomes when ESAs are dosed to a target hemoglobin ≤12 g/dL across solid tumors other than small cell lung cancer. FDA will attempt to evaluate the relationship between ESA dose and risks of adverse outcomes and between the hemoglobin level achieved and risks of adverse outcomes across completed clinical trials as data become available. However, the optimal way to address this concern would be to randomize patients to different treatment strategies, including dosing consistent with the current Center for Medicare and Medicaid Services National Coverage Decision memorandum and to compare effects on survival and tumor progression to a control arm receiving transfusion support only.

Risk Management Proposals

A more detailed discussion of additional risk management tools (beyond labeling modifications) are described in Dr. Kowarski's review in Appendix 2. The additional tools that may be considered to enhance communication and manage the risks of ESAs include:

1. Implementation of informed consent/patient agreement

   The informed consent process could be used to facilitate communication between a patient and physician. The result of this communication is the patient's authorization or agreement to undergo treatment with the ESA. In the process, the physician prescribing the ESA treatment would discuss the risks and benefits of ESA therapy as well as of alternative treatments. FDA experience with this tool is limited and its utility depends upon full implementation which can be difficult to monitor and enforce.

2. Limits in advertising and promotion

   This tool could consist of self-imposed restrictions on advertising and promotion of ESAs, includig no direct-to-consumer (DTC) advertising, restrictions on physician incentives, and limited professional promotion to specific, defined specialties and journals for very defined populations. This tool would be voluntary and not FDA-enforceable.

3. Restricted Distribution System

   Restricted distribution systems include a linkage between product access to prescribers, pharmacies, outpatient clinics, and patients with a voluntary agreement to comply with elements which assure safe use. Such systems require identification and enrollment of healthcare providers who agree to prescribe only in accordance with product labeling and who commit to patient education regarding safe use. The limitations of a restricted distribution system for ESAs involve the complexity of developing a system that covers all approved indications.

Conclusions

ESAs are supportive care agents that were approved for the treatment of anemia arising from cancer chemotherapy, based on ESAs' ability to reduce the proportion of patients requiring RBC transfusions during chemotherapy. The use of ESAs in cancer patients does not eliminate the need for RBC transfusions, since at best, an approximately 20 to 30% absolute reduction in the risk of receiving a RBC transfusion has been observed in the original approval trials for ESAs. Since the time of original approval, the risks of serious and fatal infections transmitted in blood products have decreased. At the time of approval of epoetin alfa in the oncology indication in 1993, concerns regarding adverse impact on tumor growth were theoretical. Since 1993, multiple randomized studies have demonstrated decreased survival, decreased time to tumor progression and/or poorer tumor control rates, as well as increased rate of thrombovascular events. As of February 2008, eight randomized clinical trials (BEST, ENHANCE, 2001-0103, 2000-0161, DAHANCA, EPO-CAN-20, GOG-191, PREPARE) have demonstrated decreased survival, decreased time to tumor progression, or poorer locoregional tumor control rates. Two of these trials are new studies (GOG-191 and PREPARE) presented to FDA since the May 2007 ODAC. All eight of these clinical trials targeted hemoglobins ≥12 g/dL,

but based on available data from these same studies, increased risks may be present when achieved hemoglobin values are less than 12 g/dL. There are no studies which clearly establish the effect of ESAs on survival or on tumor promotion when ESAs were administered in accordance with recommended dose in product labeling across multiple cancer subtypes.

The uncertainty regarding the risks of ESAs when used in accordance with product labeling has not been satisfactorily addressed in the four years since the 2004 ODAC. There is one actively accruing clinical trial intended to assess the risks of ESAs in patients with metastatic breast cancer, Study EPO-ANE-3010; this trial is designed adequately with respect to the 2004 ODAC's recommendations and is powered to detect a 25% decrement in progression-free survival. However, due to significant difficulty with patient accrual, results of this study may not be available for many years. One new trial, Study 2007-0782, has been proposed by Amgen since ODAC 2007 to further characterize risk of ESAs in patients with metastatic breast cancer, NSCLC, and metastatic colorectal carcinoma when used according to the dosage and administration section of the approved prescribing information. This trial protocol has not been initiated. Thus, no study establishing the safety profile of ESAs is expected in the near term.

Given the current lack of information on safety, FDA requests the Committee's advice with regards to further labeling restrictions and optimal risk management strategies.

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