FDA BRIEFING DOCUMENT

May 10, 2007
Oncologic Drugs Advisory Committee

Continuing Reassessment of the Risks of Erythropoiesis-Stimulating Agents (ESAs) Administered for the Treatment of Anemia associated with Cancer Chemotherapy

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List of Abbreviations

95% CI	95% confidence interval
AIDS	Acquired Immunodeficiency Syndrome
C	Cyclophosphamide
CA	Cancer
CEF	Cyclophosphamide, Epirubicin, 5-fluorouracil
Chemo	Chemotherapy
CLL	Chronic Lymphocytic Leukemia
CMF	Cyclophosphamide, Methotrexate, 5-fluorouracil
CSR	Clinical Study Report
DB	Double-blind
DFS	Disease-free Survival
DI	Dose Intense
DLBCL	Diffuse large B cell lymphoma
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
E	Epirubicin
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
EFS	Event free survival
EOTP	End of treatment period
ESA	Erythropoietin Stimulating Agent
ETC	Epirubicin, Paclitaxel, Cyclophosphamide
FDA	Food and Drug Administration
GVHD	Graft versus host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQOL	Health-related quality-of-life
ITT	Intent to Treat

JCO	Journal of Clinical Oncology
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LRC	Loco-regional Control
MedDRA	Medical Dictionary for Regulatory Activities
ND	Not determined
NS	Not significant
NSCLC	Non-small cell lung cancer
ODAC	Oncologic Drugs Advisory Committee
ORR	Overall Response Rate
OS	Overall Survival
PC	Placebo-controlled
PFS	Progression free Survival
Q3W	Every 3 weeks
QOL	Quality-of-life
QW	Every week
RBC	Red Blood Cell
R-CHOP	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
RFS	Relapse free survival
RR	Response Rate
RT	Radiation Therapy
SCLC	Small cell lung cancer
SMQ	Standardize MedDRA Query
T	Paclitaxel
TAC	Docetaxel, Doxorubicin, Cyclophosphamide
tiW	Three times a week
TRALI	Transfusion related acute lung injury
TVE	Thrombo-Vascular Event

Executive Summary

Erythropoiesis-stimulating agents (ESA) were first studied and licensed for the treatment of anemia in 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 the etiology of anemia in 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 anemic patients with cancer receiving myelosuppressive chemotherapy, which formed the basis for FDA approval, was reduction in the proportion of patients who require RBC transfusions; in those such patients were 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 alone 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 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 risks of blood transfusions, including the infectious risks, have decreased. In contrast, data continue to accumulate regarding the increased risks of mortality and of possible tumor promotion from the use of ESAs. As of March 2007, increased mortality has been observed both in patients with cancer (BEST, ENHANCE, 20000161, and EPO-CAN-20 studies) and in those with chronic renal failure ("Normal Hematocrit" and CHOIR studies) when ESA treatment strategies were designed to achieve and maintain hemoglobin levels above 12 g/dL. In addition, ESA treatment strategies intended to achieve and maintain hemoglobin levels above 12 g/dL have demonstrated poorer tumor outcomes (BEST, ENHANCE, and DAHANCA studies). Accumulating data from recent clinical trials, consistent with the earlier clinical trials presented to ODAC in May 2004, led to revised product labeling that includes more expansive and detailed warnings regarding use of ESA treatment strategies that are designed to maintain hemoglobin levels above 12 g/dL.

While the risks of treatment strategies in which ESAs are used to achieve and maintain hemoglobin levels in excess of that needed to avoid transfusions have been clearly demonstrated to be unacceptable, there are insufficient data from adequate and well-controlled studies designed to assess effects on survival or tumor promotion employing the *recommended* doses of ESAs. In the three years since the May 2004 ODAC meeting, the primary study data have not been submitted for **any** of the ongoing studies identified by Johnson & Johnson or Amgen as intended to assess these risks. Furthermore, many of these studies use regimens which are not consistent with current labeling and thus do not address the risks of the recommended regimen. The only data provided to FDA derives from a study with design limitations, Amgen Study 20010103, which used the

recommended dose/dose medication and demonstrated significantly shorter survival in cancer patients receiving ESAs as compared those receiving transfusion support. This study was not adequately designed to assess effects on tumor promotion or on thrombotic risks.

Given the data from recent clinical studies, it is appropriate to re-assess the safety of ESAs in patients with cancer and to re-evaluate the net clinical benefit of ESAs in this setting. This document contains: 1) summaries of the risks of transfusions and of ESAs; 2) a summary of data from studies of ESAs in patients with cancer available at the time of the May 2004 ODAC meeting, 3) an update on the status of clinical trials intended to further assess the effects of ESAs on survival, tumor promotion, and thrombotic events, and 4) enumeration of limitations of the ongoing studies intended to assess the risks of ESAs.

FDA seeks advice from the Committee regarding:

1. Whether the net clinical benefits of ESAs, given the decreasing risks of transfusions, continue to outweigh the risks of ESAs when used according to product labeling in anemic patients receiving concurrent chemotherapy. Should the results observed with off-label regimens (those intended to achieve and maintain hemoglobin levels above 12 g/dL) be generalized to the approved dosing regimens, and if so, to what extent?

2. Comment on the adequacy of the characterization of the risks of ESAs at the recommended dose and schedule. If the characterization of risks is deemed inadequate, what steps that should be taken to better characterize the risks in a timely fashion. Factors that may impact timely completion of studies include unrealistic expectations of patients and physicians regarding clinical benefit of ESAs, use of placebo controls, and studies conducted by third parties from whom Amgen and Johnson & Johnson have been unable to obtain primary study data.

3. Comment on need to re-evaluate the appropriate dose of ESAs. Should studies be conducted to assess the safety and effectiveness of dosing strategies that maintain hemoglobin levels at a level comparable to that achieved with current transfusion practices?

4. Comment on the extent of additional safety information that should be obtained. For example, the use of an ESA may increase the rate of serious or fatal thromboembolic adverse events by as much as 25 to 50% over the baseline placebo rate. Based on internal FDA calculations, the rate of excess fatal venous thromboembolic events due to an ESA may be increased 3 to 4 fold over the most likely fatal red blood cell transfusion event, transfusion acquired acute lung injury (TRALI). A study designed to exclude clinically important increases in the incidence of thrombotic-vascular events (similar to the SPINE study, which was conducted in patients receiving ESAs prior to orthopedic surgery) would require hundreds to thousands of patients. Similarly, studies intended to support expanded labeling for new dosing regiments would require up to 15,000 patients in order to characterize the increase in thrombosis rates for the new ESA dosing regimens compared with approved regimens.

5. Comment on further actions that should be undertaken by Amgen, Johson & Johnson, or FDA to minimize risks to patients.

Risks of blood transfusion

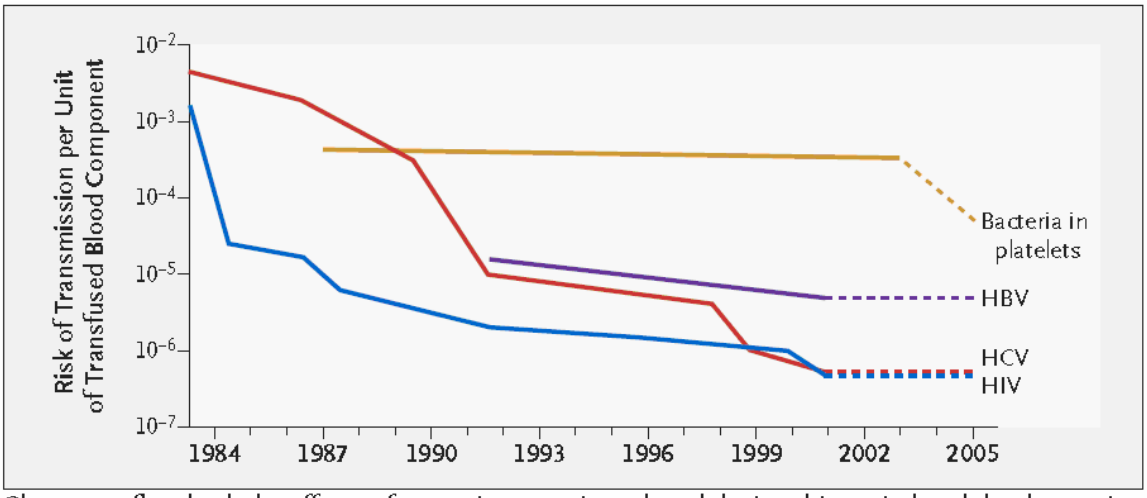
In order to weigh the current clinical benefit of ESAs (avoidance of the risks of blood transfusion), changes in the risk profile of transfusions must be taken into account. Table 1 and Figure 1 provide information on the changing incidence of infectious risks of blood transfusions over time. Due to better donor selection and improved screening, the risks have decreased, in some cases dramatically. In addition to the risks listed in Table 1 and Figure 1, red blood cell transfusions may result in transfusion-related acute lung injury (TRALI), which is now the most common serious risk of red cell transfusions. The risk of TRALI is uncertain but is estimated to be between 1 in 432 whole blood units to 1 in 557,000 red blood cell units.[1]

Table 1: Estimated Risks per Unit Blood Transfused

Risk	Retrovirus Epidemiology Donor Study (1991-1993)[2]	Dzik 2003[3]
HIV	1/493,000	<1/1,000,000
HCV	1/103,000	<1/1,000,000
HBV	1/63,000	<1/400,000
Bacterial contamination	ND	≈1:10,000-100,000*
Mistransfusion	ND	≈1:5000-10,000
GVHD	ND	<1:10,000

*Risk of transfusion associated fatal bacteremia is estimated at 1/13,898,000 units of blood transfused.[4]
ND=Not determined

Figure 1: Risk of Transfusion-Transmitted HIV, HBV, HCV, and Bacterial Infection in the United States, 1984-2005[5]



Changes reflect both the effects of screening tests introduced during this period and the decreasing incidence of HIV, HBV, and HCV infections in blood donors. Several measures to prevent the transmission of bacteria by platelet transfusion were implemented in or around 2004. Dashed lines represent estimates.

Risks and Potential Risks of ESAs

Adverse reactions of ESAs may vary in incidence by underlying disease condition. The most serious adverse events associated with ESAs include pure red cell aplasia, increased mortality associated with cardiovascular and thromboembolic events, and in patients with cancer, the potential for tumor growth promotion. In patients with chronic renal failure, the most common adverse reactions are hypertension, headache, arthralgias, and nausea. The most common adverse reactions in patients with cancer are pyrexia, nausea, vomiting, and diarrhea. Please see the full Prescribing Information on Aranesp and Epogen/Procrit for further discussion of known ESA risks.

Of the serious risks, an increased risk of thrombotic events has been consistently observed across multiple patient populations. In patients with chronic renal failure, the risks of vascular access graft thrombosis is increased and as demonstrated in the "Normal Hematocrit" and CHOIR studies, the incidence of serious thrombotic events are increased with treatment strategies intended to maintain hemoglobin levels above 12 g/dL. In patients with cancer, an increased risk of thrombotic events has not been observed consistently across clinical studies. However in a recent meta-analysis of controlled trials in patients with cancer, an increased risk of thrombotic events was demonstrated (HR 1.67) for those who received ESAs. In addition, FDA's analysis of datsets from three recently submitted Amgen studies (20010103, 20030232, 20000161) demonstrated an increased incidence of risks of arterial and venous thrombosis in a standardized medical query (SMQ) analysis. The most convincing evidence of the increased risk of thrombosis is provided by a study conducted in anemia patients receiving pre-operative ESAs prior to scheduled orthopedic surgery (SPINE study). The goal of this study was to demonstrate that there was no clinically important increase in the rate of thrombotic events in patients receiving ESAs compared with those receiving standard transfusion supports. In contrast, the study showed a significant and clinically important increase in the risks of thrombotic events, based on systematic evaluation that included non-invasive screening procedures.

In contrast to the consistent evidence of increased risks of thrombosis, the evidence for tumor proliferation is limited to the results of the clinical studies (BEST, ENHANCE, DAHANCA) which used unapproved dosing regimens. The biological plausibility of the observed findings is supported by demonstration of the presence of erythropoietin receptors on malignant cells. However a direct relationship between the presence of erythropoietin receptors on tumor and tumor proliferation in response to exogenous erythropoietin has not been established. *In vitro* and *in vivo* data do not provide convincing evidence that erythropoietin promotes tumor growth and proliferation. Please refer to the additional references for further information. [6,7,8,9,10,11,12,13,14,15,16] Because of the lack of compelling supportive data from *in vitro* and *in vivo* studies in animal models, this question can only be addressed through adequate and well-controlled clinical trials.

Regulatory History

Two erythropoietin stimulating agents (ESAs), epoetin alfa (Epogen/Procrit) and darbepoetin alfa (Aranesp), are currently licensed in the US. Both products were approved in cancer patients based on the demonstration of a reduction in the proportion of blood transfusions received during chemotherapy. These agents 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.

Two additional erythropoietin products, epoetin alfa (Eprex, Ortho Biotech) and epoetin beta (NeoRecormon, Roche) are approved for use outside the US. Epoetin alfa and epoetin beta have the same amino acid sequence but differ in glycosylation patterns. Aranesp differs from epoetins alfa and beta in its amino acid sequence and in glycosylation. The FDA considers epoetin alpha, epoetin beta, and darbepoetin alfa as members of the same pharmacologic class and for the purposes of labeling, treats all members of this class as equivalent with regards to safety issues.

Approval History of Procrit/Epogen

The first approved ESA in the US was epoetin alfa, which is manufactured, distributed and marketed by Amgen, Inc. under the proprietary name Epogen. The same epoetin alfa product is manufactured by Amgen, Inc., but is marketed and distributed by Ortho Biotech, L.P., a subsidiary of Johnson & Johnson, under the proprietary name Procrit. Under a contractual agreement with Amgen, Ortho Biotech LP has rights to development and marketing of Procrit for any indication other than for the treatment of anemia associated with chronic renal failure in patients on dialysis or use in diagnostic test kits. Epogen and Procrit have identical labeling information for all approved indications.

Epoetin alfa was licensed on June 1, 1989 and was indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis (end stage renal disease) and patients not on dialysis. Since that time, the license has been expanded to include the following additional indications:

- Treatment of anemia associated with zidovudine therapy in patients with AIDS (1991)
- Treatment of anemia associated with cancer chemotherapy (1993)
- Pre-surgical administration to reduce perioperative transfusion requirements (1996)

Additional changes to the label have been:

- Addition of a new subsection in Warnings regarding higher mortality with treatment regimens intended to maintain a hemoglobin level of 12-14 g/dL in patients with chronic renal failure.(1996)
- Revisions to Warnings and Precautions sections to include new information regarding effects on response rate, time to progression, and overall survival in solid tumors (May 2004)
- New dosing regimen (40,000 U/kg weekly) for the treatment of anemia associated with cancer chemotherapy (June 2004)
- Revisions to Warnings and Adverse reactions to include information regarding pure red cell aplasia (October 2005)

Data supporting labeling expansion for Procrit/Epogen for the treatment of anemia associated with cancer chemotherapy

The basis of approval for Procrit/Epogen for the expanded indication of treatment of anemia associated with cancer chemotherapy in April 1993 was demonstration of a

reduction in the proportion of patients transfused during chemotherapy during the second and third months of chemotherapy and Epoetin alfa administration. The analysis was conducted on data pooled from 6 randomized, placebo-controlled, double-blind, clinical trials in a total of 131 anemic cancer patients receiving at least 12 weeks of concurrent chemotherapy who were randomized (1:1) to receive Procrit 150 U/kg TIW or placebo subcutaneously for 12 weeks. Approximately half of the patients received cisplatin containing chemotherapy regimens.[17] The efficacy results from the pooled data of the 6 clinical trials are shown below:

Table 2: Proportion of Patients Transfused During Chemotherapy (Efficacy Population[a])

Chemotherapy Regimen	On Study[b]		During Months 2 and 3[c]	
	Procrit®	Placebo	Procrit®	Placebo
Regimens without cisplatin	44% (15/34)	44% (16/36)	21% (6/29)	33% (11/33)
Regimens containing cisplatin	50% (14/28)	63% (19/30)	23% (5/22)[d]	56% (14/25)
Combined	47% (29/62)	53% (35/66)	22% (11/51)[d]	43% (25/58)

[a] Limited to patients remaining on study at least 15 days (1 patient excluded from Procrit arm®, 2 patients excluded from placebo arm).
[b] Includes all transfusions from day 1 through the end of study.
[c] Limited to patients remaining on study beyond week 6 and includes only transfusions during weeks 5-12.
[d] Unadjusted 2-sided $p < 0.05$

At the time of approval for treatment of anemia associated with cancer chemotherapy, the FDA noted that Procrit could potentially serve as a growth factor for malignant tumors. Because of this concern, Amgen agreed to conduct a study (N93-004), which was designed to rule out a detrimental effect of Procrit on the response rate in patients with limited or extensive stage small cell lung cancer.[18, 19, 21] The results of Study N93-004 are summarized under the section "Data Leading to the May 2004 ODAC".

In 2004, product labeling was expanded to include a new (weekly) dosing regimen for the treatment of anemia in patients with cancer receiving chemotherapy. The approval was based on the results of a randomized, double-blind, placebo-controlled study conducted by the North Central Cancer Trial Group (NCCTG) in which 344 patients receiving myelosuppressive chemotherapy were randomized (1:1) to Procrit 40,000 IU weekly or placebo for 16 weeks. Randomization was stratified by center, primary tumor type (lung/breast/other), concurrent radiotherapy (yes/no), and baseline hemoglobin (< 9 vs. ≥9 g/dL). Procrit/placebo doses adjusted to maintain hemoglobin of 13-15 g/dL.

There were a sizable number of patients who withdrew from study prematurely. The reasons for withdrawal were variable; however, more patients withdrew in the Epoetin arm for hemoglobin levels above 15 g/dL. The results, based on multiple analyses, utilizing different imputations for patients who withdrew from study prior to a transfusion event, showed a consistent effect on reduction in the proportion of patients requiring transfusions in the Epoetin alfa treated arm. The summary results from two of these analyses are presented in the table below.

Table 3: Proportion of patients transfused

	Study Day 28 to End-of-Treatment (Worst Case Analysis)[a]		Study Day 28 to End-of-Treatment (LOCF)[b]	
	Procrit n=174	Placebo n=170	Procrit n=174	Placebo n=170
Number of patients transfused	69	84	25	48
Proportion transfused	39.7%	49.4%	14.4%	28.2%
Chi-square test	p=0.069		p=0.002	
Difference (epo-placebo)	- 9.8%		-18.9%	
Adjusted odds ratio	0.668		0.388	
95% CI for Odds ratio	0.43, 1.03		0.22, 0.68	

[a] imputed transfusion in patients who withdrew prior to week 12

[b] Last observation carried forward

Overall survival was not significantly different (p=0.35 log rank test; HR 1.13 [95% CI 0.87, 1.46]) with median survival times of 10.9 months and 10.8 months in the Procrit- and placebo-treated arms, respectively. Due to the heterogeneity of the underlying tumor, a comparison of tumor outcomes between treatment arms was not appropriate. The reported incidence of thrombotic vascular events was 6% and 4% in the Procrit- and placebo-treated arms, respectively. It is noted that a systematic attempt to capture all TVEs was not a component of the study design.

Approval History of Aranesp

Darbepoetin alfa (Aranesp) is manufactured, distributed and marketed by Amgen, Inc. Darbepoetin alfa was licensed in September 2001 for the treatment of anemia associated with chronic renal failure, including patients on dialysis (end stage renal disease) and patients not on dialysis. Since that time, the license has been expanded to include the following additional indications:

- Treatment of anemia associated with cancer chemotherapy (July 2002)

Additional changes to the label have been:

- New dosing regimen (40,000 U/kg weekly) for the treatment of anemia associated with cancer chemotherapy (June 2004)
- Revisions to Warnings and Precautions to include information regarding effects on thrombotic events and tumor promotion (December 2004)
- Revisions to Warnings and Adverse reactions to include information regarding pure red cell aplasia (October 2005)

Data supporting labeling expansion for Aranesp for the treatment of anemia associated with cancer chemotherapy

The approval of Aranesp for the treatment of anemia associated with cancer chemotherapy was based on demonstration of a significant reduction in the proportion of patients transfused during chemotherapy during week 5 through the end-of-treatment. Study 980297, a Phase 3, double-blind, placebo-controlled, randomized (1:1) study of

darbepoetin alfa that enrolled anemic patients with previously untreated non-small cell or small cell lung cancer receiving at least 12 weeks of platinum-containing chemotherapy. This was a multicenter, multinational study in 314 anemic patients (Hgb ≤ 11 g/dL) randomized to Aranesp 2.25 mcg/kg subcutaneously weekly or placebo; randomization was stratified by tumor type. The efficacy results from Study 980297 are shown below.

Table 4: Proportion of patients transfused

	From Study Day 1 through End-of-Treatment		From Week 5 through End-Of-Treatment	
	Aranesp n=156	Placebo n=158	Aranesp N=148	Placebo N=149
Number of patients transfused	53	89	39	74
KM estimated proportion	26%	60%	21%	51%
95% confidence interval	20%, 33%	52%, 68%	15%, 28%	43%, 60%

With regard to safety, there was no evidence that Aranesp-treated patients experienced poorer survival; it should be noted however, that the study was not designed to detect an impact on overall survival of a specified magnitude. It was also noted that there was no increase in the risk of thrombotic events among patients receiving Aranesp, nor was there evidence of shorter time-to-progression among patients receiving Aranesp either in the overall study or by lung cancer subtype (NSCLC or SCLC).

Table 5: Study 980297 Adverse events of interest (2002)

Events	NSCLC		SCLC	
	Aranesp n=108	Placebo n=114	Aranesp n=47	Placebo n=45
Death	19 (17.5%)	14 (12%)	3 (6.4%)	5 (11%)
Pulm embolism	1 (1%)	0 (0)	1 (2%)	0 (0)
Thrombosis	5 (5%)	4 (4%)	0 (0)	1 (2%)

Continued patient follow-up was conducted for this study and updated information was supplied on two occasions, The following analyses for overall and progression-free survival are derived from a dataset submitted March 2, 2007, which contained updated data:

Table 6: Overall Survival

ITT Analysis	**Hazard Ratio (ESA vs Control)**	**95% CI**	**p-value**
Overall	0.80	(0.61, 1.05)	0.09
SCLC	0.68	(0.41, 1.11)	0.12
NSCLC	0.86	(0.62, 1.18)	0.35

Table 7: Progression-free survival

ITT Analysis	Hazard Ratio (ESA vs Control)	95% CI	p-value
Overall	0.80	(0.63, 1.03)	0.09
SCLC	0.58	(0.36, 0.93)	0.02
NSCLC	0.92	(0.68, 1.23)	0.56

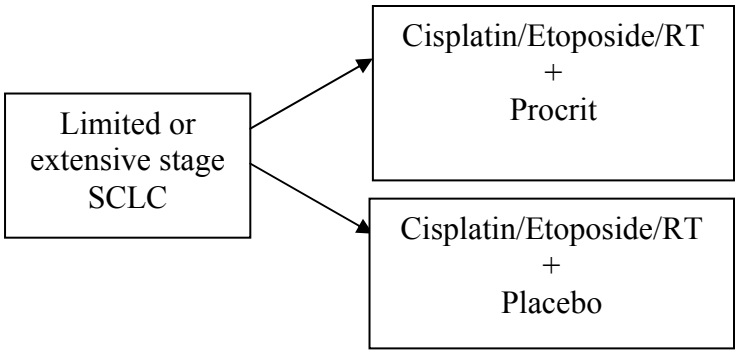
These long-term results also do not demonstrate adverse effects; however they do suggest that there may be differences in the effects of ESA on overall and progression-free survival in patients with small cell lung cancer as compared to non-small cell lung cancer. If these findings are real, it would suggest that effects on tumor outcomes in patients with small cell lung cancer may not be generalizable to patients with epidermoid tumors.

Data leading to May 2004 ODAC

The Oncologic Drugs Advisory Committee (ODAC) was convened on May 4, 2004, so that FDA could present and seek advice regarding safety signals (evidence of adverse effects on survival and shorter time-to-tumor progression) observed in the ENHANCE and BEST studies. FDA presented data used for marketing approval and labeling expansion of Procrit/Epogen and Aranesp for the treatment of anemia of cancer as well as the results of Study N93-004, which was conducted under an agreed-upon postmarketing commitment to assess the tumor-stimulating potential of Procrit/Epogen. As compared to the studies supporting marketing approval and labeling claims, the BEST and ENHANCE studies were specifically designed to test whether the use of an ESA at a dose intended to achieve and maintain a hemoglobin of >12 g/dL would improve tumor outcomes and survival compared with standard transfusion support. Instead, the ENHANCE (Henke, et al) study and the BEST (L Jones, et al) showed evidence of detrimental effects on survival and tumor outcomes. In addition to the use of a dosing strategy which was inconsistent with approved product labeling, the ENHANCE study was conducted in patients receiving concurrent radiotherapy but not chemotherapy. In contrast to the ENHANCE and BEST studies, Study N93-004 was smaller (224 vs. 351 or 939 patients) and was not designed to detect effects of a specified magnitude on overall survival or time-to-progression or progression-free survival. Rather, Study N93-004 was designed to detect a significant reduction in objective response rates. The results of these three trials are briefly summarized below.

In addition to these trials, published reports of three additional randomized trials assessing the benefits of ESA in patients with homogeneous cancers and cancer treatment were assessed. All three trials were terminated prematurely for evidence of an unacceptable increase in the risk of thrombotic and cardiovascular events in the ESA arm. These trials were EPO-CAN-15 (small cell lung cancer), PR00-03-006 (gastric and rectal cancer), and GOG 191 (cervical cancer). An additional randomized breast cancer trial (Rosenzweig) was terminated early for increased thrombotic events in the ESA arm. Additional information can be found in FDA's May 2004 ODAC briefing document.[21]

<u>Study N93-004</u>: Postmarketing Commitment Study Assessing the Tumor Stimulating potential of Procrit/Epogen



Study N93-004 was a Phase 3, randomized, double-blind, placebo-controlled trial in 224 patients with newly diagnosed limited or extensive stage SCLC who were undergoing treatment with chemotherapy and radiation therapy. These patients were randomized to receive either epoetin alpha or placebo. The study was designed as a non-inferiority study to exclude a 15% reduction in overall response rates, assuming the response rate in the control arm was 60%. Procrit was administered at a dose of 40,000 IU/kg weekly; doses were withheld for hemoglobin > 16 g/dL. The target hemoglobin was not specified, and Procrit was given over the duration of chemotherapy.

Two hundred twenty-four of a planned 400 patients were enrolled in the study between July 1993 and July 2001. Ortho Biotech LP terminated the study early due to slow accrual rates.

<u>Results</u>:

The primary objective of the study was to exclude a ≥15% reduction in the objective response rate (defined as complete and partial responses after 3 cycles of chemotherapy) among patients receiving chemotherapy with Procrit compared with those receiving chemotherapy alone. The study met its objective; data summarized in the following table:

<u>Table 8</u>: Study N93-004 Objective Response Rate

	Procrit (N=109)	Placebo (N=115)
Number of patients with CR or PR	79	77
Objective response rate (PR+CR)	73%	67%
95% CI for objective response rate	64%, 81%	58%, 76%
Observed difference in response rate	6%	
95% CI around the observed difference in objective response rates	-6%, 18%	

Table 8 illustrates that a difference in response rates between the Procrit and placebo arms of less than a - 6% has been statistically ruled out. The following limitations in the interpretation of the determination of objective response rate should be noted:

- Overall response was determined by investigators and not confirmed by independent, masked review of the images; the placebo-controlled nature of the study mitigates this concern.
- 17% of patients had missing tumor response data.
- Confirmation of tumor response through repeat evaluation at least four weeks after the first assessment was not required.

Impact on Overall Survival:

The study was not designed to detect a specified shortening in survival or in time-to-disease progression. Evaluation of effects on survival was further limited by the early termination of the study after accrual of 224 of a planned 400 patients. There was no significant difference in overall survival; median survival times were 9.7 months and 9.6 months (HR 1.17 (95% CI: 0.89, 1.55), p=NS), in the Procrit- and placebo-treated arms, respectively. [Note: the medians differ from that in prior FDA documents which used 28 days as the divisor to convert months, rather than the conventional value of 30.347 days, which is used here].

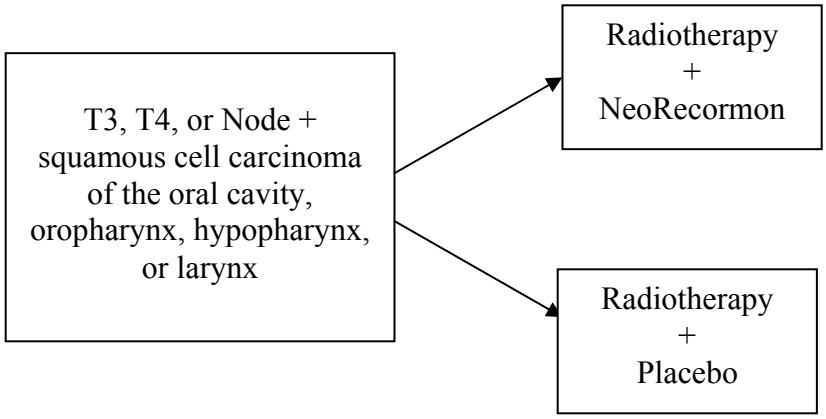
Impact on Time to Progression/Progression-free Survival

Patients with disease progression withdrew from study, however an assessment of time-to-progression could not be performed since the date of withdrawal from study was captured rather than the date of documented disease progression.

Thrombotic vascular events:

There were no differences in the rates of deep venous thrombosis or pulmonary embolism between the two arms. The protocol did not require the routine assessment of thrombovascular events.

ENHANCE Study



Design: The ENHANCE study was a Phase 3, randomized, double blind, placebo-controlled trial that enrolled 351 patients with advanced (T3, T4, or nodal involvement) squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx who were undergoing treatment with either definitive radiotherapy or postoperative radiotherapy between March 1997 and April 2001. Patients were randomized (1:1) to epoetin beta (NeoRecormon) or placebo for the duration of radiotherapy. Randomization

was stratified for tumor resection status (complete resection vs. incomplete resection vs. not resection). Epoetin beta/placebo dosing was adjusted to achieve and maintain hemoglobin values of 14.5 g/dL (women) or 15 g/dL (men).

Primary endpoint

- Locoregional progression free survival, defined as the time to loco-regional tumor progression or death, whichever occurred first.

Secondary endpoints

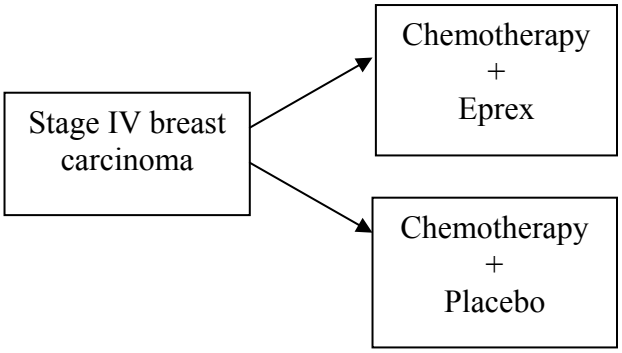
- Overall survival
- Time to loco-regional tumor progression.

Results in the intent to treat population (Lancet Oct 2003):[20]

- Significantly shorter locoregional progression free survival (HR 1.62 [95% CI 1.22, 2.14]; p=0.0008) in Epoetin beta-treated patients
    - median locoregional PFS were 406 days and 745 days, (p=0.04) in Epoetin-beta and placebo-treated patients, respectively
- Significantly shorter time-to-locoregional progression (HR 1.69 [95% CI 1.16, 2.47] p=0.007) in Epoetin beta-treated patients
- Significantly shorter overall survival (HR 1.39 [95% CI 1.05, 1.84]; p=0.02) in Epoetin beta-treated patients
- Higher incidence of "vascular disorders" (11% vs 5%) in Epoetin beta-treated patients. Vascular disorders were defined as: hypertension, hemorrhage, venous thrombosis and pulmonary embolism, and cerebrovascular disorders.
- More deaths due to "cardiac disorders" (10 vs. 5 cardiac deaths) in Epoetin beta-treated patients

For further details regarding the ENHANCE study, please see the references provided at the end of this document. [20, 21]

BEST (EPO-INT-76) Study



Design: Randomized, double-blind, placebo-controlled study in 939 patients with metastatic breast cancer receiving first line chemotherapy for metastatic breast cancer. Patients were randomized to Eprex versus placebo. Randomization was stratified by sites of metastatic disease (bone only vs. other measurable metastatic disease vs. other non-

measurable metastatic disease) but was not stratified by chemotherapy regimen. Concurrent radiotherapy and/or hormonal therapy were also permitted.

Primary endpoint

- One-year overall survival rates.

Relevant secondary endpoints:

- Objective tumor response rates
- Time to progression.

Study drug treatment: Target hemoglobin was 12-14 g/dL, and Eprex was given for 12 months. The dose of Eprex was adjusted throughout the study based on the subject's hemoglobin.

There were 939 patients enrolled between June 2000 and June 2001; the study exceeded its planned enrollment of 870 patients. Study terminated in April 2002, after review of data in the first 938 patients by the Data Monitoring Committee (DMC) due to evidence of an unexpected excess mortality in the Eprex arm. On April 24, 2002, the DMC asked Johnson & Johnson to discontinue administration of the study drug to all participating subjects. J&J also commissioned an outside consulting firm to conduct a medical chart review in August 2002, in which the primary documents were reviewed in a blinded manner in an attempt to "collect additional information concerning factors of prognostic significance for breast cancer and potentially fatal medical conditions".[21]

Results of this unplanned interim analysis yielded the following:

- Shorter 1 yr OS rates in Epoetin alfa-treated patients: 70% vs. 76%, (p=0.0117, HR= 1.359 [95% CI 1.07, 1.74])[21, 22]
    - More deaths due to thrombovascular events (TVEs) in Epoetin-treated patients within 12 months of randomization: 14 vs 4.
- Increased deaths (all-cause) in Epoetin-treated patients at 4 months after randomization: 41 deaths vs. 16 deaths.
    - Increased proportion of deaths due to thrombotic vascular and cardiovascular adverse events in Epoetin-treated patients at 4 months: 2.3% vs. 0.4%
    - Increased deaths due to disease progression in Epoetin-treated patients within 4 months of randomization: 28 vs 13.
- Time to disease progression, progression-free survival, and overall response rates (45% vs. 46%) were not significantly different between the two groups.[21,22]

Study limitations:

- Assessment of impact on tumor outcomes were limited by
    - Inadequate tumor assessments at baseline in 29% and 26% of the Eprex- and placebo-treated patients.
    - Incomplete information on imaging of lung, liver, and bone in 28% of the records.
    - The protocol did not require an assessment of all known metastatic lesions, or a set schedule for objective assessments of disease progression[23]
- Assessment of impact of TVE limited by retrospective data collection.

For further details regarding the BEST study, please see the references provided at the end of this document.[21,22,23]

Oncology Drugs Advisory Committee (ODAC) 2004

The members of the ODAC agreed that the results of these studies raised concerns that should be investigated through additional studies. In response to FDA's requests for advice, the Committee specified that the following design features be included in studies intended to further investigate the potential risks of ESAs in patients with cancer receiving chemotherapy.

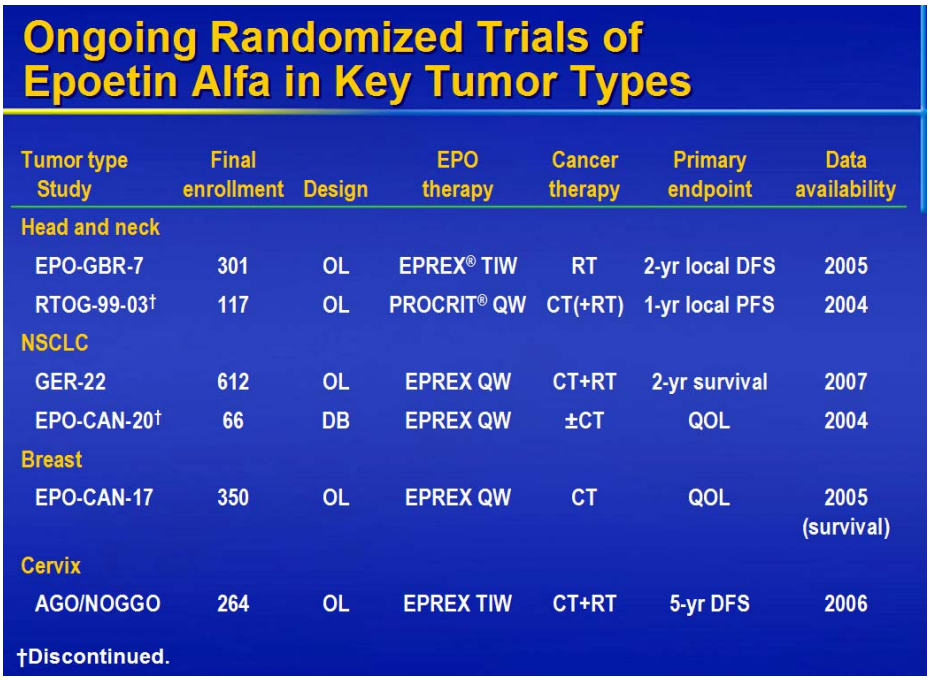
Recommendations from the Committee

- Trials should be double blind and placebo-controlled
- A survival endpoint, such as progression free survival, was the preferred primary endpoint
- Trials should be adequately powered to detect differences in survival
- Tumor progression should be routinely assessed
- Tumor type should be homogenous
- Tumor biopsies to assess for erythropoietin receptors were optional
- Studies conducted outside of the US would be generalizable to the US cancer population
- The assessment of TVEs should be a prospectively defined endpoint. Case report form should be designed to capture clinically symptomatic TVEs. TVEs should be assessed at prespecified intervals.

Presentation of Studies By Amgen and J&J PRI intended to Investigate Risk of ESAs:

During the presentations from Johnson & Johnson and Amgen at ODAC May 2004, these Sponsors identified the following studies that would be used to further investigate the risks of ESAs.

Studies Intended to Assess Risks of Epoetin Alfa as Proposed by Johnson and Johnson at 2004 ODAC

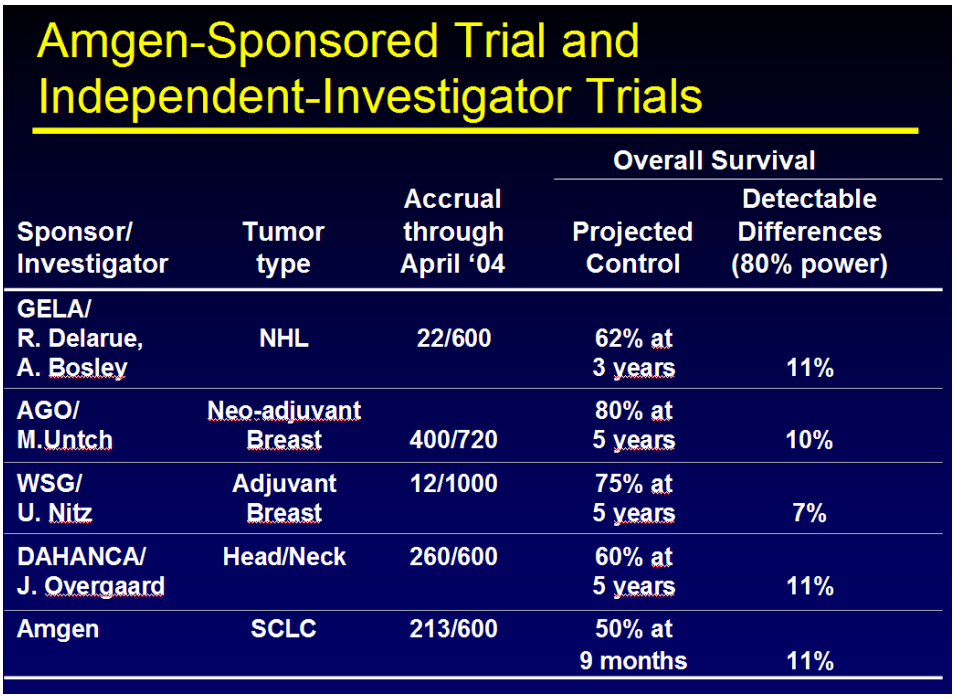


Ongoing Randomized Trials of Epoetin Alfa in Key Tumor Types

Tumor type Study	Final enrollment	Design	EPO therapy	Cancer therapy	Primary endpoint	Data availability
Head and neck						
EPO-GBR-7	301	OL	EPREX® TIW	RT	2-yr local DFS	2005
RTOG-99-03†	117	OL	PROCRIT® QW	CT(+RT)	1-yr local PFS	2004
NSCLC						
GER-22	612	OL	EPREX QW	CT+RT	2-yr survival	2007
EPO-CAN-20†	66	DB	EPREX QW	±CT	QOL	2004
Breast						
EPO-CAN-17	350	OL	EPREX QW	CT	QOL	2005 (survival)
Cervix						
AGO/NOGGO	264	OL	EPREX TIW	CT+RT	5-yr DFS	2006

†Discontinued.

Studies Intended to Assess Risks of Darbepoetin Alfa as Proposed by Amgen at 2004 ODAC



Amgen-Sponsored Trial and Independent-Investigator Trials

Sponsor/ Investigator	Tumor type	Accrual through April '04	Overall Survival: Projected Control	Overall Survival: Detectable Differences (80% power)
GELA/ R. Delarue, A. Bosley	NHL	22/600	62% at 3 years	11%
AGO/ M.Untch	Neo-adjuvant Breast	400/720	80% at 5 years	10%
WSG/ U. Nitz	Adjuvant Breast	12/1000	75% at 5 years	7%
DAHANCA/ J. Overgaard	Head/Neck	260/600	60% at 5 years	11%
Amgen	SCLC	213/600	50% at 9 months	11%

All of the studies above were initiated and accruing at the time of the May 2004 ODAC meeting. Therefore FDA did not have the opportunity to modify the protocols nor to ensure that each study contained the study design elements (above) that were

recommended by the ODAC. FDA did provide comment on an additional study EPO-ANE 3010, which was proposed by Johnson & Johnson.

March 2007: Update on Status and Results of Studies Investigating Risks of ESAs

Since May 2004, the status of the studies intended to assess the risks of ESAs, including those identified at the 2004 ODAC meeting as well as additional studies subsequently identified by Amgen or Johnson & Johnson, can be grouped into three categories: (1) study ongoing with no data provided to FDA, (2) study closed with summary data provided to FDA, and (3) accrual completed and primary data provided to FDA.

Studies that are ongoing with no data provided to FDA:

- 20010145
- DE20020015 (ARA 03 study)
- EPO ANE-3010

Studies that are closed; summary results only provided to FDA:

- EPO-GBR-7
- RTOG 9903
- EPO-GER-22
- EPO-CAN-20
- AGO/NOGGO
- Moebus study
- SE20029001 (DAHANCA study)
- EPO-CAN-17 (limited dataset containing adverse event information)
- FR20033005 (LNH 03B study)- summary data from analyses for assessment of early safety signals
- DE20010033 (PREPARE study)

Studies that are closed with primary data provided to FDA.

- 20010103
- 20000161
- 20030232

Studies 20010103, 20000161, and 20030232 were not identified by Amgen as intended to assess the impact on overall survival or tumor outcomes at the May 2004 ODAC meeting, however based on study design (randomized, controlled trial), both FDA and Amgen agree that the results may provide insight into safety concerns, despite other design limitations.

The following tables provide an overview, in tabular format, of the study design, study status, and summary results for the studies listed above. There are separate tables for studies investigating the risks of epoetin alfa and of darbepoetin alfa. This separation is intended primarily to separate the progress of each Sponsor in meeting their commitment to further assess the risks of ESAs. It should be noted that the dosing of epoetin alpha in most of the studies (EPO-GBR-7, RTOG 9903, EPO-GER-22, EPO-CAN-20, EPO-CAN-17, and AGO/NOGGO) was not consistent with the approved labeling for

Epogen/Procrit, in that dosing was titrated to achieve a hemoglobin level of 12 g/dL or higher in all of these studies. Similarly, the dosing regimen for darbepoetin alfa in the studies below (20010145, DE20010033, DE20020015, SE20029001 [DAHANCA], 20010103, 20030232) and/or the titration of dose to achieve and maintain a hemoglobin level of >12 g/dL (20010145, 20020015, SE20029001, FR20022005, 20000161) are not consistent with recommended dose in approved product and labeling. Therefore, the ability to extrapolate the findings to directions for use in approved product labeling is of concern.

Table 9: Studies using Eprex or Procrit

Study	Patient Population	Study Design	Primary Endpoint(s)	Epoetin alfa Dose & Hgb Target	Study Status	Results (ESA vs. control)
EPO-GBR-7	Head/Neck CA Baseline Hgb <15	Open-label, randomized (1:1), Radiation ± Eprex	2-yr DFS	10,000 U tiW for Hgb<12.5; 4,000 U tiW for Hgb≥12.5 Titrate to maintain Hgb 12.5-15	Terminated early for poor accrual; 301 of 800 pts enrolled. Last pt enrolled 4/02. Summary results provided 4/06; CSR expected ≈12/07	• 2 yr DFS: no results provided[a] • Local failure (in RT field): 25% vs. 29% • 1 yr OS: 77% vs. 80% • ORR: 99% vs. 99% • TVE: 3% vs. 1%
RTOG 9903	Head/Neck CA Baseline Hgb 9-12.5 (F) 9-13.5 (M)	Open-label, randomized (1:1), chemoRT or Radiation ± Procrit	2-yr loco-regional control rate	40,000 U QW Titrate to maintain Hgb 12.5-14 (F) 13.5-16 (M)	Terminated early by DSMB for trend in poorer LRC and OS in Epo arm; 148 of 372 pts enrolled. Last pt enrolled 11/03. Results published in abstract 2004.	• 1 yr LRC rates: 63% vs. 70% [b] (HR 1.18, [0.67, 2.09]) p= NS • 1 yr OS: 70% vs. 81% (HR 1.57 [0.76, 3.27]) • ORR: 73% vs. 75%
EPO-GER-22	NSCLC Baseline Hgb 10-16	Open-label, randomized (1:1), chemo→RT ± Eprex	2 yr OS	40,000 U QW Titrate to maintain Hgb 12-13	Terminated early for poor accrual; 389 of 612 pts enrolled. Last pt enrolled 12/05. Results published in abstract 2003. Summary results provided 4/06; CSR expected 2/08	• 2 yr OS: no results provided • OS: median 338 d (95% CI 242, 434) vs 299 days (95% CI 234, 364) • ORR 55% vs. 47% • TVE 17.7% vs. 8.5%; p=0.097
EPO-CAN-20	NSCLC not receiving chemo Baseline Hgb ≤12	DB, PC, Randomized (1:1) ± Eprex	QOL	40,000 U QW Titrate to maintain Hgb 12-14	Terminated early by DSMB for increased deaths in ESA arm; 70 of 300 pts enrolled. Last pt enrolled 11/03. Results published in abstract 2004 and in JCO 3/07.	• QOL: no significant difference[c] • OS: median 63 days vs. 129 days (HR 1.84 [1.01, 3.35]) p=0.04

[a] Results obtained from April 2006 BLA annual report (Reference 29)
[b] Results obtained from 2004 ASCO abstract (Reference 30)
[c] Results supplemented by Mar 2007 J Clin Oncol publication (Reference 32)

Table 9: Studies using Eprex and Procrit

Study	Patient Population	Study Design	Primary Endpoint	Epoetin alfa dose/schedule	Study Status	Results (ESA vs. control)
EPO-CAN-17	Stages I-IV breast cancer Baseline Hgb ≤ 15	Open-label, randomized (1:1), chemo±Eprex	QOL	40,000 U QW Titrate to maintain Hgb 12-14	Accrual completed; 354 of 350 pts. Last pt enrolled 5/03. Results published in JCO 4/05; Summary results provided 4/06; limited safety datasets provided 3/07	• Kaplan Meier estimates of survival curves similar (p=0.82 log rank test)[d] • ORR (stage 4 pts only): 37% vs. 30%, p=NS • TVE: 20.5% vs. 16.9% • DVT: 6.3% vs. 0.6%
AGO/NOGGO	Cervical cancer Baseline Hgb not specified	Open-label, randomized (1:1), chemo→RT ± Eprex	5 yr DFS	10,000 U tiW Titrate to maintain Hgb 13	Accrual completed; 264 of 264 planned pts. Last pt enrolled 3/01. Results published in abstract 2003; Summary results provided 4/06	• 5 yr DFS: results not provided[d, e] • 2-yr recurrence rate: 17% vs. 25%, p=0.074
Moebus	Adjuvant breast cancer Baseline Hgb not specified	Open-label, multifactorial design, randomized to dose-intensive (DI) vs. standard chemo; DI arm randomized ± Eprex	2 yr DFS for DI vs standard chemo	150 U/kg tiW Titrate to maintain Hgb 12.5-13	Accrual completed; 593 of 593 planned pts. Last pt enrolled 3/01. Results based on unpublished data in 2007; Summary results provided 4/06	• 5 yr DFS (ESA vs. no ESA): 72% vs. 71%[d,f] • 5 yr OS (ESA vs.no ESA): 81% vs. 83% • TVE (ESA vs.no ESA): 3.0% vs. 1.7%
EPO-ANE 3010	Metastatic breast cancer Baseline Hgb ≤ 11	Open-label, randomized (1:1), chemo ± Eprex	PFS	40,000 U QW Titrate to maintain Hgb 12	Study ongoing; first pt enrolled 3/06 with 111 of 1000 planned pts enrolled as of 3/07	No results available

[d] Results from April 2006 BLA annual report (Reference 29)
[e] Results supplemented by 2003 abstract (Reference 33)
[f] Results supplemented by 2007 unpublished abstract (Reference 34)

Table 10: Studies using Aranesp

Study	Patient Population	Study Design	Primary Endpoint	Aranesp Dose	Study Status	Results (Aranesp vs. control)
20010145	Untreated, SCLC Baseline Hgb 9-13	DB, PC, Randomized (1:1), Platinum + etoposide ±Aranesp	-Change in Hgb -Survival time	300µg QW x 4 → 300 µg Q3W Titrate to maintain Hgb 13-14	Accrual completed; 600 of 600 planned pts. Last patient enrolled 7/06. Two interim analyses conducted after the 165th and 248th death. No summary study results provided. CSR anticipated by 12/07	No results available
DE20010033 PREPARE	Neoadjuvant Breast CA Baseline Hgb <13	Open-label, multifactorial design; dose-intensive (E→T→CMF) ± Aranesp vs. standard dose chemotherapy (EC→T) ± Aranesp	5 yr RFS -OS	4.5 µg/kg Q2W Titrate to maintain Hgb 12-13	Accrual completed; 720 of 720 planned pts. Last patient enrolled 3/05 No summary study results provided. CSR anticipated by 12/07	No results available
DE20020015 "ARA 03"	Adjuvant Breast CA pT1-3,>3LN Baseline Hgb < 13.5	Open-label, R (1:1) CEF or TAC chemotherapy ± Aranesp	EFS	300µg QW x 4 → 300 µg Q3W Titrate to maintain Hgb > 14	Accrual ongoing. 700 of planned 1000 pts enrolled. No interim study results available. CSR anticipated June 2011	No results available
SE20029001 "DAHANCA"	Head/ Neck Baseline Hgb ≤ 14.5	Multicenter, open-label trial of radiotherapy ± Aranesp	LRC	150 µg QW Titrate to maintain Hgb 14.5-15.0	Terminated early by DMC (after 522 of 600 planned pts enrolled) based on lower LRC rates and increase deaths in ESA arm in planned interim analysis. 522 of 600 planned pts. Last patient enrolled 10/05. Summary results submitted 12/06. CSR anticipated 9/08.	• 3 yr LRC: significant reduction in Aranesp arm, p=0.01[g,h] • OS: trend towards shorter survival in Aranesp arm; p=0.08
FR20033005 "GELA LNH 03B"	DLBCL	Open-label, multifactorial design; R-CHOP 14 vs. R-CHOP 21 ± Aranesp	EFS	2.25 µg/kg QW Titrate to maintain Hgb 13-15	Study ongoing; 328 of 600 planned pts enrolled. Summary data from interim analysis 12/06 and abstract 2006. CSR anticipated 9/2010	• Interim analysis 1 yr OS: 78% vs. 70%; p=NS[g,i] • Interim analysis 1 yr EFS: 73% vs. 64%m p=NS

[g] Results from December 2006 BLA Periodic Safety Update (Reference 35)
[h] Results supplemented by February 2007 Cancer Letter (Reference 36)
[i] Results supplemented by 2006 abstract (Reference 38)

Table 10: Studies using Aranesp

Study	Cancer Subtype	Study design	Primary Endpoint	Aranesp Dose	Study Status and Results	Results (ESA vs. control)
20010103	Non-myeloid malignancies not receiving chemotherapy Baseline Hgb ≤ 11	R (1:1; 1:9), DB, PC multicenter study ± Aranesp	occurrences of transfusion	6.75 µg/kg Q4W Titrate to maintain Hgb 12-13	Study closed; 989 of 1000 planned pts. First patient enrolled 4/04; last patient enrolled 5/06. Summary data provided in flash report Jan 07; primary data submitted 3/07	• Occurences of transfusion: HR 0.85 (95% CI 0.62, 1.17)[j] • OS: HR 1.30 [1.07, 1.57] p=0.008[k] • Embolic and thrombotic events, arterial and venous 3.1 vs 1.3%[k]
20030232	Non-myeloid malignancies receiving chemotherapy Baseline Hgb ≤ 11	R (1:1), DB, PC	% transfused	300 mcg Q3W Titrate to maintain Hgb 12-13	Study closed. 391 of 380 pts enrolled. First patient enrolled 2/04, last patient enrolled 10/04. CSR submitted 4/6/07. Primary data submitted 3/07	• % transfused: 24% vs. 41%[l] • OS: HR 0.82 [0.43, 1.57]; p=NS[m] • Embolic and thrombotic events, arterial and venous: 7.1% vs. 3.6%.[m]
20000161	Lymphoprolif. malignancies receiving chemotherapy baseline Hgb≤ 11	R (1:1), DB, PC trial of patients receiving chemo ± Aranesp	Increase in Hgb ≥ 2 g/dl	2.25 µg/kg QW Titrate to maintain Hgb > 15 (M) > 14 (F)	Study closed to accrual; 344 of 340 planned pts. First patient enrolled 11/00, last patient enrolled 11/01. CSR with primary dataset submitted as a component of STN BL 103951/5097; Data cut-off 12/05; updated datset submitted 4/6/07	• OS: HR 1.37 (1.02, 1.83), p= 0.037[n] • PFS: HR 1.02 (0.80, 1.30), p= NS

[j] Based on CSR submitted in 1/07 (Reference 24)
[k] Based on FDA analysis of primary data submitted in 3/07 (Reference 25)
[l] Based on CSR submitted in 4/07 (Reference 27)
[m] Based on FDA analysis of primary data submitted in 3/07 (Reference 28)
[n] Based on FDA analysis of primary data submitted in 4/07 (Reference 26)

Since the May 2004 ODAC meeting, the following additional data regarding effects on ESAs on overall survival in patients with cancer are now available. Of the three studies demonstrating adverse effects on survival, 20010103 was the second largest controlled study (after the BEST trial) to be conducted, enrolling 939 patients. In contrast to the BEST trial, the study population was heterogeneous with respect to underlying cancer type, none of the patients were receiving active treatment for cancer and the treatment strategy was to maintain a hemoglobin level of approximately 12 g/dL rather than greater than 12 g/dL.

The 20010161 study was conducted in patients with lymphoproliferative malignancies; randomization was stratified for relevant prognostic factors. Demonstration of an adverse effect on survival was not observed in an earlier dataset but became apparent with additional follow up data.

The EPO CAN-20 study was a small quality of life trial that was terminated after 70 patients. As with the 20010103 study, it was conducted in patients not receiving chemotherapy for cancer, albeit in a homogeneous population.

Table 11: Studies demonstrating adverse effects on survival since May 2004 ODAC

Study	Results
20010103	*OS: HR 1.30 [1.07, 1.57]*
20000161	*OS: HR 1.37 (1.02, 1.83)*
EPO CAN 20	HR 1.84 (1.01, 3.35)

The following studies in Table 12 have not demonstrated an adverse effect on overall survival. FDA has reviewed the primary data from only one of these studies (2000232) and notes that for this study, there are no data for any of the 344 patients that is more than 5 months from the date of randomization. The adequacy of follow-up for the additional studies cannot be determined from the summary information provided. Another study in which a "trend" toward shorter survival was noted also demonstrated evidence of shorter time to tumor progression (SE20029001 "DAHANCA"). This study were conducted in patients with head and neck cancer and appeared to be consistent with the findings in the ENHANCE study discussed at the May 2004 ODAC meeting.

Table 12: Studies that did not demonstrate adverse effects on survival since May 2004 ODAC

Study	Results
20030232	*OS: HR 0.82 (0.43, 1.57)*
SE20029001	"trend towards shorter survival" p=0.08
FR20033005	1 yr OS: 78% vs. 70%, p=NS (ESA vs no ESA)
Moebus	5 yr OS: 81% vs. 83%, p= NS (ESA vs no ESA)
EPO CAN-17	Kaplan Meier estimates of survival curves similar (p=0.82 log rank test)
EPO GER-22	2 yr OS results (primary endpoint) not provided Median OS: 338 d (95% CI; 242, 434) vs 299 days (95% CI; 234, 364) (ESA vs no ESA)
RTOG 9903	1 yr OS 70% vs. 81% (ESA vs no ESA) OS: HR 1.57 (0.76, 3.27)
EPO-GBR-7	1 yr OS: 77% vs. 80% (ESA vs no ESA)

Since the May 2004 ODAC meeting, there is only one study which clearly demonstrates an adverse effect on time to tumor progression, Study SE20029001, which is also known as the DAHANCA study. This study was terminated as recommended by the data monitoring committee, based on both adverse effects on locoregional control rates and for a trend towards impaired survival in an interim analysis. As noted above, this study bears a number of similarities to the ENHANCE study discussed at the May 2004 ODAC meeting.

The following studies in Table 13 have not demonstrated an adverse effect on tumor outcomes. FDA is continuing its review of the primary data from study 20000161, which was submitted on April 6, 2007. The adequacy of follow-up for the additional studies cannot be determined from the summary information provided.

Table 13: Studies that did not demonstrate adverse effects on tumor outcomes since May 2004 ODAC

Study	Results
20010161	*PFS not significantly different (HR 1.02 [0.80, 1.30)*
EPO GBR 7	2-yr DFS results (primary endpoint) not provided No difference in local failure rates with radiation field and similar overall response rates
RTOG 9903	2-yr DFS results (primary endpoint) not provided 1 yr locoregional control rates 63% vs. 70%, differences not significant. Study terminated early for trend in poorer tumor outcomes.
EPO GER-22	No significant difference in overall response rates
EPO CAN 17	No significant difference in 2 yr DFS on interim analysis No significant difference in overall response rates in subset (n=74) with stage IV disease.
AGO/NOGGO	5-yr DFS results (primary endpoint) not provided Trend in 2 yr recurrence rates favor ESA arm (17% vs. 25%)
Moebus	5 yr DFS (ESA vs. no ESA) not significantly different
FR20033005	1 yr EFS not significantly different at interim analysis

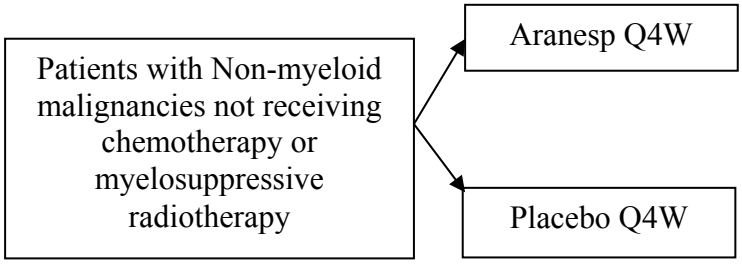
In the following section, a more detailed description of the individual studies are provided with an assessment of the limitations of each study with regard to demonstration of effects on survival, on tumor outcomes, and on thrombotic-vascular events. Specific limitations common to many of the studies are the relative infrequency and modest amount of objective (radiologic) monitoring required by most protocols for documentation of disease status and for identification of adverse drug reactions. In addition, for several studies, the case report forms capture minimal detail regarding tumor status or adverse drug reaction information. Finally, the open-label nature of many of the studies introduces the potential for bias (overt or unintentional) in reporting of tumor outcomes and adverse drug reactions.

Studies for which FDA has received primary datasets

The primary datasets for the following three studies conducted by Amgen were submitted in the past between early March and early April 2007. The results provided below, except where noted, are derived from FDA's preliminary analyses of the data.

Study 20010103

Study Design:



Study 20010103 was a phase 3, randomized (1:1), double-blind, placebo-controlled multicenter study of Aranesp in patients with anemia of cancer who were not receiving chemotherapy or myelosuppressive radiotherapy.

Primary endpoint

- Difference in proportion of red blood cell transfusions between treatment arms from study day 29 to week 17.

Secondary endpoints

- Incidence of first RBC transfusion and change in Hgb concentration.
- Safety endpoints included overall survival (deaths on study and deaths in long-term follow-up period) and adverse events.

Randomization stratified by: Hgb level (<10 g/dl versus ≥ 10 g/dl), Geographic region (Central and East Europe versus Test of the World), RBC transfusion history (yes versus no), tumor type/treatment categories (CLL or low grade lymphoma versus all other eligible patients), and ECOG status (0, 1 versus 2). Randomization ratio was modified late in the study from 1:1 to 1:9 (placebo:Aranesp). Analyses have been adjusted for randomization scheme utilized for each subject.

Study drug treatment: Aranesp was to be administered in patients with Hgb ≤ 11 g/dl at 6.75µg/kg once every 4 weeks for 16 weeks. Aranesp was to be withheld when Hgb > 13 g/dl, and resumed when Hgb falls to 12 g/dl with a 25 % reduction of previous dosage.

Amgen submitted topline summary results in January 2007.[24] A dataset containing primary data for study 20010103 was submitted on March 2, 2007.[25]

Results

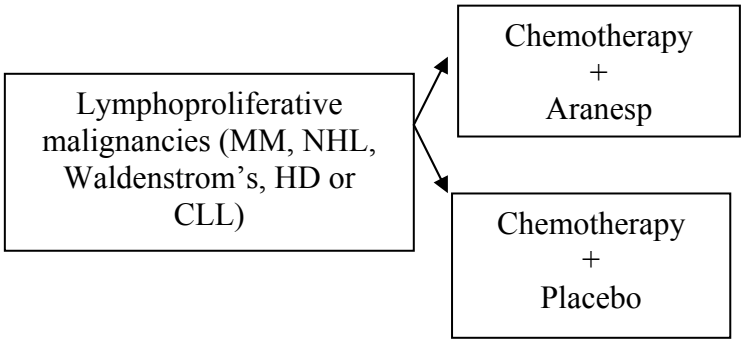
- Significantly shorter overall survival (HR 1.30; [95% CI: 1.07, 1.57], p=0.008) in Aranesp-treated patients, with median survival times of 243 days and 329 days for the Aranesp- and placebo-treated arms, respectively.
- No evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions in Aranesp arm.
- An increased incidence of arterial and venous TVEs, arterial (3.1 vs 1.3%) in Aranesp-treated patients based on a standardized medical query (SMQ) analysis.

Limitations to assessment of impact on tumor outcomes, OS, or TVE:

- The dosing regimen and adjustment rules of Aranesp employed in this study are not consistent with approved labeling Aranesp dose regimen, (2.25 ug/kg, QW or 500 ug Q3W)
- The patient population (no concurrent chemotherapy) is not consistent with the approved indication.
- The design of the study was not adequate to assess for tumor proliferation.
  - The study population included heterogeneous cancer types.

Study 20000161

Study Design:



Study 20000161 was a phase 3, randomized, double-blind, placebo-controlled, multicenter study of Aranesp in anemic patients with lymphoproliferative malignancies receiving chemotherapy.

Primary endpoint

- Proportion of subjects who achieve a Hgb response, defined as an increase of Hgb ≥ 2 g/dl by the end of treatment phase.

Secondary endpoints

- Included the correction of anemia, mean Hgb change, RBC transfusion, QOL and safety.

Randomization was stratified by: malignancy type (multiple myeloma vs. lymphoma); extent of prior chemotherapy at baseline (heavily pretreated versus not heavily pretreated), and region (Australia versus Canada versus Western Europe).

Study drug treatment: Target Hgb < 15 for men and < 14 for women. Aranesp was to be administered at 2.25 µg/kg, weekly, for 12 weeks.

At the May 4, 2004 ODAC meeting, Amgen presented the initial results of study 20000161. Amgen stated that in all histologies, the results of overall survival and progression free survival were similar for the Aranesp-treated patients and placebo patients, with a median follow up of 27 months.

In April 2005, Amgen submitted a clinical study report and primary dataset of study 20000161 containing additional information collected in long term follow up; database cutoff date was October 29, 2004.[26] Amgen stated that the safety profile of Aranesp-treated patients was comparable to that of the placebo-treated group, and consistent with that expected for a patient population receiving concomitant chemotherapy.

The following analysis is based on a dataset submitted in April 2007.

Results

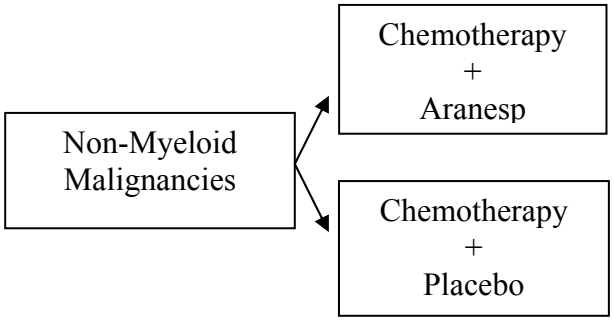
- Shorter overall survival (HR 1.37 [95% CI 1.02, 1.83]) in Aranesp-treated patients.
- No significant difference in progression free survival (HR 1.02 [0.80, 1.30]) between two arms
- The incidence of grade 3-5 TVE was higher (3.4% vs., 0.6%) for Aranesp-treated patients. TVE was defined as: thrombosis venous deep, thrombosis venous, embolism pulmonary, myocardial infarction, cardiac arrest, cerebrovascular disorder, thrombosis and angina pectoris

Limitations to assessment of impact on EFS, OS, or TVE

- The dosing adjustment rules of Aranesp employed in this study are not consistent with approved labeling.
- The design of the study was not adequate to assess for tumor proliferation.
  - Study not designed to assess PFS
  - The protocol follow-up schedule, follow-up modality, and tumor response assessment were unclear.
  - Study population included a heterogeneous patient population with mixed tumor types, disease status, and prognostic characteristics who received varied chemotherapy regimens.
- The study did not address specific monitoring for possible thrombotic/ cardiovascular events, as outlined in the ODAC recommendations on May 4, 2004

Study 20030232

Study Design:



Study 20030232 was a phase 3, randomized, double-blind, placebo-controlled study of Aranesp in anemic patients (Hgb < 11 g/dl) with non-myeloid malignancies receiving multicycle chemotherapy.

Primary endpoint

- Incidence of RBC transfusion from week 5 to end of treatment period.

Secondary endpoint

- Incidence of achieving a Hgb level ≥ 11.0 g/dl from week 5 to end of treatment period and adverse events.

Randomization stratified by: baseline Hgb level (< 10 g/dl versus ≥ 10. g/dl), region (North America versus Australia), and tumor type (lung/gynecological versus others).

Study drug treatment: Target Hgb < 13; Aranesp was to be administered at a starting dose of 300 µg, every three weeks, up to 15 weeks, and was to be increased to 500µg, every three weeks, if the week 4 Hgb level is < 9.0 g/dl, or if the week 7 Hgb increase is < 1.0 g/dl. Aranesp was to be withheld when Hgb > 13 g/dl and reinstated at a lower dose when Hgb falls to ≤ 12 g/dl. Aranesp dose was to be decreased when Hgb increase by > 1 g/dl in 2 week period in the absence of RBC transfusion.

The first patient was enrolled in February 2004, and the last patient was enrolled in October 2004. Amgen submitted a clinical study report for study 20030232 to FDA in August 2006.[27] Amgen submitted primary datasets for study 20030232 in March 2007.[28]

Results

- There was a significant reduction in the percentage of patients receiving RBC transfusions from week 5 to the EOTP (24% vs. 41%) for Aranesp-treated patients reported by Amgen. FDA has not had an opportunity to verify this result
- There is no significant difference in overall survival (HR 0.82 [95% CI 0.43, 1.57]).
- There is an increased incidence in embolic and thrombotic events, arterial and venous (7.1% vs. 3.6%) in Aranesp-treated patients based on a standardized medical query (SMQ) analysis.

<u>Limitations to assessment of impact on tumor outcomes, OS, or TVE</u>

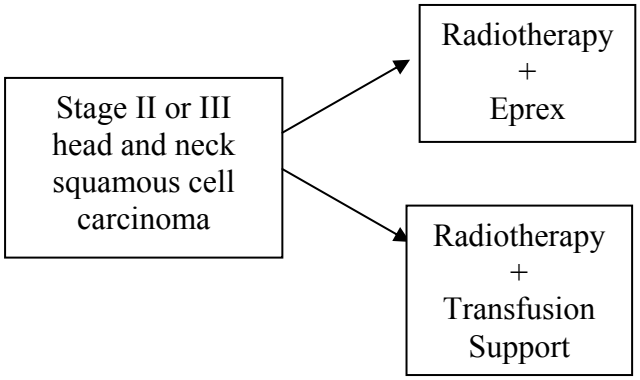
- The design of the study was not adequate to assess for tumor proliferation.
    - Study was not prospectively designed to address effects of Aranesp on tumor promotion or survival.
    - The study included a heterogeneous population with different tumor types, disease status, and prognostic factors.
    - No long term follow-up plan was stipulated in the protocol. Data collection was not adequately nor clearly specified in terms of disease status (e.g., disease stage, history of prior chemotherapy), follow-up schedule, follow-up modality, or tumor response assessment.
- The dosing regimen and dose adjustment rules for Aranesp employed in this study are not consistent with either of the approved regimens (2.25 ug/kg QW or 500 ug Q3W).

Studies which are closed with summary data available

The summary results presented below were derived from the annual reports submitted to the IND application for Procrit, periodic safety update reports to the license application for Aranesp, and/or from published literature. FDA has not received primary data and therefore cannot verify the accuracy or limitations of the summary results provided for the following studies.

EPO-GBR-7

Study Design:



EPO-GBR-7 was a Phase 3, open label, randomized study in patients with stage II or III squamous cell carcinoma of the head and neck who are undergoing treatment with curative intent radiation therapy (RT) at a dose of 60-70 Gy. Patients were randomized to either radiotherapy and epoetin alfa (Eprex) or radiotherapy with transfusion support as needed.

Primary endpoint

- Local disease free survival at 2 years defined as the absence of clinical recurrence of tumor within the RT field after 2 years.

Secondary endpoints:

- Relevant secondary endpoints in this study were overall survival at 1, 2, and 5 years.

Study drug treatment: The target hemoglobin in the study was 14.5-15 g/dL. Eprex was given over the course of RT. The dose of Eprex was based on the entrance hemoglobin, and adjusted throughout the study based on the subject's hemoglobin.

The study was stopped due to slow accrual in 2002 after 301 of a planned 800 patients were enrolled onto study between August 1999 and April 2002. Despite study closure in 4/02, primary datasets for efficacy and safety have not been submitted to FDA. Summary data regarding Study EPO-GBR-7 was contained in the annual report submitted in April 2006.[29]

Reported results:

- There was no difference between the 2 arms for local recurrence in the RT field, local recurrence outside the RT field, one-year overall survival, or response rate.
- The incidence of thrombovascular events was 1% for the RT alone arm versus 3% for the RT + Eprex arm.

Limitations to assessment of impact on tumor outcomes, OS, or TVE:

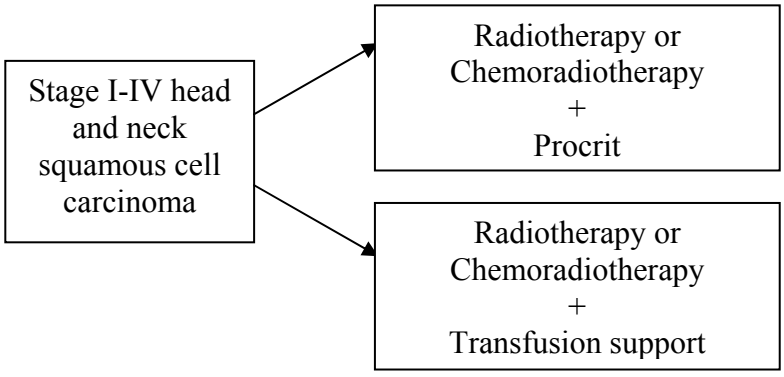
- The dosing adjustment rules of epoetin alfa employed in this study are not consistent with approved labeling.
- The design of the study was not adequate to assess tumor proliferation.

- The assessment method and the frequency of testing for local recurrence were inadequate. Tumor control was monitored by clinical assessment and not routine radiologic assessments. Clinical assessments were supplemented by radiology where appropriate, with the first follow up clinical examination occurring 1 weeks after completion of RT. Subsequent clinical follow-up was then every 4 weeks for 2 visits and then yearly for 5 years. A biopsy of the suspected recurrence site was not required to document recurrence.
- The protocol did not require assessment of survival status after subjects had been withdrawn from the study. Data regarding the number of subjects that withdrew from the study has not been submitted to the FDA.
- As noted above, responses were judged from clinical assessments, and radiographs are not required to document response. The overall response rate was noted to be 99% for both arms, an unusually high response rate for patients with Stage II/III head and neck cancer undergoing RT alone.

- The study did not address specific monitoring for possible thrombotic/ cardiovascular events, as outlined in the ODAC recommendations on May 4, 2004.
  - Routine assessments of thrombovascular events were not prespecified in the protocol.
  - The definition used for TVEs was overly broad including terms not likely to represent true thrombovascular events. Thrombovascular events as defined by the sponsor in the summary document included chest pain, cardiac arrest, angina, coronary artery disease, myocardial infarction, pulmonary embolism, and upper respiratory tract infection.

RTOG 99-03

Study Design:



RTOG 99-03 was a Phase 3, open label, randomized trial of 148 patients with Stage I-IV non metastatic squamous cell carcinoma of the head and neck who were undergoing treatment with radiation therapy (RT) at a dose of 66-72 Gy or concurrent cisplatin and RT were randomized to either epoetin alfa (Procrit) or supportive care.

Primary endpoint

- 2 year loco-regional failure

Secondary Endpoints

- Overall survival

Study drug treatment: The target hemoglobin in the study was 13.5-16 g/dL in males and 12.5-14 g/dL in females. Eprex was given over the course of RT. The dose of Eprex was adjusted throughout the study based on the subject's hemoglobin.

Study RTOG 99-03 accrued 148 of a planned 372 patients between June 2000 and October 2003. The RTOG data monitoring committee (DMC) performed an interim analysis in October 2003, following the publication of the results of the ENHANCE study, and concluded that continuation of the study was not warranted based on a trend towards shorter local-regional control rates and shorter survival in the epoetin alfa arm. Despite study closure in 10/03, a primary safety and efficacy dataset has not been submitted to FDA as of 4/07 by Johnson & Johnson. The study was published in abstract form in 2004.[30] The following safety and efficacy results were derived from the abstract:

Reported results:

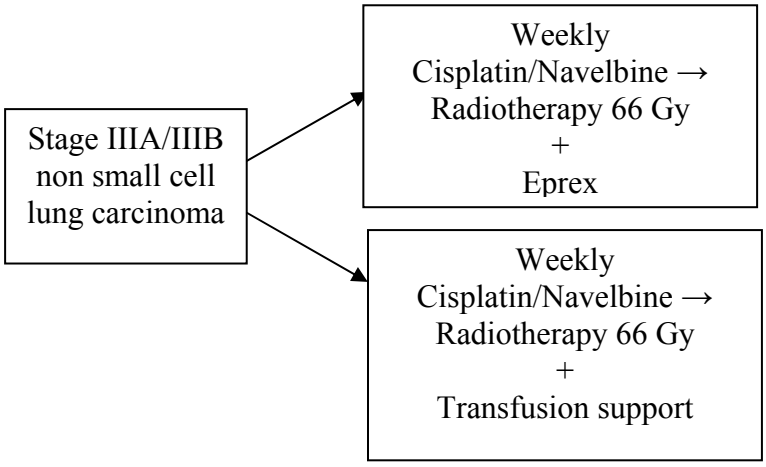
- 1 year locoregional control rates (63% vs.70%) (HR 1.18 [95% CI 0.67, 2.09]; p=NS)
- 1-year overall survival (70% vs. 81%, (HR 1.57 [0.76, 3.27]; p=NS)
- No significant differences in complete response rates.
- One fatal pulmonary embolism in the epoetin alfa arm was reported in the abstract.

<u>Limitations to assessment of impact on tumor outcomes, OS, or TVE:</u>

- The dosing adjustment rules of epoetin alfa employed in this study are not consistent with approved labeling.
- The design of the study was not adequate to assess for tumor proliferation.
    - The frequency of radiographic tumor assessments was not adequate to assess the primary endpoint, local regional control rate. A CT or MRI head and neck was required at baseline, during RT if clinically deemed necessary, and then 6-8 weeks post-RT (where scans were recommended but not required), and then every 6-12 months.
- The study did not address specific monitoring for possible thrombotic/ cardiovascular events, as outlined in the ODAC recommendations on May 4, 2004
    - Routine assessments of thrombovascular events were not prespecified in the protocol.
    - Complete data regarding thrombovascular events was not reported in the abstract published by Machtay.

EPO-GER-22

Study Design:



EPO-GER-22 was a Phase 3, open label, randomized trial of 389 patients with treatment naïve Stage IIIA/IIIB non-small cell lung cancer who were undergoing treatment with sequential chemotherapy (weekly cisplatin/navelbine) followed by RT (66 Gy) were randomized to receive either epoetin alfa (Eprex) or supportive care.

Primary endpoint

- 2 year overall survival

Secondary endpoints

- Relevant secondary endpoints were remission rate and local tumor control

Study drug treatment: The target hemoglobin in the study was 12-13 g/dL. Eprex was given over the course of chemotherapy and RT. The dose of Eprex was adjusted throughout the study based on the subject's hemoglobin.

The study was stopped dues to slow accrual in December of 2005 after 389 of a planned 612 patients were enrolled onto study between August 2001 and December 2005. As of April 2007, a primary data set on the safety and efficacy endpoints has not been provided to FDA. Summary survival and response rate data were submitted to the FDA by Johnson & Johnson in 4/06,[29] and are presented below. Interim data on median survival on 215 patients was discussed in an abstract published by Debus et al in March of 2006.[31]

Reported Results:

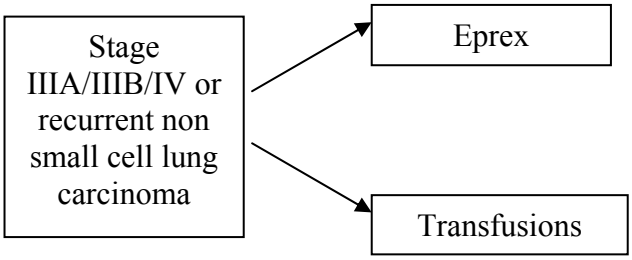
- Based on 215 of 389 enrolled patients, there was no significant difference in the median survival between the two groups.
- Based on 177 of 389 enrolled patients, the overall response rates between the two arms did not differ significantly.
- Based on 230 of 389 enrolled patients, the total number of thrombovascular events (TVEs) was 26 (23%) in the chemo-radiotherapy + epoetin alfa group, and 11 (9.4%) in the chemo-radiotherapy alone arm.

Limitations to assessment of impact on EFS, OS, or TVE:

- The dosing adjustment rules of epoetin alfa employed in this study are not consistent with approved labeling.
- No primary data available for review.

EPO-CAN-20

Study Design:



EPO-CAN-20 was a Phase 3, randomized, double-blind, placebo-controlled trial of 70 patients on palliative treatment for Stage IIIA, IIIB, IV or recurrent non-small cell lung cancer were randomized to receive either epoetin alfa (Eprex) or supportive care. Patients in this trial did not receive treatment with chemotherapy.

Primary endpoint

- Change in quality of life (FACT-An Anemia scale) from baseline to week 12.

Secondary endpoint

- No prespecified response or survival endpoints.

Study drug treatment: Target hemoglobin 12-14 g/dL. Eprex was given for 12 weeks. The dose of Eprex was adjusted throughout the study based on the subject's hemoglobin.

70 patients were enrolled into the study between February 2001 and November 2003. The study fell short of the target accrual of 300 patients, and enrollment was stopped in November 2003 due to an unplanned analysis by the data safety monitoring committee (DSMC). The unplanned analysis was conducted to assess for evidence of harm following the publication of increased mortality and poorer tumor outcomes in patients receiving ESAs in the BEST and ENHANCE studies.[20, 22] The unplanned analysis showed increased mortality in the Eprex arm. Despite study closure in November 2003, a primary efficacy and safety dataset has not been submitted to the FDA as of 4/07. The study results were published in the Journal of Clinical Oncology in March of 2007, and are presented below.[32]

Reported Results:

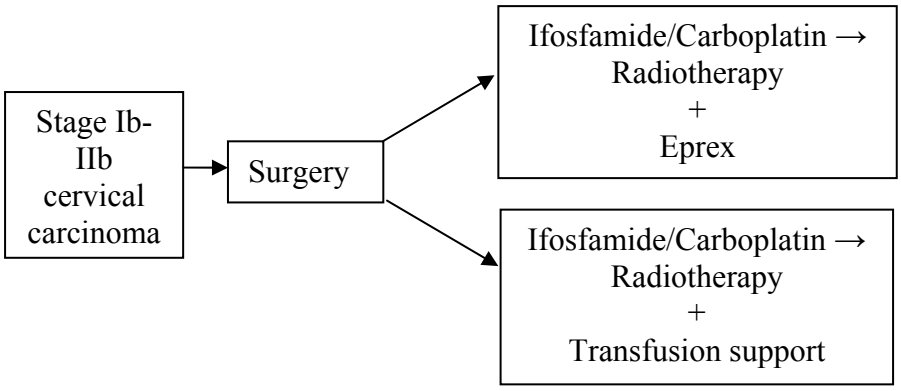
- Significantly shorter survival (HR 1.84; 95% CI, 1.01, 3.35 p= 0.04) in Epoetin-treated patients. Median survivals 63 vs. 129 days, in Epoetin and control arms, respectively
- The incidence of thrombovascular events was not reported in the Journal of Clinical Oncology article.

Limitations to assessment of impact on EFS, OS, or TVE:

- The dosing adjustment rules of epoetin alfa employed in this study are not consistent with approved labeling.
- No primary data available for review.
- The design of the study was not adequate to assess for tumor proliferation.
  - The only assessment of tumor progression was at 12 weeks and was performed by clinical assessment and chest x-ray.
- The study did not address specific monitoring for possible thrombotic/ cardiovascular events, as outlined in the ODAC recommendations on May 4, 2004

AGO/NOGGO

Study Design:



The AGO/NOGGO study was a Phase 3, randomized, open label trial of 264 patients with FIGO stage Ib-IIb cervical cancer undergoing treatment with postsurgical adjuvant sequential chemotherapy (ifosfamide and carboplatin) followed by RT (50.4 Gy) randomized to receive either epoetin alfa (Eprex) or supportive care.

Primary endpoint

- 5 year recurrence free survival.

Secondary endpoints

- Relevant secondary endpoints were overall survival and time to treatment failure

Study drug treatment: Target hemoglobin 13 g/dL. Eprex was given over the course of chemotherapy and RT. The dose of Eprex was adjusted throughout the study based on the subject's hemoglobin.

The study accrued 264 patients between January 1999 and study closure in March 2001. A primary efficacy and safety dataset has not been submitted to FDA as of April 2007.

The results below are based on summary safety and efficacy data submitted to FDA by Johnson & Johnson in 4/06.[29] In addition, an abstract was published in ASCO 2003 by Blohmer et al[33].

Reported results:

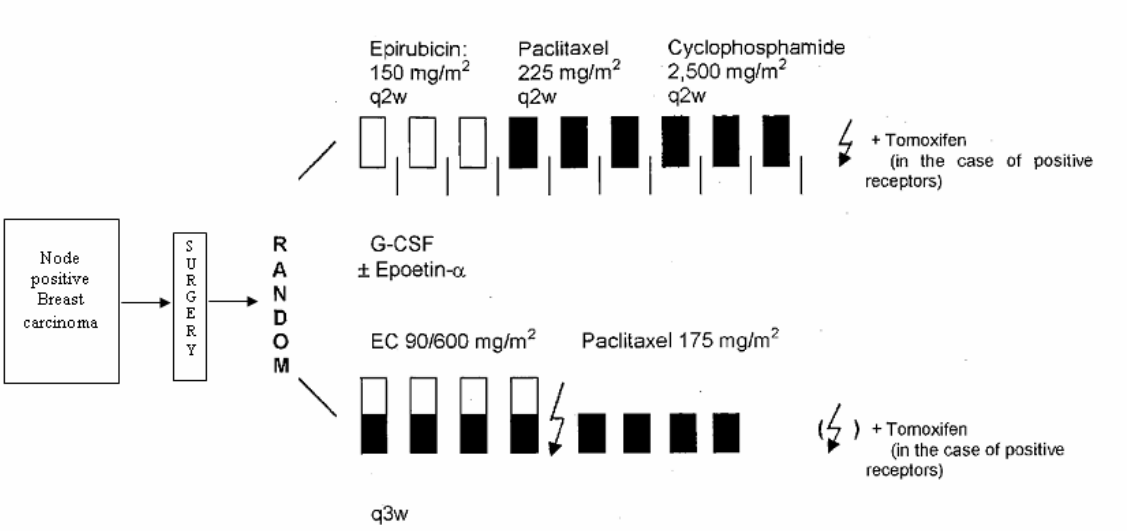
- 5 year RFS (primary endpoint): not reported
- No significant difference in relapse rates (17% vs. 25%, p= 0.074) with median follow-up of 105 weeks
- 1 yrs RFS 91% vs. 86%; 2-yr RFS 81% vs. 70% (p=0.058) reported in 2003 abstract.
- No results reported for overall survival or time to treatment failure.

Limitations to assessment of impact on tumor outcomes, OS, or TVE:

- The dosing adjustment rules of epoetin alfa employed in this study are not consistent with approved labeling.
- Primary data has not been submitted to FDA.

Moebus

Study Design:



Johnson & Johnson identified this study as one with potential to address the risks of ESAs in their annual report submitted in April of 2006. The Moebus study was a Phase 3, randomized, multifactorial design, open label trial with a planned enrollment of 1284 patients with node positive breast cancer. Patients are randomized to receive dose-intensive (every 2 week) treatment with sequential single agent courses of epirubicin, paclitaxel, and cyclophosphamide (ETC) or standard chemotherapy consisting of epirubicin and cyclophosphamide every three weeks for four cycles followed by paclitaxel every 3 weeks for an additional 4 cycles. Chemotherapy is to be followed by RT, and hormonal therapy if appropriate. Patients randomized to the dose-intensive arm were subsequently randomized to receive epoetin alfa (Eprex) or transfusion support.

Primary endpoint

- Co-primary endpoints were 2 year disease-free survival of ETC every 2 weeks vs ETC every 3 weeks, and change in hemoglobin concentration.

Secondary endpoints

- 5-year overall survival and disease free survival of ETC every 2 weeks vs ETC every 3 weeks, quality-of-life, median hemoglobin levels, and the rate of intramammary recurrence of disease.

Study drug treatment: Target hemoglobin 12.5-13 g/dL. Eprex was given over the course of chemotherapy. The dose of Eprex was adjusted throughout the study based on the subject's hemoglobin.

A total of 1284 patients were enrolled onto study between January 1999 and March 2001. Of these, 593 patients were enrolled on the every 2 week chemotherapy arm and randomized to receive Eprex versus supportive care. Despite study closure in March 2001, a primary efficacy and safety dataset has not been submitted to FDA as of 4/07. Summary results were provided in April 2006 and in an unpublished abstract in May 2007.[29,34]

Reported results:

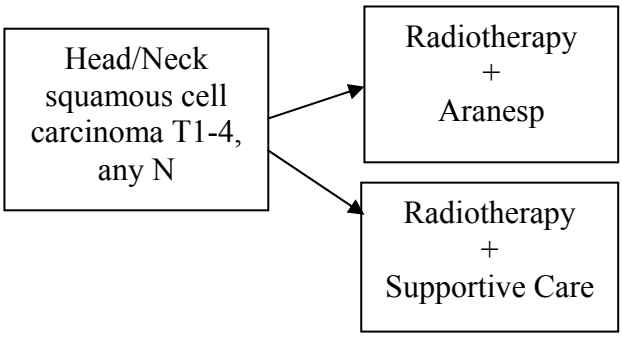
- No significant differences in 5 yr DFS and 5-yr OS within the subset randomized to Eprex versus transfusion support.
- The rate of thrombovascular events (TVEs) was 3.0% for the Eprex arm vs 1.7% for the transfusion support.

<u>Limitations to assessment of impact on EFS, OS, or TVE:</u>

- The dosing adjustment rules of epoetin alfa employed in this study are not consistent with approved labeling.
- No primary data set available for review.
- The design of the study was not adequate to assess for tumor proliferation.
    - The effects of epoetin alfa on tumor response or survival were not specified as endpoints of this study.
    - This study has a multifactorial design to study the effects of two chemotherapy regimens on event-free survival. Assessment of the impact of Eprex co-administration on disease-free or overall survival is one of multiple secondary endpoints. There are insufficient details to determine the adequacy of the analytic approach, including adjustment for multiplicity.
    - Radiographic assessments for disease-free survival were performed at baseline, at the end of chemotherapy, and then annually.
- Reliability of survival and DFS results may be impacted by "a significant number" of subjects who were lost to follow-up.
- The study did not address monitoring for possible thrombotic/ cardiovascular events, as outlined in the ODAC recommendations on May 4, 2004
    - Routine assessments of TVEs events were not prespecified in the protocol.
    - The summary materials provided are ambiguous regarding the definition of TVEs.

Study SE 2002-9001 (DAHANCA)

Study Design:



Study SE 2002-9001 (DAHANCA) was a Phase 3, open-label, randomized study in treatment-naïve patients with head and neck squamous cell carcinoma (T1-4, any N stage) and with Hgb < 14.5 g/dL who were undergoing treatment with definitive radiotherapy.

Primary endpoint

- 5 yrs locoregional control rates, defined as events occurring at least two months after completion of RT.

Secondary endpoints

- Relevant secondary endpoints included local control, overall survival, disease-specific survival, and toxicities.

Randomization stratified by

- Institution, gender, site of disease, T-classification, N-classification, intent of systemic neck node dissection, and type of treatment and group.

Study drug treatment: Aranesp was to be administered at 150 µg weekly until the completion of radiation treatment. The target Hgb level was 14 g/dl to 15.5 g/dl. Aranesp dose modification rules included Aranesp administered at 150 µg weekly when Hgb ≤14; Aranesp administered at 80 µg weekly when Hgb>14 but ≤15.5; Aranesp withheld when Hgb > 15 g/dl; and increase of Aranesp to 300 µg weekly when Hgb decreasing after 4 doses of Aranesp 150 ug injection.

Amgen informed FDA of preliminary interim results of study SE 2002-9001 on December 6, 2006. Five hundred twenty two of 600 planned patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy were randomized to receive Aranesp or transfusion support from July 2002 to October 2006. The study was terminated after a planned interim analysis in October 2006 showed no evidence of potential benefit in the Aranesp arm. Amgen projected to submit final study report to FDA by the third quarter of 2008.

Reported results:[35,36]

- An interim analysis in 484 patients demonstrated a 10% increase in locoregional failure rate among Aranesp -treated patients ($p = 0.01$).

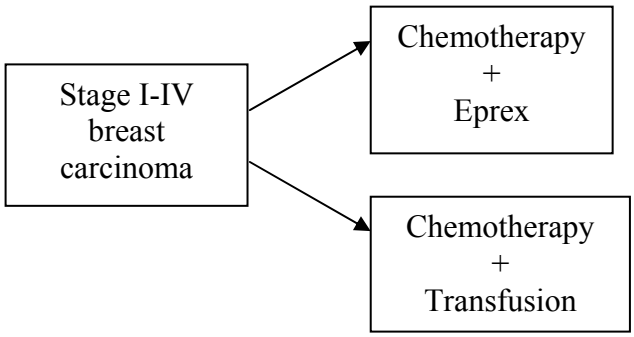
- Trend toward shorter survival in the Aranesp-treated arm (p = 0.08).

Limitations to assessment of impact on tumor outcomes, OS, or TVE:

- The dosing regimen and dose adjustment rules for Aranesp employed in this study are not consistent with either of the approved regimens (2.25 ug/kg QW or 500 ug Q3W).
- The design of the study was not adequate to assess tumor proliferation.
  - There was no uniform imaging assessment of the head and neck mandated at baseline, or for tumor recurrence.
  - Tumor biopsy was not mandated to document recurrence.
  - There was inadequate imaging assessment at baseline to exclude distant metastasis.
- The study did not address specific monitoring for possible thrombotic/cardiovascular events, as outlined in the ODAC recommendations on May 4, 2004.

EPO-CAN-17

Study Design:



EPO-CAN-17 was a Phase 3, randomized, open label trial of 354 patients with Stages I-IV breast cancer receiving chemotherapy and randomized to receive either epoetin alfa (Eprex) or supportive care.

Primary endpoint

- Quality of life

Secondary endpoints

- Response rate and overall survival.

Study drug treatment: Target hemoglobin 12-14 g/dL. Eprex was given for 16 weeks or for 4 weeks post chemotherapy, whichever was longer (to a maximum of 28 weeks). The dose of Eprex was adjusted throughout the study based on the subject's hemoglobin.

The study accrued 354 patients between February 2002 and May 2003. Despite study closure in May 2003, a primary efficacy and safety dataset has not been submitted to FDA as of April 2007. The results below are from summary data provided by Johnson &

Johnson in April 2006. The study results were published in the Journal of Clinical Oncology in April of 2005.[37]

Reported results:

- Significant improvement in multiple analyses of HRQOL
- No significant difference in overall survival.
- The overall response rate among 74 patients with Stage IV breast cancer similar (37% vs. 30%).
- Increased incidence of "deep thrombophlebitis" (6.2% vs. 0.6%) in Epoetin alfa-treated patients.
- No difference in overall incidence of thrombovascular events (TVEs)
- Significantly higher incidence of moderate to severe Neutropenia, nausea, and anorexia in Epoetin-treated patients, significantly higher incidence of fever and anemia in the transfusion support arm; similar incidence of moderate to severe fatigue in both arms.

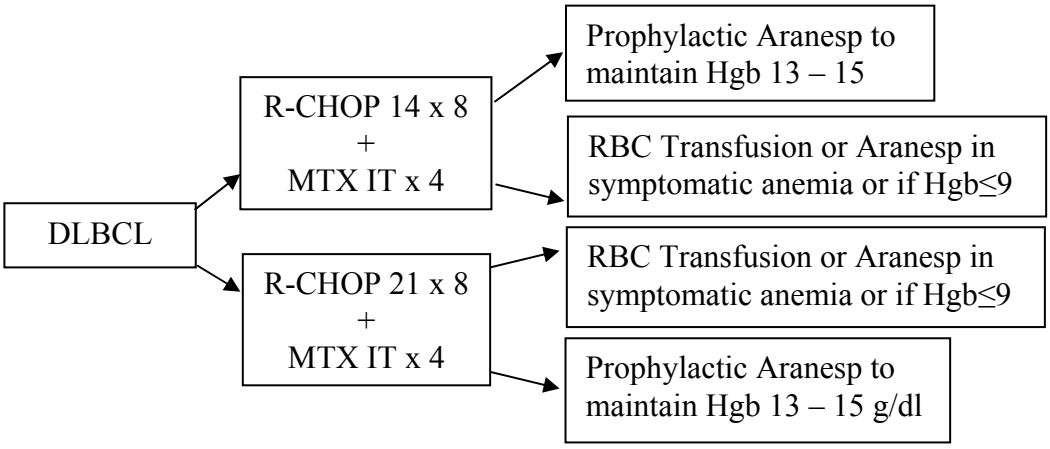
FDA analysis of adverse event data provided in March 2007 dataset demonstrated an increased incidence of TVEs in epoetin alfa treated patients (7.1% vs 3.6%). The term "TVE" included deep vein thrombosis, cardiac arrest, jugular vein thrombosis, thrombosis, arterial thrombosis, pulmonary embolism, carotid artery occlusion, intracranial hemorrhage, cerebral hemorrhage, cerebrovascular accident, cerebral ischemia, angina pectoris, acute coronary syndrome, and ischemic cardiomyopathy.

Limitations to assessment of impact on tumor outcomes, OS, or TVE:

- The dosing adjustment rules of epoetin alfa employed in this study are not consistent with approved labeling.
- Primary datasets containing information on tumor outcomes and survival have not been submitted.
- The study was not adequately designed to assess for effects on tumor proliferation
    - Tumor staging was not conducted adequately and rigorously. For the subset of patients with Stage IV disease (a total of 74 patients in the study), tumor staging was performed at baseline, week 12, and within 5 days of the last dose of Eprex. No systematic assessment of tumor response was required after last dose of Eprex.
- The study was not adequately designed to assess for effects on overall survival
    - The length of follow-up for overall survival is not adequate to assess impact in patients with early-stage breast cancer.
    - Overall survival follow-up was performed at 6, 12, 18, and 24 months in a heterogeneous population (Stage I-IV breast cancer) with the potential to receive different therapeutic regiments.
- The study did not address specific monitoring for possible thrombotic/ cardiovascular events, as outlined in the ODAC recommendations on May 4, 2004
    - Routine assessments of thrombovascular events were not prespecified in the protocol.
    - The definition used for TVEs was overly broad including terms not likely to represent true thrombovascular events.

Study FR 2003-2005 (GELA LNH03-6B)

Study Design:



Study FR 2003-2005 (GELA LNH03-6B) is a phase 3, randomized, open-label, multifactorial, multicenter study of intensified CHOP plus Rituximab given every 14 days (R-CHOP 14) versus CHOP plus Rituximab given every 21 days (R-CHOP 21) in patients with previously untreated diffuse large B cell lymphoma (DLBCL). R-CHOP was given for 8 cycles, and both arms received intrathecal (IT) methotrexate (MTX) for the first 4 cycles. A second randomization of each R-CHOP arm was performed to prophylactic Aranesp versus RBC transfusions or Aranesp in symptomatic anemia or if Hgb ≤ 9 g/dL.

Primary endpoint

- Event free survival (EFS) between the two chemotherapy arms (R-CHOP 14 versus R-CHOP 21).

Secondary endpoints

- Comparisons between the two chemotherapy arms (R-CHOP 14 versus R-CHOP 21) in response rate, progression rate, relapse rate, disease-free survival for complete responders, and overall survival.
- Relevant secondary endpoints that compared Aranesp vs *RBC transfusion or Aranesp* were response rate, progression rate, relapse rate, disease-free survival for complete responders, and overall survival.

Study drug treatment: In patients randomized to prophylactic Aranesp, the study drug was to be administered at 2.25 µg/kg, weekly, to maintain Hgb level between 13 to 15 g/dl until 4 weeks after completion of chemotherapy. Aranesp was to be increased to 4.5 µg/kg, weekly when Hgb < 13 g/dl at chemotherapy cycle 3. Aranesp was to be suspended when Hgb > 15 g/dl, and resumed at a reduced dose of 1.5 ug/kg, weekly, when Hgb decreased to below 14 g/dl. Patients randomized to the arm without prophylactic Aranesp arm were to be treated according to local practice, including RBC transfusion, or Aranesp when patients had symptomatic anemia or if Hgb < 9 g/dl.

The target hemoglobin was changed from 13-15 g/dL to 13-14 g/dL by amendment in July 2005 in order to comply with a request from European regulators.

Reported results

An unplanned analysis for safety was conducted in the first 130 patients enrolled and included in the Amgen's periodic safety update report submitted to the license application on Dec. 2006. Summary information also published in 2006 abstract in Blood.[38]

- Overall survival was similar
- Event free survival was similar.

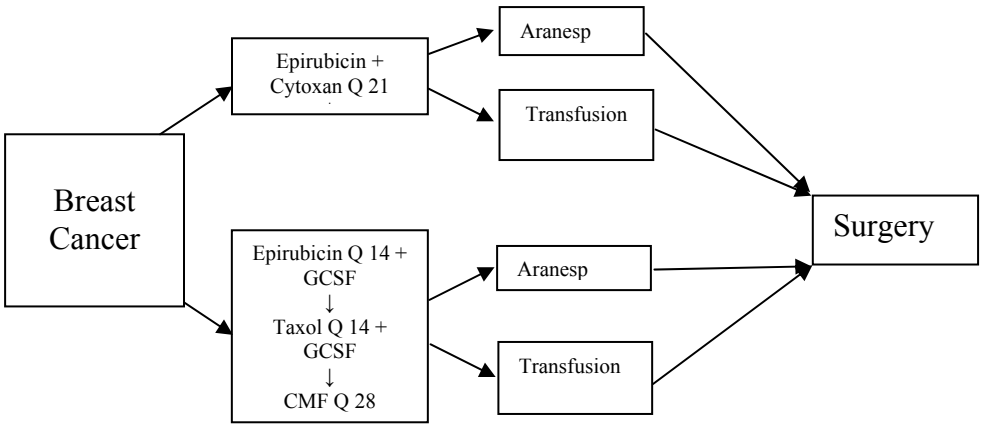
Limitations to assessment of impact on EFS, OS, or TVE

- This study has a multifactorial design to study the effects of two chemotherapy regimens on event-free survival. Assessment of the impact of Aranesp co-administration on disease-free or overall survival is one of multiple secondary endpoints. The control arm is confounded by the possible administration erythropoietin products. There are insufficient details in the protocol to determine the adequacy of the analytic approach, including adjustment for multiplicity.
- The design of the study was not adequate to assess tumor proliferation. Response rate and DFS were not clearly defined in the protocol, and criteria for tumor response, disease progression, or relapse were not provided.
- The dosing regimen and dose adjustment rules for Aranesp employed in this study are not consistent with either of the approved regimens (2.25 ug/kg QW or 500 ug Q3W).
- The study did not address specific monitoring for possible thrombotic/ cardiovascular events, as outlined in the ODAC recommendations on May 4, 2004.

The following studies are either still accruing or have failed to achieve enough events for final analysis. No data are available regarding tumor outcomes or survival for these studies.

Study DE 2001-0033 (PREPARE)

Study Design:



Study DE 2001-0033 was an open-label, randomized, 2 x 2 multifactorial design study intended to compare the efficacy of a preoperative, sequential chemotherapy with epirubicin, and cyclophosphamide followed by paclitaxel in standard dosage and dosing intervals versus a dose-intensified, interval-shortened sequential chemotherapy with epirubicin, paclitaxel, and CMF in patients with breast cancer.

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.

Study drug treatment: Aranesp/placebo administered at a dose of 4.5 μg/kg every 2 weeks until 14 days after the last cycle of chemotherapy. Aranesp was withheld when Hgb ≥ 13 g/dl and resumed when Hgb < 13 g/dl. Note: Patients randomized to Aranesp did not initiate treatment until the hemoglobin was less than 13 g/dL.

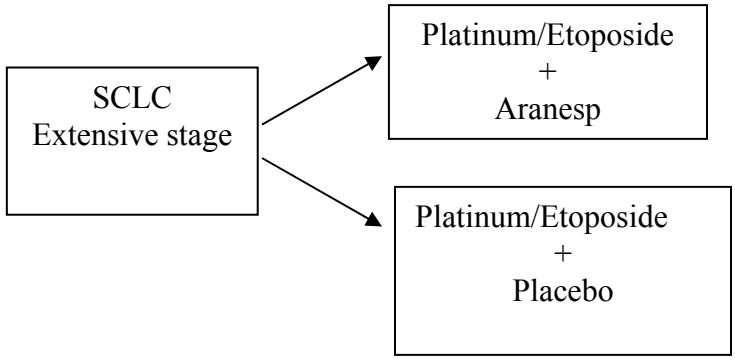
Limitations of assessment of impact on RFS, OS, and TVE:

- This study has a multifactorial design to study the effects of two neoadjuvant chemotherapy regimen on relapse-free survival and overall survival as co-primary endpoints. Assessment of the impact of Aranesp co-administration on relapse-free or overall survival is one of multiple secondary endpoints. There are insufficient details in the protocol to determine the adequacy of the analytic approach, including adjustment for multiplicity.
- The dosing regimen and dose modification rules for Aranesp employed in this study are not consistent with either of the approved regimens, (2.25 ug/kg QW or 500 ug Q3W).
- The design of the study was not adequate to assess tumor proliferation. In this protocol, subjects with breast cancer were to be given 12 weeks of neoadjuvant chemotherapy, followed by surgery, radiation, and hormonal therapy. The structure of this study would allow the determination of possible effects of darbepoetin alfa on tumor growth during the chemotherapy phase. However, since all subjects would undergo surgery, further tumor size determination would not be possible.
- Follow-up monitoring was inadequate. Routine scans or blood chemistries were not mandated as part of follow-up monitoring for disease recurrence, no imaging of the contralateral breast was mandated, and it was not stated when follow-up monitoring ended.
- The study did not address specific monitoring for possible thrombotic/cardiovascular events, as outlined in the ODAC recommendations on May 4, 2004.

Studies which are ongoing with no data provided to FDA

2001-0145 (Amgen)

Study Design:



Study 20010145 is a randomized, double-blind placebo-controlled, multicenter study of Aranesp in 583 subjects with previously untreated, extensive-stage, small cell lung cancer.

Co-primary endpoints:

- Change in hemoglobin from baseline to the end of study treatment phase.
- Survival time.

Randomization stratified by:

- Region (Western Europe, Australia, North America versus the rest of world)
- ECOG performance status (0, 1 versus 2)
- LDH level (normal versus abnormal).

Study treatment: Aranesp/ placebo at a dose of 300 µg every week for the first four weeks then every 3 weeks throughout the 6 cycles of chemotherapy and 3 weeks after the last dose of chemotherapy. Withhold study drug for Hgb ≥ 14 g/dl; resume when Hgb< 13 g/dl.

Assessment throughout the treatment phase of the study:

- Disease response assessment by CT scan of chest and abdomen was to occur approximately 1 week before cycles 3 and 5, and 2 weeks after cycle 7 of on-study chemotherapy.

End of Study treatment visit:

- Disease response assessment by CT scan of chest and abdomen, and chest X-ray.

Follow-up:

- CT of chest and abdomen every 3 months until documented disease progression.
- Collect information on additional therapy given for treatment of SCLC.

Subjects who have documented disease progression will continue to be followed every 3 months until death or the point at which all randomized subjects have completed their end of study treatment visit and 496 deaths have occurred.

Long term follow-up:

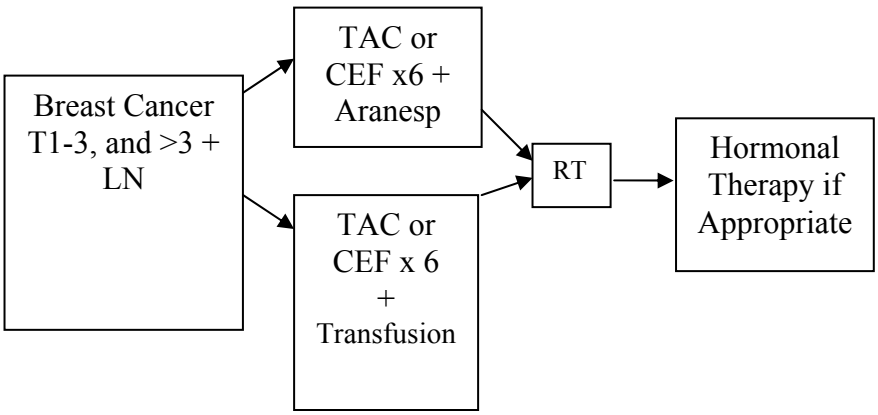
- After the end of the study, survival data were to be collected at pre-specified intervals, until all randomized subjects have died. The collection of data was to be at quarterly intervals initially, and increased to 6-12 month intervals as appropriate.

Limitations in assessment of impact on OS, PFS, or TVEs:

- The dosing regimen and adjustment rules of Aranesp employed in this study are not consistent with approved labeling Aranesp dose regimen, (2.25 ug/kg, QW or 500 ug Q3WS) and adjustment rules in this study population.
- Patients with SCLC, a disease entity with pathologic and biologic characteristics distinct from NSCLC and many other common solid tumors, may not adequately represent the general patient population receiving Aranesp for an oncology indication.
- The study did not address specific monitoring for possible thrombotic/cardiovascular events, as outlined in the ODAC recommendations on May 4, 2004.

Study DE 2002-0015 (ARA-03)

Study Design:



Study DE 2002-0015 (ARA-03) was a phase 3, open-label, randomized, multicenter study of Aranesp versus supportive care in patients with T1-3 breast cancer who had more than 3 positive lymph nodes receiving adjuvant chemotherapy with either TAC (docetaxel, doxorubicin, cyclophosphamide) or CEF (cyclophosphamide, epirubicin, fluorouracil). Randomization was to be stratified by study centers. Study investigators chose whether patients would receive adjuvant TAC or FEC chemotherapy; no stratification by type of chemotherapy.

Primary endpoint

- Event-free survival (EFS) rates between the two study arms.

Secondary endpoints:

- The relevant secondary endpoints included overall survival rate, local relapse rate, QOL, and toxicity.

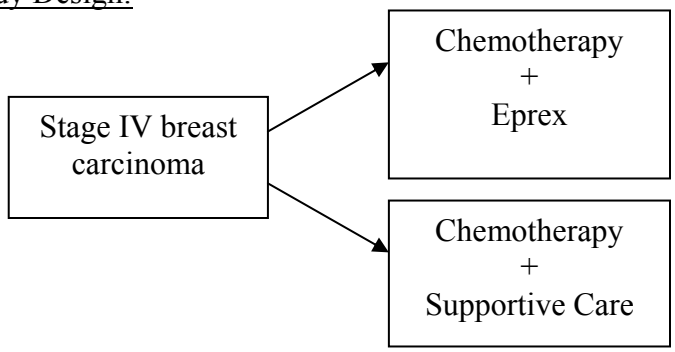
Study drug treatment: Aranesp administered concurrently with chemotherapy at 300 ug weekly for 4 weeks then at a dose of 300 μg every three weeks in patients with Hgb ≤ 13.5 g/dl until patients completed radiotherapy. Aranesp was to be withheld when Hgb > 14 g/dl and resumed when Hgb < 13.5 g/dl.

Limitations to assessment of impact on EFS, OS, or TVE:

- The dosing regimen and dose adjustment rules for Aranesp employed in this study are not consistent with either of the approved regimens (2.25 ug/kg QW or 500 ug Q3W).
- The chemotherapy regimen was not homogenous. Subjects could receive either TAC or CEF, at the discretion of the investigator. Randomization was stratified by study centers, not by chemotherapy regimen.
- The design of the study was not adequate to assess tumor proliferation. Similar to the PREPARE trial above, follow-up tumor assessment modality and frequency was inadequate: follow-up CXR, abdominal ultrasound, and bone scan were to be performed as clinically indicated, and were not routinely required. Routine laboratory exams were not included as part of follow-up.
- The study did not address specific monitoring for possible thrombotic/cardiovascular events, as outlined in the ODAC recommendations on May 4, 2004.

EPO-ANE-3010 (Johnson & Johnson)

Study Design:



EPO-ANE-3010 was presented to the May 2004 ODAC as a postmarketing commitment study, as a randomized, placebo-controlled trial in 2000 patients, designed to rule out a 15% decrement in progression-free survival. The final protocol was submitted in December 2004 and was modified as an open-label trial enrolling 1000 patients, designed to rule out a 25% decrement progression-free survival; the changes were intended to enhance accrual and rapid completion of the study. The study has accrued slowly since December 2004, and in the 27 months since the final protocol submission, has only accrued 111 patients as of 3/23/07. An outline of the study was presented by Johnson & Johnson in ODAC May 2004. EPO-ANE-3010 is a randomized, open label study of epoetin alfa (Eprex) in subjects receiving first-line standard chemotherapy for metastatic breast cancer.

Primary endpoint

- Progression Free Survival, as measured from the date of randomization to the first date of progressive disease or death from any cause, whichever occurs first.

Relevant secondary endpoints

- Overall response rate
- Response duration
- Time to progression
- Overall survival
- Incidence of thrombovascular events.

Randomization stratified by:

- Prior adjuvant chemotherapy regimen (prior anthracycline or no prior anthracycline chemotherapy).
- HER2/Neu status (positive or negative)
- Disease-free survival interval between initial diagnosis of breast cancer and metastatic disease (< 12 or ≥ 12 months)

There is no stratification for the chemotherapeutic regimen; a variety of different first-line metastatic breast cancer chemotherapy regimens are permitted.

Study treatment: The target hemoglobin is 12 g/dL.

Tumor assessments and Follow-Up:

- Assessment of response or progressive disease is performed by CT scans of the chest and abdomen (and other sites if involved with metastatic disease) every 8 weeks for 1 year and then every 12 weeks (3 months) until disease progression or the clinical cutoff, whichever comes first. Additional imaging studies are performed based on signs and symptoms of the subject for suspected new lesions.
- All subjects are evaluated weekly for clinical signs and symptoms of thrombovascular events (TVE), and will undergo specific laboratory and medical imaging studies to evaluate for TVE if clinical suspicion exists.
- After disease progression, subjects will be followed for survival every 3 months until death or end of study (3 years after the last subject is randomized).

Limitations in assessment of impact on TVEs:

- The multiple chemotherapy regimens employed may confound assessment for risks of TVEs.

CONCLUSIONS:

Information regarding effects of ESAs on survival, tumor promotion, and TVEs continue to evolve since the first ESA approval (Procrit in 1993) for the treatment of anemia associated with cancer chemotherapy, which was based on reduction in the proportion of patients receiving RBC transfusions during chemotherapy. The studies supporting labeling expansion for both Procrit and Aranesp were not designed to assess for the impact of ESAs on survival or on tumor promotion.

As of March 2007, there are five randomized clinical trials (BEST, ENHANCE, 20010103, 20000161, and EPO-CAN-20) that demonstrated decreased survival times in

cancer patients receiving ESAs compared with those receiving transfusion support. There are three randomized studies (ENHANCE, BEST, and SE 2002-9001 "DAHANCA") that demonstrate poorer tumor outcomes (locoregional control or progression-free survival) in cancer patients receiving ESAs compared with those receiving transfusion support. With the exception of one clinical trial (Study 20010103) conducted in anemic patients with cancer who were not receiving concurrent chemotherapy, the studies demonstrating detrimental effects on survival and/or tumor outcomes employed an unapproved treatment regimen designed to maintain hemoglobin levels above 12 g/dL.

There are insufficient data to characterize the effects of ESAs on survival or on tumor promotion when ESAs are administered in accordance with recommended dosing in product labeling. There are no data from adequately designed trials intended to characterize the risk of tumor promotion, and there are only two adequately designed trials that are ongoing from which such data are anticipated: Study 20010145 in patients with small cell lung cancer and Study EPO-ANE-3010 in patients with metastatic breast cancer. Results from Study 20010145 may not be generalizable to patients with epidermoid tumors and results from Study EPO-ANE-3010 may not be available for several years.

The increased risk of TVEs in patients receiving ESAs has been evident in multiple studies and across varied clinical settings. While an increase in the number of TVEs in patients receiving ESAs increases morbidity and is likely to increase mortality, the detrimental effects on survival in patients receiving ESAs can not been attributed solely to the higher rate of TVEs nor to the poorer tumor outcomes .

The uncertainty regarding the risks of ESAs when used in accordance with product labeling has not been satisfactorily addressed in the past three years. Additional efforts should be made to obtain such information in a timely manner. In addition, regular re-assessment of the net clinical benefit of ESAs (avoidance of blood transfusions and the risks of such transfusions) should continue to be weighed against the potential for detrimental effects on survival and tumor growth. Further modifications to product labeling may be appropriate to minimize risks to patients, through restrictions of the indicated patient population or further limitations on dosing to achieve the minimal hemoglobin level necessary to avoid transfusions.

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